Neural Activation During Facial Emotion Processing in Unmedicated Bipolar Depression, Euthymia, and Mania

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Background: Studies incorporating direct comparisons across all phases of bipolar (BP) disorder are needed to elucidate the pathophysiology of bipolar disorder. However, functional neuroimaging studies that differentiate bipolar mood states from each other and from healthy subjects are few and have yielded inconsistent findings.

Methods: One hundred five unmedicated adults were recruited: 30 with current bipolar depression (BPD), 30 with current bipolar hypomania or mania (BPM), 15 bipolar euthymic (BPE), and 30 healthy control subjects (HC). All subjects were diagnosed with DSM-IV BP (type I or II) using a structured clinical interview. Groups were age- and gender-ratio matched. In 3T functional magnetic resonance imaging experiments, subjects completed a negative facial emotion matching task.

Results: Bipolar euthymic and BPD groups exhibited increased amygdala activation compared with HCs in response to the negative faces; however, in the BPM group, this increase was not seen. Conversely, both BPE and BPM groups had increased activation in the insula relative to HCs, but in the BPD group, this effect was not seen. All three BP groups exhibited increased activation of the putamen compared with HCs. In the cortical areas, the BPM group exhibited decreased left lateral orbitofrontal cortex activation compared with both BPEs and HCs, increased dorsal anterior cingulate cortex activation compared with the BPD group, and increased dorsolateral prefrontal cortical activation compared with all other groups.

Conclusions: Both state- and trait-related abnormalities in corticolimbic activation were seen in response to the negative facial emotion processing in a large sample of unmedicated adults across BP mood states.

Key Words: Bipolar disorder, depression, emotion processing, euthymia, fMRI, mania, MRI, neuroimaging

To optimize treatments for the various phases of bipolar (BP) disorder, there is a need to differentiate the pathophysiology between mood states. Among functional neuroimaging studies in which the depressed phase of BP illness has been characterized using negative emotional (fearful, sad, angry) processing tasks, findings have consistently shown increased amygdala (1,2) and ventral prefrontal cortical activation (2) and decreased activation of dorsal cortical regions such as the dorsolateral prefrontal cortex (DLPFC) (2). Specifically, studies have reported: 1) increased subcortical, orbitofrontal, and ventral cortical responses to sad faces in euthymic and depressed BP adult and adolescent subjects (3–5); 2) reduction in DLPFC activation (6); and 3) an increase in amygdala activation in response to fearful facial affect (6). More recently, functional connectivity was found to be abnormally increased between the amygdala and orbitofrontal cortex (OFC) when collected during a sad facial emotion processing task (7). Thus, individuals with bipolar depression have been shown to demonstrate hyperactivation in limbic structures during negative emotion processing, likely arising from aberrant cortical homeostatic mechanisms.

Functional neuroimaging studies of BP mania have been less consistent and have shown several patterns of activation across cortical and limbic regions in response to tasks involving negative emotional stimuli, when compared with healthy or euthymic individuals. Increases in activation have been seen in ventrolateral PFC (8), caudate (9), posterior insula (10), and fusiform gyrus (11) in response to negative emotional stimuli. Conversely, patterns of decreased cortical activation have been reported in dorsal and ventral PFC (6,12), bilateral OFC (10,13), inferior frontal gyrus (14), and right frontopolar cortex (14). Activations in the anterior cingulate cortex (ACC) subregions during mania are less clear, with reports of attenuation (10), normal activation (15), and increased activation (2,9,14) relative to euthymics and/or control subjects. Studies also highlight the amygdala as a key region in the processing of emotionally salient stimuli. However, amygdala activation patterns are unclear in mania. Decreased (10,12,16), as well as increased (17), activation of the amygdala have been reported during negative facial emotion processing in mania.

Individuals in the euthymic or remitted phase of bipolar disorder have been studied less often with functional neuroimaging methods, particularly in the context of negative emotional stimuli. Hassel *et al.* (18) found decreased left DLPFC activity and elevated striatal activation in response to fearful faces in euthymic participants versus control subjects. Similarly, during fearful face processing, ventral ACC activation was significantly lower in a remitted group compared with control subjects (19). Compared with control subjects, euthymic participants showed hyperactivation in inferior PFC regions but no difference in amygdala activations during a fearful and angry facial emotion processing task (20). Thus, preliminary work suggests that dysfunctional dorsal and ventral cortical systems implicated in appraisal, encoding, and regulation of emotion may

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represent a mechanistic failure seen in BP disorder, even in the absence of an acute mood episode.

Fewer studies have directly compared activation patterns across mood states. In one such study, medicated BP participants in all mood states showed reduced activation in the bilateral OFC on a passively viewed emotional masking task (21). In this study, activation in euthymic and manic participants was significantly reduced compared with that of both control subjects and depressed groups in the bilateral amygdala and right temporal pole (21). In the right DLPFC, all groups showed an increased level of activation compared with the manic group (21). Using a nonaffective Stroop task, Blumberg *et al.* (13) showed a distinct area of decreased ventral PFC activation in BP participants compared with healthy subjects that appeared to be independent of mood state. Manic patients showed decreased right ventral PFC activation, whereas depressed patients showed increased activation, compared with euthymic patients (13). Overall, it appears that a number of imaging studies in BP disorder have implicated prefrontal cortex and amygdala in aberrant facial processing. While fewer studies have assessed striatal, thalamic, and insular regions, there is some evidence, as discussed above, that these regions play a role in emotional processing and facial emotion matching. Thus, these brain structures form the basis for the a priori regions of interest selected for the image analyses.

Despite these research advances, interpretation of the findings in terms of pathophysiology of BP disorder is limited by the potential confounding effects of medications, small numbers of participants, and, in some cases, the inadequate identification of the phase of illness (22). It remains unclear whether increased amygdala activity and decreased cortical activation in response to emotional facial expressions are trait markers of BP disorder or whether abnormal amygdala and cortical activity differentiate the different mood states. To address this question, we present data examining neural activity during emotional face processing collected from a sample of unmedicated bipolar depressed (BPD), bipolar manic (BPM), bipolar euthymic (BPE), and healthy control (HC) subjects, all closely matched for age and gender. We hypothesized that differences between groups would occur in the cortical and limbic areas activated by the face task. We further hypothesized that BPD and BPM subjects would exhibit increased limbic and decreased cortical activation compared with HC subjects, while in BPE, the abnormalities would also be present but in an attenuated form.

Methods and Materials

Participants

Bipolar subjects medication-free for at least 2 weeks and healthy control subjects closely matched for age and gender were recruited from the outpatient psychiatry clinic at Indiana University Hospital and by advertisement to the community. Demographically matched healthy control subjects ($n = 30$) were recruited via advertisements. All subjects took part in the study after signing an informed consent form approved by the Institutional Review Board at the Indiana University School of Medicine. Both patients and healthy control subjects were paid $75 for screening and $75 for a magnetic resonance imaging (MRI) scan. All subjects underwent a detailed structured diagnostic interview: the Diagnostic Interview for Genetic Studies (5) and/or the Mini-International Neuropsychiatric Interview, as well as a clinical interview by a psychiatrist (A.A.) to determine the appropriate DSM-IV Text Revision (DSM-IV-TR) diagnoses. Subjects were also rated on the 17-item Hamilton Depression Rating Scale (HDRS) (23) and Young Mania Rating Scale (YMRS) (24) at the time of the baseline scan.

Inclusion criteria for noncontrol participants were that they satisfy DSM-IV-TR criteria for BP disorder either in the 1) hypomanic or manic phase and have YMRS >10, HDRS <18; 2) depressed phase and have HDRS >15, YMRS <12; or 3) current euthymic mood state (HDRS <10 and YMRS <10). Participants whose HDRS and YMRS scores were consistent with both mania/hypomania and depression (e.g., mixed state) were excluded. Exclusion criteria for participants included the following: lifetime diagnosis of schizophrenia or schizoaffective disorder; a current primary anxiety disorder; use of psychotropic medications in the past 3 weeks; fluoxetine use over the past 4 weeks; acute suicidal or homicidal ideation or behavior; recent (<1 week) or current inpatient hospitalization; meeting DSM-IV-TR criteria for substance dependence within the past year, except nicotine; positive urinary toxicology screening at baseline; use of alcohol in the past 1 week; serious medical or neurological illness; current pregnancy or breast feeding; and metallic implants or other contraindications to MRI.

Healthy subjects (18–60 years) had no personal or family history of psychiatric illness or alcohol or substance abuse/dependence. Additional exclusion criteria were use of any centrally acting medications; use of alcohol in the past 1 week; serious medical or neurological illness; age less than 18 years of age; pregnant or breast feeding; and metallic implants or other contraindication to MRI.

Imaging Paradigm

All participants participated in a 3-minute emotion-matching task developed by Hariri et al. (25). This task focuses the subject's attention on the negative facial emotion (angry or scared) depicted and reliably activates the amygdala and limbic regions (25). Pictures were obtained from the NimStim set of facial expressions (26). Each trial consists of a presentation of three faces, all depicting a negative emotion, in which the subject is asked to match the emotion of the top picture with the emotion seen in one of the two bottom pictures (Figure 1A). In the control task (Figure 1B), oval shapes are used instead of faces. Five trials are presented in each 22.5-second-long block. Three face presentation blocks interspersed with four shape blocks were presented. Subjects' task performance (accuracy, response times) were recorded and used as covariates in the imaging analysis.

Imaging Protocol

Subjects were trained on the task on a personal computer outside the scanner before being taken to the imaging suite. After a short scout imaging scan to survey head position and center the field of view, a high-resolution three-dimensional magnetization prepared rapid acquisition gradient-echo scan was collected.

During functional activation scans, the blood oxygen level-dependent response was acquired using a T2*-weighted gradient echo-planar imaging sequence (129 measurements, repetition/

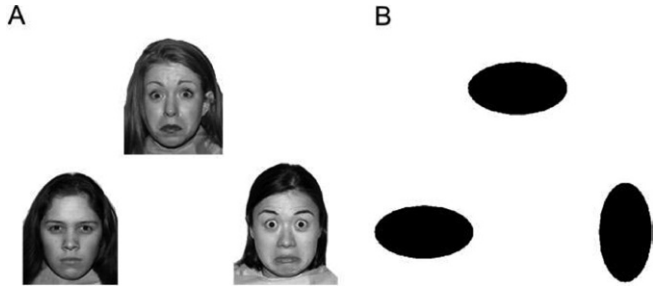

Figure 1. (A) Angry/worried faces (26) and **(B)** shapes used as experimental and control stimuli, respectively, for the functional magnetic resonance imaging task.