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Altered functional connectivity during self- and close other-reflection in patients with bipolar disorder with past psychosis and patients with schizophrenia

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ABSTRACT

Disturbances in implicit self-processing have been reported both in psychotic patients with bipolar disorder (BD) and schizophrenia. It remains unclear whether these two psychotic disorders show disturbed functional connectivity during explicit self-reflection, which is associated with social functioning and illness symptoms. Therefore, we investigated functional connectivity during explicit self-reflection in BD with past psychosis and schizophrenia. Twenty-three BD-patients, 17 schizophrenia-patients and 21 health controls (HC) performed a self-reflection task, including the conditions self-reflection, close other-reflection and semantic control. Functional connectivity was investigated with generalized psycho-physiological interaction (gPPI). During self-reflection compared to semantic, BD-patients had decreased connectivity between several cortical-midline structures (CMS) nodes (i.e., anterior cingulate cortex, ventromedial prefrontal cortex), the insula and the head of the caudate while HC showed increased connectivities. Schizophrenia-patients, during close other-reflection compared to semantic, demonstrated reduced ventral-anterior insula-precuneus/posterior cingulate cortex (PCC) functional connectivity, whereas this was increased in HC. There were no differences between BD and schizophrenia during self- and close other-reflection. We propose that decreased functional connectivity between the CMS nodes/insula and head of the caudate in BD-patients may imply a reduced involvement of the motivational system during self-reflection; and the reduced functional connectivity between the ventral-anterior insula and precuneus/PCC during close other-reflection in schizophrenia-patients may subserve difficulties in information integration of autobiographical memory and emotional awareness in relation to close others. These distinctive impaired patterns of functional connectivity in BD and schizophrenia (compared to HC) deserve further investigation to determine their robustness and associations with differences in clinical presentation.

1. Introduction

Self-processing is important for psychotic disorders including bipolar disorder (BD) with a history of psychosis and schizophrenia, given a close relationship between psychotic symptoms and impaired distinction between the internal (self) and external world (Brookwell et al., 2013). Self-processing could be either explicit or implicit. Explicit self-reflection refers to the cognitive process of judging whether certain information (e.g., traits and attitudes) describes oneself (van der Meer et al., 2010), while implicit self-reflection is related to self-reflective processing during rest. On the neural level, explicit self-reflection has consistently shown activation in areas termed as the cortical midline structures (CMS) and the insula (Modinos et al., 2009; Northoff and Bermpohl, 2004; Northoff et al., 2006; van der Meer et al., 2010). The Default Mode Network (DMN) is assumed to be related to implicit self-reflection (Gusnard and Raichle, 2001). Interestingly, it has been

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shown that explicit and implicit self-reflection have not only similarities in their underlying neural mechanisms but also differences (Qin and Northoff, 2011; Whitfield-Gabrieli et al., 2011). Previous neuroimaging studies have shown disturbed DMN connectivity in both BD and schizophrenia patients (Whitfield-Gabrieli and Ford, 2012). A direct comparison between BD with a history of psychosis and schizophrenia patients has shown both shared and unique impairments in the DMN (Khadka et al., 2013; Meda et al., 2012; Ongur et al., 2010). However, there have been no connectivity studies to further elucidate the neural correlates during explicit self-reflection in BD with a history of psychosis and schizophrenia. This is important, because it has been shown that explicit self-reflection links to symptoms such as hallucination, emotional withdrawal and depression (Lysaker et al., 2005), and may affect social cognition via its influence on thinking about other's mental states (Dimaggio et al., 2008; Mitchell et al., 2005). Therefore, the present investigation of explicit self-reflection in BD with a history of psychosis and schizophrenia might help to understand the contributions of explicit self-reflection to the symptoms and social cognition in BD and schizophrenia.

The consistently activated CMS during explicit self-reflection (hereafter self-reflection) consist of the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), dorsomedial prefrontal cortex (DMPFC) and ventromedial prefrontal cortex (VMPFC). The CMS and the insula have been suggested to work closely together in a network (Northoff and Bermpohl, 2004; van der Meer et al., 2010). Functional connectivity of these self-reflection areas has been investigated in healthy individuals. Specifically, during self-reflection, compared to valence judgment, reduced functional connectivity among the CMS areas and increased functional connectivity between the CMS and areas outside the CMS have been observed (Van Buuren et al., 2010, 2012). Furthermore, it has been shown that the DMPFC tends to have strong functional connectivity with cognitive control areas, while the VMPFC has shown strong functional connections to affective areas during self-reflection (Schmitz and Johnson, 2006). Although specific connectivities vary across studies, connections between nodes of the self-reflection network, as well as connections between these nodes and other brain areas, contribute to normal self-reflection.

However, to our knowledge, despite comparisons of the DMN between BD and schizophrenia patients, functional connectivity within the explicit self-reflective network has not been investigated in BD and schizophrenia patients. In addition, reflection on self and a close other has been shown comparable in many respects (Murray et al., 2012; van der Meer et al., 2010), but no study has shed light on functional connectivity during close other-reflection yet. Therefore, we also investigated functional connectivity during close other-reflection.

In summary, we aimed to investigate functional connectivity of self- and close other-reflection in BD patients with a history of psychosis and schizophrenia patients. Considering the findings in healthy individuals, we hypothesized BD and schizophrenia patients to show differences in connectivity between areas within the reflective network (i.e., CMS/insula), and/or between the CMS/insula nodes and non-CMS/insula areas when compared to healthy individuals. A direct comparison between BD patients with a history of psychosis and schizophrenia patients was included in order to explore whether they were comparable in functional connectivity during self- and close other-reflection.

2. Materials and methods

2.1. Participants

The study involved 23 BD patients and 17 schizophrenia patients, who were recruited from mental health care institutions in the North of the Netherlands. Around 20–50% BD patients report psychotic episodes, representing the most severe BD population (Keck et al., 2003; Pope and Lipinski, 1978). Moreover, given that self-reflection has been associated with illness insight (clinical and cognitive insight) (van der Meer et al., 2013), the current schizophrenia data were used from a previous study (van der Meer et al., 2013) that included measures of insight, in order to have comparable levels of illness insight in BD and schizophrenia patients. Clinical and cognitive insight were measured with the Schedule of Assessment of Insight-Expanded version (SAI-E; Kemp and David, 1997) and the Beck Cognitive Insight Scale (BCIS; Beck et al., 2004), respectively. Diagnosis was confirmed with the Mini International Neuropsychiatric Interview-Plus 5.0.0 (MINI-Plus; Sheehan et al., 1998). Inclusion criteria were no medication change at least one week prior to scanning, no psychiatric disorders other than BD or schizophrenia, no neurological/somatic disorders which might affect the central nervous system, no electroconvulsive therapy in the year before scanning, free from MRI-incompatibilities (e.g., metal implant, pregnancy), and for BD patients a life-time history of psychotic symptoms was required. Five BD patients with excessive head movements (more than 3° and/or 3 mm in any direction), missing log files of the task, or a lack of imaging data had to be excluded, leaving a final sample of 18 BD patients.

The Quick Inventory of Depressive Symptomatology (QIDS; Rush et al., 2003) and Young Mania Rating Scale (YMRS; Young et al., 1978) were administered in BD and schizophrenia patients to measure the current severity of depression and mania, respectively. The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) was conducted to assess the severity of current psychotic symptoms. Lower scores on the QIDS, YMRS and PANSS reflected less symptom severity. Intelligence was measured with the Dutch adult reading test (DART; Schmand et al., 1991).

Twenty-one healthy controls (HC) were recruited, who had no neurological/somatic disorders that could have influenced the central nervous system. The MINI-Plus was administered in HC to exclude participants with past or current psychiatric disorders. In addition, the QIDS and DART were also conducted in HC. In summary, 18 BD patients with a history of psychotic symptoms, 17 schizophrenia patients and 21 HC were included in our final analyses.

This study was approved by the Medical Ethics Committee of the University Medical Center Groningen and was based on the Declaration of Helsinki (2008). Informed consent was obtained from all individual participants included in the study. Differences in activation patterns during self- and close other-reflection of the BD patients, schizophrenia patients and HC were published previously (Zhang et al., 2015), while the current report concerns connectivity differences.

2.2. Self-reflection task

During the self-reflection task (Zhang et al., 2015), participants were instructed to judge whether a sentence with a trait word was applicable to them (self-reflection) or a close other (close other-reflection). Notably, a close other was named by the participant before scanning. Judgments were made on a four-point continuum (1-fully disagree; 4-fully agree). Valence (positive and negative) and quality (mental and physical) were balanced within the conditions self and close other. In the control condition, participants judged whether sentences with general knowledge were true or false (semantic control), with an equal number of true and false statements.

In each trial, a sentence was presented for 4000 ms followed by a fixation cross for 500 ms. Each condition included 60 sentences. These sentences were organized in blocks (five trials per block) semi-randomly in terms of the three conditions to avoid consecutive presentation of the same condition.

2.3. Image acquisition

fMRI scanning was performed using a 3.0 Tesla whole body scanner (Philips Intera, Best, NL). The head of the participant was kept still using an elastic band and foam cushions on each side of the head.