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Resting-state functional connectivity between right anterior insula and right orbital frontal cortex correlate with insight level in obsessive-compulsive disorder

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ABSTRACT

Few studies have explored the neurobiological basis of insight level in obsessive-compulsive disorder (OCD), though the salience network (SN) has been implicated in insight deficits in schizophrenia. This study was then designed to investigate whether resting-state (rs) functional connectivity (FC) of SN was associated with insight level in OCD patients. We analyzed rs-functional magnetic resonance imaging (fMRI) data from 21 OCD patients with good insight (OCD-GI), 19 OCD patients with poor insight (OCD-PI), and 24 healthy controls (HCs). Seed-based whole-brain FC and ROI (region of interest)-wise connectivity analyses were performed with seeds/ROIs in the bilateral anterior insula (AI) and dorsal anterior cingulate cortex (dACC). The right AI-right medial orbital frontal cortex (mOFC) connectivity was found to be uniquely decreased in the OCD-PI group, and the value of this aberrant connectivity correlated with insight level in OCD patients. In addition, we found that the OCD-GI group had significantly increased right AI-left dACC connectivity within the SN, relative to HCs (overall trend for groups: OCD-GI > OCD-PI > HC). Our findings suggest that abnormal right AI-right mOFC FC may mediate insight deficits in OCD, perhaps due to impaired encoding and integration of self-evaluative information about OCD-related beliefs and behaviors. Our findings indicate a SN connectivity dissociation between OCD-GI and OCD-PI patients and support the notion of considering OCD-GI and OCD-PI as two distinct disorder subtypes.

1. Introduction

Obsessive-compulsive disorder (OCD) is a relatively common mental disorder with a lifetime prevalence of 1–3%; it is characterized by the presence of unwanted, intrusive thoughts termed obsessions and/or repetitive, ritualistic behaviors known as compulsions (DSM-V; APA, 2013). Previously, patients with OCD who did not have the ability to recognize the excessiveness or unreasonableness of their OCD behaviors were classified as having poor insight (DSM-IV; APA, 1994). Because, OCD patients have been described historically as having preserved insight into their symptoms, the notion of poor insight in OCD is a relatively new feature in OCD research relative to, for instance, schizophrenia, wherein poor insight has long been regarded as a hallmark of psychosis.

The portion of patients with OCD who are classified as having poor insight has been estimated to be in the range of 15–36% of the OCD population (Matsunaga et al., 2002; Kishore et al., 2004; Catapano et al., 2010). Poor insight in OCD has been associated with early age of onset (Catapano et al., 2010), intense symptom severity (Storch et al., 2008; Catapano et al., 2010), co-morbidity with schizotypal personality disorder and body dysmorphic disorder (Catapano et al., 2010; Costa et al., 2012), unfavorable responses to behavioral and pharmacological interventions (Erzegovesi et al., 2001; Himle et al., 2006), and poor prognosis (Matsunaga et al., 2002; Catapano et al., 2010). Furthermore, relative to their counterparts with good insight, OCD patients with poor insight have been reported to have more severe neuropsychological deficits in conflict resolution/response inhibition and verbal memory (Tumkaya et al., 2009; Kashyap et al., 2012). These results suggest that

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poor insight in OCD may represent an important neuropsychological characteristic. If so, understanding insight may be helpful for OCD management.

The neural underpinnings of insight in OCD have not been well elucidated. The only two neuroimaging studies examining this characteristic explicitly pointed to different specific brain regions. Aigner et al. (2005) found evidence for the involvement of the basal ganglia and parietal lobe, whereas Fan et al. (2017) found evidence for involvement of temporal regions. Thus, clarification of the neurobiological basis of insight in OCD is desperately needed.

In recent years, psychiatric disorders have come to be examined extensively on the level of brain-network dysfunction. In particular, analyses of functional connectivity (FC) during a resting-state (rs) within brain networks (intra-rsFC) or between different networks (inter-rsFC) have gained favor as methods for clarifying the phenomenology of mental illness (Shin et al., 2014). Notably, emerging recent evidence has linked intra- and inter-rsFC of the salience network (SN) to insight in psychosis and schizophrenia (Lena Palaniyappan et al., 2012; Raij et al., 2016).

The SN, a stable core brain network, is a large-scale paralimbic-limbic system anchored to the anterior insula (AI) and dorsal anterior cingulated cortex (dACC). It has been shown to be involved in detecting, processing, and integrating internal and external salient information (Sridharan et al., 2008; Menon, 2011). Besides the intra network function, SN was also found to play a crucial role in controlling interactions between task-negative (usually known as default mode network [DMN]) and task-positive (usually known as central executive network [CEN]) networks, which was achieved by initiating transient control signals that engage the CEN to mediate cognitive control processes while disengaging the DMN (Menon and Uddin, 2010; Menon, 2011). SN-related intra- and inter-rsFC alternations have been associated with psychosis in several psychiatric disorders, including schizophrenia, depression, and bipolar disorder (Skaf et al., 2002; Ellison-Wright and Bullmore, 2010; Manoliu et al., 2013; Wotruba et al., 2013).

To examine psychopathology insight directly, Raij et al. (2016) designed a clinical insight task wherein participants evaluate statements about insight content, such as “whether an individual's psychosis-related experiences should be described as a mental illness”. They found that SN activation was related to evaluation of insight-related questions in first-episode psychosis patients. van der Meer et al. (2010) also found that AI activation was associated with clinical insight in schizophrenic patients. Though not found in OCD cohorts, these results suggest that SN connectivity data could be helpful for understanding the neural underpinnings of insight in OCD.

To the best of our knowledge, no prior study has investigated the relationship between SN connectivity and insight in OCD directly. The a few studies that have explored FC of the SN in OCD patients have yielded inconsistent results (Stern et al., 2011; Stern et al., 2012; Weber et al., 2014; Posner et al., 2016; Matsumoto et al., 2010; Song et al., 2011a; Tan et al., 2013; de Wit et al., 2014). These inconsistencies may be related, perhaps in part, to methodological differences. Additionally, given the evidence implicating SN connectivity in psychopathology insight, we supposed that the lack of consideration of the participants' insight presentation may help explain the aforementioned discrepant findings. Thus, we hypothesized that patients with OCD with differing insight levels might differ with respect to the involvement of intra- and inter-rsFCs of the SN in OCD.

The aim of the present study was to investigate whether intra- and/or the inter-rsFC of the SN may underlie insight presence in OCD. To explore specific alterations in intra- and inter-rsFC of the SN that may distinguish between OCD patients with poor insight (OCD-PI) versus those with good insight (OCD-GI), we compared seed-based whole-brain FC of the SN—using the regions of interest (ROIs) of the AI and dACC as seeds—and ROI-wise connectivity within the SN among OCD-GI, OCD-PI, and HC groups. The bilateral AI and bilateral dACC were selected as ROIs because they exhibit stable, reliable SN properties (Pannekoek et al., 2014; Posner et al., 2016). Subsequently, to identify core connectivity changes that could account for degree of insight in OCD, we examined whether the insight levels of patients with OCD correlated with altered FCs involving the SN. Given the exploratory nature of this preliminary study, we chose an unbiased approach with no a priori hypothesis regarding the specific FC pathways that may be associated with insight in OCD.

2. Materials and methods

2.1. Participants

Forty-four patients fulfilled the DSM-IV criteria for OCD participated in the current study. Twenty-two of them were OCD-GI, and the other 22 were OCD-PI.

All the patients were recruited from the psychological clinic at Second Xiangya Hospital of Central South University. The diagnoses of OCD and comorbidity of axis I psychiatric disorder were established by an experienced psychiatrist according to the Structured Clinical Interview for the DSM-IV (SCID), wherein insight quality was also rated and according to which the patients were dichotomized into OCD-GI and OCD-PI groups. The exclusion criteria were: (1) any axis I psychiatric disorder comorbidity, such as schizophrenia, schizoaffective disorder, major depression disorder, bipolar disorder, autism spectrum disorder, drug dependence and eating disorders; (2) a history of major medical or neurological problems (e.g., hypothyroidism, seizure disorder, or brain injury). To control for potential medication effects on our results, only patients who were drug-naïve (19 patients) or did not take psychotropic medications for a minimum of 3 months at the time of enrollment were recruited.

Twenty-five age- and gender-matched students or staff members at Central South University were recruited to form the HC group. The exclusion criteria for HCs were: (1) a history of any psychiatric illnesses; and (2) any major medical or neurological problems.

All participants were right-handed, 16–35 years of age, with ≥ 9 years of formal education. This study was approved by Ethics Committee of the Second Xiangya Hospital of Central South University and all the subjects signed written consent forms before they participated in the study.

2.2. Clinical assessments and verification of OCD-GI vs. OCD-PI classification

After being diagnosed, each participant then underwent a semi-structured interview conducted by an experienced research psychiatrist. During the interview, demographic data and information related to clinical variables were recorded; handedness was classified using the Edinburgh Handedness Inventory (EHI; Oldfield, 1971); and general intelligence was evaluated with the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). All of the participants completed the Beck Depression inventory (BDI; Beck et al., 1961) and the State Trait Anxiety Inventory (STAI; Spielberger et al., 1983) to determine their depression and anxiety levels. OCD severity was assessed with the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989).

Verification of OCD-GI vs. OCD-PI classification was based on the Brown Assessment of Beliefs Scale (BABS; Eisen et al., 1998). The BABS is a clinician-administrated 7-item scale that was developed to assess insight across a variety of psychiatric disorders. The Chinese version of the BABS has been confirmed to have good reliability and validity (Niu et al., 2016). Specific probes of this scale included conviction, perception of other's views or beliefs, explanation of differing views, fixity of ideas, attempts to disprove beliefs, insight, and ideas/delusions of reference. In the BABS, each item is rated on a scale ranging from 0 (non-delusional or least pathological) to 4 (delusional or most patho-