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Aberrant emotional processing in posterior cortical midline structures in bipolar II depression

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ABSTRACT

Bipolar II depression is a serious and disabling illness associated with significant impairment and high rates of suicide attempts. However, mechanisms underlying emotional dysregulation in this condition are poorly characterized. The goal of this work was to investigate one component of emotional processing in this disorder, brain activation associated with exposure to emotional faces. Functional MRI was used to study 16 unmedicated male subjects with bipolar II depression and 19 healthy male controls. The activation paradigm exposed subjects to happy, fearful and neutral faces. The two key findings of this study were as follows. First, bipolar subjects demonstrated significantly decreased activation in response to happy facial expression in the left posterior cortical midline structures (CMS) and frontal cortex. Second, depression severity was positively correlated with activation of the posterior CMS and other regions. Our results suggest that mechanisms involving CMS dysfunction may play a role in the neurobiology of bipolar II depression as has been demonstrated for unipolar illness. Further investigations of CMS function in bipolar spectrum disorders are warranted.

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1. Introduction

Emotional dysregulation is associated with bipolar disorder (Green et al., 2007), however specific aberrant mechanisms of affective control associated with bipolar II depression are incompletely characterized. An enhanced understanding of the emotional processing deficits underlying this illness may eventually lead to advances in treatment. Research investigating the neurobiology of bipolar II depression is needed because this is an understudied disorder with impairment comparable to bipolar I disorder (Judd et al., 2005) as well as frequent suicide attempts (Novick et al., 2010; Valtonen et al., 2005). The goal of this work was to investigate one component of emotional processing in this condition, brain activation associated with exposure to emotional faces.

Studies utilizing functional neuroimaging and exposure to emotional faces have provided insights into aberrations of emotional processing associated with bipolar I disorder, for example (Chen et al., 2006; Foland et al., 2008; Lawrence et al., 2004; Surguladze et al., 2010; Versace et al., 2010). However to our knowledge, no studies have used this approach to investigate a cohort consisting exclusively of unmedicated adult subjects with bipolar II depression.

We reasoned that investigating brain activation patterns associated with exposure to emotional faces might contribute to our understanding of the neural processes underlying this illness. The medial surface of the cortex was an area of particular interest. Much of the anterior and posterior midline cortex has been characterized as an anatomical and functional unit known collectively as the cortical midline structures (CMS) (Northoff and Bermpohl, 2004). The CMS are thought to be important in affective disorders because of extensive involvement in both self-referential (Northoff and Bermpohl, 2004; Northoff et al., 2006) and emotional processing (Grimm et al., 2009a; Heinzel et al., 2005). Further, these regions are components of the default mode network (Gusnard and Raichle, 2001; Raichle et al., 2001). There is compelling evidence that self-perception and processing of self-referent information are abnormal in both bipolar and unipolar spectrum illness (Blairy et al., 2004; Gara et al., 1993; Nilsson et al., 2010; Shestyuk and Deldin, 2010). In particular, individuals with unipolar illness demonstrate increased self-focus (Ingram, 1990; Northoff, 2007). In other words, attention is shifted to focus primarily on the self rather than on the environment and environmental events (Northoff, 2007). Furthermore, there is now direct evidence that self-referential processing activates the CMS and that this neural response is associated with negative affectivity in healthy controls (Lemogne

Abbreviations: CMS, cortical midline structures; MMSE, Mini-mental state exam; EHI, Edinburgh Handedness Inventory; PTSD, posttraumatic stress disorder; ADHD, attention-deficit/hyperactivity disorder; SCID, Structured Clinical Interview for DSM-IV-TR Axis I Disorders—Research Version; MADRS, Montgomery–Asberg Depression Rating Scale; YMRS, Young Mania Rating Scale; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; MRI, magnetic resonance imaging; MNI, Montreal Neurological Institute; ROI, region-of-interest; FWE, Family Wise Error.

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et al., 2010a). Finally, studies indicate that abnormal self-referential processing in unipolar illness is mediated by neural response in cortical and subcortical midline structures (Grimm et al., 2009b; Yoshimura et al., 2010). Thus, we hypothesized that the CMS response to emotional faces might be abnormal among individuals suffering from bipolar II depression.

2. Methods

2.1. Subjects

Subjects were recruited from the community using recruitment fliers and other advertising. Fliers used to recruit bipolar subjects stated that participants who had, or thought they might have, bipolar disorder were needed. Written informed consent was obtained, as approved by both the Institutional Review Board at the University of Utah and the Research Review Committee of the George E. Wahlen Veterans Administration Medical Center. All subjects underwent a study evaluation during which the Structured Clinical Interview for DSM-IV-TR Axis I Disorders—Research Version (SCID) and the Mini-mental state exam (MMSE) (Folstein et al., 1975) were administered and demographic information and psychiatric history were obtained. The SCID was utilized to confirm the presence of bipolar II disorder and the absence of current psychiatric comorbidity for the illness group as well as to establish the absence of any past or current psychiatric disorder among the control subjects. The SCID was administered by either practicing psychiatrists or psychiatry residents. Diagnoses were confirmed by the principal investigator, a senior psychiatrist with over 20 years of clinical experience. Subjects were only enrolled if there they were clearly able to recall prior episodes of mood elevation that unmistakably met all criteria for hypomania. For the bipolar subjects, mood symptoms were assessed using the Montgomery–Asberg Depression Rating Scale (MADRS) for depressive symptoms (Montgomery and Asberg, 1979) and the Young Mania Rating Scale (YMRS) for manic symptoms (Young et al., 1978) at the time of the scan.

Exclusionary criteria for both groups were contraindications to MRI as well as any history of head injury or of medical or neurological disease that might impact the central nervous system. MMSE score of ≤ 24 was also an exclusionary criteria to rule out cognitive impairment. For the control group, other exclusionary criteria were any history of: 1) a psychiatric or substance use disorder, 2) treatment with any psychotropic medication or psychotherapy, 3) a self-harm attempt or 4) a first-degree relative with a psychiatric disorder. Potential bipolar subjects were excluded if they would have met DSM-IV-TR criteria for any comorbid psychiatric or substance abuse disorder within 1 month of the study evaluation or were currently being treated with psychiatric medications. Finally, all subjects were strongly right-handed as evidenced by a score of ≥ 80 on the Edinburgh Handedness Inventory (Oldfield, 1971) and male to avoid any possible confound secondary to handedness or gender-specific activation patterns (Bell et al., 2006).

Sixteen male subjects with bipolar II disorder and 19 male controls were studied. Subject variables for both groups are listed in Table 1. There were no significant between group differences in regard to age ($p = 0.83$), MMSE score ($p = 0.26$) or Edinburgh Handedness Inventory score ($p = 0.80$). Bipolar subjects were all scanned during a ≥ 2 week episode of depression defined as a MADRS score of ≥ 18 and an YMRS score of ≤ 6. Bipolar subjects had not taken any psychotropic medication within 3 weeks of being scanned and none of the subjects was taking any medication that might impact the central nervous system at the time of scanning. Bipolar II subject clinical variables are listed in Table 2.

2.2. Activation paradigms and experimental procedure

The activation paradigm consisted of 18 blocks of male and female emotional faces, taken from a standard set (Ekman and Friesen, 1976). Each block had a duration of 20 s and exposed subjects to only one emotional expression (happy or fearful or neutral). Faces were presented in pseudorandom order. Each face was displayed for 1.5 s, and separated by 0.5 s of blank screen. The task lasted 6 min. In order to maintain attention to the task, subjects were asked to press a button when two identical faces with identical expressions were displayed sequentially. Each 20-second block contained two sets of matched faces/expressions.

Visual stimuli for the tasks were presented on a translucent slide screen at the back of the magnet, which was viewed through a mirror mounted on top of the head coil. Stimulus presentation and response recordings were controlled by E-prime software (Psychology Software Tools, Inc., Pittsburgh, USA; www.pstnet.com/eprime). Subjects pressed a button in response to visual cues and responses were recorded in E-prime.

Subjects were trained on the task immediately prior to scanning. This was done utilizing a computer to display the visual stimuli while instructions were given. Subjects practiced the task using the actual button boxes used during the scan. Subjects were not informed that the faces had an emotional valence prior to the scan. Training and orientation to the scan required approximately 10 min per subject. Task compliance was confirmed during the scanning session by way of a remote control box that indicated subject button presses by illuminating a light color coded for each button.

2.3. Functional image acquisition

Subjects were scanned on a Siemens 3T Trio MR scanner with a quadrature transverse electromagnetic (TEM) head coil (MR Instruments, Minneapolis, MN). Functional MRI data were acquired with a susceptibility weighted gradient echo EPI sequence (field-of-view 22 cm, matrix 64×64, repetition time $TR = 2.08$ s, echo time $TE = 30$ ms, slice thickness 3 mm with 10% gap, flip angle 75°). Thirty-five slices were acquired during each repetition time. The first five image volumes of each task were discarded to ensure signal equilibrium. Distortions caused by variations in magnetic susceptibility were removed during post-processing using fieldmap data acquired with a separate sequence. Anatomic T1-weighted images were acquired using an MPRAGE sequence (field-of-view 22 cm,

Table 1
Bipolar II and control subject variables.

	Bipolar II (n = 16 males)	Control (n = 19 males)	p value
	Mean (range) SD	Mean (range) SD	
Age	32.9 (21–45) ± 7.5	33.7 (22–60) ± 12.5	0.83
MMSE	29.3 (26–30) ± 1.3	29.7 (28–30) ± 0.6	0.26
EHI	91.3 (80–100) ± 7.9	91.9 (80–100) ± 8.3	0.80

SD = standard deviation; MMSE = Mini-mental state exam; EHI = Edinburgh Handedness Inventory.

Table 2
Bipolar II subject clinical variables (n = 16).

	Mean (range) SD	n (percent of total)
MADRS at time of scan	27.5 (18–44) ± 7.3	–
YMRS at time of scan	2.8 (0–6) ± 1.6	–
Age of mood symptom onset	15 (5–35) ± 8.5	–
Prior comorbidity[a]	–	11 (69%)
Prior substance use disorder[a]	–	10 (63%)
Prior anxiety disorder[a]	–	3 (19%)
Prior ADHD[a]	–	1 (1%)
Prior suicidal ideation	–	10 (63%)
Prior suicide attempts	–	3 (19%)
Prior pharmacotherapy	–	13 (81%)
Prior psychotherapy	–	7 (44%)

[a] Some subjects had more than one prior comorbid psychiatric condition. MADRS = Montgomery–Asberg Depression Rating Scale; YMRS = Young Mania Rating Scale.