



Cortical thickness is associated with poor insight in first-episode psychosis

Lisa Buchy^{a,b,c}, Yasser Ad-Dab'bagh^{d,e}, Ashok Malla^{b,f}, Claude Lepage^c, Michael Bodnar^{a,b,c},
Ridha Joobar^{b,f}, Karine Sergerie^{a,c}, Alan Evans^c, Martin Lepage^{a,b,c,f,*}

^a Brain Imaging Group, Douglas Mental Health University Institute, 6875 LaSalle Blvd., Verdun, Quebec, Canada H4H 1R3

^b Prevention and Early Intervention Program for Psychoses, Douglas Mental Health University Institute, 6875 LaSalle Blvd., Verdun, Quebec, Canada H4H 1R3

^c Department of Neurology & Neurosurgery, Montreal Neurological Institute, 3801 University Street, Montreal, Quebec, Canada H3A 2B4

^d Department of Psychiatry, University of Ottawa, 1145 Carling Avenue, Ottawa, Ontario, Canada K1Z 7K4

^e Children's Hospital of Eastern Ontario, 401 Smyth Road, Ottawa, Ontario, Canada K1H 8L1

^f Department of Psychiatry, McGill University, 1033 Pine Avenue West, Montreal, Quebec, Canada H3A 1A1

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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 first-episode psychosis. Insight was rated in 79 people with a first-episode psychosis 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 and efficacy suggests that the neural signature of insight involves a network of brain structures, and not only the frontal lobes as previously suggested.

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1. 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 (Amador et al., 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 (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 (2004, 2006) 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

* Corresponding author. Douglas Mental Health University Institute, 6875 LaSalle Blvd., Verdun, Quebec, Canada H4H 1R3. Tel.: +1 514 761 6131x4393; fax: +1 514 888 4064.

E-mail address: martin.lepage@mcgill.ca (M. Lepage).

is evidence for associations between poor insight and parietal and temporal neuropsychological dysfunction (Goodman et al., 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 et al., 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 morphometric 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 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 (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 and 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.

2. Materials and methods

2.1. Participants

All participants were part of a longitudinal naturalistic outcome study of first-episode psychosis 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 first-episode psychosis (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, 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.

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 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) (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 (Riskind et al., 1987). Parental SES was estimated using the Hollingshead SES Rating Scale (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.

2.3. MRI acquisition

Scanning was carried out at the Montreal Neurological Institute (MNI) on a 1.5 T 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 = 22 ms, echo time = 9.2 ms, flip angle = 30°, 180 1 mm contiguous sagittal slices). The rectangular field of view (FOV) for the images was 256 mm (SI) × 204 mm (AP).

2.4. Statistical analyses

2.4.1. 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

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