Investigating the structural neural correlates and psychological determinants of clinical insight in enduring schizophrenia

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I. Abstract

Objectives. The main objective of this thesis is to contribute to a better understanding of clinical insight by refining our understanding of its psychological and neuroanatomical determinants in enduring schizophrenia, through the integration of current knowledge on the etiology of insight, and by addressing limitations of previous work in this field. In pursuit of this objective, two studies were performed using data collected from the same sample of enduring schizophrenia patients. The aims of the first study were to 1) examine the relative contribution of different social cognitive abilities and self-reflectiveness to clinical insight, and 2) to identify the strongest predictors of clinical insight by elucidating the relative contribution of known predictors of insight, including social cognition and self-reflectiveness. The aims of the second study were to investigate the structural neuroanatomical correlates of clinical insight using structural magnetic resonance imaging (MRI) and a comprehensive measure of clinical insight by investigating 1) the link between whole-brain cortical thickness and clinical insight levels, and 2) the link between volumes of 4 subcortical structures and clinical insight levels.

Results. Results of the first study indicated that affective empathy, medication dosage, and self-reflectiveness are the strongest unique predictors of clinical insight. In the second study, no associations between both insight factors and cortical thickness were found. Bilateral hippocampal volumes were positively correlated with higher scores on an assessment of clinical insight. No other significant associations emerged between neuroanatomical markers and clinical insight.

Conclusions. The findings presented in this thesis are significant because they shift the emphasis from previous notions that poor clinical insight can be mainly attributed to neurocognitive deficits or positive symptoms. Instead, these studies suggest that levels of insight may not have a

clear neuroanatomical basis, and that this phenomenon may be largely determined by psychological variables such as self-reflectiveness and affective empathy. It is hoped that the studies presented in this thesis pave the way for the development of more targeted interventions that address the underlying psychological bases of clinical insight. Moreover, the findings of these studies which represent clinical insight as a complex, multi-determined phenomenon, provide a stepping stone toward more integrative approaches to research on clinical insight that elucidates the specific ways in which different factors are related to insight.

Résumé

Objectifs. L'objectif de cette thèse est de contribuer à une meilleure compréhension du phénomène de l'*insight* clinique, en raffinant nos connaissances sur ses déterminants psychologiques et neuroanatomiques chez les patients ayant un diagnostic de schizophrénie, à travers l'intégration des connaissances actuelles sur l'étiologie de l'insight, et en adressant les limitations des études précédentes sur ce sujet. Afin d'atteindre cet objectif, deux études ont été réalisées à partir d'un échantillon de patients ayant un diagnostic de schizophrénie chronique. Les objectifs de la première étude étaient 1) d'évaluer la contribution relative de la cognition sociale et l'auto-réflexion sur le niveau d'insight des patients ayant la schizophrénie, et 2) d'identifier les prédicteurs principaux de l'insight, en évaluant la contribution relative de prédicteurs d'insight connus, ainsi que la cognition sociale et l'auto-réflexion. Les objectifs de la deuxième étude étaient d'élucider les corrélats neuroanatomiques de l'insight clinique, par l'utilisation de l'imagerie à résonance magnétique en étudiant 1) le lien entre l'épaisseur du cortex et le niveau d'insight, ainsi que 2) le lien entre le volume de 4 structures cérébrales sous-corticales, et le niveau d'insight.

Résultats. Les résultats de la première étude ont démontré que l'empathie affective, la dose de médicaments antipsychotiques, et l'auto-réflexion sont les prédicteurs uniques et principaux du niveau d'insight chez des patients ayant un diagnostic de schizophrénie chronique. Les résultats de la deuxième étude ont démontré qu'il n'existe pas de lien entre l'épaisseur du cortex et le niveau d'insight. Cependant, un meilleur insight était associé à une augmentation du volume bilatéral de l'hippocampe. Aucune autre association entre le volume de structures sous-corticales et l'insight n'a été trouvé.

Conclusions. Les résultats présentés dans cette thèse sont importants car ils amènent une nouvelle perspective sur l'étiologie des déficits d'insight en schizophrénie, en changeant l'emphase sur les déficits neurocognitifs en tant que cause principale de l'insight. Les deux études suggèrent au contraire que l'insight n'aurait pas une base neuroanatomique précise, et que ce phénomène pourrait être largement basé sur des facteurs psychologiques, tels que la cognition sociale et l'empathie. Les résultats de ces études représentent l'insight clinique comme étant un phénomène complexe et multidéterminé. Il est à espérer que les études présentées dans cette thèse ouvriront la voie au développement d'interventions davantage ciblées, qui abordent les bases psychologiques sous-jacentes de l'insight clinique identifiés dans ces études.

II. Acknowledgements

I take the opportunity of having my work written in ink and made public to acknowledge the guidance and invaluable support that I have received from several people throughout my Master's degree. First and foremost, I would like to thank Dr. Martin Lepage, my supervisor, for his guidance and mentoring in the preparation of this thesis. Most importantly, I am grateful for the opportunity to complete the projects presented in this thesis and to have had the ability to pursue my own research interests.

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III. Preface and Contribution of Authors

Martin Lepage designed the larger project on which this thesis is based. Sophie Béland and Martin Lepage developed the research questions presented in this thesis. Data analyses were completed by Sophie Béland, under Martin Lepage's guidance. The entirety of the text presented in this document was written by Sophie Béland. Two written manuscripts comprise Chapters 3 and 4, as follows. In Study #2, CM contributed to the processing of the neuroimaging data. SK contributed to the development of the clinical insight measure used in this study. LB and ML participated in the formulation of the research question and provided supervision and guidance throughout the completion of the project. Finally, SB completed the writing of the article and conducted all analyses.

Chapter 3 Study #1:

The relative contributions of social cognition and self-reflectiveness to clinical insight in enduring schizophrenia

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Chapter 4 Study #2:

Clarifying associations between cortical thickness, subcortical volumes, and a comprehensive assessment of clinical insight in enduring schizophrenia

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Chapter 1: Introduction and objectives

Poor insight is a defining feature of schizophrenia and related psychoses (Amador, Strauss, Yale, & Gorman, 1991). It has indeed been shown that between 40-60% of individuals with schizophrenia lack the awareness that the symptoms or difficulties they are experiencing are related to a mental illness, and this phenomenon has been termed poor clinical insight (Amador & Gorman, 1998; Fennig, Naisberg-Fennig, & Craig, 1996). Individuals with poor clinical insight have been shown to have less favorable functional and clinical outcomes, and therefore it represents a major obstacle for therapeutic interventions and for recovery (Erol, Delibas, Bora, & Mete, 2015; Wittorf et al., 2009). Given that these associations have been found in both enduring and first-episode schizophrenia (Drake et al., 2007; Saravanan et al., 2010), this testifies to the significance of poor clinical insight in psychosis, and emphasizes this as an important target for intervention.

Not surprisingly, the significance of poor clinical insight in schizophrenia has triggered research efforts to better understand this phenomenon by identifying its determinants, both at the psychological and neurobiological level. However, the large body of literature on insight so far indicates that clinical insight does not have a clear etiology, and is instead associated with a range of illness-related factors, from the severity of positive symptoms (Mintz, Dobson, & Romney, 2003), to the degree of neurocognitive deficits (Stratton, Yanos, & Lysaker, 2013). The multi-dimensionality of clinical insight, and the plethora of different factors associated with this phenomenon poses a challenge to the development of clear definitions of clinical insight, and to the creation of well-targeted intervention strategies for deficits in clinical insight in schizophrenia. Moreover, the variables associated with clinical insight are all factors that share

common conceptual and etiological bases. It is therefore difficult to delineate the unique contribution of different variables to levels of clinical insight. Similarly, the available literature on the neural correlates of clinical insight reveals a complex picture, with many studies contributing contradictory evidence. Potential explanations for this contradictory evidence may arise from the significant limitations of previous literature, which include small sample sizes, inadequate or inconsistent assessments of clinical insight, and variation in imaging methodology.

The premise of this thesis was therefore to contribute to a better understanding of clinical insight by refining our understanding of the potential psychological and structural neural determinants of clinical insight by offering a more integrative approach to investigating this phenomenon and addressing limitations of previous work.

The two studies that make up this thesis and that were used to address the main objective of this thesis were conducted as part of a larger project focused on the study of insight in schizophrenia. As part of this larger study, a large amount of data was collected from a sample of 141 schizophrenia patients, and 72 healthy controls, from the administration of a comprehensive set of clinical, psychological, and neurocognitive assessments. Moreover, structural neuroimaging data for most participants (114 patients and 71 controls) was acquired using structural magnetic resonance imaging (MRI). The data that collected as part of this study thus offered the possibility to achieve the two major goals of the present thesis, namely: 1) to refine our understanding of the psychological determinants of clinical insight by bridging findings from previous research and examining the relative contributions of previously identified predictors of clinical insight, with a focus on social cognition and metacognition **(Chapter 3**, **Study #1**) and 2) to examine the neuroanatomical correlates of clinical insight at the level of the cortex and

subcortex, using structural MRI, in a large sample of patients, and using a novel and comprehensive assessment of clinical insight (**Chapter 4, Study #2**).

By completing these studies, the premise of this thesis was to provide a better model for understanding insight, with high quality clinical and neuroimaging data, in the hopes of guiding future research on insight, as well as informing the potential development of psychological interventions that target the predictors of insight identified in the present research. It is hoped that with this new knowledge, functional and clinical outcomes in individuals with schizophrenia can be improved by targeting deficits in insight.

Chapter 2: Literature Review

2.1 Defining Schizophrenia

The endeavor of defining and characterizing schizophrenia as a definable entity is the subject of intensive debate and research (Boyle, 2014). Nevertheless, it is generally agreed upon that schizophrenia refers to an enduring mental illness that involves a loss of touch with reality and distorted thinking, and which is associated with marked impairment in cognitive, occupational, and social functioning. It is thought that currently, between 0.2 to 2% of the Canadian population suffers from this illness (http://www.phac-aspc.gc.ca/publicat/miic-mmac/chap_3-eng.php), a rate that is also consistent globally. The illness tends to affect predominantly males, with a male to female ratio estimated to be around 1.4 (McGrath, Saha, Chant, & Welham, 2008). The onset of schizophrenia most often occurs around late adolescence and early adulthood, and the magnitude of psychopathological symptoms tend to be relatively stable in the long-term (Lang, Kosters, Lang, Becker, & Jager, 2013). Nevertheless, although schizophrenia is often discussed in terms of its enduring nature, a significant proportion of patients can achieve remission, conceptualized as a reduction in the severity of symptoms, below a certain threshold required for diagnosis (Andreasen et al., 2005; Lang et al., 2013).

Individuals who live with schizophrenia often have difficulty maintaining an expected level of social and occupational functioning. For example, it is estimated that the employment rate amongst individuals with schizophrenia is only about 10% (Evensen et al., 2016), compared to approximately 60% for the general Canadian population(Canada, 2017). In line with the disabling nature of this illness, schizophrenia thus represents an important global economic and health burden (Chong et al., 2016).

The main categories of symptoms that make up the diagnostic criteria for schizophrenia, include positive symptoms (e.g. delusions, hallucinations), negative symptoms (e.g. social withdrawal, flat affect) and thought disorder (American Psychiatric Association, 2013). Although these latter symptoms make up the diagnostic criteria for the illness, schizophrenia is also very frequently accompanied by other notable impairments in cognitive functioning, neurobiological abnormalities, and impaired insight. These core aspects of schizophrenia are detailed below. Given that this diverse cluster of symptoms is used to characterize schizophrenia, and given that individuals with schizophrenia will experience differing degrees of severity or presence of these symptoms, this emphasizes the heterogeneity of this disorder, and results in a large variety of illness presentation across patients.

2.1.1. Course of illness

In both clinical and research fields, schizophrenia is often defined and operationalized in terms of distinct stages, including a *prodromal phase*, the *first-episode of psychosis,* and *enduring schizophrenia*. The prodromal phase is characterized by an extended period of time when an individual experiences attenuated psychotic symptoms. Attenuated psychosis implies the presence of symptoms whose severity does not necessarily reach the threshold for a diagnosis of schizophrenia, but still cause significant distress, and is not explained by other medical conditions (Tsuang et al., 2013; Woods, Walsh, Saksa, & McGlashan, 2010). Individuals who present with such experiences are often characterized as being at "high risk" for psychosis, and approximately 30% will convert to a first episode of psychosis after 3 years (Fusar-Poli et al., 2012). This prodromal phase has been of special interest in terms of intervention, and has led to the emergence of early intervention clinics, because it has been shown that the longer the duration of this phase, the poorer the outcomes, such as increased negative symptom severity

(Boonstra et al., 2012), and reduced response to medication (Perkins, Gu, Boteva, & Lieberman, 2005).

The *first-episode* of psychosis/schizophrenia marks the first occurrence of a psychotic episode, where there is presence of symptoms that meet criteria for the disorder. Following the first episode, individuals may go on and experience multiple episodes, and may eventually reach a stable or *enduring* phase. In this latter more prolonged stable phase, the presence of positive symptoms will often gradually reduce, whereas negative symptoms will predominate and persist (Association, 2013; Tandon, Nasrallah, & Keshavan, 2009). Approximately 13.5% of individuals with schizophrenia will achieve recovery, which can be defined as maintained symptom remission and adequate overall functioning for a period of at least 2 years (Liberman, Kopelowicz, Ventura, & Gutkind, 2002)

2.1.2. Positive and negative symptoms

One of the most characteristic feature of schizophrenia is the loss of touch with reality, which can take the form of hallucinations and delusions. Hallucinations represent disturbances in perception, which can involve hearing, feeling, or seeing things that others cannot perceive or without any external stimuli (e.g. auditory hallucinations or hearing voices), whereas delusions refer to firmly held ideas or beliefs that do not necessarily reflect reality, despite contradictory evidence (American Psychiatric Association, 2013). Although these symptoms are often the most emphasized aspects of schizophrenia and can cause significant distress, they often do not represent the most burden in terms of outcomes (Fenton & McGlashan, 1991).

Whereas positive symptoms can be conceptualized as an "addition" of a dysfunctional behavior or thought, negative symptoms refer to a dampening of behaviors considered to be

normative in multiple domains, including language, motor function, and social behavior. Negative symptoms can include impairments in expressiveness such as alogia (poverty of speech) and lack of expressive affect or eye contact, loss of motivation (avolition) and interest (apathy), or an inability to experience pleasure (anhedonia), and social withdrawal(American PsychiatricAssociation, 2013). In the clinical and research fields, a distinction can be made between primary negative symptoms, which are symptoms that are considered to be part of the psychopathology of schizophrenia, and secondary negative symptoms, which are thought to be the result of external factors that often accompany the illness, such as the use of certain prescription medication, or comorbid disorders such as mood disorders (Kirkpatrick, Fenton, Carpenter, & Marder, 2006; Peralta, Cuesta, Martinez-Larrea, & Serrano, 2000). Contrary to positive symptoms, negative symptom severity shows strong associations with poorer quality of life (Norman et al., 2000), and poorer overall outcomes, particularly in terms of social functioning (Milev, Ho, Arndt, & Andreasen, 2005). Moreover, negative symptoms are often persistent in nature whereas a remission of positive symptoms is most likely to be observed. Unfortunately, although pharmacological interventions are effective in alleviating positive symptoms, effective pharmacological interventions for negative symptoms are lacking (Kane & Correll, 2010). Alleviating negative symptoms in schizophrenia thus represents an unmet need, and there has been an increased interest in the development of psychological interventions, which have demonstrated some effectiveness (Lutgens, Gariepy, & Malla, 2017).

2.1.3. Positive formal thought disorder

Another core aspect of schizophrenia and its diagnosis involves disorders of thought, which can affects an individual's pattern of speech and lead to impairments in communication (Andreasen, 1984; American PsychiatricAssociation, 2013). Such phenomenon includes

instances where an individual may fail to iterate ideas that are associated with each other and may jump from one unrelated subject to another (derailment). Moreover, individuals may respond to questions in a tangential manner, with no relationship to the question asked (tangentiality), or may require a lot of time to reach goal ideas by including unnecessary details or comments (circumstantiality). Finally, positive formal thought disorder may also take the shape of incoherent speech, such as in the form of a word salad, where an individual will combine unrelated words within the same sentence.

2.1.4. Cognitive dysfunctions in schizophrenia

Impairments in cognitive functioning are not part of the diagnostic criteria of schizophrenia, but they represent an important predictor of functional and clinical outcomes in patients (Green, 1996; Lepage, Bodnar, & Bowie, 2014; Lystad et al., 2016). Moreover, cognitive impairments often precede the onset of illness (Reichenberg et al., 2010), and past research has consistently and robustly shown that individuals with schizophrenia perform poorer on a variety of cognitive abilities when compared to healthy controls (Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005). Cognitive deficits therefore have garnered much interest in terms research and as a potential target of pharmacological (Bervoets et al., 2012; Lopez-Munoz & Alamo, 2011) and psychological interventions (Bowie, Grossman, Gupta, Oyewumi, & Harvey, 2014).

Evidence suggests that these deficits remain relatively stable throughout the illness (Bora & Murray, 2014) with no significant deterioration with illness progression, as has been shown from studies demonstrating that deficits in first-episode psychosis do not differ in magnitude compared to those seen in individuals with enduring schizophrenia (Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009). Nevertheless, some improvements are observed following

pharmacological(Desamericq et al., 2014) and psychological treatment (Bowie et al., 2014; Kurtz, Mueser, Thime, Corbera, & Wexler, 2015). Impairments in cognition are generalized, but deficits seem most prominent in the domain of verbal and working memory (Fatouros-Bergman, Cervenka, Flyckt, Edman, & Farde, 2014; Saykin et al., 1991; Schaefer, Giangrande, Weinberger, & Dickinson, 2013).

Although verbal and working memory are most severely affected in schizophrenia, social cognition deficits are also frequently observed in schizophrenia. Social cognition refers to the "set of cognitive processes involved in perceiving and using social information" (Green, Horan, & Lee, 2015). Impairments in social cognition are observed across a wide range of abilities, such as the ability to infer other people's mental states (theory of mind), or to recognize emotion. This specific feature of schizophrenia has received a lot of attention primarily because it seems that social cognition is the domain of neurocognition that is the most predictive of outcome(Fett et al., 2011; Mancuso, Horan, Kern, & Green, 2011), and is most associated with levels of social skills, community functioning, and vocational achievement (Couture, Penn, & Roberts, 2006; Green et al., 2008).

Finally, it is important to note that the observed cognitive deficits in schizophrenia may not be inherent to the illness, but can be affected by aspects of the illness, and caution has recently been suggested when interpreting observations of cognitive deficits in research (Moritz et al., 2017). Indeed, factors such as, lack of motivation or defeatist attitudes (Foussias et al., 2015; Grant & Beck, 2009; Moritz et al., 2017), as well as distraction from the presence of certain positive symptoms have been shown to affect a patient's performance cognitive assessments. Therefore, although cognitive impairments are indeed observed, it is important to keep a nuanced understanding and discourse regarding cognitive deficits in schizophrenia.

2.1.5. Neurobiological alterations

Schizophrenia is often described in terms of a brain disorder, owing to evidence demonstrating changes both at the functional and structural brain levels. In terms of structural abnormalities, one of the earliest, and most replicated finding is that patients with a diagnosis of schizophrenia haver larger ventricular size compared to healthy controls (Fusar-Poli et al., 2013; Johnstone, Crow, Frith, Husband, & Kreel, 1976), and this enlargement has been associated with poorer neurocognitive performance and the severity of negative symptoms (Andreasen, Olsen, Dennert, & Smith, 1982; Keilp et al., 1988; Owens et al., 1985).

Reductions in grey matter volume and cortical thickness compared to healthy controls have also been frequently reported in past literature, and have been predominantly found in frontal and temporal regions, as well as in the insular cortex (Goldman et al., 2009; Kuperberg et al., 2003; Narr et al., 2005; Nesvag et al., 2008; Rimol et al., 2010; Shenton, Dickey, Frumin, & McCarley, 2001), including medial structures such as the anterior cingulate cortex and medial prefrontal cortex(Ellison-Wright & Bullmore, 2010; Ellison-Wright, Glahn, Laird, Thelen, & Bullmore, 2008; Fornito, Yucel, Patti, Wood, & Pantelis, 2009). These patterns of grey matter alterations have been related to relevant psychopathology in schizophrenia. For example, grey matter volume reductions in the frontal regions of the brain are thought to underlie deficits in executive functioning and working memory that are characteristic of schizophrenia (Antonova, Sharma, Morris, & Kumari, 2004), although abnormalities in frontal grey matter have also been associated with the severity of negative symptoms (Venkatasubramanian, Jayakumar, Gangadhar, & Keshavan, 2008). Moreover, reductions in the left superior temporal gyrus volume and cortical thickness have been positively correlated with the severity of thought disorder (Shenton et al., 1992) and positive symptoms (Walton et al., 2017).

Studies investigating potential neuroanatomical correlates of schizophrenia have also indicated that individuals with schizophrenia exhibit abnormalities in subcortical and limbic structures, including reduced volume of the amygdala, thalamus, and hippocampus (Rimol et al., 2010; Shenton et al., 2001; van Erp et al., 2016). In line with evidence for a role of the hippocampus in memory processes, it has been shown that reduced volume of the hippocampus in particular may be related to the memory deficits characteristic of the illness (Wang, Montchal, Yonelinas, & Ragland, 2014). Finally, there is also evidence for greater basal ganglia volumes in schizophrenia, which may be mediated by extended exposure to antipsychotic medication in enduring schizophrenia samples (Corson, Nopoulos, Miller, Arndt, & Andreasen, 1999; Ellison-Wright & Bullmore, 2010; Hokama et al., 1995; Rimol et al., 2010; van Erp et al., 2016; Zampieri, Bellani, Crespo-Facorro, & Brambilla, 2014).

Reviewing the literature on the neural structural correlates of schizophrenia therefore reveals a complex picture, where abnormalities are found in widespread areas around the brain. From this observation, it has been suggested that schizophrenia may be more accurately understood as a disorder of brain connectivity (Fornito & Harrison, 2012; Stephan, Friston, & Frith, 2009). Indeed, structural and functional connectivity analyses have shown that schizophrenia patients show aberrant connectivity, particularly in networks relaying frontal, temporal and limbic regions, in line with structural anatomical features discussed above (Andreasen et al., 1996; Garrity et al., 2007; Weinberger, Berman, Suddath, & Torrey, 1992). In turn, these alterations in brain networks are thought to give rise to the set of symptoms observed in schizophrenia.

2.2. Insight in schizophrenia

Another one of the distinguishing features of schizophrenia is the observation that patients are often unaware of different aspects of their illness experience. Indeed, studies have

demonstrated that approximately 50% of patients with schizophrenia are unaware of their illness experiences (Amador et al., 1994; Fennig et al., 1996). This phenomenon has been termed clinical insight, a concept thought to be composed of multiple dimensions of awareness including: 1) awareness of having a mental illness or psychological disturbances, 2) awareness of the need or of effectiveness of treatment, 3) awareness of their symptoms, 4) attributing symptoms to a mental illness and 5) awareness of the social, occupational, or functional consequences of the illness (Amador and David, 1998). Moreover, it is generally accepted that levels of clinical insight can vary along a continuum, as opposed to being a categorical dimension (A. S. David, 1990).

Schizophrenia patients who have poor levels of awareness on these dimensions have been shown to have less favorable functional and clinical outcomes (Erol et al., 2015, Wittorf et al., 2009) such as higher frequency of rehospitalization and relapse (Drake et al., 2007; Olfson, Marcus, Wilk, & West, 2006). Moreover, it has been shown that better clinical insight is associated with better medication adherence and overall improved clinical outcomes (Mohamed et al., 2009, Novick et al., 2015, Schwartz et al., 1997). This literature therefore has provided an impetus to study the nature of poor insight in schizophrenia in order to improve outcomes in this population. Much research has therefore been conducted to aim to better understand and define insight as a phenomenon by exploring the correlates and potential determinants of clinical insight.

2.2.1. Insight and course of illness

Levels of clinical insight have been explored in individuals with a first episode of psychosis (FEP) as well as those with more enduring forms of schizophrenia. The literature shows that levels of clinical insight in those with a FEP is less stable and is lower than individuals who have

enduring schizophrenia (Thompson, McGorry, & Harrigan, 2001), although insight levels tend to improve over time (McEvoy et al., 2006). One potential explanation for this finding is that because individuals with a FEP have had less experience dealing with relapses than enduring schizophrenia patients, they may experience more denial, which may represent a coping mechanisms to protect one's self-esteem in the face of stigma (Lally, 1989). Alternatively, individuals with a FEP may lack the terminology to describe and define their experiences, appearing as low insight levels. On the other hand, levels of clinical insight in enduring schizophrenia are more stable, presumably because of having lived with the illness for a longer time (Koren, Viksman, Giuliano, & Seidman, 2013). Consequently, the unstable nature of insight in FEP has rendered its study difficult, and this suggests that investigating clinical insight may be most appropriate in enduring schizophrenia samples. Hence, the studies presented in this thesis are focused on exploring clinical insight in an enduring schizophrenia sample.

2.2.2. Cognitive and clinical insight

In the literature, an important distinction can be made between *clinical* and *cognitive* insight in schizophrenia. Whereas clinical insight reflects awareness or beliefs specific to one's illness as described earlier, cognitive insight is a concept that reflects more general tendencies in terms of cognitive style. More specifically, cognitive insight represents two cognitive dimensions: one's openness to reevaluating their opinions or interpretations, considering other's feedback or alternative interpretations of one's experiences (*self-reflectiveness*), and one's level of certainty in their own opinions as well as levels of dogmatic attitudes (*self-certainty)*. The concept of cognitive insight was advanced by Beck, Baruch, Balter, Steer, and Warman (2004) as an alternative to the concept of clinical insight due to critiques of the way clinical insight is conceptualized and assessed. Indeed, one argument is that the assessment, and therefore the study

of clinical insight, may be obscured by what someone with schizophrenia has been told by their treatment team, as opposed to directly assessing beliefs regarding their illness or the ability to reflect and understand their experiences. Thus, examining one's ability to evaluate one's beliefs and be opened to other interpretations (i.e. cognitive insight) has been conceptualized as a better method of understanding insight deficits in schizophrenia.

Cognitive insight and clinical insight have been shown to have weak, and sometimes no correlations (Ekinci, Ugurlu, Albayrak, Arslan, & Caykoylu, 2012; Pedrelli et al., 2004; Riggs, Grant, Perivoliotis, & Beck, 2012), which suggests that they assess different dimensions. This is also supported by a recent factor analyses conducted in our group which identified both concepts as separate factors (Konsztowicz, Schmitz, & Lepage, submitted), and the fact that clinical and cognitive insight predict different factors in schizophrenia (O'Connor et al., 2013). Therefore, in the schizophrenia literature, cognitive and clinical insight are often investigated as independent factors. The subject of the current thesis is focused on clinical insight.

2.3. Etiology of clinical insight

Multiple theories of clinical insight have been advanced, conceptualizing poor insight as 1) a side effect of the presence of psychotic symptoms, 2) an impairment in metacognition and social cognition, 3) a result of neurocognitive deficits and associated neurobiological alterations and 4) a coping mechanism. These theoretical approaches have guided much of earlier research attempting to understand the etiology of clinical insight in schizophrenia. This research has garnered a plethora of findings relating levels of clinical insight to different psychological, neurocognitive, and neurobiological factors, as reviewed below.

2.3.1. Symptoms

It has been argued that levels of clinical insight may reflect the severity of an individual's illness, and that poor clinical insight may itself represent a delusional belief (Van Putten, Crumpton, & Yale, 1976). Past research has indeed revealed associations between levels of clinical insight and severity of both positive and negative symptoms (Mintz et al., 2003). In particular, there is consistent evidence of a relationship between higher positive symptom severity and lower levels of clinical insight. The presence of positive symptoms may indeed make it more difficult for an individual to be aware of their illness experiences. Indeed, it is reasonable to expect that an individual who has firmly held delusional thoughts (a positive symptom) would be unlikely to automatically attribute their thoughts to an illness, considering that by definition, delusions are firmly held beliefs despite contradictory evidence. Nevertheless, research has also been inconsistent, with some studies finding no relationship with symptoms, and a meta-analysis by Mintz et al. (2003) revealed that symptom severity rarely explains more than 7% of variance in clinical insight, suggesting that other factors come into play in determining levels of clinical insight.

2.3.2. Metacognition and social cognition

Metacognition broadly refers to the act of thinking about one's own or others' thinking (P. H. Lysaker, Olesek, et al., 2011), and the ability to integrate information to create more complex and abstract representations of the self, others, or objects (P. H. Lysaker & Dimaggio, 2014; Vohs, George, Leonhardt, & Lysaker, 2016). As part of the umbrella construct of metacognition is the ability to reflect or monitor one's own thinking, an ability referred to as self-reflectiveness. Conceptually, the relationship between the ability to self-reflect and clinical insight is easy to make. The ability to be aware of one's illness and attribute symptoms to an illness requires reflections on one's mental state history and knowledge of social or cultural

norms, and then make use of this information to formulate an explanation for this unusual experiences. Therefore, at its base, explaining one's thoughts and experiences requires one to self-reflect. If somebody is less able to reflect on the self, or take different information into account while trying to make sense of their unusual experiences, then this presumably would result in a less accurate understanding of one's experiences and hence, poorer insight. In support of this theoretical link between clinical insight and metacognition, it has indeed been found that levels of clinical insight are associated with metacognitive dimensions, with strongest associations found with the dimension of self-reflectiveness (P. H. Lysaker, Dimaggio, et al., 2011).

Similarly, social cognition has also been argued to underlie clinical insight deficits. Social cognition refers to the mental processes involved in the perception and interpretation of social information (Green et al., 2015), and impairments in social cognition are common in schizophrenia, and are found across different phases of the illness (J. Addington, Saeedi, & Addington, 2006; Bora, Yucel, & Pantelis, 2009; Lee, Hong, Shin, & Kwon, 2015). One rationale for this hypothesized relationship with clinical insight is the idea that the ability to take the perspective of another person into account when evaluating one's illness experiences can lead to a more representative and "insightful" explanation of one's symptoms. Moreover, being able to understand that one's experiences are unusual requires the ability to use information from their social environment to come up to the latter conclusion. For example, poor social cognition might make it difficult for someone to take into account feedback from close others that worry about a patient's symptoms, or to use knowledge of social norms to understand that one's illness experiences are unusual, and this may lead to a restricted understanding of one's illness experiences. Moreover, poorer social cognition in schizophrenia is associated with poorer social

functioning(Couture et al., 2006). Therefore, if patients have poorer social functioning, then presumably they would be less likely to have meaningful social interactions with others. If this is the case, then this person would have less opportunities to discuss, name and explain their experiences to others, which would lead to a restricted or isolated understanding of their experiences.

In support of these hypotheses, several studies have found a relationship between higher levels of social cognition and better clinical insight (Ng, Fish, & Granholm, 2015; Pijnenborg, Spikman, Jeronimus, & Aleman, 2013; Vaskinn et al., 2013). Nevertheless, one gap in the literature on a potential social cognition and insight relationship is that the literature has focused on the relationship between theory of mind and clinical insight. Theory of mind (TOM) represents a social cognitive dimension thought to underlie the ability to understand and infer the mental states of others. The specific interest on the TOM-insight link is guided by the idea that awareness of illness experiences may be improved if one can understand the perspective of others around them, and use these perspectives to have a better understanding of their illness. Nevertheless, few studies have looked at other domains of social cognition in relation to clinical insight, and therefore it remains unknown whether clinical insight is also related to other social cognitive abilities such as the recognition of social/emotional information (i.e. emotion recognition/social perception) or the ability to relate affectively with others (i.e. empathy). A more detailed review of the association between metacognition and social cognition with clinical insight can be found in Chapter 2 of this thesis.

2.3.3. Neurocognition and neural correlates of clinical insight

Beyond psychological factors, neurobiological and neurocognitive factors may also contribute to poor insight. A primary impetus for the interest in this relationship came from the

hypothesis that clinical insight may be the result of deficits in frontally-mediated cognitive functioning (Laroi et al., 2000), due to the resemblance of poor insight to the phenomenon of *anosognosia,* or lack of insight*,* in certain neurological disorders involving frontal-lobe damage (Amador et al., 1991). As mentioned above, individuals with schizophrenia exhibit differences in neuroanatomy compared to healthy controls, and these neuroanatomical alterations have been suggested to be a potential basis for clinical insight deficits. In effect, neuroimaging studies have provided evidence that clinical insight is associated with total brain size (Flashman, McAllister, Andreasen, & Saykin, 2000), grey (M. A. Cooke et al., 2008; Morgan et al., 2010) and white matter volumes (Palaniyappan, Balain, & Liddle, 2012), with many studies suggesting specific abnormalities in frontal regions (Laroi et al., 2000; Shad, Muddasani, & Keshavan, 2006; Shad, Muddasani, Prasad, Sweeney, & Keshavan, 2004).

Consistent with evidence for an association with neuroanatomical features in the frontal lobes, there is also evidence for a relationship between neurocognitive performance and clinical insight levels, including executive functioning, attention and memory performance (Boyer et al., 2012; Drake & Lewis, 2003; Sapara et al., 2014; Stratton et al., 2013). A recent meta-analysis conducted by Nair, Palmer, Aleman, and David (2014) revealed that the strongest relationship was between a measure of mental flexibility, set-shifting, and clinical insight, a neurocognitive ability thought to primarily require frontal lobe functioning.

Although much of the previous research has focused on frontal lobes as region of interest in associations with insight, recent studies have also revealed that individuals with poor clinical insight have reduced grey matter volume of temporal gyri and insula (Emami, Guimond, Mallar Chakravarty, & Lepage, 2016). The latter brain structures have been involved in self-reflective processes and therefore these findings may underlie the link between clinical insight and self-

reflectiveness ability as described above (van der Meer, Costafreda, Aleman, & David, 2010). Therefore, this suggests the need for more research examining the association between clinical insight levels and neuroanatomy in regions other than the frontal lobes.

2.3.4. Insight as coping mechanism

One consistent finding in the insight literature is the link between better clinical insight and greater distress (Schwartz & Smith, 2004), as well as lower quality of life (Hasson-Ohayon, Kravetz, Roe, David, & Weiser, 2006). One explanation for this relationship is the role of internalized stigma: individuals who see themselves as mentally ill (i.e. intact clinical insight), may be more likely to appropriate to themselves stigmatizing beliefs that are often attached to serious mental illnesses (Rusch, Angermeyer, & Corrigan, 2005). Consequently, by holding these beliefs, individuals who believe that they are mentally ill and thus that have good insight, have lower self-esteem and lower affect (Staring, Van der Gaag, Van den Berge, Duivenvoorden, & Mulder, 2009). Therefore, one approach to understanding clinical insight has been to argue that individuals with schizophrenia deny that they suffer from an illness and attribute their symptoms to causes other than a mental illness to protect their self-esteem (Moore, Cassidy, Carr, & O'Callaghan, 1999). It has indeed been shown that an individual's coping style is associated with their level of clinical insight. More specifically, M. Cooke et al. (2007) demonstrated that individuals whose coping styles are characterized by positive reinterpretation and growth have lower levels of clinical insight. These findings indicate that an individual's attitude towards their illness plays a role in determining their levels of clinical insight, and therefore that clinical insight should not be solely understood as a "deficit" or as a side effect of some of the impairments observed in schizophrenia, but as a phenomenon that reflects one's approach to dealing with unusual and difficult experiences.

2.4. Reconceptualization of clinical insight

As can be concluded from the above review, there are many factors involved in predicting levels of insight. While earlier research on insight has focused on formulating theories on what neurocognitive deficit or symptom determine poor or good insight, research has shown that insight is likely not a function of either one of these things, but likely represents a phenomenon that it determined by a combination of these factors. This therefore highlights the need for more integrative research on how different factors come together to explain levels of insight. Moreover, it directs attention to a new conceptualization of insight not as a single deficit or single phenomenon in schizophrenia, but that is likely a *latent* phenomenon that cannot be defined or measured directly, but can be inferred from a variety of factors. More specifically, being aware of one's illness does not only imply that one accepts a 'fact' that one is suffering from an illness. To the contrary, clinical insight is conceptualized as a phenomenon which involves the construction of a complex illness narrative. This illness narrative, in turn, needs to incorporate different information regarding past and current mental events, and requires that an individual makes sense of the flow of complex events that led to an illness, to make sense of their present condition. If viewed in this way then, clinical insight is not a process unique to schizophrenia, but represents a combination of different kinds of abilities that humans use in general to understand and make sense of their difficult experiences.

Therefore, rather than define clinical insight as a specific ability or deficit, it may help to define insight more broadly as the ability to identify, perceive and combine information of different kinds (social, personal, cultural), using different mental processes and available resources (social environment, personal attitudes) – to then create a global and coherent understanding of one's condition.

This conceptualization of clinical insight has already led to the emergence of research interest in analyzing patient's discourse and their narratives of their illness as a means of understanding and investigating clinical insight in schizophrenia, as opposed to quantitatively assessing an individual's correctness of their beliefs (Paul H Lysaker, Clements, Plascak-Hallberg, Knipscheer, & Wright, 2002; Macnaughton, 2008). Qualitative research represents a potential means to better understand insight, and has already shown that clinical insight represents an active process of choice of how to interpret their illness, rather than an inability to be aware of their illness. That is, insight represents a process of constructing and re-constructing self-understandings depending on experienced levels of distress with their current illness, and the degree to which alternative interpretations can offer plausible and helpful explanations of current mental states.

In addition, if we conceptualize insight in this manner, then this also suggests a need for integrative research to uncover the specific mechanisms that contribute to poor or good insight, rather than research focused on specific correlates. That is, more research needs to be done that examines multiple factors simultaneously to determine how they each relate to insight levels, and to determine whether certain factors are more important than others in predicting insight. Similarly, research that aims to understand the neurobiological basis of clinical insight should remain alert to the fact that insight's neural correlates may not reside in a single brain region or structure. Instead, research should be directed towards taking a whole-brain approach to understanding the neural basis of insight, by investigating the whole brain, both at the level of the cortex and subcortex, and not be limited to a priori regions of interest.

It is therefore with this reconceptualization of insight in mind that this Master's project was conducted. The attempt was to investigate both neural and psychological aspects of clinical

insight, by integrating knowledge from past research and conceptualizing insight as a complex phenomenon, determined by multiple factors. The first study in Chapter #3 attempts to build on previous research on psychological correlates of clinical insight and better understand the unique contribution of different psychological factors, with an emphasis on social cognition and self-reflectiveness, due to relative lack of research on those factors as potential determinants of insight. Moreover, the second study presented in Chapter #4 attempts to address limitations of previous research by exploring the whole-brain, using cortical thickness and subcortical volumes as potential neural markers of insight levels.

Chapter 3: Article #1

The relative contributions of social cognition and self-reflectiveness to clinical insight in enduring schizophrenia

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3.1. Introduction

Individuals with schizophrenia and other psychoses often exhibit a lack of awareness of their illness, a phenomenon termed poor clinical insight, and this is associated with an array of less favorable functional and clinical outcomes (Erol et al., 2015; Wittorf et al., 2009). Conversely, higher levels of clinical insight are associated with improved community functioning, better medication adherence, and overall improved clinical outcomes (Mohamed et al., 2009; Novick et al., 2015; Schwartz, Cohen, & Grubaugh, 1997). Given that these associations have been found in both enduring and first-episode schizophrenia (Drake et al., 2007; Saravanan et al., 2010), this testifies to the significance of poor clinical insight in psychosis, and emphasizes this as an important target for intervention.

Not surprisingly, the significance of poor clinical insight in schizophrenia has triggered research efforts to further our understanding of this phenomenon, and identify its determinants at the neurobiological and psychological level. The literature to date indicates that clinical insight is a multidimensional concept and is multi-determined, which poses a challenge to the development of clear definitions of this phenomenon, and to the elaboration of well-targeted intervention strategies. In particular, the complex etiology of insight poses a challenge because known predictors of clinical insight are often overlapping constructs or factors that influence each other,

such as social cognition and neurocognition (Sergi et al., 2007), or positive symptoms and neurocognition (Ventura, Thames, Wood, Guzik, & Hellemann, 2010). Therefore, research that aims to identify the factors that independently and uniquely contribute to clinical insight, while accounting for known predictors, has the potential to refine our understanding of the concept of clinical insight in schizophrenia, and thus, guide the development of therapeutic interventions.

Recently, one promising avenue of research on clinical insight has been the study of its relationship with social cognition. Theories on the formation of one's self-concept have often revolved around that idea that self-knowledge is based in part on our social interactions, such as through comparison, or direct feedback (Carruthers, 2009; Decety & Sommerville, 2003; Markus & Wurf, 1987). Similarly, poor clinical insight has been conceptualized as an inaccurate or incomplete perception of the self that might arise from the inability to "see ourselves as others see us", which may arise from deficits in social cognition (A. S. David, 1999). Therefore, one premise of the hypothesis of a social cognition-insight relationship is that clinical insight may be improved if one can more effectively recognize and make use of information derived from the social environment.

To date, there is substantial evidence supporting a link between social cognition and insight in schizophrenia, irrespective of which dimension of clinical insight is studied (Bora, Sehitoglu, Aslier, Atabay, & Veznedaroglu, 2007; P. H. Lysaker, Dimaggio, et al., 2011), the stage of illness (J. L. Vohs et al., 2015), and independent of the shared variance with other predictors including neurocognition and symptomatology (Konstantakopoulos et al., 2014; Ng et al., 2015). Nevertheless, studies have so far largely focused on theory of mind (TOM) as an index of social cognitive ability. This can be attributed to the fact that deficits in TOM are the most pronounced social cognitive deficits in schizophrenia (Sprong, Schothorst, Vos, Hox, & van Engeland, 2007),

and that TOM involves the ability to take the perspective of the other, the latter having been proposed to be a psychological process that contributes to intact awareness of illness (A. S. David, 1999).

According to the socio-emotional processing stream, TOM relies on the output of more basic sociocognitive abilities, such as the perception and recognition of social-emotional stimuli (Ochsner, 2008). Yet, it is still unclear whether clinical insight is also related to more basic social cognitive abilities, including emotion recognition, or if this relationship is specific to the higher-order capacity to make inferences about others' thinking. Moreover, affective empathy represents another kind of higher-order social cognitive ability that requires perspective-taking through an affective route and that has also been associated with clinical insight (Pijnenborg et al., 2013). Nevertheless, few studies have examined how different social cognitive abilities, such as emotion recognition, TOM, and affective empathy, relate to clinical insight and whether their influence can be differentiated. To the best of our knowledge, only two studies have examined more than one level of social cognitive ability in relation to clinical insight (Quee et al., 2011; Vaskinn et al., 2013). However, the relative contribution of distinct social cognitive abilities was not explored. Therefore, it is still unknown whether clinical insight is specifically related to the non-affective perspective-taking aspect of TOM, or also to affective perspective-taking (ie. affective empathy) and social perception.

Similar to the rationale behind studying the relationship between TOM and insight, it has been suggested that metacognitive abilities, such as self-reflectiveness, may facilitate clinical insight. Self-reflectiveness is an introspective act that entails the process of thinking about one's own thinking, and which is thought to promote the integration of different information in order to create more complex and abstract representations and understandings of the self (P. H. Lysaker

& Dimaggio, 2014; P. H. Lysaker, Olesek, et al., 2011; Vohs et al., 2016). Accordingly, the ability to engage in self-reflective thought has been hypothesized to contribute to the elaboration of well-rounded narratives and understandings of illness experiences, and hence to greater clinical insight.

Research to date supports a relationship between self-reflectiveness and clinical insight both at the behavioral (A. S. David, Bedford, Wiffen, & Gilleen, 2012; P. H. Lysaker et al., 2005; P. H. Lysaker, Dimaggio, et al., 2011) and neurobiological level (Curcic-Blake, van der Meer, Pijnenborg, David, & Aleman, 2015; Morgan et al., 2010; van der Meer et al., 2010). However, it is unclear whether the perspective-taking process involved in social cognitive abilities like empathy and TOM is the same aspect that relates self-reflectiveness to clinical insight. Indeed, an idea within "simulation theory" is that in order to infer other people's thoughts, we use the same thought processes we use as when we reflect about the self (Gallese & Goldman, 1998; Mitchell, Banaji, & Macrae, 2005). This question of whether understanding other people's minds and self-reflectiveness engages similar cognitive processes has been a subject of debate in the social cognition literature (Carruthers, 2009; Decety & Sommerville, 2003; Mitchell et al., 2005). Nevertheless, recent evidence supports the idea that social cognition and metacognition, including self-reflectiveness, likely reflect distinct processes (P. H. Lysaker et al., 2013). It therefore remains unanswered whether higher-order social cognition like empathy and TOM still contribute to clinical insight after controlling for the capacity for self-reflectiveness.

In order to address these gaps in the literature, the primary objective of this study was to investigate the independent and relative contribution of different social cognitive abilities to clinical insight, including TOM, emotion recognition, and affective empathy, in a large sample

of enduring schizophrenia patients. By including these three different social cognitive abilities, we also aimed to differentiate the relative contribution of lower-order social cognitive ability (emotion recognition) compared to higher-order abilities that involve perspective-taking abilities, using cognitive (TOM) and affective routes (affective empathy).

The second objective of this study was to clarify whether the contribution of social cognitive abilities could be distinguished from the contribution of self-reflectiveness ability in explaining levels of clinical insight. Finally, we also aimed to examine the relative contribution of social cognition abilities and self-reflectiveness while controlling for known predictors of clinical insight. To answer these questions, we conducted separate exploratory hierarchical regression analyses to investigate the relative contribution of these factors in a large sample of enduring schizophrenia patients.

3.2. Methods

3.2.1. Participants.

One hundred thirty-nine subjects (73% male) meeting diagnostic criteria for schizophrenia or schizoaffective disorder for a duration of at least 4 years, and aged between 18 to 50 years old, were recruited from inpatient and outpatient units of the Douglas Mental Health University Institute and affiliated community centers. Participants were recruited as part of a larger study examining the neurobiological and psychological determinants of insight in enduring schizophrenia. Information on diagnosis, antipsychotic dosage (converted to chlorpromazine equivalent), and duration of illness were collected by medical chart review, or directly confirmed with patients' medical teams. An abbreviated version of the Structured Clinical Interview for DSM-IV Axis I Disorders was also administered to all patients to confirm patients' illness history.

Exclusion criteria for the schizophrenia group included 1) very low performance on the neuropsychological assessment defined as less than two standard deviations below the mean; 2) personal or familial history of neurological conditions that can affect cognition; 3) head injury with loss of consciousness; 4) diagnosis of substance dependence in the past 3 months.

All clinical assessments were administered by trained research assistants with a minimum of an undergraduate degree in psychology or related field. All participants provided written informed consent, and the study procedures were approved by the Douglas Mental Health University Institute human ethics review board.

3.2.2. Clinical Insight

Clinical insight was assessed using the Schedule for the Assessment of Insight-Expanded (SAI-E), an interviewer-rated scale that uses a multi-dimensional approach to evaluate clinical insight (A. David, Buchanan, Reed, & Almeida, 1992). The last two items of the SAI-E were not included in assessing insight levels as they require feedback from the patient's health care practitioner and family member. Item 9 was also omitted as its content closely reflects metacognition, which was a variable of interest in this study. A total score representing the sum of items 1 to 8 was used as an index of clinical insight, with higher sum scores indicating higher clinical insight.

3.2.3. Social Cognition.

TOM was assessed using the Hinting Task, an interviewer-rated scale which assesses one's capacity to infer other people's intentions through indirect speech (Corcoran, Mercer, & Frith, 1995). The task comprises of 10 stories that contain a dialogue between two or more characters and that are read out loud to participants. Participants are asked to identify the hidden meaning behind characters' remarks. The Hinting Task produces a total score out of 20, with higher scores indicating better TOM performance.

Affective empathy was assessed using the Empathic Concern (EC) subscale of the Interpersonal Reactivity Index (IRI), a 28-item self-report questionnaire designed to assess one's belief regarding their empathic abilities (M. H. David, 1980). The EC subscale comprises of 7 items scored from 1 (*does not describe me well)* to 5 (*describes me very well)*, on a 5-point Likert scale. The EC subscale has been shown to be a valid and reliable measure of empathy, and has a high degree of internal reliability (α=0.80) (Pulos, Elison, & Lennon, 2004).

Emotion recognition ability was assessed using a task of facial emotion recognition (FERT) administered on a computer using E-Prime (Psychological Software Tools, Inc.). In this task, 56 color images of males and females expressing 7 different emotions were presented to participants. Each emotion was presented 8 times. Participants were asked to identify the emotion represented by the picture from a list of 7 emotions displayed on the right of the screen (Olbert et al., 2013). Stimuli were obtained from the standardized photograph set created by Ekman (Ekman P. Subtle Expression Training Tool (SETT) & Micro Expression Training Tool (METT) (computer program. Version 2004. www.paulekman.com). In this study, global accuracy (defined as the percentage of correctly identified emotions) was used as an index of emotion recognition ability, with higher scores indicating better performance.

3.2.4. Self-reflectiveness.

The Self-Reflectiveness subscale of the Beck Cognitive Insight Scale (BCIS) was used as an index of self-reflectiveness ability (Beck et al., 2004). The Self-Reflectiveness subscale assesses the ability to be open to feedback, acknowledge fallibility, and consider alternative explanations to one's experiences. This subscale consists of 15 statements that participants rate on a 4-point scale from "*Do not agree at all*" to "*Agree completely*". Higher scores indicate higher self-reflectiveness.

3.2.5. Known predictors of clinical insight

We also assessed participants' neurocognitive performance, and positive and negative symptoms in order to include them as potential confounds in analyses, as these factors have been previously associated with clinical insight. Neurocognitive performance was assessed using the CogState Research Battery (CS)(Lees et al., 2015). The CS is a computerized test battery that assesses performance on the following cognitive abilities: working memory, speed of processing, verbal

learning and memory, attention, visual learning and memory, executive function, and emotion recognition. Standardized scores (z-scores) were computed for each cognitive ability, for each participant, based on the normative data from 35 healthy subjects that were collected in a separate study done in our group (Benoit et al., 2015). Finally, a composite score representing general cognitive performance, was obtained by averaging z-scores on each cognitive ability. Scores on the emotion recognition task of the CS were removed from calculations of the composite score as it was a variable of interest in our analyses assessed using a separate task.

Negative and positive symptoms were assessed using the sum of each global symptom scores from the Scale for Assessment of Negative symptoms (SANS) (Andreasen, 1984) and Scale for Assessment of Positive symptoms (SAPS)(Andreasen, 1983), respectively. The global score for the attention domain of the SANS was excluded from the latter calculations (Hovington, Bodnar, Joober, Malla, & Lepage, 2012).

3.2.6. Statistical Analyses.

Descriptive analyses were first conducted to characterize the demographic and clinical characteristics of the participants. Second, Spearman's rho correlations were conducted between measures of social cognition and self-reflectiveness, and clinical insight to ensure a linear relationship between these variables in order to determine whether to include them in the following regression analyses. Correlations were also applied between clinical insight and neurocognition, symptoms, and demographics to identify potential confounds to include in subsequent analyses.

To address our research objectives, hierarchical multiple regressions were used. Prior to conducting the analyses, the assumptions of multicollinearity, homoscedasticity and normality,

and the presence of outliers were verified. All of the latter assumptions were met, with the exception of normality. However, because of the large sample size, we determined that a regression would remain an adequate statistical method (Lumley, Diehr, Emerson, & Chen, 2002). For our primary objective, emotion recognition was entered in the first step of a hierarchical regression, followed by TOM and affective empathy in the second and third steps, respectively. Entering these variables in this order enables us to see whether TOM and affective empathy predict unique variance in insight, over and above lower-order sociocognitive abilities.

For the second research objective, self-reflectiveness was entered in the first step of a hierarchical multiple regression. In Step 2, the social cognition variables found to be unique predictors of clinical insight in the previous analyses were included. Finally, the latter regression was repeated to address the third objective, with the addition of potential confounds identified in previous correlational analyses in Step 1 of the regression model. All analyses were conducted using SPSS Version 20.0 with a critical p value of 0.05.

3.3. Results

3.3.1. Demographic and clinical characteristics

Means and standard deviations of demographic and clinical characteristics of patients are listed in Table 1.

3.3.2. Relationships with Clinical Insight

Correlations between clinical insight and social cognition measures, self-reflectiveness, and known predictors are listed in Table 2.

3.3.3. First Objective: Relative contribution of social cognition abilities

Results of the hierarchical multiple regression (Table 3) revealed a significant effect of emotion recognition on clinical insight in Step 1, $F(1,133)=6.124$, $p=0.020$, accounting for 4.4% of variance in clinical insight levels. Adding TOM in Step 2 explained an additional 0.8% of variance in insight levels, which was not significant $F(1,132)=1.14$, $p=0.290$. Adding affective empathy in Step 3 explained an additional 6.6% of variance in insight, over and above emotion recognition and TOM, and this change was significant, $F(1,131)=9.79$, $p=0.002$. Together, the three social cognition measures explained 10% of variance in clinical insight (adjusted $R^2=0.098$), with affective empathy making the largest unique contribution to clinical insight (beta=0.257, $p=0.002$), followed by emotion recognition, although this was a nonsignificant trend (beta=0.17, $p=0.056$). There was no significant effect of TOM on clinical insight in the final model.

3.3.4. Second objective: Relative contribution of higher-order social cognition and self-reflectiveness

Results from the hierarchical regression (Table 4) indicated a significant effect of self-reflectiveness, accounting for 8% of unique variance in clinical insight, $F(1,135)=11.98$, $p<0.001$. Adding TOM performance in Step 2 did not predict any significant additional portion of variance in clinical insight, $F(1,134)=2.92$, $p=0.100$. The addition of affective empathy in Step 3 contributed an additional 6% of variance in clinical insight, which was significant, $F(1,133)=9.90$, $p=0.002$. In the final model, self-reflectiveness made the largest contribution to clinical insight (beta=0.276, $p=0.001$), followed by affective empathy (beta=0.250, $p=0.002$). TOM performance did not predict a significant unique amount of variance in clinical insight (beta=0.121, $p=0.131$).

3.3.5. Third Objective: Relative contribution of social cognition, self-reflectiveness, and known predictors of clinical insight

Results from the third hierarchical multiple regression (Table 5) indicated that general cognitive performance, negative symptoms, and antipsychotic dosage predict 14.8% of the variance in clinical insight levels, $F(3,125)=7.249$, $p<0.001$. Adding self-reflectiveness in Step 2 explained an additional 5% of variance in clinical insight, $F(1,124=7.39)$, $p=0.007$. In Step 3, emotion recognition and affective empathy together predicted an additional 6% of variance in clinical insight, $F(2,122)=4.22$, $p=0.007$. The final model explained 22% of variance in clinical insight levels (adjusted $R^2=0.223$), in which only 3 variables made a significant unique contribution to clinical insight: affective empathy (beta=0.239, $p=0.004$), followed by antipsychotic dosage (beta=0.234, $p=0.004$), and self-reflectiveness (beta=0.225, $p=0.007$). In this final model, general

cognitive performance, negative symptoms, and emotion recognition did not predict significant unique variance in clinical insight.

3.4. Discussion

The main purpose of this study was to determine the relative contribution of social cognition abilities, and self-reflectiveness, to clinical insight levels in enduring schizophrenia patients. Our results showed that affective empathy and self-reflectiveness make the strongest unique contribution to clinical insight levels, independent of other known predictors. Moreover, we found that amongst social cognition predictors of insight, affective empathy is the only social cognitive ability that contributes unique variance in clinical insight levels.

Contrary to previous findings, our results suggest that clinical insight may not be specifically related to the perspective-taking aspect of TOM. Indeed, while our analyses showed that TOM performance is correlated with clinical insight levels, when controlling for emotion recognition, TOM did not have any additional effect. This suggests that the relationship between TOM and clinical insight may be driven solely by the capacity to recognize relevant social information, a capacity required for, and inherent in both TOM and emotion recognition tasks (Ochsner, 2008). Nevertheless, we found that emotion recognition does not predict unique variance in clinical insight when controlling for other known predictors. One factor that may have reduced the influence of emotion recognition on clinical insight is neurocognition. Indeed, it has been shown that although social cognition is distinct from neurocognition (van Hooren et al., 2008), emotion recognition has been shown to be the social cognition ability that relies the most on nonsocial neurocognition (Fanning, Bell, & Fiszdon, 2012).

It is also possible that the relationship of both emotion recognition and TOM with clinical insight may be mediated by neurocognition. The TOM and emotion recognition tasks may have assessed similar underlying neurocognitive abilities, as opposed to purely social cognitive capacities, and this may explain why the contribution of TOM to clinical insight was nulled by

the addition of the emotion recognition variable. In support of this, it has been suggested that the Hinting Task may significantly rely on story comprehension skills, which itself requires adequate neurocognitive ability (Langdon & Ward, 2009; Scherzer, Achim, Leveille, Boisseau, & Stip, 2015). Nevertheless, a link between TOM and clinical insight has been found in studies in which different TOM tasks were used (Langdon & Ward, 2009; P. H. Lysaker, Dimaggio, et al., 2011; Ng et al., 2015), and one study demonstrated that this relationship is independent from neurocognition (Chan, 2016). Due to the demonstrated relationship between neurocognition and clinical insight, the relationship with TOM may thus best be studied with a task that does not significantly rely on neurocognitive skills.

By contrast, the link between affective empathy and clinical insight remained even after accounting for its potential shared variance with other known predictors. This finding replicates results from Pijnenborg et al. (2013), which demonstrated that affective empathy is more predictive of clinical insight levels than cognitive empathy, or TOM. Awareness of one's illness may not only require the capacity to take others' perspective, but may specifically require the ability to relate affectively with others. Indeed, affective empathy has been argued to require a person to simulate how another person is feeling by adopting a first-person perspective (Scherzer, Leveille, Achim, Boisseau, & Stip, 2012). Accordingly, taking a first-person perspective may facilitate the acceptance of another person's point of view, why may promote better clinical insight (Pijnenborg et al., 2013).

Another interpretation for the relationship between affective empathy and insight may be that a third variable mediates this relationship, such as better social functioning. It has been shown that empathic abilities are related to better maintenance of social relationships and social functioning (Couture et al., 2006; Michaels et al., 2014; Ofir-Eyal, Hasson-Ohayon, & Kravetz,

2014). Therefore, by promoting greater frequency of social contact, better empathic abilities may provide individuals with schizophrenia with more opportunities to be exposed to opposing views concerning their illness experiences. Moreover, a richer social life may also diversify the information one uses to explain one's experiences, and thereby lead to a more well-rounded understanding of the illness. It is also possible that different types of social contact may vary in their potential to improve insight. For example, more structured types of social contact such as peer support may provide a unique opportunity to develop one`s illness narrative. Peer support groups represent a specific type of social contact which involves active sharing and discussions of participants' illness experiences. As such, by verbalizing one another's experiences, and through the promotion of relating to other's stories, peer support groups may provide a unique opportunity for individuals to gain a better understanding of their experiences or promote the use of other approaches in making sense of difficult experiences. In line with this, participation in peer support or psychoeducation groups has shown promise in helping certain individuals acknowledge their illness, as indicated by qualitative research (Lal, Ungar, Malla, Leggo, & Suto, 2017).

Another objective of this study was to investigate whether the variance in clinical insight explained by self-reflectiveness, is independent from the variance explained by higher-order social cognition. Our findings indicate that self-reflectiveness ability makes a significant and unique contribution to variance in clinical insight, independent from the variance explained by higher-order social cognition, and other known predictors. This suggests that despite their conceptual similarity, social cognition and self-reflectiveness contribute to clinical insight in unique ways. On the one hand, social cognition might furnish one with the capacity to

understand and effectively use information from the social world, which can permit a better grasp of one's experiences by understanding how it is perceived by others or what impact they have on them (Vohs et al., 2016). On the other hand, better self-reflectiveness ability may encourage awareness of illness by facilitating introspection and critical thinking, which may lead one to integrate information regarding current and past mental states, and this may permit a more elaborate illness narrative.

From these findings, we can propose a tentative model for the maintenance or development of clinical insight in schizophrenia. Self-reflectiveness ability may provide the foundations for an individual to attain a thorough understanding of one's illness. However, self-reflectiveness alone may not necessarily be conducive of good clinical insight. Without the capacities to identify and make use of information derived from the environment (i.e. because of neurocognitive or social cognitive deficits), or without the opportunities to be exposed to different or opposing views (ie. social withdrawal), one may not have the opportunity to construct an adequate understanding of their illness, even in the presence of intact self-reflectiveness abilities. Therefore, multiple factors may contribute to determining what kind of information is used to reflect on the self, and if this information is lacking, then this could also lead to poor clinical insight.

In line with this, close to 80% of variance in clinical insight remains unexplained in our study, even when accounting for the variance explained by neurocognition, social cognition, positive and negative symptoms, and self-reflectiveness. This is at the image of the plethora of evidence that insight is associated with a range of factors, both psychological (De Hert et al., 2009; Mohamed et al., 2009; Schwartz, 1998; Stratton et al., 2013) and neurobiological (Emami et al., 2016; Sapara et al., 2007). Importantly, the relationship between insight and other factors

often exhibit small effect sizes and seldom explain a large amount of variance in insight levels (Aleman, Agrawal, Morgan, & David, 2006; Mintz et al., 2003; Nair et al., 2014). This supports the notion that clinical insight is an emergent or latent phenomenon, rather than a deficit in a single modality, and it likely arises from the combination of neural, psychological, and neurocognitive factors factors.

The very fact that clinical insight is a phenomenon determined by many factors that have small effects makes the exploration of its predictors challenging, as one factor may be crucial in some patients but not in others. As our results illustrated, in our sample of schizophrenia patients characterized by relatively high levels of clinical insight and low levels of positive symptoms, clinical insight was only associated with negative symptoms, but not positive symptoms. This is in contrast with previous research that has consistently shown a link between clinical insight and positive symptoms (Buchy, Torres, Liddle, & Woodward, 2009; De Hert et al., 2009). Therefore, perhaps for individuals with schizophrenia who have less pronounced positive symptoms, insight may be more highly dependent on other factors such as negative symptoms or neurocognition. Accordingly, an important goal of future research on clinical insight should be to investigate how predictors of clinical insight vary according to different illness profiles.

Finally, the findings of this current study help shift the emphasis from neurocognitive deficits and symptom severity, toward self-reflectiveness and social cognition as main contributors to insight. This study therefore positions interventions that target metacognitive skills and social cognition abilities as viable options for individuals with schizophrenia with poor clinical insight, as well as other forms of social contact such as peer support groups. Moreover, by emphasizing the multi-determined nature of clinical insight, this study provides new insights for the development of more targeted interventions for poor clinical insight that address its

underlying bases. Future studies investigating the efficacy of such interventions should therefore aim to include assessments of clinical insight in order to confirm these findings.

Limitations

First, our sample of schizophrenia patients had relatively high levels of clinical insight, and consisted of mostly individuals with enduring schizophrenia under the age of 50 years old. Considering that levels of insight may vary by age (Gerretsen et al., 2014) and illness phase(Quee et al., 2011), it is possible that different factors predict insight levels in different groups, and therefore this limits the generalizability of present findings.. Nevertheless, our findings are largely in line with previous findings on the predictors of clinical insight, such as its correlation with social cognition, self-reflectiveness, negative symptoms, and neurocognition, indicating that the predictive power of some factors may exhibit a dose-response relationship with insight. Second, certain factors that have been related to clinical insight were not evaluated in our study, such as depression (Belvederi Murri et al., 2016). It is possible that including other factors might modulate the magnitude of the relationship between social cognition, self-reflectiveness, with clinical insight. Finally, a limitation of the study is its cross-sectional nature. It needs to be confirmed whether the predictors identified in this study actually precede the development of good and poor insight. This highlights the need to further investigate whether interventions aimed at improving patient's social cognition or self-reflectiveness can modulate insight levels longitudinally.

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Conflict of interest

ML reports having received financial assistance/compensation for research and educational events from Janssen-Ortho, Eli Lilly, Roche, and Otsuka/Lundbeck Alliance. SB, CM, SK, and LB declare that they have no conflicts of interest.

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Chapter 4 Article #2:

Clarifying associations between cortical thickness, subcortical volumes, and a comprehensive assessment of clinical insight in enduring schizophrenia

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4.1. Introduction

Poor clinical insight in schizophrenia is associated with an array of unfavorable clinical and functional outcomes (Drake et al., 2007; Erol et al., 2015). The potential neuroanatomical basis of poor clinical insight in schizophrenia has attracted considerable attention over the past decade and there is evidence that clinical insight is associated with various neuroanatomical markers such as total brain size (Flashman et al., 2000), grey matter (M. A. Cooke et al., 2008; Morgan et al., 2010) and white matter volumes (Palaniyappan et al., 2012). While many findings suggest specific abnormalities in frontal regions related to the neurocognitive deficits associated with poor insight (Laroi et al., 2000; Shad et al., 2006; Shad et al., 2004), studies have also shown that insight levels are associated with regions hypothesized to be engaged with the capacity for self-reflectiveness, a metacognitive ability which is thought to include the ability to reflect on one's experiences, evaluate one's own beliefs, and acknowledge fallibility. These regions include the precuneus (Buchy et al., 2012; Morgan et al., 2010), anterior cingulate cortex (Shad, Keshavan, Tamminga, Cullum, & David, 2007), and insula (Palaniyappan, Mallikarjun, Joseph, & Liddle,

2011). These findings are in line with the idea that the capacity for clinical insight may be largely determined by one's ability to reflect on the self, and to evaluate one's own beliefs, and not solely by neurocognitive abilities (Vohs et al., 2016)).

Nevertheless, to date, the literature on the structural neural correlates of clinical insight has been largely inconsistent, with a subset of studies revealing no relationship with neuroanatomy, despite using relatively similar neuroimaging techniques and a focus on similar neuroanatomical markers as studies that do find a relationship (Bassitt, Neto, de Castro, & Busatto, 2007; Buchy, Makowski, Malla, Joober, & Lepage, 2016; McFarland et al., 2013; Rossell, Coakes, Shapleske, Woodruff, & David, 2003). Moreover, to our knowledge, no study has yet examined whether clinical insight levels are associated with the anatomy of subcortical structures in enduring schizophrenia. These inconsistencies in the literature, as well as the lack of exploration of potential links to subcortical structure, have posed a challenge in drawing clear conclusions about the potential neuroanatomical basis of clinical insight.

A possible explanation for the inconsistencies found in past neuroimaging research on insight may largely stem from the existence of multiple tools to assess clinical insight, an issue that is exacerbated by the multi-dimensionality of this phenomenon. Available assessments of clinical insight in schizophrenia often vary in the types and number of questions used to evaluate a single insight dimension. This makes it difficult to compare scores between scales and prevents inference that an association with insight found in one study would also be found when using different assessments. For example, Bassitt et al. (2007) found no correlation between a measure of clinical insight and grey matter volume using voxel-based morphometry (VBM) analyses and a 1.5 Tesla magnetic resonance imaging (MRI) scanner in a sample of 50 schizophrenia patients. On the other hand, a study conducted by M. A. Cooke et al. (2008), using similar imaging and

VBM processing techniques with an approximately equivalent sample size, found that clinical insight was related to grey matter volume in temporal and parietal gyri, and the precuneus. The key ingredient differentiating these studies was the method of assessing clinical insight, with one study employing a combination of self-rated and observer-rated measures, and another employing only an observer-rated measure. This illustrates the complexity of bridging findings from this literature given the variability in clinical insight assessment. Moreover, several studies have relied on single item (Shad et al., 2004), or global measures of clinical insight (Rossell et al., 2003), that do not necessarily capture specific dimensions of clinical insight. Given the multi-dimensional and complex nature of the concept of clinical insight, examining the neural correlates of scores of general measures of insight may not accurately depict this phenomenon's neural basis.

Another potential reason for the inconsistency in the literature is that studies on the neuroanatomy of clinical insight have often been limited by small sample sizes, with most studies including a sample size smaller than 57 schizophrenia patients (Antonius et al., 2011; Bassitt et al., 2007; M. A. Cooke et al., 2008; Flashman et al., 2001; Gerretsen et al., 2015; Laroi et al., 2000; Palaniyappan et al., 2012; Sapara et al., 2007; Shad et al., 2004). This low statistical power may significantly weaken the reliability of available research (Button et al., 2013), especially in the face of contradictory findings in this particular literature.

Finally, the available literature on insight is limited by the fact that many analyses have been restricted to the frontal lobes as regions of interest due to the hypothesis that poor insight may reflect frontally-mediated neurocognitive deficits (Flashman et al., 2001; Sapara et al., 2007; Shad et al., 2006). However, this focus prevents us from identifying potential associations of clinical insight with other brain structures. This latter point is especially important given

evidence that clinical insight is associated with psychological processes whose correlates may lie in regions other than the frontal lobes (e.g. social cognition (Vaskinn et al., 2013)).

It is clear that additional studies of clinical insight are warranted, specifically improving upon the abovementioned limitations. These include i) including a large sample size, ii) a comprehensive, reliable assessment of insight, and iii) a more exhaustive exploration of the whole brain, including both whole-brain analyses, and complementary region of interest analyses that are not limited to the frontal lobe, and subcortical volumes analyses.

Recently, we conducted a large cross-sectional study to address these limitations by recruiting a large number of schizophrenia patients and healthy controls, administering multiple assessments of clinical insight, and acquiring over 100 high quality controlled structural MRI scans. Using this data, our first aim was to specifically address the limitations that stem from the existence of multiple assessments of insight, by conducting a factor analysis using the performance of 141 patients with a diagnosis of schizophrenia on 4 self-report and observer-rated scales of insight (Konsztowicz et al., submitted). Results of this study revealed that clinical insight is largely driven by two factors: Awareness of Illness and Need for Treatment (AINT) and Awareness of Symptoms and Consequences of the illness (ASC). These statistically derived factors, obtained from a range of self-report and interviewer-rated assessments, yielded a more comprehensive and statistically reliable assessment of the dimensions of clinical insight, bridging information that one can obtain from most available clinical insight assessments.

Thus, the second objective of this project, and the focus of this manuscript, was to examine the neuroanatomical correlates of insight in schizophrenia, both at the level of the cortex and subcortex, using the two factors identified previously by our group (Konsztowicz et al., submitted). The general aim of this project was to strengthen our ability to identify neural

correlates of clinical insight by conducting this study in a large sample of schizophrenia patients, good quality 3T MRI data, and established methods of analyzing grey matter morphology by investigating whole-brain cortical thickness, and subcortical structures.

To address the objective of this study, we examined the relationship between whole-brain cortical thickness and scores on two dimensions of clinical insight previously identified by our group (Konsztowicz et al., submitted), Awareness of Illness and Need for Treatment, and Awareness of Symptoms and Consequences, in a large sample of well-characterized enduring schizophrenia patients. As a means of comparison, we also included a healthy control group. In addition, as a way to reduce the burden of multiple comparison correction, and as an attempt to replicate previous findings from ROI analyses, we also conducted vertex-wise region-of-interest analysis in 7 brain regions that have been the most associated with clinical insight and self-reflective processes: insula (Morgan et al., 2010; Palaniyappan et al., 2011; van der Meer et al., 2010)), dorsolateral prefrontal gyrus (Buchy et al., 2012; Shad et al., 2007; Shad et al., 2004), medial superior frontal gyrus (Flashman et al., 2001; Sapara et al., 2007), anterior cingulate cortex (Bassitt et al., 2007; Emami et al., 2016; Flashman et al., 2001; Shad et al., 2007), precuneus (Buchy et al., 2012; M. A. Cooke et al., 2008; Morgan et al., 2010), inferior parietal lobe (M. A. Cooke et al., 2008; Morgan et al., 2010; Shad et al., 2007), and orbitofrontal gyrus (Buchy et al., 2012; Sapara et al., 2007; Shad et al., 2007). Cortical thickness, as opposed to grey matter volume, was used as a neuroanatomical marker, as it provides a robust index of grey matter morphology, and has been argued to reflect the laminar structure of the cortex (Lerch & Evans, 2005). Moreover, cortical thickness has been shown to be associated with relevant clinical phenomena in schizophrenia (Oertel-Knochel et al., 2013; Rimol et al., 2010; Xiao et al., 2015).

Finally, in line with our objective to examine associations between clinical insight using a more comprehensive whole-brain approach, we also conducted exploratory analyses of association between two clinical insight dimensions and volumes of 4 subcortical structures: the hippocampus, striatum, thalamus, and amygdala. To our knowledge, this is the first study examining associations between insight and subcortical structures in a sample of enduring schizophrenia patients.

In line with previous studies, and with the association of clinical insight levels with self-reflectiveness and metacognitive processes (P. H. Lysaker, Dimaggio, et al., 2011; J. L. Vohs et al., 2015), our primary hypothesis was that higher clinical insight would be associated with greater cortical thickness in multiple cortical regions associated with self-reflectiveness, including the temporal lobes and cortical midline structures such as the medial prefrontal and anterior cingulate gyri. For replication purposes, we also compared vertex-wise cortical thickness between healthy controls and patients, where we predicted that patients would exhibit reductions in cortical thickness in temporal, occipital, and cortical midline structures, as previously demonstrated (Rimol et al., 2010). As analyses of subcortical structures were exploratory in nature, no a priori hypotheses were formulated.

4.2. Methods

4.2.1. Subjects.

One hundred forty-one subjects (73% male) meeting diagnostic criteria for schizophrenia or schizoaffective disorder for a duration of at least 4 years, and aged between 18 to 50 years old, were recruited from inpatient and outpatient units of the Douglas Mental Health University Institute and affiliated community centers. Participants were recruited as a part of a larger cross-sectional study investigating the determinants of insight in schizophrenia. Of this group, 114 patients accepted to participate in the neuroimaging portion of the study. Information on diagnosis, antipsychotic dosage (converted to chlorpromazine equivalent), and duration of illness were collected by medical chart review, or directly confirmed with patients' medical teams. An abbreviated version of the Structured Clinical Interview for DSM-IV Axis I Disorders was also administered to all patients to confirm patients' illness history. Exclusion criteria for the schizophrenia group included 1) very low performance on the neuropsychological assessment (less than two standard deviations below the mean); 2) a lifetime history of neurological conditions that may affect cognition (e.g. epilepsy); 3) head injury with loss of consciousness for more than 10 minutes, 4) family history of hereditary neurological conditions (e.g., Huntington's disease); 5) diagnosis of substance dependence in the past 3 months; 6) score of 8 or more on the Calgary Depression Scale (CDS); 7) presence of metallic objects in the body. Diagnosis, antipsychotic dosage, hospitalization history, and duration of illness were confirmed by medical chart review, or directly confirmed with the patients' medical team.

An additional 71 healthy control participants, without any personal or familial history of psychotic illness were recruited by means of ads in local newspapers and classified ads website. The Structured Clinical Interview for DSM-IV-TR Axis 1 Disorders, non-patient version (SCID-

NP) was administered to all healthy controls during the first assessment to rule out the presence of current mental illness, including substance abuse or dependence. Healthy subjects were also recruited based on their education level, age, and sex, to match the demographic characteristics of the patient group. All participants provided written informed consent, and the study procedures were approved by the Douglas Mental Health University Institute human ethics review board.

4.2.2. Clinical insight

Levels of clinical insight were obtained by computing sum scores on the items included in the two AINT and ASC insight dimensions as per Konsztowicz et al. (submitted) recommendation. Items included in the AINT factor, which explained 15.2% of total variance, were derived from 3 scales designed to assess clinical insight: one self-report scale Birchwood Insight Scale (BIS) (Birchwood et al., 1994), and two interviewer-rated scales, the Scale for Unawareness of Mental Disorder (SUMD) (Amador et al., 1993) and the Schedule for the Assessment of Insight – expanded version (SAI-E) (A. David et al., 1992). Scores on this factor were calculated by summing scores on items 1, 2a, and 2b from the SUMD, item 1 from the SAI-E, and items 6,8, and 4 on the BIS. Because higher scores on the SUMD indicate lower insight, scores on SUMD items were reverse-coded before calculating sum scores. Higher scores on this factor indicate higher levels of clinical insight into illness and need for treatment, with a possible range of scores from 3 to 25. Items included in the ASC factor were derived from items 7, 8, 4, and 5 of the SAI-E, which were defined to represent a dimension comprising both awareness and attribution of symptoms, as well as awareness of the consequences of the illness. Together, these items explained 9.5% of variance, and ASC was the second most reliable factor in the factor

analysis. Also on this dimension, higher scores indicate better awareness of symptoms and consequences of illness.

4.2.3. Clinical and neuropsychological assessment

Negative and positive symptoms were assessed using the sum of each global symptom scores from the Scale for Assessment of Negative symptoms (SANS) (Andreasen, 1984) and Scale for Assessment of Positive symptoms (SAPS)(Andreasen, 1983), respectively. The global score for the attention domain of the SANS was excluded from the latter calculations (Hovington et al., 2012). Moreover, the Weschler Abbreviated Scale of Intelligence (WASI), the Calgary Depression Scale (CDS) (D. Addington, Addington, & Maticka-Tyndale, 1993), and the Hamilton Anxiety Scale (HAS) (Riskind, Beck, Brown, & Steer, 1987) were administered to both patient and control groups in order to assess intellectual quotient (IQ) and general clinical symptoms.

4.2.4. Statistical analyses of demographic, clinical, and neuropsychological data

Statistical analyses of demographic and clinical data were done in three stages. First, descriptive statistics were computed to characterize the patient and control groups. Second, independent samples t-tests (2-tailed) were performed to compare demographic and psychological characteristics of the patient and control groups. Third, Pearson correlations were conducted between the ASC and AINT scores, and demographic and clinical variables in the patient group to identify covariates to add in subsequent cortical thickness analyses.

4.2.5. MRI acquisition and processing.

T1-weighted structural images were acquired on a Siemens 3T Tim trio MRI at the Brain Imaging Center of the Douglas Mental Health University Institute. The scans were MPRAGE

(TR = 2300 ms, TE = 2.98 ms, FOV 256 mm, 1 mm × 1 mm × 1 mm voxels, flip angle = 9) and lasted 9 min. All raw T1-weighted scans were visually inspected by one rater (S.B.) to ensure that no artefacts were present due to motion, and that the grey/white matter delineation was sufficiently clear for extraction of cortical thickness. Any scan that did not pass this first step of quality control was not further processed or analyzed. Quality-controlled scans were then submitted to the CIVET processing pipeline to extract cortical thickness (version 2.0, Montreal Neurological Institute at McGill University, Montreal, Quebec, Canada) (Ad-Dab'bagh et al., 2005; Kim et al., 2005). Processing steps included 1) registration of T1-weighted images to the ICBM152 nonlinear template and correction for uniformity; 2) tissue classification; 3) extraction of grey and white matter surfaces within 40,962 vertices from each hemisphere; 4) distance between white and grey surfaces was measured and smoothed using a 30-mm kernel. Detailed description of processing steps from our group can be found elsewhere (Emami et al., 2016; Makowski, Bodnar, Malla, Joober, & Lepage, 2016). Regions of interests were defined using the Automated Anatomical Labeling (AAL) atlas using the AAL labeling package in CIVET.

Quality-controlled scans were also submitted to the Multiple Automatically Generated Templates (MAGeT)-Brain algorithm to extract subcortical volumes (striatum, amygdala, hippocampus, thalamus) (Chakravarty et al., 2015; Pipitone et al., 2014). Previous studies have been conducted to validate the use of MAGeT (Chakravarty et al., 2013; Pipitone et al., 2014), including a study from our group showing its applicability in a first episode psychosis sample (Makowski et al, 2016). All scans processed through CIVET were visually inspected to ensure quality of grey/white matter surface extraction. One hundred and ten, and 69 MRI scans of patients and controls, respectively, were retained for subsequent analyses following quality control.

4.2.6. Cortical thickness analyses.

The RMINC statistical package was used to conduct cortical thickness analyses (https://github.com/Mouse-Imaging-Centre/RMINC). First, patients and controls were compared using whole-brain vertex-wise linear models, controlling for age, handedness and sex. Second, in the patient group, AINT and ASC factor scores were regressed against cortical thickness, additionally controlling for antipsychotic dosage. Finally, vertex-wise bilateral region-of-interest regression analyses were conducted in the following brain regions: 1) insula, 2) medial superior frontal gyrus, 3) orbitofrontal gyrus, 4) superior temporal gyrus, 5) dorsolateral prefrontal gyrus, 6) anterior cingulate gyrus, and 7) precuneus. We did not control for total intracranial volume in our analyses, because cortical thickness and brain volume have been shown to be poorly correlated (Sowell et al., 2007). All analyses were corrected for multiple comparisons using the False Discovery Rate procedure, with a threshold of q=0.05 (Genovese, Lazar, & Nichols, 2002).

4.2.7. Subcortical volume analyses.

Analyses of subcortical volumes were conducted in SPSS (version 20) and were conducted in two stages. First, two multivariate general linear models (GLM) were conducted to compare subcortical volumes between the two groups (healthy control vs patients). Included covariates were sex, age, and total brain volume (without ventricles). Second, partial correlations were conducted between scores on the AINT and ASC factors and bilateral hippocampus, striatum, thalamus, and amygdala volumes, including antipsychotic dosage, sex, age, and total brain volume as covariates. Significant findings were corrected for the family-wise error rate using Bonferroni-Holmes correction.

4.3. Results

4.3.1. Demographic and clinical data

Descriptive statistics of demographic and clinical variables are listed in **Table 1**.

4.3.2. Associations with clinical insight

Correlations between clinical and demographic variables and clinical insight are listed in **Table 2.**

4.3.3. Whole-brain cortical thickness analyses

Patients vs controls

Analyses revealed a significant difference in cortical thickness between schizophrenia patients and healthy controls in regions of the left hemisphere (p=0.05, FDR corrected). Specifically, the patient group displayed significantly thinner cortex in the left superior and middle temporal gyri, insula, precuneus, and cingulate cortex (**Figure 1 & Table 2**). No significant group differences between the two groups were observed in the right hemisphere.

Associations with insight factors

No associations were observed between scores on insight factor and cortical thickness in both the left and right hemisphere, after FDR correction.

4.3.4. Region of interest cortical thickness analyses

Associations with insight factors

No significant associations were observed when regressing AINT and ASC factors against mean cortical thickness in any of the regions of interest (p>0.05, FDR corrected).

4.3.5. Subcortical volume analyses

Patients vs controls

Results of the GLM are presented in Table 4. Analyses revealed significantly larger left ($F(1,173)=16.17$, $p<0.001$) and right ($F(1, 173)=15.44$, $p<0.001$) striatum volumes in schizophrenia patients compared to controls (**Table 4**). These latter findings survived correction using the Bonferroni-Holmes procedure. No other effect of group was seen on volume of the amygdala, hippocampus, or thalamus (all $p>0.05$).

Associations with Insight factors

Partial correlations revealed a significant positive correlation between scores on the AINT factor and left ($r=0.224$, $p=0.024$) and right ($r= .202$, $p=.043$) hippocampal volumes. However, the latter findings did not survive Bonferroni Holmes correction. Although not significant, there was also a trend correlation between AINT scores and left amygdala volume ($r=.193$, $p=0.053$) and right amygdala volume ($r=.178$, $p=.075$), and with right thalamus volume ($r=.181$, $p=0.070$). Finally, no significant correlations emerged between scores on the ASC factor and bilateral subcortical volumes (all $p>0.05$).

4.4. Discussion

The aim of this project was to clarify the relationship between clinical insight and neuroanatomical correlates, namely cortical thickness and subcortical volumes. In doing so, we also hoped to address limitations of previous studies conducted in this field. Findings of this study highlight the complexity of identifying structural neural correlates of clinical insight. At the level of the cortex, no relationship between two comprehensive assessments of clinical insight and cortical thickness was observed, both at the whole-brain and ROI level. These results are in line with the negative findings of Bassitt et al. (2007), which found no relationship between grey matter volume and insight. Current results shed light on the possibility that previous findings of a link between insight and the cortex may have been inflated by small sample sizes, liberal statistical thresholds, and inadequate assessment of clinical insight.

It is also likely that potential correlates of insight observed at the level of the cortex may be better isolated using network analyses. This latter proposition is supported by two factors. First, insight likely represents dynamic thought processes and the interplay of different cognitive abilities (e.g. social cognition, working memory, etc.), rather than a specific neurocognitive deficit. Second, mounting evidence is pointing towards understanding schizophrenia as a disorder of dysconnectivity, as opposed to a disorder characterized by localized alterations of neuroanatomy (Fornito & Harrison, 2012; Friston, Brown, Siemerkus, & Stephan, 2016). Consequently, it may not be possible to isolate clear structural neuroanatomical markers of poor or good clinical insight. It may instead be more fruitful to investigate the phenomenon of insight using network approaches to studying neuroanatomy, or functional neuroimaging.

Our findings of reduced left hemisphere cortical thickness in patients compared to controls replicate findings from numerous studies demonstrating cortical atrophy and grey matter

volume deficits in the insula, temporal regions, and cortical midline structures including the precuneus and cingulate cortex in schizophrenia patients compared to healthy subjects (Palaniyappan et al., 2012; Rimol et al., 2010; Torres et al., 2016). As such it suggests that our cortical thickness metric was sensitive enough to detect group differences, but failed to reveal a significant link between insight and cortical thickness.

Our findings also show that cortical thinning was observed only in the left hemisphere in schizophrenia patients. Although previous research has revealed bilateral cortical thinning of equivalent effect sizes in schizophrenia (Rimol et al., 2010), one potential explanation for this finding may be related to the reduced hemispheric asymmetry that has been noted in schizophrenia (Crow et al., 1989; Pearlson et al., 1997). Hemispheric asymmetry has been documented in healthy controls in favor of the left hemisphere (Wada, Clarke, & Hamm, 1975), but schizophrenia patients do not exhibit the expected asymmetry. In the current study, we found that individuals exhibited predominantly cortical thinning in the left hemisphere compared to controls. This hemispheric specificity of our results could thus be taken as reflecting this lack of asymmetry in patients compared to controls. Nevertheless, previous studies have also demonstrated larger effect sizes of cortical thinning in schizophrenia patients compared to patient in left hemisphere regions including the cingulate cortex, which was also a region exhibiting cortical thinning in the current study (Rimol et al., 2010). Finally, it has also been shown that the neurocognitive deficits that schizophrenia patients demonstrate are mainly abilities that are hypothesized to engage more of left hemisphere function(Carter, Robertson, Nordahl, Chaderjian, & Oshora-Celaya, 1996), therefore the current finding may reflect this

It is interesting to note that in this study, there was a trend toward higher antipsychotic dosage intake in individuals with greater levels of insight, an association which has been documented previously (Bianchini et al., 2014; Pijnenborg et al., 2015). While antipsychotic dosage was

controlled for in our analyses, it is possible that previously established links between brain measures and clinical insight may have been mediated by this relationship with antipsychotic medication, as many previous studies conducted on the neuroanatomical basis of clinical insight did not include medication as potential covariate (M. A. Cooke et al., 2008; Palaniyappan et al., 2011; Sapara et al., 2007). Indeed, it has been shown that cortical thickness (van Haren et al., 2011), and both grey and white matter volumes (Ho, Andreasen, Ziebell, Pierson, & Magnotta, 2011) may vary as a function of antipsychotic intake in schizophrenia patients over time.

In the same vein, the potential relationship between insight, neuroanatomy, and antipsychotic dosage may also explain why our results are in contrast with findings from a previous study done in our group, which examined the relationship between awareness of symptoms and cortical thickness (Emami et al., 2016). Emami et al. (2016) reported thinner right insular cortex in individuals with low insight into symptoms, compared to those with higher insight using vertex-wise cortical thickness analyses. Differences between our findings may be attributed to differences in covariates included in analyses, and specifically antipsychotic dosage. On the other hand, both sample sizes and assessments of clinical insight differed between our two studies. Emami et al. (2016) findings were restricted to the dimension of symptom awareness as assessed by the SAI-E whereas in the current study, associations with cortical thickness were examined using a more comprehensive measure of clinical insight which included both the dimension of symptom awareness and attribution, and awareness of consequences of the illness. Finally, Emami et al. (2016) took a categorical approach to insight levels, whereas in the current investigation, clinical insight levels were examined as a continuous phenomenon. These inconsistencies further emphasize the impact of slight differences across assessments of insight on exploration of this phenomenon's etiology.

A second objective of this study was to explore the relationship between clinical insight levels and subcortical volumes. Present findings suggest an association between greater AINT and larger bilateral hippocampal volumes, although these results do not survive multiple comparison correction. This result contrasts with the findings of a study conducted by Buchy et al. (2010) which did not find evidence of a relationship between clinical insight and hippocampal volume in a sample of first-episode psychosis patients. The discrepancy between our findings may be the result of using different clinical populations. Moreover, a different measure of clinical insight was used. Nevertheless, in line with the established role of the hippocampus in memory processes (Lepage, Habib, & Tulving, 1998; Scoville & Milner, 1957), the trend identified in the current study may reflect the relationship between greater memory performance and better clinical insight in schizophrenia (Nair et al., 2014). In individuals with enduring schizophrenia, reductions in hippocampal volume may contribute to memory deficits, which in turn may make it difficult for individuals to make use of knowledge of past mental states to inform their current self-perceptions and illness narrative, leading to poorer clinical insight.

A trend-like association also emerged between greater amygdala volumes and better AINT. A proposed role of the amygdala is the processing of emotionally relevant or salient stimuli (Anderson & Phelps, 2001; Cunningham & Brosch, 2012). Although this is the first study to show an association between insight and amygdala volume, one speculation is that this relationship may reflect the affective component of clinical insight. Indeed, the presence of depressive symptoms has been shown to predict insight levels (Lincoln, Lullmann, & Rief, 2007; Staring et al., 2009). On the other hand, having awareness of one's illness experiences may require one to be able to identify information relevant to the self, and being able to make connections between salient past and current mental events, which may inform individuals of

schizophrenia that their psychological states have changed. Future studies should further explore this trend and examine whether potential network alterations between the amygdala and hippocampus may be related to clinical insight.

Finally, although associations between subcortical volumes and levels of AINT were observed, no associations emerged between subcortical volumes and the ASC dimension. This further testifies to the importance of examining correlates of insight dimensions separately, as it has already been shown that levels of awareness for different dimensions of the illness have been shown to be predicted by different sets of psychological and clinical factors (Ritsner & Blumenkrantz, 2007). Moreover, the specificity of a link between neuroanatomy and AINT further supports the heuristic value of the factors identified by Konsztowicz et al. (submitted), and suggest that ASC and AINT do indeed reflect separate dimensions. One speculation is that being aware of one's illness might require more introspective and self-reflectiveness abilities, and drawing on past and current mental states using working memory to create a global understanding of the self. On the other hand, awareness of specific symptoms may be more influenced by personal attitudes and coping styles towards the experience of symptoms, psychological variables which may not be amenable to isolation in the brain.

Clinical insight is determined by a range of psychological, clinical and cognitive factors (Vohs et al., 2016). Therefore, one potential explanation for the lack of a pronounced relationship between clinical insight and neuroanatomy is that it may not be possible to isolate precise neuroanatomical determinants of clinical insight levels that are generalizable to all schizophrenia patients. It is possible that the factors that are found to predict clinical insight levels, and the weight that they have in determining clinical insight, may differ between certain individuals depending on their illness profiles. Accordingly, the variance in clinical insight levels

that is explained by neuroanatomical features, such as cortical thickness or subcortical volumes, may vary depending on illness profiles, even within patients with enduring schizophrenia. Moreover, it is possible that the psychological characteristics that have bene found to determine insight may not have a clear neuroanatomical basis, thus making it difficult to find precise neuroanatomical markers of insight. Accordingly, investigating insight using a network approach may also facilitate the understanding of the potential neural basis of insight.

Results of the contrast between patients and controls in subcortical volumes are not as extensive as previously shown. A recent paper investigating subcortical volumes in a sample of over 2000 schizophrenia patients across North America and Europe demonstrated that individuals with schizophrenia have significantly reduced volume of the hippocampus, thalamus and amygdala. Some potential explanations for the discrepancies with the null findings of the current study include a difference in the tools use to process the MRI scans, as it has been shown that different automated pipelines vary in their segmentation of subcortical compared to the manually segmented "gold standard" (Makowski et al., 2017). Second, the healthy control participants included in the current study were recruited so that their education level, age, and sex matched those of the patient group. It is possible that the similarity of these characteristics might be represented at the level of the brain as well. Third, our sample was restricted to individuals from the same community, compared to a more global representation in the study by van Erp et al. (2016). Finally, a crucial point to note in the literature on schizophrenia is the fact that this disorder is marked by extreme heterogeneity in terms of psychopathology. Pooling patients on the sole basis of having a diagnosis of schizophrenia may obscure some slight differences within this clinical population. Accordingly, in future endeavors, it will be important

to investigate the neural correlates of schizophrenia-related phenomenon like clinical insight, in groups or clusters of patients that present with similar pathology.

As of now, investigating the neural correlates of insight in a heterogeneous sample of enduring schizophrenia patients may not be the most fruitful endeavor. Efforts should be geared towards developing a clearer definition of, and better understanding of the mechanisms of the etiology of this complex phenomenon in a disorder as heterogeneous as schizophrenia. Future studies should therefore aim to determine whether different etiological patterns, including patterns of neuroanatomy, of clinical insight can be identified across different clinical profiles in schizophrenia. For example, in some groups of patients with more severe neurocognitive deficits, neurobiology might explain more variance in insight levels than individuals with schizophrenia who only present with psychotic symptoms. Understanding the different routes towards achieving good or poor clinical insight will better equip the field to probe neuroanatomical correlates in a more directed and profitable manner.

Limitations

One limitation of this study is that only the association between total subcortical volumes and clinical insight were examined. Given the present evidence for an association between clinical insight and hippocampal volume, future research should aim to explore whether associations with levels of clinical insight are specific to certain subfields, given the emerging interest in the field at dissecting this structure. This could extend as well to thalamic subnuclei (Van Buren & Borke, 2013). It should also be noted that the current study was restricted to structural neural correlates only. However, clinical insight is a phenomenon that likely represents dynamic thought processes, as opposed to a “state” phenomenon. Functional brain imaging may therefore offer a more appropriate method to better understand the neural roots of clinical

insight. Finally, this is the first study to investigate the correlates of the insight factors AINT and ASC. Due to the issue of assessment variability in the field of clinical insight, additional studies conducted with different samples and that examine the correlates of these two factors are needed to replicate and confirm the validity of these findings.

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Conflict of interest

ML reports having received financial assistance/compensation for research and educational events from Janssen-Ortho, Eli Lilly, Roche, and Otsuka/Lundbeck Alliance. SB, CM, SK, and LB declare that they have no conflicts of interest.

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Chapter 5

General conclusions

5.1. Summary and Conclusions

The main objective of this thesis was to clarify the psychological determinants and neural correlates of clinical insight, by using an approach that helps integrate different theories of insight as well as findings from previous literature, and by addressing limitations of previous insight research. In Chapter 3, the relative contribution of different social cognition domains and self-reflectiveness to clinical insight were examined while accounting for previously established predictors of clinical insight. While previous research had mostly focused on identifying single correlates of clinical insight guided by distinct theoretical approaches on insight, a more integrative approach was taken, with the idea in mind that clinical insight likely is not a result of a single deficit in a single modality, but reflects a combination of factors. Results of the study presented in Chapter 3 clarified the contributions of individual factors, and demonstrated that affective empathy, medication dosage, and self-reflectiveness make the largest unique contribution to variance in clinical insight. These findings are significant because they shift the emphasis from previous notions that poor clinical insight can be mainly attributed to neurocognitive deficits or symptom severity. Instead, this study suggests that clinical insight is largely determined by 1) one's self-reflective/introspection abilities, and 2) by one's ability to take another person's perspective and to relate affectively with others. This therefore identifies metacognition and social cognition as primary targets of interventions aimed at improving insight amongst schizophrenia patients. Moreover, this is one of the first study to highlight the role of medication dosage in predicting levels of clinical insight. Although the directionality of the latter relationship cannot be inferred from results of this study, this finding provides a stepping stone for more research to be conducted on the potential role of medication on levels of clinical insight.

A more general implication of the findings presented in Chapter 3 is the fact that this study paves the way for the development of more targeted interventions that address the underlying bases of clinical insight, as opposed to targeting insight itself. Moreover, it is hoped that this work provides a stepping stone toward more integrative approaches to research on clinical insight that elucidates the specific ways in which different factors are related to insight, given that findings confirm the multi-determined nature of this phenomenon.

In **Chapter 4**, limitations of previous studies on neural correlates of insight were addressed by examining the neuroanatomical correlates of clinical insight, through an extensive examination of the brain at the level of cortex and subcortex, and using a comprehensive assessment of clinical insight. Results of this study did not replicate previous findings obtained with smaller samples, and instead suggest that insight into illness may not have a clear neuroanatomical basis at the level of the cortex. In fact, this lack of neuroanatomical basis is in line with the behavioral results presented in Chapter 3, which highlighted the fact that multiple factors come into play in predicting clinical insight levels. Indeed, considering the findings presented in Chapter 3, it is unsurprising that no clear neural correlate of clinical insight emerged in our result. If clinical insight is a latent factor, determined by a multitude of factors that are primarily psychological in nature, then it may not be possible to isolate a specific brain structure responsible for poor or good clinical insight.

The lack of a clear association between neuroanatomy and clinical insight, and the finding that clinical insight is determined by multiple factors have several implications. First, it suggests that a different approach to examining the neural correlates of clinical insight should be taken. Rather than grouping a heterogeneous group of schizophrenia patients and examining broad associations between clinical insight levels and the brain, the etiology of clinical insight

and how it potentially differs in certain groups of patients should be more clearly understood. In particular, it is possible that clinical insight levels have different determinants depending on the illness profiles of certain patients. Therefore, cluster analyses should be conducted in order to uncover whether certain factors have more weight in predicting insight levels in subgroups of patients with similar psychopathology. When, and if, different etiologies of insight are identified in patient subgroups, then it can be more precisely determined whether neurobiology may play a role in explaining levels of clinical insight. For example, perhaps for individuals with severe neurocognitive deficits, clinical insight is more determined by neuroanatomical alterations, compared to patients with normative neurocognitive performance but whose level of insight may be solely determined by their coping styles.

Another major implication of the findings presented in this dissertation is the importance of negative results in understanding the nature of psychological phenomena. There is often a bias in the scientific literature for the publication of solely significant findings. Nevertheless, it is crucial that both negative and positive findings be made accessible to the scientific community as this provides a more complete picture of what is going on. The negative findings presented in this thesis have the opportunity to add a lot of value to the current state of the literature on the current understanding of the neural and psychological basis of insight, especially given the strengths of the study, such as the large sample size, conservative statistical analyses, quality controlled imaging data, and an exhaustive exploration of the whole brain and multiple psychological predictors of insight.

5.2. Limitations

Like any research project, there are limitations to the work outlined in this thesis that limit interpretations that can be made from this thesis. A first limitation concerns the fact that the levels of clinical insight in the schizophrenia patient sample used in both studies were high. Therefore, the factors that were found to predict clinical insight levels in this study may not be representative of the factors that predict clinical insight in individuals with more severe insight impairments. This aspect of the sample may have been determined by the fact that individuals who chose to take part in a study, which included long assessments and an MRI scan, may represent less severe cases, or simply by the fact that individuals with very poor insight may not want to participate in a study on 'schizophrenia'. Future studies should therefore aim to adjust the characteristics of the study to enable the recruitment of a more varied sample of patients.

A second limitation concerns the study presented in Chapter 3. The objective of this study was to use an integrated approach to examining the determinants of clinical insight, by examining the relative contribution of multiple psychological variables. Nevertheless, some factors that have been shown to play a role in levels of clinical insight were not included in this study. For example, coping styles have been shown to explain variance in insight levels as mentioned in Chapter 1, but this variable was not included in our analyses. It is therefore possible that by including more known predictors of insight, the relative contribution of the social cognition and self-reflectiveness would have differed.

Third, in Chapter 4, the associations between subcortical structure volumes and clinical insight were examined, but only whole volumes were examined, and the potential associations with subregions of different subcortical structures were not examined. It has nevertheless been shown that different subnuclei of the thalamus and hippocampus, in particular, may subserve

different functions in the brain. Therefore, examining associations between insight and subcortical structures at the subnuclei level may provide a more accurate and precise depiction of a potential link between insight and subcortical volumes.

5.3. Future directions

The findings presented in this thesis highlight the complexity of investigating the etiology of the insight phenomenon in schizophrenia, and emphasize the idea that clinical insight may not represent a single phenomenon but a combination of different individual characteristics in the illness. In light of these findings, and the fact that schizophrenia is demarcated by its heterogeneity, it will be important in the future to design studies that can disentangle whether some factors are more important than others in determining levels of insight in subgroups of schizophrenia patients. That is, cluster analyses could be used to identify subgroups of patients with similar psychopathology, followed by an investigation of how levels of clinical insight within each subgroup is determined. In line with this, it will also be important to conduct studies that investigate the relative contribution of both neuroanatomical *and* psychological factors to clinical insight levels. Examining both factors simultaneously may uncover a specific interplay between them that can help elucidate clearer mechanisms of the formation of insight. More specifically, examining the directionality of the relationship between the different psychological and neuroanatomical predictors identified in this research and clinical insight will help elucidate the etiology of insight. This kind of project could be achieved using longitudinal designs.

Another important future direction, particularly in relation to results of Chapter 3, will be to assess whether psychological interventions that target social cognitive abilities and self-reflectiveness in particular could lead to improvements in clinical insight. Affective empathy was found to be the strongest predictor of clinical insight in this thesis. Interventions have already

been developed that target these deficits in schizophrenia, such as Social Cognitive and Interaction Training (SCIT), and these have shown to lead to improvements in targeted social cognitive abilities and social functioning (Combs et al., 2007; Roberts et al., 2014). On the other hand, other types of interventions that facilitate social contact without necessitating direct intervention on patients' social skills may also have beneficial effects for clinical insight. For example, peer support groups involve interactions between individuals who have significantly improved from a mental illness and others who still struggle with psychological difficulties. This type of intervention promotes social interactions as well as reflecting on one's illness experiences by considering other individuals' interpretations of their own struggles with mental illness (Davidson, Chinman, Sells, & Rowe, 2006). Therefore, peer support groups may work both on social skills as well as on an individual's capacity to reflect on the self in a flexible way, integrating other perspectives from peers in their interpretation of their own experiences. Peer support groups may thus hold great promise in promoting better clinical insight in individuals with schizophrenia through the promotion of social contact and self-reflectiveness.

In addition, more active psychological interventions have also been developed to improve aspects of a patient's metacognition, including self-reflectiveness, such as Metacognition Reflection Insight Therapy (MERIT) (Van Donkersgoed et al., 2014), and there is preliminary evidence for their efficacy in improving clinical insight, which supports the present finding that self-reflectiveness represents an important predictor of clinical insight (Leonhardt et al., 2016; Jenifer L. Vohs et al., 2015). In sum, these findings highlight the importance of conducting more studies that investigate the potential efficacy of these kinds of therapeutic interventions or peer support groups in improving clinical insight, and the potential factors that mediate these improvements, as this could also strengthen the reliability of the findings presented in Chapter 3.

Also in line with findings from Chapter 3, a potential avenue of future research would be to examine whether social functioning may mediate the relationship between affective empathy and clinical insight. It is possible that those who are more frequently exposed to social situations, and who have better quality of social relationships are more exposed to opposing views concerning their illness. Moreover, they may have more opportunities to discuss their illness experiences and therefore more opportunities to make sense of them in an appropriate manner. Therefore, future studies should attempt to determine whether there is a relationship between social functioning and clinical insight, and whether this relationship mediates the relationship between self-reflectiveness, affective empathy, and clinical insight.

One implication of the findings presented in Chapter 4 is the fact that there does not seem to be a clear structural neuroanatomical basis to clinical insight. Therefore, as alluded to throughout Chapter 4 of this thesis, network approaches to examining neuroanatomy, such as examining the covariation of cortical thickness of different related brain regions, as well as functional neuroimaging have the potential to advance our understanding of clinical insight. The reasons for this are two-fold: schizophrenia is increasingly seen as a disorder of network connectivity, and so it is likely that a phenomenon that occurs as part of this illness is also mediated by alterations in connectivity. Second, clinical insight likely represents a dynamic thought process that requires a wide range of abilities, from neurocognition to affective empathy, as evidenced by findings of Chapter 3. Consequently, the relationship between brain and insight could perhaps be better understood by examining whether the psychological/clinical predictors of insight can be understood as a dysfunction of specific brain networks, and how these can relate to insight levels. For example, findings in Chapter 3 highlight self-reflectiveness ability as predictor of clinical insight levels, and it has been shown that self-reflectiveness abilities are

subserved by the activation of a specific network, the 'default mode network' (Gusnard, Akbudak, Shulman, & Raichle, 2001; Johnson et al., 2002). Therefore, future studies should aim to investigate whether clinical insight are specifically related to aberrant functioning of the default mode network.

Although there are ample opportunities for future directions in relation to research on clinical insight, the work presented in this dissertation provides a stepping stone towards a more integrative understanding of clinical insight as a *latent* phenomenon, as opposed to a specific neurocognitive deficit or symptom. By understanding insight in this way, this can open more opportunities to the investigation of insight, without restricting research to specific correlates or determinants, and remaining open to the possibility that clinical insight has multiple determinants, and that these determinants may vary across individuals. For example, this work provides more support for qualitative approaches to studying insight, as analyzing discourses may reveal exactly how individuals may use self-reflectiveness or affective empathy to gain an understanding of their illness. Through this reconceptualization of clinical insight, this work provides a stepping stone towards more comprehensive approaches to the research on insight, and therefore knowledge gained from this research can be applied to future endeavors.

Appendix 1:

Study #1 Tables

Table 1:Demographic and clinical characteristics of subjects. Sample size is 139 schizophrenia patients unless otherwise specified.

	Mean	**SD**	**Range**
Male (%)	101 (73%)	-	-
Years of age	35.70	7.98	21 - 50
Illness Duration (n=137)	13.39	7.73	4 – 37
Antipsychotic dosage (n=131)	798.30	849.98	10.70 - 4835.00
CogState (standardized score)	-1.29	0.95	-4.52 - 0.98
SAPS total score	6.75	4.31	0 – 16
SANS total score	9.02	3.08	0 – 17
SAI-E total score	13.83	4.40	1.33 – 20.00
Ekman global accuracy (n=137)	79	12	25 – 100
Hinting Task total score (n=137)	15.90	3.27	4 – 20
Affective Empathy subscale – total score	18.10	4.66	5 – 38
Self-reflectiveness subscale score	12.30	4.34	2 – 26

Table 2: Spearman rho correlations between clinical characteristics, social cognition, neurocognition, self-reflectiveness, and clinical insight. Sample size is 139 schizophrenia patients, unless otherwise specified. Positive correlations indicate that higher scores on associated variable is related to higher clinical insight.

Variable	**Clinical insight**	
	r	*p*
Years of age	0.003	0.969
Illness duration (n=137)	0.085	0.322
Antipsychotic dosage (n=131)	0.309	<0.001
CogState (standardized score)	0.199	.019
SAPS total score	0.034	0.687
SANS total score	-0.239	0.005
Ekman global accuracy (n=137)	0.253	0.003
Hinting Task total score (n=137)	0.180	0.035
Affective empathy subscale – total score	0.236	0.005
Self-reflectiveness subscale score	0.326	<0.001

Table 3: Relative contribution of social cognition measures to clinical insight: hierarchical regression analysis (N=135)

Block	**β**	***R*² change**	***F* change**	**Significance of *F* change**
Block 1		0.044	6.124	0.015
Ekman global accuracy	0.210**			
Block 2		0.008	1.140	0.288
Ekman global accuracy	0.172			
Hinting Task total score	0.098			
Block 3		0.066	9.799	0.02
Ekman global accuracy	0.172*			
Hinting Task total score	0.081			
Affective Empathy subscale score	0.257**			

**p*=0.056, ***p<0.05

Table 4:Relative contribution of social cognition and self-reflectiveness to clinical insight: hierarchical regression analysis (N=137)

Block	**β**	***R*² change**	***F* change**	**Significance of *F* change**
Block 1		0.081	11.975	0.001
Self-reflectiveness subscale score	0.285**			
Block 2		0.020	2.917	0.090
Self-reflectiveness subscale score	0.275**			
Hinting Task total score	0.140			
Block 3		0.062	9.895	0.002
Self-reflectiveness subscale score	0.276**			
Hinting Task total score	0.121			
Affective empathy subscale score	0.250*			

*p<0.005, **p<0.001

Table 5: Relative contribution of known predictors, social cognition, self-reflectiveness, to clinical insight: Hierarchical regression analysis (N=129)

Block	**β**	**R^2 change**	***F* change**	**Significance (*p*)**
Block 1		0.148	7.249	<0.001
Cogstate (standardized score)	0.160			
SANS total score	-0.232**			
Antipsychotic dosage	0.254***			
Block 2		0.048	7.393	0.007
Cogstate (standardized score)	0.181*			
SANS total score	-0.167*			
Antipsychotic dosage	0.231***			
Self-reflectiveness subscale score	0.229**			
Block 3		0.063	5.217	0.007
Cogstate (standardized score)	0.122			
SANS total score	-0.102			
Antipsychotic dosage	0.234***			
Self-reflectiveness subscale score	0.225**			
Affective empathy subscale score	0.239***			
Ekman global accuracy	0.119			

*p<0.05, **p<0.01, ***p<0.005

Appendix 2:

Study #2 Figures and Tables

Table 1: Descriptive statistics of demographic and clinical characteristics of the patient and healthy control groups. Sample sizes are n=110 for the patient group, and n=69 for healthy controls, unless otherwise specified.

		Patients			**Controls**			
			Range	**SD**		**Range**	**SD**	***p***
Male (%)		83 (76%)	-	-	48 (70%)			
Age (years)		35.24	21-50	8.17	34.19	21-50	8.97	0.42
Handedness	**Right**	85 (77%)	-	-	54 (81%)	-	-	
	Left	16 (15%)	-	-	7 (10%)	-	-	
	Ambidextrous	9 (8%)			6 (9%)			
Education (years)		11.36	4-22	2.51	13.48	9-22	2.40	<0.001
WASI full-scale IQ		95.23	66-134	14.58	108.84	72-134	13.60	<0.001
Age of onset (years)		22.40	8-44	6.85	-	-	-	-
Illness duration (years)		12.66	3-37	7.58	-	-	-	-
Antipsychotic medication (dose, mg) (n=105)*		797.59 (n=105)	10.7-4835	820.48	-	-	-	-
SAPS total score		18.27	0-16	17.53	-	-	-	-
SANS total score		24.58	0-17	10.53	-	-	-	-
AINT**		12.44	7-21	2.38	-	-	-	-
ASC[e]**		7.71	.75-12	2.73	-	-	-	-
Calgary Depression Scale		2.65	0-15	2.846	.65	0-7	1.28	<0.001
Hamilton Anxiety Scale		6.41	0-20	4.556	2.12	0-11	2.67	<0.001

*Antipsychotic dosage reported as chlorpromazine equivalent in milligrams. **Higher scores on the AI&NT and ASC factors indicate better performance.

Table 2: Pearson correlations between clinical and demographic characteristics and clinical insight, in the patient group only (n=110). Positive correlations indicate that better insight is associated with greater scores on the associated variable.

	AINT scores		**ASC scores**	
	R	*p*	*r*	*p*
Age	-.005	.956	-.017	.863
Illness duration (years)	-.063	.514	.104	.306
Education (years)	.100	.296	-.006	.950
Antipsychotic medication (dose, mg)	.180	.066	.212	.038*
WASI Full-scale IQ	-.017	.857	.188	.060
SAPS total score	.024	.805	-.126	.210
SANS total score	.069	.472	-.238	.017*
CDS	.081	.399	.177	.077
HAS	-.050	.607	.086	.391

Figure 1: Differences in left hemisphere whole-brain cortical thickness between 110 schizophrenia patients and 69 healthy controls (t = -2.8, p<0.05, FDR corrected).

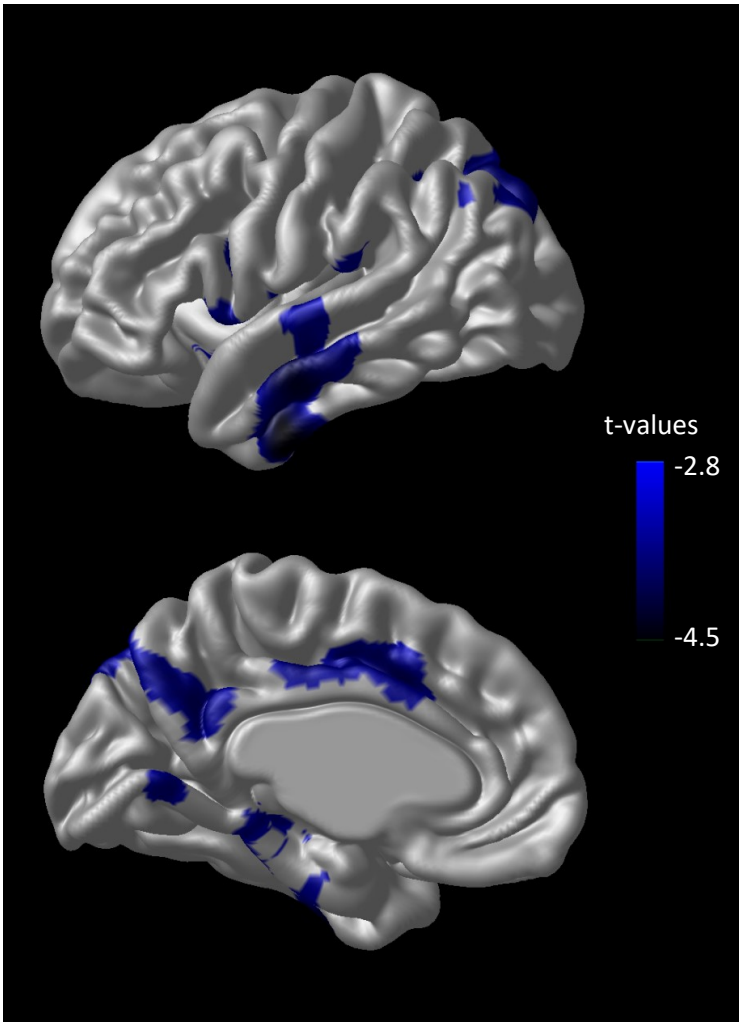

Table 3: Regions where schizophrenia (n=110) patients exhibited significantly thinner cortex compared to healthy controls (n=69). MNI space coordinates represent the maxima.

Region	**Stereotaxic coordinates (MNI space)**		
Patients < Healthy controls	*x*	*y*	*z*
L middle temporal gyrus	-69.911	-10.531	-24.190
L inferior temporal gyrus	-54.957	-11.147	-40.482
L superior occipital gyrus	-28.874	-66.898	31.405
L median cingulate gyrus	-9.615	7.581	41.402
L precuneus	-7.050	-56.889	31.944
L lingual gyrus	-5.141	-65.998	2.641
L parahippocampal gyrus	-24.889	-40.528	-12.754

Table 4: Differences in means subcortical volumes in the patient and control groups.

Structure	**Patients**	**Controls**	
	Volume in mm³ (SD)	**Volume in mm³ (SD)**	***p***
L hippocampus	3209.2 (300.9)	3265.7 (349.5)	.906
L amygdala	1786.9 (144.5)	1809.1 (146.6)	.850
L striatum	12928.3 (1057.2)	12581.6 (1052.3)	<.001
L thalamus	7657.6 (585.4)	7943.9 (683.1)	.902
R hippocampus	3211.8 (297.3)	3299.0 (313.5)	.566
R amygdala	1778.1(145.9)	1784.2(143.8)	.349
R striatum	12968.3 (1065.8)	12651.8 (992.8)	<.001
R thalamus	8252.9 (622.6)	8582.0 (716.3)	.850

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