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DISSERTATION

Neural Substrates of Social and Self-Referential Stimulus Processing in Mania as investigated with fMRI

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To my family

Abstract

Introduction: Patients with mania show alterations of social behaviour, characterized by excessive involvement in pleasurable social activities and inappropriate social communication and interaction. These deficits in social competence may be caused by underlying impairments in social cognitive functions. Manic patients also exhibit feeling of grandiosity, that hint at an impaired processing of self-referential stimuli. Based on clinical observations and previous behavioural findings of social deficits in mania, we studied the neural substrates of (1) impaired social cognition and (2) self-referential processsing for the first time in patients with mania in their acute phase. We focused on areas such as the medial prefrontal cortex and the temporo-parietal junction, which are involved in social cognition in healthy subjects, and the cortical midline structures, especially the medial prefrontal cortex, which is implicated in self-referential processing.

Methods: In the first paradigm the neuronal response to standardized pictures with social and non-social content was compared in 14 patients with bipolar 1 disorder in mania to healthy controls using BOLD-fMRI as a surrogate marker of neuronal activity. In the second paradigm we investigated the self-referential processing in the same design, by asking the patients to indicate, whether the presented pictures personally related to them or not. In the group analysis the results of both experiments were contrasted with those of 14 matched healthy volunteers.

Results: The study (1) found in the group contrast diminished response in patients with mania in the dorsomedial prefrontal cortex and increased response in the temporo-parietal junction in response to social stimuli. The response in the temporo-parietal junction correlated positively with the score of delusional ideation. The study (2) found decreased activation to self-referential stimuli in mania in ventromedial prefrontal cortex and increased response in precuneus/posterior cingulate cortex.

Discussion: The finding of decreased activation to social stimuli in patients with mania in the dorsomedial prefrontal cortex may be related to deficits in making cognitive

inferences about others' mental states. The finding of increased activation of the temporo-parietal junction in manic patients is likely related to exaggerated attribution of meaning to social stimuli. The pattern of increased activation in precuneus/posterior cingulate cortex and decreased activation in ventromedial prefrontal cortex to self-referential stimuli in mania may reflect the clinical presentation of increased focus on external content, resulting in increased distractibility and flight of ideas in mania.

Zusammenfassung

Hintergrund: Patienten mit Manie zeigen Veränderungen des sozialen Verhaltens, die durch übermäßige Einbindung in angenehme soziale Aktivitäten und unangemessene soziale Kommunikation und Interaktion geprägt sind. Diese Beeinträchtigungen der sozialen Kompetenz gründen in Störungen der sozialen kognitiven Funktionen. Ebenso kann das Gefühl der Grandiosität bei Patienten mit Manie als Hinweis auf eine gestörte Verarbeitung von selbst-referenziellen Stimuli verstanden werden. Basierend auf klinischen Beobachtungen und früheren Verhaltensstudien zu sozialen Defiziten bei Manie adressiert die vorliegende Arbeit das mögliche neuronale Substrat (1) gestörter sozialer Kognition und (2) selbst-referenzieller Verarbeitung erstmals bei Patienten mit Manie in ihrer manischen Phase. Dabei wird ein Schwerpunkt auf die Untersuchung von Arealen gelegt, die wie der mediale präfrontale Kortex und temporo-parietaler Übergang ausgehend von bildgebenden Untersuchungen bei Gesunden in sozialer Kognition beteiligt sind, während kortikale Mittellinienstrukturen - hier insbesondere der mediale präfrontale Kortex - bei selbst-referenzieller Verarbeitung eine Rolle zu spielen scheinen.

Methoden: Bei 14 Patienten mit einer bipolaren 1 Erkrankung wurde im ersten Paradigma zur sozialen Kognition die neuronale Antwort auf standardisierte Bilder mit sozialen und nicht-sozialen Inhalt mittels BOLD-fMRI als Surrogatparameter neuronaler Aktivität in einem ereigniskorrelierten Design verglichen. In einem zweiten Paradigma untersuchten wir selbst-referenzielle Verarbeitung im gleichen Design, indem die Patienten angaben, ob die präsentierten Bilder für sie einen persönlichen Bezug hatten oder nicht. In einer Gruppenanalyse wurden die Ergebnisse beider Untersuchungen dann mit denen von 14 gleichaltrigen Gesunden kontrastiert.

Ergebnisse: In Studie (1) zeigte sich im Gruppenkontrast eine verminderte Aktivierung bei Patienten mit Manie im dorsomedialen präfrontalen Kortex und eine erhöhte Aktivität im temporo-parietalen Übergang in Antwort auf soziale Stimuli. Die Aktivierung im temporo-parietalen Übergang korrelierte dabei positiv mit den skalierten wahnhaften

Vorstellungen. Studie (2) ergab eine verminderte Aktivierung in Antwort auf selbst-referenzielle Stimuli bei den manischen Patienten im ventromedialen präfrontalen Kortex, während sie im Precuneus / posterioren cingulären Cortex vermehrt aktivierten.

Diskussion: Die verminderte Aktivierung auf soziale Stimuli im dorsomedialen präfrontalen Kortex bei Patienten mit Manie kann zu Defiziten bei Rückschlüssen auf mentale Zustände anderer in Beziehung gesetzt werden. Die vermehrte Aktivierung des temporo-parietalen Übergangs bei manischen Patienten spiegelt wahrscheinlich eine übertriebene Bedeutungsattribution zu den sozialen Stimuli wider. Ebenso kann das Muster der erhöhten Aktivierung in Precuneus / posterioren cingulären Cortex und die verminderte Aktivierung im ventromedialen präfrontalen Kortex auf selbst-referenzielle Stimuli den verstärkten Fokus auf externe Inhalte reflektieren, was klinisch mit einer erhöhten Ablenkbarkeit und Ideenflucht korreliert.

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Abbreviations

MPFC	Medial prefrontal cortex
TPJ	Temporo-parietal junction
CMS	Cortical midline structures
vMPFC	Ventromedial prefrontal cortex
dMPFC	Dorsomedial prefrontal cortex
ACC	Anterior cingulate cortex
PCC	Posterior cingulate cortex
fMRI	Functional magnetic resonance imaging
BOLD	Blood Oxygen-Level Dependent
ToM	Theory of mind
FFA	Fusiform face area
OFA	Occipital face area
STS	Superior temporal sulcus
TP	Temporal poles
BD	Bipolar disorder
pACC	Perigenual anterior cingulate cortex
DMN	Default-mode network
SACC	Supragenual anterior cingulate cortex
SN	Salience network
DSM-IV	Diagnostic and statistic manual of mental disorders, IV edition
SCID I	Structured Clinical Interview for DSM-IV Part I
IQ	Intelligence quotient
MWT-B	Mehrfachwahl-Wortschatz-Intelligenztest
IAPS	International Affective Picture System
PDI	Peters Delusion Inventory
TAS	Toronto Alexithymia Scale
MNI	Montreal Neurological Institute
GLM	General linear model
HRF	Hemodynamic response function
ANOVA	Analysis of variance
FDR	False discovery rate
ROI	Region of Interest
ALE	Activation Likelihood Estimation
SVC	Small volume correction
FWE	Family-wise error
SD	Standard deviation
VBM	Voxel-based morphometry
BA	Brodmann area
CEN	Central executive network

1. INTRODUCTION

1.1. General Overview

In everyday life, we process information differently based on whether it is related to ourselves or to others. The neural basis of self-referential and social stimulus processing has increasingly become the focus of neuroscience, particularly, neuroimaging in the recent years. Social stimuli are those, that a person identifies as relevant to interpersonal relationships. For example, pictures including other people will be processed differently from pictures with objects or landscapes. Previous studies in healthy participants mostly studied explicit social processing. However, processing of such stimuli also occurs implicitly, without an explicit instruction. Previous studies have identified medial prefrontal cortex (MPFC) and the temporo-parietal junction (TPJ) as areas consistently involved in social cognition.

Social and self-referential stimulus processing are interconnected functions of the human brain. Previous studies have identified brain areas, collectively referred to as cortical midline structures (CMS), consistently involved during exposure to self-relevant stimuli as opposed to non-self-relevant ones. Self-specific stimuli are those that a person identifies as highly personally relevant. An identification of a stimulus as self-specific, or, self-referential, can happen through a variety of mechanisms. For example, a picture with a snowboarder going down the fresh slope can be self-referential if a person is a snowboarder herself and can relate to the feeling evoked by the picture, or, she wishes to learn snowboarding, or, she has a fear of snowboarding. The cortical midline structures involved in self-referential processing include the ventromedial prefrontal cortex (vMPFC), dorsomedial prefrontal cortex (dMPFC), anterior cingulate cortex (ACC), and the posterior cingulate cortex (PCC).

As social and self-referential stimulus processing underlies the social behaviour of individuals, we chose to study patients with bipolar disorder in mania, who show alterations of social behaviour and who, hence, would show alterations of brain region

activation in comparison to healthy participants during social- or self-referential stimulus processing.

Here I present the results of two experiments that investigate the neural signature of (1) implicit social and (2) self-referential stimulus processing in patients with bipolar disorder in mania. To investigate the neural correlates, we analyze the human brain data obtained by functional magnetic resonance imaging (fMRI) during picture viewing and performance of a self-referential judgement task.

The first study found diminished Blood Oxygen-Level Dependent (BOLD) responses to social stimuli in patients with mania in the dMPFC, an area associated with cognitive aspects of social cognition. This may be related to deficits in making cognitive inferences about others' mental states. At the same time, manic patients revealed increased activation of the TPJ, compared to healthy controls, likely related to exaggerated attribution of meaning to social stimuli. The second study found diminished BOLD responses to self-referential stimuli in mania in vMPFC and precuneus/PCC, regions, consistently implicated in self-referential processing in healthy controls. This pattern may reflect the clinical presentation of no increased self-focus in mania. Furthermore, the finding of increased activation in precuneus/PCC could reflect the clinical finding of external focus with increased distractibility and flight of ideas in mania.

In the first chapter, I will provide an introduction to the previous literature and the hypotheses of these two experiments. In the second chapter I will describe the methods. The results of the two experiments will be presented in detail in the third chapter, and, finally, I will discuss the results of both experiments and the limitations in chapter four.

1.2. Social cognition in healthy participants

Social cognition refers to the processes that subserve behavior in response to other individuals of the same species (Adolphs, 1999). These are the processes involved in perceiving, interpreting and responding to the social world (van Rheenen and Rossell, 2014).

Within research on social cognition there is no conclusive categorization of processes yet, but five dimensions have been delimited and extensively studied so far: theory of mind (ToM), social perception, social knowledge, attributional bias and emotion processing (Green and Leitman, 2008). There is some overlap among these social cognitive areas. Furthermore, social cognition may encompass a larger set of components that have not been sufficiently addressed in research studies conducted so far.

In the previous neuroimaging studies of social perception human faces were used as stimuli as opposed to the perception of objects. These studies have found fusiform face area (FFA) and occipital face area (OFA) being especially involved while processing human faces (Peelen and Downing, 2007; van Overwalle, 2009). Further studies investigating the brain areas active while perceiving human body revealed extra-striate body area to be specifically involved during perception of human body as opposed to human face or to non-human body (Peelen and Downing, 2007). Furthermore, while using moving stimuli it was revealed that areas such as posterior superior temporal sulcus and occipital and fusiform face areas underlie the perception of biological motion (Grossman and Blake, 2002).

Extensive neuroimaging work in healthy subjects has found very consistently involvement of the medial prefrontal cortex (MPFC) and the temporo-parietal junction (TPJ), the superior temporal sulcus (STS) and the temporal poles (TP) during social cognitive tasks (Amodio and Frith, 2006; van Overwalle, 2009) (Figure 1). This research suggests that the MPFC has a special role in social cognition, whereas other regions in

the network serve more general functions. Furthermore, it has been proposed that a dorsal-ventral distinction within MPFC during social cognition might exist. On the basis of previous meta-analyses (Koski and Paus, 2000; Steele and Lawrie, 2004) it has been suggested that the MPFC, including the anterior cingulate cortex (ACC), might be distinguished in a posterior cognitive zone and an anterior emotional region (Amodio and Frith, 2006; Koski and Paus, 2000; Ochsner *et al.*, 2004). Similarly, emotional in contrast to cognitive social cognition activated ventral versus dorsal MPFC, respectively (Hynes *et al.*, 2006; Keysers and Gazzola, 2007).

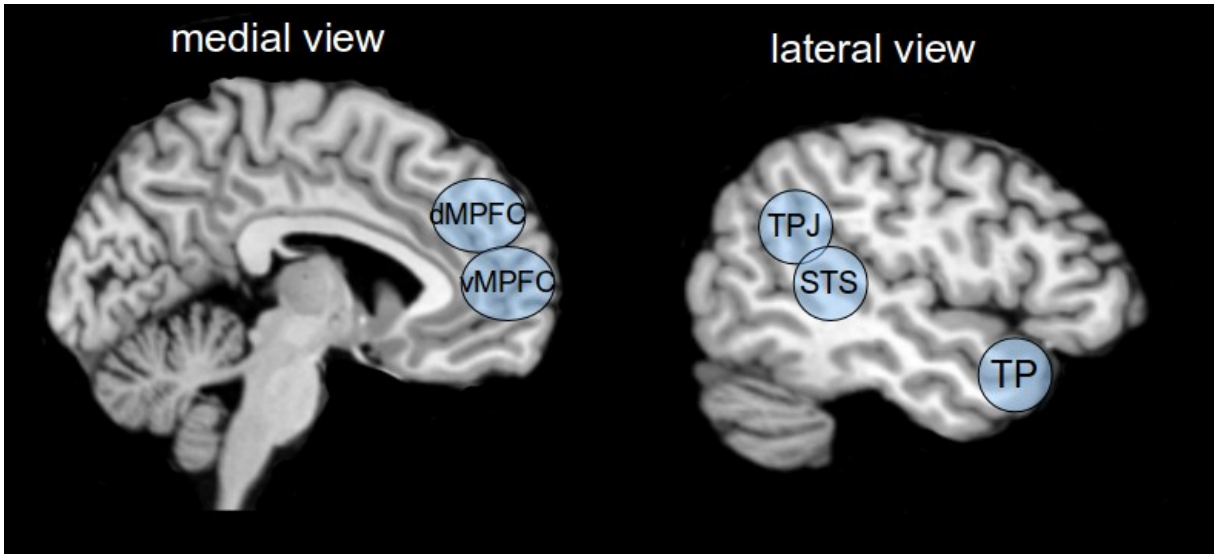

Figure 1: Brain areas, activated during social cognitive tasks in healthy subjects. Dorsomedial prefrontal cortex, dMPFC; ventromedial prefrontal cortex, vMPFC; temporo-parietal junction, TPJ; superior temporal sulcus, STS; the temporal poles, TP.

1.3. Social cognition in bipolar disorder

Clinical observations suggest altered social behaviour in manic patients with bipolar disorder (BD), characterized by excessive involvement in pleasurable social activities and inappropriate social communication and interaction. Many people with BD have difficulties in carrying out work functions (Judd *et al.*, 2008) and in some cases are

unable to work (Dion *et al.*, 1988). They report difficulties in social activities (Morriss *et al.*, 2007) and social skills performance (Goldstein *et al.*, 2006), as well as maladjustment in marital or romantic relationships (Blairy *et al.*, 2004; Tsai *et al.*, 1999; Van Rheenen and Rossell, 2014). Poor social functioning is reported in up to two-thirds of bipolar patients (Goldberg and Harrow, 2004; Huxley and Baldessarini, 2007; Wingo *et al.*, 2010a) and persists even during periods of sustained and substantial remission (Jaeger and Vieta, 2007).

In Bipolar 1 disorder as opposed to bipolar 2 disorder the primary symptom presentation is manic. Manic episodes are characterized by a distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary). During the period of mood disturbance, three (or more) of the following symptoms have persisted (4 if the mood is only irritable) and have been present to a significant degree: increased self-esteem or grandiosity, decreased need for sleep, more talkative than usual or pressure to keep talking, flight of ideas or subjective experience that thoughts are racing, distractibility, increase in goal-directed activity or psychomotor agitation, excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments) (APA, 2000).

Bipolar 1 disorder affects approximately 1% of adults (Merikangas *et al.*, 2007) with an immense personal and economic burden imposed on the society (Gustavsson *et al.*, 2011; Whiteford *et al.*, 2015). Studying social cognition in mania therefore might help identify the underlying pathology and possible targets for intervention.

The deficits in social competence in mania may in part be caused by underlying impairments in social cognitive functions, such as the cognitive ability to mentalize about other people’s mental states (‘theory of mind') or to empathize with others, mostly regarding their emotional experiences (Cusi *et al.*, 2010). Social cognition has the potential to represent a more proximal and complex predictor of psychosocial outcome

than neurocognition (van Rheenen and Rossell, 2014). In the same line, Samamé in her review (2013) argues that social cognition in BD might become a possible endophenotype of BD. So far the key finding of neuropsychological research is that emotion processing and ToM deficits are present even in euthymic BD subjects and might thus present a trait marker.

BD is one of the most highly heritable psychiatric disorders, with genetic influences accounting for 65-80% of variance in risk (Smoller and Finn, 2003). Nevertheless, its exact genetic profile remains unknown, which is due, in part, to not having identified endophenotypes: traits that are more proximal to the genetic substrate than are diagnostic categories (Gottesman and Gould, 2003). It is thus important to determine whether impaired social cognition is a trait marker and candidate endophenotype that could facilitate research of the illness (Samamé, 2013).

Recently, behavioural studies investigating social cognitive capacities in BD have found impairments in various ToM paradigms (Cusi *et al.*, 2012), although in general this still remains an under-researched topic. Bipolar patients show deficits in social cognitive tests even in the euthymic state (Samamé *et al.*, 2012). Wingo et al. found that 54% of 65 investigated BD-patients retained social cognitive deficits while returning to the euthymic state (Wingo *et al.*, 2010b). Kerr et al found ToM deficits in BD (Kerr *et al.*, 2003) and Bazin et al. found deficits in attribution of intentions to others in manic patients in comparison to depressed patients (Bazin *et al.*, 2009).

To specify these deficits in BD, several studies have distinguished cognitive and affective aspects of social cognition, based on findings in healthy participants and individuals with brain lesions (Hynes *et al.*, 2006; Shamay-Tsoory *et al.*, 2009) suggesting two separable aspects of social cognition. Concordantly, these behavioural findings indicated that individuals with BD were only impaired when they had to cognitively ascribe mental states to others or adopt someone else's point of view, but were not affected when identifying or empathizing with the emotional state of another

person (Barrera *et al.*, 2012; Cusi *et al.*, 2010; Montag *et al.*, 2010; Seidel *et al.*, 2012; Shamay-Tsoory *et al.*, 2009).

In BD, this dissociation between cognitive and affective aspects of social processes has only been investigated at the behavioural level, but not yet with neuroimaging methods which would allow the identification of underlying brain regions. To date only two functional magnetic resonance (fMRI) studies examined the neural correlates of social cognition in BD. These studies examined euthymic bipolar patients and did not distinguish between cognitive and affective social cognitive processes.

In the study of Kim et al. (2009) 14 euthymic patients with bipolar 1 disorder and 14 healthy controls underwent functional MRI while performing a virtual reality social cognition task, which incorporated both cognitive and emotional dimensions, simulating real-world social situations. During the scanning, subjects had to guess possible reasons for expressed emotion of virtual humans, just after observing their verbal and nonverbal expressions which were emotionally valenced (happy, angry and neutral). In comparison to healthy controls BD patients showed delayed reaction times in emotional conditions with comparable response accuracy. Relative to healthy controls, BD patients showed reduced activations in the 'mirror neuron system', including the right inferior frontal cortex, premotor cortex, and insula, mainly in angry or happy condition. These results suggest that, even during euthymic state, BD patients have difficulties in recruiting brain regions for the utilization of emotional cues as a means for understanding others (Kim *et al.*, 2009).

Malhi et al. (2008) examined 20 euthymic bipolar patients and 20 matched healthy controls using fMRI while subjects were engaged in a Theory of Mind task. The activation paradigm involved observing ToM and random-motion animated sequences in a block design. Patients were compromised in their ability to appropriately rate the ToM stimuli and assess them for intention as compared to healthy subjects. This was reflected in the fact that patients had few within-group significant activations in response to ToM animated sequences, namely, left anterior cingulate, and precuneus and cuneus

bilaterally. In contrast, robust activations in response to ToM animated sequences in healthy subjects were widespread and involved regions recognized for mental state reasoning, in particular the insula, inferior frontal, supramarginal and angular gyri, and temporal cortex. This findings suggest that in a social context, euthymic bipolar patients, though seemingly well and capable of engaging aspects of ToM, are perhaps constrained in their ability to mentalize fully, and furthermore cannot reliably adopt an alternate cognitive perspective when appropriate. Impairment of this capacity, though subtle, may in effect compromise their ability to understand the emotions and intentions of others, and also may limit appreciation of their own illness and symptoms. Such a deficit in bipolar disorder perhaps impacts upon interpersonal relationships and adversely affects social cognition and clinical functioning (Malhi *et al.*, 2008).

In summary, both studies found diminished activation within the mirror system in euthymic BD patients, related to lower-level action perception processing, but no differences in comparison with controls in regions of the well-established 'ToM network'.

1.4. Self-referential processing in healthy participants

Philosophers, psychologists and, most recently, neuroscientists have been extensively investigating the concept of the self (Gillihan and Farah, 2005; Legrand and Ruby, 2009; Metzinger and Gallese, 2003; Northoff *et al.*, 2006; Northoff and Bermpohl, 2004). Northoff distinguishes in his summary of previous research (Northoff *et al.*, 2011) three content-based concepts of the self. First, the „proto-self" (Damasio, 2000; J, 1997; Panksepp, 2003), which corresponds to the physical self of William James (James, 1890), outlines one's body in affective and sensory-motor terms; second, the ''minimal self" (Gallagher, 2000; Gallagher and Frith, 2003) or ''core or mental self" (Damasio, 2000), which roughly corresponds to the mental self of William James, is determined by one's own mental contents; and, third, Damasio's ''autobiographical self" (Damasio, 2000) and Gallagher's ''narrative self" (Gallagher, 2000; Gallagher and Frith, 2003),

which corresponds to the spiritual self of William James, relies on linking past, present, and future events.

A common approach to studying the processing of self-referential stimuli so far has been to study the content-based concepts of the self. The subjects were asked to judge the stimuli as being self-referential (personally related to them) or not (Churchland, 2002; Gallagher, 2000; Gallagher and Frith, 2003; Keenan *et al.*, 2003; Kelley *et al.*, 2002; Lambie and Marcel, 2002; LeDoux, 2003; Northoff and Bermpohl, 2004; Qin *et al.*, 2010; Schneider *et al.*, 2008; Turk *et al.*, 2002, 2003). Northoff argues that this judgement task implicates self-awareness or self-consciousness, the ability to become aware of that stimulus being specific or non-specific to the self. Imaging studies thus combine a content-based view of the self, be it bodily, mental or autobiographical, with the recruitment of higher-order cognitive functions required in the task. Since subjects must reference themselves in self-consciousness or self-awareness, one may speak of 'self-referential processing' (Northoff *et al.*, 2011).

Brain imaging studies have implicated various medial cortical regions in self-referential processing, including the perigenual anterior cingulate cortex (pACC), dorsomedial prefrontal cortex (dMPFC) and posterior cingulate cortex (PCC) (Kelley *et al.*, 2002; Mitchell *et al.*, 2005; Northoff *et al.*, 2006; Northoff and Bermpohl, 2004; Platek *et al.*, 2006; Uddin *et al.*, 2007; Yaoi *et al.*, 2009; Zhu *et al.*, 2007) (Figure 2). In addition, self-referential processing has been found to be associated with resting state activity in the default-mode network (DMN) (Buckner *et al.*, 2008; Raichle *et al.*, 2001). Since the regions of the DMN strongly overlap with those of the cortical midline structures, some authors speak even of 'default-self' arguing that the self may be more or less identical with the high resting state activity observed in these regions (Boly *et al.*, 2008; Christoff *et al.*, 2003; Gusnard *et al.*, 2001; Wicker *et al.*, 2003).

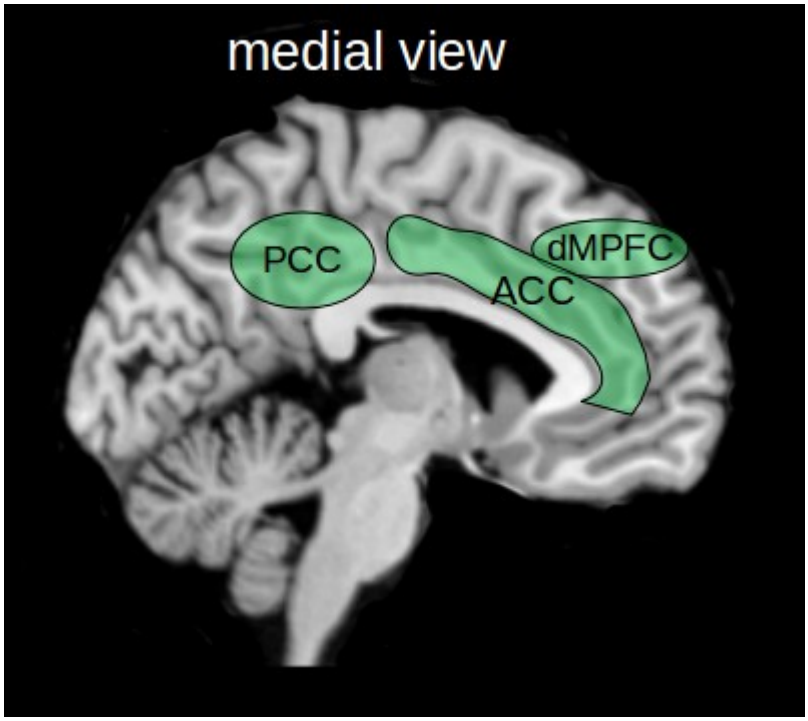

Figure 2: Brain areas, activated during self-referential processing in healthy subjects. Anterior cingulate cortex, ACC; dorsomedial prefrontal cortex, dMPFC; posterior cingulate cortex, PCC.

1.5. Self-referential processing in affective disorders

Neural correlates of self-referential processing have recently attracted increased research interest in the context of affective disorders. Most studies so far focused on self-referential processing in depressed patients. To my knowledge, there is no study so far investigating self-referential processing in patients with bipolar mania. However, manic patients exhibit clinical characteristics, such as an inflated self-esteem or feeling of grandiosity, that hint at an impaired processing of self-referential stimuli.

Studies investigating the neural basis of self-referential processing in depressed patients (Grimm *et al.*, 2009; Johnson *et al.*, 2009; Lemogne *et al.*, 2009; Yoshimura *et al.*, 2010) found altered activation of cortical midline structures. Lemogne et al. (Lemogne *et al.*, 2009) and Yoshimura et al. (Yoshimura *et al.*, 2010) found increased activation of MPFC during self-referential processing in depressed patients, while

Grimm et al. (Grimm *et al.*, 2009) and Johnson et al. (Johnson *et al.*, 2009) found decreased activation of MPFC for the same contrast. A recent meta-analysis focused on changes in DMN activation in depressed patients, found that depressed patients have an increased activation of vMPFC during resting state condition compared to healthy individuals (Kühn and Gallinat, 2013).

In summary, all studies so far point towards an altered functioning of MPFC in depression, which is connected to the increased tendency of depressed patients to ruminate, that is, to repeat negative thoughts with high self-relevance. As such, increased activation of MPFC in depression can be seen as a central factor in the perpetuation of the disease (Lemogne *et al.*, 2012).

A few studies have investigated the neural basis of resting state condition in bipolar disorder (Das *et al.*, 2014; Magioncalda *et al.*, 2015). Magioncalda et al. (Magioncalda *et al.*, 2015) found mood state dependent alteration in resting state functional connectivity in DMN. While in bipolar depression during resting state there is hypoconnectivity between perigenual ACC (PACC) and supragenual ACC (SACC), in bipolar mania there is hypoconnectivity between PACC and PCC. This decreased resting state functional connectivity found in depressed patients between PACC and SACC may reflect decreased anterior DMN- salience network (SN) connectivity. Such altered connectivity between DMN and SN might lead to an abnormal shifting towards the DMN and hypothetically intensive focusing on internal contents as manifested in depression in the increased tendency to ruminate. The decreased resting state functional connectivity in manic patients between PACC and PCC may reflect a deficit in posterior DMN associated with a shift toward central executive network (CEN) going along with excessive focusing on external contents at the expense of internal contents as reflected by flight of ideas and distractibility in mania (Magioncalda *et al.*, 2015).

1.6. Study design and hypotheses

Experiment I: Implicit processing of social stimuli in mania

Previous neuroimaging studies in healthy individuals mostly used social tasks, which predominantly necessitated explicit social processing. However, social processing does also occur implicitly without an explicit instruction. Social processing is automatically triggered, for example, when perceiving humans or moving stimuli, which imply animacy and intentionality (Castelli *et al.*, 2000; Heider and Simmel, 1944). fMRI findings showed that tasks, which involved implicit mentalizing, also activated the same network as during explicit processing (German *et al.*, 2004; Mitchell *et al.*, 2002). In the present study in manic patients, we thus chose a task involving implicit processing of social scenes, which is especially suited for the investigation of this patient population, as it is easy to understand and perform and is largely independent of additional cognitive processes.

In this study, we used fMRI to compare social stimulus processing in manic patients with age- and IQ- matched healthy controls. The present study investigating social processing in symptomatic BD patients extends the existing neuroimaging studies on social cognition conducted in the euthymic state. During fMRI, participants viewed stimuli with social content, i.e. involving one or more humans. Scenes without humans (e.g., nature scenes, objects) served as a control condition. We hypothesized that regions implicated in social cognition, namely the medial prefrontal cortex and the temporo-parietal junction, would show differential activation patterns for the mania group compared to the control group. This hypothesis was based on clinical observations and previous behavioural findings of social deficits in mania. We furthermore wanted to specifically investigate whether group differences particularly concerned the dorsal (i.e., cognitive), but not the ventral (i.e., affective) part of the MPFC. It may be possible that patients with mania especially show deficits only in the more cognitive, dorsal part of the MPFC, in line with previous behavioural reports (Montag *et al.*, 2010). Furthermore, patients with mania often show an enhanced

responsivity to social cues and, in extreme cases, also delusions of reference. Therefore, questionnaire data on delusional ideation (including ideas of reference) was correlated with brain activation in the regions of interest to identify regions, which show higher activation when enhanced delusional ideation is present.

Experiment II: Self-referential processing in mania

One of the common ways to study self-referential processing in healthy individuals is to ask the participants to judge stimuli as being „self-referential“, i.e. personally related to them. In this study, we used fMRI to compare self-referential stimulus processing in manic patients with age- and IQ- matched healthy controls. The present study investigating self-referential processing in symptomatic BD patients extends the existing neuroimaging studies on the self conducted in healthy participants and in patients with depression. During fMRI, participants viewed pictures with various contents (e.g., landscapes, objects, people) and were asked to judge these stimuli as being personally related to them or not. Based on previous research in patients with depression, we hypothesized that regions implicated in self-referential processing, namely the cortical midline structures, would exhibit altered activations for the mania group compared to the control group.

2. METHODS

2.1. Participants

Experiment I and II

14 right-handed (assessed with Edinburgh Handedness Inventory) patients with bipolar 1 disorder, at the time of experiment in mania according to DSM-IV (APA, 2000) participated in the experiments. Patients were assessed using the SCID I (Structured Clinical Interview for DSM-IV Part I) (First, Michael B., Spitzer, Robert L, Gibbon Miriam, and Williams, Janet B.W., 2002). They did not fulfill the criteria for a mixed episode, had no diagnosis of any other axis I psychiatric disorder and no history of any neurological disorder. We used the Young Mania Rating Scale (YMRS) (Young *et al.*, 1978) to quantify manic symptoms. In addition, we used Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960) to rule out the possibility that participants were in a mixed episode. A HAM-D score < 7 was considered normal. The patients could use antimanic (e.g. antipsychotics, mood stabilizers) medication, but no benzodiazepines. The medication on the day of examination was taken after the scanning session early in the morning upon previous agreement with the patient's psychiatrist. Out of 33 manic patients who were screened for the study, 14 were finally included. Common exclusion criteria for fMRI studies were considered (pregnancy, metal implants, tattoos and permanent make-up, unremovable piercing).

The 14 mentally healthy right-handed control subjects were matched for age, gender, verbal IQ, duration of education and smoking status (Table 1). The verbal IQ was measured with Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B) (Lehrl, 2005). The healthy subjects had been interviewed with the SCID I (Structured Clinical Interview for DSM-IV Part I) to ensure that they had no current or previous axis I psychiatric disorder. They were medication free.

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. Stimuli and design

Experimental stimuli comprised 160 standardized non-erotic pictures selected from the International Affective Picture System (IAPS) (Lang *et al.*, 2008) so that the normative valence scores of the presented pictures (9-point rating scale from 1, very negative over 5, neutral to 9, very positive) were neutral to positive and the variance of normative valence and arousal (9 point rating scale) scores was reduced to a minimum ($mean_{valence}$ $\pm Sd_{valence}$: 7.0±0.55; $mean_{arousal}$ $\pm SD_{arousal}$: 5.0±0.49) (Figure 3). The IAPS pictures were selected as stimulus material, because they have produced robust effects in previous social cognition tasks (Gusnard *et al.*, 2001; Northoff *et al.*, 2009; Phan *et al.*, 2004). We chose pictures of neutral to positive valence because a prior study (Northoff *et al.*, 2009) indicated that this type of material would produce a sufficient number of trials for both levels of self-relatedness, i.e., rated as 'self-referential' or 'non-self-referential' by the study participants.

Experiment I: Implicit processing of social stimuli in mania

In total, 90 social and 70 non-social pictures were chosen. Social and non-social pictures did not differ in standard valence (t(158)=-0,728, p= 0.468) or arousal ratings (t(158)=1.388, p=0.167). During the fMRI experiment IAPS photographs of social and non-social scenes were randomly presented. Pictures classified as social depicted scenes containing one or more persons, while non-social pictures showed for instance landscapes or scenes containing objects (e.g., food items).

Experiment II: Self-referential processing in mania

Arousal of pictures rated as self-referential or non-self-referential showed no significant difference in both groups as revealed in repeated measures ANOVA for the self condition ($F(1,26)=0.20$, $p=0.887$) and self*group interaction ($F(1,26)=0.960$, $p=0.336$). The valence of pictures showed significant difference between the 'self' and 'non-self' condition ($F(1,26)=28.512$, $p<0.001$), indicating that both patients in mania and healthy study participants rated more positive pictures as self-referential, but showed no significant effect in self*group interaction ($F(1,26)=0.009$, $p=0.925$).

Experiment I and II:

Participants passively viewed each picture for 4 s, followed by an episodic memory and a self-reference task (3 s each; randomised order of tasks). After the two judgements a fixation-cross period (range: 13.65-19.5 s; mean: 15.99 s) was shown prior to the next trial (Figure 3).

Debriefing after fMRI revealed that study participants had started to carry out the tasks implicitly during the period of picture presentation, i.e., prior to presentation of the question screens. Implicit task processing during the picture period should not have affected the comparison between experimental conditions, because the same two tasks were performed in response to each picture stimulus. The paradigm consisted of four runs each comprising 40 trials. All 160 pictures were presented in a pseudo-randomized order. Prior to scanning participants were familiarized with the paradigm in a training session with a different set of pictures. The stimuli were presented using the Presentation® Software (Neurobehavioral Systems, CA, USA).

Experiment II: Self-referential processing in mania

In the self-reference task participants were asked to answer the question: „Does this picture relate to you?“. In the memory performance task the question was: „Is this picture familiar to you?“.

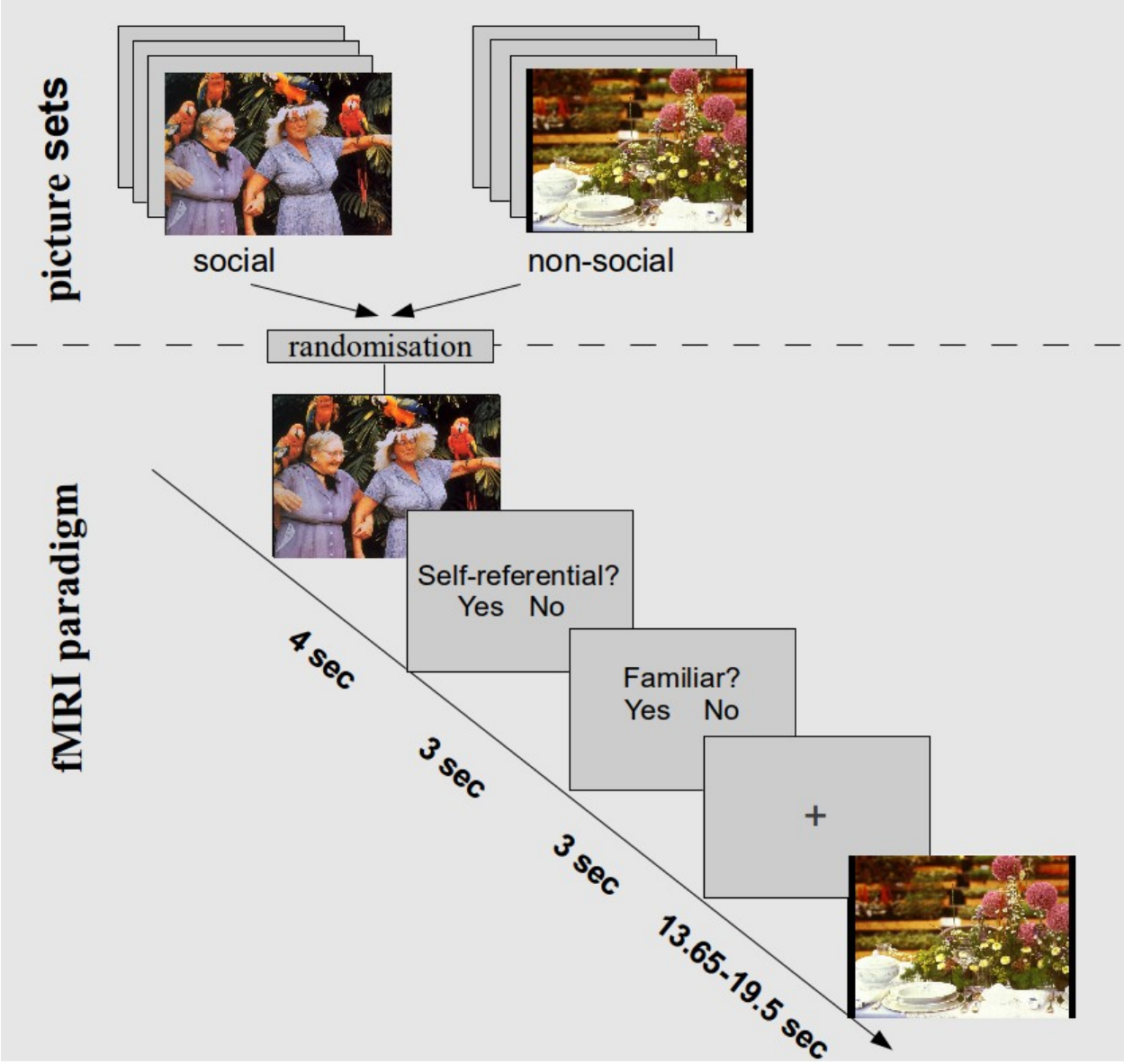

Figure 3: fMRI paradigm: picture stimulus followed by the two forced-choice-tasks.

Experiment I and II:

For the purpose of the studies, the memory performance task following stimulus presentation served to direct the participants' attention to the stimuli and ensure, that manic patients paid attention to the task same as healthy individuals.

The participants' performance in the memory task as quantified with d' was 1.88 (±0.61, mean d'± SD) in the healthy and 1.59 (±0.74, mean d'± SD) in the mania group and was not significantly different between two groups in a T test (T=1.154, p=0.259).

2.3. Peters Delusion Inventory (PDI)

After the scanning session participants completed the Peters Delusion Inventory (PDI-40) (Peters *et al.*, 1999), designed to measure the presence of delusional ideation. For example, items include the presence of delusions of reference ("Do you ever feel as if things in magazines or on TV were written especially for you?"). PDI scores were compared between two groups using a t-test for independent groups (healthy, manic). To test for association of the severity of delusional ideation in manic patients and BOLD responses in our regions of interest, single-subject parameter estimates from the contrast 'social > non-social' were correlated with individual PDI scores using a Pearson correlation. One participant had to be excluded based on extreme values in standard outlier measures for linear regression analysis (studentized residuals ≥ 3, leverage value > 1.5, Cooks distance > 1).

2.4 Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) was used in this study as an imaging method. Magnetic resonance (MR) measures how radio frequency electromagnetic waves act upon dipoles in a magnetic field. Nuclei with an odd number of protons, such as the hydrogen nuclei in water, can be viewed as magnetic dipoles. The hydrogen nuclei are the only dipoles present in significant density in the brain to support

measurements at high spatial resolution. Such dipoles arise due to the fact that protons possess angular momentum or nuclear spin. When exposed to an external static magnetic field, the randomly oriented dipoles line up with and precess around the field's direction, thus creating a macroscopic magnetization. The rate of precession is given by the so-called Larmor relationship. The hydrogen nucleus has two permissible states with orientations parallel (lower energy) and anti-parallel (higher energy) to the main magnetic field. The tissue magnetization that MRI uses arises due to the tiny fractional excess of the population in the lower energy level and varies with temperature and magnetic field strength. The lower the temperature or the stronger the field, the stronger the tissue magnetization.

The magnetic resonance measurement begins with the introduction of a radio frequency pulse into the tissue. This pulse excites nuclei away from their resting state into a higher energy state. Information about the nearby tissue is derived from the rate at which the hydrogen nuclei return to the low-energy state following the excitation. The relaxation back to the original state can be described as changes in two dimensions, longitudinal and transverse relaxation. Two exponential processes with time constants (T1 and T2) describe the relaxation back to the low-energy state. The T1 constant measures the relaxation in the direction of the B0 magnetic field (longitudinal relaxation). The T2 constant measures the transverse relaxation of the dipole in the plane that is perpendicular to the B0 field. These changes in the local magnetic field are measured by special equipment (coils) that is placed within the scanner.

The transverse relaxation is of special significance for fMRI. In physiological tissue the transverse relaxation is more rapid than in an ideal homogeneous magnetic field because of local field inhomogeneities including those caused by the tissue itself. When inhomogeneities are present, the decay constant is T2*. Field variations randomly alter the frequency of the proton's precession, disturbing the phase coherence and speeding the transverse relaxation. In the brain, the size of these inhomogeneities depends upon the physiological state and in particular the composition of the local blood supply. This physiological state depends, in turn, on the neural activity. For this reason,

measurement of the T2* parameter is an indirect measurement of neural activity. These measurements are obtained by superimposing small gradients upon the main B0 magnetic field (Logothetis, 2002; Logothetis and Wandell, 2004).

2.5 The Blood Oxygen- Level Dependent (BOLD) Contrast

The BOLD contrast refers to the difference in signal on T2*-weighted images as a function of the amount of deoxygenated hemoglobin (Huettel *et al.*, 2004). Hemoglobin consists of two pairs of polypeptide chains, each of which is attached to a complex of protoporphyrin and iron. In deoxygenated hemoglobin the iron is in a paramagnetic high-spin state, as four of its six outer electrons are unpaired and act as an exogenous paramagnetic agent. When oxygenated, the haem iron changes to a low-spin state by receiving the oxygen's electrons. Paramagnetic deoxygenated hemoglobin is confined in the intracellular space of the red blood cells that in turn are restricted to the blood vessels. Magnetic susceptibility differences between the compartments, containing deoxygenated hemoglobin, and the surrounding space generate magnetic feld gradients across and near the compartment boundaries. Pulse sequences designed to be highly sensitive to such susceptibility differences generate signal alterations whenever the concentration of deoxygenated hemoglobin changes. The BOLD signal does not correlate perfectly with action potentials, but rather measures a mix of continuous membrane potentials and action potentials (Logothetis, 2002, 2002; Logothetis and Wandell, 2004).

Fast pulse sequences have been developed to approximately match the rate of the physiological changes underlying brain function. Mansfield and colleagues (Mansfield, 1977) proposed a method, known as echo-planar imaging (EPI), in which an entire image is created using rapid gradient switching following a single excitatory pulse (Huettel *et al.*, 2004).

2.6. FMRI data acquisition and preprocessing

Brain images were acquired using a T2*-weighted gradient echo-planar imaging (EPI) sequence sensitive to blood oxygen level dependent (BOLD) contrast on a 1.5 Tesla Scanner (Sonata, Siemens, Erlangen, Germany) with a standard head coil. Repetition time (TR) was 1950 ms, echo time (TE) was 40 ms and flip angle was 90°. Thirty-five oblique axial slices aligned to the plane connecting the anterior and posterior commissure were collected with voxel dimensions of 3 x 3 x 3.5 mm^3 providing full brain coverage. For each study participant 341 volumes were recorded, the first three were excluded from the analysis because of the expected T1- saturation effects. Thus, for every study participant 338 volumes were included in the analysis.

fMRI data was analysed using the Statistical Parametric Mapping (SPM8) software (Wellcome Department of Imaging Neurosciences, London, UK). Preprocessing included slice time correction, realignment to the mean volume, spatial normalization to a standard MNI template and spatial smoothing using a Gaussian kernel of full width at half maximum (FWHM) = 8 mm. A 128 s highpass filter was applied to the time series in each voxel to remove low-frequency drifts.

2.7. fMRI data analysis

2.7.1.First level analysis

Preprocessed fMRI data of each subject was submitted to a two-level procedure. First, condition and subject effects were estimated using the general linear model (GLM) approach (Friston *et al.*, 1994).

Experiment I: Implicit processing of social stimuli in mania

The trials were assigned to experimental conditions based on the factor ‘social content’ of the stimulus. The picture onsets of the resulting two conditions (social, non-social) were modeled as regressors of interest.

Experiment II: Self-referential processing in mania

The trials were assigned to experimental conditions based on online responses to the self-referentiality question. The picture onsets of the resulting two conditions (self-referential, non-self-referential) were modelled as regressors of interest.

The six movement parameters (three rotational and three translational) and the regressors for left-hand and right-hand button press during the task were included as regressors of no interest. The regressors were convolved with a hemodynamic response function (HRF) provided by SPM8. The regressors were simultaneously regressed against the BOLD signal in each voxel using the least squares criteria, and contrast images were computed from the resulting parameter estimates.

2.7.2. Second level analysis

Experiment I: Implicit processing of social stimuli in mania

For the second-level random-effects analysis single-subject contrasts were entered in a two-way factorial analysis of variance (ANOVA) model with a main effect of group (healthy versus manic), a main effect of condition (social versus non-social), and a group* condition interaction.

In a first step, we tested in healthy participants whether our paradigm produced activations in brain areas typically associated with social cognition, such as the MPFC and TPJ. A whole-brain analysis ($p< 0.05$, FDR-corrected) comparing social versus non-social pictures revealed, amongst other regions, indeed significant activations in the MPFC, including dorsal and ventral parts (12 54 42, 4 60 -10), right and left TPJ (58 -42 14, -44 -62 16).

Region of Interest Analysis

To analyse our fMRI data on the group level we used a Region of Interest (ROI) approach, specifically focusing on our predefined relevant brain areas (dMPFC, vMPFC, TPJ). To define these functional regions we used coordinates from previous neuroimaging studies on social cognitive functions (Theory of Mind beliefs, inference of traits of others, interactive games) reported in a recent meta-analysis (van Overwalle, 2009). A total of 46 studies with 91 activation peaks were used for an Activation Likelihood Estimation (ALE) using the software Brainmap GingerALE (http://brainmap.org/ale/). The goal of this approach is to identify brain areas where the reported foci of activation converge across published experiments. This method is based on the idea that peak activations of neuroimaging studies can be viewed as probability distributions around those coordinates (Turkeltaub *et al.*, 2002). By transforming activation peaks into such three dimensional probability distributions a map can be created, which displays for each voxel the probability that one or more peaks were located in this voxel in the meta-analysis. The statistical significance of this map can further be assessed to identify above-chance activations. This results in a statistical map coding for the assessed voxels the significance of the estimation likelihood of activation. Here, we employed the false discovery rate method to correct our results for multiple comparisons at a significance threshold of $P < 0.05$ (cluster threshold 100 mm^3). The obtained peak coordinates (dMPFC: 8 52 30 (right), -10 50 36 (left); vMPFC: 6 56 14 (right), -10 50 0 (left); TPJ: 56 -54 18 (right), -52 -62 22 (left)) were then used to conduct a ROI analysis by creating 8 mm spheres around them and applying a small volume correction (SVC). Only regions surviving a FWE-correction ($p < 0.05$) for multiple comparisons are reported as significant.

Experiment II: Self-referential processing in mania

At the group level of analysis, contrast images of the single subjects were subjected to one-sample-t-test to calculate main effects of self-referentiality in both groups independently.

Then, a two-sample-t-test was calculated for the main effect of 'self' comparing the resulting activations between the groups. Significant activations were identified at a threshold of $p<0.001$, uncorrected with a cluster extend of $k \geq 5$ voxels.

Experiment I and II:

We extracted parameter estimates for the peak voxels of the contrast images. We used the SPM toolbox RFXplot (Gläscher, 2009) For the anatomical labeling of the clusters we used the SPM toolbox MNI Space Utility (MSU), and Talairach-Daemon (Lancaster *et al.*, 1997, 2000). The conversion of the coordinates between the MNI- and Talairach-space was carried out with the SPM toolbox WFUpickatlas (Maldjian *et al.*, 2003, 2004).

3. RESULTS

Experiment I and II:

3.1. Clinical and demographic results

Groups did not differ in age, gender, smoking status, duration of education or verbal intelligence. Clinical and demographic characteristics of study populations are summarized in Table 1. In the mania group the mean Young Mania Rating Scale score was 19.7 (SD = ± 6.1), the mean Hamilton Rating Scale for Depression score was 4.4 (SD = ± 3.9).

Characteristic	**Manic (n=14)**	**Controls (n=14)**	**P**
Sex, F/M, n	4 / 10	4 / 10	1.000
Age, mean +/- SD, y	33.4 +/- 10.4	38.1 +/- 5.8	0.192
Smoker, n	10	6	0.127
Verbal IQ (WST), mean +/- SD*	107.2 +/-12.1	114.1+/- 13.1	0.168
Duration of education in years, mean +/- SD*	15.2 +/- 2.0	17.2 +/- 3.6	0.085
Duration of illness in years, mean +/- SD**	8.8 +/- 9.7	-	-
Manic episodes, mean +/- SD**	3.6 +/- 2.4	-	-
Depressive episodes, mean +/- SD***	2.8 +/- 2.8	-	-
Psychotropic medication, n			-
Lithium	6	-	
Valproic acid	7	-	
Carbamazepine	1	-	
Clozapine	1	-	
Quetiapine	4	-	
Olanzapine	5	-	
Risperidone	4	-	
Biperiden	2	-	
Flupentixol	1	-	

Table 1. Clinical and demographic characteristics of study populations.
Abbreviations: * Data was missing for one manic subject.
** Data was missing for 4 subjects.
***Data was missing for 3 subjects.
n number

In the PDI questionnaire, the mania group showed more delusional ideation (mean: 20.07±10.37 SD) compared with healthy participants (mean: 8.14 ±4.96 SD) ($t(26)= -3.884$, $p= 0.001$). 3.2. Experiment I: Implicit processing of social stimuli in mania

3.2.1. Behavioural data

Trial distribution and memory task performance.

The percentages of stimuli judged as self-referential were 40 (±12, mean ± SD) in social condition and 40 (±18, mean ± SD) in non-social condition in healthy and 51 (±21, mean ± SD) in social condition and 53 (±21, mean ± SD) in non-social condition in mania group. A repeated measures ANOVA revealed no significant effect for the factor condition ($F(1, 26)= 0.104$, $p=0.750$) and the social*group interaction ($F(1,26)= 0.092$, $p=0.764$), indicating that the percentage of pictures judged as self- or non-self-referential was comparable across groups and conditions.

3.2.2. Neuroimaging results

Main effect of group

The comparison 'manic > healthy' and 'healthy > manic' didn't show any significant differences in ROI analysis.

Main effect of condition (ROI analysis): Regions, showing higher activation during social processing as compared to non-social in ***both groups (pooled groups)***

In both groups, the comparison 'social > non-social' revealed significant activations in the right vMPFC ($T=3.34$; $x=10$ $y=60$ $z=12$), right TPJ (Tmax 10.06; $x=52$ $y= -52$ $z=12$) and left TPJ ($Tmax=7.65$; $x= -48$ $y= -64$ $z=16$) ROI.

Main effect of condition (ROI analysis): regions, showing higher activation during social processing compared to non-social in ***mania group***

The comparison 'social > non-social' in mania group produced significant activation in the right vMPFC (T=3.25; x=10 y=60 z=12), right TPJ (Tmax 7.69; x=58 y= -48 z=14) and left TPJ (Tmax=4.07; x= -48 y= -64 z=16) ROI.

Main effect of condition (ROI analysis): regions, showing higher activation during social processing compared to non-social in ***healthy group***

The comparison 'social > non-social' in healthy group produced significant activation in the left dMPFC (T=3.45; x= -8 y=54 z=38), right vMPFC (T=3.26; x=6 y=52 z=20), right TPJ (Tmax 9.81; x=54 y= -60 z=14) and left TPJ (Tmax=7.82; x= -48 y= -64 z=16) ROI.

*Group * condition interaction: Regions, showing higher activation in the* ***healthy group*** *during social compared to non-social processing (ROI analysis)*

For the contrast 'social > non-social processing', the comparison 'healthy > manic' revealed a significant activation in the right dMPFC *(T=3.17, coordinates: 14 50 26, p uncorrected = 0.001, p (FWE) = 0.042)* (Fig. 4A). Plots of parameter estimates indicate, that healthy subjects showed a larger BOLD signal in this area during social as opposed to non-social stimuli in comparison to manic patients (Fig. 5A). The comparison 'healthy > manic' revealed no significant effects for the contrast 'social > non-social processing' in any ROI, i.e. neither in the left and right TPJ, nor in the left and right vMPFC, nor in the left dMPFC. In the right vMPFC (Fig. 5B), an effect was not even observed when the threshold was tentatively lowered to $p < 0.01$ uncorrected, underlining the specificity of the finding in the right dMPFC.

*Group * condition interaction: Regions, showing higher activation in the **mania group** during social compared to non-social processing (ROI analysis)*

For the contrast 'social > non-social processing', the comparison manic > healthy revealed a significant activation during social versus non-social stimuli in the right TPJ *(T=3.29, coordinates: 60 -50 14, p uncorrected = 0.001, p (FWE) = 0.032)* (Fig. 4B, Fig. 5C). This comparison revealed no significant effects in the left TPJ, the right and left dMPFC, the right and left vMPFC. The effect was not even observed when the threshold was tentatively lowered to $p < 0.01$ uncorrected, underlining the specificity of the finding in the right TPJ.

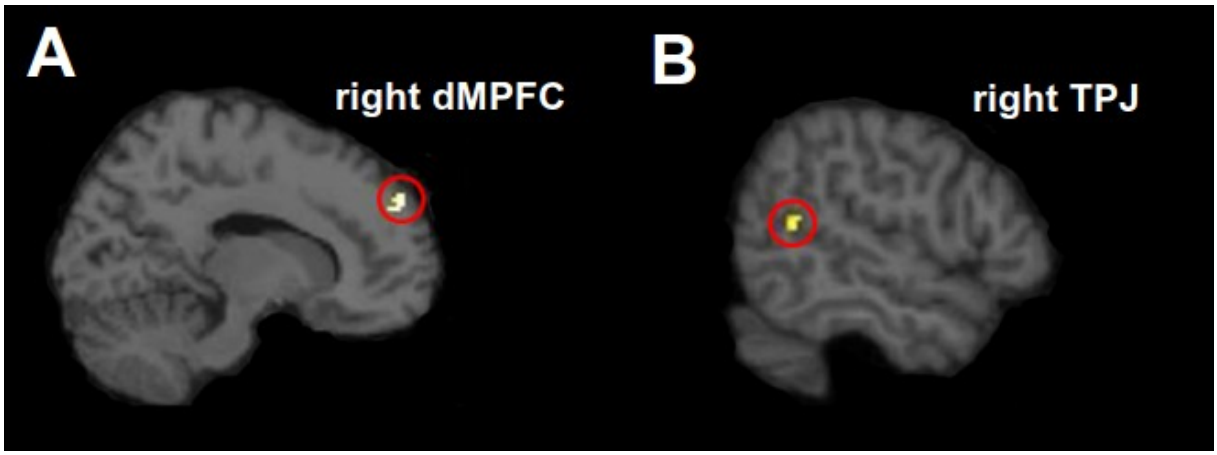

Figure 4: Group differences in BOLD signal for the contrast 'social > non-social' in the ROI analysis. A) Diminished BOLD signal in the right dMPFC (*T=3.17, Talairach coordinates: 14 50 26, p uncorrected = 0.001, p (FWE-corrected) = 0.042*) for the contrast 'social > non-social' in the mania group in comparison to the healthy group. B) Higher BOLD signal in the right TPJ (*T=3.29, Talairach coordinates: 60 -50 14, p uncorrected = 0.001, p (FWE-corrected) = 0.032*) for the contrast 'social > non-social' in the mania group in comparison to the healthy group.

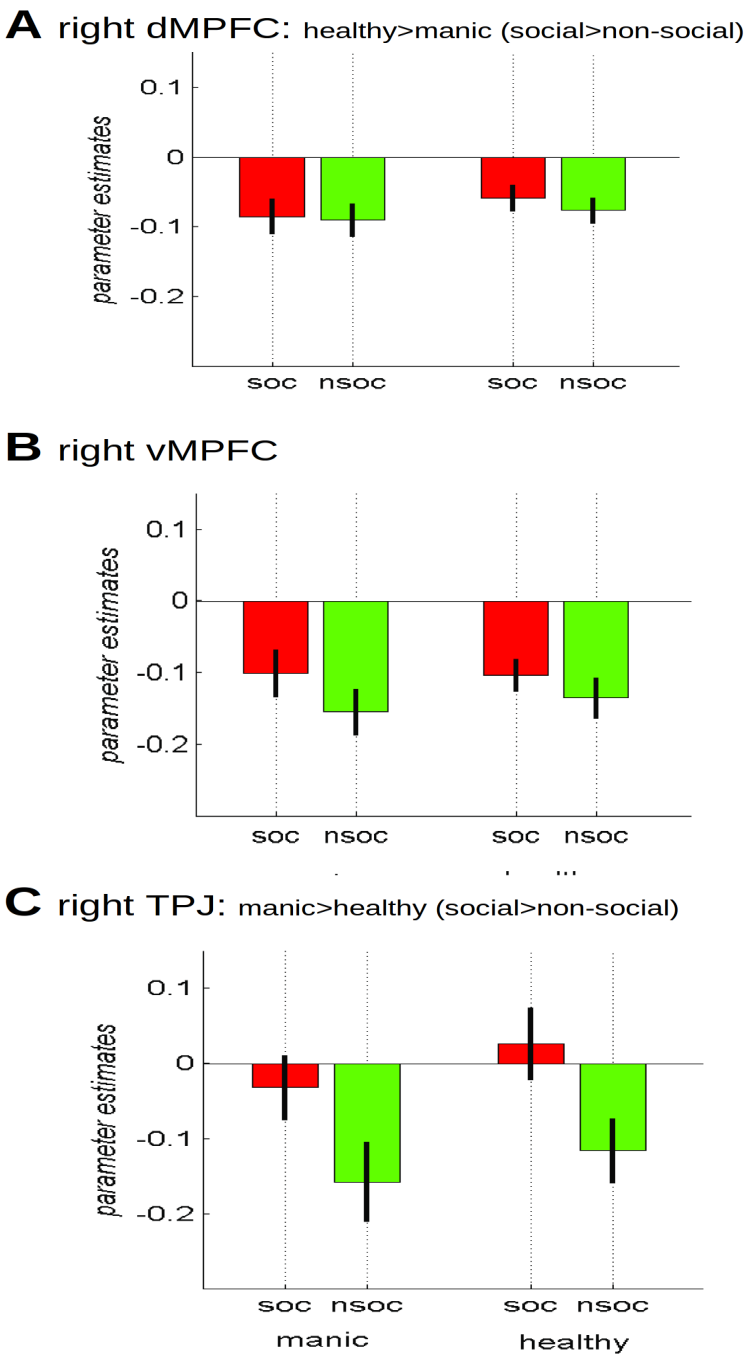

Figure 5: Parameter estimates for the contrast 'social > non-social' in the ROI analysis. A) Parameter estimates (in arbitrary units) and 95% confidence intervals for the manic and healthy group for the social (red bars) and non-social (green bars) conditions in the right dMPFC ROI (*p uncorrected = 0.001, p (FWE-corrected) = 0.042)*. B) Parameter estimates (in arbitrary units) and 95% confidence intervals for the manic and healthy group for the social (red bars) and non-social (green bars) conditions in the right vMPFC ROI. C) Parameter estimates (in arbitrary units) for the manic and healthy group for the social (red bars) and non-social (green bars) conditions in the right TPJ ROI (*p uncorrected = 0.001, p (FWE-corrected) = 0.032)*.

Exploratory whole-brain analysis

Whole-brain results are presented for the interaction contrast 'social > non-social' in healthy > manic and 'social > non-social' in manic > healthy, uncorrected, with $p < 0.001$ and cluster size ≥ 5 (Table 2).

Region (Brodman Area)	**Coordinates (MNI)**			**Peak T Value**	**N of voxels (k)**
	x	y	z		
Contrast social > non-social, healthy > mania					
Right subcallosal gyrus (11)	12	22	-14	3.84	14
Left anterior cingulate gyrus (24)	-14	32	18	3.89	13
Right anterior cingulate gyrus (32)	18	28	26	3.73	11
Right posterior cingulate gyrus (31)	26	-46	28	3.67	25
Right superior frontal gyrus (8)	22	20	52	3.38	6
Contrast social>nonsocial, mania>healthy					
Right superior temporal gyrus (22)	60	-48	12	3.59	10
Right superior parietal lobule (7)	22	-64	54	4.13	20
Left postcentral gyrus (5)	4	-46	64	3.85	16

Table 2. Exploratory whole brain analysis for the contrast 'social > non-social'. Peak voxel coordinates, $P < 0.001$ uncorrected, cluster size (k) ≥ 5.

Relationship between delusional ideation and brain activation

Finally, we were interested in the relationships between delusional ideation (measured with the PDI questionnaire) and brain activation. We found that the PDI scores were selectively correlated with the activity in right TPJ during social versus non-social pictures ($r = 0.52$, $p < 0.05$, one tailed).

3.3. Experiment II: Self-referential processing in mania

Clinical and demographic results

We used the samples as in the Experiment I. (See Table 1)

3.3.1. Behavioural data

Trial distribution and task performance

The mean number of trials rated as self-referential did not differ significantly between the groups, as revealed by the self*group interaction in the repeated measures ANOVA ($F(1,26)=2.496$, $p=0.126$).

3.3.2. Neuroimaging results

*Group * condition interaction: Regions, showing higher activation in the mania group during self-referential compared to non-self-referential processing*

For the contrast 'self-referential > non-self referential processing', the comparison manic patients > healthy controls revealed a significant difference in activation in precuneus/PCC *(T=3.95, coordinates 10 -44 40, p uncorrected < 0.001)* (Figure 6A). Plots of parameter estimates indicate, that manic patients showed a larger BOLD signal in this area during self-referential as opposed to non-self-referential processing (Figure 7A, Table 3). This contrast revealed no significant differences in vMPFC, dMPFC or TPJ.

*Group * condition interaction: Regions, showing higher activation in the healthy control group during self-referential compared to non-self-referential processing*

For the contrast 'self-referential > non-self-referential processing', the comparison healthy controls > manic patients revealed a significant difference in activation in vMPFC *(T= 4.15, coordinates -6 54 10, p uncorrected < 0.001)* (Figure 6B). Plots of parameter estimates indicate, that healthy controls exhibited larger BOLD signal in this area during self-referential as opposed to non-self-referential processing (Figure 7B, Table 3). This contrast produced no significant effects in precuneus/PCC, dMPFC and TPJ.

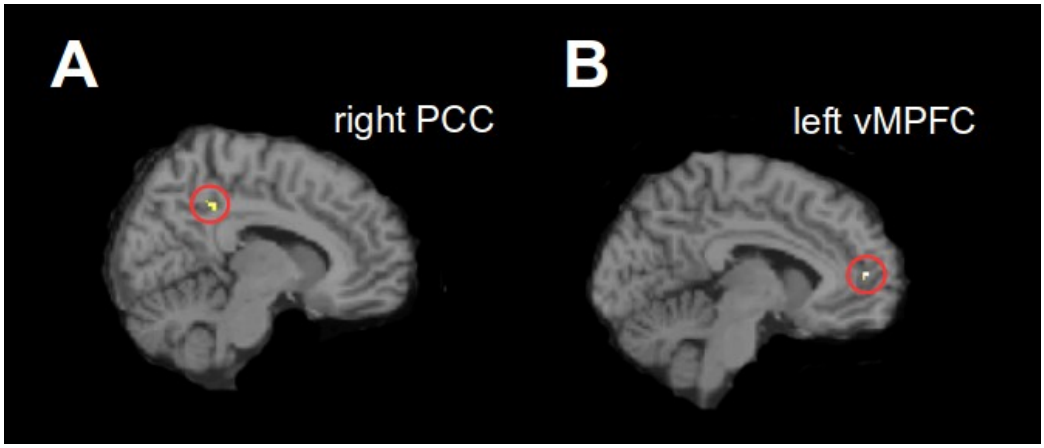

Figure 6: Group differences in BOLD signal revealed by the contrast 'self-referential > non-self-referential processing'. A) Increased BOLD signal in the right precuneus/ PCC (*T=3.95, Talairach coordinates 10 -44 40, p uncorrected < 0.001)* for the contrast 'self-referential > non-self-referential processing' in the manic group in comparison to the healthy group. B) Increased BOLD signal in the left vMPFC (*T= 4.15, Talairach coordinates -6 54 10, p uncorrected < 0.001*) for the contrast 'self-referential > non-self-referential processing' in the healthy group in comparison to the mania group.

Region (Brodman Area)	**Coordinates (MNI)**			**Peak T Value**	**N of voxels (k)**
	x	y	z		
Contrast self-referential > non-self-referential, mania > healthy					
Right PCC, Precuneus (31,7)	10	-44	40	3.95	13
Left primary motor cortex: precentral gyrus (4)	-50	-14	34	3.75	6
	38	-14	46	3.84	10
	50	-12	34	4.18	19
Left cerebellum: culmen	-8	-36	14	4.86	18
Contrast self-referential>non-self-referential, healthy>mania					
Left vMPFC: medial frontal gyrus (10)	-6	54	10	4.15	16

Table 3. Coordinates of the maxima, cluster sizes and t-values of the BOLD-activations produced by the contrast 'self-referential>non-self-referential processing'. All activations are reported p<0.001 uncorrected, k≥5 voxels.

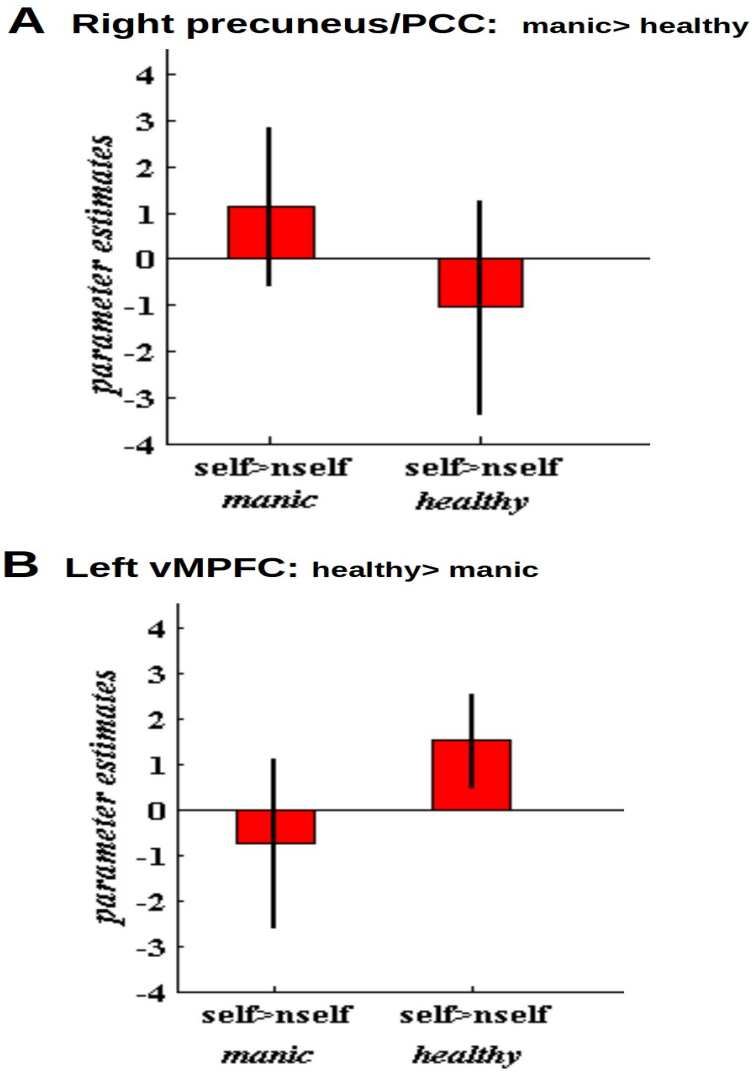

Figure 7: Parameter estimates for the 'self-referential > non-self-referential' condition. A) Parameter estimates (in arbitrary units) and 95% confidence intervals for the manic and healthy group for the 'self-referential > non-self-referential' condition in the right PCC (*T=3.95, Talairach coordinates 10 -44 40, p uncorrected < 0.001)*. B) Parameter estimates (in arbitrary units) and 95% confidence intervals for the manic and healthy group for the 'self-referential > non-self-referential' condition in the left vMPFC (*T= 4.15, Talairach coordinates -6 54 10, p uncorrected < 0.001*).

4. DISCUSSION

4.1. Social Stimulus Processing in Mania

This is the first study to investigate the neural profile of social stimulus processing targeting well-known social regions in patients with mania. The main findings of this study are, first, less activation in right dMPFC to social (versus non-social) stimuli in the mania group compared to healthy controls, while no group difference was observed in the vMPFC. Secondly, we found increased activation in the right TPJ to social (versus non-social) stimuli in manic patients as compared to healthy controls.

Previous neuroimaging studies in healthy participants have found the MPFC to be associated with social cognitive processes, such as person perception and making inferences about others' thoughts (Amodio and Frith, 2006). In addition, these studies have revealed a dorsal-ventral axis within the MPFC, with more dorsal regions being involved in cognitive aspects of social cognition and ventral areas being implicated in emotional facets (Hynes *et al.*, 2006; Shamay-Tsoory *et al.*, 2006). This functional dissociation between cognitive and emotional aspects of social cognition is strengthened also by recent behavioural reports in BD patients, which found impairment only for cognitive, but not for emotional social cognition (Montag *et al.*, 2010). Our results extend these previous findings by revealing that manic patients compared to healthy participants show exclusively decreased activation of the dMPFC, but not of the vMPFC during social processing. Impairment in cognitive aspects of social processing may concern for instance less or faulty inferences regarding possible beliefs or intentions of another person. Supporting this view, Montag and colleagues characterized the mentalizing deficits of BD patients in detail and found evidence for reduced or lacking mental state reasoning in BD patients ('undermentalizing'), but no 'overmentalizing' as it has been shown for example in schizophrenic patient groups (Fyfe *et al.*, 2008). Furthermore, deficits of BD patients on a cognitive perspective-taking questionnaire suggest that their difficulty may lie in the weakened ability of voluntarily shifting from an egocentric viewpoint to adopt the perspective of someone else (Seidel

et al., 2012). In BD, an inability to disengage from self-oriented thought processes may also contribute to difficulties maintaining successful social relationships, as well as occupational activities (Cusi *et al.*, 2010). In contrast, BD patients can readily relate to feelings of another person and may in some cases even show evidence for enhanced affective social cognition (Shamay-Tsoory *et al.*, 2009). The present finding of reduced activation to social stimuli in the cognitive (i.e., dorsal), but not the emotional (i.e., ventral) section of the MPFC may correspond to these previous behavioural observations of impairments in cognitive, but not emotional aspects of social processing.

Furthermore, it has been proposed that dorsal in contrast to ventral areas of MPFC are preferentially involved in the control and monitoring of social cognition (Forbes and Grafman, 2010; Olsson and Ochsner, 2008; Satpute and Lieberman, 2006). As social processing moves from ventral to dorsal regions, it may become less stimulus driven and increasingly controlled and reflective, for example, enabling us to actively take other peoples' perspectives and to judge explicitly one's own or others' mental states while considering prior knowledge. In mania, abnormal functioning of dMPFC, together with impaired executive functions, such as response inhibition (Bora *et al.*, 2009), could ultimately lead to a deficit in the control of social cognitive processes and voluntary regulation of social behavior.

In healthy individuals, the TPJ, and the nearby posterior superior temporal sulcus (pSTS), have shown activations in theory of mind and visual and cognitive perspective-taking tasks (Aichhorn *et al.*, 2006; Saxe and Wexler, 2005), but also during the attribution of intentionality to perceptual displays of moving inanimate objects, such as moving triangles (Castelli *et al.*, 2000). For example, activity in pSTS increased with the perception of animacy and interaction when viewing objects (Schultz *et al.*, 2005), supporting the involvement of STS in automatic identification of animate entities (Frith and Frith, 2008). TPJ activation has also been reported in non-social tasks, which require to redirect attention or to detect salient or unexpected events in the environment (Astafiev *et al.*, 2006; Corbetta and Shulman, 2002; Downar *et al.*, 2000; Mitchell,

2008). Interestingly, we found an overactivation of the right TPJ in patients with mania compared to controls during the perception of social stimuli and in the mania group this activation in the right TPJ was positively correlated with enhanced delusional ideation measured by the PDI questionnaire. It may thus be possible that in patients with mania there is a heightened saliency of external, social stimuli and that furthermore more intentionality is attributed to those social scenes. As the TPJ has been found in healthy controls to support the automatic visual detection and identification of agents from movement, this function may be chronically overactive in mania which could lead to an exaggerated attribution of meaning to social stimuli, so that these are perceived as particularly salient and personally significant. This may clinically manifest itself in an enhanced responsivity to social cues and, in extreme cases, also in delusions of reference.

In line with this, our finding of enhanced activation of the TPJ area in mania shows commonalities with previously reported overactivation of this region in schizophrenia. Schizophrenic patients, who suffered from passivity symptoms, in which patients feel that their own thoughts and actions are controlled by an external entity, showed sustained hyperactivation of the inferior parietal region (Spence *et al.*, 1997), as well as abnormal activation of this region during action-attribution judgements and the amount of these symptoms was correlated with higher activity in the TPJ region (Farrer *et al.*, 2004). Blakemore and colleagues (Blakemore *et al.*, 2003) also showed that patients with delusions of persecution attributed intentionality to moving objects when healthy controls detected no such intentional behaviour. This suggests an overactive perception of agency in schizophrenia, possibly related to abnormal activation of the TPJ region, which could also underlie the observed hyperactivation of this region in our study during a manic phase.

The present study used a task, which captures implicit processing of social scenes. This has the advantages, first, that it is a paradigm that is easy to understand and perform (which is critical for manic patients who often show attentional deficits), and, second, that it is largely independent of additional cognitive processes (in relation to the social

stimuli), especially executive functions, which have been found to be impaired in mania (Bora *et al.*, 2009). Such additional cognitive impairments could potentially confound group differences in more complex social tasks. While critical for this first neuroimaging study on this topic to bypass these confounds, future studies may employ explicit social tasks to capture further aspects of social processing.

Several studies in BD patients found positive correlation between performance on social cognition tasks and psychosocial functioning (Hoertnagl *et al.*, 2011; Lahera *et al.*, 2012; Martino *et al.*, 2009). The present findings might contribute to the understanding of the neural foundation of social processing in mania and may help to identify disorder-specific impairments for intervention. Psychotherapeutic procedures may be more effective, if they are specifically focused on the underlying functional deficit. For instance, meta-cognitive training (Moritz *et al.*, 2010) may be considered an approach tailored to improve cognitive social functions in BD.

In summary, this is the first study investigating the neural signature of social processing during a manic episode. In accordance with previous behavioural reports, we found diminished activation during social processing in mania only in the dMPFC, a region which has previously been linked to cognitive aspects of social cognition, but no difference in the ventral part of MPFC, related to affective processing of social information. This abnormal activation profile in mania may be related to reported deficits in making inferences about others' mental states and possibly also to controlling and regulating social processes in mania. Furthermore, hyperactivation of the TPJ shows commonalities with overactivation of this region in schizophrenia and may be related to exaggerated attribution of meaning to social stimuli.

4.2. Self-referential processing in mania

This is the first study, directly investigating the neural correlates of self-referential stimulus processing in patients with mania. The task required judgements of self-referentiality of pictures and thus was designed to investigate explicit self-referential

processing. The main findings of this second experiment are, first, more activation in precuneus/PCC to self-referential (versus non-self-referential) stimuli in the mania group compared to healthy controls. Secondly, we found decreased activation in the vMPFC to self-referential (versus non-self-referential) stimuli in manic patients as compared to healthy controls.

Previous neuroimaging studies in healthy participants report increased activity in the vMPFC during tasks which require self-reflective thought, e.g. yes/no evaluation of the self or significant other based on individually presented adjectives, such as „shy“ or „intelligent“. (Schmitz *et al.*, 2004), yes/no decisions concerning statements like 'I forget important things' (Johnson *et al.*, 2002) or taking the first-person perspective (Vogeley *et al.*, 2004). In addition, previous studies found no general failure to activate vMPFC in manic patients during an n-back task (Pomarol-Clotet *et al.*, 2012) or go/no-go-tasks (Elliott *et al.*, 2004; Strakowski *et al.*, 2008). Therefore we interpret our finding of decreased activation in vMPFC in manic patients as being specific to self-referential processing.

Another interesting aspect in interpretation of this finding arises from the literature on altered MPFC activation in depressed patients (Grimm *et al.*, 2009; Johnson *et al.*, 2009; Lemogne *et al.*, 2009; Yoshimura *et al.*, 2010). Lemogne et al (2012) combined the results from these studies into one model of tonic vMPFC and phasic dMPFC hyperactivation in depressed patients to account for the differences in the experimental designs. Elevated tonic vMPFC activation may embody automatic aspects of depressive self-focus, or, in other terms, a lack of deactivation of the default mode network during externally-oriented tasks. This increased automatic self-focus may reflect the clinical finding of rumination in depressed patients, i.e., a form of self-focused attention on negative aspects of one's self, which is associated with acute depressive states and an increased risk of depressive relapse (Lemogne *et al.*, 2012; Nolen-Hoeksema *et al.*, 2008; Watkins, 2008). Our finding of decreased BOLD-response in vMPFC in manic patients in self-referential processing might reflect the well-known clinical presentation of decreased self-focus in mania and increased focus on external stimuli. Behavioural

findings of the present study support this hypothesis, as manic patients show no significant increase in the number of trials rated as self-referential compared to healthy controls.

Second finding of this study is an increased BOLD-response in precuneus/PCC during self-referential processing in manic patients compared to healthy controls. Previous studies found evidence for structural alteration and dysfunction of precuneus/PCC in bipolar patients. A structural MRI study reported decreased volumes of bilateral PCC in patients with pediatric bipolar disorder (Kaur *et al.*, 2005), two studies using voxel-based morphometry (VBM) reported decreased gray matter volume in superior parietal lobule (BA 7) in manic patients (Adler *et al.*, 2005) and reduced volumes in precuneus/PCC in first-episode drug-naive manic patients (Yatham *et al.*, 2007).

In a recent functional study Magioncalda and colleagues found resting state hypoconnectivity in manic patients between PACC and PCC, which the authors interpreted in network terms with a deficit in the posterior default-mode network (DMN) and consequent abnormal shifting toward the central executive network (CEN), hypothetically resulting in excessive focusing on external contents at the expense of internal contents that can manifest in distractibility and flight of ideas, characteristic of mania (Magioncalda *et al.*, 2015).

In psychopathological terms, thought disorders are a well-established feature of mania. Both the disorder of formal thought and the disorder of thought content are found in mania. Normally, the brain's selective attention mechanism filters and prioritizes incoming stimuli by excluding from consciousness extraneous, low-priority stimuli and grading the importance of more relevant data. Because this “filter/prioritizer” becomes defective in mania, tangential stimuli are processed without appropriate prioritization. This defect is observed clinically as manic distractibility, poor judgment, and lack of insight. The level of distractibility provides a clinical index reflecting the severity of the information-processing defect in manic patients. Increasing distractibility in mania leads to disorganization of thought and behavior and to psychosis (Lake, 2008) Here, our

findings of hypoactivation of vMPFC and hyperactivation in PCC offer possible neural correlates of the thought disorders found in mania.

In summary, this second study is the first investigation of the neural signature of self-referential processing during a manic episode. We found diminished activation in vMPFC in mania, a region, consistently implicated in self-referential processing in healthy participants and showing no failure of activation during other tasks in mania. We conclude therefore, that this finding is specific for self-referential processing in mania. As vMPFC hyperactivation was described to be characteristic of self-referential processing and increased rumination in depressed patients, we conclude that vMPFC hypoactivation in mania could reflect the clinical presentation of focus on external contents and high distractibility, i.e. no increased ruminative self-focus, in mania. Similarly, the finding of hyperactivation in precuneus/PCC could reflect the clinical finding of external focus with increased distractibility and flight of ideas in mania.

4.3. Limitations

One of the limitations of our study is that all manic patients were administered psychotropic medication, which cannot be withdrawn in a manic episode due to ethical reasons. Unfortunately, our sample size did not allow the statistically powerful analysis of medication effects. However, a meta-analysis on social cognition in BD patients found no medication effects on behavioural indicators (Samamé *et al.*, 2012). More importantly, most neuroimaging studies in patients with BD have not found an effect of psychotropic medication exposure status on neuroimaging results (Hafeman *et al.*, 2012). The studies, that found differences based on medication status, indicated that medication exposure tends to mitigate the observed differences between the BD patients and healthy controls. Specifically concerning the PFC, Hafeman et al. (2012) found in several studies with schizophrenia patients, that atypical antipsychotic agents tended to increase the BOLD signal in the PFC, reversing the deficit observed in schizophrenia. Our data reveals a pattern, which makes it very unlikely that our effects

are influenced by medication effects. We found a differential effect with decreased activation in mania in the dMPFC (Experiment I) and vMPFC (Experiment II), which cannot be attributed to atypical antipsychotics, as they would rather increase the BOLD signal in the PFC, and we found an increased activation in the TPJ (Experiment I) and the PCC (Experiment II) in the patient group, whereas medication effects would rather normalize the BOLD response. Still better ways to deal with possible medication effects on neuroimaging results would be to adjust for medication in analysis and to conduct longitudinal studies to assess medication effects.

Longitudinal studies with BD patients in euthymic and, possibly, in depressed state would be interesting also for another reason. Such studies would be helpful in understanding whether the neuroimaging effects we have observed during social and self-referential stimulus processing are state- or trait-dependent. An enduring trait marker represents the properties of the behavioural and biological processes that play a more proximal role in the pathophysiology of the psychiatric disorder, whereas a transient state marker reflects the clinical manifestations in patients. Apart from studying BD patients in different mood states, a possible way to differentiate between trait or state markers would be to study also close relatives of BD patients and patients with other similar disorders, e.g. with schizophrenic psychosis.

Another limitation arises from the definitions of the social or self-referential stimuli, which could have been different. It is possible, that seeing according to our definition non-social stimuli, e.g. a beach or food, study participants could imagine walking there or eating it with another person. Such stimuli then could partially elicit activation of social networks as well, even though there are no faces of other people on them. Furthermore, it is unclear, whether the social networks would be active while viewing pictures of animals, e.g. monkeys. On a similar note, IAPS stimuli are complex and even those labelled as social include apart from people some objects or animals, or picture different activities. These differences could be confounding factors while determining areas, responsive to social stimuli.

Conclusions

In summary, the first study investigated the neural signature of social processing during a manic episode. In accordance with previous behavioural reports, we found diminished activation during social processing in mania only in the dMPFC, a region which has previously been linked to cognitive aspects of social cognition, but no difference in the ventral part of MPFC, related to affective processing of social information. This abnormal activation profile in mania may be related to reported deficits in making inferences about others' mental states and possibly also to controlling and regulating social processes in mania. Furthermore, hyperactivation of the TPJ shows commonalities with overactivation of this region in schizophrenia and may be related to exaggerated attribution of meaning to social stimuli.

The second study investigated the neural signature of self-referential processing during a manic episode. In accordance with previous reports, we found diminished activation in vMPFC in mania, a region, consistently implicated in self-referential processing in healthy participants in previous studies and showing no failure in activation during other tasks in mania. We conclude therefore, that this finding is specific for self-referential processing in mania. As vMPFC hyperactivation was described to be implicated in self-referential processing in depressed patients, we conclude that vMPFC hypoactivation in mania could reflect the clinical presentation of no increased self-focus in mania. Furthermore, the finding of hyperactivation in precuneus/PCC could reflect the clinical finding of external focus with increased distractibility and flight of ideas in mania.

References

Adler CM, Levine AD, DelBello MP, Strakowski SM. Changes in Gray Matter Volume in Patients with Bipolar Disorder. Biol. Psychiatry 2005; 58: 151–157.

Adolphs R. Social cognition and the human brain. Trends Cogn. Sci. 1999; 3: 469–479.

Aichhorn M, Perner J, Kronbichler M, Staffen W, Ladurner G. Do visual perspective tasks need theory of mind? NeuroImage 2006; 30: 1059–1068.

Amodio DM, Frith CD. Meeting of minds: the medial frontal cortex and social cognition. Nat. Rev. Neurosci. 2006; 7: 268–277.

Association AP. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR. American Psychiatric Association; 2000.

Astafiev SV, Shulman GL, Corbetta M. Visuospatial reorienting signals in the human temporo-parietal junction are independent of response selection. Eur. J. Neurosci. 2006; 23: 591–596.

Barrera A, Vázquez G, Tannenhaus L, Lolich M, Herbst L. Theory of mind and functionality in bipolar patients with symptomatic remission. Rev. Psiquiatr. Salud Ment. 2012

Bazin N, Brunet-Gouet E, Bourdet C, Kayser N, Falissard B, Hardy-Baylé M-C, et al. Quantitative assessment of attribution of intentions to others in schizophrenia using an ecological video-based task: a comparison with manic and depressed patients. Psychiatry Res. 2009; 167: 28–35.

Blairy S, Linotte S, Souery D, Papadimitriou GN, Dikeos D, Lerer B, et al. Social adjustment and self-esteem of bipolar patients: a multicentric study. J. Affect. Disord. 2004; 79: 97–103.

Blakemore SJ, Sarfati Y, Bazin N, Decety J. The detection of intentional contingencies in simple animations in patients with delusions of persecution. Psychol. Med. 2003; 33: 1433–1441.

Boly M, Phillips C, Tshibanda L, Vanhaudenhuyse A, Schabus M, Dang-Vu TT, et al. Intrinsic brain activity in altered states of consciousness: how conscious is the default mode of brain function? Ann. N. Y. Acad. Sci. 2008; 1129: 119–129.

Bora E, Yucel M, Pantelis C. Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. J. Affect. Disord. 2009; 113: 1–20.

Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. Ann. N. Y. Acad. Sci. 2008; 1124: 1–38.

Castelli F, Happé F, Frith U, Frith C. Movement and mind: a functional imaging study of perception and interpretation of complex intentional movement patterns. NeuroImage 2000; 12: 314–325.

Christoff K, Ream JM, Geddes LPT, Gabrieli JDE. Evaluating self-generated information: anterior prefrontal contributions to human cognition. Behav. Neurosci. 2003; 117: 1161–1168.

Churchland PS. Self-representation in nervous systems. Science 2002; 296: 308–310.

Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. 2002; 3: 201–215.

Cusi A, Macqueen GM, McKinnon MC. Altered self-report of empathic responding in patients with bipolar disorder. Psychiatry Res. 2010; 178: 354–358.

Cusi AM, Macqueen GM, McKinnon MC. Patients with bipolar disorder show impaired performance on complex tests of social cognition. Psychiatry Res. 2012; 200: 258–264.

Damasio A. The Feeling of What Happens: Body and Emotion in the Making of Consciousness. 1 edition. Mariner Books; 2000.

Das P, Calhoun V, Malhi GS. Bipolar and borderline patients display differential patterns of functional connectivity among resting state networks. NeuroImage 2014; 98: 73–81.

Dion GL, Tohen M, Anthony WA, Waternaux CS. Symptoms and functioning of patients with bipolar disorder six months after hospitalization. Hosp. Community Psychiatry 1988; 39: 652–657.

Downar J, Crawley AP, Mikulis DJ, Davis KD. A multimodal cortical network for the detection of changes in the sensory environment. Nat. Neurosci. 2000; 3: 277–283.

Elliott R, Ogilvie A, Rubinsztein JS, Calderon G, Dolan RJ, Sahakian BJ. Abnormal ventral frontal response during performance of an affective go/no go task in patients with mania. Biol. Psychiatry 2004; 55: 1163–1170.

Farrer C, Franck N, Frith CD, Decety J, Georgieff N, d'Amato T, et al. Neural correlates of action attribution in schizophrenia. Psychiatry Res. 2004; 131: 31–44.

First, Michael B., Spitzer, Robert L, Gibbon Miriam, and Williams, Janet B.W. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-patient Edition. (SCID-I/NP). N. Y. Biom. Res. N. Y. State Psychiatr. Inst. 2002

Forbes CE, Grafman J. The role of the human prefrontal cortex in social cognition and moral judgment. Annu. Rev. Neurosci. 2010; 33: 299–324.

Friston KJ, Holmes AP, Worsley KJ, Poline J-P, Frith CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: A general linear approach. Hum. Brain Mapp. 1994; 2: 189–210.

Frith CD, Frith U. Implicit and explicit processes in social cognition. Neuron 2008; 60: 503–510.

Fyfe S, Williams C, Mason OJ, Pickup GJ. Apophenia, theory of mind and schizotypy: perceiving meaning and intentionality in randomness. Cortex J. Devoted Study Nerv. Syst. Behav. 2008; 44: 1316–1325.

Gallagher null. Philosophical conceptions of the self: implications for cognitive science. Trends Cogn. Sci. 2000; 4: 14–21.

Gallagher HL, Frith CD. Functional imaging of 'theory of mind'. Trends Cogn. Sci. 2003; 7: 77–83.

German TP, Niehaus JL, Roarty MP, Giesbrecht B, Miller MB. Neural correlates of detecting pretense: automatic engagement of the intentional stance under covert conditions. J. Cogn. Neurosci. 2004; 16: 1805–1817.

Gillihan SJ, Farah MJ. Is self special? A critical review of evidence from experimental psychology and cognitive neuroscience. Psychol. Bull. 2005; 131: 76–97.

Gläscher J. Visualization of group inference data in functional neuroimaging. Neuroinformatics 2009; 7: 73–82.

Goldberg JF, Harrow M. Consistency of remission and outcome in bipolar and unipolar mood disorders: a 10-year prospective follow-up. J. Affect. Disord. 2004; 81: 123–131.

Goldstein TR, Miklowitz DJ, Mullen KL. Social skills knowledge and performance among adolescents with bipolar disorder. Bipolar Disord. 2006; 8: 350–361.

Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am. J. Psychiatry 2003; 160: 636–645.

Green MF, Leitman DI. Social Cognition in Schizophrenia. Schizophr. Bull. 2008; 34: 670–672.

Grimm S, Ernst J, Boesiger P, Schuepbach D, Hell D, Boeker H, et al. Increased self-focus in major depressive disorder is related to neural abnormalities in subcortical-cortical midline structures. Hum. Brain Mapp. 2009; 30: 2617–2627.

Grossman ED, Blake R. Brain Areas Active during Visual Perception of Biological Motion. Neuron 2002; 35: 1167–1175.

Gusnard DA, Akbudak E, Shulman GL, Raichle ME. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. Proc. Natl. Acad. Sci. U. S. A. 2001; 98: 4259–4264.

Gustavsson A, Svensson M, Jacobi F, Allgulander C, Alonso J, Beghi E, et al. Cost of disorders of the brain in Europe 2010. Eur. Neuropsychopharmacol. 2011; 21: 718–779.

Hafeman DM, Chang KD, Garrett AS, Sanders EM, Phillips ML. Effects of medication on neuroimaging findings in bipolar disorder: an updated review. Bipolar Disord. 2012; 14: 375–410.

Hamilton M. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 1960; 23: 56–62.

Heider F, Simmel M. An experimental study of apparent behavior. Am. J. Psychol. 1944; 57: 243–259.

Hoertnagl CM, Muehlbacher M, Biedermann F, Yalcin N, Baumgartner S, Schwitzer G, et al. Facial emotion recognition and its relationship to subjective and functional outcomes in remitted patients with bipolar I disorder. Bipolar Disord. 2011; 13: 537–544.

Huettel SA, Song AW, McCarthy G. Functional Magnetic Resonance Imaging. Sinauer Associates; 2004.

Huxley N, Baldessarini RJ. Disability and its treatment in bipolar disorder patients. Bipolar Disord. 2007; 9: 183–196.

Hynes CA, Baird AA, Grafton ST. Differential role of the orbital frontal lobe in emotional versus cognitive perspective-taking. Neuropsychologia 2006; 44: 374–383.

J P. The periconscious substrates of consciousness. Affective states and evolutionary origins of the SELF. J. Conscious. Stud. 1997; 5: 566–582.

Jaeger J, Vieta E. Functional outcome and disability in bipolar disorders: ongoing research and future directions. Bipolar Disord. 2007; 9: 1–2.

James W. The principles of psychology [Internet]. New York : Holt; 1890. [cited 2016 Apr 12] Available from: http://archive.org/details/theprinciplesofp01jameuoft

Johnson MK, Nolen-Hoeksema S, Mitchell KJ, Levin Y. Medial cortex activity, self-reflection and depression. Soc. Cogn. Affect. Neurosci. 2009; 4: 313–327.

Johnson SC, Baxter LC, Wilder LS, Pipe JG, Heiserman JE, Prigatano GP. Neural correlates of self-reflection. Brain J. Neurol. 2002; 125: 1808–1814.

Judd LL, Schettler PJ, Solomon DA, Maser JD, Coryell W, Endicott J, et al. Psychosocial disability and work role function compared across the long-term course of bipolar I, bipolar II and unipolar major depressive disorders. J. Affect. Disord. 2008; 108: 49–58.

Kaur S, Sassi RB, Axelson D, Nicoletti M, Brambilla P, Monkul ES, et al. Cingulate cortex anatomical abnormalities in children and adolescents with bipolar disorder. Am. J. Psychiatry 2005; 162: 1637–1643.

Keenan JP, Wheeler M, Platek SM, Lardi G, Lassonde M. Self-face processing in a callosotomy patient. Eur. J. Neurosci. 2003; 18: 2391–2395.

Kelley WM, Macrae CN, Wyland CL, Caglar S, Inati S, Heatherton TF. Finding the self? An event-related fMRI study. J. Cogn. Neurosci. 2002; 14: 785–794.

Kerr N, Dunbar RIM, Bentall RP. Theory of mind deficits in bipolar affective disorder. J. Affect. Disord. 2003; 73: 253–259.

Keysers C, Gazzola V. Integrating simulation and theory of mind: from self to social cognition. Trends Cogn. Sci. 2007; 11: 194–196.

Kim E, Jung Y-C, Ku J, Kim J-J, Lee H, Kim SY, et al. Reduced activation in the mirror neuron system during a virtual social cognition task in euthymic bipolar disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry 2009; 33: 1409–1416.

Koski L, Paus T. Functional connectivity of the anterior cingulate cortex within the human frontal lobe: a brain-mapping meta-analysis. Exp. Brain Res. Exp. Hirnforsch. Expérimentation Cérébrale 2000; 133: 55–65.

Kühn S, Gallinat J. Resting-state brain activity in schizophrenia and major depression: a quantitative meta-analysis. Schizophr. Bull. 2013; 39: 358–365.

Lahera G, Ruiz-Murugarren S, Iglesias P, Ruiz-Bennasar C, Herrería E, Montes JM, et al. Social cognition and global functioning in bipolar disorder. J. Nerv. Ment. Dis. 2012; 200: 135–141.

Lake CR. Disorders of Thought Are Severe Mood Disorders: the Selective Attention Defect in Mania Challenges the Kraepelinian Dichotomy—A Review. Schizophr. Bull. 2008; 34: 109–117.

Lambie JA, Marcel AJ. Consciousness and the varieties of emotion experience: a theoretical framework. Psychol. Rev. 2002; 109: 219–259.

Lancaster JL, Rainey LH, Summerlin JL, Freitas CS, Fox PT, Evans AC, et al. Automated labeling of the human brain: a preliminary report on the development and evaluation of a forward-transform method. Hum. Brain Mapp. 1997; 5: 238–242.

Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L, et al. Automated Talairach atlas labels for functional brain mapping. Hum. Brain Mapp. 2000; 10: 120–131.

Lang P, Bradley M, Cuthbert B. International affective picture system (IAPS): Affective ratings of pictures and instruction manual [Internet]. 2008. [cited 2013 Apr 23] Available from: http://csea.phhp.ufl.edu/Media.html

LeDoux J. Synaptic Self: How Our Brains Become Who We Are. Penguin Books; 2003.

Legrand D, Ruby P. What is self-specific? Theoretical investigation and critical review of neuroimaging results. Psychol. Rev. 2009; 116: 252–282.

Lehrl S. Mehrfachwahl-Wortschatz-Intelligenztest: MWT-B. 5th ed. Spitta; 2005.

Lemogne C, le Bastard G, Mayberg H, Volle E, Bergouignan L, Lehéricy S, et al. In search of the depressive self: extended medial prefrontal network during self-referential processing in major depression. Soc. Cogn. Affect. Neurosci. 2009; 4: 305–312.

Lemogne C, Delaveau P, Freton M, Guionnet S, Fossati P. Medial prefrontal cortex and the self in major depression. J. Affect. Disord. 2012; 136: e1–e11.

Logothetis NK. The neural basis of the blood-oxygen-level-dependent functional magnetic resonance imaging signal. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 2002; 357: 1003–1037.

Logothetis NK, Wandell BA. Interpreting the BOLD signal. Annu. Rev. Physiol. 2004; 66: 735–769.

Magioncalda P, Martino M, Conio B, Escelsior A, Piaggio N, Presta A, et al. Functional connectivity and neuronal variability of resting state activity in bipolar disorder--reduction and decoupling in anterior cortical midline structures. Hum. Brain Mapp. 2015; 36: 666–682.

Maldjian JA, Laurienti PJ, Burdette JH. Precentral gyrus discrepancy in electronic versions of the Talairach atlas. NeuroImage 2004; 21: 450–455.

Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. NeuroImage 2003; 19: 1233–1239.

Malhi GS, Lagopoulos J, Das P, Moss K, Berk M, Coulston CM. A functional MRI study of Theory of Mind in euthymic bipolar disorder patients. Bipolar Disord. 2008; 10: 943–956.

Mansfield P. Multi-planar image formation using NMR spin echoes. J. Phys. C Solid State Phys. 1977; 10: L55–L58.

Martino DJ, Marengo E, Igoa A, Scápola M, Ais ED, Perinot L, et al. Neurocognitive and symptomatic predictors of functional outcome in bipolar disorders: a prospective 1 year follow-up study. J. Affect. Disord. 2009; 116: 37–42.

Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RMA, Petukhova M, et al. Lifetime and 12-Month Prevalence of Bipolar Spectrum Disorder in the National Comorbidity Survey Replication. Arch. Gen. Psychiatry 2007; 64: 543–552.

Metzinger T, Gallese V. The emergence of a shared action ontology: building blocks for a theory. Conscious. Cogn. 2003; 12: 549–571.

Mitchell JP. Activity in right temporo-parietal junction is not selective for theory-of-mind. Cereb. Cortex N. Y. N 1991 2008; 18: 262–271.

Mitchell JP, Banaji MR, Macrae CN. General and specific contributions of the medial prefrontal cortex to knowledge about mental states. NeuroImage 2005; 28: 757–762.

Mitchell JP, Heatherton TF, Macrae CN. Distinct neural systems subserve person and object knowledge. Proc. Natl. Acad. Sci. U. S. A. 2002; 99: 15238–15243.

Montag C, Ehrlich A, Neuhaus K, Dziobek I, Heekeren HR, Heinz A, et al. Theory of mind impairments in euthymic bipolar patients. J. Affect. Disord. 2010; 123: 264–269.

Moritz S, Vitzthum F, Randjbar S, Veckenstedt R, Woodward TS. Detecting and defusing cognitive traps: metacognitive intervention in schizophrenia. Curr. Opin. Psychiatry 2010; 23: 561–569.

Morriss R, Scott J, Paykel E, Bentall R, Hayhurst H, Johnson T. Social adjustment based on reported behaviour in bipolar affective disorder. Bipolar Disord. 2007; 9: 53–62.

Nolen-Hoeksema S, Wisco BE, Lyubomirsky S. Rethinking Rumination. Perspect. Psychol. Sci. 2008; 3: 400–424.

Northoff G, Bermpohl F. Cortical midline structures and the self. Trends Cogn. Sci. 2004; 8: 102–107.

Northoff G, Heinzel A, de Greck M, Bermpohl F, Dobrowolny H, Panksepp J. Self-referential processing in our brain--a meta-analysis of imaging studies on the self. NeuroImage 2006; 31: 440–457.

Northoff G, Qin P, Feinberg TE. Brain imaging of the self--conceptual, anatomical and methodological issues. Conscious. Cogn. 2011; 20: 52–63.

Northoff G, Schneider F, Rotte M, Matthiae C, Tempelmann C, Wiebking C, et al. Differential parametric modulation of self-relatedness and emotions in different brain regions. Hum. Brain Mapp. 2009; 30: 369–382.

Ochsner KN, Knierim K, Ludlow DH, Hanelin J, Ramachandran T, Glover G, et al. Reflecting upon feelings: an fMRI study of neural systems supporting the attribution of emotion to self and other. J. Cogn. Neurosci. 2004; 16: 1746–1772.

Olsson A, Ochsner KN. The role of social cognition in emotion. Trends Cogn. Sci. 2008; 12: 65–71.

Panksepp J. At the interface of the affective, behavioral, and cognitive neurosciences: decoding the emotional feelings of the brain. Brain Cogn. 2003; 52: 4–14.

Peelen MV, Downing PE. The neural basis of visual body perception. Nat. Rev. Neurosci. 2007; 8: 636–648.

Peters ER, Joseph SA, Garety PA. Measurement of delusional ideation in the normal population: introducing the PDI (Peters et al. Delusions Inventory). Schizophr. Bull. 1999; 25: 553–576.

Phan KL, Taylor SF, Welsh RC, Ho S-H, Britton JC, Liberzon I. Neural correlates of individual ratings of emotional salience: a trial-related fMRI study. NeuroImage 2004; 21: 768–780.

Platek SM, Loughead JW, Gur RC, Busch S, Ruparel K, Phend N, et al. Neural substrates for functionally discriminating self-face from personally familiar faces. Hum. Brain Mapp. 2006; 27: 91–98.

Pomarol-Clotet E, Moro N, Sarró S, Goikolea JM, Vieta E, Amann B, et al. Failure of de-activation in the medial frontal cortex in mania: evidence for default mode network dysfunction in the disorder. World J. Biol. Psychiatry Off. J. World Fed. Soc. Biol. Psychiatry 2012; 13: 616–626.

Qin P, Di H, Liu Y, Yu S, Gong Q, Duncan N, et al. Anterior cingulate activity and the self in disorders of consciousness. Hum. Brain Mapp. 2010; 31: 1993–2002.

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc. Natl. Acad. Sci. U. S. A. 2001; 98: 676–682.

Samamé C. Social cognition throughout the three phases of bipolar disorder: a state-of-the-art overview. Psychiatry Res. 2013; 210: 1275–1286.

Samamé C, Martino DJ, Strejilevich SA. Social cognition in euthymic bipolar disorder: systematic review and meta-analytic approach. Acta Psychiatr. Scand. 2012; 125: 266–280.

Satpute AB, Lieberman MD. Integrating automatic and controlled processes into neurocognitive models of social cognition. Brain Res. 2006; 1079: 86–97.

Saxe R, Wexler A. Making sense of another mind: the role of the right temporo-parietal junction. Neuropsychologia 2005; 43: 1391–1399.

Schmitz TW, Kawahara-Baccus TN, Johnson SC. Metacognitive evaluation, self-relevance, and the right prefrontal cortex. NeuroImage 2004; 22: 941–947.

Schneider F, Bermpohl F, Heinzel A, Rotte M, Walter M, Tempelmann C, et al. The resting brain and our self: self-relatedness modulates resting state neural activity in cortical midline structures. Neuroscience 2008; 157: 120–131.

Schultz J, Friston KJ, O'Doherty J, Wolpert DM, Frith CD. Activation in posterior superior temporal sulcus parallels parameter inducing the percept of animacy. Neuron 2005; 45: 625–635.

Seidel E-M, Habel U, Finkelmeyer A, Hasmann A, Dobmeier M, Derntl B. Risk or resilience? Empathic abilities in patients with bipolar disorders and their first-degree relatives. J. Psychiatr. Res. 2012; 46: 382–388.

Shamay-Tsoory S, Harari H, Szepsenwol O, Levkovitz Y. Neuropsychological evidence of impaired cognitive empathy in euthymic bipolar disorder. J. Neuropsychiatry Clin. Neurosci. 2009; 21: 59–67.

Shamay-Tsoory SG, Aharon-Peretz J, Perry D. Two systems for empathy: a double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions. Brain J. Neurol. 2009; 132: 617–627.

Shamay-Tsoory SG, Tibi-Elhanany Y, Aharon-Peretz J. The ventromedial prefrontal cortex is involved in understanding affective but not cognitive theory of mind stories. Soc. Neurosci. 2006; 1: 149–166.

Smoller JW, Finn CT. Family, twin, and adoption studies of bipolar disorder. Am. J. Med. Genet. C Semin. Med. Genet. 2003; 123C: 48–58.

Spence SA, Brooks DJ, Hirsch SR, Liddle PF, Meehan J, Grasby PM. A PET study of voluntary movement in schizophrenic patients experiencing passivity phenomena (delusions of alien control). Brain J. Neurol. 1997; 120 (Pt 11): 1997–2011.

Steele JD, Lawrie SM. Segregation of cognitive and emotional function in the prefrontal cortex: a stereotactic meta-analysis. NeuroImage 2004; 21: 868–875.

Strakowski SM, Adler CM, Cerullo MA, Eliassen JC, Lamy M, Fleck DE, et al. Magnetic resonance imaging brain activation in first-episode bipolar mania during a response inhibition task. Early Interv. Psychiatry 2008; 2: 225–233.

Tsai SY, Lee JC, Chen CC. Characteristics and psychosocial problems of patients with bipolar disorder at high risk for suicide attempt. J. Affect. Disord. 1999; 52: 145–152.

Turk DJ, Heatherton TF, Kelley WM, Funnell MG, Gazzaniga MS, Macrae CN. Mike or me? Self-recognition in a split-brain patient. Nat. Neurosci. 2002; 5: 841–842.

Turk DJ, Heatherton TF, Macrae CN, Kelley WM, Gazzaniga MS. Out of contact, out of mind: the distributed nature of the self. Ann. N. Y. Acad. Sci. 2003; 1001: 65–78.

Turkeltaub PE, Eden GF, Jones KM, Zeffiro TA. Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. NeuroImage 2002; 16: 765–780.

Uddin LQ, Iacoboni M, Lange C, Keenan JP. The self and social cognition: the role of cortical midline structures and mirror neurons. Trends Cogn. Sci. 2007; 11: 153–157.

van Overwalle F. Social cognition and the brain: a meta-analysis. Hum. Brain Mapp. 2009; 30: 829–858.

van Rheenen TE, Rossell SL. Phenomenological predictors of psychosocial function in bipolar disorder: is there evidence that social cognitive and emotion regulation abnormalities contribute? Aust. N. Z. J. Psychiatry 2014; 48: 26–35.

Vogeley K, May M, Ritzl A, Falkai P, Zilles K, Fink GR. Neural correlates of first-person perspective as one constituent of human self-consciousness. J. Cogn. Neurosci. 2004; 16: 817–827.

Watkins ER. Constructive and unconstructive repetitive thought. Psychol. Bull. 2008; 134: 163–206.

Whiteford HA, Ferrari AJ, Degenhardt L, Feigin V, Vos T. The global burden of mental, neurological and substance use disorders: an analysis from the Global Burden of Disease Study 2010. PloS One 2015; 10: e0116820.

Wicker B, Ruby P, Royet J-P, Fonlupt P. A relation between rest and the self in the brain? Brain Res. Brain Res. Rev. 2003; 43: 224–230.

Wingo AP, Baldessarini RJ, Compton MT, Harvey PD. Correlates of recovery of social functioning in types I and II bipolar disorder patients. Psychiatry Res. 2010a; 177: 131–134.

Wingo AP, Baldessarini RJ, Compton MT, Harvey PD. Correlates of recovery of social functioning in types I and II bipolar disorder patients. Psychiatry Res. 2010b; 177: 131–134.

Yaoi K, Osaka N, Osaka M. Is the self special in the dorsomedial prefrontal cortex? An fMRI study. Soc. Neurosci. 2009; 4: 455–463.

Yatham LN, Lyoo IK, Liddle P, Renshaw PF, Wan D, Lam RW, et al. A magnetic resonance imaging study of mood stabilizer- and neuroleptic-naïve first-episode mania. Bipolar Disord. 2007; 9: 693–697.

Yoshimura S, Okamoto Y, Onoda K, Matsunaga M, Ueda K, Suzuki S, et al. Rostral anterior cingulate cortex activity mediates the relationship between the depressive symptoms and the medial prefrontal cortex activity. J. Affect. Disord. 2010; 122: 76–85.

Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. Br. J. Psychiatry J. Ment. Sci. 1978; 133: 429–435.

Zhu Y, Zhang L, Fan J, Han S. Neural basis of cultural influence on self-representation. NeuroImage 2007; 34: 1310–1316.

CURRICULUM VITAE

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

PUBLICATIONS

Publications in scientific journals (in chronological order)

- Herold D, Spengler S, Sajonz B, **Usnich T**, Bermpohl F. Common and distinct networks for self-referential and social stimulus processing in the human brain. Brain Struct Funct. 2015 Sep 13.

- Ostwaldt AC, **Usnich T**, Nolte CH, Villringer K, Fiebach JB. Case report of a young stroke patient showing interim normalization of the MRI diffusion-weighted imaging lesion. BMC Med Imaging. 2015 Aug 25;15:33.

- **Usnich T***, Spengler S*, Sajonz D, Herold D ,Bauer M, Bermpohl F. The perception of social stimuli in mania: an fMRI study. Psychiatry Res. 2015 Jan 30;231(1):71-6.
  **equally contributed to publication*

- Braemswig TB*, **Usnich T***, Albach FN, Brunecker P, Grittner U, Scheitz JF, Fiebach JB, Nolte CH. Early new diffusion-weighted imaging lesions appear more often in stroke patients with a multiple territory lesion pattern. Stroke. 2013 Aug;44(8):2200-4.
  **equally contributed to publication*

- Albach FN, Brunecker P, **Usnich T** , Villringer K, Ebinger M, Fiebach JB, Nolte CH. Complete early reversal of diffusion-weighted imaging hyperintensities after ischemic stroke is mainly limited to small embolic lesions. Stroke. 2013 Apr;44(4):1043-8.

- **Usnich T**, Albach FN, Brunecker P, Fiebach JB, Nolte CH. Incidence of new diffusion-weighted imaging lesions outside the area of initial hypoperfusion within 1 week after acute ischemic stroke. Stroke. 2012 Oct;43(10):2654-8.

Presentations in scientific meetings as first author (in chronological order)

- **Usnich T**, Spengler S, Sajonz D, Herold D ,Bauer M, Bermpohl F. Poster “The perception of social stimuli in mania: an fMRI study.” 03/2014 ECNP Workshop for Junior Scientists in Europe, Nice, France.

- **Usnich T**, Albach FN, Brunecker P, Braemswig TB, Fiebach JB, Nolte CH. Talk “Diabetes mellitus increases risk for new early diffusion-weighted imaging lesions outside the initially affected vascular territory in acute stroke patients.” 06/2013 ENS Congress, Barcelona, Spain.

- **Usnich T**, Albach FN, Brunecker P, Fiebach JB, Nolte CH. Talk “Neue DWI Läsionen nach akutem ischämischen Schlaganfall in Relation zum initial bestehenden Perfusionsdefizit.” 09/2012 DGN Kongress, Hamburg.

- **Usnich T**, Spengler S, Herold D, Sajonz B, Bermpohl F. Talk “Social stimulus processing in manic patients: an fMRI study. ” 09/2012 Emotional Neuroscience Conference, Berlin.

- **Usnich T**, Heinzle J, Haynes JD. Poster: “Predictability of free decisions- how cognitive load limits our ability to make unpredictable choices. ” 03/2010 FENS/IBRO SfN School “Brain evolution and its consequences for brain pathology” Naples, Italy.

Eidesstattliche Versicherung

„Ich, **Tatiana Usnich**, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: **Neural Substrates of Social and Self-Referential Stimulus Processing in Mania as investigated with fMRI** selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
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Anteilserklärung an etwaigen erfolgten Publikationen

Tatiana Usnich hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1:

Usnich T*, Spengler S*, Sajonz D, Herold D ,Bauer M, Bermpohl F. The perception of social stimuli in mania: an fMRI study. Psychiatry Res. 2015 Jan 30; 231(1):71-6.

* These authors contributed equally to this publication.

Beitrag im Einzelnen: Beteiligung an der Entwicklung der Studienidee und des Studienkonzepts, Rekrutierung von insgesamt 35 manischen Patienten auf den psychiatrischen Stationen, Testung von 14 Patienten in je drei Testterminen (welche fMRT-Messungen und psychologische Tests beinhalteten), Analyse und Interpretation der klinischen und bildgebenden Daten (unter Supervision von Spengler und Bermpohl), Abfassung des Manuskripts und Entwicklung der Bearbeitungsstrategie für die Revision (unter Supervision von Spengler und Bermpohl).

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Herold D, Spengler S, Sajonz B, **Usnich T**, Bermpohl F. Common and distinct networks for self-referential and social stimulus processing in the human brain. Brain Struct Funct. 2015 Sep 13.

Beitrag im Einzelnen: Beteiligung an der Entwicklung der Studienidee und des Studienkonzepts, Beteiligung an Analyse der bildgebenden Daten, Beteiligung an Diskussion und Interpretation der Befunde, Beteiligung an Abfassung und Revision des Manuscripts.

Unterschrift, Datum und Stempel des betreuenden Hochschullehrers

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