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Research paper

Decreased medial prefrontal cortex activation during self-referential processing in bipolar mania

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ABSTRACT

Background: Patients with bipolar disorder in mania exhibit symptoms pointing towards altered self-referential processing, such as decreased self-focus, flight of ideas and high distractibility. In depression, the opposite pattern of symptoms has been connected to increased activation of medial prefrontal cortex (mPFC) during self-referential processing. In this study, we hypothesized that (1) patients with mania will exhibit decreased activation in the mPFC during self-referential processing and (2) will be more alexithymic and that levels of alexithymia will correlate negatively with mPFC activation.

Methods: The neural response to standardized pictures was compared in 14 patients with bipolar I disorder in mania to 14 healthy controls using blood oxygen level dependent contrast magnetic resonance imaging. Participants were asked to indicate with button press during the scanning session for each picture whether the pictures personally related to them or not. Toronto alexithymia scale (TAS) scores were recorded from all participants.

Results: In the group analysis, patients with mania exhibited decreased activation in a predefined region of interest in the mPFC during self-referential processing compared to healthy controls. Patients with mania showed significantly higher levels of alexithymia, attributable to difficulties in identifying and describing emotions. Activation in the mPFC correlated negatively with levels of alexithymia.

Limitations: Results presented here should be replicated in a larger group, potentially including unmedicated patients.

Conclusions: The finding of decreased mPFC activation during self-referential processing in mania may reflect decreased self-focus and high distractibility. Support for this view comes from the negative correlation between higher alexithymia scores and decreased mPFC activation. These findings represent an opposite clinical and neuroimaging pattern to findings in depression.

1. Introduction

Self-referential processing, the processing of stimuli related to one's own self, and its neural correlates have recently attracted increased research interest in the context of affective disorders, especially depression (Grimm et al., 2009; Lemogne et al., 2012, 2009; Yoshimura et al., 2010). There are a number of important aspects in the clinical presentation of patients with mania, which suggest altered processing of self-referential stimuli, especially disorders of thought content and disturbances in the form or process of thinking. Regarding the thought content, patients with mania present with decreased self-focus and external orientation of attentional focus. Coherent with this decreased self-focus, the disturbances in the form of thinking are characterized by increased distractibility and flight of ideas, the opposite of rumination, which is observed during depression and has been connected to an increased self-focus (Lemogne et al., 2012; Nolen-Hoeksema et al., 2008).

In healthy individuals, tasks involving the processing of stimulus

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material related to the own self (i.e., self-referential processing) activates the medial and lateral prefrontal cortex, orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), precuneus, posterior cingulate cortex (PCC) and temporoparietal junction (TPJ) (Denny et al., 2012; Northoff et al., 2006; Northoff and Bermpohl, 2004).

To our knowledge, to date, no study has investigated self-referential processing in bipolar mania using functional magnetic resonance imaging (fMRI). Only few studies have investigated resting state brain activity in bipolar disorder (Das et al., 2014; Magioncalda et al., 2014). Magioncalda et al. (Magioncalda et al., 2014) found mood state dependent alterations in resting state functional connectivity in the default mode network pointing towards a dysfunction of mPFC and ACC in bipolar disorder. In their systematic review of resting state network-functional MRI in bipolar disorder Vargas and colleagues (Vargas et al., 2013) found that studies consistently reported alterations in the connectivity patterns of PFC areas in bipolar patients compared to healthy controls. Some authors found increased connectivity of mPFC (Chai et al., 2011), and others decreased (Anand et al., 2009). Further evidence for mPFC dysfunction in bipolar disorder comes from neurochemical and neuropathological studies, which found reduced levels of metabolites and a volume decrease in mPFC in patients with bipolar disorder compared to healthy controls (Ozdel et al., 2012; Savitz et al., 2014).

Studies investigating the neural basis of self-referential processing in patients with depression (Grimm et al., 2009; Johnson et al., 2009; Kross et al., 2009; Lemogne et al., 2009; Yoshimura et al., 2010), for a review see Lemogne et al. (2012) found altered activation of the medial prefrontal cortex (mPFC). Lemogne et al. (2009) and Yoshimura et al. (2010) examined self-referential processing in patients with depression using a block design and found increased activation of dorsal mPFC. Using an event-related design Grimm et al. (2009) and Johnson et al. (2009) found decreased activation of mPFC during self-referential processing in patients with depression. These studies also report increased activation of the mPFC during the control condition in patients with depression, meaning that the finding of decreased mPFC activation during self-referential processing might be relative due to statistical contrast. Lemogne et al. (2012) interpreted these findings as phasic (as revealed by a block design) and tonic (as revealed by an event-related design) hyperactivation of mPFC.

A recent meta-analysis (Kuhn and Gallinat, 2011) focused on changes in resting state brain activity in patients with depression and schizophrenia, revealing that patients with depression exhibit increased activation in a ventromedial prefrontal region during rest compared to healthy individuals.

In summary, there are no studies examining self-referential processing in bipolar mania, but studies investigating the resting state network point towards mPFC dysfunction in bipolar disorder. Studies of self-referential processing in depression suggest an increased activation of mPFC, which clinically may correspond to the increased self-focus and the increased tendency to ruminate, that is, to repeat negative thoughts with high self-relevance. The opposite, namely decreased self-focus, flight of ideas, high irritability, and externally oriented attentional focus characterizes mania; therefore, we hypothesized that mPFC activation would be decreased in mania.

The concept of alexithymia refers to difficulties in identifying and describing emotions, constricted (self-referential) imaginal processes and an externally oriented focus of attention (Taylor, 1984; Taylor and Taylor, 1997). The ability to recognize and experience emotions allows an individual to form a representation of his own emotions (Damasio, 2003; Northoff et al., 2006). Such self-referential emotion processing has been associated with the mPFC (Phan et al., 2002), which is a key part of the default mode network (DMN) (Gusnard and Raichle, 2001). Lieburg et al. (2012) investigated the connectivity within DMN in alexithymic compared to non-alexithymic study participants. Alexithymic participants showed lower connectivity within medial frontal and temporal areas as compared to non-alexithymic participants. This suggests a link between high levels of alexithymia and altered, possibly reduced, frontal activation. Given the above-mentioned clinical alterations in mania, one may expect higher levels of alexithymia in patients with mania, which may be related to altered PFC activation.

Here we conducted an fMRI study examining the neural correlates of self-referential processing in patients with mania. We hypothesized that (1) during self-referential versus non-self-referential processing there would be decreased mPFC activation in patients with mania, (2) patients with mania would exhibit higher levels of alexithymia as measured by the Toronto Alexithymia Scale (TAS) (Bagby et al., 1994a, 1994b; Kupfer et al., 2001), which would correlate negatively with mPFC activation.

2. Materials and methods

2.1. Participants

We included 14 subjects diagnosed with bipolar I disorder according to DSM-IV (American Psychiatric Association 2000) as well as 14 healthy controls in the study. Out of 17 patients with bipolar mania who underwent fMRI scanning, 14 were finally included. We excluded 3 patients due to excessive movement (> 4 mm per run).

All subjects were right-handed as assessed with the Edinburgh Handedness Inventory (Oldfield, 1971) and general MRI exclusion criteria (pregnancy, metal implants, tattoos and permanent make-up, irremovable piercing) were considered.

No subject in the mania nor in the healthy control group had a (comorbid) psychiatric axis-I disorder, as assessed with SCID-I (Structured Clinical Interview for DSM-IV) (First et al., 1997). Further exclusion criteria were limiting general medical condition or history of neurological disease.

Patients were diagnosed with bipolar I disorder and at inclusion date fulfilled the criteria for a manic episode according to DSM IV, but not mixed or depressive episode. We used the Young Mania Rating Scale (YMRS) (Young et al., 1978) to quantify manic symptoms.

Patients were allowed to take antimanic medication such as neuroleptics or mood stabilizers (Table 1), but no benzodiazepines. Upon the day of fMRI examination, in agreement with their psychiatrist, patients took their prescribed medication after scanning, which took place early in the morning.

Groups did not differ significantly with regard to age, gender, verbal IQ and smoking status (Table 1).

The study was conducted in compliance with the Declaration of Helsinki and was authorized by the local ethics committee of Charité-Universitätsmedizin Berlin. Written informed consent was obtained from all participants. The study was conducted in accordance with current safety guidelines and no known risks were associated with the participation.

2.2. Experimental design

During fMRI scanning subjects performed the following experimental task: each trial started with a passive picture viewing phase (4 s), followed by questions related to self-referentiality of the stimulus (“Does this picture personally relate to you?”) and episodic memory retrieval (“Is this picture familiar to you?”) (Fig. 1). The questions were presented for 3 s each in randomized order. Participants were instructed to consider an answer carefully and reply within the 3 s time frame, when the question appeared on the screen.

Participants responded with a “yes” or “no” button press with the left or right index finger, respectively. Each trial ended with a fixation cross period (range: 13.65–19.5 s; mean: 15.99 s). This rather slow task design has been chosen, because behavioural pilot experiments showed that participants needed relatively long to process the rather complex stimulus material and to come to a decision in the self-referential as well as the memory task.