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Brain activation during self- and other-reflection in bipolar disorder with a history of psychosis: Comparison to schizophrenia

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ABSTRACT

Objectives: Reflecting on the self and on others activates specific brain areas and contributes to metacognition and social cognition. The aim of the current study is to investigate brain activation during self- and other-reflection in patients with bipolar disorder (BD). In addition, we examined whether potential abnormal brain activation in BD patients could distinguish BD from patients with schizophrenia (SZ).
Methods: During functional magnetic resonance imaging (fMRI), 17 BD patients, 17 SZ patients and 21 healthy controls (HCs) performed a self-reflection task. The task consisted of sentences divided into three conditions: self-reflection, other-reflection and semantic control.
Results: BD patients showed less activation in the posterior cingulate cortex (PCC) extending to the precuneus during other-reflection compared to HCs ($p = 0.028$ FWE corrected on cluster-level within the regions of interest). In SZ patients, the level of activation in this area was in between BD patients and HCs, with no significant differences between patients with SZ and BD. There were no group differences in brain activation during self-reflection. Moreover, there was a positive correlation between the PCC/precuneus activation during other-reflection and cognitive insight in SZ patients, but not in BD patients.
Conclusions: BD patients showed less activation in the PCC/precuneus during other-reflection. This may support an account of impaired integration of emotion and memory (evaluation of past and current other-related information) in BD patients. Correlation differences of the PCC/precuneus activation with the cognitive insight in patients with BD and SZ might reflect an important difference between these disorders, which may help to further explore potentially distinguishing markers.

1. Introduction

Several studies have demonstrated disturbed metacognitive processing in patients with bipolar disorder (BD) (Batmaz et al., 2014; Samamé, 2013; Thaler et al., 2013). Self- and other-reflection can be considered metacognitive processes and refer to the evaluation process by which people determine to what extent certain cues (e.g. traits and attitudes) apply to themselves or others respectively (Van der Meer et al., 2010). Patients with BD may show comparable impairments in several metacognitive domains as patients with schizophrenia (SZ) (Brüne, 2005; Rabin et al., 2014; Thaler et al., 2013) in whom self- and other-reflection have been investigated more abundantly (Bedford et al., 2012; Holt et al., 2011; Murphy et al., 2010; Pauly et al., 2013; Van der Meer et al., 2013). However, little is known about self- and other-reflection and the underlying neural correlates in BD patients.

Self-reflection and other-reflection are related to the function of cortical midline structures (CMS). The CMS consist of the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), dorsal medial prefrontal cortex (DMPFC) and ventral medial prefrontal cortex (VMPFC) (Northoff & Bermpohl, 2004). The *cognitive neuropsychiatric self-reflection/self-appraisal model* (Van der Meer et al., 2010) suggests that these different structures each have a specific contribution to reflective processing. According to this model, directing attention is associated with activation of the ACC. The PCC is involved in consultation of autobiographical memory to facilitate decisions whether the confronted stimuli apply to self or others. Ultimately, the final decision is proposed to be related to activation of the DMPFC. In addition, the insula seems to be involved in reflective processing and is associated with evaluation of internal self-state and somatic feedback (Craig, 2009). These processes are similar in both self- and other-reflection (Van der Meer et al., 2010). Moreover, a specific role in tagging self-relevant information

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has been hypothesized for the VMPFC. Murray et al. (2012) have reported evidence that the level of activation in the VMPFC is mediated by the degree of self-relatedness. They demonstrated that the VMPFC is activated by stimuli related to self and, to a lesser extent, a close other, but not by stimuli referring to a public other.

There are currently, to our knowledge, no studies investigating the neural correlates of self- and other-reflection in BD patients. However, studies conducted in SZ patients have revealed abnormal brain activations during self- and other-reflection that occur during psychotic periods and seem to persist during stable periods after psychotic symptoms disappear. Compared to healthy individuals, SZ patients have shown less activation during self-reflection in the PCC (Van der Meer et al., 2013), inferior temporal gyrus extending to the middle temporal gyrus (Pauly et al., 2013) and precuneus (Murphy et al., 2010), but also hyper-activation in the PCC has been reported (Holt et al., 2011). During other-reflection, less activation in the VMPFC, ACC, insula and cuneus (Pauly et al., 2013) and PCC/precuneus (Van der Meer et al., 2013) has been reported. In addition, comparing self to other has shown less activation in the DMPFC (Bedford et al., 2012), and higher activation in the PCC/precuneus (Shad et al., 2012). These studies suggest that the self- and other-reflective network is abnormally activated in SZ patients during reflective processing, even in the absence of current symptoms (Holt et al., 2011).

Lichtenstein et al. (2009) have reported that the same genes could lead to vulnerability for both of these disorders and some authors even suggest that BD and SZ are an expression of different levels of severity on the same disease continuum rather than two completely different diseases (Craddock & Owen, 2005). It has indeed been shown that patients with BD and SZ share several clinical features (e.g. anhedonia, psychotic symptoms; American Psychiatric Association, 2013; Kempf et al., 2005). Moreover, patients with both BD and SZ have shown disturbed metacognitive processing in social and emotional domains such as theory of mind (e.g. Brüne, 2005; Rabin et al., 2014; Thaler et al., 2013) which is closely associated with self- and other-reflection (Happé, 2003; Mitchell et al., 2005; Saxe et al., 2006). In addition, while healthy individuals tend to attribute more positive than negative events to themselves during self-reflection (self-serving bias; Mezulis et al., 2004), this tendency is disturbed in both SZ patients (Mehl et al., 2014; Mizrahi et al., 2008) and BD patients (Lyon et al., 1999). However, BD and SZ have been classified as two different disorders for a long time. SZ patients have shown worse cognitive functioning than BD patients (Krabbendam et al., 2005), which also implies differences between BD and SZ. Therefore, it would be interesting to explore whether potential abnormal activations during self- and other-reflection in BD patients are comparable to those in SZ patients or whether these represent unique neurobiological features distinguishing BD patients from SZ patients.

In order to maximize comparability between BD and SZ groups, and also potentially get more pronounced differences compared to healthy individuals, we recruited a relatively homogeneous group of BD patients who had a history of psychosis, but were not currently experiencing a psychosis. Notably, it has been found that activation during reflective processing is associated with level of illness insight (Van der Meer et al., 2013). BD patients have generally a good level of illness insight when they are not in a manic episode (Cassidy, 2010), while in SZ patients illness insight could be low during all phases of illness (Arango & Amador, 2011; Yen et al., 2002). Therefore, we aimed to investigate differences between BD and SZ in brain activation during self- and other-reflection in patients with good insight only.

In the present study, we aimed to investigate the neural correlates during a self-reflection task in BD patients with a history of psychotic symptoms. Based on the importance of the self-reflective network during both self- and other-reflective processing and their established deficiencies in relation with psychotic symptomatology, we hypothesized that BD patients would show abnormal activation within the self-reflection network compared to healthy individuals. Additionally, differences between patients with BD and SZ in brain activation during reflective processes, as well as correlations with insight, were explored in order to examine whether the potential abnormalities in BD were specific for BD.

2. Methods

2.1. Participants

This study included BD patients, SZ patients and healthy controls (HCs). The following inclusion criteria were applied to both BD and SZ patients: (1) Being stable on current medication and no medication change in the week before scanning; (2) no electroconvulsive therapy in the year prior to the scan; (3) having no psychiatric disorders other than BD or SZ (e.g. substance use disorder); and (4) for BD patients, having a history of an episode with psychotic symptoms, lifetime. A specific inclusion criterion for HCs was no current or past psychiatric disorders. Additional inclusion criteria for all participants were: (1) No somatic or neurological disorders that may have impacted the central nervous system; and (2) no MRI-incompatibilities (e.g. metal implants, claustrophobia or pregnancy).

Following these criteria, 21 BD patients (8 males, 13 females) were recruited from several mental health care institutions in the North of the Netherlands. Diagnosis of BD was confirmed with the Mini International Neuropsychiatric Interview-Plus 5.0.0 (MINI-Plus; Sheehan et al., 1998).

Based on the final BD patient sample (see Section 3.1 Patient disposition), 17 SZ patients (11 males, 6 females) were selected from a sample of a previous study (Van der Meer et al., 2013). These participants were not significantly different from the BD sample on intelligence (measured with the Dutch reading test for adults (NLV); Schmand et al., 1991), age, gender and level of education. Diagnosis of SZ was confirmed with the MINI-Plus. Because self-reflection is also associated with insight into illness (both clinical insight and cognitive insight) (Van der Meer et al., 2013), it is important to match patients with BD and SZ on insight to exclude alternative explanations for any potential group differences. We matched SZ patients with BD patients on illness insight, based on the Schedule of Assessment of Insight-Expanded version (SAI-E, clinical insight; Kemp & David, 1997) and the Beck Cognitive Insight Scale (BCIS, cognitive insight; Beck et al., 2004). The BCIS is composed of a self-reflectiveness subscale and a self-certainty subscale. Cognitive insight is measured by a composite score of these two sub-scales (i.e. score on the self-reflectiveness minus the self-certainty score). BD and SZ patients were matched on the BCIS subscales and the BCIS composite score. Higher scores on the SAI-E and BCIS indicate better insight.

In addition, we included a group of 21 HCs (12 males, 9 females) matched on intelligence, gender and level of education with both patient groups. The HC group was the same as in a previous study (Van der Meer et al., 2013).

The present study was performed in accordance with the Helsinki Declaration of 1975 and was approved by the Medical Ethics Committee of the University Medical Center Groningen (UMCG). All participants gave written informed consent and received monetary compensation (€45) for participation.

2.2. Clinical assessment and measures

Current severity of depression and mania was measured by the Quick Inventory of Depressive Symptomatology (QIDS-SR; Rush et al., 2003) and Young Mania Rating Scale (YMRS; Young et al., 1978), respectively. A depressive state was defined as a score of >10 on the QIDS-SR (Rush et al., 2006) and a mania state was defined as a score of >8 on the YMRS (Mercer & Becerra, 2013). Current psychotic symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). The PANSS is composed of three dimensions: