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Symptom Attribution in first episode psychosis: A cortical thickness study

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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) are correlated with 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 magnetic resonance imaging study, 52 people with a first-episode psychosis (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 was associated with thickness in the OFC [Brodmann's area (BA) 11/47]. Delusion, flat affect and asociality misattribution were associated with cortical thinness in the dorsolateral prefrontal cortex (BA 9/46). Differential associations emerged between each attribution item and cortical thickness/thinness in a 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.

1. Introduction

Lack of insight is a central clinical characteristic of schizophrenia (Carpenter et al., 1973) and other psychoses (Amador et al., 1994; Ghaemi and 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 composed of several related but partially independent elements (David et al., 1992; Amador et al., 1993). 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 (David, 1990; David et al., 1992; Amador et al., 1993).

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-based 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) (Flashman et al., 2001; Shad et al., 2004; Shad et al., 2006a; Buchy et al., 2011) 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 et al., 2006a) have hypothesized that the DLPFC may mediate poor insight via deficits in conceptual organization and self-monitoring. Flashman et al. (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 et al., 2011). 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 and Trimble, 2006; Hassabis et al., 2007; Wolf et al., 2009), while decreased coordination of the left temporal

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cortex–DLPFC pathway may lead to insight-associated memory and executive dysfunctions in psychosis (Aleman et al., 2006; Buchy et al., 2011).

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 et al., 2006a). 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 into particular signs and symptoms of their illness but not others (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 into delusions and hallucinations results from different processes (Amador et al., 1994; Beck et al., 2004; Buchy et al., 2009). Fourth, functional and structural MRI data suggest that neural networks underlying different schizophrenia symptoms are partially overlapping but not homogeneous (Kasai et al., 2002; Gur et al., 2007; Hulshoff Pol and Kahn, 2008; Knobel et al., 2008; Harvey et al., 2010). 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). The measurement of 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 (Zilles, 1990; Parent and Carpenter, 1995). 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) tested a general hypothesis that the regional distribution of cortical thickness or thinness would be partially dissociable across the four symptom attribution items.

2. 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 the PEPP were that subjects be aged 14–35, suffering from either affective or non-affective psychosis, and not have taken antipsychotic medication for more than 1 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 the 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 (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, $n = 37$.

2.2. 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 assessment through consensus between two senior psychiatrists (A.M. and R.J.). Clinical insight was quantified with an abbreviated version of the SUMD (Amador et al., 1994). The SUMD assesses both awareness and attribution of symptoms, and in the current study, only attribution scores were used. These items were (3b) hallucinations, (4b) delusions, (5b) flat affect and (6b) asociality. Items are rated on a 5-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 (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 (Miller, 1991) and handedness with the Edinburgh Handedness Inventory (Oldfield, 1971). MR scans were performed on average within 21.2 days (S.D. = 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.

2.3. MRI acquisition

Scans were acquired at the Montreal Neurological Institute 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 for images was 256 mm (SI) × 204 mm (AP).

2.4. Statistical analyses

MRIs were submitted to the CIVET processing pipeline (Version 1.1.9) (http://wiki.bic.mni.mcgill.ca/index.php/CIVET) (Zijdenbos et al., 2002; Ad-Dab'bagh et al., 2006). Native T1-weighted images were first registered to the ICBM152 template using linear transformation (Collins et al., 1994; Grabner et al., 2006) and simultaneously corrected for non-uniformity artifacts 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 the CLASP algorithm (MacDonald et al., 2000; Kabani et al., 2001; Kim et al., 2005). 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 (Robbins, 2004; Lyttelton et al., 2007). 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 and 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 $t = 2.04$ ($r = 0.28$).