Blunted Activation in Orbitofrontal Cortex During Mania: A Functional Magnetic Resonance Imaging Study

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Background: *Patients with bipolar disorder have been reported to have abnormal cortical function during mania. In this study, we sought to investigate neural activity in the frontal lobe during mania, using functional magnetic resonance imaging (fMRI). Specifically, we sought to evaluate activation in the lateral orbitofrontal cortex, a brain region that is normally activated during activities that require response inhibition.*

Methods: *Eleven manic subjects and 13 control subjects underwent fMRI while performing the Go-NoGo task, a neuropsychological paradigm known to activate the orbitofrontal cortex in normal subjects. Patterns of whole-brain activation during fMRI scanning were determined with statistical parametric mapping. Contrasts were made for each subject for the NoGo minus Go conditions. Contrasts were used in a second-level analysis with subject as a random factor.*

Results: *Functional MRI data revealed robust activation of the right orbitofrontal cortex (Brodmann's area [BA] 47) in control subjects but not in manic subjects. Random-effects analyses demonstrated significantly less magnitude in signal intensity in the right lateral orbitofrontal cortex (BA 47), right hippocampus, and left cingulate (BA 24) in manic compared with control subjects.*

Conclusions: *Mania is associated with a significant attenuation of task-related activation of right lateral orbitofrontal function. This lack of activation of a brain region that is usually involved in suppression of responses might account for some of the disinhibition seen in mania. In addition, hippocampal and cingulate activation seem to be decreased. The relationship between this reduced function and the symptoms of mania remain to be further explored.*

Key Words: Functional magnetic resonance imaging, mania, orbitofrontal cortex

In addition to an alteration in mood, the clinical state of mania comprises a cluster of symptoms involving increased impulsivity (e.g., overspending, hypersexual behavior, increased risk-taking behavior), impaired attention (distractibility), and increased motor activity (e.g., increased movement, increased talkativeness). Because many of these symptoms suggest an impairment in normal brain inhibitory mechanisms, impairment in orbitofrontal function might contribute to this symptom presentation (Damasio 2000; Horn et al 2003). Human studies have shown that patients with orbitofrontal lesions can present with disinhibition, distractibility, hyperactivity, euphoria, and impulsivity (Fuster 1989; Starkstein et al 1988, 1990). Animal studies demonstrate a role for the orbitofrontal cortex in inhibition of movement, and lesions in this brain region might result in increased motor activity (Kawashima et al 1996a).

Resting-state imaging studies have implicated disturbances in functioning in the lateral and medial prefrontal cortex and in limbic regions in patients with mania (al Mousawi et al 1996; Baxter et al 1985, 1989; Blumberg et al 2000; Drevets et al 1992; Goodwin et al 1997; Gyulai et al 1997; Kishimoto et al 1987; Migliorelli et al 1993; O'Connell et al 1995). Very few activation studies have been performed with neurocognitive paradigms to probe the function of specific brain regions during mania. This is probably owing to the difficulty of having a manic patient remain still during scanning. The few activation imaging studies, however, suggest an attenuation of orbitofrontal functioning during mania (Blumberg et al 1999, 2003; Elliott et al 2004; Rubinsztein et al 2001). The aim of the present study was to further evaluate orbitofrontal functioning in manic subjects compared with control subjects, with the use of a standard neuropsychological task that specifically requires behavioral inhibition.

Methods and Materials

Study Subjects

Our study protocol was approved by the institutional review boards at the University of California, Los Angeles (UCLA) and at the Department of Veterans Affairs (VA) Greater Los Angeles Healthcare System, and each subject gave written consent before their inclusion in the study. We recruited subjects with bipolar I disorder through the UCLA Mood Disorders Clinic and the Bipolar Disorders Clinic of the VA Greater Los Angeles Healthcare System in West Los Angeles, as well as the inpatient units of both hospitals; subjects enrolled in other research projects of the UCLA Mood Disorders Research Program were also invited to participate. We recruited control subjects by advertisements placed in local newspapers and campus flyers. All subjects were interviewed with the Structured Clinical Interview for DSM-IV (Spitzer et al 1996). Control subjects were excluded if they had a current or past psychiatric diagnosis (including history of substance abuse) or were taking any medications for medical reasons. Subjects with bipolar illness were included if they met criteria for bipolar I disorder and had current mania or hypomania. They were excluded if they had any other active Axis I comorbidity. Additional exclusion criteria for both control and bipolar subjects included left-handedness, hypertension, neurologic illness, metal implants, and a history of skull fracture or

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Received March 30, 2005; revised August 9, 2005; accepted September 14, 2005.

0006-3223/05/$30.00
doi:10.1016/j.biopsych.2005.09.012

head trauma with loss of consciousness for more than 5 min. On the day of the scan, we rated mood symptoms in the bipolar subjects, using the Young Mania Rating Scale (YMRS; Young et al 1978) and the 21-item Hamilton Depression Rating Scale (Hamilton 1960) to assess for current severity of mania and depression (dysphoric mania).

In total, 11 subjects (7 [64%] women) with bipolar I disorder, currently manic or hypomanic, and 13 control subjects (8 [62%] women) were included. The mean (±SD) age for the 11 manic subjects was 36 ± 7.6 years, and the mean age for the 13 control subjects was 31 ± 6.7 years ($t = 1.94$, $p = .07$). Both groups were primarily Caucasian [manic subjects were 63% Caucasian, 18% Hispanic, 9% African American, 9% Asian; control subjects were 69% Caucasian, 13% Hispanic, 8% African American; $\chi^2(3) = 1.3$, $p = .73$].

At the time of the scan, 4 manic subjects were not taking any medication, and 7 manic subjects were taking a range of medications, including lithium ($n = 1$) anticonvulsants (divalproex sodium, lamotrigine; $n = 6$), and antipsychotics (olanzapine; $n = 2$) to treat their mania. The mean YMRS score for the 11 manic subjects at the time of the scan was 16.9 ± 3.9, and the mean 21-item Hamilton Depression Rating Scale score was 5.36 ± 4.41. Mean duration of the current manic episode at the time of the scan was 6.3 ± 4.29 weeks.

Imaging Procedure

Magnetic resonance imaging scans were obtained on a 3-T instrument (General Electric, Waukesha, Wisconsin) with echo planar imaging (EPI) capability (Advanced NMR Systems, Wilmington, Massachusetts). Functional MRI (fMRI) scanning was conducted with a gradient echo, echo planar acquisition sequence. First, an automated shim procedure was applied to maximize magnetic field homogeneity. Second, a sagittal scout (T_2 weighted) was obtained to identify locations for both structural and functional images. Third, coplanar EPI high-resolution structural images were obtained, consisting of 26 slices (time to repetition/time to echo [TR/TE] = 4000 msec/54 msec, 4 mm thick, 1-mm gap, matrix 128^2, field of view [FOV] = 20 cm) coplanar to the functional imaging scans. Finally, functional images were obtained with an asymmetric spin echo sequence (Hoppel et al 1993). This sequence was used to reduce susceptibility artifacts and covered 16 slices from the midtemporal lobe region and upward (TR/TE/180° pulse offset = 2500 msec/70 msec/25 msec, 4 mm thick, 1-mm gap, matrix 64^2, FOV = 20 cm).

Activation Task

The Go-NoGo paradigm was used to assess orbitofrontal activation. A central feature of the task is the requirement to inhibit a prepotent motor response. This task also requires the recruitment of anterior cingulate cortex and prefrontal cortex function related to attention response conflict (Cabeza and Nyberg 2000). Prior imaging studies in normal subjects have reported selective activation in the orbitofrontal cortex (Brodmann's areas [BA] 10, 11, 47) and cingulate (BA 24, BA 31) during the response inhibition component (i.e., the NoGo minus the Go task) of the paradigm (Elliott et al 2004; Horn et al 2003; Kawashima et al 1996b).

During both the control and experimental tasks, subjects monitored a sequence of letters presented visually one at a time, evaluated their identity, and responded to a target by pressing or not pressing a button. Before beginning the task, subjects were instructed to use their right index finger to press the key of a button box. The task began with a 30-sec rest block followed by eight alternating 30.5-sec blocks of Go and NoGo conditions, ending with a 30-sec rest block. During the rest block, subjects passively viewed the word "Rest" at the center of a white screen. During the experiment, each condition was preceded by an instruction that lasted 2.5 sec. The Go (control) condition was preceded by the instruction "Press for all Letters." In the control condition, subjects were presented with a series of random letters, to which they would press the button. The NoGo (experimental) condition was preceded by the instruction "Press for all except X." During the NoGo condition, subjects were shown random letters 50% of the time and the letter "X" 50% of the time. Subjects were instructed to press the button for each letter as it appeared on the screen but to refrain from pressing the button for the letter "X." The order of the appearance of the letter "X" in the experimental block was random. Thus, the task required the subject to sometimes respond and sometimes refrain from responding to a trigger letter (in this case the letter "X"). Within each condition (Go and NoGo), stimulus presentation was .5 sec, with an interstimulus interval of 1.5 sec, so that the subjects would see a letter appear on the screen every 2 sec.

Data Analysis

Performance Data. Response times and accuracy of performance of the task were recorded for patients and control subjects for both the Go and NoGo conditions. Differences between groups on each task were assessed with a mixed-effects analysis of variance model (unconstrained covariance matrix), with diagnosis as a grouping variable and task as a repeated measure.

Preprocessing and Statistical Parametric Mapping. All functional image volumes were examined closely for time points containing severe motion or spike artifacts. Single corrupted volumes (i.e., those containing spike artifacts and volume series or runs containing significant head motion of 2 voxels or greater) were removed from further analysis. Head motion correction and spatial normalization were performed with automated image registration (AIR) tools (Woods et al 1998). First, the images from the high-resolution echo planar anatomic scans were aligned automatically to a site-specific atlas (Woods et al 1999). The coplanar functional scans were concatenated and corrected for linear head motion with a six-parameter algorithm in AIR. After this, the data were smoothed with a 6-mm full width at half maximum Gaussian kernel. The high-resolution file was then resampled to match the functional files. Next, all transformation parameters from realignment and spatial normalization were applied to the functional files, which were now realigned to correct for head motion in atlas space. Within-subject masking was then applied, retaining only those voxels for which there was signal in all images/scans.

The group preprocessing consisted of cropping images not shared across all subjects (i.e., eliminating planes that did not have brain images across all subjects). Next we cropped the functional files and then processed the group data statistically with statistical parametric mapping (SPM). Contrasts were run in SPM99 (http://www.fil.ion.ucl.ac.uk/spm/).

The NoGo compared with Go condition (NoGo minus Go) was used in the current analysis to evaluate degree of brain activation specific for response inhibition, as opposed to general attention or processes associated with letter identification and motor output. Contrasts were first made for the NoGo minus Go comparison within each group (patients and control subjects separately). The output from this analysis was then entered into a second-level analysis with subject as a random factor (random-effects analysis). Random-effects comparisons were constrained

Table 1. Mean Behavioral Scores for Reaction Time and Accuracy

	Go Task[a]		NoGo Task[a]	
	Manic	Control	Manic	Control
Reaction Times (msec)	.39 ± .07	.43 ± .11	.50 ± .06	.48 ± .07
Accurate Responses (%)	93 ± 19	99 ± 2	91 ± 10	92 ± 7

Data are presented as mean ± SD.
[a]Behavioral data unavailable on two manic and two control subjects.

with a mask, such that only voxels demonstrating significant activity in the within-group analyses were entered into the between-groups comparisons. This approach minimizes false-positive errors due to random differences in pixel values between groups and reduces the need to correct for multiple comparisons.

In addition, to determine whether the duration and the severity of the manic episode affected fMRI activity, we performed correlational analyses that identified brain voxels whose magnitude of activation in the NoGo versus Go comparisons were significantly related to duration (measured by weeks of the episode) and severity (measured by the YMRS scores).

Results

Performance data (response time and accuracy) are given in Table 1. For response times, there was the expected significant main effect of task, with response time being significantly faster in both groups during performance of the Go task compared with the NoGo task [$F(1,18) = 16.31$, $p = .0009$]. There was, however, no significant main effect of diagnosis (patient vs. control groups) on response times during performance of either the Go or NoGo tasks [$F(1,18) = .07$, $p = .8$], and there was no significant diagnosis × task interaction [$F(1,18) = 2.17$, $p = .16$]. Similarly, in regard to accuracy, there was the expected main effect of task, with the Go task being performed significantly more accurately than the NoGo task in both groups [$F(1,18) = 6.42$, $p = .02$]. But again, there was no main effect of diagnosis on the accuracy of performance for either the Go or NoGo tasks [$F(1,18) = .8$, $p = .38$] (although accuracy was more variable in the manic subjects), and there was no significant task × diagnosis interaction [$F(1,18) = 1.24$, $p = .28$].

SPM Analyses of fMRI Results During NoGo Minus Go

Table 2 indicates the location, spatial extent, and magnitude of activation separately for manic and control subjects, based on the within-group SPM analysis uncorrected for multiple comparisons. When significance levels were set at $p < .001$ corrected for multiple comparisons, no activation in any brain region was seen in subjects with mania. Even when significance thresholds were lowered to $p < .001$ uncorrected for multiple comparisons, manic subjects exhibited no significant regions of activation with an extent threshold of 10 pixels or more. Thus, lack of activation in the manic group could not be explained readily by the use of an overly stringent statistical threshold. Evaluation by SPM of the four manic subjects who were not taking medications continued to demonstrate this blunted activation in lateral orbitofrontal cortex (BA 47) ($z = 4.16$ for manic vs. $z = 7.36$ for control subjects).

Control subjects showed significant activation in the right lateral orbitofrontal cortical region (BA 47), right lateral prefrontal cortex (BA 45), and right hippocampus that seemed not to be activated in the manic group. Both groups also demonstrated significant activation in the left rostral cingulate (BA 24), although manic subjects' activation was attenuated (k < 10) compared with control subjects. Figure 1 demonstrates SPM orbitofrontal activation and hippocampal activation in the control versus manic subjects.

Table 3 and Figure 2 illustrate results from the random-effects analyses of the control versus manic subjects masked for the control region of activation in the NoGo minus Go task. The differences in activation between control subjects and manic

Table 2. Regions of Significant Activation Within Groups from SPM on the NoGo Compared with Go Tasks (NoGo Minus Go)[a]

	Maximally Activated Voxel Coordinates									
	Bipolar, Manic ($n = 11$)					Control Subjects ($n = 13$)				
Region	k	x	y	z	*z* Score	k	x	y	z	*z* Score
Frontal Lobe										
Orbital										
Lateral										
L BA 47										
R BA 47						107	36	28	−4	7.36
Medial										
L BA 10										
R BA 10	(7)	(36)	(36)	(10)	(4.27)					
Lateral										
L BA 45										
R BA 45						12	38	28	4	4.60
Cingulate										
L BA 24	(5)	(−4)	(−4)	(28)	(3.88)	19	−2	−14	34	5.01
R BA 24										
Temporal Lobe										
L hippocampus										
R hippocampus						18	24	−30	−2	4.35

SPM, statistical parametric mapping; L, left; R, right; BA, Brodmann's area.
[a]Height threshold T = 3.73, extent threshold >10 voxels, $p < .0001$, uncorrected. Values in parentheses show subthreshold activation (k < 10).

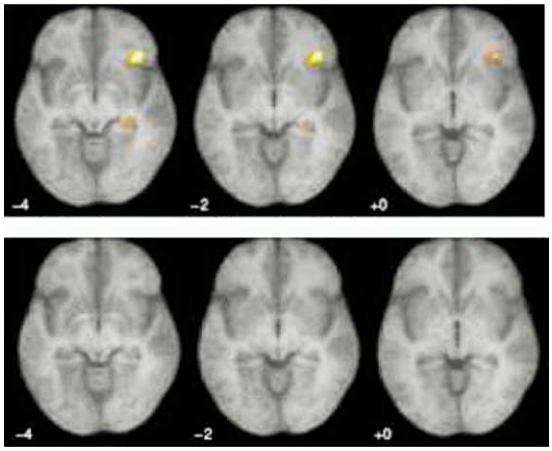

Figure 1. Statistical parametric mapping results for control and manic subjects on NoGo minus Go task. **Top:** Activation in control subjects (n = 13) during NoGo minus Go condition (p = .0001, uncorrected, k = 10 voxels). **Bottom:** Manic patients (n = 11) show no activation during NoGo minus Go condition (p = .0001, uncorrected, k = 10 voxels).

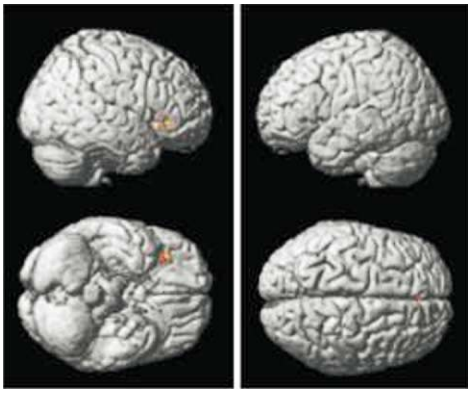

Figure 2. Statistical parametric mapping random-effects analysis of control versus manic subjects on NoGo minus Go task. Statistical parametric mapping surface renderings show random effects results, comparing activation of control subjects with that of manic patients on NoGo minus Go task. Results were masked with activation of control subjects on the same condition.

subjects remained significant with random-effects analyses in right BA 47 and right hippocampus, as well as left cingulate (BA 24) ($p < .01$, uncorrected).

Relationship of fMRI Activity and Episode Duration and Severity

Correlational analyses showed no significant relationship between mania severity, as measured by the YMRS, and fMRI activity on the NoGo versus Go comparison. There was, however, a significant negative correlation between the duration of the manic episode and fMRI activity, such that patients with the longest duration of the current episode showed the least activity in the right frontal lobe, whereas those with shorter episode duration had relatively greater fMRI increases in this region (k = 20 voxels; x, y, z = 38, 38, 8; p = .005, uncorrected).

Discussion

Performance of the NoGo task requires behavioral inhibition, in that prepotent responses to distractors must be suppressed. The neural substrates involved in this inhibition response have previously been reported to include activation of ventral prefrontal regions and specifically the right lateral orbitofrontal cortex in normal subjects (Cabeza and Nyberg 2000; Casey et al 1997; Elliott et al 2004; Garavan et al 2002; Horn et al 2003; Kawashima et al 1996a). Animal studies have shown single unit neuronal firing in specific prefrontal cortical regions in relation to the NoGo response during the Go-NoGo task (Kubota and Komatsu 1985; Sakagami and Niki 1994; Watanabe 1986). These animal findings are similar to the human findings of the current study, in which a strong activation of the right prefrontal cortex was seen in relation to the NoGo minus Go conditions (e.g., response inhibition).

Table 3. Regions of Significantly Greater SPM Activation in Controls Versus Manic Subjects on Random-Effects Analysis: The NoGo Minus Go Tasks[a]

Region	k	x	y	z	*z* Score
R BA 47 (OFC)	57	34	30	−4	3.55
L BA 24 (cingulate)	36	−6	−20	34	3.22
R hippocampus	24	22	−34	−4	3.45

SPM, statistical parametric mapping; R, right; L, left; BA, Brodmann's area; OFC, orbitofrontal cortex.

[a]Masked for control regions of activation (height threshold T = 2.51, extent threshold k > 10 voxels, $p < .01$, uncorrected).

The increased blood oxygenation level–dependent response seen in our control group while performing the NoGo task was robust and was similar to that previously reported. Our results suggest that there are specific cortical fields in the right prefrontal cortex that are activated in the generation of the NoGo response in normal subjects but not in manic subjects. Subjects with mania demonstrated significantly less magnitude in signal intensity in the right orbital region compared with the control subjects. Other functional imaging studies of subjects with mania in which cognitive probes of frontal lobe function were used have similarly reported an attenuation in orbital activity. In one study in which $H_2{}^{15}O$ positron emission tomography (PET) during a word-generation activation paradigm was used, decreases in orbitofrontal activity bilaterally during rest and a decrease in right rostral and orbital prefrontal cortex activity during activation were found in 5 manic subjects (Blumberg et al 1999). In another PET activation study assessing the role of the frontal lobe in a decision-making task, Rubinsztein et al (2001) found that task-related activation was decreased in the right frontopolar (BA 10) and right lateral orbital (BA 47) regions in 6 manic subjects compared with 10 control subjects. In a recent fMRI study in which the Stroop paradigm was used to measure activation in the prefrontal cortex, Blumberg et al (2003) found a relative decrease in right prefrontal cortical activation in 11 manic subjects compared with 15 euthymic subjects, suggesting that the finding is state related. Most recently, Elliott et al (2004) used the Go-NoGo paradigm to assess 8 manic and 11 control subjects. Manic subjects demonstrated an attenuated orbitofrontal response when a semantic task, similar to our design, was given. Given the small number of activation imaging studies performed to date with manic subjects, the degree of overlap in findings is striking. Our study adds to this literature.

The functional significance of decreased orbitofrontal activation in mania—and the meaning of the negative correlation between weeks manic and this activation—is unclear. Neuroimaging studies have demonstrated a role for medial and lateral regions of the orbitofrontal cortex in mood regulation (Baker et al

1997; Northoff et al 2000) and in associative emotional memory functions (Bookheimer 2002; Cabeza and Nyberg 2000; Dapretto and Bookheimer 1999; Price 2003). The orbitofrontal cortex also plays an important role in the regulation of aggressive behavior, and activation of BA 10 and BA 47 might enable persons to inhibit aggressive behavioral responses (Dougherty et al 1999, 2004; Pietrini et al 2000). Lesions in orbital prefrontal cortex often have resulted in behavioral disinhibition: dramatic behavioral changes that resemble mania, including impulsivity, poor planning, poor judgment, irritability, and high risk-taking, reckless behaviors (Clark and Davison 1987; Fuster 2001; Joseph 1986; Paradiso et al 1999; Starkstein et al 1987; Stuss 1991).

How attenuation of orbitofrontal activation might pathophysiologically be associated with manic symptomatology requires further exploration. It is possible that a defect in frontal lobe functioning might have effects in neural circuits that regulate mood. In primates, reciprocal connections exist between the lateral edge of the orbitofrontal cortex and the medial prefrontal network (Amaral and Price 1985; Carmichael and Price 1995, 1996). Interestingly, the amygdala contributes as one component in this distributed neural network (Price 2003). Medial and ventrolateral orbitoprefrontal areas exchange sensory information through extensive reciprocal connections with the amygdala, anterior temporal, and anterior cingulate brain regions (Mega et al 1997; Ongur and Price 2000). Several groups have reported that bipolar disorder might be associated with alterations in structure or function in the anterior limbic network (Altshuler et al 1998; Blumberg et al 2003; Ketter et al 2001; Strakowski 2002; Strakowski et al 1999). Recent work by our group found a significantly greater activation of the amygdala in manic versus control subjects while performing a task that normally activates the amygdala (Altshuler et al 2005). Hariri et al (2000) have shown that the right prefrontal cortex modulates (inhibits) the intensity of the amygdala response bilaterally to stimuli that usually activate this brain structure. In light of these findings, our current finding of reduced activation in the right lateral orbital prefrontal cortex is intriguing when considering the etiology of our recent findings of amygdala hyperreactivity. Although it is possible that amygdala hyperreactivity is part of a primarily pathologic process in mania, it is alternatively possible that a primary deficit (hypoactivity) in a brain region, such as the orbitofrontal cortex, that might normally exert an inhibitory/modulatory effect on the amygdala could result in a disruption of a primarily inhibitory prefrontal–amygdala circuit. One clinical result (symptom) of this functional neuroanatomic dysregulation could be an increase in impulsivity or unstable mood.

The cause of reduced activation of the orbitofrontal cortex in mania also requires further study. An attenuated functional response of frontal lobe activation in mania could occur owing to structural dysfunction. Deficits in white matter volume (Kieseppa et al 2003) and white matter tracts (Adler et al 2004) have both been recently reported in the prefrontal region of subjects with bipolar disorder. Disruption in the integrity of white matter tracts connecting specific areas in the frontal lobe to other brain regions could result in an apparent functional frontal lobe deficiency, even if neurons in the orbitofrontal lobe are intact. Further evaluation of the underlying reasons for orbitofrontal hypoactivity is needed.

Manic subjects in our study also demonstrated an attenuated response in left cingulate and right hippocampus compared with normal control subjects. The attenuation in cingulate response might represent in part a pathophysiologic correlate of the symptom of distractibility seen in manic subjects. A role for the anterior cingulate in modulating attention and a role for the hippocampus in memory have been well described. Interactions between attentional and emotional brain networks have been described and are believed to be neuroanatomically moderated through the anterior cingulate (Mayberg et al 1999; Mega et al 1997; Strakowski et al 2004; Yamasaki et al 2002). Several recent studies in euthymic bipolar subjects have demonstrated persistent attentional difficulties in bipolar subjects even during euthymia (Clark and Goodwin 2004; Clark et al 2002). Additional euthymic subjects seem to have limbic system circuits that are overly active compared with control subjects when performing non-emotional, attentional tasks (Strakowski et al 2004). These studies suggest that both attentional difficulties and limbic hyperreactivity might be trait related rather than state related, which might represent a disturbed neural circuitry in subjects with bipolar disorder. The cingulate changes might play a role in these clinical findings. How these systems contribute to vulnerability to mood episodes is currently not known. Furthermore, the interactive associations, if any, between alterations in activity in these brain regions and the attenuation seen in the orbitofrontal region remain to be further studied.

Several limitations exist in the present study. First, the number of patients scanned in our study was small; however, in previously published studies that, like ours, involve the use of activation paradigms in subjects who are manic in the scanner, the number of subjects reported has been 5 (Blumberg et al 1999), 6 (Rubinsztein et al 2001), 11 (Blumberg et al 2003), and 8 (Elliott et al 2004). The logistical problem of having a manic patient remain at rest for a period of time no doubt accounts for the relatively small number of imaging studies, as well as the small group sizes of subjects in the manic phase of bipolar disorder in each of these studies. In this regard, our study is no exception, but it nonetheless represents one of the larger studies involving manic subjects ($n = 11$). Despite the small number of studies and the small number of subjects in each study, a pattern indicating pathological function in orbitofrontal cortex during mania has consistently been reported. In our study, no significant correlations were found, however, between severity of mania and any SPM regional activation. The range of YMRS scores was narrow because the more severely manic subjects had data that could not be included in the current study owing to motion artifact. Thus, if there were a relationship, it might not have been revealed because of the restricted range of YMRS scores.

A second limitation of the present study is that most of the manic patients studied were taking antimanic medications at the time of scanning, and the impact of these medications on cortical blood flow has not been well established. Divalproex sodium (the most commonly used medication by the manic group) and lithium have been shown to either decrease cerebral blood flow (Gaillard et al 1996; Leiderman et al 1991) or to have no effect (Oliver and Dormehl 1998; Theodore 2000). It is possible that medication contributed to our finding of decreased frontal responsivity; however, the signal intensity changes in the four subjects taking no medication also showed blunted response. A third limitation of the present study is that the manic subjects were slightly (not significantly) older, and this could have contributed to a reduced response. A fourth possibility for reduced activation could be that manic subjects were attending less to the task; however, response times of patients and control subjects during the task suggest that all subjects were attending to the task and make this explanation of our findings unlikely.

Mania is a mood state associated with overall disinhibition. This manifests itself as an increased reactivity to social and

emotional stimuli, increased impulsivity, and increased motor activity. The present study adds to converging data suggesting orbitofrontal dysfunction during mania. A blunting of orbitofrontal function might be a physiologic marker of some of the symptoms seen during mania. Functional neuroimaging studies involving activation paradigms that probe orbitofrontal function in bipolar depression and euthymia might help distinguish state versus trait functional neuroanatomic abnormalities in this brain region. A lack of activation in an orbitofrontal region might affect other brain regions (e.g., amygdala, basal ganglia, hippocampus, cingulate) in ways that result in the composite of emotional, motoric, and attentional symptoms seen in mania. Studies involving paradigms that specifically activate other brain regions are needed to help evaluate the neural circuitry in mania. Whether the blunted activation in orbitofrontal cortex is a primary source of neurobiologic, pathophysiologic vulnerability to developing mania or represents a pathologic change that has occurred as a result of a primary pathologic process elsewhere in the brain (e.g., the cingulate, amygdala) remains to be further elucidated.

Funding for this study was provided by The Stanley Medical Research Institute, the National Alliance for Research on Schizophrenia and Depression, and the National Institute of Mental Health (grant K24 MH01848). For generous support, we also thank the Brain Mapping Medical Research Organization, Brain Mapping Support Foundation, Pierson-Lovelace Foundation, The Ahmanson Foundation, Tamkin Foundation, Jennifer Jones-Simon Foundation, Capital Group Companies Charitable Foundation, Robson Family, Northstar Fund, the National Institute of Drug Abuse (grant DA13054), and the National Center for Research Resources (grants RR12169, RR13642, and RR08655).

We thank Joaquin Fuster, M.D., Ph.D., for consultation during the development of this manuscript, and Teri English for editorial assistance during manuscript preparation.

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