CLINICAL, NEUROCOGNITIVE, AND STRUCTURAL AND FUNCTIONAL MRI CORRELATES OF INSIGHT IN FIRST EPISODE PSYCHOSIS

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To
Rita and Jordy

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CONTRIBUTIONS OF AUTHORS

The experiments presented in this thesis were designed, conducted and written as manuscripts by myself and my PhD supervisor **Martin Lepage**. I was responsible for image processing and statistical analyses. The following list identifies the contributions of the other authors located at the *Douglas Mental Health University Institute.*

1. **Michael Bodnar.** Assisted in the statistical analyses and interpretation of results for experiments 1, 2 and 7.
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ABSTRACT

Background. Poor insight is primary symptom of psychosis that can be characterized along clinical and cognitive dimensions. Clinical insight describes ones awareness of illness, awareness of treatment need/efficacy, and ability to relabel unusual mental events, while cognitive insight reflects ones self-reflectiveness and self-certainty in beliefs.

Purpose. Our overall aim was to map the psychopathological correlates and cognitive and neural systems underlying poor clinical and cognitive insight in FEP using behavioural analyses, and MRI-based cortical thickness, diffusion tensor imaging and functional imaging measurements.

Methods. We carried out the following experiments: **1.** Assessing the trajectory of clinical insight at multiple time points over the first year of a FEP **2–3.** Mapping the extent of cortical thinning in FEP patients with poor clinical insight. **4.** Analyzing the role of the hippocampus in cognitive insight in FEP **5.** Analyzing the integrity of the fornix in relation to self-certainty in FEP. **6.** Assessing the significance of delusional severity for cognitive insight in FEP. **7.** Analyzing the role of source memory for cognitive insight in FEP using a virtual reality cognitive activation paradigm during fMRI data acquisition.

Results. 1. Clinical insight improved concurrently with positive, negative and anxious symptoms between baseline and month 1. Five patient subgroups were discriminated: good, increasing, decreasing, moderate poor and very poor. **2–3.** Cortical thinning was associated with clinical insight. **4.** Verbal memory associated with self-reflectiveness, while hippocampal volume was associated with self-certainty. **5.** Fornix integrity associated to self-certainty. **6.** Delusions were associated with self-reflectiveness. **7.** FES patients demonstrated statistically similar source memory performance to that of healthy controls. Despite this, within-group analyses revealed BOLD signal differences in frontal and parietal regions in correlation with higher self-reflectiveness and lower self-certainty in FES and controls during source memory recognition.

Conclusions and significance. 1. Specific longitudinal insight trajectories appeared to be driving the observed associations between clinical insight and negative and depressive symptoms in the entire FEP cohort. **2–3.** The findings suggest that the neural signature of clinical insight in FEP involves a network of semi-independent brain structures. **4–5**. Structural deficits in the hippocampus and its circuitry, including fornix integrity, appear to be emerging as an intermediate phenotype for self-certainty in FEP. In individuals with a FEP, cognitive insight may rely on memory whereby current experiences are appraised based on previous ones. **6.** Self-reflection may be important for delusion severity. **7.** The disparate regional brain activity in FES might reflect the use of an alternate cognitive stratagem to achieve adaptive self-reflectiveness and self-certainty levels, or may reflect underlying neuropathology in frontal and parietal areas.

RÉSUMÉ

Contexte. Le manque d'auto-critique (*insight*) est un symptôme primaire de psychose qui peut être caractérisé sur les plans cliniques et cognitifs. L'*insight* clinique décrit la conscience qu'a une personne de sa maladie, la conscience du besoin ou de l'efficacité du traitement et l'habileté d'une personne à catégoriser des événements mentaux inhabituels, alors que l'*insight* cognitif représente la capacité de réflexion sur soi et le niveau de certitude par rapport à ses propres croyances.

Objectif. Notre objectif général était de définir les corrélats psychopathologiques et cognitifs ainsi que les systèmes neuronaux impliqués dans le manque d'*insight* clinique et cognitif chez les premiers épisodes psychotiques (PEP) en utilisant des analyses comportementales ainsi que des mesures basées sur l'IRM comme l'épaisseur corticale, l'imagerie par tenseur de diffusion et l'imagerie fonctionnelle.

Méthodes. Nous avons fait les expériences suivantes : **1.** Évaluer la progression de l'*insight* clinique à plusieurs moments de la première année d'un PEP **2–3.** Définir l'ampleur de l'amincissement cortical chez les patients PEP avec un manque d'*insight* clinique. **4.** Analyser le rôle de l'hippocampe dans l'*insight* cognitif chez les PEP **5.** Analyser l'intégrité du fornix en relation avec la certitude de soi chez les PEP. **6.** Évaluer le rôle de la sévérité des délires par rapport à l'*insight* cognitif des PEP. **7.** Analyser le rôle de la mémoire de la source dans l'*insight* cognitif chez les PEP en utilisant un paradigme d'activation cognitive en réalité virtuelle durant une acquisition de données d'IRMf.

Résultats. 1. L'*insight* clinique s'est amélioré simultanément avec les symptômes positifs, négatifs et d'anxiété entre l'évaluation initiale et le premier mois. Cinq sous-groupes de patients ont été identifiés : bon, croissant, décroissant, modérément faible et très faible. **2–3.** L'amincissement cortical était associé avec l'*insight* clinique **4.** La mémoire verbale était associée avec la réflexion sur soi alors que le volume de l'hippocampe était associé avec la certitude de soi, indépendamment des effets de la

mémoire verbale chez les PEP. **5.** L'intégrité du fornix était associée à la certitude de soi. **6.** Les délires étaient associés avec la réflexion sur soi. **7.** Les patients PEP démontraient une performance de leur mémoire source similaire aux contrôles sains. Malgré ceci, les analyses à l'intérieur de chaque groupe ont révélé une différence du signal BOLD dans les régions frontales et pariétales en corrélation avec une plus grande réflexion de soi et une plus faible certitude de soi chez les PEP et les contrôles durant une tâche de reconnaissance de la mémoire source.

Conclusions et importance. 1. La progression longitudinale spécifique de l'*insight* semble entraîner les associations entre l'*insight* clinique et les symptômes négatifs et dépressifs dans l'ensemble de la cohorte PEP. **2–3.** Les résultats suggèrent que la signature neuronale de l'*insight* chez les PEP implique un réseau de structures cérébrales semi-indépendantes. **4–5**. Les déficits structuraux de l'hippocampe et de ses circuits, incluant l'intégrité du fornix, semblent émerger en tant que phénotype de la certitude de soi chez les PEP. Chez les individus avec un PEP, l'*insight* cognitif pourrait reposer sur la mémoire puisque les expériences actuelles sont jugées sur la base des expériences précédentes. **6.** La réflexion sur soi pourrait être importante pour la sévérité des délires. **7.** L'hétérogénéité de l'activité des régions du cerveau chez les PEP peut refléter l'utilisation d'une stratégie cognitive alternative pour adapter la réflexion de soi ou la certitude de soi. Ceci pourrait aussi refléter une neuropathologie sous-jacente dans les régions frontales ou pariétales.

ORIGINAL CONTRIBUTIONS

Experiment 1: Documenting the progression of clinical insight and psychopathology at multiple time points over the first year of treatment for a psychosis using a general estimating equation of change. Using latent group based trajectory analysis to identify distinct subgroups of patients based on clinical insight levels, and describing the impact of psychopathology over time on the different trajectory groups.

Experiment 2: Mapping the distribution of cortical thinning in people with a FEP who show impairment on the awareness of illness and awareness of treatment need/efficacy dimensions of clinical insight. Regressing cortical thickness values on clinical insight scores in FEP.

Experiment 3: Mapping the distribution of cortical thickness and thinness in people with a FEP with symptom misattribution. Regressing cortical thickness values on symptom attribution scores in FEP.

Experiment 4: Analyzing the brain system that underlies cognitive insight in FEP by correlating hippocampal volumes with cognitive insight scores. Analyzing the link between hippocampal volume and cognitive insight in FEP controlling statistically for verbal memory performance.

Experiment 5: Assessing the degree to which fornix integrity associates to self-certainty in FEP using DTI based probabilistic tractography. Correlating fornix fractional anisotrophy (FA) to self-certainty scores in FEP.

Experiment 6: Comparing cognitive insight in FEP patients with active delusions and those with no active delusions.

Experiment 7: Analyzing the functional neural activation of cognitive insight during source recognition memory in FEP patients as compared to healthy participants using virtual reality technology.

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ABBREVIATIONS

BCIS	Beck Cognitive Insight Scale
CIVET	Cortical thickness at each vertex using the t-link metric pipeline
CLASP	Constrained Laplacian Anatomic Segmentation using Proximity algorithm
CSF	Cerebro-spinal fluid
DLPFC	Dorsolateral **PFC**
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
FEP	First episode psychosis
FDR	False discovery rate
fMRI	functional **MRI**
FWHM	Full-width-at-half-maximum
GM	Gray matter
M	Mean
MD	Mean diffusivity
MRI	Magnetic Resonance Imaging
OFC	Orbitofrontal cortex
PFC	Prefrontal cortex
SD	Standard deviation
TE	Echo time
TR	Repetition time
VBM	Voxel-based morphometry
WM	White matter

PART I

INTRODUCTION

CHAPTER 1

INTRODUCTION

Psychotic Disorders are disabling illnesses that cause distortions in perception and thought. The term Psychotic Disorders includes schizophrenia, bipolar disorder, major depression with psychotic features, schizoaffective disorder, delusional disorder, and psychosis not otherwise specified. A plethora of findings have linked poor insight to the emergence of psychotic symptoms (Mintz, Dobson, & Romney, 2003). Early intervention is key to minimizing the effects of psychosis on individuals, their families and communities, and an understanding of the brain changes that lead to poor insight during a first episode of psychosis (FEP) is important for prophylactic developments.

Insight is a cardinal feature of psychosis that can be described along "clinical" and "cognitive" dimensions. *Clinical insight* focuses on the patient's awareness of their mental disorder, awareness of treatment effects, and ability to label unusual mental events as pathological and attributable to a mental disorder. This form of insight is determined by observing individuals' behaviour in the context of a clinical examination and is valuable for determining diagnosis (Carpenter, Strauss, & Bartko, 1973), clinical outcome (X. F. Amador et al., 1994; Lincoln, Lullmann, & Rief, 2007) and treatment adherence (Buckley et al., 2007; B. J. Miller, 2008). A complementary approach, coined *cognitive insight* (Beck, Baruch, Balter, Steer, & Warman, 2004), addresses patients' capacity to re-evaluate their anomalous experiences and correct their aberrant interpretations. This aspect of meta-cognition is important for patients' clinical insight and awareness of their symptoms (Beck, et al., 2004; Engh et al., 2009; Warman, Lysaker, & Martin, 2007).

In spite of its clinical importance, the neural bases of clinical and cognitive insight have been scantily explored. An understanding of the brain systems primarily affected in poor

insight may lead to important applications such as prediction of first episode, relapse prevention and medication efficacy.

The goal of this thesis was to gain an understanding of the psychological, neurocognitive and neuroanatomical underpinnings of clinical and cognitive insight in FEP. We studied the neurocognitive correlates of insight using a comprehensive neuropsychological battery, its relation to clinical symptoms both cross-sectionally and longitudinally, its structural neural architecture using magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) tractography, and its functional neural basis using functional MRI (fMRI).

We conducted the following **seven** experiments:

1. Assessing the longitudinal trajectory of clinical insight and its relation to psychopathology at multiple time points over the first year of a psychosis. Subgroups of patients with different courses of insight were identified using latent group-based trajectory analysis and group differences in symptom severity were evaluated (p15).
2. Mapping the distribution of cortical thinning in FEP patients with poor clinical insight. Scores on two aspects of clinical insight, awareness of illness and awareness of treatment need and efficacy, were correlated with thickness measurements across the cortical mantle (p25).
3. Mapping the distribution of cortical thinning in FEP patients displaying symptom misattribution. Scores on attribution for four specific symptoms – delusions, hallucinations, flat affect and asociality – were correlated with thickness measurements across the surface of the cortex (p52).
4. Assessing the role of the hippocampus in cognitive insight in FEP. Using manually traced hippocampal volume measurements we performed a correlational analysis between hippocampal volumes and cognitive insight, controlling statistically for the effects of verbal memory ability (p74).

5. Analyzing the role of the fornix in the neural network underlying the self-certainty dimension of cognitive insight in FEP using probabilistic tractography on diffusion tensor imaging data and statistically relating these data to self-certainty scores (p97).
6. Assessing the psychopathological correlates of cognitive insight in FEP by comparing patients with and without delusions on cognitive insight scores (p109).
7. Analyzing the role of source memory for cognitive insight in FEP using functional magnetic resonance imaging (fMRI). A virtual city containing 20 characters paired with 20 objects in 20 different locations was designed to measure the functional neural activity of source memory in FEP patients with high vs. low self-certainty (p121).

The dissertation is organized as follows: Chapter 2 (p5) reviews the background literature. Chapters 3 to 5 are a string of manuscripts describing our clinical insight experiments. The manuscripts of chapters 6 to 9 describe the experiments we carried out on the topic of cognitive insight. Chapter 10 is a manuscript that describe our experiments using virtual reality technology. The final chapter (p140) summarizes the key findings and the significance of this work.

* * *

CHAPTER 2

BACKGROUND

Clinical insight

Lack of clinical insight is a central clinical characteristic of schizophrenia (Carpenter, et al., 1973) and the psychoses (X. F. Amador, et al., 1994; Ghaemi & Rosenquist, 2004). Several large field studies have confirmed the high prevalence of poor clinical insight in about 40-60% of this population. Although early theorists (Carpenter, et al., 1973; Van Putten, Crumpton, & Yale, 1976) conceptualized insight as an all or nothing phenomenon, whereby the patient either had insight or they did not have insight, modern psychological assessments regard insight as a multidimensional construct that occurs on a continuum (X. F. Amador et al., 1993; A. David, Buchanan, Reed, & Almeida, 1992). Recent writers have concentrated on the patient's awareness, or more aptly, unawareness, of several related but partially independent elements. These include awareness of one's illness, awareness of the need for treatment and an understanding of its efficacy, the ability to relabel anomalous perceptions and experiences (e.g., hallucinations, delusions) as pathological (A. David, et al., 1992), and recognition by the individual that their symptoms are attributable to a mental disorder (X. F. Amador, et al., 1993; A. S. David, 1990). This form of insight is determined by observing individuals' behaviour in the context of a clinical examination and is valuable for determining diagnosis (Carpenter, et al., 1973), prognosis (X. F. Amador, et al., 1994; Lincoln, et al., 2007) and treatment adherence (Buckley, et al., 2007; Lepage, Bodnar, Buchy, Joober, & Malla, 2010; B. J. Miller, 2008).

Clinical insight in psychosis: theoretical models

In recent years there have been three main theoretical approaches of insight which have stimulated empirical studies. The psychopathology account of clinical insight holds that insight impairments emerge with positive, negative, manic and disorganization symptom exacerbation (Buchy, Torres, Liddle, & Woodward, 2009; Mintz, et al., 2003; Osatuke, Ciesla, Kasckow, Zisook, & Mohamed, 2008). The neurocognitive account attributes lack of insight to an impaired prefrontal cortex, which subserves cognitive flexibility, self-reflection, planning and abstract thinking, as well as other executive functions (Aleman, Agrawal, Morgan, & David, 2006). That lack of insight is attributable to a deficit in prefrontally-mediated neurocognitive abilities is attested to by findings of volumetric reductions in this region (Shad, Muddasani, & Keshavan, 2006; Shad, Muddasani, Prasad, Sweeney, & Keshavan, 2004), suggesting poor insight is reducible to a neuroanatomical deficit. Lastly, the defence account of insight holds that impaired clinical insight is a coping strategy whereby patients deny the presence of their illness to psychologically protect themselves. Studies demonstrating that depressive and anxious symptoms emerge with improvements in insight corroborate this theory (Mintz, et al., 2003).

Longitudinal course of clinical insight in psychosis: relation to psychopathology

Studies tracking changes in clinical insight over the first few years following an onset of psychosis have found that a majority of individuals show full insight or improvement in insight, while others lose insight or show persistently poor insight (Fennig et al., 1996; McEvoy et al., 2006; Saeedi, Addington, & Addington, 2007). For example, poor insight has been linked to greater positive symptoms after 1 (Mintz, Addington, & Addington, 2004; Saeedi, et al., 2007), 2 and 3 years (Saeedi, et al., 2007), after 4 years (Crumlish et al., 2005), but may not be associated to positive symptom severity after 6 months (Fennig, et al., 1996). Studies have reported that greater negative symptoms are associated with

lack of insight after 1, 2 and 3 years (Saeedi, et al., 2007), but not at 6 months (Fennig, et al., 1996) or 4 years (Crumlish, et al., 2005). Finally, depression has been reported to be significantly associated to poor insight after 6 months (Crumlish, et al., 2005), though another study failed to observe this relation (Fennig, et al., 1996). Taken together, the clinical state of patients appears to be correlated with level of insight or pattern of insight change when measured simultaneously. Whether longitudinal course of insight (e.g., persistently poor insight over 12 months) is associated with symptom severity at multiple assessment points (month 3, month 6, etc.) has not been studied. This is clinically relevant as in people with a FEP the level of negative symptoms at 1 year is more likely to be associated with outcome than positive symptoms alone (A. K. Malla et al., 2004), and depression and anxiety are associated with subjectively experienced distress (Vracotas, Schmitz, Joober, & Malla, 2007).

Another important consideration is the timing of insight change after a FEP. Level of insight on admission has been shown to significantly improve after 1 year (Saeedi, et al., 2007), after 6 months (Crumlish, et al., 2005) and as soon as 3 months (Mintz, et al., 2004). The dynamic of insight changes over the first 3 months of a FEP has not been studied. A joint analysis of proximal changes in insight and psychopathology may reveal important determinants of longitudinal course of illness and outcome.

Structural neural correlates of clinical insight in psychosis: insights from manually traced prefrontal volumetry

As described above, over the first year of a psychosis the majority of people show full insight or improvement in insight, while others lose insight or show persistently poor insight. It is therefore quite possible that there may be important anatomical differences in the brains of insightful and insightless individuals.

A series of research reports has linked poor insight with structural alterations in cortex. Investigations conducted in patients with chronic psychosis have observed diminished volume in several specific regions of the prefrontal cortex, namely the left anterior

cingulate gyrus (Bassitt, Neto, de Castro, & Busatto, 2007; Flashman et al., 2001; Ha et al., 2004), superior and middle frontal gyri (Flashman, et al., 2001) and medial frontal gyrus (Bassitt, et al., 2007). The focus on prefrontal regions of interest is motivated by accounts holding that poor insight is a reflection of prefrontally mediated cognitive dysfunction (Aleman, et al., 2006).

Research on the neural systems of poor insight early in the disease process has received only scant attention. Two recent studies have suggested that structural alterations in cortex may be associated with impaired insight in people with first episode schizophrenia. In an initial study, Shad and coworkers (Shad, et al., 2004) examined in 31 patients the relationship between volume of the dorsolateral prefrontal cortex (DLPFC) and level of insight as measured by a unitary item from the Hamilton Depression Scale. Results revealed that impaired insight was correlated to volumetric reductions in the right DLPFC. The authors suggested that a diminished right DLPFC may lead to unawareness of illness via deficits in self-monitoring and conceptual organization. Further, the data fit well with the account suggesting that poor insight is the psychological analog of anosognosia (Babinski, 1914), the unawareness of neurological disorder, observed in right hemisphere neurological lesions. In a follow-up study (Shad, Muddasani, et al., 2006), this group assessed the association between two specific dimensions of insight, awareness of illness and symptom attribution (ability to correctly attribute symptoms to a mental illness), and DLPFC and orbitofrontal cortex (OFC) volumes in 14 first episode schizophrenia participants. A dissociation across insight dimensions emerged: poorer awareness of illness scores correlated with decreased volume of the right DLPFC, and poorer symptom attribution scores associated to increased left OFC volume. The DLPFC finding corroborated the authors' previous (2004) suggestion that insight may rely on DLPFC mediated self-monitoring processes. The authors posited that larger OFC volume may confer aberrant salience to perceptions and experiences (i.e., perceived symptomatology) causing inaccurate symptom attribution. An important limitation here is that analyses were limited to the DLPFC and OFC, two spatially inclusive prefrontal regions. The general contribution of gray matter (GM) disruptions outside of frontal cortex to clinical insight levels is unknown.

Whole brain analysis of structural correlates of clinical insight: merits and shortcomings of voxel-based morphometry

The abovementioned first-episode schizophrenia studies assessed the prefrontal GM underpinnings of clinical insight through manual delineation of single brain structures. Although this technique can provide a highly sensitive measure of GM volumetry or concentration, it represents a labour intensive method that suffers from inter and intra-rater reliability issues, thereby compromising the reliability of the technique. The manual delineation approach is also limited to predetermined regions of interest and therefore inappropriate for a whole cortex search. An automated, whole brain structural analysis can be achieved using the technique of voxel-based morphometry (VBM), without predefining regions of interest. The basic approach employs a series of automated processing steps including linear registration, tissue classification (white matter (WM), GM and cerebral spinal fluid (CSF)), and spatial normalization to a standard template. This allows the statistical comparison of voxels with an independent parameter of interest (e.g., insight). Although VBM provides important neuroanatomical information, it has several limitations. Most notably is the fact that typical VBM results communicate information about size, position and morphology concurrently. The analysis is also sensitive to registration differences, the size of smoothing kernel, shape differences that arise from systematic registration errors during spatial normalization, and image noise (Bookstein, 2001; D. K. Jones, Symms, Cercignani, & Howard, 2005), which may confound volume/density estimates. Moreover, VBM blurring is 3 dimensional, meaning it does not respect boundaries between tissue classes, leading to an increased likelihood of diluting existing signal or misinterpreting boundary shift as signal. Some VBM determined volumetric data are available suggesting a role for parietal and temporal cortices for insight in chronic psychosis (Cooke et al., 2008). Since syntheses of first episode and chronic psychosis work have concluded that frontal cortical dysfunction is at the core of poor insight in psychosis (Shad, Tamminga, Cullum, Haas, & Keshavan, 2006), the role of non-frontal brain areas for insight in this population has not been examined.

Cortical thickness measurements of clinical insight in psychosis: a biologically meaningful index of brain structure

Compared to VBM, measurements of cortical thickness can provide a direct and biologically meaningful index of cortical structure as they respect the anatomy of the folded cortical surface. Cortical thickness analyses are performed at the vertices of a three dimensional polygonal mesh, rather than on a 3D voxel grid. A deformable model characterized by 40,096 vertices per hemisphere is used to create inner WM and outer GM surfaces of the cortex. The thickness metric is defined as the distance between linked vertices on the two surfaces, and communicates in millimetres the actual thickness of the cortex, providing qualitatively meaningful results. The technique provides an opportunity to assess the cortical morphometry of insight across the entire cortex in people with psychosis.

Cognitive insight in psychosis: the Beck Cognitive Insight Scale (BCIS)

Fundamental to an understanding of clinical insight is the study of patients' capacity to distance themselves from their distorted beliefs and misinterpretations, reflect on them rationally, and recognize erroneous conclusions. These "higher level" metacognitive processes have only recently been studied under the rubric of cognitive insight (Beck, et al., 2004). The evaluation and correction of distorted beliefs and misinterpretations is essential for clinical insight. If patients have impaired capacity to detect their anomalous experiences and correct their erroneous interpretations, they are compelled to believe that their perceptions - what others label as symptoms - are real, that their perceptual appraisals are facts, and that their thinking is rational. Cognitive insight includes the capacity to detect and correct distorted beliefs and misinterpretations, and these metacognitive processes are believed to obstruct awareness of a mental illness requiring treatment (i.e., clinical insight). Independent studies suggest that cognitive insight has adequate convergent validity with self-rated (Pedrelli et al., 2004) and clinician rated

measures of clinical insight (Beck, et al., 2004; Bora, Erkan, Kayahan, & Veznedaroglu, 2007; Engh et al., 2007).

Recently, Beck and colleagues have developed the Beck Cognitive Insight Scale (Beck, et al., 2004) (BCIS) to psychometrically assess this construct. A first of two domains, self-reflectiveness, captures the willingness to acknowledge fallibility, consider alternate explanations, and recognize dysfunctional reasoning. The second, self-certainty, taps overconfidence in current beliefs and judgments. It has been hypothesized that higher certainty may reduce the capacity for self-reflection, and thus a Composite index is calculated that adjusts for this bias (self-reflectiveness score – self-certainty score). The original study on the BCIS compared psychotic patients (schizophrenia, schizoaffective or major depression with psychotic features) to non-psychotic psychiatric patients (major depression) on levels of cognitive insight. Relative to the psychiatric control group, in-patients with psychotic disorders endorsed greater self-certainty and less self-reflectiveness, suggesting these thinking styles may be particularly important for psychosis. Cognitive insight is of great clinical significance as it directly taps into thinking styles underlying distorted cognitions, which are increasingly acknowledged as target for intervention in people with psychosis (Turkington, Kingdon, & Turner, 2002).

Cognitive insight in psychosis: the role of active delusions

In cognitive insight studies, an association between active delusions and increased self-certainty has been reported for chronic patients with psychosis (Engh, et al., 2009; Warman, et al., 2007) and for healthy people who report delusion proneness (Warman et al., 2006). The rationale posited for this link has been that high levels of conviction may contribute to delusions via an inability to cast doubt on fallible information (Moritz & Woodward, 2002; Moritz, Woodward, & Ruff, 2003; Moritz, Woodward, Whitman, & Cuttler, 2005; Warman, et al., 2007). The initial study to investigate the delusions–cognitive insight link (Warman, et al., 2007) reported higher self-reflectiveness in delusional compared to non-delusional patients, suggesting these people are less willing

to think flexibly about their beliefs and interpretations. However, this result was at variance with theoretical expectations (i.e., overconfidence suppresses the capacity to self-reflect), and could have been influenced by sampling characteristics of the non-delusional group (they were quite chronic (mean age = 50.5 years) and underrepresented in the study (n = 13)). Interestingly, delusional patients had self-reflectiveness equivalent to healthy controls. From this perspective, it would appear that the cognitive process underlying self-reflectiveness is functioning similarly in delusions and normal cognition. A more recent study (Engh, et al., 2009) observed an expected delusions-associated dampening of self-reflection in a larger (N=143 including 79 non-delusional patients) and hence more representative sample of patients with chronic psychosis. Earlier work by this group (Engh, et al., 2007) found that self-certainty and self-reflectiveness failed to differentiate between schizophrenia and bipolar patients. In this study the schizophrenia group had significantly higher delusion severity, and although the impact of delusions was not directly assessed, this result may question the claim that aberrations in cognitive insight are stronger for delusional patients. Other studies have provided evidence for an association between the positive symptom dimension and self-certainty (Bora, et al., 2007; Pedrelli, et al., 2004), and a negative correlation between positive symptoms and self-reflectiveness (Bora, et al., 2007), in people with psychosis. Taken together, it seems that high self-certainty, and perhaps low self-reflectiveness, are more pronounced in deluded chronic psychotic patients. The impact of delusions on cognitive insight has not been investigated at the time of a FEP.

Cognitive insight in FEP: a selective role for verbal memory

The study of cognitive insight has recently been employed to identify aspects of the neurocognitive architecture that may contribute to aberrant thinking styles and cognitive distortions in psychosis (Lepage et al., 2008). In an initial study, we evaluated in individuals with a FEP associations between cognitive and clinical insight and seven domains of cognition (verbal learning and memory, visual learning and memory, working

memory, speed of processing, reasoning and problem solving, attention, and social cognition) (Lepage, et al., 2008). Results showed that participants who had higher BCIS composite index scores (indicating better cognitive insight) had better verbal learning and memory than individuals who scored lower on the composite index. We proposed that cognitive insight may rely selectively on verbal memory as it requires reflection and self-searching in memory. Further, the magnitude of verbal learning and memory deficits corresponded with the degree of self-certainty (overconfidence). We suggested that high belief certainty may cause memories to be held with strong conviction, which may dissuade elaborate searches for previous experiences in memory. Taken together, these data support the conclusion that cognitive insight may rely on memory processes whereby current experiences are appraised based on previous ones.

* * *

PART II

EXPERIMENTS

CHAPTER 3

LONGITUDINAL TRAJECTORY OF CLINICAL INSIGHT AND RELATION TO PSYCHOPATHOLOGY

Preface

Studies tracking changes in clinical insight over the first few years following an onset of psychosis have found that a majority of individuals show full insight or improvement in insight, while others lose insight or show persistently poor insight (Fennig, et al., 1996; McEvoy, et al., 2006; Saeedi, et al., 2007). Relations between clinical insight and negative and depressive symptoms have been reported at various time points during the first year of a psychosis (Crumlish, et al., 2005; Fennig, et al., 1996; Saeedi, et al., 2007), suggesting that the clinical state of patients appears to be correlated with level of insight or pattern of insight change when measured simultaneously. Another important consideration is the timing of insight change after a FEP. Level of insight on admission has been shown to significantly improve after 1 year (Saeedi, et al., 2007), after 6 months (Crumlish, et al., 2005) and as soon as 3 months (Mintz, et al., 2004). A joint analysis of proximal changes in insight and psychopathology may reveal important determinants of longitudinal course of illness and outcome.

In this study, we first evaluated whether individuals' 12 month insight profile is associated with symptom severity at multiple time points: baseline, and months 1, 2, 3, 6, 9 and 12. Secondly, we used latent-class trajectory analysis to identify subgroups of patients with different course of insight over 12-months, and compared their psychopathology.

3.1 Abstract

We first aimed to evaluate the progression of insight and psychopathology over the first year of treatment for a psychosis. We hypothesized that improvement in insight would associate with improvement in positive and negative symptoms, and depressive and anxious symptom exacerbation. Secondly, in an exploratory analysis, we aimed to identify quantitatively distinct insight trajectory groups and to describe the impact of psychopathology over time on the different trajectory groups. One-hundred and sixty-five patients were administered a comprehensive clinical evaluation and insight was rated on the Scale for Assessment for Unawareness of Mental Disorder (SUMD), item 1 (awareness of mental disorder), at admission and after 1, 2, 3, 6, 9, and 12 months. In a generalized estimating equation (GEE) model of change, insight improved concurrently with positive, negative and anxious symptoms between baseline and month 1 in the entire cohort. Latent group-based trajectory analysis revealed five insight groups: good, increasing, decreasing, moderate-poor and very-poor. GEE modeling revealed that the very-poor and moderate-poor insight groups displayed greater overall negative symptoms than patients with good and increasing insight trajectories. The good insight group showed significantly greater overall depressive symptoms than the diminished and very-poor insight groups. The results suggest that specific longitudinal insight trajectories were driving the observed associations between insight and negative and depressive symptoms in the entire FEP cohort. Persistently poor insight may be an important factor in negative symptom maintenance. Good or increasing course of insight may be early clinical indicators of a liability to depression.

3.2 Introduction

Impaired insight, or unawareness of illness, is a hallmark clinical feature of psychosis (X. F. Amador, et al., 1994; Carpenter, et al., 1973). Studies tracking changes in insight over the first few years following an onset of psychosis have found that a majority of patients show full insight or improvement in insight, while others lose insight or show persistently poor insight (Fennig, et al., 1996; McEvoy, et al., 2006; Saeedi, et al., 2007).

Recent studies have begun to investigate the influence of severity of psychotic symptoms on insight of patients with a first episode of psychosis (FEP) to determine which aspects of psychopathology are associated with level or longitudinal course of insight. These investigations have yielded inconsistent results, which may arise from variation in experimental designs and statistical analyses. For example, in one large study (Saeedi, et al., 2007), 278 FEP patients were separated into good and poor insight groups and compared with regard to mean psychopathology ratings at admission and 1-, 2-, and 3-years later. The authors found that relative to those with poor insight, those with good insight showed fewer positive and negative symptoms at each assessment, and higher depression at baseline. The former result is consistent with the account holding that insight deteriorates with psychotic symptom exacerbation, while the latter supports the defense account of insight, which holds that the realization of having a mental illness and awareness of its long-term consequences leads to depression. Another study (Crumlish, et al., 2005) examined correlation of insight and illness severity at multiple time points and found that higher awareness of illness associated with high depression at intake and after 6-months, but not 4-years later. In two investigations, regression analysis was used to determine whether level of insight at intake was associated with severity of psychotic symptoms over time (Crumlish, et al., 2005; Fennig, et al., 1996). Crumlish and colleagues (Crumlish, et al., 2005) found that lack of insight at initial clinical evaluation significantly predicted higher positive but not negative and depressive symptom severity 4-years later in 101 FEP patients. On the other hand, in Fennig et al.'s (Fennig, et al., 1996) sample of 189 patients with a FEP, no consistent relationship emerged between insight and positive, negative or depressive symptoms. Finally, Mintz et al. (Mintz, et al.,

2004) attempted to determine whether severity of psychopathology at 1-year after onset of first psychotic symptoms differentiated between patients grouped according to patterns of insight rated at 3, 6, 9 and 12 months. The main finding was that patients who showed persistent good insight or whose insight improved over 12-months had greater improvement on positive symptoms compared to patients with persistent poor insight. Taken together, these prospective longitudinal studies suggest that clinical state of patients is correlated with level of insight or pattern of insight change when measured simultaneously.

These studies have clearly established a psychopathological basis of insight. However, this research suffers from two methodological limitations. First, the majority of studies focused on the average level of insight for the entire FEP cohort (Crumlish, et al., 2005; Fennig, et al., 1996; Saeedi, et al., 2007). Group mean course, however, may be misleading in that it disregards the heterogeneity of insight over time, masking subgroups of patients who show differing insight trajectories. In an attempt to circumvent this concern, Mintz and colleagues (Mintz, et al., 2004) classified a subset of their FEP participants according to 1-year course of insight into consistent good and consistent poor insight groups, and a group whose insight diminished over time. While these groupings may be intuitive, the rationale was unsubstantiated and groups were not derived using probability-based statistical modeling. The second limitation of these previous studies is the correlational approach to studying insight-psychopathology relations. Although this strategy provides information about the immediate impact of symptom severity on insight, it forfeits exploration of potential longitudinal relationships, such as whether course of insight may influence the progression of psychotic symptoms over multiple phases of illness. The assessment of insight across distinct insight trajectory groups and the comparison of psychopathology across groups using multivariate statistical techniques for repeated measures may prove useful to overcome these methodological shortcomings.

Another important consideration in the insight literature is the timing of insight change after a first psychosis. Four studies (Crumlish, et al., 2005; McEvoy, et al., 2006; Mintz, et al., 2004; Saeedi, et al., 2007) have evaluated insight longitudinally, and all revealed that when group means are analyzed, improvement in insight occurs within two years of a

FEP. However, the precise timing of insight change observed across studies is variable and obviously limited by the frequency of assessments. For example, in a recent study Saeedi et al. (Saeedi, et al., 2007) demonstrated that level of insight on admission significantly improved 1-year later. Crumlish et al. (Crumlish, et al., 2005) rated insight at baseline and observed a significant improvement after 6-months. Mintz et al. (Mintz, et al., 2004) conducted the only study to date which has evaluated and analyzed insight change 3-months after a FEP, and reported a significant improvement in insight at this time. Thus, the dynamic of insight changes over the first 3-months of a FEP have not been studied. It has been reported that in patients with schizophrenia spectrum disorders substantial improvement in psychotic symptoms occurs within the first weeks of antipsychotic drug treatment (Agid, Kapur, Arenovich, & Zipursky, 2003). A joint analysis of proximal changes in insight and psychotic symptoms may reveal important determinants of longitudinal course of illness and symptomatic outcome.

The purpose of the present study was two-fold. The first goal was to examine the course of insight and psychopathology ratings obtained on a large sample of participants with a FEP assessed at admission and 1, 2, 3, 6, 9, and 12 months later. This allowed us to test whether changes in insight are specifically and temporally associated with changes in core symptoms of psychosis. In line with the literature, we hypothesized that improvement in insight would associate with improvement in positive and negative symptoms, and with depressive and anxious symptom exacerbation. The second goal was to identify subgroups of patients with different course of insight over 12-months. To achieve this goal, latent-class trajectory analysis was applied to insight ratings. The statistic fits a mixture model to identify subgroups of observations based on course of a variable of interest. Subgroups can then be described along a number of clinically meaningful dimensions, including time-dependent factors (e.g., symptom severity). We then tested whether symptom severity over time could differentiate between groupings of patients with distinct insight trajectories. These latter analyses were exploratory in nature; thus no specific hypotheses were made for insight group-psychopathology associations.

3.3 Methods

Participants

FEP patients were recruited from the Prevention and Early Intervention for Psychoses Program (PEPP-Montréal) at the Douglas Mental Health University Institute. The program involves a comprehensive approach with intensive medical and psychosocial management, where treatment is modified per client through case manager. Individuals aged 14–30 years from the local catchment area suffering from either affective or non-affective psychosis who have not taken antipsychotic medication for more than one month were consecutively admitted to the program as either in or out patients. There is no competing service and treatment is publicly funded. Written informed consent was obtained from all participants, and from a parent/guardian for participants aged 14-18. Research protocols were approved by the Douglas Institute human ethics review board.

Diagnoses were based on a Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 1998) conducted by a trained interviewer and confirmed through a consensus meeting attended by at least two senior research psychiatrists (R.J. and A. M.). Duration of untreated psychosis (DUP) was calculated as the time between onset of psychotic symptoms to the time of adequate treatment with antipsychotics (A. Malla et al., 2006). Adequate treatment was defined as taking antipsychotic treatment for a period of 1 month or until significant response was achieved, whichever came first (A. K. Malla et al., 2002). Duration of untreated illness (DUI) (Arduini et al.) was calculated as the time between onset of first ever psychiatric symptoms and onset of adequate antipsychotic therapy. The type and dosage of antipsychotic taken at each clinical assessment were converted to a standard chlorpromazine equivalent (Woods, 2003). Medication adherence was based on a 5-point scale ranging from 0 (never) to 4 (fully compliant) (A. Malla, et al., 2006). Patients were asked how often they missed a dose over the past month and adherence was calculated as a percent of prescribed doses taken. Similar methodology was employed by clinical staff and adherence recorded as a percentage in clinical notes. Correlational analyses among scores based on information

obtained from patients and clinical notes, and a more objective measure of pill counting, available for a subset of the sample were found to be high (Cassidy, Rabinovitch, Joober, & Malla, 2008). Ratings were averaged over the 12-month period to provide an overall mean adherence score. In addition to pharmacotherapy, case managers provide individualized supportive psychotherapy and education to patients with one aim being an increase in awareness (i.e. insight) of the nature of their symptoms.

Clinical assessment

The Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987) was used to measure severity of positive (sum of items P1-P7) and negative (sum of items N1-N7) symptoms. Research assistants and graduate students who performed the symptom ratings were not involved with the treatment of the patient and have established an intra-class correlation coefficient (ICC) = 0.75 on the PANSS. Depression and anxiety were quantified with total scores on the Calgary Depression Scale (Addington, Addington, & Schissel, 1990) and Hamilton Anxiety Scale (J. Riskind, A. Beck, G. Brown, & R. Steer, 1987), respectively. All scales were administered at baseline and after 1, 2, 3, 6, 9 and 12 months.

Measure of insight

Degree of insight was quantified using the SUMD (X. F. Amador, et al., 1994), item 1, awareness of mental disorder. The item is rated from 1 (aware) to 5 (unaware). Although inter-rater reliability data for the SUMD is not available, this scale is administered by the same research assistants and graduate students who administer the PANSS. Our raters receive extensive training and supervision with reliability measured at least once a year for the PANSS. Inter-rater reliability for the PANSS insight item (G12) which share similarities with the SUMD Q1 was found to be high (ICC = 0.79).

Statistical analysis

Baseline characteristics of patients who did and patients who did not provide insight ratings at each month were compared using regression equations. Availability for follow-up was entered as the dependant variable. Age, gender, DUP, DUI, and baseline insight were entered as independent variables.

In the first analysis on all FEP participants, to characterize symptom severity we used generalized estimating equation (GEE) analyses, which take into account multiple assessments per patient and correlations owing to repeated examinations. Positive, negative, anxious, and depressive symptom scores at each month were entered as dependent variables. The independent variable was insight.

In the second analysis, latent group-based trajectory analysis was performed with the PROC TRAJ macro in SAS version 9.2 (B. F. Jones, Nagin, & Roeder, 2001). The program segregates participants who share distinct trajectories in to groups, or latent classes. Participants with similar trajectories are clustered into the same group. The shape of each group's trajectory is modeled by a polynomial function over time (intercept, linear, quadratic or cubic). PROC TRAJ uses maximum likelihood to estimate model parameters, thus participants with some missing data values are included in model.

To characterize symptom severity between latent trajectory groups, we used generalized estimating equation (GEE) analyses. Positive, negative, anxious, and depressive symptom scores at each month were entered as dependent variables. Independent variables were group, month, and the group X month interaction. A significant group effect would suggest a difference in symptom scores between latent trajectory groups. A significant interaction term would suggest differential rates of symptom change among latent trajectory groups. Tukey's Standardized Range Test post-hoc comparisons with pair-wise contrasts (Least Significant Difference) were performed where appropriate. The GEEs were performed using SPSS 17.0.

3.4 Results

Characteristics of the sample

Two-hundred and forty-five patients were assessed with the SUMD. We restricted analyses to participants who provided the baseline rating and at least three of the six possible follow-up ratings. This resulted in the exclusion of 80 participants, for a final total sample size of N=165. On average 5.8 insight ratings were provided per patient. When analysing whether availability for follow-up could be explained in part by baseline demographic variables, baseline insight predicted 2-month follow-up, $F(1,162)=3.79$, $P=0.05$, $R^2=0.02$, and education predicted 12-month follow-up, $F(1,164)=4.69$, $P=0.03$, $R^2=0.03$. No other variables reached significance in the regression analyses suggesting that data were missing-at-random (Enders, 2001; Startup, Jackson, & Startup, 2006). Table 3.1 presents demographic and diagnostic descriptions of the sample (N=165).

	FEP	
	M	SD
Age (years)	22.5	4.0
Education (years)	11.4	2.4
DUP (days)	46.8	84.7
DUI (days)	292.1	266.0
	N	%
Gender	110M, 55F	67:33
Diagnostic category		
Schizophrenia	79	47.9
Schizoaffective disorder	21	12.7
Schizophreniform disorder	4	2.4
Psychosis not otherwise specified	15	9.1
Delusional disorder	1	0.6
Bipolar disorder	27	16.4
Major depression with psychotic features	16	9.7
Undetermined	2	1.2

Table 3.1: Demographic and clinical characteristics of the sample.

Insight and course of psychopathology in all participants

The means for insight, positive, negative, anxious and depressive symptoms for the 165 participants are presented in Figure 3.1.

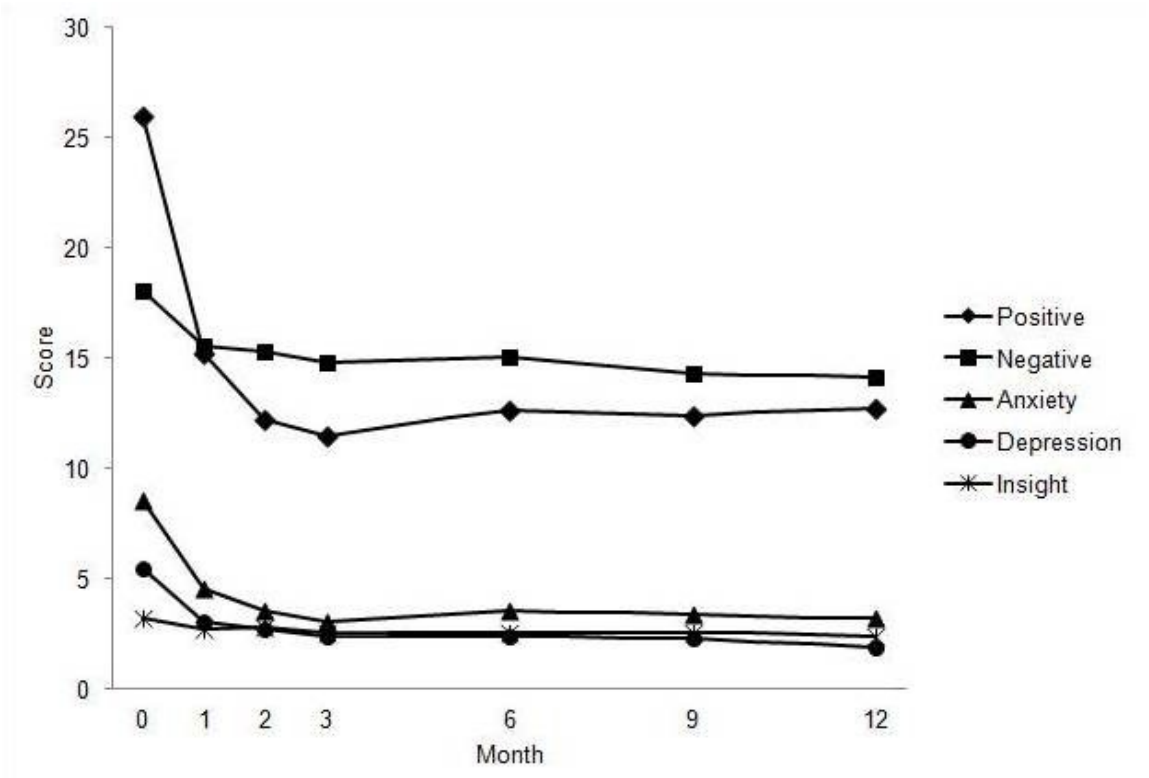

Figure 3.1: Means for insight, positive, negative, anxious and depressive symptoms over 12-months for 165 participants with a FEP.

GEE analyses were utilized to test changes in symptom severity over time. Considering insight, a significant main effect emerged, $\beta = -0.13$, $p < 0.001$, reflecting improvement in the early phase of treatment between baseline and 1 month ($p < .001$). A significant main effect emerged for positive symptoms, $\beta = -2.22$, $p < 0.001$. Significant improvement occurred between baseline and month 1 ($p = 0.001$), and months 1 and 2 ($p = 0.001$), with no subsequent improvement in the following months. The main effect for negative symptoms achieved significance, $\beta = -0.68$, $p < 0.001$, reflecting significant improvements between baseline and month 1 ($p = 0.001$), months 1 and 2 ($p = 0.02$), and months 6 and 9 ($p = 0.04$). Considering anxious symptoms, the main effect achieved significance, $\beta = -0.99$, $p < 0.001$, reflecting significant symptom improvement between baseline and month 1 ($p = 0.001$), months 1 and 2 ($p = 0.001$), and months 2 and 3 ($p =$

0.001). Finally, considering depressive symptoms, the main effect was nonsignificant, β = -0.38, $p > 0.05$, suggesting depressive symptoms remained stable over 12-months.

Latent trajectory groups

Using the censored normal distribution model, we began with a basic one group model and continued until we had fit a five group model. The highest Bayesian Information Criterion (Park et al.) value was relied on for model selection as described in Jones et al. (B. F. Jones, et al., 2001). Using this approach, a five group solution comprised of three linear groups, one quadratic group and one cubic group was favoured for the best model fit (BIC = -1533.99). Mean insight scores for the five groups are displayed in Figure 3.2. The first group reflected a good insight trajectory and was the largest (n = 61, 40.0%). The second group showed an increasing insight trajectory, and was relatively small (n = 12, 0.7%). A decreasing insight trajectory was represented in the third group (n = 24, 14.5%). The fourth and fifth groups reflected moderate-poor (n = 34, 20.6%) and very-poor (n = 34, 20.6%) insight trajectories, respectively. Average probabilities of belonging to each group were as follows: good (M = 0.91), increasing (M = 0.72), decreasing (M = 0.77), moderate-poor (M = 0.77) and very-poor insight (M = 0.86).

As shown in Table 3.2, the five insight groups did not significantly differ on age, $F(4,160) = 0.76$, $p = 0.56$, gender, $\chi^2(4) = 8.09$, $p = 0.08$, diagnosis (affective vs. non-affective psychosis), $F(4, 160) = 0.84$, $p = 0.50$, DUP, $F(4,155) = 0.18$, $p = 0.95$, DUI, $F(4,155) = 1.34$, $p = 0.26$, and education, $F(4,159) = 0.65$, $p = 0.62$. Groups significantly differed on medication adherence, $F(4,159) = 4.19$, $p < 0.01$, and this reflected greater adherence in the good and decreasing insight groups relative to both the moderate-poor (both ps < .05) and very-poor insight groups (both ps < .01). Groups significantly differed on mean chlorpromazine equivalent antipsychotic dosage at month 6, $F(4,116) = 2.56$, $p = 0.04$. The very-poor insight group was taking a greater mean dosage than the decreasing (p = .01) and good insight groups (p = .01).

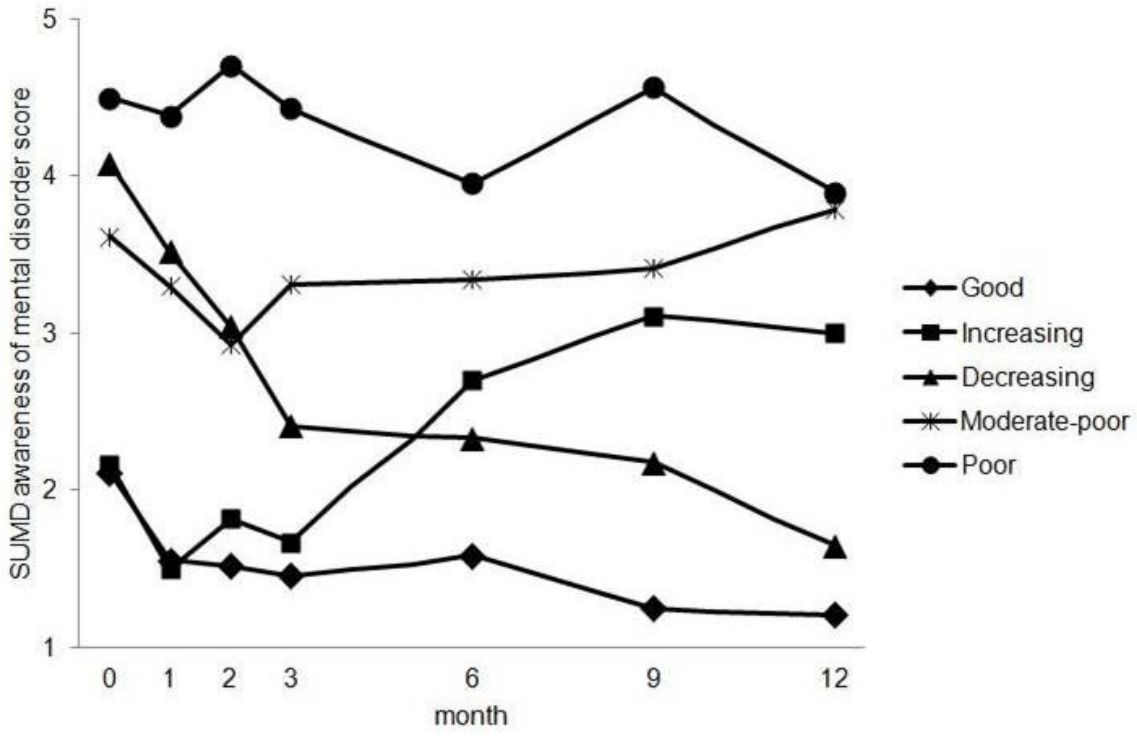

Figure 3.2: Mean insight ratings for FEP patients over 12 months by group.

Latent-class trajectory groups: psychopathological profiles

Means on positive, negative, anxious and depressive symptoms for the five insight trajectory groups are presented in Table 3.3.

	Insight group				
	Good (n=61)	**Improving** (n=12)	**Decreasing** (n=24)	**Moderate -poor** (n=34)	**Very-poor** (n=34)
Age (years)	22.7 (4.5)	24.1 (3.8)	22.7 (3.7)	22.5 (3.7)	21.8 (3.9)
Gender (M:F)	48:13	7:5	17:7	19:15	19:15
Education (years)	11.5 (2.8)	11.9 (2.1)	11.8 (2.5)	11.6 (2.0)	10.8 (1.8)
DUP (days)	43.8 (88.8)	32.1 (34.0)	61.1 (126.9)	22.5 (33.7)	44.4 (63.1)
DUI (days)	295.4 (281.2)	370.8 (306.1)	194.5 (179.8)	335.6 (275.2)	287.7 (260.5)
Antipsychotic medication[a]	289.4 (259.4)	350.9 (617.7)	258.3 (195.7)	291.9 (253.8)	414.8 (429.9)
Medication adherence	3.6 (0.8)	3.2 (1.1)	3.5 (0.9)	2.9 (1.2)	2.9 (1.2)
Diagnostic category (N)					
Schizophrenia	27	7	11	13	21
Schizoaffective disorder	9	-	4	4	4
Schizophreniform disorder	1	-	2	1	-
Psychosis not otherwise specified	4	-	2	8	1
Delusional disorder	1	-	-		-
Bipolar disorder	11	2	3	5	6
Major depression with psychotic features	7	3	2	3	1
Undetermined	1	-	-	-	1

Table 3.2: Demographic and clinical characteristics of the five insight groups. Results expressed as means with standard deviation in brackets. [a] Mean dose in chlorpromazine equivalents over 12-months.

	Insight group				
	Good (n=61)	**Increasing** (n=12)	**Decreasing** (n=24)	**Moderate -poor** (n=34)	**Very-poor** (n=34)
PANSS positive					
Baseline	25.4 (5.2)	26.1 (7.1)	26.3 (6.0)	27.1 (6.0)	25.8 (6.3)
1 month	15.0 (6.7)	13.3 (5.6)	16.3 (6.5)	15.7 (6.8)	15.2 (6.5)
2 months	12.1 (5.3)	10.0 (3.5)	13.5 (6.7)	12.6 (5.0)	12.2 (4.7)
3 months	11.1 (3.9)	9.5 (3.8)	11.2 (5.1)	12.3 (4.6)	12.4 (5.1)
6 months	13.0 (5.7)	11.7 (5.8)	12.0 (6.1)	13.7 (6.7)	12.0 (4.7)
9 months	12.1 (5.1)	12.2 (5.6)	12.7 (6.6)	10.4 (5.5)	14.2 (7.0)
12 months	13.6 (7.9)	11.7 (4.1)	10.9 (4.3)	12.4 (6.2)	13.4 (6.5)
PANSS negative					
Baseline	17.5 (6.2)	16.8 (7.4)	17.7 (5.6)	18.5 (7.5)	19.3 (7.3)
1 month	14.4 (5.1)	16.1 (8.0)	16.1 (6.2)	16.0 (5.7)	16.8 (7.0)
2 months	14.7 (4.9)	16.7 (9.7)	15.7 (5.5)	15.2 (6.6)	15.9 (6.6)
3 months	14.1 (5.1)	16.3 (7.4)	15.8 (5.6)	14.5 (6.5)	15.3 (5.9)
6 months	15.2 (6.5)	13.6 (7.5)	15.4 (6.2)	14.6 (7.0)	15.6 (6.0)
9 months	14.1 (5.2)	13.1 (7.2)	14.6 (5.1)	12.3 (6.3)	16.2 (6.0)
12 months	14.1 (5.2)	13.1 (6.9)	14.5 (5.1)	14.0 (6.0)	14.4 (5.0)
Hamilton anxiety					
Baseline	7.7 (6.8)	6.8 (6.8)	7.0 (5.7)	10.4 (7.0)	10.3 (6.2)
1 month	3.9 (4.1)	6.1 (4.5)	5.9 (5.9)	4.5 (3.6)	4.4 (3.8)
2 months	2.4 (2.3)	3.8 (3.9)	5.6 (5.6)	4.1 (3.9)	4.1 (3.8)
3 months	2.8 (3.7)	2.5 (3.8)	3.7 (4.3)	3.6 (4.3)	3.0 (4.2)
6 months	3.4 (4.2)	3.7 (3.3)	2.8 (3.5)	3.4 (4.2)	4.5 (4.7)
9 months	4.0 (5.0)	3.3 (3.8)	2.7 (3.1)	1.5 (2.3)	4.5 (5.4)
12 month	3.4 (4.2)	3.3 (2.9)	2.1 (3.3)	3.9 (4.1)	3.1 (3.0)
Calgary depression					
Baseline	5.7 (6.1)	3.6 (4.1)	5.8 (5.2)	5.4 (5.0)	5.6 (4.4)
1 month	2.8 (3.9)	4.2 (3.9)	4.1 (4.1)	2.9 (3.9)	2.7 (4.2)
2 months	2.1 (2.8)	3.0 (2.8)	2.9 (2.7)	3.1 (4.3)	3.3 (3.8)
3 months	2.2 (3.2)	4.2 (3.2)	1.3 (1.7)	2.6 (3.8)	2.7 (4.4)
6 months	1.9 (3.9)	3.5 (3.9)	1.8 (3.2)	2.6 (4.2)	3.2 (4.1)
9 months	2.5 (3.5)	3.8 (3.5)	1.6 (2.6)	1.6 (2.9)	2.7 (4.7)
12 months	2.6 (4.2)	1.2 (4.2)	1.1 (2.3)	2.0 (3.5)	1.7 (2.9)

Table 3.3: Mean PANSS symptom scores over 12 months as a function of group (SD in brackets).

The five groups did not differ on positive symptoms as indicated by a nonsignificant group effect, β = .52, p = 0.07, and a nonsignificant group X assessment interaction, β = .10, p = 0.13. When considering negative symptoms, a significant group effect emerged, β = 1.18, p > 0.001. The very-poor and moderate-poor insight groups showed greater negative symptoms than both the good (both *ps* = 0.01) and increasing insight groups (both *ps* = 0.01). The diminishing insight group showed significantly fewer negative symptoms than the increasing insight group (p = 0.04). The assessment X group interaction was nonsignificant for negative symptoms, β = 0.09, p = 0.38. No group differences emerged for anxious symptoms; the group effect was nonsignificant, β = -0. 60, p = 0.10, as was the assessment X group interaction, β = 0.14, p = 0.33. Finally, with regard to depressive symptoms, the group effect achieved significance, β = -0.51, p = 0.01. The good insight group showed significantly greater depressive symptoms than the diminished (p = 0.02) and very-poor (p = 0.01) insight groups. The assessment X group interaction was nonsignificant for depressive symptoms, β = -0.06, p = 0.15.

3.5 Discussion

The study set out to examine the joint progression of insight and psychopathology over 12-months from our data on 165 people with a FEP. Patients showed simultaneous improvement in insight and severity of positive, negative, and anxious symptoms between the initial assessment and after 1 month. Severity in these three symptom domains continued to attenuate over months 1 and 2. Secondly, the study set out to model latent trajectory groups according to pattern of insight change over 12-months, and to identify the impact of psychopathology over time on the different trajectory groups. Several significant findings emerged: five co-occurring insight groups were identified (good, increasing, decreasing, moderate-poor and very-poor). Negative symptoms were more pronounced in FEP patients with very-poor and moderate-poor insight trajectories, relative to patients with a good or increasing course of insight. Depressive symptoms were marked in patients with good and increasing insight trajectories, relative to patients with a diminishing or very-poor course of insight.

Insight and course of psychopathology in all participants

The psychopathological account of insight holds that insight impairments emerge with symptom exacerbation. Our finding that significant improvement in insight occurs as early as 1 month after treatment initiation, concurrently with improvements in three core symptom dimensions – positive, negative and anxious – supports this framework for understanding insight. This set of results is in agreement with a previous investigation demonstrating improvement in insight and symptoms 3-months after a FEP (Mintz, et al., 2004). In contrast to this study, we included clinical assessments at 1 and 2 months post-FEP, allowing us to detect insight and symptom change very soon (within 1 month) after psychosis onset.

It has been suggested that longitudinal studies tracking changes in insight and symptoms over time could test hypotheses related to causation (i.e., whether insight facilitates symptom decline or vice versa). In the current work, insight improved in tandem with positive, negative and anxious symptoms after 1 month. Interestingly, in the ensuing months, positive, negative and anxious symptoms continued to attenuate. It can be speculated that during the early stages of the illness, insight may be the mechanism on the pathway from a psychotic episode to symptom remission, facilitating and maintaining symptom reduction and/or protecting against its exacerbation. The evolution of insight and psychotic symptoms at more chronic stages of the illness remains unknown and merits investigation.

Latent insight trajectory groups

The latent-class group based modeling strategy permitted the observation of five qualitatively distinct courses of insight in our FEP sample. Two major subgroups of patients displayed very-poor (22.6%) and moderate-poor (45.9%) insight, while insight decreased over time in 14.5% of patients. Course of insight was good for 40.0% and increased in 0.7% of patients, respectively. This is the first report to reveal such groupings in FEP using a longitudinal data modeling procedure. The results establish that

insight is a heterogeneous clinical feature of psychosis with variable prognosis during its first year. A clinical application is that FEP patients who show continuously poor insight or early and persistent deterioration in insight may be identified at 12-months and recommended for adjunctive psychosocial treatments (Turkington, et al., 2002).

Psychopathological distinctions between insight trajectory groups

The results strongly suggest that specific longitudinal insight trajectories were driving the observed association between insight and psychopathology in the first analysis on entire FEP cohort. Participants with 12-month poor insight showed the greatest negative symptoms, while participants with preserved insight showed depression. It can be noted that in the first analysis on the entire FEP cohort this relation was not apparent; rather, negative symptoms decreased in early months and depressive symptoms appeared stable. Therefore, conflicting claims that insight shares either no clear relationship (Fennig, et al., 1996) or a reliable relation (Crumlish, et al., 2005; Mintz, et al., 2004; Saeedi, et al., 2007) with negative symptoms over time, or a positive (Crumlish, et al., 2005; Saeedi, et al., 2007) or null relation (Fennig, et al., 1996) with depression, may be explained by the fact that a single group of FEP patients was evaluated without considering the heterogeneity of insight over time.

The finding that depression emerged in patients with good and increasing insight profiles extends findings from other FEP samples (Crumlish, et al., 2005; Saeedi, et al., 2007). The idea that insight provides fertile soil for depressive thoughts fits in well with results demonstrating that patients with good insight report reduced emotional well being (Hasson-Ohayon, Kravetz, Roe, David, & Weiser, 2006) and poor psychosocial and global quality of life (Karow et al., 2008; Lysaker, Bell, Bryson, & Kaplan, 1998). The findings are also in line with studies showing that insight may increase hopelessness and lower self-esteem (Hasson-Ohayon, et al., 2006), and enhance a risk for suicidality (Schwartz, 2000; Schwartz & Petersen, 1999; Schwartz & Smith, 2004). At the theoretical level, these data provide further evidence for the defense account of insight, which holds that the realization of having a mental illness and awareness of its long-term

consequences leads to demoralization, feelings of worthlessness and hopelessness, and subsequent depression.

One interpretation of our negative symptom-insight finding is that impaired insight may be a symptomatic marker for a vulnerability to persistent negative symptoms. This interpretation is congruent with the finding that FEP patients with persistent negative symptoms demonstrate reduced cortical volumes (Hirayasu et al., 2001) and lower remission rate after one year (A. K. Malla, et al., 2004), relative to non-affected patients. Group differences appeared stable over time, due to the non-significant group X assessment interaction, raising the possibility that the specificity of negative symptoms for insight may reflect "trait" aspects of the disease process. Moreover, the present insight–negative symptom link supports a role for insight as an independent and core feature of the illness, and not a mere epiphenomenon of positive symptoms as posited by some theorists (Jaspers, 1963). A final possible explanation of this finding is that in their strongest forms, the constellation of negative symptoms of psychosis may combine to contribute to a susceptibility to impaired insight in FEP.

Unlike some (Crumlish, et al., 2005; Mintz, et al., 2004; Saeedi, et al., 2007), but not all (Fennig, et al., 1996), previous studies, the current analyses revealed no significant relationships between positive and anxious symptom severity and insight. A previous study that segregated patients a priori in to 12-month persistent good and persistent poor insight groups reported higher positive symptom severity in the latter at 12-months (Saeedi, et al., 2007). In contrast to this study design, our study measured symptom severity at multiple time-points. On the basis of the present longitudinal analysis it appears that such a link between insight and positive symptoms is not generalizable across multiple phases of the illness. Rather, state of positive symptom severity may be associated with level of insight in a proportion of patients during various phases of illness, including in early (Crumlish, et al., 2005; Mintz, et al., 2004) and chronic (Mintz, et al., 2003) psychosis, while these relations may vary over time at the individual level. Further, the positive syndrome reflects a mixture of many different psychopathological features, including delusions, hallucinations and disordered thought, which may obfuscate potential associations between any one of these symptoms, and insight.

Finally, it can be noted that the current findings emerged in patients with both affective and non-affective FEP disorders. In accord with the literature (X. F. Amador, et al., 1994; Pini, Cassano, Dell'Osso, & Amador, 2001), our data suggest that insight may associate to discrete symptom dimensions, irrespective of the combination of symptoms an individual may display (e.g., presence of mood and psychotic symptoms vs. psychotic symptoms only).

A potential limitation of the present work is that we confined our analyses to the SUMD item1, the awareness of illness. Longitudinal associations between the symptoms of psychosis and other insight dimensions, such as awareness of the need for treatment, current and retrospective insight, and awareness and attribution of specific symptoms (X. F. Amador, et al., 1993) remain unknown. Future work will be necessary to determine whether the reported relationships hold over multiple dimensions of insight or remain generalizable to awareness of illness.

The interplay between insight and psychopathology has been demonstrated on longitudinal analysis using a latent-class group modeling procedure. The results suggest that specific longitudinal insight trajectories underpinned the observed association between insight and negative and depressive symptoms in our first analysis on the entire FEP cohort. Negative symptoms may promote or culminate from the establishment of insight impairments, while good and improving insight may point toward an impending depression. Course of insight appears immutable to patients' 12-month positive and anxiety symptom profiles in our sample. The prognostic significance is that at patients' 1-year clinical assessment clinicians may pay careful attention to one's history of insight when considering other psychosocial interventions. Future research may examine whether a longitudinal coupling of insight and symptom severity persists over chronic phases of psychosis. Understanding how the symptoms of psychosis contribute to the maintenance of good and/or poor insight over prolonged phases of illness may reveal important links in the current framework for understanding long-term variation in insight.

* * *

CHAPTER 4

CLINICAL INSIGHT IN FEP: PATTERNS OF CORTICAL THINNING

Preface

The longitudinal analysis of the previous study showed that over the first year of a psychosis the majority of people show full clinical insight or improvement in insight, while others lose insight or show persistently poor insight. This leads to the question of whether clinical insight may have a biological cause. Indeed, people with a FEP with poor insight have been shown to have volumetric reductions in prefrontal cortical areas on manually traced volumetric analyses (Shad, Muddasani, et al., 2006; Shad, et al., 2004). The impact of extra-frontal cortices on clinical insight remains unknown. Traditional MRI measures, such as manual tracing and VBM, may be of limited use for a whole cortex search. Manual tracing of regions of interest introduces rater variability issues, thereby limiting the ability to delineate consistent cortical boundaries, and its labour intensiveness is impractical for a whole-brain search. Although VBM enables an automated cerebral-wide analysis of estimated GM concentration in a given voxel, its sensitivity tends to diminish in areas with high anatomical variability, such as cortical gyri and sulci.

Modern advances in MRI-based measurements of cortical thickness offer a direct and biologically meaningful index of cortical structure at tens of thousands of points across the cortical surface. In FEP, these measurements can be used to map the cortical topography underpinning poor and intact clinical insight.

In this project, we regressed cross sectional cortical thickness data on clinical insight scores in a group of FEP participants. We also studied whether scores on the SUMD

awareness of illness and awareness of treatment need and efficacy items would associate with common or separable patterns of cortical topography.

4.1 Abstract

Through conceptualizing poor insight in psychotic disorders as a form of anosognosia (neurological deficit), frontal lobe dysfunction is often ascribed a vital role in its pathogenesis. Whether non-frontal brain regions are important for insight remains to be investigated. We used a multi-method approach to examine the neural morphometry of all cortical regions for insight in FEP. Insight was rated in 79 people with a FEP with the awareness of illness and awareness of treatment need and efficacy items of the Scale for assessment of Unawareness of Mental Disorder. Participants were assessed with magnetic resonance imaging. Cortical thickness analysis and voxel-based morphometry were utilized to identify the possible neuroanatomical basis of insight. Cortical thickness technique revealed that poorer awareness of illness was associated with regional thinning in left middle frontal and inferior temporal gyri. Poorer awareness of treatment need and efficacy was associated with cortical thinning in left medial frontal gyrus, precuneus and temporal gyri. No significant associations emerged between any insight measure and gray matter density using voxel-based morphometry. The results confirm predictions derived from the anosognosia/ neuropsychology account and assert that regional thickness in frontal cortex is associated with awareness of illness in the early phase of psychosis. The fact that prominent thickness reductions emerged in non-frontal regions of the brain in parietal and temporal cortices for both awareness of illness and awareness of treatment need/efficacy suggests that the neural signature of insight involves a network of brain structures, and not only the frontal lobes, as previously suggested.

4.2 Introduction

A substantial proportion of people with psychosis demonstrate lack of insight into their illness, including difficulty recognizing the pathological nature of their symptoms and acknowledging the need for treatment. One longstanding view states that impaired insight in psychosis is similar to anosognosia (X. F. Amador, Strauss, Yale, & Gorman, 1991; Babinski, 1914), the unawareness of symptoms in neurological disorders observed following right frontal, parietal or temporal lobe lesions. Research on the neural correlates of insight has been motivated by this anosognosia account, which regards poor insight to be a reflection of prefrontally mediated neuropsychological or neurological dysfunction (A. S. David, 1999; Lewis, 1934). Consistent with this model, neuroimaging studies have established that volumetric reductions in circumscribed frontal cortical regions are at the core of poor insight in chronic schizophrenia (Bassitt, et al., 2007; Flashman, et al., 2001; Ha, et al., 2004; Lee et al., 2006; Sapara et al., 2007).

In two first episode schizophrenia studies, Shad's group (2006; 2004) showed that patients with poor awareness of illness showed volumetric reductions in right dorsolateral prefrontal cortex (DLPFC), relative to patients with good insight. The authors concluded that volumetric reductions in frontal cortex are an integral part of poor insight, supporting the anosognosia account of impaired insight. However, looking only at the frontal cortex, by definition, forfeits exploration of potential structural alterations in posterior brain areas underlying insight, such as parietal and temporal cortices. This is an important consideration because there is evidence of an association between poor insight and parietal and temporal neuropsychological dysfunction (Goodman, Knoll, Isakov, & Silver, 2005; McEvoy et al., 1996). Moreover, executive dysfunction – part and parcel of poor insight in psychosis (Aleman, et al., 2006) – may reflect impairment in a distributed cortical-subcortical network (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009). Further, morphometric studies in chronic schizophrenia have demonstrated a relationship between insight and gray matter (GM) volumes in non-frontal brain regions, including parietal and temporal cortices (Cooke, et al., 2008; Ha, et al., 2004). Theoretically, as anosognosia is classically observed following parietal and temporal lesions, an anosognosic model for

the neurological underpinnings of poor insight would predict structural deficits in parietal and temporal regions.

At a methodological level, the abovementioned morphometry studies have employed voxel-based analyses of magnetic resonance images (MRIs), capturing the volume of structures by the totality of voxels it encompasses or by examining gray matter density. With recent advances in neuroimaging methods, it is now possible to perform fully automated cortical thickness measurements of MRIs at a subvoxel resolution. This metric provides a direct measurement in millimeters of gray matter morphology, and moreover, is anatomically meaningful, reflecting cortical laminar structure and integrity. In vivo cortical thickness measurements have not been used to address the question of whether gray matter integrity is associated with insight in psychosis.

In this study we tested predictions derived from the anosognosia account and hypothesized that poor insight in people with a first episode psychosis would associate with structural deficits in 1) DLPFC and 2) parietal and temporal cortices. We further explored whether awareness of treatment need and treatment efficacy, two insight dimensions partially independent from awareness of illness (A. David, et al., 1992), would associate with certain neuroanatomical deficits. We applied cortical thickness analyses and voxel-based morphometry (VBM) of MRIs. The VBM analysis provided a voxel-based estimate of GM density (Ashburner & Friston, 2000, 2001) and allowed us to compare directly our results to those from previous insight–neuroimaging studies. Cortical thickness measurements are performed at a subvoxel resolution and provide a direct measurement in millimeters of GM morphology, and have not been used to address the question of whether GM integrity is associated with insight in psychosis.

4.3 Materials and Methods

Participants

All participants were part of a longitudinal naturalistic outcome study of FEP treated in a specialised early intervention service, the Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), Douglas Hospital, in Montreal, Canada. The program involves a comprehensive approach with intensive medical and psychosocial interventions provided within the context of a modified assertive case management program. Individuals aged 14 – 30 years from the local catchment area suffering from either affective or non-affective psychosis who have not taken antipsychotic medication for more than one month were consecutively admitted to the program as either in- or out-patients. This service is entirely publicly funded and there are no competing services within the system.

MR scans and insight ratings were acquired for 79 people with a FEP as part of a larger study on cognitive and neuroimaging predictors of outcome. Inclusion criteria were those set by PEPP with additional restrictions of between ages 18 – 30, right handed, clinically stable (number of days between entry into PEPP and the symptom assessment, M = 184.3 days, SD = 134.5, range = 52 – 728; patients were receiving active treatment during this period and symptoms were not interfering with administration of clinical scales), no major medical disorders (based on medical history and physical examination) and able to provide informed consent. Exclusion criteria were lifetime history of neurologic condition including loss of consciousness that could affect cognition, family history of hereditary neurologic disorders, and lifetime diagnosis of substance dependence or presence of neurological disorder.

The type and dosage of antipsychotic taken at each clinical assessment were recorded and converted to a standard chlorpromazine equivalent for statistical analysis. Eight patients were taking anticholinergic medications and one patient was unmedicated.

Clinical assessment

A Structured Clinical Interview for DSM-IV (First, et al., 1998) was performed by a trained interviewer and confirmed through a consensus meeting attended by at least two senior research psychiatrists (R.J. and A.M.) to determine diagnostic status. Psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay, et al., 1987). The research assistants and graduate students who perform symptom ratings using the PANSS have established an intra-class correlation coefficient (ICC) of 0.75. Clinical insight was quantified with an abbreviated version of the Scale for Assessment of Unawareness of Mental Disorder (SUMD) (X. F. Amador, et al., 1994). Items are rated on a five point scale from 1 (aware) to 5 (unaware). We limited our exploration of the SUMD to items 1, awareness of mental disorder, 2a, awareness of treatment need, and 2b, awareness of treatment efficacy. In the present sample, scores on Q2a and Q2b were found to be strongly correlated ($r = 0.84$, $p < 0.01$) and were thus combined into a single global score. Weaker correlations emerged between Q1 scores and both Q2a ($r = 0.46$, $p < 0.01$) and Q2b scores ($r = 0.48$, $p < 0.01$); thus item Q1 was considered separately in all analyses. The SUMD is administered by the same research assistants and graduate students who administer the PANSS. Although inter-rater reliability data for the SUMD are not available, our raters receive extensive training and supervision with reliability measured at least once a year for the PANSS. Inter-rater reliability for the PANSS insight item (G12) was found to be high (ICC = 0.79). Depression was measured with the Calgary Depression Scale (Addington, et al., 1990) and anxiety with the Hamilton Anxiety Scale (J. Riskind, et al., 1987). Parental SES was estimated using the Hollingshead SES Rating Scale (D. C. Miller, 1991) and handedness with the Edinburgh Handedness Inventory (Oldfield, 1971). MR scans were performed on average within 10 days of insight assessments ($M = 9.9$, SD = 24.9). All participants provided written informed consent in accordance with the Douglas Mental Health University Institute human ethics review board.

MRI acquisition

Scanning was carried out at the Montreal Neurological Institute on a 1.5T Siemens Sonata whole body MRI system. Structural T1 volumes were acquired for each participant using a three-dimensional gradient echo pulse sequence with sagittal volume excitation (repetition time = 22ms, echo time = 9.2ms, flip angle = 30º, 180 1mm contiguous sagittal slices). The rectangular field of view (FOV) for the images was 256mm (SI) x 204mm (AP).

Statistical analysis

a) Measurements of Cortical Thickness. MRIs were submitted to the CIVET processing pipeline (Version 1.1.9) (http://wiki.bic.mni.mcgill.ca/index.php/CIVET) (Ad-Dab'bagh et al., 2006; Zijdenbos, Forghani, & Evans, 2002). Native T1-weighted images were first registered to the ICBM152 template using linear transformation (D. L. Collins, Neelin, Peters, & Evans, 1994; Grabner et al., 2006) and simultaneously corrected for non-uniformity artefacts using N3 (Sled, Zijdenbos, & Evans, 1998). The transformed images were then segmented into GM, WM, CSF and background using a neural net classifier (INSECT) (Zijdenbos, et al., 2002). GM and WM surfaces were extracted using CLASP algorithm (Kabani, Le Goualher, MacDonald, & Evans, 2001; J. S. Kim et al., 2005; MacDonald, Kabani, Avis, & Evans, 2000). A spherical-mesh deformation algorithm was used to produce a surface mesh of 81 924 polygons (40 962 nodes or vertices) for each hemisphere. Non-linear registration of both cortical surfaces to a high resolution average surface template generated from the ICBM152 data set was performed to establish inter-subject correspondence of vertices (Lyttelton, Boucher, Robbins, & Evans, 2007; Robbins, 2004). Reverse linear transformation of volumes was performed to allow vertex-based corticometric (VBC) measurements in native space for each subject's MRI (Ad-Dab'bagh et al., 2005). The deformation algorithm first fits the white matter surface and then expands to the outer GM and cerebral spinal fluid intersection. From these surfaces, cortical thickness was computed in native space using the t-link method (Lerch & Evans,

2005), which determines the linked distance between the inner and outer cortical surfaces at each of 40 962 vertices. Each participant's cortical thickness map was subsequently blurred using a 20-mm full-width half-maximum surface-based diffusion smoothing kernel (Chung et al., 2003).

Statistics were performed at all 40 962 vertices, regressing cortical thickness against SUMD awareness of illness and the composite awareness of treatment need/awareness of treatment efficacy scores. Total intracranial volume was not included as a covariate, as cortical thickness and brain volume are poorly correlated (Ad-Dab'bagh, et al., 2005; Sowell et al., 2007). Statistical maps were thresholded and multiple comparisons were taken in to account using the false discovery rate procedure, with q = 0.05 (Genovese, Lazar, & Nichols, 2002). Results were considered significant at $t = 1.98$ ($p < 0.05$).

b) Voxel-based morphometry. T1 images were linearly registered to the ICBM152 nonlinear sixth generation template with a 12-parameter linear transformation (D. L. Collins, et al., 1994; Grabner, et al., 2006), then RF inhomogeneity corrected (Sled, et al., 1998) and tissue classified (Tohka, Zijdenbos, & Evans, 2004; Zijdenbos, et al., 2002). GM was averaged across subjects to create a GM template, which was nonlinearly registered with a 16-mm node spacing between vectors in the deformation grid (D. Collins, Peters, & Evans, 1994). Resulting GM images were smoothed with a 10-mm full-width at half-maximum Gaussian kernel. Results were considered significant at a $t = 1.98$ ($p < 0.05$).

4.4 Results

Demographic and clinical details are reported in Table 4.1. Mean insight scores indicated that insight was moderately impaired in our sample.

	FEP (N = 79)		
	M	SD	Range
Age at hospitalization (years)	23.3	3.7	16.1 – 30.1
Education (years)	11.8	2.4	7 – 18
Hollingshead Index score	2.9	1.1	1 – 5
SUMD			
Awareness of Mental Disorder	2.4	1.4	1 – 5
Awareness of Response to Medication	2.2	1.5	1 – 5
Awareness of Need for Treatment	2.4	1.5	1 – 5
PANSS			
Positive score	12.3	5.3	7 – 28
Negative score	13.6	5.0	7 – 30
General psychopathology score	26.6	7.1	16 – 56
Calgary Depression Scale (total)	2.4	3.3	0 – 16
Hamilton Anxiety Scale (total)	3.2	3.4	0 – 15
Antipsychotic (dose, mg)[a]	292.1	356.4	25 – 1875
	N	%	
Anticholinergics (receiving/ not receiving)	8/71	10/90	
Gender (M:F)	57:22	72:28	
Handedness			
Right	63	84.0	
Left	4	5.3	
Ambidextrous	8	10.7	
Diagnostic category			
Schizophrenia	44	55.7	
Schizoaffective disorder	12	15.2	
Schizophreniform disorder	2	2.5	
Psychosis not otherwise specified	9	11.4	
Bipolar	8	10.1	
Major depression with psychotic features	3	3.8	
Undetermined	1	1.3	

Table 4.1: Demographic and clinical characteristics of the sample. [a] Anti-psychotic medication reported as chlorpromazine equivalent dosage in mg. One patient was unmedicated.

Cortical thickness

Mean awareness of illness scores (1 = aware, 5 = unaware) were significantly and inversely associated with cortical thickness (t = -1.98, p = 0.05), as shown in Figure 4.1 and Table 4.2. Significant inverse associations (poorer insight with cortical thinning) emerged in the left hemisphere in the middle frontal gyrus (DLPFC), inferior frontal gyrus, inferior temporal gyrus, and precentral gyrus. In the right hemisphere, significant inverse associations were observed in the precentral gyrus and inferior occipital gyrus.

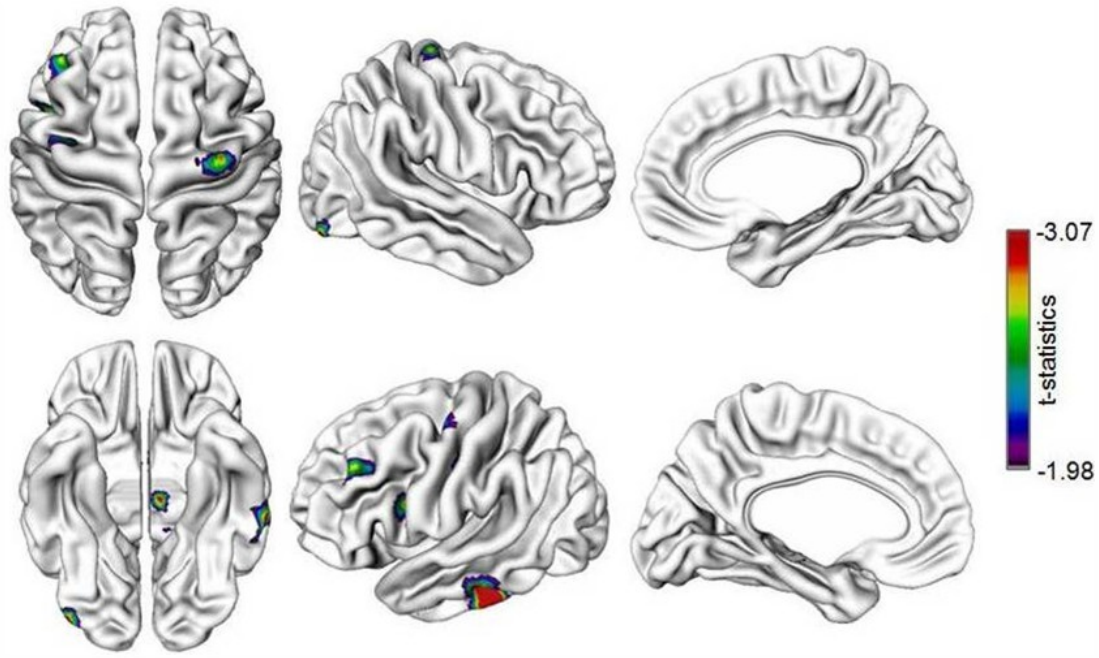

Figure 4.1: *T*-statistical maps of the SUMD Q1 (awareness of mental disorder) regression against cortical thickness in 79 people with FEP. Significant negative correlations (poorer insight with cortical thinning) can be found most pronouncedly in the left frontal and temporal lobes.

	Stereotaxic coordinates (MNI space)			
	x	y	z	*t*-value
Awareness of illness				
Left hemisphere				
Middle frontal gyrus (9)	-39	35	34	-2.45
Inferior frontal gyrus (44)	-47	9	20	-2.55
Precentral gyrus (6)	-36	-7	55	-2.58
Inferior temporal gyrus (20)	-59	-32	-21	-3.07
Right hemisphere				
Precentral gyrus (6)	34	-15	70	-2.57
Inferior occipital gyrus (18)	40	-86	-15	-2.65
Awareness of treatment need/efficacy				
Left hemisphere				
Middle frontal gyrus (10)	-41	46	23	-2.08
Middle frontal gyrus (6)	-34	-8	57	-2.99
Medial frontal gyrus (6)	-7	-10	61	-3.29
Medial frontal gyrus (11)	-4	39	-15	-2.02
Medial frontal gyrus (25)	-3	24	-17	-1.99
Rectal gyrus (11)	-4	38	-20	-2.06
Precuneus (7)	-8	-57	52	-2.51
Paracentral lobule (4)	-4	-42	67	-2.49
Supramarginal gyrus (40)	-60	-48	31	-2.31
Superior temporal gyrus (38)	-48	19	-21	-2.25
Superior temporal gyrus (38)	-50	15	-14	-2.20
Middle temporal gyrus (39)	-52	-60	12	-2.34
Inferior temporal gyrus (20)	-65	-19	-20	-2.88
Parahippocampal gyrus	-29	-5	-20	-2.50
Middle occipital gyrus (19)	-46	-77	-3	-2.01
Right hemisphere				
Inferior frontal gyrus (47)	30	24	-4	-2.72
Precuneus (7)	22	-79	47	-2.34
Superior Parietal lobule (7)	21	-67	64	-2.24
Supramarginal gyrus (40)	60	-51	30	-2.14
Paracentral lobule (4)	8	-43	69	-2.83
Superior temporal gyrus (38)	34	19	-32	-2.49
Parahippocampal gyrus (35)	23	-25	-26	-2.10
Fusiform gyrus (20)	40	-25	-28	-2.74
Lingual gyrus (18/19)	21	-63	-10	-2.09

Table 4.2: Regions where awareness of illness and awareness of treatment need/ efficacy scores significantly associated to cortical thinning in 79 FEP patients. Brodmann areas are shown in parentheses. MNI coordinates reflect the maxima.

Mean scores on the composite awareness of treatment need/efficacy measure were significantly and inversely associated with cortical thickness (t = -1.98, p = 0.05), and these results are displayed in Figure 4.2 and Table 4.2. Significant inverse associations (poorer insight with cortical thinning) can be found in the left hemisphere in the middle and medial frontal gyri, precuneus, paracentral lobule, supramarginal gyrus, superior, middle and inferior temporal gyri, parahippocampal gyrus and the middle occipital gyrus. Significant associations in the right hemisphere emerged in the inferior frontal gyrus, precuneus, superior parietal and paracentral lobules, supramarginal gyrus, superior temporal gyrus, parahippocampal gyrus, and fusiform and lingual gyri.

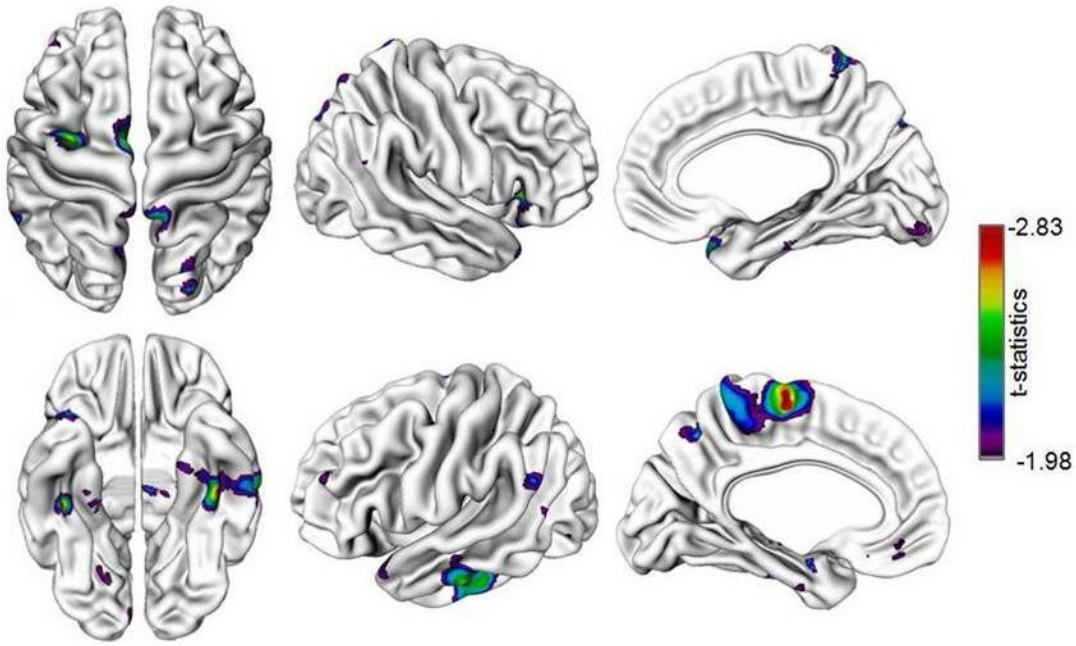

Figure 4.2: *T*-statistical maps of the SUMD Q2a + Q2b composite (awareness of need for treatment, awareness of treatment efficacy) regression against cortical thickness in 79 people with FEP. Significant associations (poorer insight with cortical thinning) emerged most pronouncedly in the left frontal, parietal and temporal lobes.

All brain regions retained significance when limiting the analysis to patients with non-affective psychosis (n = 68). Medication dose did not significantly associate to cortical thickness in any region that significantly correlated with awareness of mental disorder or awareness of treatment need/efficacy scores.

Voxel-based morphometry – regional GM density

When considering GM density, no significant inverse associations (poorer insight with density reductions) emerged with either awareness of mental disorder scores or awareness of treatment need/efficacy scores (all *p*s > 0.05).

Limiting the VBM analysis to patients with non-affective psychosis did not change interpretation of results.

4.5 Discussion

We used cortical thickness technique to assess the neural correlates of poor awareness of illness in a FEP sample, and as predicted, thinning in frontal cortex was observed, supporting our first hypothesis. Cortical thinning emerged most prominently in parietal and temporal cortices in association with poor awareness of illness and treatment need/efficacy, confirming our second hypothesis.

The left DLPFC effect strengthens the account holding that the neural pattern of insight may be similar to that for anosognosic syndromes (X. F. Amador, et al., 1991; Babinski, 1914). Two previous studies have reported associations between insight and the right DLPFC using manual tracing technique in first episode schizophrenia (Shad, Muddasani, et al., 2006; Shad, et al., 2004). One explanation for the hemispheric discrepancy is that we assessed insight multidimensionally while previous works correlated averaged SUMD awareness of symptoms item scores (Shad, Muddasani, et al., 2006) or used a global

rating (Shad, et al., 2004). Second, our sample size may have yielded greater statistical power to detect the left DLPFC effect (present study, N = 79; Shad et al., 2004, N = 35; Shad et al., 2006, N = 14). Third, we included affective and non-affective psychoses, while previously only schizophrenia patients had been studied (Shad, Muddasani, et al., 2006; Shad, et al., 2004). Fifth, preceding studies used manual segmentation technique, limited by labor intensiveness, inter- and intra-rater variability and the use of different anatomical borders, yielding GM volumes that may provide a mixed measure of cortical surface area, cortical folding and cortical thickness (Hutton, Draganski, Ashburner, & Weiskopf, 2009). At a cognitive level, the DLPFC is ascribed a vital role in normal (i.e., healthy) executive functions (Minzenberg, et al., 2009). The current DLPFC finding fits nicely with a meta-analytic finding that executive dysfunction is a core feature of poor insight in psychosis (Aleman, et al., 2006).

The finding that awareness of treatment need/efficacy associated with cortical thinning in left precuneus is in accord with volumetric reductions reported in chronic schizophrenia patients with poor insight (Cooke, et al., 2008). Functional imaging studies in healthy samples have suggested that the precuneus subserves self-processing operations (Cavanna & Trimble, 2006; Hassabis, Kumaran, & Maguire, 2007; Wolf, Dziobek, & Heekeren, 2009), including evaluating one's emotional experiences (Ochsner et al., 2004), considering self-referential personality/psychological attributes (Kircher et al., 2002; Kircher et al., 2000; Kjaer, Nowak, & Lou, 2002), and first- (Vogeley et al., 2001) and third-person perspective taking (Lombardo et al., 2009). This interpretation fits with the hypothesis that insight requires the metacognitive capacity "to see ourselves as others do" (Langdon & Ward, 2009). We hypothesize that cognizance of the effects of treatments on symptom intensity/frequency may invoke internal representations of one's mental states, and adopting another's mental perspective toward the self may be invoked in order to judge correctly one's mental health. It is of note that the precuneus is also important for episodic memory retrieval (Cavanna & Trimble, 2006). In this regard, our precuneus finding may support the hypothesis that inaccurate reflection on previous symptom related experiences may compromise the ability to compare accurately past and current symptoms and consequentially treatment effects over time (Flashman, et al., 2001).

Perhaps the strongest thickness effects were seen in left inferior temporal cortex, an area implicated in insight impairments in chronic schizophrenia (Cooke, et al., 2008; Ha, et al., 2004). Here it is relevant that early post-mortem studies in schizophrenia patients have shown that laminar patterning of Dopamine 1 (D1) and D2 receptors (Domyo, Kurumaji, & Toru, 2001) is altered in the inferior temporal cortex (BA20) (Goldsmith, Shapiro, & Joyce, 1997). Our current result may extend the theorized temporal cortex–insight relationship to FEP.

In the VBM analysis, no insight–GM density associations emerged for any tissue compartment. Although this is inconsistent with two previous chronic schizophrenia studies (Cooke, et al., 2008; Ha, et al., 2004), it can be noted that Cooke's group reported GM volumes, whereas Ha et al. characterized GM density. It has been shown meta-analytically that VBM analyses of GM volume and density produce different results (Fornito, Yucel, Patti, Wood, & Pantelis, 2009). Secondly, insight was quantified dissimilarly across the three studies, defined with four different scales yielding seven different insight dimensions. Third, VBM analysis is sensitive to registration differences, the size of smoothing kernel, shape differences that arise from systematic registration errors during spatial normalization, and image noise (Bookstein, 2001; D. K. Jones, et al., 2005), which may confound volume/density estimates. Moreover, blurring of cortical thickness data takes place in a topologically correct manner along the cortical surface, whereas VBM blurring is 3 dimensional, meaning it does not respect boundaries between tissue classes, leading to an increased likelihood of diluting existing signal or misinterpreting boundary shift as signal. Further, cortical thickness analysis communicates in millimeters the actual thickness of the cortex, providing qualitatively meaningful results. Finally, there could be a difference between first episode versus chronic psychosis that is specific to frontal lobe GM; for example, aging or cumulative effects of psychotic episodes may lead to progressive frontal GM loss that would not be detected in FEP. It may also be that continued impaired insight across multiple psychotic episodes, in combination with symptoms, is biologically toxic, possibly leading to stronger insight–GM volume/density associations in chronic populations.

The present study is limited partly by the cross-sectional analysis. Longitudinal studies suggest that insight changes early in the illness (Buchy, Bodnar, Malla, Joober, & Lepage, 2010), and our analysis cannot address whether insight and cortical mophometry change in tandem. Further, a main disadvantage of the cortical thickness metric is that it cannot index alterations in non-cortical brain regions previously associated with insight, such as intracranial volume (Flashman, McAllister, Andreasen, & Saykin, 2000) or ventricle/brain ratio (Takai, Uematsu, Ueki, Sone, & Kaiya, 1992). Whether changes in sub-cortical structures such as the basal ganglia, lead to poor insight cannot be studied.

In conclusion, these data provide greater support for an anosognosia theory of poor insight, suggesting that the neural signature of insight involves a widespread neural network and not only the frontal lobes as previously suggested (Shad, Muddasani, et al., 2006; Shad, et al., 2004). The results provide preliminary evidence for the existence of several insight-related mechanisms hosted in multiple cortical regions, and suggest the existence of separable neural systems underlying awareness for illness and treatment related experiences in FEP. The SUMD has acceptable correlations to other scales used in previous insight-neuromorphometry studies, such as the Schedule for Assessment of Insight (Andreasen, 1984b), Hamilton Depression Scale insight item (X. F. Amador, et al., 1993) and the Birchwood Insight Scale (Birchwood et al., 1994), suggesting our results may be compared with other works using different assessment tools. Further work will use patient samples with longer illness history who provide a more stable level of insight (i.e., pervasively poor or good insight) and whose trajectory has been impacted by variations in number of subsequent episodes. Moreover, a fuller account of insight will require the systematic investigation of psychological factors such as attributional bias, self-esteem, social cognition, etc. in addition to neuroanatomical measures within the same cohort of participants.

* * *

CHAPTER 5

SYMPTOM ATTRIBUTION IN FEP: PATTERNS OF CORTICAL THINNING

Preface

The cortical thickness analysis of the previous chapter pointed to partially independent topography for the awareness of illness and awareness of treatment related experiences items in our FEP sample. A third insight dimension, the ability to attribute symptoms to a mental disorder, has been relatively understudied neuroanatomically, aside from one study which associated global symptom misattribution to volumetric enlargement in the orbitofrontal cortex (OFC) (Shad, Muddasani, et al., 2006). Given insight can be modality specific, in that patients may express insight in-to particular signs and symptoms of their illness but not others (X. F. Amador, et al., 1994; Pini, et al., 2001), and that a global rating may obfuscate potential associations between misattribution for any one symptom and structural neuroanatomy, we appraised the neural architecture underlying misattribution for different symptoms of psychosis.

In the present work, we analyzed cortical thickness data in correlation with symptom attribution scores for four discrete symptoms: delusions, hallucinations, flat affect and asociality. We predicted that greater OFC thickness would associated with higher misattribution for one or more symptoms. We furthermore tested a general hypothesis that the regional distribution of cortical thickness or thinness would be partially dissociable across the four symptom attribution items.

5.1 Abstract

One dimension of insight in psychosis is the ability to attribute correctly one's symptoms to a mental disorder. Recent work suggests that gray matter volumes of the orbitofrontal cortex (OFC) correlate to aggregate symptom attribution scores in first episode schizophrenia. Whether regions beyond the OFC are important for symptom attribution remains to be established. Further, whether common or separable neural systems underlie attribution of specific symptoms (e.g., delusions, asociality) has not been studied. In the current work, 52 people with a FEP were rated with the Scale for assessment of Unawareness of Mental Disorder on attribution of hallucinations, delusions, flat affect and asociality. Attribution ratings were regressed on cortical thickness at 81,924 vertices. Mapping statistics revealed that delusion misattribution associated with thickness in OFC (BA 11/47). Delusion, flat affect and asociality misattribution associated with cortical thinness in the dorsolateral prefrontal cortex (BA 9/46). Differential associations emerged between each attribution item and cortical thickness/thinness in variety of frontal, temporal, parietal and occipital areas. The results imply a selective role for the OFC in delusion misattribution in FEP. Evidence for cortical thickness covariation in a variety of regions suggests partial-independence in the neural architecture underlying attribution for different symptoms in FEP.

5.2 Introduction

Lack of insight is a central clinical characteristic of schizophrenia (Carpenter, et al., 1973) and other psychoses (X. F. Amador, et al., 1994; Ghaemi & Rosenquist, 2004). Although early theoretical models suggested that insight can be split into an all or nothing phenomenon (Carpenter, et al., 1973; Van Putten, et al., 1976), more recent evidence suggests that insight is a continuous construct comprised of several related but partially independent elements (X. F. Amador, et al., 1993; A. David, et al., 1992). Insight elements typically involve awareness of illness, awareness of treatment effects, and an ability to label unusual mental events as pathological and attributable to a mental disorder (X. F. Amador, et al., 1993; A. David, et al., 1992; A. S. David, 1990).

Consistent with current multidimensional models, neuroimaging studies suggest the existence of partially separable neural systems underlying different insight dimensions in psychosis. These studies have employed voxel- or region-of-interest based analyses of magnetic resonance images (MRIs) to estimate gray matter volume or concentration. Two aspects of insight that have received attention in the literature include awareness of illness and awareness of treatment effects. Proposed brain regions relevant for illness awareness include bilateral dorsolateral prefrontal cortex (DLPFC) (Buchy, Ad-Dab'bagh, et al., in press; Flashman, et al., 2001; Shad, Muddasani, et al., 2006; Shad, et al., 2004) and the gyrus rectus (Flashman, et al., 2001). To understand these findings, it has been conceptualized that alterations in regional gray matter likely disturb their subserved cognitive functions, and this presumably contributes to poor insight. Shad and colleagues (Shad, et al., 2004; Shad, Tamminga, et al., 2006) have hypothesized that the DLPFC may mediate poor insight via deficits in conceptual organization and self-monitoring. Flashman and colleagues (2001) have hypothesized that the DLPFC and gyrus rectus orchestrate comparison of current and past experiences for accurate symptom interpretation. Awareness of treatment effects, on the other hand, may engage left precuneus and inferior temporal cortex (Buchy, Ad-Dab'bagh, et al., in press). The precuneus may support accurate reflection on one's mental states or adopting another's mental perspective to judge correctly one's mental health (Cavanna & Trimble, 2006;

Hassabis, et al., 2007; Wolf, et al., 2009), while decreased coordination of the left temporal cortex–DLPFC pathway may lead to insight associated memory and executive dysfunctions in psychosis (Aleman, et al., 2006; Buchy, Ad-Dab'bagh, et al., in press).

A third insight dimension, the ability to attribute symptoms to a mental disorder, has been relatively understudied. The only study examining this question found that symptom misattribution was associated with increased left orbitofrontal cortex (OFC) volume in first episode schizophrenia (Shad, Tamminga, et al., 2006). The authors suggested that a larger OFC, vis-à-vis its direct connections with limbic structures, may confer aberrant salience to symptom related perceptions and experiences causing incorrect attribution. However, symptom misattribution as measured by the Scale to assess Unawareness of Mental Disorder (SUMD) (Amador et al., 1993) was quantified with an aggregate score from attribution ratings on many different symptoms, and this may limit interpretation of results. First, a global rating may obfuscate potential associations between misattribution for any one symptom and structural neuroanatomy. Second, modern theorists have argued that insight can be modality specific, in that patients may express insight in-to particular signs and symptoms of their illness but not others (X. F. Amador, et al., 1994; Pini, et al., 2001), and this is presumably due to dissociable features of their pathophysiology. Third, investigations taking a specific symptom awareness approach suggest that different cognitive and psychopathological processes contribute to different dimensions of insight, for example, that insight for delusions and hallucinations result from different processes (X. F. Amador, et al., 1994; Beck, et al., 2004; Buchy, Joober, Malla, & Lepage, 2009). Fourth, functional and structural MRI data suggest that neural networks underlying different schizophrenia symptoms are partially overlapping but not homogeneous (Gur et al., 2007; Harvey, Armony, Malla, & Lepage, 2010; Hulshoff Pol & Kahn, 2008; Kasai et al., 2002; Knobel, Heinz, & Voss, 2008). Another relevant point here is that healthy adults activate qualitatively dissociable neural networks to different attributional tasks, for example, during internal versus external attribution for events (Blackwood et al., 2000), and to attributions about one's own versus others' emotional states (Ochsner, et al., 2004). This presents a strong case for a symptom-specific approach to studying the neural architecture of insight.

In the present work, we used a fully automated, objective measure of cortical thickness across the entire cerebrum to address whether common or separable neural systems underlie misattribution for symptoms seen in people with psychosis (delusions, hallucinations, flat affect, asociality). Cortical thickness confers several benefits over previously employed manual analyses: it provides a direct quantitative index in millimeters of cortical integrity and reflects the structure, density and arrangement of cells (Parent & Carpenter, 1995; Zilles, 1990). In line with the literature, we (1) predicted that greater OFC thickness would be associated with higher misattribution for one or more symptoms, and (2) also tested a general hypothesis that the regional distribution of cortical thickness or thinness would be partially dissociable across the four symptom attribution items.

5.3 Methods

Participants

Participants were part of a longitudinal naturalistic outcome study of first episode psychosis (FEP) treated in a specialised early intervention service, the Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), Douglas Institute in Montreal, Canada. The program involves a comprehensive approach with intensive medical and psychosocial interventions provided within the context of a modified assertive case management program. Inclusion criteria for PEPP were aged 14-35, suffering from either affective or non-affective psychosis and not taken antipsychotic medication for more than one month. This service is entirely publicly funded and there are no competing services within the system.

MR scans were acquired for FEP participants as part of a larger study on cognitive and neuroimaging predictors of outcome. Inclusion criteria were those set by PEPP with additional restrictions of ages 18–30, clinically stable (patients were receiving active treatment during this period), no major medical disorders (based on medical history and

physical examination) and able to provide informed consent. Exclusion criteria were history of neurological illnesses and head trauma resulting in loss of consciousness that could affect cognition, family history of hereditary neurological disorders, presence of neurological disorder and lifetime diagnosis of substance dependence. Participants were included in the present study if the symptom of interest was present and if they showed full (score = 1) to partial awareness (score = 2 or 3) on the corresponding symptom awareness item of the SUMD, as per instructions by the original authors (X. F. Amador, et al., 1993). Misattribution scores used in the main analysis were taken from participants who satisfied these inclusion criteria, and ranged from correct (score = 1) to incorrect attribution (score = 5).

Numbers of participants who met inclusion criteria at time of scanning were: hallucinations, n = 27, delusions, n = 25, flat affect, n = 22, and asociality, n = 29. The final sample size was 52 as 30 people were excluded: symptom of interest was not present: hallucinations, n = 48, delusions, n = 26, flat affect, n = 18, asociality, n = 10; did not show full to partial awareness on corresponding SUMD awareness item: hallucinations, n = 2, delusions, n = 11, flat affect, n = 15, asociality, n = 6; and SUMD ratings not acquired: hallucinations, n = 5, delusions, n = 20, flat affect, n = 27, asociality, n = 37.

Clinical assessment

Patient diagnoses were conducted at baseline based on the Structured Clinical Interview for DSM-IV (First, et al., 1998) and confirmed at 1–year through consensus between two senior psychiatrists (A.M. and R.J.). Clinical insight was quantified with an abbreviated version of the SUMD (X. F. Amador, et al., 1994). The SUMD assesses both awareness and attribution of symptoms, and in the current work attribution scores were utilized only. These items were 3b hallucinations, 4b delusions, 5b flat affect and 6b asociality. Items are rated on a five point scale from 1 = aware to 5 = unaware. Symptom severity was determined with the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984b), Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984a),

Calgary Depression Scale (Addington, et al., 1990) and Hamilton Anxiety Scale (J. Riskind, et al., 1987) by research assistants and graduate students who had received extensive training. Parental Socioeconomic status (SES) was estimated using the Hollingshead SES Rating Scale (D. C. Miller, 1991) and handedness with the Edinburgh Handedness Inventory (Oldfield, 1971). MR scans were performed on average within 21.2 days (*SD* = 20.5) of insight and symptom assessments. Participants provided informed consent and the Douglas Mental Health University Institute Human Ethics Review Board approved the study.

MRI acquisition

Scans were acquired at the Montreal Neurological Institute on a 1.5T Siemens Sonata whole body MRI system. Structural T1 volumes were acquired for each participant using a three-dimensional gradient echo pulse sequence with sagittal volume excitation (repetition time = 22ms, echo time = 9.2ms, flip angle = 30º, 180 1mm contiguous sagittal slices). The rectangular field of view for images was 256mm (SI) X 204mm (AP).

Statistical Analyses

MRIs were submitted to the CIVET processing pipeline (Version 1.1.9) (http://wiki.bic.mni.mcgill.ca/index.php/CIVET) (Ad-Dab'bagh, et al., 2006; Zijdenbos, et al., 2002). Native T1-weighted images were first registered to the ICBM152 template using linear transformation (D. L. Collins, et al., 1994; Grabner, et al., 2006) and simultaneously corrected for non-uniformity artefacts using N3 (Sled, et al., 1998). Transformed images were segmented into gray matter, white matter, cerebral spinal fluid and background using a neural net classifier (INSECT) (Zijdenbos, et al., 2002). Gray matter and white matter surfaces were extracted using CLASP algorithm (Kabani, et al., 2001; J. S. Kim, et al., 2005; MacDonald, et al., 2000). A spherical-mesh deformation algorithm was used to produce a surface mesh of 40,962 vertices for each hemisphere. Non-linear registration of both cortical surfaces to a high resolution average surface

template generated from the ICBM152 data set was performed to establish inter-subject correspondence of vertices (Lyttelton, et al., 2007; Robbins, 2004). Reverse linear transformation of volumes was performed to allow vertex-based corticometric measurements in native space for each subject's MRI (Ad-Dab'bagh, et al., 2005). The deformation algorithm first fits the white matter surface and then expands to the outer gray matter/cerebral spinal fluid intersection. From these surfaces, cortical thickness was computed in native space using the t-link method (Lerch & Evans, 2005) which determines the linked distance between inner and outer cortical surfaces at each vertex. Each participant's cortical thickness map was subsequently blurred using a 20-mm full-width half-maximum surface-based diffusion smoothing kernel (Chung, et al., 2003).

Statistics were performed at 40,962 vertices, regressing cortical thickness against attribution scores. Total intracranial volume was not included as a covariate as cortical thickness and brain volume are weakly correlated (Ad-Dab'bagh, et al., 2005; Sowell, et al., 2007). Statistical maps were thresholded and multiple comparisons taken into account using the false discovery rate procedure with $q = 0.05$ (Genovese, et al., 2002), and thus results were considered significant at $t = 2.04$ ($r = 0.28$).

5.4 Results

Demographic and clinical details are reported in Table 5.1. Participants showed moderate misattribution for hallucinations, delusions, flat affect and asociality. All results are reported as negative and positive correlations indicating regions where greater misattribution associated with cortical thinness and cortical thickness, respectively.

	FEP (N = 52)		
	M	SD	Range
Age at inclusion (years)	23.2	3.8	17 – 30
Education (years)	11.7	2.1	7 – 18
Hollingshead Index score	3.7	0.8	2 – 5
SUMD			
Awareness of mental disorder	2.5	1.4	1 – 5
Awareness of response to medication	2.4	1.4	1 – 5
Awareness of need for treatment	2.4	1.5	1 – 5
Hallucination attribution[a]	2.2	1.3	1 – 5
Delusion attribution[b]	3.2	1.5	1 – 5
Flat affect attribution[c]	4.2	1.9	1 – 5
Asociality attribution[d]	3.3	1.4	1 – 5
SAPS			
Global rating of hallucinations	2.7	1.2	1 – 5
Global rating of delusions[b]	2.2	2.0	1 – 5
SANS			
Global rating of flat affect[c]	3.1	0.4	2 – 5
Global rating of asociality[d]	3.6	0.6	3 – 5
Calgary Depression Scale (total)	3.0	3.7	0 – 16
Hamilton Anxiety Scale (total)	3.8	3.8	0 – 17
Antipsychotic (dose, mg)	310.9	405.4	25 – 1875
Seroquel XR	1	2	

Table 5.1: Demographic and clinical characteristics of the sample. [a] Scores reported for the hallucination attribution group only, n = 27. [b] Scores reported for the delusion attribution group only, n = 25. [c] Scores reported for the flat affect attribution group only, n = 22. [d] Scores reported for the asociality attribution group only, n = 29. Antipsychotic medication reported as chlorpromazine equivalent dosage in mg. Medication information was unavailable for one participant. Handedness was not recorded for one participant.

	FEP (N = 52)	
	N	%
Gender (M:F)	40:12	77:23
Handedness: Left/Right/Ambidextrous[f]	2/43/6	4/84/12
Diagnostic category		
Schizophrenia	30	42.2
Schizoaffective disorder	9	17.3
Schizophreniform disorder	1	1.9
Psychosis not otherwise specified	6	11.5
Bipolar	4	7.7
Major depression with psychotic features	2	3.8
Antipsychotic		
Risperidone	23	45
Olanzapine	14	27.4
Clozapine	2	4
Seroquel	6	11.8
Ziprasidone	1	2
Paliperidone	4	7.8
Seroquel XR	1	2

Table 5.2: Demographic and clinical characteristics of the sample.

Attribution ratings did not significantly correlate with severity on the corresponding SAPS/SANS symptom item for any item (hallucinations, r = 0.01, p =0.93, delusions, r = 0.19, p = 0.37, flat affect, r = 0.35, p = 0.11, asociality, r = 0.15, p = 0.14).

Figures 5.1 and 5.2 display cortical thickness maps for the four attribution items.

a) Hallucination misattribution: Within the hallucination misattribution group, significant negative effects emerged in frontal (BA 4/6), temporal (BA 20) and occipital gyri (BA 17), cingulate gyrus (BA 24) and parahippocampal gyrus, shown in Table 5.3. Significant positive effects emerged in frontal (BA 24), temporal (BA 21/22/39/20) and parietal gyri (BA 40), parahippocampal gyrus and uncus.

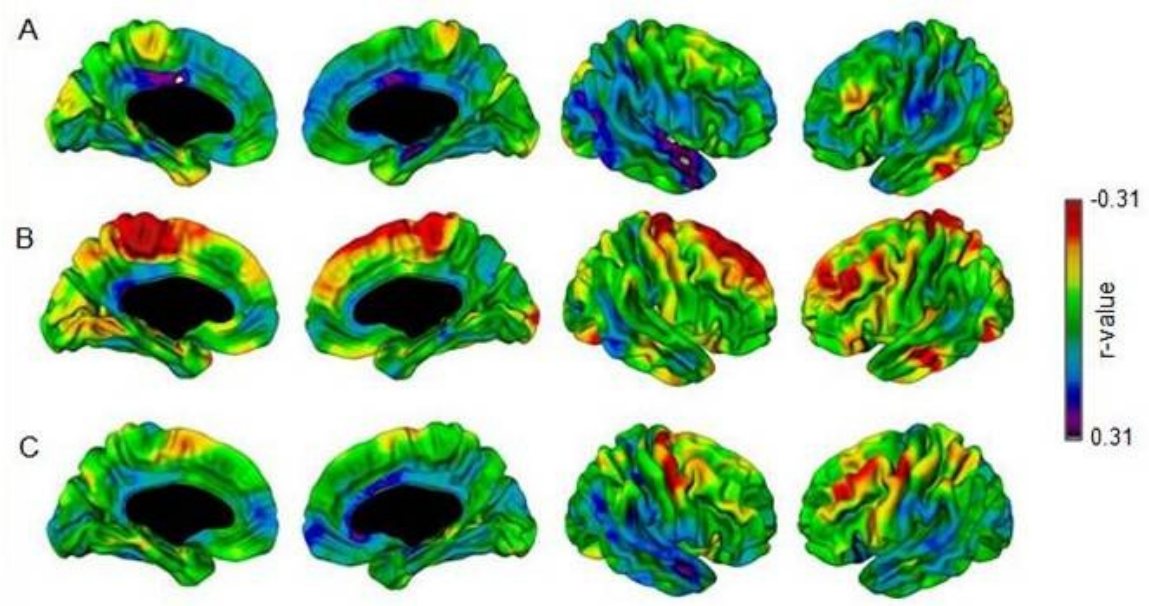

Figure 5.1: Correlation maps showing significant results from the regression of attribution scores on cortical thickness in 52 FEP participants. Images display correlations between cortical thickness and attribution scores for A) hallucinations, B) flat affect, and C) asociality. Vertices with negative effects (greater misattribution correlated to cortical thinness) are shown in red, and those with positive effects (greater misattribution correlated to cortical thickness) in purple.

	Brodmann Area (BA)	Hemisphere	Stereotaxic coordinates (MNI space)			r-value at peak vertex
			x	y	z	
Negative associations (greater misattribution correlated with cortical thinness)						
Inferior temporal gyrus	20	Left	-58	-33	-20	-0.49
Middle occipital gyrus	19	Left	-36	-83	8	-0.44
Precentral gyrus	4	Left	-51	-14	44	-0.49
Precentral gyrus	6	Left	-58	-7	28	-0.43
Cingulate gyrus	24	Left	-2	-7	33	-0.52
Parahippocampal gyrus	-	Left	-32	-37	-5	-0.56
Positive associations (greater misattribution correlated with cortical thickness)						
Middle temporal gyrus	21	Right	54	2	-14	0.54
Superior temporal gyrus	22	Right	57	-2	1	0.55
Inferior parietal Lobule	40	Right	38	-33	41	0.46
Superior temporal gyrus/ angular gyrus/ middle temporal gyrus	39/21	Right	49	-63	19	0.58
Inferior temporal gyrus	20	Right	56	-58	-15	0.44
Cingulate gyrus	24	Right	2	5	33	0.50
Parahippocampal gyrus/ uncus	-	Right	35	-12	-19	0.50

Table 5.3: Regions where hallucination attribution scores significantly associated to cortical thinness and thickness in 27 FEP participants.

b) Delusion misattribution: Within the delusion misattribution group, significant negative effects emerged in frontal gyri (BA 9/44), shown in Table 5.4. Significant positive effects emerged in frontal (BA 6/4/10/11/47/9), parietal (BA 2/40/5/43/40/39), temporal (BA 42/20/19/22/) and occipital gyri (BA 18), cingulate gyrus (BA 24/31) and uncus (BA 28).

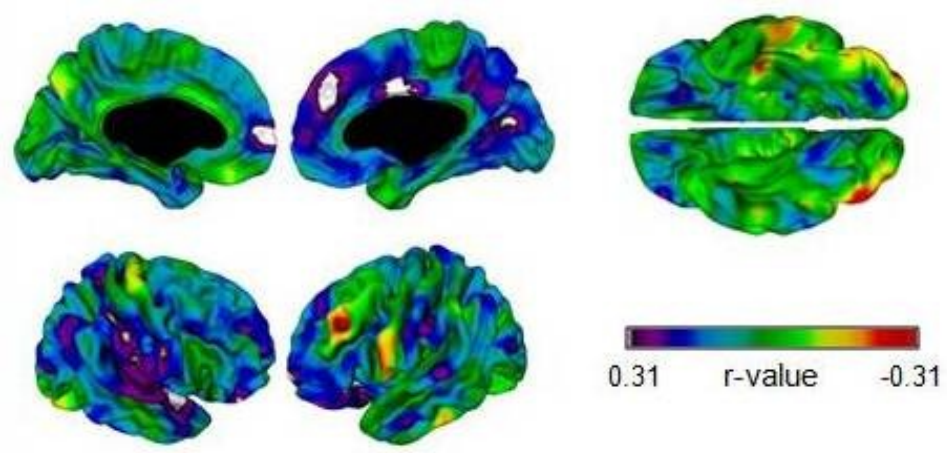

Figure 5.2: Correlation maps showing significant results from the regression of delusion attribution scores on cortical thickness in 52 FEP participants. Images display correlations between cortical thickness and attribution scores for A) hallucinations, B) flat affect, and C) asociality. Vertices with negative effects (greater misattribution correlated to cortical thinness) are shown in red, and those with positive effects (greater misattribution correlated to cortical thickness) in purple.

	Brodmann Area (BA)	Hemisphere	Stereotaxic coordinates (MNI space)			r-value at peak vertex
			x	y	z	
Negative associations (greater misattribution correlated with cortical thinness)						
Middle frontal gyrus	9	Left	-38	32	34	-0.50
Inferior frontal gyrus	44	Left	-57	9	18	-0.45
Positive associations (greater misattribution correlated with cortical thickness)						
Precentral gyrus	6	Left	-53	-11	34	0.47
Cingulate gyrus	31	Left	-17	44	40	0.45
Precentral gyrus	4	Left	-28	-27	60	0.48
Postcentral gyrus	2	Left	-54	-22	36	0.53
Inferior parietal lobule	40	Left	-41	-59	47	0.50
Superior temporal gyrus	42	Left	-67	-25	10	0.46
Inferior temporal gyrus	20	Left	-63	-8	-22	0.44
Middle temporal gyrus	19	Left	-42	-80	17	0.44
Superior/medial frontal gyri	10/11	Left	-12	69	-3	0.60
Uncus	28	Left	-28	3	-25	0.57
Orbital gyrus	47	Left	-11	32	-27	0.44
Middle frontal gyrus	11	Left	-43	47	-15	0.45
Inferior frontal gyrus	47	Left	-39	32	-3	0.66
Inferior frontal gyrus	47	Left	-31	20	-20	0.58
Middle frontal gyrus	11/47	Right	43	43	-17	0.55
Middle frontal gyrus	10	Right	28	59	10	0.44
Superior frontal gyrus	10	Right	25	50	22	0.44
Middle frontal gyrus	9	Right	43	17	32	0.65
Precentral gyrus	6	Right	59	-1	25	0.55
Inferior parietal lobule	5/43/40	Right	26	-42	64	0.54
Superior temporal gyrus	22	Right	55	2	-2	0.59
Angular gyrus/ precuneus	39	Right	51	-66	37	0.47
Middle temporal gyrus	19	Right	41	-85	14	0.48
Orbital gyrus	11	Right	14	39	-27	0.57
Medial frontal gyrus	9	Right	7	47	28	0.59
Cingulate gyrus	24	Right	2	5	33	0.65
Cuneus	18	Right	3	-72	15	0.55
Precuneus/ cingulate gyrus	31	Right	6	-66	24	0.55
Superior frontal gyrus	10	Right	7	61	2	0.45

Table 5.4: Regions where delusion attribution scores significantly associated with cortical thinness and thickness in 25 FEP participants.

c) Flat affect misattribution: Within the flat affect misattribution group, significant negative effects can be seen in frontal (BA 9/10/46/8/6/47/11), parietal (BA 5/7/31) and temporal gyri (BA 20), and parahippocampal gyrus as presented in Table 5.5. Significant positive effects can be seen in frontal (BA 6/4/9/8) and occipital gyri (BA 18).

	Brodmann Area (BA)	Hemisphere	Stereotaxic coordinates (MNI space)			r-value at peak vertex
			x	y	z	
Negative associations (greater misattribution correlated with cortical thinness)						
Superior and middle frontal gyri/ precuneus	9/31/10/46/8	Left	-38	35	35	-0.57
Middle frontal gyrus	6	Left	-42	13	52	-0.43
Inferior frontal gyrus	47	Left	-54	30	-1	-0.42
Middle frontal gyrus	11	Left	-28	41	-15	-0.41
Precentral gyrus	6	Left	-43	-13	34	-0.45
Inferior temporal gyrus	20	Left	-64	-22	-20	-0.50
Middle occipital gyrus	37	Left	-41	-66	-2	-0.52
Precuneus	19	Left	-36	-82	37	-0.47
Postcentral gyrus/ superior parietal lobule	5/7	Left	-29	-50	69	-0.44
Paracentral lobule/ cingulate gyrus/ superior and medial frontal gyri/ postcentral gyrus	6/24/5/4/7	Left	-4	-30	54	-0.60
Parahippocampal gyrus	-	Left	-29	-5	-21	-0.57
Positive associations (greater misattribution correlated with cortical thickness)						
Superior, middle and medial frontal gyri/ precentral gyrus/ paracentral lobule	6/4/9/8/31	Right	15	23	55	-0.68
Cuneus	18	Right	8	-102	1	-0.46

Table 5.5: Regions where flat affect attribution scores significantly associated with cortical thinness and thickness in 22 FEP participants.

d) Asociality misattribution: Finally, within the asociality misattribution group, significant negative effects emerged in frontal (BA 9/44/8/6/4) and parietal gyri (BA 40), and parahippocampal gyrus, shown in Table 5.6. Significant positive effects emerged in temporal gyrus (BA 38) and anterior cingulate (BA 24).

	Brodmann Area (BA)	Hemisphere	Stereotaxic coordinates (MNI space)			r-value at peak vertex
			x	y	z	
Negative associations (greater misattribution correlated with cortical thinness)						
Superior frontal gyrus	9	Left	38	34	35	-0.40
Inferior frontal gyrus	44	Left	-48	6	19	-0.44
Middle frontal gyrus	8	Left	-34	21	48	-0.41
Middle frontal gyrus	6	Left	-39	-6	57	-0.48
Inferior parietal lobule	40	Left	-50	-38	51	-0.38
Parahippocampal gyrus		Left	-28	-5	-20	-0.38
Precentral gyrus	6	Right	28	-18	74	-0.49
Precentral gyrus	4	Right	50	-10	50	-0.47
Positive associations (greater misattribution correlated with cortical thickness)						
Anterior cingulate	24	Right	3	15	27	0.47
Superior temporal gyrus	38	Right	52	-1	-16	0.44

Table 5.5: Regions where asociality attribution scores significantly associated with cortical thinness and thickness in 29 FEP participants.

Medication dose did not significantly associate to cortical thickness in any region that significantly correlated with SUMD attribution scores. Limiting the four cortical thickness analyses to patients with non-affective psychosis did not change interpretation of results. To examine influences of demographic variables on the results, we regressed SUMD attribution scores on cortical thickness, controlling statistically for the following variables: SAPS and SANS total scores, age, gender, diagnosis (affective vs. non-affective psychosis), handedness and medication dose (chlorpromazine equivalents). The analyses did not change interpretation of the main findings of the study for any of the four attribution items.

5.5 Discussion

The use of a sophisticated surface-extraction method in a FEP sample has generated results that both corroborate and disconfirm previous findings based on manual segmentation. Further, some novel findings have emerged.

First, as predicted, cortical thickness in OFC (BA 11/47) was associated with symptom misattribution, though this was statistically significant for the delusion item only. Second, thickness reductions emerged in several regions theoretically important for insight, including left middle frontal gyrus in an area of the dorsolateral prefrontal cortex (DLPFC BA 9/46) in association with delusion, flat affect and asociality misattribution. Thinning in left temporal cortex (BA 20) was associated with hallucination and flat affect misattribution, and thinning in bilateral precuneus (BA 7/19) was associated with flat affect misattribution. Taken as a whole, the novel contribution of the corticometric analysis over and above previous manual analyses of MRIs in correlation with misattribution data was: (1) whole brain statistical mapping at a sub-voxel resolution leading to higher statistical sensitivity, (2) evidence confirmation that the OFC is involved in symptom misattribution, (3) evidence that frontal, parietal and temporal cortical morphometry is also associated with symptom misattribution, and (4) the

observation that the brain systems underlying attribution for different symptoms are partially-independent in our FEP sample.

Intriguingly, our sample showed significant thickness enlargements in medial OFC in correlation with delusion misattribution only. This finding contrasts with a volumetric study reporting orbitofrontal enlargement in first episode schizophrenia patients with global symptom misattribution (Shad, Muddasani, et al., 2006). Our result is consistent with disrupted orbitofrontal-based dopamine-mediated assignment of salience to external and internal stimuli (elaborated on in the "motivational salience" model (Kapur, 2003)) that leads to disruption in the ability to correctly attribute delusions to a mental illness (Kapur, 2003; Shad, Muddasani, et al., 2006). The result also accords with functional neuroimaging findings that the OFC activates when healthy individuals make attributions of mental states to other people (Elliott et al., 2006) and correct memory attributions for emotional items (Kensinger & Schacter, 2005). Another research stream has placed the medial OFC/amygdala/striatum triad as key nodes in the network subserving reward processes, including the valence and motivational value of rewards (Berridge & Kringelbach, 2008) and social rewards such as smiling (O'Doherty et al., 2003). In the context of delusions, OFC pathology could potentially lead patients to utilize socially desirable explanations for their anomalous perceptions and experiences.

Beyond this a priori hypothesized region, cortical thinness in left DLPFC was correlated with misattribution for three symptoms. The DLFPC has previously been implicated in awareness of illness deficits in analyses on first episode antipsychotic naïve schizophrenia (Shad, Muddasani, et al., 2006; Shad, et al., 2004), FEP (Buchy, Ad-Dab'bagh, et al., in press) and chronic schizophrenia populations (Flashman, et al., 2001). It would appear that DLPFC thinning constitutes a common element in the topographic basis for multiple insight dimensions. This conforms with convergent reports that the DLPFC is the nexus of cognitive dysfunction in schizophrenia patients who lack insight (Aleman, et al., 2006), most pronouncedly in memory, cognitive set switching and flexibility in abstract thinking. Inferences regarding how frontal cortical structure and function are linked to symptoms misattribution will be best appreciated in functional MRI studies during cognitive activation paradigms.

The temporal lobe has likewise exhibited reduced volume in correlation with unawareness of illness in a range of chronic schizophrenia studies (Cooke, et al., 2008; Ha, et al., 2004), and reduced cortical thickness in correlation with unawareness of treatment need/efficacy in a FEP sample (Buchy, Ad-Dab'bagh, et al., in press), overlapping with that of this study, particularly in left inferior and middle temporal gyri. Interestingly, in the current work, hallucination and flat affect misattribution were associated with cortical thinness in left DLPFC and left temporal cortices. Cortical thinning may reflect compromised cortical laminar structure and integrity or neuronal cell count, but could also reflect a loss of cortico-cortical circuitry through diminished neuropil volume (Selemon & Goldman-Rakic, 1999). This raises the question of the status of white matter structure in the frontotemporal network. Indeed, in a very recent study our group used diffusion tensor imaging tractography to demonstrate that frontotemporal connectional architecture (uncinate fasciculus, superior longitudinal fasciculus) is compromised in FEP patients who show misattribution for hallucinations and delusions (Buchy L et al., 2010). This could be compatible with the "dysconnectivity" hypothesis of schizophrenia. Interestingly, 14 patients (52% and 64% of those in the hallucinating and flat affect groups, respectively) were in both groups, suggesting independent contributions of frontal and temporal cortices to attribution processes in some of our participants.

Flat affect misattribution-related thinness also emerged in bilateral precuneus and surrounding middle and medial frontal cortices. Cortical abnormalities in this network suggest that flat affect misattribution may be explained as the failure of self-processing mechanisms (Cavanna & Trimble, 2006; Hassabis, et al., 2007; Kircher, et al., 2002; Kircher, et al., 2000; Kjaer, et al., 2002; Wolf, et al., 2009). In this scenario, affective judgments may rely on the capacity to reflect upon the self from the perspective of another (A. S. David, 1990, 1999; Langdon & Ward, 2009), seeing as others do one's emotional reactivity. Therefore, when parts of this structural network function suboptimally, as in our participants with flat affect misattribution, the appropriate 'see ourselves as others see us' response may not be activated, and incorrect attribution may occur.

Taken together, the finding of morphometric effects in areas outside the predicted misattribution relevant region of the OFC suggests incorrect attribution may be associated with disruption in a dynamic circuitry. Cortical thickening was seen in frontal and temporal gyri, inferior parietal lobule, precuneus, pre- and post-central gyri and parahippocampal gyrus. Cortical thinning was evident in superior, middle and inferior frontal gyri, medial frontal gyrus, superior temporal gyrus, precentral gyrus, parahippocampal gyrus and occipital gyri. This latter network is in part comparable with brain regions important for awareness of illness and treatment related experiences (Buchy, Ad-Dab'bagh, et al., in press; Cooke, et al., 2008; Flashman, et al., 2001; Lee, et al., 2006; Sapara, et al., 2007), and this fits with the current view of insight as multidimensional encompassing different but related elements (X. F. Amador, et al., 1994; A. S. David, 1990). The results are also compatible with the popular anosagnosia hypothesis of insight (X. F. Amador, et al., 1991; Babinski, 1914), which posits the prefrontal cortex as a core deficit. In an extension of this account, we have argued on both empirical and theoretical grounds (Buchy, Ad-Dab'bagh, et al., in press) that an anosagnosic model of insight would predict structural impairments in frontal, parietal and temporal cortices, and the current data support this contention.

The study is subject to several limitations. Psychosis is a heterogeneous disorder, and symptom attribution is just one manifestation of the underlying pathology. While evidence from volumetric studies suggests that psychopathological variables such as auditory hallucinations (Garcia-Marti et al., 2008; Neckelmann et al., 2006; Shapleske et al., 2002), delusions (Whitford et al., 2009) and negative symptoms (Koutsouleris et al., 2008) are associated with cortical morphology, we feel false positives are unlikely given that symptom attribution ratings were not statistically associated with symptom severity. Notwithstanding, cortical thickness effects appear relatively subtle (range, r = 0.38 – 0.68). A large standard deviation can be seen between insight ratings and MR scans (*M* = 21.2 days, *SD* = 20.5); however, we have documented that our FEP patients show little change in insight and symptom severity after 1-month of antipsychotic treatment (Buchy et al., 2010), suggesting patients' clinical state was likely stable between their MR scan and clinical assessment. Even so, gray matter could be changing during the time between assessment and scanning, and changes in neuroanatomy may precede detectable changes

in clinical status or behavioral ratings. It is also relevant that in recent-onset schizophrenia a relation between insight and IQ has been documented (David et al., 1995; Parellada et al., 2010), and its impact on neural morphometry was not considered in the current dataset. Further, in future studies it would be helpful to analyze the regions identified in this study in comparison to controls to see if there are differences in cortical thickness in FEP patients vs. controls or whether FEP patients have cortical thickness essentially within the range of normal but with variance that relates to symptoms. A technical limitation is that in cortical thickness analysis the focus is restricted to cortex, and involvement of noncortical gray matter and white matter will not be detected. It is also worth noting that any exploratory analysis across the entire cerebrum has less statistical power than a predefined region-of-interest approach, owing to the increased number of multiple comparisons. Even so, the results suggest that semi-independent neural systems differentially underlie misattribution for distinct symptoms of psychosis. Future studies using functional neuroimaging may help to further explain the pathology that underlies misattribution, and tasks tapping executive and self-processing functions may be particularly insightful in this regard. Studies in ultra-high risk psychosis samples will provide a unique opportunity to study insight, which may yield neural markers for transition to psychosis and/or "trait" markers of poor insight across multiple psychosis stages (i.e., ultra-high risk, first episode antipsychotic naïve, and FEP). To conclude, cortical thickness is emerging as an intermediate phenotype for multiple insight dimensions in FEP, including awareness of illness, awareness of treatment efficacy and now symptom attribution.

5.7 Appendix: Supplementary Table

Attribution scores	Attribution scores			
	Hallucations	Delusions	Flat affect	Asociality
Hallucations	–	r = 0.82, p < 0.001, n = 17	r = 0.50, p = 0.10, n = 12	r = 0.45, p = 0.12, n = 13
Delusions	–	–	r = 0.52, p = 0.06, n = 14	r = 0.87, p < 0.001, n = 17
Flat affect	–	–	–	r = 0.74, p < 0.001, n =2 1
Asociality	–	–	–	–

Table 5.6: Correlations between symptom attribution scores. N represents the number of first-episode psychosis participants who satisfied inclusion criteria for both attribution items (see text for inclusion criteria).

* * *

CHAPTER 6

ROLE OF HIPPOCAMPAL VOLUME AND VERBAL MEMORY FOR COGNITIVE INSIGHT IN FEP

Preface

Chapters 3 to 5 described several experiments on the topic of clinical insight in FEP. Over the past eight years or so, it has become apparent that patients' capacity to distance themselves from their distorted beliefs and misinterpretations, reflect on them rationally, and recognize erroneous conclusions, is essential for clinical insight. These metacognitive processes are considered to reflect one's *cognitive insight*. Cognitive insight includes the capacity to detect and correct distorted beliefs and misinterpretations, and these metacognitive processes are believed to obstruct awareness of a mental illness requiring treatment (i.e., clinical insight), and the two show adequate convergent validity (Beck, et al., 2004; Bora, et al., 2007; Engh, et al., 2007; Pedrelli, et al., 2004).

Our previous work (Lepage, et al., 2008) linked verbal learning and memory with cognitive insight, but not clinical insight, in individuals with a FEP. An important question that is yet to be investigated is whether the brain systems underlying cognitive insight in FEP overlap with those underlying verbal memory. In view of evidence that the verbal memory cognitive system and the hippocampus are functioning suboptimally in schizophrenia (Achim & Lepage, 2005; Boyer, Phillips, Rousseau, & Ilivitsky, 2007; Steen, Mull, McClure, Hamer, & Lieberman, 2006; Weiss & Heckers, 2001), and that the hippocampus is critical for verbal memory (Lepage, Habib, & Tulving, 1998; Schacter &

Wagner, 1999; Scoville & Milner, 1957), in the present study we set out to investigate their role for cognitive insight in FEP. Against a background of evidence that clinical insight is correlated with neurocognitive ability (Aleman, et al., 2006) and with gray matter volumes (Shad, et al., 2004; Shad, Tamminga, et al., 2006), we also investigated whether correlations appear with neurocognitive performance and hippocampal volumes.

6.1 Abstract

Our previous work has linked verbal learning and memory with cognitive insight, but not clinical insight, in individuals with a first episode psychosis (FEP). The current study reassessed the neurocognitive basis of cognitive and clinical insight and explored their neural basis in 61 FEP patients. Cognitive insight was measured with the Beck Cognitive Insight Scale (BCIS) and clinical insight with the Scale to assess Unawareness of Mental Disorder (SUMD). Global measures for seven domains of cognition were examined. Hippocampi were manually segmented in to three parts: the body, head, and tail. Verbal learning and memory significantly correlated with the BCIS composite index. Composite index scores were significantly associated with total left hippocampus (HC) volume; partial correlations, however, revealed that this relationship was attributable largely to verbal memory performance. The BCIS self-certainty subscale significantly and inversely correlated with bilateral HC volumes, and these associations were independent of verbal learning and memory performance. The BCIS self-reflectiveness subscale significantly correlated with verbal learning and memory, but not with HC volume. No significant correlations emerged between the SUMD and verbal memory or HC volumes. These results strengthen our previous assertion that in individuals with a FEP cognitive insight may rely on memory whereby current experiences are appraised based on previous ones. The hippocampus may be a viable location among others for the brain system which underlies aspects of cognitive insight in individuals with a FEP.

6.2 Introduction

Lack of clinical insight is a central clinical characteristic of schizophrenia (Carpenter, et al., 1973). The clinical concept of insight focuses on the patient's awareness that their symptoms and behaviour are abnormal and attributable to a mental disorder, of the social consequences of the disorder and the need for treatment (1993; A. S. David, 1990). This form of insight is determined by observing individuals' behaviour in the context of a clinical examination and is valuable for determining diagnosis, prognosis and treatment (X F Amador & David, 1998; Mintz, et al., 2003).

Fundamental to an understanding of clinical insight is the study of patients' capacity to distance themselves from their distorted beliefs and misinterpretations, reflect on them rationally, and recognize erroneous conclusions. These metacognitive processes are studied under the rubric of cognitive insight. To psychometrically assess such cognitions, Beck and colleagues (Beck, et al., 2004) developed the brief self-reported Beck Cognitive Insight Scale (BCIS). These authors argue that the mental operations underlying cognitive insight can be divided into two mechanisms: self-reflectiveness, which includes a willingness to acknowledge fallibility, corrigibility and recognition of dysfunctional reasoning, and self-certainty, which refers to a tendency to be overconfident. These authors propose that higher levels of certainty may diminish the capacity for self reflection, and thus a composite index is calculated through subtracting the individual's self-certainty score from her/his self-reflectiveness score. Cognitive insight is of great clinical significance as it directly taps into thinking styles underlying distorted cognitions, which are increasingly acknowledged as target for intervention (Turkington, et al., 2002). Cognitive insight has adequate convergent validity with clinical measures of insight (Beck, et al., 2004).

The study of cognitive insight has recently been employed to identify aspects of the neurocognitive architecture that may contribute to aberrant thinking styles and cognitive distortions in psychosis (Lepage, et al., 2008). In an initial study, in individuals with a first episode of psychosis (FEP), we evaluated associations between cognitive and clinical insight and seven domains of cognition (verbal learning and memory, visual learning and

memory, working memory, speed of processing, reasoning and problem solving, attention, and social cognition) (Lepage, et al., 2008). Results showed that participants who had higher BCIS composite index scores had better verbal learning and memory than individuals who scored lower on the composite index. We proposed that cognitive insight may rely selectively on verbal memory as it requires reflection and self-searching in memory. Further, the magnitude of verbal learning and memory deficits corresponded with the degree of self-certainty. We suggested that belief inflexibility may cause memories to be held with strong conviction, which may dissuade elaborate searches for previous experiences in memory. Notably, no associations emerged for self-reflectiveness or two clinical insight measures, namely the Scale for assessment of Unawareness of Mental Disorder (SUMD) item 1 (awareness of mental disorder) and the insight item (G12) from the PANSS. We concluded that cognitive insight, but not clinical insight, may rely on memory processes whereby current experiences are appraised based on previous ones.

An important question that is yet to be investigated is whether the brain systems underlying cognitive insight in FEP overlap with those underlying verbal memory. Lesion studies have provided evidence for a critical role of the hippocampus (HC) for verbal memory function (Scoville & Milner, 1957). Moreover, functional neuroimaging studies have demonstrated that the HC is a key neural correlate when normal subjects engage in both memory encoding and memory retrieval (Lepage, et al., 1998; Schacter & Wagner, 1999). In comparison, people with schizophrenia show a lack of normal memory-related activity in the HC (Achim & Lepage, 2005; Boyer, et al., 2007; Weiss & Heckers, 2001) as well as volumetric reductions in this region (Steen, et al., 2006). Despite the absence of studies on the neural basis of cognitive insight, the pattern of associations between verbal memory and cognitive insight reported may lead to some tentative hypotheses. First, the finding that increased self-certainty was correlated with poorer verbal memory may imply inefficient HC function in FEP participants with higher certainty judgments. Second, self-reflectiveness and verbal memory were found to be uncorrelated, which may imply that the HC does not play an important role in self-reflectivity.

The aim of this study was to gain an anatomical understanding of the brain systems that underlie cognitive insight in individuals with a FEP. In view of evidence that the verbal memory cognitive system and the HC are functioning suboptimally in schizophrenia, and that the HC is critical for verbal memory, an investigation in to their role for cognitive insight seemed particularly worthwhile. Against a background of evidence that clinical insight is correlated with neurocognitive ability and with gray matter volumes(Shad, Tamminga, et al., 2006), we also investigated whether correlations would appear with neurocognitive performance and HC volumes. Our prior study detected no substantial influence of verbal memory on clinical insight; thus we expected no significant impact of verbal memory or HC volume on clinical insight in FEP.

6.3 Methods

Participants

All participants (N = 61) were part of a longitudinal naturalistic outcome study of FEP (FEP) treated in a specialised early intervention service, the Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), Douglas Hospital in Montreal, Canada. FEP participants were diagnosed based on a Structured Clinical Interview for DSM-IV(First, et al., 1998), conducted by a trained interviewer and confirmed through a consensus meeting attended by at least two senior research psychiatrists (R.J. and A. M.). Duration of untreated psychosis (DUP) was calculated as part of the initial assessment as the time between onset of psychotic symptoms to the time of adequate treatment with antipsychotics(A. Malla, et al., 2006). The research assistants and graduate students who perform symptom ratings using the PANSS have established an intra-class correlation coefficient (ICC) = 0.75. The SUMD is administered by the same research assistants and graduate students who administer the PANSS. Although inter-rater reliability data for the SUMD is not available, our raters receive extensive training and supervision with reliability measured at least once a year for the PANSS. Inter-rater reliability for the PANSS insight item (G12) was found to be high (ICC = 0.79). Inter-rater reliability for

estimating DUP independently by two raters was conducted on 12 randomly selected cases and was found to be high (ICC = 0.81 – 0.98).

The type and dosage of antipsychotic taken at each clinical assessment were recorded, and converted to a standard chlorpromazine equivalent (see Table 1). At the time of testing, patients were receiving mostly (n = 54) novel antipsychotic medications. One patient was receiving typical antipsychotic medication and six were unmedicated. Medication adherence was based on a 5-point scale ranging from 0 (never) to 4 (fully compliant) (A. Malla, et al., 2006). Patients were asked how often they missed a dose over the past month and adherence was calculated as a percent of prescribed doses taken. Similar methodology was employed by clinical staff and adherence recorded as a percentage in clinical notes. Correlational analyses among scores based on information obtained from patients and clinical notes, and a more objective measure of pill counting, available for a subset of the sample were found to be high (Cassidy, et al., 2008). In addition to pharmacotherapy, case managers provide individualized supportive psychotherapy and education to individuals with an aim to increase awareness (i.e. insight) of the nature of their symptoms. Demographic and clinical descriptions of the sample are reported in Table 6.1.

MR scans were acquired for 61 people with a FEP. All participants completed the BCIS scales, 54 provided completed SUMD and 59 completed neurocognitive assessments. In the current investigation, we report neurocognitive data for the same 50 participants as in our first study (Lepage, et al., 2008) plus an additional nine participants who were tested since the previous publication.

	FEP (N = 61)		
	M	SD	Range
Age at hospitalization	23.4	3.7	17.5 – 30.8
Education	11.8	2.6	7 – 18
PANSS positive total	12.1	5.2	7 – 28
PANSS negative total	13.5	4.8	7 – 30
DUP (days)	53.2	94.2	2 – 591
Calgary Depression Scale (total)	2.0	2.9	0 – 11
Hamilton Anxiety Scale (total)	3.6	3.6	0 – 14
BCIS			
Self-reflectiveness	13.3	4.0	3 – 22
Self-certainty	8.3	3.2	2 – 18
Composite index	5.0	5.7	-11 – 19
SUMD			
awareness of mental disorder	2.4	1.4	1 – 5
Awareness of Response to Medication	2.1	1.4	1 – 5
Awareness of Need for Treatment	2.5	1.5	1 – 5
Medication adherence	3.1	1.4	0 – 4
Antipsychotic (dose (mg))	235.9	277.7	0 – 1250.0
	N	%	
Gender (M:F)	43:18	70:30	
Diagnostic category			
Schizophrenia	37	60.7	
Schizoaffective disorder	9	14.8	
Schizophreniform disorder	1	1.6	
Psychosis not otherwise specified	7	11.5	
Delusional disorder	1	1.6	
Bipolar disorder	5	8.2	
Undetermined	1	1.6	

Table 6.1: Demographic and clinical characteristics of the sample. Medication adherence: 0 (never taken) to 4 (always taken). Antipsychotic medication reported as chlorpromazine equivalent dosage in mg. Six patients were unmedicated.

Cognitive insight was assessed with the Beck Cognitive Insight Scale (BCIS) (Beck, et al., 2004), a 15-item self-report inventory. Self-reflectiveness (ability to reflect on previous experiences), self-certainty (overconfidence), and composite index (self-reflectiveness – self-certainty) scores were computed. Each question is rated on a 4-point scale from 0 (do not agree at all) to 3 (agree completely). Clinical insight was quantified with an abbreviated version of the SUMD (X. F. Amador, et al., 1994). We limited our exploration of the SUMD to item 1, awareness of mental disorder, but for completeness we report descriptive data for the first three items (see Table 1). Items are rated on a five point scale from 1 (aware) to 5 (unaware). Psychotic symptom severity was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay, et al., 1987), depression with the Calgary Depression Scale (Addington, et al., 1990), and anxiety with the Hamilton Anxiety Scale (J. Riskind, et al., 1987).

Neurocognitive assessment

Neurocognitive assessments were incomplete for some of the participants as they either refused or were unable to complete some of the tasks. FEP individuals were assessed within an average of 11.3 weeks (*SD* = 15.2) after treatment initiation and only when in a stable though not necessarily asymptomatic condition.

Cognitive ability was examined by separating various neuropsychological tests into seven cognitive domains as suggested by the NIMH-Measurement and Treatment Research to Improve Cognition in Schizophrenia group (MATRICS, 2003; Nuechterlein et al., 2004). Verbal learning and memory was derived from the Logical Memory (Brinkenkamp & Zillmer) subtests of the Wechsler Memory Scale - Third Edition (WMS-III) (Wechsler, 1997). Other domains were visual learning and memory, working memory, speed of processing, reasoning/problem solving, attention, and social cognition. The neuropsychological tests that comprise these domains are and listed in Table 6.2 and described in detail elsewhere (Bodnar, Malla, Joober, & Lepage, 2008).

	M	SD	Range
Verbal learning and memory			
Logical Memory I Immediate Recall	34.8	10.9	10 – 60
Logical Memory II Delay Recall	20.5	8.2	4 – 39
Logical Memory II Recognition	25.0	2.9	17 – 30
Visual learning and memory			
Visual Reproduction I Immediate Recall	89.2	13.3	37 – 104
Visual Reproduction II Delay Recall	72.2	20.5	14 – 104
Visual Reproduction II Recognition	44.9	2.8	36 – 48
Working memory			
Digit Span Forward	9.5	2.2	4 – 14
Digit Span Backward	6.2	2.4	2 – 12
Spatial Span Forward	8.5	2.2	4 – 14
Spatial Span Backward	7.6	2.1	2 – 13
Speed of processing			
Trail A	35.6	10.4	19 – 61
Digit Symbol	62.7	15.0	38 – 107
Reasoning and problem solving			
Trail B	77.4	32.2	34 – 228
Block Design	44.2	11.6	21 – 64
Tower of London: Number of Movements [a]	8.8	2.9	5 – 17
Attention			
D2 Test of Attention	147.6	43.8	61 – 279
Social cognition			
4 Factor Tests of Social Intelligence	31.1	7.6	12 – 46
Hinting Task	15.5	2.9	8 – 20

Table 6.2: Neurocognitive performance of the sample. [a] The mean and SD exclude the results of the 3-movement subtest.

MRI acquisition

Structural magnetic resonance data were acquired at the Montreal Neurological Institute (MNI) on a 1.5 Tesla Siemens Sonata whole body system magnetic resonance imaging (MRI) scanner outfitted with a standard head coil (Siemens, Germany). Participants' heads were stabilized by a vacuum cushion. High-resolution T1-weighted anatomical MR images were acquired from each participant using the standard MNI structural acquisition protocol. Contiguous sagittal slices perpendicular to the anterior-posterior commissure line, with 1mm slice thickness, were acquired using a gradient echo pulse sequence (TR = 22ms, TE = 9.2ms, flip angle = 30º, voxel size 1 x 1 x 1 mm^3). MR images were transferred to an external workstation for image processing.

Manual segmentation of the hippocampus

Prior to manual HC segmentation, the following preprocessing steps were performed: non-uniformity correction, registration into standard stereotaxic space, and signal intensity normalization. Volumetric analyses were performed with the interactive software package DISPLAY developed at the Brain Imaging Center of the MNI. HC volumes were calculated automatically by the software. Manual tracing of the HC was performed using a validated protocol (Pruessner et al., 2000), and manual segmentation into HC body, head and tail regions was performed according to an updated protocol by the same author (2006, unpublished) (Figure 6.1). Measurements were performed by a trained rater (Y.C.) who was blind to clinical information. To assess intra-rater reliability of the obtained volumes, volumetric measurements of the HC were performed twice for 10 participants, and was found to be high (left HC, ICC = 0.98, right HC, ICC = 0.99). Inter-rater reliability for estimating HC volumes independently by one rater (C.C.) was conducted on five randomly selected cases and was found to be high (left HC, ICC = 0.98; right HC, ICC = 0.98).

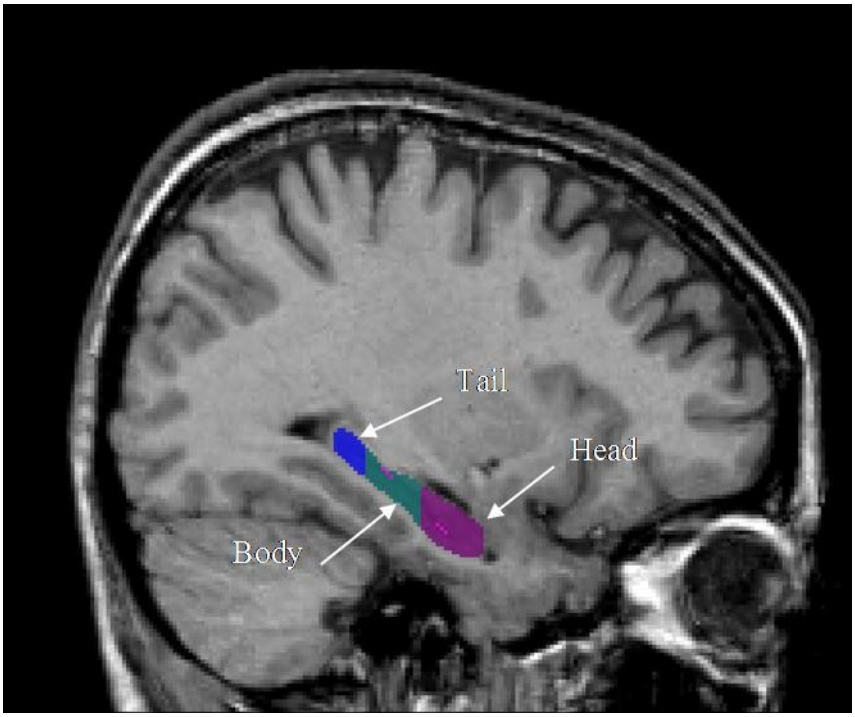

Figure 6.1: Saggital section of the brain and delineation of the hippocampus into body, head and tail subregions.

Procedure

Clinical interviews and the neuropsychological assessment were administered by a trained professional who was not involved with the patient's treatment. The BCIS and SUMD/PANSS were performed within three weeks of each other (M = 20.6 days, SD = 51.4). The MRI scan was performed within two weeks of the insight assessments (BCIS, M = 11.3 days, SD = 25.2; SUMD/PANSS, 7.3 days, SD = 61.4). The neurocognitive assessment was administered within 57.0 days (SD = 120.6) of the SUMD/PANSS interviews and within 78.4 days (SD = 125.1) of the BCIS interviews. The difference between these latter assessment dates was significant, $t(52) = 2.60$, $p = 0.01$. Owing to the stability of neurocognitive functions in FEP (Albus et al., 2002; S. Gold, Arndt, Nopoulos, O'Leary, & Andreasen, 1999; Hoff et al., 1999) it is unlikely that this difference was of direct significance for the primary purpose of this study. Moreover,

virtually all individuals were tested at least 3 months after admission to PEPP and were clinically relatively stable at the time of insight evaluation.

After a comprehensive description of the study, written informed consent was obtained from all participants. Research protocols were approved by the Douglas Hospital human ethics review board.

Statistical analyses

Pearson's correlations were used to evaluate associations between HC volumes and cognitive and clinical insight scores. The critical *p*-value was set at 0.05 for analyses of total left and right HC volumes. When considering HC head, body and tail volumes the critical *p*-value was set at 0.02 following Bonferroni correction. Calculations of the seven cognitive domains are described elsewhere (Lepage, et al., 2008). All statistical tests were two-tailed and performed using SPSS version 16.0 (SPSS, 2007).

6.4 Results

Relations between cognitive and clinical insight and verbal memory

Table 2 presents the mean performance of the tests or subtests used in each of the different neurocognitive domains. The global measure of verbal learning and memory was significantly correlated with the BCIS composite index, $r(57) = 0.33$, $p = 0.01$ and with the BCIS self-reflectiveness subscale, $r(58) = 0.31$, $p = 0.02$. No significant correlations emerged for self-certainty or awareness of mental disorder scores, $r(57) = -0.22$, $p = 0.10$; $r(52) = -0.11$, $p = 0.45$, respectively. The only other modestly significant correlation between any of the insight variables and the cognitive domains was between the global measure of social cognition and the BCIS composite index, $r(50) = 0.28$, $p = 0.05$.

Relations between cognitive and clinical insight and hippocampal volumes

Mean and standard deviations, minimum and maximum HC volumes are shown in Table 6.3. HC volumes for our FEP participants appear to be bigger than those reported in studies of HC volumes in FEP (Steen, et al., 2006). However, these studies have employed a variety of different methods for calculating HC volumes than the current manual tracing technique. Differences in anatomical boundaries across protocols need to be taken in to account and this hinders the comparison of results. Notably, the current protocol has been shown to allow a more precise definition of the HC (Pruessner, et al., 2000).

	M	SD	Minimum	Maximum
Right hippocampus				
Total	4208.6	417.3	3303	5370
Head	2207.6	338.6	1396	2881
Body	1257.1	238.7	623	1998
Tail	743.8	163.2	392	1245
Left hippocampus				
Total	4106.5	368.3	3296	5017
Head	2029.0	346.6	1292	2841
Body	1337.0	220.8	797	1929
Tail	740.4	197.9	295	1194

Table 6.3: Mean and standard deviations, minimum and maximum volumes for the right and left hippocampus in 61 people with FEP. All values are in mm^3.

a) Self-reflectiveness. The analyses revealed no significant correlations between self-reflectiveness scores and HC volume in either hemisphere (left HC, $r(59) = 0.11$, $p = 0.40$, right HC, $r(59) = 0.07$, $p = 0.61$). An examination of the subdivisions of the HC revealed no significant effects (left HC, head, $r(59) = 0.18$, $p = 0.16$, body, $r(59) = -0.11$, $p = 0.42$, tail, $r(59) = 0.01$, $p = 0.97$; right HC, head, $r(59) = 0.12$, $p = 0.37$, body, $r(59) = -0.18$, $p = 0.17$, tail, $r(59) = 0.18$, $p = 0.16$).

b) Self-certainty. Negative correlations revealed that FEP individuals with smaller HC volumes had higher self-certainty scores (left HC, $r(59) = -0.34$, $p < 0.01$, right HC, $r(59) = -0.29$, $p = 0.02$) (see Figure 2). When the subdivisions of the HC were examined, no regional specificity of this effect was observed (left HC, head, $r(59) = -0.16$, $p = 0.22$, body, $r(59) = -0.14$, $p = 0.30$, tail, $r(59) = -0.19$, $p = 0.14$; right HC, head, $r(59)=-0.17$, $p = 0.19$, body, $r(59) = -0.12$, $p = 0.38$, tail, $r(59) = -0.24$, $p = 0.07$).

c) Composite index. The analysis revealed a significant correlation such that individuals with a FEP with higher composite index scores showed greater HC volume in the left hemisphere, $r(59) = 0.25$, $p = 0.05$ (see Figure 2). No significant effect emerged for the right hemisphere, $r(59) = 0.21$, $p = 0.11$. Examination of the subdivisions of the HC revealed a positive correlation between composite index scores and right HC tail volume, $r(59) = 0.29$, $p = 0.03$; however, this became non-significant following a Bonferroni correction. No other effects emerged (left HC, head, $r(59) = 0.21$, $p = 0.11$, body, $r(59) = -0.02$, $p = 0.91$, tail, $r(59) = 0.12$, $p = 0.35$; right HC, head, $r(59) = 0.18$, $p = 0.17$, body, $r(59) = -0.09$, $p = 0.51$).

d) Awareness of mental disorder. The analyses revealed no significant correlations between awareness of mental disorder scores and HC volume in either hemisphere (left HC, $r(52) = -0.08$, $p = 0.58$; right HC, $r(52) = -0.11$, $p = 0.43$) or with subdivisions of the HC (left HC, head, $r(52) = 0.00$, $p = 0.98$, body, $r(52) = -0.15$, $p = 0.30$, tail, $r(52) = 0.02$, $p = 0.92$; right HC, head, $r(52) = -0.05$, $p = 0.71$, body, $r(52) = -0.19$, $p = 0.14$, tail, $r(52) = 0.09$, $p= 0.50$).

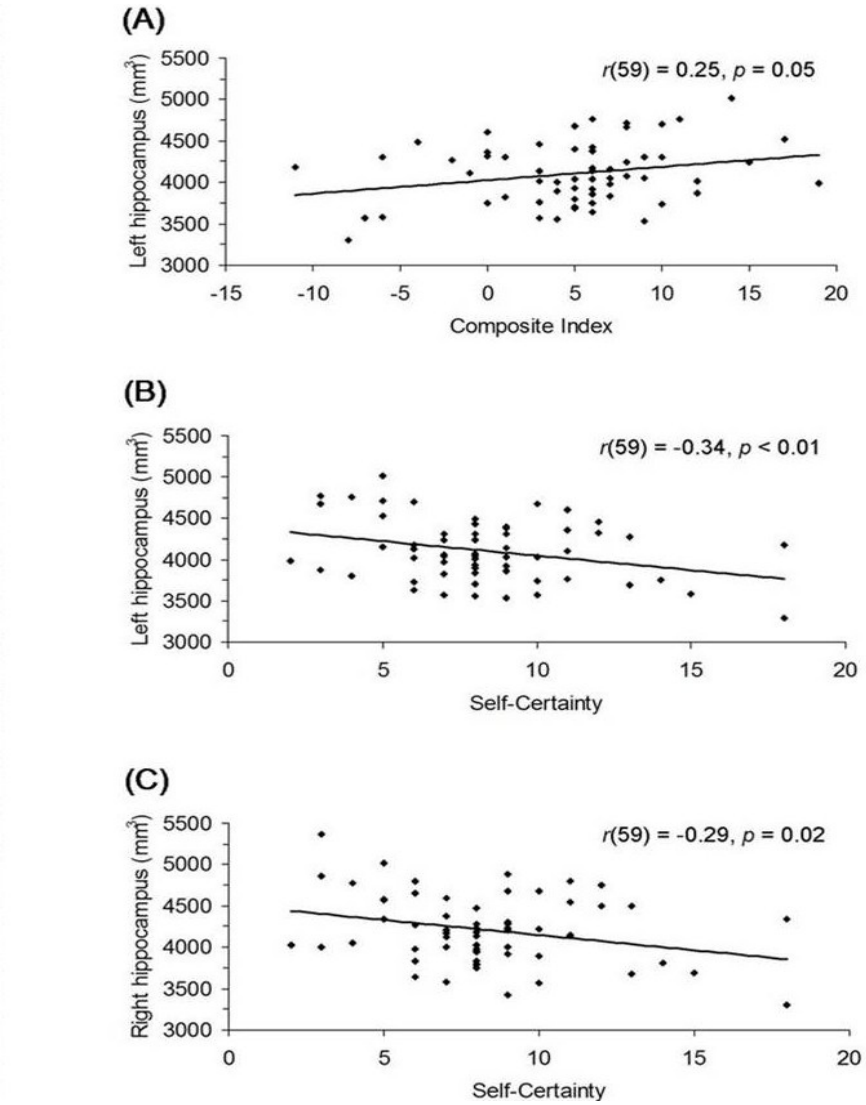

Figure 6.2: Significant correlations between BCIS scores and hippocampal volume in FEP patients. (A) Correlations of composite index scores and hippocampal volume in the left hemisphere. (B and C) Correlations of self-certainty scores and hippocampal volume in left and right hemispheres.

e) Complementary analyses. Against the background of severe problems with verbal memory (Aleman, et al., 2006; Heinrichs & Zakzanis, 1998) and reduced HC volumes in individuals with schizophrenia (Steen, et al., 2006), and in view of the association

between verbal memory and cognitive insight in FEP (Lepage, et al., 2008), we directly tested the specificity of the HC to cognitive insight when controlling statistically for verbal memory performance.

First, we followed up on the significant correlation between the BCIS composite index and left HC volume. Partial correlations were computed between composite index scores and left HC volume, with verbal memory performance as a covariate. The result became a non-significant trend, $r(56) = 0.25$, $p = 0.06$. Second, we followed up on the significant correlations between BCIS self-certainty and HC volumes. Partial correlations performed between self-certainty scores and both left and right HC volumes, with verbal memory as a covariate, did not change interpretation of results (left HC, $r(55) = -0.32$, $p = 0.01$; right HC, $r(55) = -0.27$, $p = 0.04$).

The impact of positive symptomatology as a possible mediating variable was also explored. Entering PANSS positive scale scores as a second covariate in all abovementioned analyses did not affect interpretation of results, with the exception of the following: left HC volume re-emerged as a significant correlate of composite index scores, $r(56) = 0.28$, $p = 0.04$.

When correlating the verbal memory scores with HC volumes, no significant correlations were observed in either hemisphere (left HC, $r(57) = 0.02$, $p = 0.86$; right HC, $r(57) = 0.09$, $p = 0.50$ nor with the subdivisions of the HC (left HC, head, $r(57) = 0.00$, $p = 0.99$, body, $r(57) = -0.01$, $p = 0.94$, tail, $r(57) = 0.06$, $p = 0.67$; right HC, head, $r(57) = 0.15$, $p = 0.27$, body, $r(57) = -0.15$, $p = 0.26$, tail, $r(57) = 0.15$, $p = 0.27$). PANSS positive scale score did not correlate with verbal memory, $r(56) = -0.15$, $p = 0.27$, or any index of HC volume, $rs(59) = -0.02–0.23$, $ps > 0.49$.

6.5 Discussion

To our knowledge, this is the first demonstration that in individuals with a first episode of psychosis cognitive insight is associated with HC volume. Most importantly, our volumetric analysis revealed that greater self-certainty correlated with diminished bilateral HC volumes and this relationship was independent of verbal memory performance. Self-reflectiveness correlated with verbal memory but not with HC volume. Further, higher BCIS composite index scores were associated with greater volume of the left HC. A modest proportion of this relationship was attributable to verbal memory performance. When considering clinical insight, no correlations were observed between awareness of mental disorder scores and verbal memory or HC volumes. The results strengthen the claim that the neurocognitive system involved in verbal memory is important for cognitive insight, but perhaps not for clinical insight, in individuals with a FEP. The hippocampus may be a viable location among others for the brain system which underlies aspects of cognitive insight in individuals with a FEP.

The current analysis revealed that higher self-reflectiveness was associated with better verbal memory performance. This result was not seen in our previous work (r = 0.22 for self-reflectiveness and verbal memory in our initial published study) (Lepage, et al., 2008), and presumably the larger sample size yielded increased statistical power to detect this effect. A possible explanation of this finding is that in individuals with a FEP poor verbal memory ability precludes accurate reflection on the mental episodes of previous experiences (Lepage, et al., 2008), possibly through impaired discrimination of valid from invalid information in memory (Moritz & Woodward, 2002). Consequentially, aberrant memory information is used to guide current beliefs and judgments. A related possibility is that self-reflectiveness is achieved through recognition that memories are internally generated (Gibbs & David, 2003). It has been recognized that for 4 of 9 items on the Self-reflectiveness subscale reflection on past life experiences is required, for example, *Some of my experiences that have seemed very real may have been due to my imagination,* and *I have jumped to conclusions too fast*. At a conceptual level it may be that in individuals with a FEP distorted memory for specific experiences may influence everyday judgments.

This may occur by compromising the capacity to consider alternative explanations, acknowledge others' superior objectivity, and by promoting belief inflexibility (the remaining 5 self-reflectiveness items address these biases). Replication is needed to strengthen this hypothesis.

The neural substrates underlying self-reflectiveness do not appear to include the HC in FEP. As mentioned above, we propose that self-reflectiveness relies on discrimination of accurate from inaccurate information in memory, and that information in memory, irrespective of its validity, is used to guide current beliefs and judgments. These cognitive functions clearly draw on episodic memory, for which the hippocampus is thought to play a major role (Scoville & Milner, 1957; Squire, 1992). This interpretation would suggest an association between HC volume and self-reflectiveness; however, this finding did not emerge in the current FEP sample. One explanation of the negative results may be the non-significant correlation between verbal memory and HC volumes; that is to say, our verbal memory task was not sensitive to hippocampal integrity. Alternatively, other neural regions beyond the HC may mediate the association between verbal memory performance and self-reflection. Regions in the prefrontal cortex (PFC) are thought to play a role in episodic memory processes, for example, the ventrolateral PFC supporting memory of items (Badre & Wagner, 2007) and the dorsolateral PFC facilitating relational processing between items (Blumenfeld & Ranganath, 2007). This may place the involvement of PFC as a candidate mechanism for self-reflectiveness. Another factor is that, relative to healthy participants, patients with schizophrenia often show decreased hippocampal recruitment during episodic memory performance (Achim et al., 2007; Achim & Lepage, 2005). The absence of an expected triangulated relationship between self-reflectiveness, HC volume and verbal memory may have been due in part to this factor. The precise role of the HC for self-reflectiveness in normal cognition (i.e., in healthy participants) compared with participants with a FEP merits investigation.

Although in our initial study poorer verbal memory was associated with self-certainty (Lepage, et al., 2008), in the current work this relationship was non-significant. The significant result in our previous study may be attributable to the sensitivity of the verbal memory effect to a smaller sample size. Furthermore, all 6 items on the self-certainty

subscale appraise current judgments (Warman, et al., 2007), supporting conceptually the negative result in the current study. One plausible explanation is related to the fact that 3 of 6 Self-certainty items require comparison of one's own beliefs and judgments to those of another individual *(I know better than anyone else what my problems are; When people disagree with me, they are generally wrong; and I cannot trust other people's opinion about my experiences)*. In this regard, it may be that the cognitive system involving source memory (Bentall, Baker, & Havers, 1991; M. K. Johnson, Hashtroudi, & Lindsay, 1993), and in particular the ability to distinguish self-generated from externally perceived information (reality monitoring) or imagined versus actual events (internal source monitoring) in memory, may be important for understanding self-certainty. This hypothesis is an extension of Moritz et al.'s (2003) observation that individuals with schizophrenia hold false source attributions in high conviction, relative to healthy individuals. It can also be noticed that the self-certainty subscale taps overconfidence in the context of everyday social interactions. This leads to a proposal that source misattributions for an incident involving a personal problem or a disagreement (the scale includes items that directly address both of these) may form the basis for increased confidence in one's current judgments. To illustrate, consider a disagreement in which a person attributes self-generated information (e.g., I think that she is at fault) as external (She admitted that she was at fault) (Bentall, et al., 1991; Woodward, Menon, Hu, & Keefe, 2006), thus demonstrating fallible source memory. In subsequent disagreements this person will likely show higher confidence that others are wrong, than a person who has reliable source memory. Exploration of the relationship of source monitoring to self-certainty may be of interest for future studies.

Bilateral HC volume reductions were associated with increased self-certainty – independent of memory performance – in our FEP sample. The observation that cognitive insight is associated with HC volumes in individuals experiencing a FEP suggests this association is not an artifact of illness chronicity or lengthy psychotropic medication use. Reduced volume of the HC could reflect disturbances in neuronal cell count, distribution or size, or failed adult hippocampal neurogenesis (Kempermann, Krebs, & Fabel, 2008). One interpretation is that larger HC volumes may be a protective factor for appropriate confidence levels. A related suggestion is that the HC may form part of a neural circuit

whose dysfunction manifests as overconfidence in individuals with psychosis. Our postulate that self-certainty engages source memory processes is congruent with previous findings that the HC, along with distributed neural networks, contributes to (1) successful avoidance of source misattributions (Ross & Slotnick, 2008), (2) source memory for spatial contextual information (Ross & Slotnick, 2008), (3) source recollection for an item's contextual details (Davachi, Mitchell, & Wagner, 2003; Dougal, Phelps, & Davachi, 2007), (4) later ability to distinguish the task performed on an item during encoding (Kensinger & Schacter, 2006) and (5) hearing another person's voice when expecting to hear one's own voice (Fu et al., 2006). We propose that the decreased HC volumes seen in this study in relation to overconfidence is related to inadequate monitoring of self- versus other-generated information (reality monitoring) and/or imagined versus actual events (internal source monitoring) in memory. That is, engaging false memory information to direct current thinking may bias individuals to hold their own beliefs and judgments in high confidence via the HC. This hypothesis deserves further investigation.

It should be noted that overconfidence may relate to other hippocampal-mediated cognitive functions such as working and/or spatial memory. This hypothesis, however, was not supported, given the absence of a correlation between self-certainty and our working memory domain (which incorporated a spatial memory task). Moreover, it is possible that overconfidence relates to symptoms of psychosis via the HC. In line with Warman et al.'s (2007) suggestion that self-certainty applies preferentially to delusions, structural abnormalities in the HC (Degreef et al., 1992) and pathology in its connectivity (Prasad, Patel, Muddasani, Sweeney, & Keshavan, 2004; Prasad, Rohm, & Keshavan, 2004), as well as global medial temporal lobe dysfunction (Liddle et al., 1992) have been associated with delusions.

In agreement with our forerunner investigation (Lepage, et al., 2008), the BCIS composite index correlated with verbal memory, suggesting that, as we previously hypothesized, in individuals with a FEP enhanced cognitive insight may depend on an ability to retrieve past memories. At a conceptual level, it is possible that individuals scoring at antipodal extremes on the composite index may display different cognitive profiles. For example,

the presence of low composite index scores, reflecting low self-reflectiveness (poor memory accuracy) and concurrent high self-certainty (inappropriate confidence), may relate to *knowledge corruption* typically observed in individuals with schizophrenia (Moritz & Woodward, 2002, 2006), whereby false judgments are held with strong conviction.

Composite index scores and left HC volume were positively correlated in our FEP sample. This association remained significant when variance due to verbal memory and positive symptom severity was subtracted out. When proposing a neural system for global cognitive insight as indexed by the composite index, it is important to emphasize that composite index scores reflect the synthesis of self-reflectiveness and self-certainty scores. An apposite explanation would be that the brain system that underlies global cognitive insight reflects those that underpin its individual components (self-reflectiveness and self-certainty). The present neurological view of cognitive insight traces hyper-confidence at least in part to HC pathology and posits an empirically testable role for the PFC in self-reflectiveness. It should be highlighted that the composite index and self-certainty, but not self-reflectiveness, correlated with HC volumes, raising the possibility that overconfidence is driving the left HC result for the global cognitive insight measure. A related point is that self-certainty may capture more of a deficit-like "trait" process that is detectable as a structural brain change. On the other hand, the neural system of self-reflectiveness may be better captured in a more fluid process such as Positron Emission Tomography or other physiologically-based imaging procedures (S. C. Johnson et al., 2002). The functional basis of cognitive insight remains to be explored.

The lack of significant correlation between awareness of mental disorder scores and HC volume is in agreement with the only other study that has examined this relationship in schizophrenia (Shad, et al., 2004). The negative finding is strengthened by the non-significant correlation between awareness of mental disorder scores and verbal memory, a hippocampal mediated cognitive measure (Scoville & Milner, 1957). This set of results may support the view that clinical insight impairments relate to dysfunction of PFC regions (Flashman, et al., 2001; Lee, et al., 2006; Sapara, et al., 2007; Shad, Muddasani, et al., 2006; Shad, et al., 2004). In line with this argument, there is consistent evidence

linking clinical insight to prefrontally-mediated cognitive tasks such as the Wisconsin Card Sorting Task (Aleman, et al., 2006; Shad, Tamminga, et al., 2006). Other recent data suggest a role for the parietal and temporal cortices in clinical insight in schizophrenia (Cooke, et al., 2008). Alternatively, the patient's unwillingness to admit their mental disorder may be contingent on psychological characteristics. Evidence for this suggestion comes from the observations that poor insight in schizophrenia is associated with a tendency to give self-reports that are honest but positively biased (Moore, Cassidy, Carr, & O'Callaghan, 1999), present oneself in a socially desirable manner (Subotnik et al., 2005), and attribute negative events to an external source (Langdon, Corner, McLaren, Ward, & Coltheart, 2006).

One issue when interpreting the behavioural results of this study is that we did not apply a correction for multiple comparisons to our statistical threshold. However, we did calculate global measures for each of the seven neurocognitive domains which afforded a better construct validity. Secondly, we did not include a healthy comparison group. Future research needs to explore the role of verbal memory and HC volumes for cognitive insight in normal cognition to understand how this system becomes dysfunctional in psychosis. Third, it should be noted that the neurocognitive evaluation and the BCIS interviews were conducted on different test dates (average 78.4 days). Further study is necessary to evaluate other areas of the neural network that supports cognitive insight, such as prefrontal, temporal and parietal cortical regions, to shed light on some of the hypotheses made above and to strengthen the current model.

The results strengthen our account holding that the cognitive processes underlying verbal memory are compatible with those involved in cognitive insight. Our data suggest that hippocampal pathology may adversely affect certainty judgments. These data place cognitive insight among other metacognitive problems observed in individuals with psychosis, including *knowledge corruption* (Moritz, et al., 2003). It remains to be explored whether poorer cognitive insight occurs in conjunction with this metacognitive problem in FEP individuals. Examination of the cognitive insight-metacognition link at both the behavioural and neural levels will be important for cognitive insight modeling.

* * *

CHAPTER 7

SELF-CERTAINTY IN FEP: RELATIONSHIP TO MICROSTRUCTURAL WHITE MATTER INTEGRITY OF THE FORNIX

Preface

The previous cognitive insight study demonstrated hippocampal structural pathology in FEP patients displaying high self-certainty. Given in psychosis self-certainty has been negatively correlated with verbal memory, (Lepage, et al., 2008; Orfei, Spoletini, Banfi, Caltagirone, & Spalletta, 2010), a fronto-hippocampal task, and executive cognitive functions including set switching (Orfei, et al., 2010) and strategy formation (Cooke et al., 2010), associated with frontal-lobe functioning, abnormal connectivity between these brain regions may be expected in patients with high self-certainty.

In this project, we explore the relation between microstructural organization of the fornix, the main white matter pathway connecting the hippocampus with other brain regions, and self-certainty in FEP. DTI followed by fornix tractography was performed on high-resolution structural MRI scans. DTI enables the examination of white matter fiber tracts interconnecting gray matter regions of the brain *in vivo*, and DTI tractography assembles local diffusion tensor data to infer the paths of fiber tracts. With DTI technique we tested the hypothesis that disturbed fornix connectivity would be correlated with high self-certainty in our FEP sample.

7.1 Abstract

Previous studies have demonstrated that patients with psychosis are more confident in beliefs and judgments compared to healthy participants and psychiatric controls with major depression. A recent study conducted by our research group has provided evidence for hippocampal pathology in association with overconfidence in a first episode psychosis (FEP) sample. The fornix is the primary efferent neural pathway of the hippocampus and may also play a role in self-certainty pathophysiology. The current investigation applied diffusion tensor imaging tractography to a FEP sample to explore whether integrity of the fornix is associated with self-certainty. High resolution structural magnetic resonance and diffusion tensor images were obtained in 44 people with a FEP. Diffusion tensor imaging tractography was used to estimate fractional anisotrophy (FA), a measure of white matter integrity, in the fornix. Confidence in beliefs and judgments was measured with the self-certainty subscale of the Beck Cognitive Insight Scale (BCIS). The analysis showed that self-certainty significantly correlated to FA values in the right fornix but was nonsignificant for the left fornix. The findings indicate anatomical dysconnectivity of the right fornix in correlation with BCIS-rated self-certainty in our FEP sample. When considered with our previously published self-certainty–hippocampus result in a FEP sample, overlapping with that of this study, the results indicate a concurrence of volumetric reductions in hippocampus and fornix pathology in correlation with self-certainty.

7.2 Introduction

A plethora of studies has demonstrated biases in reasoning and cognitive distortions in people with schizophrenia (Garety et al., 2005). For example, it has repeatedly been shown that schizophrenia patients show an enhanced need for closure (Colbert et al., 2006), jump to conclusions (Garety, 1991) and attribute failure to others (Fornells-Ambrojo and Garety, 2009). Recently, the Beck Cognitive Insight Scale (BCIS) has proven to be helpful in our understanding of reasoning processes and cognitive distortions in psychosis (Beck, et al., 2004; Riggs, Grant, Perivoliotis, & Beck, 2010). In the BCIS, participants rate how much they agree with statements tapping two dimensions of cognitive insight: self-reflectiveness and self-certainty. Self-reflectiveness captures the willingness to acknowledge fallibility, corrigibility and recognition of dysfunctional reasoning, and self-certainty refers to overconfidence in beliefs and judgments. Relative to healthy people and patients with major depression, individuals with psychotic disorders endorse significantly lower self-reflectiveness and higher self-certainty (Beck, et al., 2004; Martin, Warman, & Lysaker, 2010), suggesting these reasoning styles may play an important role in psychosis.

There is now evidence to suggest a relationship between cognitive insight in psychosis and neurocognitive deficits of hippocampal and frontally mediated functions. Several investigators have found self-certainty to be negatively correlated with performance on verbal memory, (Lepage, et al., 2008; Orfei, et al., 2010), a fronto-hippocampal task, and executive cognitive functions including cognitive set switching (Orfei, et al., 2010) and strategy formation (Cooke, et al., 2010), associated with frontal-lobe functioning. In an earlier study we have also reported a positive association between self-reflectiveness and verbal memory performance (Buchy et al., 2009). In order to address the question whether cognitive insight and memory and/or executive functions share qualitatively similar neural networks, we examined inter-relationships between self-certainty, verbal memory and hippocampal morphology in a FEP sample (Buchy, Czechowska, et al., 2009). Our results showed that participants who endorsed higher BCIS domain of self-certainty had smaller bilateral hippocampal volumes than individuals who scored lower

on self-certainty, independent of the effect of verbal memory, suggesting a selective contribution of hippocampal structure to self-certainty. In contrast, the data suggested no association of hippocampal structure with self-reflectivity. Taken together, the current literature suggests an involvement of hippocampus and frontal cortex in the basic neuropathology of self-certainty in psychosis. Therefore, abnormal connectivity between these regions can be expected in patients with psychotic disorders.

It is unknown whether functional and/or structural disruptions of the hippocampus and frontal cortex observed in patients with high self-certainty may indicate underlying structural dysconnectivities. The fornix is the main white matter pathway connecting the hippocampus with other brain regions. It projects to medial prefrontal cortex and septal areas, as well as to the mamillary bodies and nucleus accumbens. Fornix integrity is known to be correlated with hippocampal volumes (Kuroki et al., 2006; Zahajszky et al., 2001) and is believed to play a role in verbal memory in both healthy individuals and those with schizophrenia (Fitzsimmons et al., 2009; Gaffan, 2005; McMackin, Cockburn, Anslow, & Gaffan, 1995). Of further note, white matter tracts interconnecting frontal and temporal cortices have long been implicated in the pathogenesis of schizophrenia (Ellison-Wright & Bullmore, 2009). A fiber abnormality could potentially increase the vulnerability of aberrant reasoning styles, or could be marking a concomitant secondary effect from psychosis. In either case, such finding would suggest a circuit-based biomarker for self-certainty in psychosis.

In the present study we explore the relation between fornix connectional architecture and self-certainty in a first episode psychosis (FEP) sample. In particular, diffusion tensor imaging (DTI) followed by fornix tractography was performed on high-resolution structural magnetic resonance imaging (MRI) scans. DTI enables the examination of white matter fiber tracts interconnecting gray matter regions of the brain, while DTI tractography assembles local diffusion tensor data to infer the paths of fiber tracts. White matter integrity was quantified using fractional anisotropy (FA) values, which provide information about microstructural organization of white matter, incorporating information on fiber structure and fiber orientation. With DTI technique we tested the hypothesis that

disturbed fornix connectivity would be correlated with high Self-certainty in our FEP sample.

7.3 Methods

Participants

Participants were part of a longitudinal naturalistic outcome study of FEP treated in a specialised early intervention service, the Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), Douglas Institute in Montreal, Canada. The program involves a comprehensive approach with intensive medical and psychosocial interventions provided within the context of a modified assertive case management program. Individuals aged 14-35 years from the local catchment area suffering from either affective or non-affective psychosis who have not taken antipsychotic medication for more than one month were consecutively admitted as either in- or out-patients.

MR scans were acquired for 44 individuals with a FEP as part of a larger study on cognitive and neuroimaging predictors of outcome. Inclusion criteria were those set by PEPP with additional restrictions of ages 18-30, clinically stable (patients were receiving active treatment during this period), no major medical disorders (based on medical history and physical examination) and able to provide informed consent. Exclusion criteria were lifetime history of neurologic condition including loss of consciousness that could affect cognition, family history of hereditary neurologic disorders, presence of neurological disorder and lifetime diagnosis of substance dependence.

Clinical assessment

Patient diagnoses were conducted at baseline based on the Structured Clinical Interview for DSM-IV (First, et al., 1998) and confirmed at 1-year through consensus between two

senior psychiatrists (A.M. and R.J.) when appropriate. Cognitive insight was assessed with the BCIS (Beck et al., 2004), a 15-item self-report inventory. Self-reflectiveness, self-certainty, and composite index (self-reflectiveness – self-certainty) scores were computed. Each question is rated on a 4-point scale from 0 (do not agree at all) to 3 (agree completely). Symptom severity was determined with the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984b), Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984a), Calgary Depression Scale (Addington, et al., 1990) and Hamilton Anxiety Scale (J. Riskind, et al., 1987) by research assistants who had received extensive training and achieved a high level of inter-rater reliability. Parental SES was estimated using the Hollingshead SES Rating Scale (D. C. Miller, 1991) and handedness with the Edinburgh Handedness Inventory (Oldfield, 1971). Participants provided informed consent and the Douglas Mental Health University Institute Human Ethics Review Board approved the study.

MRI and DTI acquisition

Scans were acquired at the Montreal Neurological Institute on a 1.5T Siemens Sonata whole body MRI system. Structural T1 volumes were acquired for each participant using a three-dimensional gradient echo pulse sequence with sagittal volume excitation (repetition time = 22ms, echo time = 9.2ms, flip angle = 30º, 180 1mm contiguous sagittal slices). The rectangular field of view for images was 256mm (SI) x 204mm (AP). Two successive whole-brain DTI images were acquired using a single-shot echo planar imaging sequence parallel to the anterior–posterior commissural plane. Diffusion sensitive gradients were applied in 60 non-collinear, non-coplanar directions (b=1000s/mm2), together with one acquisition with no diffusion weighting (b=0 s/mm^2). Each direction was scanned twice and then averaged to improve the signal-to-noise ratio. The acquisition parameters were as follows: TR = 9800 ms, TE = 102 ms, and image matrix 112 × 128. These parameters resulted in 2.2 × 2.2 × 2.2 mm^3 acquisition voxel dimensions.

Statistical analysis

a) Image processing. DTI data were pre-processed using MNI in-house software. FA maps were obtained as per the method described by Basser (1995). The fornix was reconstructed using Fiber Assistance by Continuous Tracking (FACT) method (Mori, Crain, Chacko, & van Zijl, 1999). Fornix tractography was performed by seeding voxels with an FA greater than 0.15 and a constraining angle lower than 45°.

b) Region of interest definition. Two regions of interest (ROI) were drawn on FA-weighted colour maps. ROI locations were adapted from Concha et al. (Concha, Gross, & Beaulieu, 2005) and the protocol has been published (Luck, Malla, Joober, & Lepage, 2010). The first ROI was placed on the most inferior axial slice in which the crus of fornix was visible. This portion was selected as the first ROI. The second ROI was placed on the coronal slice in which the cerebral peduncules were most visible. Fibers inferior to the corpus callosum were selected as the second ROI. ROI sizes ranged from 10 to 20 voxels. After positioning the two ROIs, an in-house implementation of the FACT algorithm was applied so that each fiber passing through the two ROIs of each tract was selected. Figure 7.1 illustrates trajectory of the fornix obtained using these ROIs.

c) Inter-rater and intra-rater reliabilities. For intra-rater reliability, a subset of five subjects pseudo-randomly selected was replicated three times by the investigator (D.L.). For inter-rater reliability, tractographies were performed by another rater (Y.C.) on the same subset. Inter-rater and intra-rater correlations reached 0.99 and 0.94 for the left fornix respectively, and 0.95 and 0.95 for the right fornix respectively.

d) Statistical Analyses. Pearson correlations were used to evaluate associations between fornix FA values and cognitive insight scores. Statistical tests were 2-tailed and performed using PASW Statistics version 18.0.

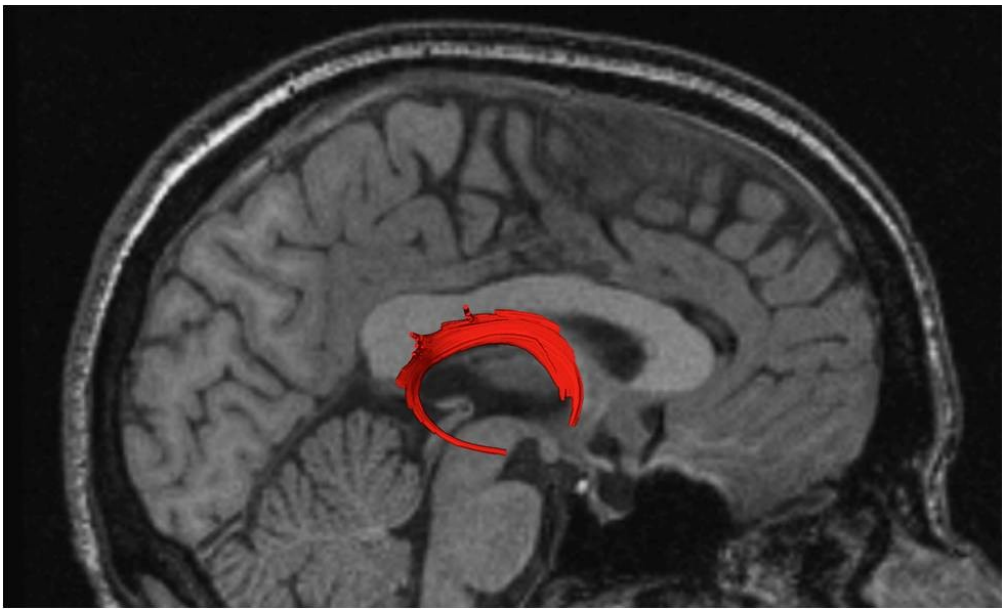

Figure 7.1: Representative image of the fornix

7.4 Results

Table 7.1 displays clinical and demographic characteristics of the sample as well as FA values of left and right fornices.

Figure 7.2 displays correlations between self-certainty scores and FA values of the left and right fornices. The analysis showed that Self-certainty was positively correlated to FA values in right fornix, r(43) = 0.32, p = 0.04. The correlation between self-certainty and left fornix FA values was nonsignificant, r(43) = 0.01, p = 0.96. No significant effects emerged between self-reflectiveness and FA values in fornix in either hemisphere, left, r(43) = -0.12, p = 0.44; right, r(43) = -0.26, p = 0.09. When considering the composite index, a negative correlation revealed that participants with higher scores had lower FA values in right fornix, r(43) = -0.38, p = 0.01. No significant effect emerged for the left hemisphere, r(43) = -0.10. p = 0.54.

	M	SD	Range
Age (years)	23.3	3.8	17.5 – 31
Education (years)	11.8	2.5	7 – 18
IQ[a]	94.8	14.7	72 – 128
Hollingshead Index score	3.8	0.77	2 – 5
Beck Cognitive Insight Scale Scores			
Self-certainty	8.6	3.4	3 – 26
Self-reflectiveness	13.5	4.5	3 – 26
Composite index	4.9	6.1	-11 – 19
SAPS total score	7.1	10.3	0 – 54
SANS total score	23.2	12.4	0 – 49
Duration of untreated psychosis (days)	53.2	100.1	2 – 591.2
Duration of untreated illness (days)	270.3	273.0	1 – 1101.6
Antipsychotic (dose, mg)[b]	310.9	405.4	25 – 1975
Fornix[c]			
Left	0.30	0.05	0.18 – 0.38
Right	0.41	0.04	0.24 – 0.41
	N	**%**	
Gender (M:F)	31:13	71:29	
Handedness			
Right	36	82	
Left	4	9	
Ambidextrous	4	9	
Diagnostic category			
Schizophrenia	27	61.4	
Schizoaffective disorder	6	13.6	
Schizophreniform disorder	1	2.3	
Psychosis not otherwise specified	7	15.9	
Bipolar Disorder	2	4.5	
Delusional disorder	1	2.3	

Table 7.1: Demographic and clinical characteristics of the sample as well as FA values of left and right fornices.

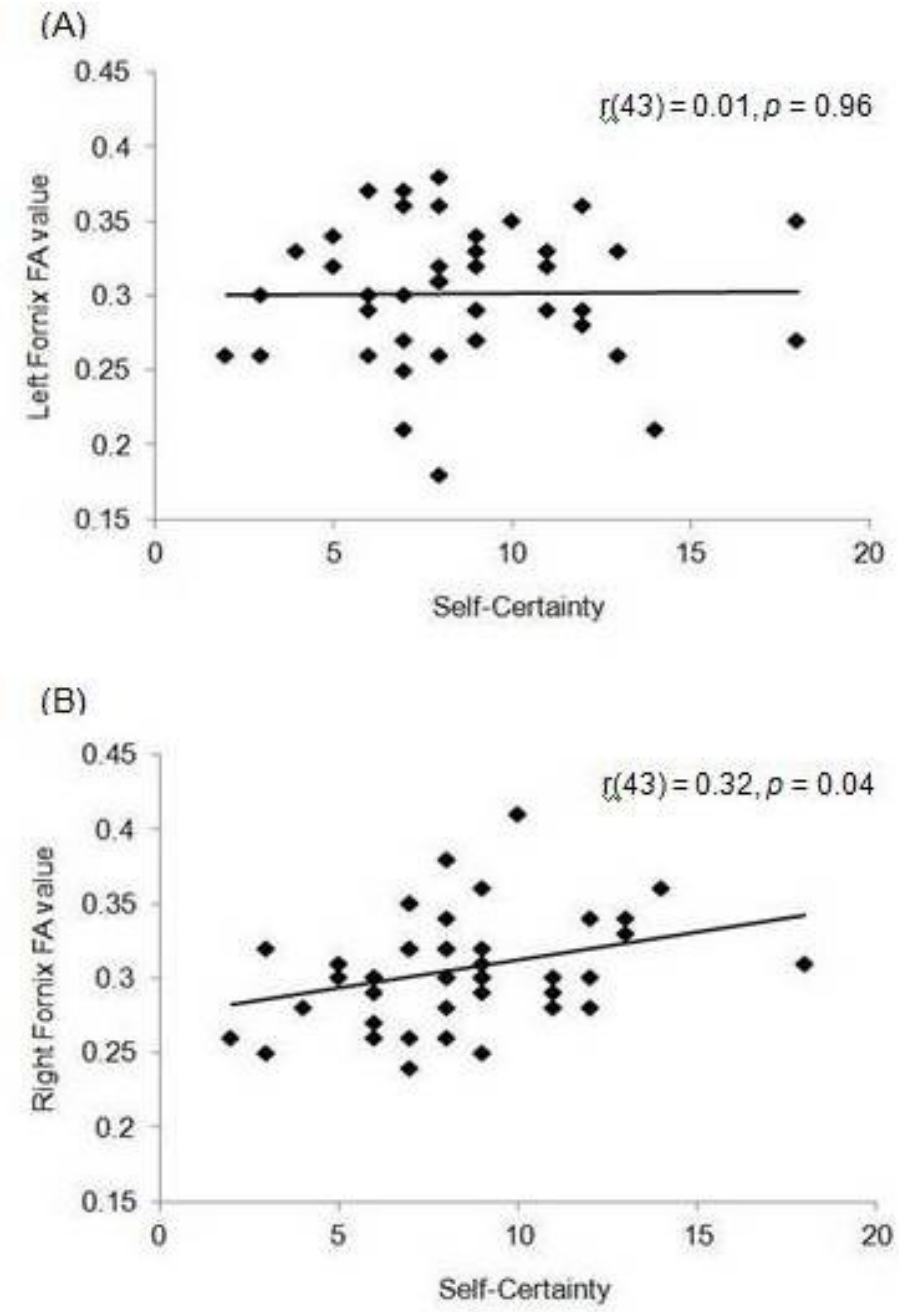

Figure 7.2: Correlations between BCIS self-certainty scores and FA values of the fornix in FEP. (A) Left hemisphere; (B) Right hemisphere.

7.5 Discussion

The present study used DTI tractography to explore whether disruptions in fornix integrity, as inferred by FA, may relate to high self-certainty in a FEP sample. Our finding of a significant positive correlation between right fornix FA values and self-certainty scores indicates that, in addition to previously demonstrated gray matter deficits in hippocampal volume in a sample overlapping with this study, anatomical dysconnectivity among the hippocampal network may contribute to maladaptive self-certainty in FEP.

The correlation between fornix FA and self-certainty scores confirms our a-priori hypothesis of frontal-temporal structural dysconnectivity in high self-certainty in psychosis. When considered with our previously published self-certainty–hippocampus and –memory results in a FEP sample (Buchy, Czechowska, et al., 2009; Lepage, et al., 2008) who overlap with the sample of this study, the findings indicate a concurrence of altered fornix connectivity and volumetric reductions in hippocampus in correlation with self-certainty. This set of findings is consistent with reports of a role for the fornix in subjective memory confidence (Rudebeck et al., 2009). The results are also corroborated by functional neuroimaging studies that demonstrate increased frontal cortex activation for memories held in high confidence in patients with schizophrenia (J. Kim, Matthews, & Park, 2010). In addition, several studies have revealed positive correlations between memory confidence and both hippocampal (H. Kim & Cabeza, 2009; Mickes, Wais, & Wixted, 2009; Moritz, Glascher, Sommer, Buchel, & Braus, 2006), and frontal cortical activation in healthy samples (H. Kim & Cabeza, 2007, 2009; Moritz, Glascher, et al., 2006). The majority of these neuroimaging studies have demonstrated bilateral neural effects; therefore, the current right fornix–overconfidence result should be interpreted with caution. Reports of increased activity in right prefrontal cortex during high compared to low confidence ratings (Camchong et al., 2007) offers some support to the present finding. However, virtually no studies have looked at the neural correlates of self-certainty aside from our own previously published work (Buchy L, et al., 2010), and for that reason it is difficult to provide a convincing explanation for the lateralization effect.

Nonetheless, taking these findings in to account, hippocampal circuitry, including the fornix, may be an anatomical substrate for overconfidence in psychosis.

A number of studies of schizophrenia patients have reported microstructural abnormalities of FA in the fornix (Chance, Highley, Esiri, & Crow, 1999; Davies, Wardell, Woolsey, & James, 2001; Fitzsimmons, et al., 2009; Kuroki, et al., 2006). A divergence in FA may reflect several factors, including the density and degree of myelination of fibres (Basser & Jones, 2002; Beaulieu, 2002), and indicates disruption in connectivity between the hippocampus and other brain regions. The current data suggest that fornix integrity is particularly important for the modulation of belief confidence, at least in our FEP sample. Structural neuroimaging of the fornix and its projections, such as the prefrontal cortex, striatum and mamillary bodies, will be important to further understand the relation between hippocampal circuitry and self-certainty in psychosis.

A limitation of DTI tractography is that it does not account for the extent of white matter alterations. Tractography allows measurement of FA along white matter tracts, but does not discriminate whether the whole tract or subdivisions relate to the self-certainty measure. A second limitation is that we did not include a healthy control group. Future research needs to explore the role of hippocampal circuitry for cognitive insight in healthy samples to understand how this system functions in psychosis.

In conclusion, the current results support our theoretical model of cognitive insight suggesting that abnormal hippocampal related circuitry may contribute to high self-certainty in FEP (Buchy, Czechowska, et al., 2009). Neuroanatomy appears to be emerging as an intermediate phenotype for self-certainty in FEP.

* * *

CHAPTER 8

IMPACT OF DELUSIONS ON COGNITIVE INSIGHT IN FEP

Preface

The previous two studies defined the hippocampus in its structure, function and connectivity, as a key player in cognitive insight in FEP. In addition to neurocognition and neuroanatomy, cognitive insight studies have turned to patients' psychopathology to better understand its pathogenesis. In these studies, an association between active delusions and increased self-certainty has been reported for chronic patients with psychosis (Engh, et al., 2009; Warman, et al., 2007) and for healthy people who report delusion proneness (Warman et al., 2006), as well as a delusions-associated dampening of self-reflection in chronic psychosis (Engh, et al., 2009). The role of delusions for cognitive insight in people experiencing a FEP who are free of potential confounds of lengthy medication use, hospitalization and relapse, is unknown.

The current work explored the impact of delusions on cognitive insight at the time of a FEP by comparing people with active delusions vs. no active delusions on self-certainty and self-reflectiveness. We hypothesized that participants with active delusions would score higher on self-certainty and lower on self-reflectiveness than non-delusional participants.

8.1 Abstract

Previous work on chronic psychosis patients has suggested that low self-reflectiveness and overconfidence in judgments may be associated with delusions. In the present study we evaluated whether this extends to a first episode psychosis (FEP) sample. Thirteen actively delusional and 53 non-delusional participants with a FEP completed the Beck Cognitive Insight Scale. Relative to non-delusional participants, delusional participants endorsed greater self-reflectiveness, though their confidence in their judgments was the same as non-delusional participants. These results suggest that the capacity to self-reflect and refrain from overconfidence may interact with delusions differentially across multiple phases of psychosis. The cognitive system involved in self-reflectiveness may be important for delusional thinking during a FEP.

8.1 Introduction

Cognitive insight involves an ability to distance from distorted beliefs and misinterpretations, reappraise them, and to recognize erroneous conclusions. Recently, Beck and colleagues have developed the Beck Cognitive Insight Scale (BCIS) (Beck, et al., 2004) to assess this construct. A first of two domains, self-reflectiveness, captures the willingness to acknowledge fallibility, consider alternate explanations, and recognize dysfunctional reasoning. The second, self-certainty, taps overconfidence in current beliefs and judgments. It has been hypothesized that higher certainty may reduce the capacity for self-reflection, and thus a composite index is calculated that adjusts for this bias (self-reflectiveness score – self-certainty score). The original study on the BCIS compared psychotic patients (schizophrenia, schizoaffective or major depression with psychotic features) to nonpsychotic psychiatric patients (major depression) on levels of cognitive insight. Relative to the psychiatric control group, in-patients with psychotic disorders endorsed greater self-certainty and less self-reflectiveness, suggesting these thinking styles may be particularly important for psychosis.

In cognitive insight studies, an association between active delusions and increased self-certainty has been reported for chronic patients with psychosis (Engh, et al., 2009; Warman, et al., 2007) and for healthy people who report delusion proneness (Warman et al., 2006). The rationale posited for this link has been that high levels of conviction may contribute to delusions via an inability to cast doubt on fallible information (Moritz & Woodward, 2002; Moritz, et al., 2003; Moritz, et al., 2005; Warman, et al., 2007). The initial study to investigate the delusions–cognitive insight link (Warman, et al., 2007) reported higher self-reflectiveness in delusional compared to non-delusional patients. However, this result was at variance with theoretical expectations (i.e., overconfidence suppresses the capacity to self-reflect), and could have been influenced by sampling characteristics of the non-delusional group (they were quite chronic (mean age = 50.5 years) and underrepresented in the study (n = 13)). Interestingly, delusional patients had Self-reflectiveness equivalent to healthy controls. From this perspective, it would appear that the cognitive process underlying self-reflectiveness is functioning similarly in

delusions and normal cognition. A more recent study (Engh, et al., 2009) observed an expected delusions-associated dampening of self-reflection in a larger (N = 143 including 79 non-delusional patients) and hence more representative sample of patients with chronic psychosis. Earlier work by this group (Engh, et al., 2007) found that Self-certainty and self-reflectiveness failed to differentiate between schizophrenia and bipolar patients. In this study the schizophrenia group had significantly higher delusion severity, and although the impact of delusions was not directly assessed, this result may question the claim that aberrations in cognitive insight are stronger for delusional patients. Other studies have provided evidence for an association between the positive symptom dimension and self-certainty (Bora, et al., 2007; Pedrelli, et al., 2004), and a negative correlation between positive symptoms and self-reflectiveness(Bora, et al., 2007), in people with psychosis. Taken together, it seems that high self-certainty, and perhaps low self-reflectiveness, are more pronounced in deluded chronic psychotic patients.

These previous cognitive insight studies predominantly assessed chronic patients, leaving open the possibility that delusional patients in these settings may be affected by the effects of institutionalization, lengthy antipsychotic treatment, or stigmatization, and that these factors contributed to the difference between the delusional and non-delusional groups. A second important point is that over time some chronic patients may begin to entertain the possibility of being mistaken (i.e., show greater self-reflection), an important reasoning process in delusional belief persistence and change (Garety, Kuipers, Fowler, Freeman, & Bebbington, 2001), after being repeatedly given negative feedback regarding the false nature of their beliefs. Once these false ideas are replaced with alternate explanations, the path back to healthy self-reflection may become unblocked. On the other hand, cognitive insight may operate very differently at the time of a first episode psychosis (FEP). For example, first episode patients have had fewer opportunities to reflect on their false beliefs and therefore may be more likely to give undue credence to them (i.e., show lower self-reflectiveness and higher belief certainty, respectively). While high self-certainty and low self-reflectiveness may represent candidate mechanisms for the emergence of delusions (Moritz & Woodward, 2002; Warman, et al., 2007), a direct assessment of the cognitive insight–delusions link after a first psychotic episode has not yet been done. A study in FEP has a methodological advantage over chronic patient

studies, as antipsychotic response rates are high (Robinson, Woerner, Delman, & Kane, 2005; Robinson et al., 2006) and confounding effects of long periods of hospitalization, treatments and stigma have less of an effect on the interpretation of results.

The aim of the current investigation was to evaluate in a FEP sample levels of cognitive insight in participants with active delusions and with no current delusions. We predicted that participants with active delusions would score higher on self-certainty and lower on self-reflectiveness than non-delusional participants.

8.2 Methods

Participants

All participants were part of a longitudinal naturalistic outcome study of FEP treated in a specialised early intervention service, the Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), Douglas Mental Health University Institute in Montreal, Canada. The program involves a comprehensive approach with intensive medical and psychosocial management provided primarily through modified case management. Individuals aged 14-30 years from the local catchment area suffering from either affective or non-affective psychosis who have not taken antipsychotic medication for more than one month were consecutively admitted to the program as either in or out patients. There is no competing service and treatment is publicly funded.

Seventy people at PEPP with a FEP were contacted to complete the BCIS as part of a larger study on cognitive and neuroimaging predictors of outcome. Inclusion criteria were those set by PEPP with the additional restrictions of between ages 18-30, right handed, clinically stable (number of days between entry into PEPP and the symptom assessment, M = 129.9 days, SD = 87.1, range = 29-379; FEP participants were receiving active treatment during this period and symptoms were not interfering with the administration of neuropsychological or clinical scales and tests), physically healthy (based on medical history and physical examination) and able to provide informed consent. Exclusion

criteria were lifetime history of neurologic condition including loss of consciousness that could affect cognition, family history of hereditary neurologic disorders, lifetime diagnosis of substance dependence, presence of depression as indexed by a Calgary Depression Scale (J. H. Riskind, A. T. Beck, G. Brown, & R. A. Steer, 1987) total score greater than 5, or presence of Parkinsonism. Sixty-six people agreed to participate and all provided corresponding symptom data.

Clinical assessment

FEP participants were diagnosed based on a Structured Clinical Interview for DSM-IV (First, et al., 1998), conducted by a trained interviewer and confirmed through a consensus meeting attended by at least two senior research psychiatrists (R.J. and A.M.). The type and dosage of antipsychotic taken was recorded and converted to a standard chlorpromazine equivalent (Woods, 2003).

Cognitive insight was assessed with the 15-item self-report Beck Cognitive Insight Scale (BCIS) (Beck, et al., 2004). Self-reflectiveness, self-certainty and composite index (self-reflectiveness – self-certainty) scores were computed. Each question is rated on a 4-point scale from 0 (do not agree at all) to 3 (agree completely). Symptom severity was assessed with the Positive and Negative Syndrome Scale (Kay, et al., 1987). Participants scoring a 4 (moderate) or above on the PANSS Delusions item were classified as having active delusions. Participants scoring 3 (mild) or below on this item were classified as non-delusional. As the impact of depression and anxiety on cognitive insight in FEP is unknown, measures assessing these symptoms were included so that a between group effect, if it emerged, could be controlled for. Thus, the Calgary Depression Scale and Hamilton Anxiety Scale (J. H. Riskind, et al., 1987) were administered. Symptom ratings are performed by research assistants and graduate students (intra-class correlation coefficient (ICC) = 0.75) who receive extensive training and supervision with reliability measured at least once a year. Symptom raters were not involved with the treatment of the patient. The interviews for collection of data relevant to this study were conducted on average within 6 months of entry in to the program (BCIS, M = 174.1 days, SD = 102.7,

range = 59 – 612; symptom assessments) when antipsychotic treatment response is known to be high (Agid, et al., 2003; Robinson, et al., 2005; Robinson, et al., 2006).

All participants provided written informed consent in accordance with the Douglas Hospital University Institute human ethics review board.

8.3 Results

Thirteen participants were classified as actively delusional and 53 as non-delusional. A comparison of demographic and clinical information is presented in Table 8.1. The delusional and non-delusional groups did not differ on age, $t(64) = 0.71$, $p = 0.48$, gender, $\chi^2(1) = 0.10$, $p = 0.75$, or depression, $t(64) = -1.41$, $p = 0.12$. Significantly higher anxiety was reported for the delusional group, $t(64) = 4.30$, $p < 0.001$. In order to accurately measure the unique relationship of cognitive insight to delusion groups, anxiety scores were partialled out of the main effects of interest by using Analysis of Covariance (ANCOVA). Anxiety was not significantly associated with any of the BCIS measures (rs = 0.01 – 0.11, all ps > 0.40).

All results are reported as ANCOVA, with delusional group as the between-group factor, cognitive insight (Composite index and two subscales) scores as dependent variables, and anxiety as the covariate. The ANCOVAs were tested at $p = 0.05$ under the hypothesis that participants in the delusional group would show decreased self-reflectiveness and increased self-certainty. These analyses indicated a main effect for self-reflectiveness, $F(1, 63) = 4.43$, $p = 0.04$. Participants in the non-delusional group were significantly more self-reflective than those in the delusional group. The main effect for Self-certainty was nonsignificant, $F(1, 63) = 1.12$, $p = 0.30$, indicating that delusional and non-delusional groups showed similar confidence in judgments. Considering the composite index, a significant effect emerged, $F(1, 63) = 4.48$, $p = 0.04$. Participants in the non-delusional group scored significantly higher on the composite index than those in the delusional group. Mean ratings for the composite index and two subscales are displayed in Figure 8.1.

	Active delusions		**No active delusions**	
	M	SD	*M*	SD
Age	23.2	4.6	23.4	3.2
PANSS positive (total)	18.8	4.7	10.0	3.2
PANSS negative (total)	15.8	6.1	12.9	4.3
PANSS general psychopathology (total)	33.2	8.6	24.4	5.8
Calgary Depression Scale (total)	2.9	3.1	1.6	2.5
Hamilton Anxiety Scale (total)	6.5	3.6	2.4	2.9
BCIS				
Self-reflectiveness	11.9	4.3	13.7	3.7
Self-certainty	8.7	3.2	8.2	3.3
Composite index	3.2	6.2	5.6	5.3
Antipsychotic medication	325.3	278.2	230.3	273.5
	N	%*	N	%
Gender (M:F)	9:4	69:31	39:14	74:26
Diagnostic category				
Schizophrenia	10	78	29	54.7
Schizoaffective disorder	–	–	9	17.0
Schizophreniform disorder	–	–	1	1.9
Psychosis not otherwise specified	3	23	5	9.4
Delusional disorder	–	–	1	1.9
Bipolar disorder	–	–	5	9.4
Undetermined	–	–	3	5.7

Table 8.1: Demographic and clinical characteristics of the sample. *Percentages are reported for number of participants within each group. Antipsychotic medication reported as chlorpromazine equivalent dosage in mg.

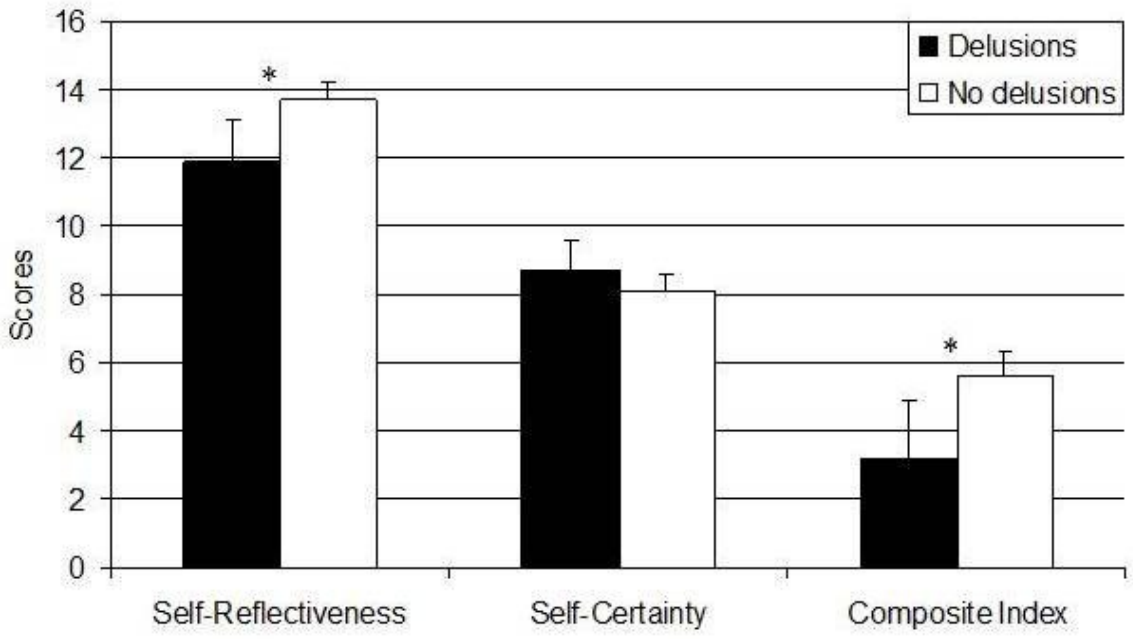

Figure 8.1: Mean ratings for BCIS self-reflectiveness, self-certainty and composite index for FEP patients with active delusions and no active delusions.

At the onset of psychosis, 59 participants (89%) scored a 4 (moderate) or above on the PANSS Delusions item, while the remaining participants scored a 3 (mild, n = 5 (8%)) and a 2 (minimal, n = 2 (3%)) on the Delusions item.

8.5 Discussion

Previous work has suggested that high self-certainty in beliefs and judgments, and both high and low self-reflection, are associated with delusions in chronic psychosis (Engh, et al., 2009; Warman, et al., 2007). In the present study in FEP our hypotheses based in part on these previous findings were only partially confirmed. Non-delusional participants were more willing to acknowledge fallibility, consider alternate explanations, and

recognize dysfunctional reasoning (i.e., higher in self-reflectiveness) compared to delusional participants, but did not differ on their belief certainty (i.e., self-certainty) ratings. These results suggest that the capacity to refrain from overconfidence may interact with delusions differentially across multiple phases of psychosis. Poor Self-reflectiveness may be important for delusional thinking during a FEP.

When interpreting the negative self-certainty/delusions finding, it is helpful to compare Self-certainty scores in the present first episode sample with those reported for Warman et al.'s (2007) and Engh et al.'s (2009) chronic psychosis samples. Inspection of the datasets suggests that certainty judgments for delusional first episode and chronic patients are comparable (Warman et al., $M = 8.6$ vs. $M = 8.7$, respectively, difference = 0.1 point; Engh et al., $M = 8.7$ vs. $M = 9.0$, respectively, difference = 0.3 points). However, considering non-delusional participants, first episode participants scored more than 1.5 points higher than Warman's chronic patients ($M = 8.2$ vs. $M = 6.6$, respectively), and nearly 1 point higher than Engh's patients on this measure ($M = 8.2$ vs. $M = 7.3$, respectively). It may be that high belief certainty spans both the presence and absence of delusions in the early disease process, suggesting that this thinking style may represent a vulnerability factor for a FEP rather than for psychotic delusions per se. The finding that high confidence in judgments is associated to high delusion proneness in healthy people (Warman & Martin, 2006) may in part corroborate this theory. Another possibility relates to the fact that in our first episode participants the non-delusional status was attained relatively recently, within 129.9 days of entry in to the program, and certainty scores may remain high for a bit longer while in chronic patients with time belief inflexibility may extinguish or diminish. Our data may suggest that self-certainty is particularly pronounced at the onset of a FEP, and this may simply be because patients have had minimal contact with psychiatric services and received little feedback regarding the false nature of their beliefs. In support of recent contemporary models of delusion maintenance (Bentall, Corcoran, Howard, Blackwood, & Kinderman, 2001), higher certainty in the validity of interpretations and explanations may contribute to the fixity of delusions (Huq, Garety, & Hemsley, 1988; Moritz & Woodward, 2002), while over time non-delusional patients may be better able to cast doubts on certainty judgments (Moritz & Woodward, 2002). Another possibility is that high certainty in beliefs may lead to an acceptance of

implausible delusional explanations for unusual events and experiences, and a reciprocal rejection of counter-evidence (Moritz, Woodward, & Hausmann, 2006). Longitudinal studies tracking self-certainty over time will be needed to empirically test these hypotheses.

Non-delusional FEP participants were significantly more self-reflective than delusional participants, and this difference appeared to be driving the (non-delusional > delusional) group difference for the Composite index. This results has recently been confirmed by Engh's group (Engh, et al., 2009) though it should be noted that there is evidence against it (Warman, et al., 2007). Nevertheless, it seems intuitive that when beliefs become as strongly held as delusions, one's ability to think flexibly about his/her experiences may be impeded. In fact, incorrigibility is one core clinical feature of delusions necessary for its current definition (Association, 2000; Jaspers, 1963). The Self-reflectiveness subscale includes items that directly address belief inflexibility, for example, "If somebody points out that my beliefs are wrong, I am willing to consider it". Other items parallel cognitive biases typically associated with schizophrenia delusions, such as the tendency to make strong judgments on the basis of poor evidence (Mickes, et al., 2009; Moritz & Woodward, 2005) ("I have jumped to conclusions too fast"), and the ability to distinguish imagined versus actual events in memory (internal source monitoring; "Some of my experiences that may have seemed very real may have been due to my imagination"). Our finding that self-reflectiveness inversely associates with delusions is conceptually supported in the literature, as delusional beliefs are thought to capture the information processing resources necessary to distance from and reframe erroneous interpretations (Hasher & Zacks, 1979). Against a background of evidence that delusions underlie a decreased willingness to re-evaluate previously held positions (Buchy, Woodward, & Liotti, 2007; Moritz, Woodward, & Chen, 2006; Moritz, Woodward, & Hausmann, 2006; Woodward, Buchy, Moritz, & Liotti, 2007), it may be suggested that the present result fits with theoretical expectations. As a final point, it could be considered that high Self-reflectiveness at the time of a first psychotic episode may permit a better response to medication, and to the mitigation of delusions.

There are limitations to the generalizability of this study's sample, since it was composed of a low number of participants with delusions. This sampling difference may reflect the fact that these data were collected within months after treatment of an initial psychotic episode when antipsychotic treatment response is high (Robinson, et al., 2005). However, caution in interpretation is warranted and results need replication. In addition, we did not recruit a healthy comparison group. In the study conducted by Warman and colleagues (Warman, et al., 2007), normal people were as self-reflective as delusional chronic patients, and scored tantamount to non-delusional chronic patients on Self-certainty. A greater understanding of cognitive insight in normal cognition will be important to model its interaction with first episode delusions.

It can be expected that delusions will abate for a subgroup of our delusional first episode participants, leaving open the possibility that self-reflectiveness and self-certainty may operate differently in persistent versus short-term delusions. In this regard, it would be instructive to examine the longitudinal association between cognitive insight and delusional belief persistence and change. Recently, we demonstrated in FEP that dysfunctions in verbal memory may compromise cognitive insight (Buchy, Czechowska, et al., in press; Lepage, et al., 2008), and future research may conduct a tripartite investigation between cognitive insight, verbal memory and delusions. Data collected by Moritz, Woodward and colleagues (Moritz & Woodward, 2002; Moritz, et al., 2003; Moritz, et al., 2005) have shown repeatedly that relative to healthy people, schizophrenia patients show a reduced "confidence gap", in that they show high confidence in memory errors and less confidence in correct responses. This may reflect a more liberal internal threshold for acceptance of multiple response options in schizophrenia (Moritz, Woodward, Jelinek, & Klinge, 2008; Moritz, Woodward, & Lambert, 2007). It remains to be explored whether self-certainty, tapped via a self-assessed questionnaire, is compatible with deviances on memory confidence, which reflect a subjective evaluation of one's behavioural performance. Finally, other patient characteristics (thinking styles, overall inflexibility even before onset of psychosis) may determine whether patients' delusions persist or not. These factors remain to be incorporated in to the current model and may enhance its validity. Metacognitive therapy in schizophrenia (Moritz & Woodward, 2007)

may consider adding a module targeting poor self-reflectiveness which could aid in alleviating delusional severity.

* * *

CHAPTER 9

THE ROLE OF SOURCE MONITORING FOR COGNITIVE INSIGHT IN FEP: A FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY

Preface

In chapters 6–7, using clinical assessments, neurocognitive tasks and structural neuroimaging techniques, we pinpointed delusional severity as well as hippocampal structure and function as key components in the cognitive and brain system underlying cognitive insight in FEP. The current study applied functional magnetic resonance imaging (fMRI) to identify the functional neural circuits that underlie these metacognitive processes in healthy cognition, and how their dysfunction manifests as poor cognitive insight in first-episode schizophrenia (FES).

To achieve this goal, we used virtual reality technology to develop a source encoding and recognition memory paradigm for use during fMRI data acquisition. Virtual reality confers particular benefits over traditional pen-and-pencil paradigms. First, memory performance can be captured in a simulated real-world environment. Virtual reality, unlike traditional cognitive assessment procedures, can achieve by way of photorealistic graphics an environment that captures the richness of the external world. On a related note, while standard tasks sacrifice ecological validity for maximal experimental control, virtual reality can achieve both by way of careful design. Third, the ability to interact freely with the surroundings is a defining feature of real world performance, and virtual reality permits participants to have full control over their environment.

In this study we evaluated the behavioural relationship between cognitive insight levels and performance on an external source monitoring task involving social interactions in FES and in healthy comparison participants. We hypothesized that higher self-certainty and/or lower self-reflectiveness would be associated with increased source memory errors. Secondly, we used fMRI to investigate brain activation changes during source memory attributions and its association with cognitive insight. We hypothesized that lower self-certainty and/or higher self-reflectiveness would correlate to neural activation in prefrontal and parietal cortices and mesial temporal regions, during source recognition memory.

9.1 Abstract

Previous research has linked cognitive insight in psychosis with neurocognitive and neuroanatomical disturbances in the fronto-hippocampal neural network. The authors' goal was to use functional magnetic resonance imaging (fMRI) to investigate the functional neural correlates of cognitive insight during a source memory cognitive activation paradigm. Participants navigated a virtual city where they encountered 20 people each paired with a distinct object at distinct locations. At test, fMRI data was acquired while participants viewed static images of the city and carried out source memory attributions for where and with whom objects were seen. Participants were 19 people with first-episode schizophrenia (FES) and 19 healthy comparison subjects. Cognitive insight was assessed with the Beck Cognitive Insight Scale. Results revealed that FES patients demonstrated statistically similar source memory performance to that of healthy controls. Despite this, within-group analyses revealed BOLD signal differences in frontal and parietal regions in correlation with higher self-reflectiveness and lower self-certainty in FES and controls during source memory recognition. Neural activity did not correlate with any cognitive insight variable during object recognition in either group. By means of virtual reality technology and in the context of a source memory paradigm, the study identified different functional neural bases for cognitive insight in FES and healthy comparison subjects. The disparate regional brain physiological activity in FES might reflect the use of an alternate cognitive stratagem to achieve adaptive self-reflectiveness and self-certainty levels, or may reflect underlying neuropathology in frontal and parietal areas and/or the putative neural network underlying cognitive insight, or both.

9.2 Introduction

Reasoning biases in schizophrenia affect a diverse set of cognitive processes, including hasty decision making, overconfidence in errors, biases in data gathering, and resistance to corrective information from others (Bentall, et al., 1991; Bentall, et al., 2001). Theses thinking styles and impairments were used to construct the Beck Cognitive Insight Scale (BCIS) (Beck, et al., 2004). In the BCIS, participants rate how much they agree with statements tapping two dimensions of cognitive insight: *self-reflectiveness*, which captures the willingness to acknowledge fallibility, corrigibility, and recognition of dysfunctional reasoning, and *self-certainty* which evaluates overconfidence. People with psychosis tend to endorse lower self-reflectiveness and greater self-certainty than psychiatric controls with major depression (Beck, et al., 2004) and healthy people (Basser, 1995; Engh, et al., 2007; Martin, et al., 2010; Morgan et al., 2010; Warman, et al., 2007), suggesting the BCIS is a sensitive measure of reasoning biases in people with psychosis.

Over the last few years, neurocognitive and neural mechanisms involved in cognitive insight in psychosis, particularly of the hippocampus and frontal cortex, have been a growing subject of research. Two independent datasets found a negative association between self-certainty and verbal memory performance (Lepage, et al., 2008; Orfei, et al., 2010), a fronto-hippocampal task. A follow-up study from our laboratory in a larger sample failed to replicate the self-certainty–verbal memory result (Buchy, Czechowska, et al., 2009), which presumably was due to a sensitivity of the verbal memory effect to sample size. The study however demonstrated a positive association between self-reflectiveness and verbal memory. Two other laboratories have reported an association between self-certainty and executive cognitive functions of cognitive set switching (Orfei, et al., 2010) and strategy formation (Cooke, et al., 2010), associated with frontal-lobe functioning. Taken together, existing studies are sparse and mixed, but suggest that memory and executive functions are at least in part linked with cognitive insight in psychosis. Further replication and extension under a broader range of memory/executive cognitive conditions will be necessary before any strong conclusions can be drawn.

Research on the interface of neuroanatomy and cognitive insight has provided converging evidence for a role of the hippocampus and frontal cortex. In a first study, we used a voxel-based manual segmentation approach to examine the contribution of hippocampal structure to cognitive insight in a first-episode psychosis sample. We demonstrated that patients with high self-certainty have smaller bilateral hippocampal volumes, independent of verbal memory effects, than those with low self-certainty (Buchy, Czechowska, et al., 2009). No significant correlations emerged between self-reflectiveness and hippocampal volumes. In a follow-up study, using diffusion tensor imaging tractography our group reported an association between microstructural white matter integrity of the fornix, the main white matter output pathway of the hippocampus, and self-certainty in a first-episode sample. A third very recent study used voxel-based morphometry and diffusion tensor imaging techniques to explore the gray and white matter correlates of cognitive insight across the entire brain in chronic schizophrenia (Orfei, Piras, Macci, Caltagirone, & Spalletta, 2012). The authors reported a positive association between self-reflectiveness and volumes of the right ventrolateral prefrontal cortex. No significant associations emerged between gray matter volumes and self-certainty scores. Diffusion tensor imaging failed to detect any association between white matter integrity and either cognitive insight index. Taken together, the available data place the fronto-hippocampal network at the core of cognitive insight in psychosis.

Since frontal and hippocampal structure and associated neurocognitive functions account for the majority of cognitive insight levels in psychosis, the question immediately arises whether neural activation in nodes of this network is also associated with cognitive insight. When designing a cognitive activation paradigm to tap the neurocognitive systems involved in cognitive insight, it is helpful to focus on the individual BCIS items. It can be observed that all 6 self-certainty items tap confidence in the context of everyday social interactions, and 3 of 6 self-certainty items require comparison of one's own beliefs and judgments to that of another person *(I know better than anyone else what my problems are*; *When people disagree with me, they are generally wrong*; *I cannot trust other people's opinion about my experiences)*. In this regard, self-certainty may depend in part on episodic source memory, such as the ability to distinguish imagined from actual events (internal source monitoring), to distinguish self-generated and externally-generated

events (reality monitoring), or to distinguish between information from outer sources in memory (external source monitoring). In addition, 4 of 9 self-reflectiveness items require reflection on past life experiences *(At times I have misunderstood people's attitudes towards me; I have jumped to conclusions too fast; Some of the ideas I was certain were true turned out to be false; Some of my experiences that have seemed very real may have been due to my imagination.* This leads to the suggestion that impairments in source memory, including the content and/or external context of events under which the memory was acquired (e.g., the people and places involved), may influence cognitive insight in people with psychosis. In other words, engaging false source mnestic information to direct current thinking may bias patients to hold their own beliefs and judgments in high certainty, or hinder their self-reflective capacities.

Syntheses of human functional neuroimaging studies, lesion data and neuropsychological work have concluded that the mesial temporal lobes, including the hippocampus and parahippocampal gyrus, play a predominant role in source memory attributions (Davachi, 2006; R. Henson, 2005; Mayes, Montaldi, & Migo, 2007; Mitchell & Johnson, 2009). Prefrontal areas including dorsolateral, anterior and ventrolateral cortices have also been implicated in source memory in healthy people (R. N. Henson, Shallice, & Dolan, 1999; Rugg, Fletcher, Chua, & Dolan, 1999; Shimamura, 1995), and may reflect the strategic organization of memory retrieval (Simons & Spiers, 2003). Functional magnetic resonance imaging (fMRI) activation studies and lesion patient data indicate that posterior parietal areas including the precuneus often activate in source monitoring tasks either alone or in conjunction with the parahippocampal gyrus (Bisiach & Luzzatti, 1978; Bohbot et al., 1998; Fletcher et al., 1995; Guariglia, Padovani, Pantano, & Pizzamiglio, 1993; Maguire, 1997). These regions appear to be involved in representing spatial information in visual scenes and in memory-related imagery. In schizophrenia, several fMRI studies have shown that patients have difficulty using contextual information to recall the source of information, and tend to activate different neural pathways during memory retrieval of source information (Wang, Metzak, & Woodward, 2011; Weiss et al., 2006). These data suggest that source memory and related neurocircuitry may be candidate mechanisms of cognitive insight in people with schizophrenia.

The aims of the study were twofold. We first sought to investigate, in a sample of stable, well-characterized first-episode schizophrenia patients, the behavioural relationship between cognitive insight levels and performance on an external source monitoring task involving social interactions. We hypothesized that higher self-certainty and/or lower self-reflectiveness would be associated with increased source memory errors. Secondly, we used fMRI to investigate brain activation changes during an external source memory paradigm and its association with cognitive insight. We created a virtual reality experiment using a similar paradigm to King and colleagues (King, Hartley, Spiers, Maguire, & Burgess, 2005) in which memories for lifelike events and its context can be assessed under controlled conditions. We hypothesized that lower self-certainty and/or higher self-reflectiveness would correlate to neural activation in prefrontal and parietal cortices, and mesial temporal regions during source recognition memory.

9.3 Methods

Participants

All the participants with schizophrenia were treated at the Douglas Mental Health University Institute in Montreal, Canada, at the Prevention and Early Intervention Program for Psychoses (PEPP) – a specialised service providing treatment to individuals aged 14–30 years from a local catchment area with either affective or non-affective psychosis. Individuals with an IQ higher than 70 who had not taken antipsychotic medication for more than 1 month were consecutively admitted as in- or out-patients. See Malla et al. (A. Malla, Norman, McLean, Scholten, & Townsend, 2003) or visit www.douglas.qc.ca/ pages/view?section_id=165 for more details.

For the neuroimaging study, only individuals aged 18–30 years with no previous history of neurological disease, head trauma causing loss of consciousness, or lifetime diagnosis of substance dependence were eligible. Twenty people with schizophrenia spectrum disorders were recruited, diagnosed according to the Structured Clinical Interview for

DSM-IV (First, et al., 1998) confirmed between two senior research psychiatrists (A.M. and R.J.). Twenty healthy controls were recruited through advertisements in local newspapers and were included only if they had no current or previous history of (a) any Axis I disorders, (b) any neurological diseases, (c) head trauma causing loss of consciousness, and (d) a first-degree family member with schizophrenia or related schizophrenia-spectrum psychosis. One patient and one control were subsequently removed due to excessive movement during scanning.

Cognitive insight was assessed with the BCIS (Beck et al., 2004), a 15-item self-report inventory. Self-reflectiveness and self-certainty scores were computed. Each question is rated on a 4-point scale from 0 (do not agree at all) to 3 (agree completely). Participants completed the cognitive insight questionnaire before encoding the experimental task. Parental Socioeconomic Status (SES) was estimated using the Hollingshead SES Rating Scale (D. C. Miller, 1991) and handedness with the Edinburgh Handedness Inventory (Oldfield, 1971). Participants provided written informed consent and the Douglas Mental Health University Institute and McGill University Human Ethics Review Board approved the study.

Experimental task

A modified version of the virtual city developed by Burgess and colleagues (Burgess, Becker, King, & O'Keefe, 2001; King, et al., 2005) was created using 3Ds Max (3Ds Max, 2011) and Unity software (Unity, 2011). Scenes were displayed using Unity webplayer. The encoding phase involved navigating through a virtual city. Participants used their right hand to use the mouse to change field of view, and their left hand to press the forward arrow key to move forward. All participants started from the same location in the virtual town and followed a path indicated by green arrows to the location of a first encounter, where 1 of 20 characters was waiting. After approaching the character within five virtual meters, the participants' view was frozen, the character moved to one side of the screen (fixed) and a life-size object appeared on the opposite side on a small table. The object appeared with a glow to enhance its visibility against the surround.

Participants were instructed to pay careful attention to the object, character and location and try to remember them. After a 5s study delay the person and object disappeared, allowing participants to follow the arrows to the site of the next encounter. In total, 20 people with 20 different objects were encountered in 20 different locations in the city.

fMRI data acquisition was carried out while participants performed a total of 80 recognition tests. Test stimuli were images of viewpoints typically encountered during encoding in the virtual environment. Each recognition trial consisted of two objects positioned on either side of a virtual character. Four types of questions were asked: (1) Person (which object was paired with this person), (2) Place (which object did you view in this location), (3) Object (which object was viewed in the city; the other object was new), and (4) Bright (which object is brighter in appearance). The Person and Place conditions were designed to assess source memory, and the Object condition assessed object recognition. Recognition trials were presented in one run of 80 trials. Each trial consisted of a fixation cross presented for 1000 to 5000 ms in 100 ms increments, followed by presentation of the encoding question for 8000 ms. Recognition trials were presented in a constrained pattern of Person, Place, Object, Bright, and each group of four contained no repeats of any person, place or object. The average trial length was 10 seconds. Participants indicated their response via a left/right keypad with their right hand always. Stimuli were presented and results recorded through E-Prime 1.0 software.

A practice route was designed to allow participants to become familiar with the arrow key and mouse, and to practice following the arrows and encounter two characters with objects in independent locales. Participants also practiced answering two of each of the four forced-choice recognition questions regarding the objects collected.

fMRI scanning parameters

Echo-planar images were collected on a Siemens 3T Tim trio MRI (TR = 2000 ms, TE = 30 ms, flip angle = 90, 36 slices of 4 mm thick, 64 x 64 voxel plane with an FOV of 256 mm, giving 4 mm x 4 mm x 4 mm voxels). Each BOLD run was preceded by 4 volumes that were later discarded to allow a magnetic steady state. A mouse connected to the

computer recorded participants' responses. The functional run of 80 trials included 312 whole brain volumes, and lasted 17.53 minutes. The anatomical scan was an MPRAGE (TR = 2300 ms, TE = 2.98 ms, FOV 256 mm, 1mm x 1mm x 1 mm voxels, flip angle = 9) and lasted 5.21 minutes.

Functional MRI data analysis

Data analysis was performed using SPM 8 on a Windows-based workstation. Images from all encoding runs were realigned to the first scan from the first encoding run. Realigned images were then normalized using the ICBM template and smoothed with an 8mm FWHM isotropic Gaussian kernel to account for differences in individual anatomy across participants. Statistical analysis was implemented in customized Matlab scripts which automated the standard voxel-wise least squares general linear model, using the standard canonical HRF plus the derivative and dispersion. Low frequency drifts were removed by applying a high-pass filter with a cut-off of 128 seconds. Statistical contrasts were created comparing the three recognition conditions (Person > Bright, Place > Bright, Object > Bright) within the patient and control groups. Only successfully remembered trials were included in fMRI analyses. The blood oxygen level dependent signal changes in activated areas were then correlated with cognitive insight scores for each group. Once the fixed effects model for each participant was completed, the data was subjected to a random effects analysis across participants to produce a group t-map using the Beta value for the HRF. For the multiple regression, statistical significance was defined at the cluster level with a t-value=3.6, p=0.001 uncorrected at the single voxel level. Results of a monte-carlo simulation (Slotnick, Moo, Segal, & Hart, 2003) of 1000 iterations indicated a cluster of 43 contiguous voxels (960 mm^3) corresponded to a cluster significance of FDR < 0.05, corrected for multiple comparisons.

9.4 Results

Sociodemographic and clinical results

The FES and control groups did not significantly differ in age, parental socioeconomic status, gender or handedness, as shown in Table 1. The FES group had significantly fewer years of education compared with the control group.

	FES n=19	Controls n=19	Statistic			
			t	χ^2	d.f.	*p*
Age (years): mean (s.d.)	25.3 (4.1)	24.7 (4.2)	.41		34	.69
Education (years)	11.3 (1.5)	14.0 (1.8)	5.2		35	.01
Hollingshead Index score: mean (s.d.)	40.2 (12.9)	46.2 (16.0)	1.2		30	.25
Gender: M:F (%)	15:4 (79:21)	17:2 (90:10)		.79	1	.37
Right handed: n (%)	16 (84)	17 (89)		.51	2	.77
BCIS scores						
Self-reflectiveness	11.5	13.0	1.00		37	.31
Self-certainty	7.6	7.1	.63		37	.54
Composite index	3.9	5.9	1.12		37	.27

Table 1. Demographic and clinical characteristics of the first-episode schizophrenia (FES) group and healthy control group

Behavioural fMRI results

The FES and control groups did not significantly differ on self-reflectiveness (t = 1.0, p = .32) or self-certainty scores (t = -.63, p = .54), or on response accuracy for any memory condition, as shown in Table 1. Cognitive insight variables did not significantly correlate with memory accuracy in any condition, as shown in Table 2.

	Self-reflectiveness	Self-certainty
First-episode schizophrenia		
Person	.07 (.79)	-.11 (.69)
Place	.35 (.19)	-.05 (.85)
Object	-.06 (.82)	.32 (.23)
Healthy controls		
Person	-.22 (.40)	-.46 (.06)
Place	.20 (.43)	.27 (.29)
Object	.31 (.23)	.26 (.31)

Table 2. Correlations between memory measures and cognitive insight variables. Data are presented as Pearson's r with corresponding p values in brackets

fMRI results

A second level analysis was performed within the FES group and control group alone to correlate signal changes for the three memory conditions with cognitive insight variables.

Self-reflectiveness

In healthy controls, when correlating self-reflectiveness scores with neural activation in the Person condition, significant effects emerged in right middle frontal gyrus (Brodmann's area 8; x=36, y=16, z=50; t=4. 89, p<.001; 43 voxels), as shown in Figure 9.1, as well as right inferior parietal lobule (Brodmann's area 40; x = 40, y = -46, z = 54; t = 4.44, p < .001; 83 voxels). Self-reflectiveness did not significantly correlate with activation in any brain area in the Place or Object conditions in controls.

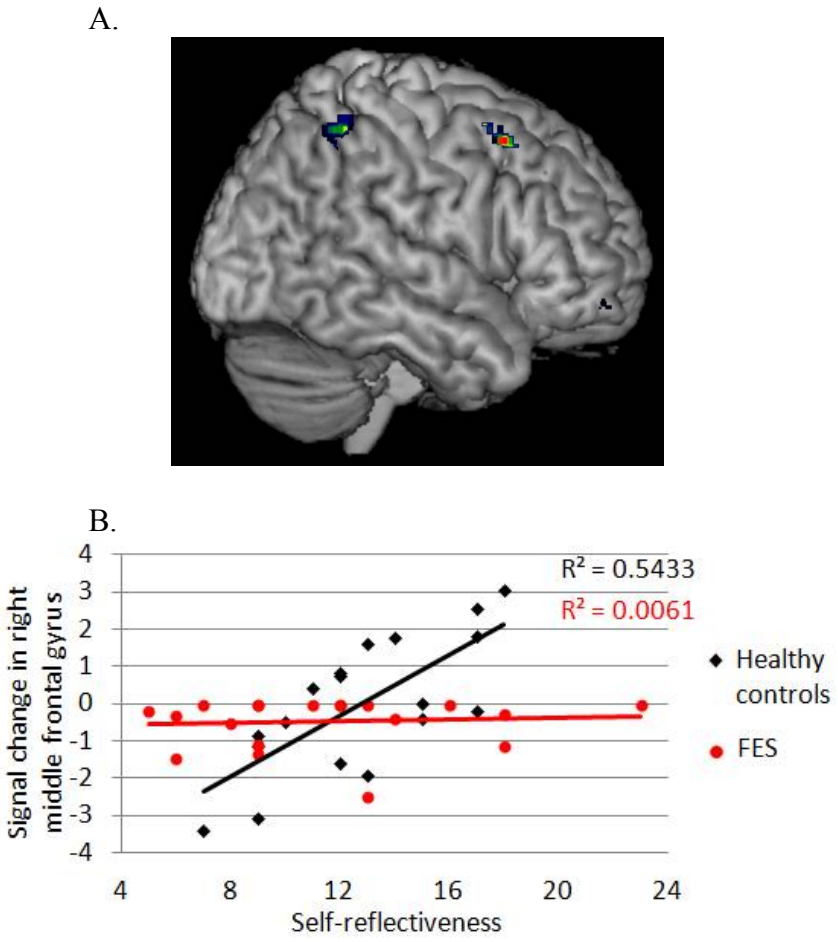

Figure 9.1. A) Right middle frontal gyrus (x = 36, y = 16, z = 50) exhibiting increased activation in response to source memory judgments and its association with self-reflectiveness in the Person condition in healthy participants. B) Regression of self-reflectiveness scores on right middle frontal gyrus activity in healthy controls and FES.

In FES, when correlating self-reflectiveness scores with neural activation in the Person condition, a significant effect emerged in right superior frontal/precentral gyri (Brodmann's area 6; x = 22, y = -14, z = 4; t = 4.22, p < .001; 52 voxels) as shown in Figure 9.2. In the Place condition, significant correlations were observed in left superior parietal lobule/postcentral gyrus (Brodmann's area 5; x=-24, y=-46, z=72; t=5.91, p<.001; 76 voxels), as well as right postcentral gyrus (Brodmann's area 3; x = 26, y = -36, z = 62; t = 5.00, p < .001; 64 voxels). Self-reflectiveness did not significantly correlate with activation in any brain area in the Object condition in FES.

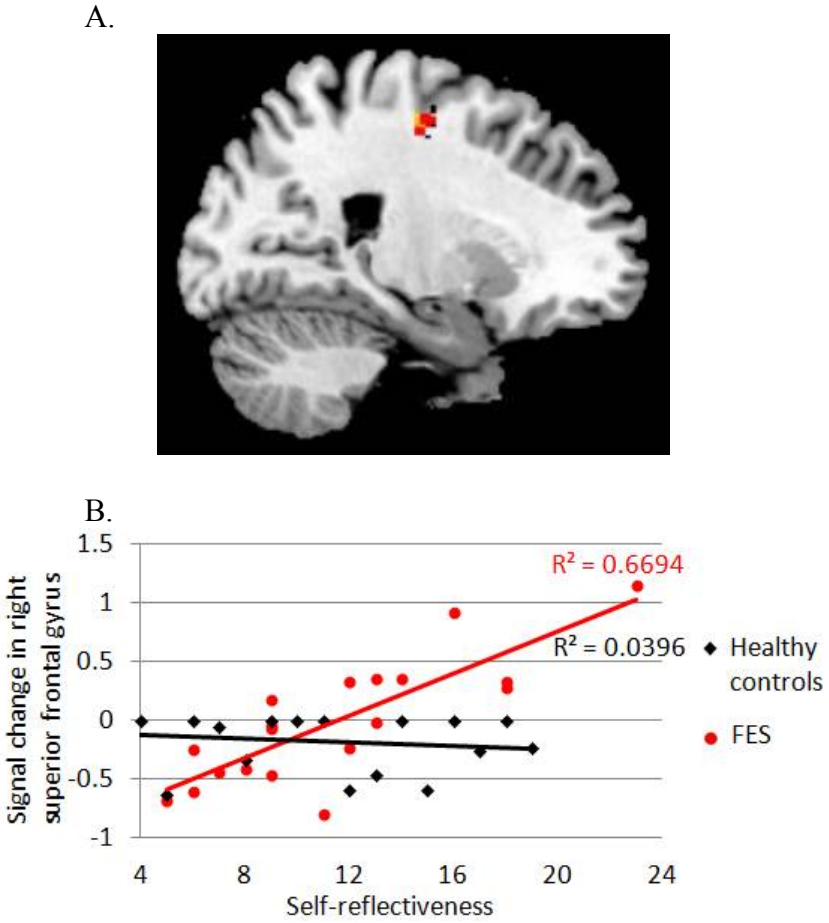

Figure 9.2. Right superior frontal/precentral gyrus (x = 22, y = -14, z = 54) exhibiting increased activation in response to source memory judgments in the Person condition and its association with self-reflectiveness in participants with first-episode schizophrenia (FES). B) Regression of self-reflectiveness scores on right superior frontal gyrus activity in FES and healthy controls.

Self-certainty

In healthy controls, in the Person condition lower self-certainty correlated with increased activation in the right thalamus (x = 4, y = -26, z = 10; t = 5.02, p < .001; 62 voxels). Lower self-certainty did not significantly correlate with activation in any brain area in the Place or Object conditions.

In FES, lower self-certainty did not significantly correlate with activation in any brain area for any of the three memory conditions.

9.5 Discussion

The study employed functional magnetic resonance imaging to investigate the neural basis of cognitive insight during source recognition memory. FES patients demonstrated statistically similar source memory performance to that of healthy controls. Despite this, within-group analyses indicated differential associations between neural activation during source recognition and higher self-reflectiveness in FES and healthy controls, particularly within the frontal and parietal cortices. Task-related cerebral activity was also associated with self-certainty in frontal cortex in controls, but not in FES. The results suggest that the path to high self-reflectiveness and low self-certainty may be different for patients with FES relative to the healthy control group.

The finding that self-reflectiveness was modulated by right middle frontal gyrus activity during source memory recognition in healthy controls is consistent with our hypothesis that cognitive insight relies on accurate memory for specific life experiences, which in turn influence everyday beliefs and judgments (Buchy, Czechowska, et al., 2009; Lepage, et al., 2008). In this model, engaging false source memory information to direct current thinking may hinder one's self-reflective capacities via impaired functions in middle frontal gyrus. Consistent with this view, individual differences in middle frontal activation correlate with superior task performance among healthy participants in source memory studies (R. N. Henson, et al., 1999). As noted in the introduction four of nine

self-reflectiveness items require reflection on past life experiences (eg, Q1, *At times I have misunderstood other people's attitudes towards me*; Q12, *If somebody points out that my beliefs are wrong, I am willing to consider it*). These questions also tap on theory of mind, that is the ability to attribute mental states to others and to appreciate that others have independent beliefs from one's own. This hypothesis accords with studies focused on healthy people which report increased middle frontal regional activity during theory of mind task processing (Vollm et al., 2006). In the context of our healthy control participants, failure to consider others' perspectives may bias low self-reflective individuals to discount others' corrective feedback and deny their objectivity, resulting in incorrigibleness and ultimately a rigid, inflexible belief system.

During correct source memory attributions FES participants showed significant correlations between self-reflectiveness and activation in right superior parietal lobule as well as bilateral postcentral gyri, areas of the brain implicated in successful source monitoring and episodic memory retrieval in schizophrenia (Ragland, Valdez, Loughead, Gur, & Gur, 2006) and in healthy people (R. N. Henson, et al., 1999; Spaniol et al., 2009; Vilberg & Rugg, 2009). At a cognitive level, the frontal lobes are ascribed a vital role in normal (i.e. "healthy") executive functions (Minzenberg, et al., 2009; Stuss, 2011) and memory processes (Wager & Smith, 2003), and disturbances in these cognitive domains and associated brain physiological activity are a robust correlate of schizophrenia (J. M. Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997; Tek et al., 2002). The current self-reflectiveness–superior frontal gyrus result could suggest an underlying executive dysfunction in patients with schizophrenia with low self-reflective capacities, as is seen in schizophrenia patients with poor clinical insight (Aleman, et al., 2006). The finding also accords with our postulate that self-reflectiveness engages theory of mind processes, as superior frontal areas activate during human-to-human competition (Polosan et al., 2011), inferring a protagonist's intention in sentence passages (Mason & Just, 2011) and creating vignettes about the mental state of a to-be-encountered imaginary stranger (Calarge, Andreasen, & O'Leary, 2003). The lack of experimental research in this field precludes confident conclusions at this time. Nevertheless, exploration of the relationship of theory of mind to self-reflectiveness in healthy and schizophrenia populations may be of interest for future studies.

In healthy controls, low self-certainty modulated activation in right thalamus during source memory evaluations. fMRI studies have shown that the cognitive processes involved in attention, including the selection of behaviorally relevant information from the environment and the conscious awareness of visual stimuli, modulate neural activity in thalamic nuclei (O'Connor, Fukui, Pinsk, & Kastner, 2002). It has been recognized that 3 of 6 self-certainty items require comparison of one's own beliefs to that of another individual (eg, Q10, *When people disagree with me, they are generally wrong*). In relation to the thalamus, it may be that in healthy people failure to attend adequately to specific details of others' overt behaviors, such as situation-relevant components of audible speech (ie, conversational details), may bias one's memory leading to an inability to cast doubt on one's own erroneous convictions, or to resist corrective feedback. That overconfidence was associated with neural activity in our healthy comparison participants fits with recent models of cognitive insight which suggest high confidence may reflect a realistic grasp of facts and events in healthy people (Buchy, Brodeur, & Lepage, 2012; Martin, et al., 2010). This fits with a recent evolutionary model of confidence in humans, which posits that overconfidence maximizes individual fitness and leads to evolutionary stability in a wide range of environments (D. D. Johnson & Fowler, 2011). Our data suggest the thalamus may be one component of the neural circuitry underlying self-certainty in our healthy comparison participants.

Self-certainty did not significantly associate with neural activation in any brain area during source memory evaluations in our FES participants. This might reflect the use of an alternate cognitive stratagem to achieve adaptive confidence levels, or may reflect underlying neuropathology in the thalamus and/or the putative neural network underlying self-certainty, or both. High self-certainty is thought to impede distorted belief correction in patients with psychosis (Beck, et al., 2004), and the underlying features of its pathophysiology merits investigation.

That self-reflectiveness and self-certainty were associated with neural activation, but did not correlate with source memory accuracy, suggests that source memory ability cannot entirely explain the relationship between cognitive insight and neural activation, at least in this sample. Verbal memory and executive function disturbances are a correlate of self-

reflectiveness and self-certainty in psychosis samples (Buchy, Czechowska, et al., 2009; Lepage, et al., 2008; Orfei, et al., 2010) and are featured in two prominent theories of cognitive insight (Buchy, Czechowska, et al., 2009; Riggs, et al., 2010). It remains unknown whether these relationships can be traced to physiological disturbances in particular components of cognitive insight circuitry.

The results of this investigation into the functional neural basis of cognitive insight in FES and healthy comparison participants should be interpreted with caution, in part due to the relatively small sample size, and partly the need for replication. In marked contrast to previous works (Beck, et al., 2004; Engh, et al., 2007; Warman, et al., 2007), our FES participants were statistically indistinguishable from comparison subjects in terms of cognitive insight, suggesting our patient sample may be biased toward high functioning individuals. Future studies may examine whether neural activation couples with cognitive insight levels in chronic phases of psychosis, to better understand its brain systems across multiple phases of the disease process.

* * *

PART III

CONCLUSIONS AND SIGNIFICANCE

This thesis presents a series of behavioral and neuroimaging studies of clinical and cognitive insight in FEP. The goal was to characterize insight in relation to patients' severity of psychopathology, neurocognitive abilities, structural neuroanatomy and functional brain activity.

Experiment 1 (p.15) measured the trajectory of clinical insight and psychopathology at seven time points over the first year of a FEP. Insight changed in tandem with positive, negative, depressive and anxious symptoms, and the greatest improvement was observed between the baseline assessment and one month later. This result, together with previous findings demonstrating joint progression of insight and symptom change in people with psychosis, supports the hypothesis that symptom exacerbations contribute to poor insight in this population. Latent group-based trajectory analysis revealed five discrete insight trajectories representing good, increasing, decreasing, moderate-poor and very-poor insight profiles. Moreover, the former two groups displayed the greatest depressive symptoms, while the latter two groups showed the greatest negative symptoms. The results described a sundry course of clinical insight that varies closely with symptom of psychosis over the first year of a psychosis.

In *Experiment 2* (p.25), we used a cross-sectional statistical regression analysis of clinical insight scores on cortical thickness in a FEP sample. We mapped a pattern of thinning that associated with patients' awareness of their illness that encompassed inferior temporal and occipital neocortices, as well as a lateral frontal region. Regression of awareness of treatment related experiences on cortical thickness mapped thinning in parietal, inferior temporal and lateral frontal regions, a pattern that partially overlapped with the distribution of cortical thinning observed in the awareness of illness analysis. These data suggested that the cortical signature of clinical insight cannot be entirely explained in terms of frontal lobular pathology as maintained by several leading insight theorists (X. F. Amador, et al., 1991; A. S. David, 1999; Lewis, 1934), rather that pathogenic processes in parietal, temporal and occipital neocortices may also play a key role in clinical insight in FEP. Although our image-based results would ideally require longitudinally designed studies of insight and cortical structural change, they are in general agreement with published volumetric reports in first-episode (Shad, et al., 2004)

and chronic schizophrenia samples (Bassitt, et al., 2007; Flashman, et al., 2001; Ha, et al., 2004; Sapara, et al., 2007) showing GM reductions in frontal and temporal neocortices in patients with poor clinical insight.

Using a cross-sectional thickness analysis in *Experiment 3* (p.52), we showed that misattribution for delusions is associated with neocortical thickness in the OFC. We further observed evidence of cortical thinning in the DLPFC in association with misattribution for hallucinations, flat affect and asociality. These findings demonstrate that incorrect attribution of one's symptoms is connected to large-scale cortical disruptions in our FEP sample, which include regions known to be associated with poor awareness of illness and treatment related experience in psychosis. Moreover, the findings provide support for our extended account of the anosognosia theory of insight which holds the frontal, parietal and temporal cortices as core deficits.

Partial correlations in *Experiment 4* (p.74) showed that greater self-certainty in FEP correlated with bilateral total hippocampal volumes after removing the effects of verbal memory performance. We proposed that the decreased hippocampal volumes in relation to overconfidence are related to inadequate source monitoring. Moreover, self-reflectiveness was significantly associated with verbal memory scores, leading to the suggestion that in FEP aberrant memory information which may include distorted memory for specific life experiences is used to guide current beliefs and judgements.

In *Experiment 5* (p.97), we investigated the relationship between self-certainty in FEP and microstructural disruptions in underlying white matter of the fornix assessed by probabilistic diffusion tensor imaging. We observed a positive correlation between fractional anisotropy of the right fornix and self-certainty. These data, together with our previous finding demonstrating hippocampal and verbal memory pathologies in correlation with high self-certainty (Buchy L, et al., 2010), suggest suboptimal structure and function in the hippocampal network in people with psychosis biased towards overconfidence.

In *Experiment 6* (p.109), we assessed the contribution of psychopathology to cognitive insight in a FEP sample. We compared self-certainty and self-reflectiveness in people with active delusions to people with no active delusions. Our finding that delusional participants endorsed greater self-reflectiveness than non-delusional participants disaccords with previous findings in chronic psychosis (Engh, et al., 2009; Warman & Martin, 2006), suggesting that the capacity to self-reflect and refrain from overconfidence may interact with delusions differentially across multiple phases of psychosis.

In *Experiment 7* (p.121), using a virtual reality-based source memory task and fMRI, we exposed differential patterns of the neural activation in correlation with cognitive insight in FES and healthy comparison subjects, in the absence of group differences in memory performance. The disparate regional brain physiological activity in FES might reflect the use of an alternate cognitive strategy to achieve adaptive self-reflectiveness and self-certainty levels, or may reflect underlying neuropathology in frontal and parietal areas and/or the neural circuitry of cognitive insight, or both.

The cortical thickness analyses of Experiments 2 and 3 establish a biological basis of clinical insight in FEP on cross sectional analysis. The results indicate that clinical insight is at least in part reducible to a neuroanatomical dysfunction, and that different dimensions of insight rely on partially overlapping neural systems. For example, in Experiment 3 thickness reductions emerged in left middle frontal gyrus in an area of the DLPFC in association with delusion, hallucination and flat affect misattribution, and in Experiment 2 with unawareness of illness and unawareness of treatment need and efficacy in our FEP patients. This region also supports executive cognitive functions, which in people with psychosis with poor insight are known to be functioning at lower levels than to those with good insight (Aleman et al., 2006). This suggests an overall deficit in the DLPFC observable at the neuroanatomical and cognitive levels, which may contribute to poor insight in some people with psychosis. The results also indicate that different dimensions of insight rely on partially separable neural systems. Here we observed thinning in an inferior temporal region for only a few insight dimensions, namely hallucination and flat affect misattribution in Experiment 3, and unawareness of mental disorder in Experiment 2. The temporal lobe has been implicated in insight

impairments in chronic psychosis samples (Cooke et al., 2003; Ha et al., 2004), and receptor dysfunction has been noted in this region in schizophrenia on post-mortem analysis (Domyo et al., 2001). Together, this leads to the suggestion that for ones attribution of hallucinations and flat affect as well as awareness of illness may reflect dysfunction in a fronto-temporal neural network, as these dimensions showed thinning in both frontal and temporal cortical regions in our FEP sample. We observed preliminary evidence for such disconnection in the same sample using DTI tractography (Buchy et al., 2010), and future work could map the white matter microstructure in first- and multi-episode samples to better understand the neural architecture of insights multiple dimensions. Moreover, it is likely that a diverse neural architecture can be observed across individual FEP patients, which in the present group analyses is masked through averaging. In future it will be clinically meaningful to measure cortical thickness at multiple time points in the brains of people with psychosis, to predict and/or track changes in clinical insight at the individual level, either alone or as a function of response to antipsychotic treatment.

A similar argument can be made for the volumetric and microstructural WM analyses of Experiments 4 through 7. The four studies provide a strong argument that the source of cognitive insight impairments is heterogeneous, and may include the presence of delusions, deficits in the verbal memory cognitive system, and altered structure and function in the hippocampal neural network. In particular, lower self-reflectiveness associated with active delusions as well as neural activity in the left superior parietal lobule and right superior frontal gyrus in our FES sample. It is possible that when beliefs become held as strongly as delusions the ability to think flexibly may be compromised, and this may rely on functioning in superior parietal and superior frontal gyri. Self-certainty, on the other hand, associated with microstructural integrity in the fornix as well as hippocampal structure, but did not associate with neural activity during source memory recognition in FES. This may suggest that a deficit in structure rather than function per se may in part contribute to high self-certainty in some FES patients, although a relatively small sample size may limit the ability to detect significant effects. A connectivity analysis of our fMRI data may provide greater insight into the neural systems important for self-reflectivess and self-certainty in FES. It would be interesting to monitor whether

changes in cognitive insight associate with commensurate changes in brain structure and/or function among individuals affected with psychotic disorders. As technology advances and statistical analyses become increasingly sensitive, the tracking of biological changes underlying changes in insight over time will become possible at the level of the individual.

Taken together, the seven experiments of this thesis expose insight as a multifaceted construct in terms of its psychopathological, neurocognitive, and neurobiological mechanisms. We have provided evidence for multiple routes to poor insight in FEP. These include cognitive abilities in verbal memory, structural integrity of the fronto-hippocampal neural network, and the presence or absence of delusions. What is more, the pathway to poor insight is likely to differ across individuals with psychosis, through psychotic symptoms, cognitive capacity, neuroanatomy, neurophysiology or more likely through some combination of these mechanisms. It is also relevant that external factors not addressed in this thesis may impact ones insight, including length of illness, attitude toward feedback from others, and response to antipsychotic treatment and/or cognitive therapies. For example, insight has been shown to increase after 1-year of cognitive behavioral therapy in people experiencing a FEP (Lecomte, Leclerc, & Wykes, 2012). Moreover, a broad literature exists on the role of self-esteem for insight in people with psychosis, and that was not considered in the current thesis (eg, Lysaker, Buck, Salvatore, Popolo, & Dimaggio, 2012).

It is important to consider whether the neural correlates of insight may be partially dissociable across different DSM-IV diagnoses. First-episode psychosis includes multiple diagnoses including schizophrenia and bipolar disorder, and the presence or absence of mood or psychotic symptoms may impact patients underlying neuroanatomy and neurophysiology. However it can be argued that the two disorders have many commonalities in terms of symptom profiles as compared to other DSM-IV diagnostic categories, such as anxiety (eg, generalized anxiety disorder, post-traumatic stress disorder) or mood disorders (eg, major depressive disorder). This leads to the speculation that the neural correlates of insight are likely closer in topography among the psychosis than compared with anxiety or mood disorders. A similar argument could be applied to

psychosis vs neurologic illnesses such as Alzheimer's disease and terminal disorders such as cancer and cardiac disease. A study examining the neural correlates of insight as a function of DSM-IV diagnosis using psychosis vs psychiatric controls (eg, major depressive disorder) and non-psychiatric controls (eg, cancer) might be of interest for future studies, and will contribute a broader understanding of awareness of illness across multiple diseases.

PART IV

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PART V

APPENDIX