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Association of medial prefrontal resting state functional connectivity and metacognitive capacity in early phase psychosis

Michael M. Francis[a,b,c,*], Tom A. Hummer[a], Bethany L. Leonhardt[a,b,c], Jenifer L. Vohs[a,b,c], Matt G. Yung[a], Nicole F. Mehdiyoun[a,b,c], Paul H. Lysaker[d], Alan Breier[a,b,c]

[a] Department of Psychiatry, Indiana University School of Medicine, 355 W. 16th St., Suite 4800, Indianapolis, IN 46202, USA
[b] Prevention and Recovery Center for Early Psychosis, Eskenazi Health Midtown Community Mental Health Center, 720 Eskenazi Avenue, Outpatient Care Center, Lower Level, Indianapolis, IN 46202, USA
[c] Larue D. Carter Memorial Hospital, IU Psychotic Disorders Program, 2601 Cold Spring Rd., Research Unit (8-2048), Indianapolis, IN 46222, USA
[d] Department of Psychiatry, Indiana University School of Medicine, Roudebush VA Medical Hospital, 1481 W 10th St., Indianapolis, IN 46202, USA

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ABSTRACT

Metacognition refers to a range of cognitive processes that allow one to form complex ideas of self and others and to use this information to navigate psychosocial challenges. Several studies in both early-phase and prolonged schizophrenia have demonstrated not only that significant deficits in metacognitive ability are present, but importantly that they are associated with significant functional impairment and decreased quality of life. In spite of the importance of metacognitive impairment in schizophrenia, relatively little is known about the biological substrates that may contribute to this dysfunction. In this study, we examined the relationship between resting state functional connectivity of the medial prefrontal cortex (mPFC), a structure shown in prior voxel-based morphometry studies to be associated with metacognition, with metacognitive function in an early-phase psychosis cohort (n=18). Analyses revealed a positive association of resting state functional connectivity between the mPFC and precuneus and posterior cingulate structures and metacognitive ability. These results provide evidence of disrupted resting state connectivity in structures relevant to metacognitive dysfunction in early-phase psychosis, which may have implications for pathophysiological models of complex cognitive deficits in this illness.

1. Introduction

Metacognition is a term referring to a wide range of mental activities which involve some form of reflection about one's own mental states or the mental states of others. Since its introduction in the 1970s, metacognition has been increasingly used to describe a spectrum of activities ranging from the consideration of discrete mental experiences, such as a specific thought or emotion, the synthesis of discrete perceptions and integration of the representations of self and others as unique agents in the world (Dimaggio et al., 2013; Lysaker et al., 2013; Semerari et al., 2003). These discrete and synthetic acts are thought to bi-directionally inform one another as persons evolve ideas of themselves and others in the flow of daily life. For example, noticing the emergence of a specific emotion or wish may affect a person's larger sense of self, just as that larger sense of self affects how an emergent emotion or wish is interpreted. Metacognitive function is foundational for adaptive function. It allows individuals to create meaning, develop and act upon personal motivations, regulate thoughts and emotions and ultimately to form the interpersonal connections which support community function (Dimaggio et al., 2015; Luther et al., 2016; Semerari et al., 2003, 2007; Vohs et al., 2015b).

Deficits in metacognition have been broadly observed in schizophrenia and theorized (Lysaker et al., 2015) to be similar to what Bleuler (1950) identified as the first of four core features of schizophrenia, namely disturbances in the associative processes needed to create viable complex ideas. Metacognitive deficits have been found to distinguish individuals with schizophrenia from others with prolonged non-psychiatric medical illness (Lysaker et al., 2014) and are related to but not synonymous with disturbances in neurocognition (Lysaker et al., 2005). Additionally, poorer metacognitive functioning in individuals with prolonged schizophrenia has been associated with a range of poor outcomes including increased negative symptoms (Pickup and Frith, 2001), decreased motivation (Vohs et al., 2014), learning impairment (Tas et al., 2012), and, ultimately, with worse psychosocial

* Corresponding author at: Larue D. Carter Memorial Hospital, IU Psychotic Disorders Program, 2601 Cold Spring Rd., Research Unit (8-2048), Indianapolis, IN 46222, USA.
E-mail addresses: mmfranci@iupui.edu (M.M. Francis), thummer@iupui.edu (T.A. Hummer), blleonha@iupui.edu (B.L. Leonhardt), jvohs@iupui.edu (J.L. Vohs), mgyung@iupui.edu (M.G. Yung), nmehdiyo@iupui.edu (N.F. Mehdiyoun), plysaker@iupui.edu (P.H. Lysaker), abreier@iupui.edu (A. Breier).

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function (Koren et al., 2006; Langdon et al., 2001; Lysaker et al., 2005, 2011a).

More recent work focusing on early-phase psychosis (EPP) has revealed that metacognitive deficits are present even in the beginning phase of the illness (Vohs et al., 2014, 2015a, 2015c). Importantly, these studies have demonstrated that diminished metacognition represents a risk factor for poor outcomes and functioning early on in the course of the disorder (MacBeth et al., 2014; McLeod et al., 2014; Vohs et al., 2015c; Vohs and Lysaker, 2014). Moreover, these studies indicate that metacognitive capacity may be a potentially modifiable disease factor and call for an improved understanding of the substrates underlying this phenomenon.

Currently, understanding of the neural processes subserving metacognition is incomplete. A number of studies in non-psychotic populations suggest that the medial prefrontal cortex (mPFC) may play an important role in mediating metacognitive ability (Fleming et al., 2014; Fleming and Dolan, 2012), though less work has been done to examine the neurobiology of metacognition in schizophrenia. The mPFC is associated with processes related to metacognition, such as self-referential thinking (Mitchell et al., 2005; Spreng and Grady, 2010) and socio-emotional processing (Bzdok et al., 2013). Furthermore, the mPFC is a significant hub in various cortical networks (van den Heuvel and Sporns, 2013), receiving information from regional afferents and providing a venue through which information from wide ranging brain systems can interact. This role is well suited for metacognition, which involves the interpretation and processing of information at a variety of levels.

Preliminary work provides evidence that the mPFC is involved in metacognitive deficits in schizophrenia. A recent study by Vohs and colleagues was the first to examine how gray matter density (GMD) was related to metacognition in EPP. Higher metacognitive capacity was associated with increased GMD in the mPFC suggesting that mPFC impairments play a key role in metacognitive deficits in this group (Vohs et al., 2015a). These results contribute to the biological understanding of metacognitive dysfunction in schizophrenia, yet merit further investigation of this symptom domain. Improved understanding of the biological processes involved in metacognition would be an important step towards the development of novel therapeutic interventions for metacognitive impairments and may also elucidate the brain based correlates of other related cognitive dysfunction.

The present investigation sought to build upon our previous studies and examine how the interaction of the mPFC with disparate brain regions is related to metacognitive capacity in EPP. To this end, we utilized functional magnetic resonance imaging (fMRI) to characterize mPFC resting-state functional connectivity (FC). Resting-state fMRI, which examines correlations in low-frequency (< 1 Hz) fluctuations in the blood-oxygen level-dependent (BOLD) signal, is thought to reflect intrinsic functional relationships between brain regions (Fox and Raichle, 2007). Therefore, possible metacognitive impairments may be related to the integrity of networks encompassing the mPFC and other related brain regions. We hypothesized that increased connectivity between the mPFC other neural structures would be associated with better overall metacognitive ability. As schizophrenia has been conceptualized as arising from disrupted neural integration and connectivity (Beaumont and Dimond, 1973; Bullmore et al., 1997; Friston, 1998; Konrad et al., 2009), linking mPFC connectivity to metacognition in EPP may be particularly helpful in highlighting neural abnormalities that significantly contribute to deficits in cognition and overall well-being early in the progression of the disorder.

2. Methods

2.1. Participants

Subjects were recruited through the Indiana University Psychotic Disorders Program, within the Indiana University School of Medicine. All study procedures were completed via two concurrent studies both approved by the Indiana University Institutional Review Board, protocol numbers 1112007648 (initially approved 9 February 2012) and 1011002975 (initially approved 14 September 2010). After receiving an explanation of study procedures, subjects gave their written informed consent prior to enrollment. Eighteen subjects ages 18–35 were enrolled, all within the first five years of psychotic illness onset, and diagnosed with schizophrenia (n=14), schizophreniform disorder (n=2), or schizoaffective disorder (n=2) as determined by the Structured Clinical Interview for DSM-IV (SCID) (First et al., 2002). Both patients with schizoaffective disorder were without significant affective symptoms for at least one month prior to enrollment in the study. All participants were on outpatient antipsychotic medication, including risperidone (n=1), paliperidone (n=4), quetiapine (n=1), olanzapine (n=3), and lurasidone (n=2). One patient was on antidepressant medication. All patients were determined to be clinically stable via a Clinical Global Impression-Severity (CGI-S) (Guy, 1976) score of 4 or less. Diagnosis of substance abuse or dependence within three months of testing, history of mental retardation as documented in the medical record, and contraindication to scanning procedures were exclusionary.

2.2. Procedures

2.2.1. Measure of metacognitive capacity

Metacognitive capacity was determined in two distinct steps. Subjects first provided a narrative of the self and illness, elicited using the Indiana Psychiatric Illness Interview (IPII) (Lysaker et al., 2002). The IPII is a semi-structured interview, generally lasting 30–60 min. Responses are audio recorded, transcribed, and later rated by trained investigators using the Metacognition Assessment Scale-Abbreviated (MAS-A) (Lysaker et al., 2005). The MAS-A was developed in conjunction with the authors of the MAS (Semerari et al., 2003) in an attempt to create an instrument with which to assess metacognition as manifest in personal narratives. Good inter-rater reliability (intraclass correlation=0.82) and validity has been presented elsewhere (Lysaker et al., 2011b). The MAS-A is comprised of subscale domains which examine an individual's ability to understand his or her own mental state ("self-reflectivity"), understand the mental state of others ("understanding the mind of the other"), see the world as existing with others having independent motives ("decentration"), and the utilization of complex understandings of self and others to respond to psychosocial challenges ("mastery"). These domains were combined to create a MAS-A total score that is representative of overall metacognitive capacity and was used for analyses with resting state fMRI data.

2.2.2. Measurement of symptoms

Symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Well-trained, masters-level clinicians conducted PANSS assessments with adequate inter-rater reliability (intraclass correlations: 0.85–0.93). Since previous work has shown that MAS-A ratings, and thus metacognitive capacity, are correlated with degree of negative symptomatology (Hamm et al., 2012), the PANSS Negative subscale (derived from previous factor analysis; (Bell et al., 1994) was utilized in statistical analyses.

2.3. MRI acquisition and analysis

High-resolution structural images were acquired with a Siemens 3 T Tim Trio scanner (Siemens, Erlangen, Germany) using a magnetization prepared rapid acquisition gradient-echo (MPRAGE) T1-weighted sequence. Scans were comprised of 160 sagittal slices with voxel dimensions 1×1×1.2 mm. Resting-state fMRI data was captured during a 6–min resting-state scan with a T2*-weighted gradient echo-planar imaging (EPI) sequence, with the following parameters: 39 interleaved slices, TR/TE 2250/29 ms, flip angle of 79°, field-of-view