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## A longitudinal study of cognitive insight and cortical thickness in first-episode psychosis

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### ABSTRACT

Among individuals with psychosis, those with poor cognitive insight (lower Self-Reflectiveness, higher Self-Certainty) show volumetric reductions in cortical structure. We evaluated whether changes in cognitive insight are associated with progressive changes in cortical structure in first-episode psychosis (FEP) and control subjects. Beck Cognitive Insight Scale ratings and magnetic resonance imaging scans were acquired at baseline for 130 FEP and 52 controls, 59 FEP and 28 controls at 1-year, and 53 FEP and 20 controls at 2-years. Cortical thickness was computed across scans and analyzed with linear mixed models. At baseline, groups did not differ on Self-Reflectiveness or Self-Certainty. At baseline, higher Self-Reflectiveness significantly correlated with thinner right occipital cortex in FEP, and higher Self-Certainty was significantly negatively correlated with cortical thickness in left posterior cingulate in controls. Longitudinal analysis showed that Self-Reflectiveness and Self-Certainty did not change over time in either group. Interestingly, the lack of change in cognitive insight aligned with longitudinal cortical thickness results, where no interaction effects were seen with cortical thickness between time and either Self-Reflectiveness or Self-Certainty. Exploratory analyses with a reduced threshold found that in FEP, across all time-points, higher Self-Certainty associated with thinner cortex in left posterior cingulate/precuneus. Results suggest that the posterior cingulate may be a common neural correlate for Self-Certainty in FEP and non-clinical subjects.

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### 1. Introduction

The past 100 years has seen a significant evolution in how patients with psychosis conceptualize insight about their illness. Whereas initial accounts viewed insight as an all-or-nothing phenomenon, such that individuals either did or did not have complete insight, recent accounts view insight as a multifaceted and dimensional concept. *Clinical insight* is characterized along dimensions that include individuals' awareness of their illness, the need and efficacy of their treatment, and ability to recognize symptoms as attributable to a mental disorder (Amador et al., 1991; David et al., 1992; David, 1999). This form of insight is typically determined by observing individual's behaviour during a clinical interview and is useful for determining diagnosis, prognosis and treatment (Amador and David, 1998). A more recent account of insight, termed *cognitive insight*, assesses individuals' capacity to evaluate their unusual

experiences, recognize and reflect upon their errors in thinking, and correct them. The Beck Cognitive Insight Scale (Beck et al., 2004) was developed to psychometrically assess these cognitions in individuals with psychotic disorders. This self-report scale taps into two facets of cognitive insight: *Self-Reflectiveness*, a measure of objectivity, reflection and openness to feedback, and *Self-Certainty*, which captures overconfidence. Beck et al. (2004) in their seminal study showed that people with psychotic disorders endorse significantly lower Self-Reflectiveness and higher Self-Certainty than individuals without a psychotic disorder, and collectively interpreted this as "poor" cognitive insight.

Beck's initial study on cognitive insight (Beck et al., 2004) was followed by many investigations with varying evidence that in people with psychosis, poorer cognitive insight is associated with greater severity of delusions, greater negative symptoms, higher depression, and lower functional outcome (Phalen et al., 2015; Riggs et al., 2012). Neuroimaging studies indicate that higher Self-Certainty is associated with smaller total hippocampal volumes (Buchy et al., 2010b) and higher fractional anisotropy within the fornix in people with FEP (Buchy et al., 2012b). Higher Self-Certainty has been correlated with increased volume in right ventrolateral prefrontal cortex (VLPFC) in schizophrenia

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(Orfei et al., 2013), and higher Self-Reflectiveness has been linked to increased neural activation in VLPFC in FEP (Buchy et al., 2015a) and enduring schizophrenia samples (Pu et al., 2013). Very recent evidence suggests that cognitive insight is associated with cortical thickness (Buchy et al., 2016) and activation (Lee et al., 2015) in widespread cortical regions in people with psychosis. Recent cross-sectional data on cognitive insight in non-clinical samples has shown that Self-Certainty is positively correlated with cortical thickness in left VLPFC (Buchy and Lepage, 2015), and that higher Self-Reflectiveness is modulated by right VLPFC activation (Buchy et al., 2014). Other research has shown that functional abnormalities in the posterior insula is associated with self-experience process and insight in people with schizophrenia (Chen et al., 2016).

Several studies have now characterized cognitive insight levels in non-clinical samples. In particular, one study has reported of typical levels of cognitive insight in the general population (Buchy et al., 2012a), and another study has reported an association between Self-Certainty and executive functions in a non-clinical sample (Orfei et al., 2011). Using functional magnetic resonance imaging (fMRI), a third study (Buchy and Lepage, 2015) demonstrated that Self-Reflectiveness was modulated by right VLPFC activity while non-clinical subjects performed an external source memory task. Another recent report linked higher Self-Certainty with lower cortical thickness in left VLPFC (Buchy and Lepage, 2015). Thus the exploration of cognitive insight and its link with neural structure and function is an emerging area of interest in this field.

Amongst the cognitive insight literature, there is a significant gap in knowledge of the dynamic nature of cognitive insight amongst both people with psychosis and non-clinical subjects. Amongst the limited research on this topic, studies have shown that cognitive insight improves alongside reductions in positive symptoms following psychosocial therapies (Granholm et al., 2006; Granholm et al., 2005; Perivoliotis et al., 2010) and does not spontaneously change within a 6-month time period (Lysaker et al., 2011) in people with enduring schizophrenia. Longitudinal studies in the clinical insight literature have shown that clinical insight is dynamic over the first few years of a psychosis (Buchy et al., 2010a; Fennig et al., 1996; McEvoy et al., 2006; Saeedi et al., 2007). Neuroimaging research has documented progressive cortical changes after the onset of a FEP, most notably in anterior cingulate cortex, superior temporal cortex and insula (Chan et al., 2011; Ellison-Wright et al., 2008; Fusar-Poli et al., 2012; Radua et al., 2012; Shepherd et al., 2012; Steen et al., 2006). No studies have evaluated the longitudinal covariation between cognitive insight and neural structure during the first few years following a FEP, or in non-clinical subjects. Such a study has the potential to reveal whether progressive brain changes covary with changes in cognitive insight soon after the onset of a psychosis, as well as in otherwise healthy individuals.

The first aim of this study was to evaluate the longitudinal course of cognitive insight over 2-years in FEP and control samples. The second aim was to examine the cross-sectional association between cognitive insight and neural structure at baseline in FEP and control samples. Our third aim was to examine covariations between cognitive insight and cortical thickness between baseline and 1-year and 2-year follow-ups in FEP and control participants. Aim 1 was exploratory; thus no hypothesis was formed. For aims 2 and 3, we hypothesized that higher Self-Reflectiveness and lower Self-Certainty would be associated with greater cortical thickness in VLPFC.

## 2. Materials and methods

### 2.1. Participants

Participants were part of a longitudinal naturalistic outcome study of FEP treated in a specialized 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 entry to PEPP were that subjects be aged 14–35, suffering from either affective or non-affective psychosis, and not have taken antipsychotic medication for >1 month. This service is entirely publicly funded, and there are no competing services within the system.

Non-clinical participants were recruited through advertisements in local newspapers and were included only if they had no current or past history of 1) any Axis I disorder, 2) any neurological diseases, 3) head trauma causing loss of consciousness, and 4) a first-degree family member suffering from schizophrenia or related schizophrenia spectrum psychosis.

MR scans were acquired at baseline for 130 FEP and 52 control subjects, at 1-year in 59 FEP and 28 controls, and at 2-years in 53 FEP and 20 controls, 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, 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, lifetime diagnosis of substance dependence, and IQ < 70.

Reasons for attrition is as follows for the 71 patients who were not included in analysis after Baseline, with the number of cases in brackets: no BCIS data (32), refused (23), unavailable for follow-up/not followed at the PEPP clinic anymore (6), unable to contact (4), failed MRI QC (2), major brain trauma (1), moved (1), pregnant (1), or excluded from the study for other clinical reasons (1).

### 2.2. 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 Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984b) and Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984a). The research assistants and graduate students who perform symptom ratings using the SAPS and SANS have established an intra-class correlation coefficient (ICC) of 0.75. Cognitive insight (Self-Reflectiveness and Self-Certainty) was rated with the 15-item self-report Beck Cognitive Insight Scale (Beck et al., 2004). Each question is rated on a 4-point scale from 0 (does not agree at all) to 3 (agree completely), with higher scores indicating higher Self-Reflectiveness and Self-Certainty. Depression was measured with the Calgary Depression Scale (Addington et al., 1990) and anxiety with the Hamilton Anxiety Scale (Riskind et al., 1987). Parental socioeconomic status (SES) was estimated using the Hollingshead SES Rating Scale (Miller, 1991) and handedness with the Edinburgh Handedness Inventory (Oldfield, 1971). Duration of untreated psychosis (DUP) was calculated as the time between onset of psychotic symptoms to the time of adequate treatment with antipsychotics (Malla et al., 2006). Adequate treatment was defined as taking antipsychotic treatment for a period of 1 month or until remission of positive symptoms was achieved, whichever came first (Malla et al., 2002). Duration of untreated illness (DUI) was calculated as the time between onset of first-ever psychiatric symptoms and onset of adequate antipsychotic therapy. Antipsychotic dosage was recorded, and calculated as chlorpromazine equivalents according to published guidelines (Leucht et al., 2014; Patel et al., 2013), while taking into consideration medication adherence percentage. Medication adherence [0 = never (0%), 1 = very infrequently (1% to 25%), 2 = sometimes (26% to 50%), 3 = quite often (51% to 75%), 4 = fully (76% to 100%)] was determined using a validated protocol based on composite information obtained from the patient, family

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