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Original Article

Deficits in inferior frontal cortex activation in euthymic bipolar disorder patients during a response inhibition task

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Objectives: The inferior frontal cortical–striatal network plays an integral role in response inhibition in normal populations. While inferior frontal cortex (IFC) impairment has been reported in mania, this study explored whether this dysfunction persists in euthymia.

Methods: Functional magnetic resonance imaging (fMRI) activation was evaluated in 32 euthymic patients with bipolar I disorder and 30 healthy subjects while performing the Go/NoGo response inhibition task. Behavioral data were collected to evaluate accuracy and response time. Within-group and between-group comparisons of activation were conducted using whole-brain analyses to probe significant group differences in neural function.

Results: Both groups activated bilateral IFC. However, between-group comparisons showed a significantly reduced activation in this brain region in euthymic patients with bipolar disorder compared to healthy subjects. Other frontal and basal ganglia regions involved in response inhibition were additionally significantly reduced in bipolar disorder patients, in both the medicated and the unmedicated subgroups. No areas of greater activation were observed in bipolar disorder patients versus healthy subjects.

Conclusions: Bipolar disorder patients, even during euthymia, have a persistent reduction in activation of brain regions involved in response inhibition, suggesting that reduced activation in the orbitofrontal cortex and striatum is not solely related to the state of mania. These findings may represent underlying trait abnormalities in bipolar disorder.

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Despite the prevalence (1) and morbidity (2) of bipolar disorder, the neurophysiologic underpinnings of the disorder remain unknown. The cluster of symptoms demonstrated in the disorder, however, may provide clues to the affected underlying neural circuits. The inferior frontal cortex (IFC) is involved in the modulation or inhibition of a range of impulsive behaviors. The IFC consists of the pars opercularis [Brodmann's area (BA) 44], pars triangularis (BA45), and pars orbitalis (BA47). Animal studies demonstrate that lesions to the IFC result in increased perseverative motor activity,

supporting a role for this region in the inhibition of movement (3). Furthermore, lesions to this area in human subjects may result in dramatic behavioral changes resembling mania, including hyperactivity, elevated mood, disinhibition, and reckless behavior (4). Impulsivity in healthy subjects is modulated by IFC activity, with greater impulsivity associated with attenuated IFC activity (5). A recent study found that differences in anatomical connectivity between the IFC and subcortical regions predicted response inhibition performance in healthy subjects (6). Given these findings, impairment in the IFC has been suspected to contribute to the bipolar manic presentation. Functional imaging data support this suspicion, demonstrating IFC hypoactivation in bipolar disorder patients while manic (7–10).

Studies suggest that even when bipolar disorder patients are euthymic, trait impulsivity remains elevated (11). Whether this is reflective of continued neural impairment in IFC function is not known. While several functional magnetic resonance imaging (fMRI) studies have been reported in euthymic bipolar disorder patients performing attention or interference tasks (7, 12, 13), there are only two published studies, to our knowledge, that examined brain function in euthymic bipolar disorder patients during the performance of a response inhibition task (14, 15). Results from these studies are conflicting. One study found decreased activation in the left frontal cortex in patients with bipolar disorder (15) and the other found no significant differences between groups during response inhibition, but did find differences in temporal lobe activation during emotional response inhibition (14). In the current study, using a large sample of euthymic bipolar disorder patients, we sought to further elucidate whether the lack of IFC activation observed during the same response inhibition task used in our prior study in mania (9) persists in the state of euthymia. We hypothesized that, even during euthymia, patients with bipolar disorder would exhibit significant reductions in IFC activation relative to healthy subjects and would show abnormalities in the frontal–striatal network.

Patients and methods

This study was approved by the institutional review boards at the University of California, Los Angeles (UCLA) (Los Angeles, CA, USA) and at the Department of Veterans Affairs (VA) Greater Los Angeles Healthcare System (Los Angeles, CA, USA). Each participant provided written consent. Participants with a DSM-IV diagnosis of bipolar I disorder, currently euthymic, were recruited through the UCLA Mood Disorders Outpatient Clinic, the Bipolar Disorder Outpatient Clinic of the VA Greater Los Angeles Healthcare System, and local advertising. Healthy subjects were recruited by local newspaper advertisements and campus fliers. All participants were interviewed using the Structured Clinical Interview for DSM-IV (16) to confirm a bipolar diagnosis or absence thereof. Patients with bipolar illness were included if they met criteria for bipolar I disorder and were currently euthymic, and were excluded for other active Axis I disorders. Patients with a prior history of alcohol or drug abuse/dependence were eligible if they had > 3 months of sobriety. Healthy subjects were excluded if they had any current or past psychiatric diagnosis or were taking medications. Additional exclusion criteria for all participants included left-handedness, hypertension, neurological illness, metal implants, and a history of head trauma with loss of consciousness > 5 min.

On the day of the scan, mood symptoms were evaluated in the patients with bipolar disorder using the Young Mania Rating Scale (YMRS) and the 21-item Hamilton Depression Rating Scale (HDRS). Patients eligible for this study had a YMRS score of ≤ 7, a 21-item HDRS score of ≤ 7, and had been euthymic for at least two months prior to scanning based on self-report and the Structured Clinical Interview for DSM-IV (SCID).

Thirty-nine patients with bipolar disorder and 32 age- and gender-matched healthy subjects participated, but seven bipolar disorder patients and two healthy subjects were excluded due to excessive motion during the scan. Thus, the final data analysis included 32 euthymic patients with bipolar disorder (21 males, mean $\pm$ standard deviation (SD) 37 $\pm$ 13 years) and 30 healthy subjects (17 males, 37 $\pm$ 13 years). Mean mood rating scale scores for the patients with bipolar disorder were 1.4 $\pm$ 2.0 for the YMRS and 3.8 $\pm$ 2.0 for the HDRS. Sixteen of the 32 patients with bipolar disorder had a prior history of substance abuse, and they had been free of meeting the criteria for an average of 4.3 years. Eight of the 32 patients (25%) met criteria for a past anxiety disorder. Nine of the 32 patients (28%) were unmedicated at the time of scanning. The remaining 23 patients (72%) were taking anticonvulsants (n = 14: divalproex sodium, lamotrigine, or oxcarbazepine), antipsychotics (n = 16: aripiprazole, olanzapine, quetiapine, or risperidone), or antidepressants (n = 9: bupropion, or selective serotonin reuptake inhibitors) to treat their bipolar illness. Patients were euthymic for a range of 2–84 months

(mean = 15 months, median = 6 months) prior to scanning.

Imaging procedure

Patients underwent an fMRI scan on a 3-Tesla Siemens Allegra scanner. The blood oxygenation level dependent (BOLD) contrast was evaluated using a T2-weighted echo planar imaging (EPI) gradient-echo pulse sequence [repetition time (TR) = 2500 msec, echo time (TE) = 35 msec, flip angle = 90°, matrix = 64×64, field of view (FOV) = 20 cm, in-plane voxel size = 3.12 mm × 3.12 mm, slice thickness = 3 mm, 1 mm gap, and 28 total slices]. EPI high-resolution structural images were obtained co-planar to the functional imaging scans (TR = 5000 msec, TE = 33 msec, 3 mm thick, 1 mm gap, matrix = 128^2, FOV = 20 cm, and 28 total slices).

Activation task

A Go/NoGo paradigm was used to assess IFC activation. This specific paradigm has been shown by our group to reliably activate the IFC in healthy subjects (9). Participants monitored a sequence of letters presented visually one at a time and responded to a target by pressing or not pressing a button box key. The task began with a 30-sec rest block followed by eight alternating 30.5-sec blocks of Go (control) and NoGo (experimental) conditions, ending with 30-sec rest. During rest, participants passively viewed the word 'Rest' at the center of a white screen. Each Go and NoGo block was preceded by an instruction lasting 2.5 sec. The Go condition began with the instruction 'Press for all Letters', followed by a series of random letters, in response to which participants would press the button. The NoGo condition began with the instruction 'Press for all Letters except X', following which, participants were shown random letters 50% of the time and the letter 'X' 50% of the time, thus requiring participants to sometimes respond and sometimes refrain from responding to the trigger letter (X). Participants were instructed to press the button as a letter appeared on the screen, but to refrain from pressing for the letter 'X.' The order of appearance of the letter 'X' in the experimental block was random. Within each condition (Go and NoGo), stimulus presentation lasted 0.5 sec, with an inter-stimulus interval of 1.5 sec.

Behavioral data analysis

Differences between groups in the response times and accuracy of performance for condition (Go and NoGo) were assessed using a mixed effects analysis of variance model (unconstrained covariance matrix), using diagnosis as a grouping variable and task as a repeated measure.

fMRI analysis

Functional images were examined closely for motion or spike artifacts. Any scans having greater than half a voxel (< 1.5 mm) of motion over the time series were excluded. fMRI data processing was performed using fMRI Expert Analysis Tool (FEAT) version 5.91, part of FSL 4.0 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The following pre-statistics processing was applied: motion correction using MCFLIRT (17), non-brain removal using BET, spatial smoothing using a Gaussian kernel of full-width half-maximum (FWHM) 5 mm, grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, and high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 65.0 sec).

Time-series statistical analysis was performed using FILM with local autocorrelation correction (18). Registration to standard space was performed using a two-step transformation in FLIRT (17). A 7 degree of freedom (df) transform was used to register participants' functional images to the co-planar high-resolution structural image, and a 12 df transform to register co-planar high-resolution structural images to standard space. All images were manually inspected to ensure proper registration.

Whole-brain analyses were run for all participants, as we were interested in potential differences between groups across frontal (including the IFC and cingulate cortex) and striatal regions. Contrasts were first made for the NoGo minus Go comparison for each participant, which was carried to a within-group analysis (cluster threshold of $Z > 2.3$, $p = 0.05$ corrected for multiple comparisons). The output from this analysis was entered into a second-level analysis with participant as a random factor using FMRIB's Local Analysis of Mixed Effects 1 + 2 (FLAME) (19). All of the between-group results were masked with the within-group results to isolate just those areas that were significant in the first-level analysis (cluster threshold of $Z > 1.7$, $p = 0.05$ corrected) and to avoid false positive emerging at the between-group level. To assess the role of medication status, if any, on regional activation, a whole-brain between-group analysis compared the medicated and unmedicated euthymic patients with bipolar disorder directly. Unmedicated euthymic patients (six males/three

females, average age = 35 ± 16 years) were compared directly to the entire group of healthy subjects, as well as to a subset of age- and gender-matched healthy subjects (six males/three females, age = 34 ± 15 years).

Results

Behavioral data analyses revealed no significant differences in response times or accuracy between the euthymic bipolar and healthy groups. Accuracy for the healthy and bipolar groups was 97.3 ± 2.9% and 98.4 ± 2.7%, respectively (t = 1.55, df = 59, p = 0.13). Reaction times were 0.42 ± 0.07 sec for the healthy subjects and 0.42 ± 0.07 sec for the bipolar disorder patients (t = 0.26, df = 59, p = 0.80).

Within-group results

Figure 1 shows the within-group activations for bipolar and healthy subjects during response inhibition (Go/NoGo). As seen in Figure 1A, there was considerable bilateral IFC (BA45/47) activation in the healthy group. Other frontal regions activated in the healthy subjects included the bilateral middle frontal gyrus (BA10), left precentral gyrus motor (BA6 and BA4), bilateral superior frontal gyrus (BA9/46), left insula, and right cingulate (BA32) (see Table 1). Healthy subjects activated bilateral subcortical structures including the caudate, putamen, thalamus, and subthalamic nucleus (STN). Additionally, activation was seen bilaterally in the parietal lobe (BA40), the middle temporal gyrus (BA22), and throughout primary and associative visual regions in the occipital lobe (BA17, 18, and 19).

Figure 1B shows within-group activations for all euthymic bipolar disorder subjects. In the frontal lobe, these subjects showed similar activation patterns to that of healthy subjects, including activation in the bilateral inferior frontal gyrus (BA45/47), bilateral middle frontal gyrus (BA10), bilateral superior frontal gyrus (BA9/46), left insula, and right cingulate (BA32). Within-group results revealed unilateral activation of subcortical structures including the right putamen and right caudate. Additionally, activation was seen in the right inferior and superior parietal lobules (BA40 and BA7), the right middle temporal gyrus (BA21), and throughout the occipital lobe (BA18 and 19).

Between-group results

Between-group results are displayed in Figure 2 and Table 2. In the frontal lobe, there was a significant reduction in activation in bipolar disorder subjects compared to healthy subjects in the

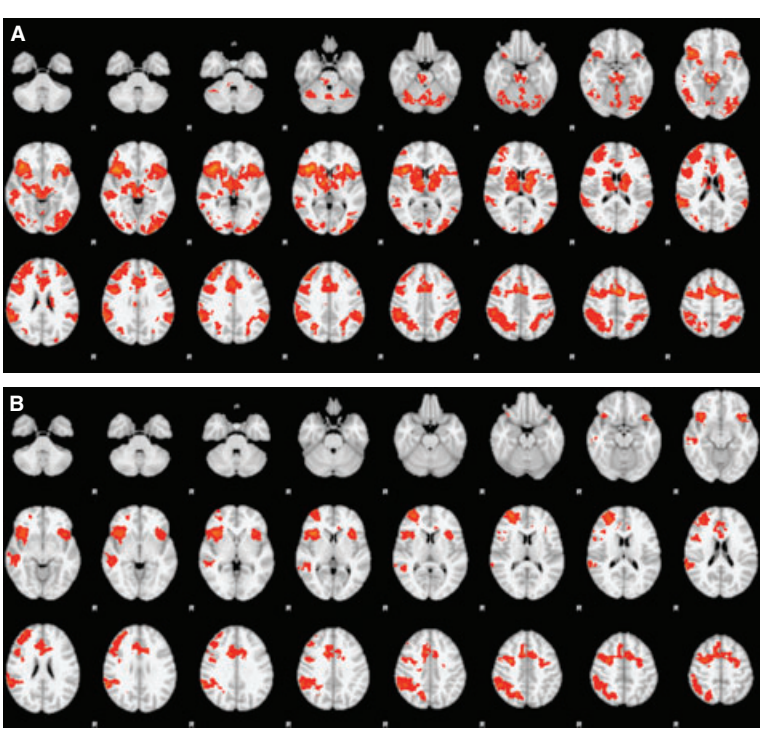

Fig. 1. Within-group results for healthy and euthymic bipolar I disorder subjects for the Go/NoGo contrast show extensive activation of the inhibition network, including the inferior frontal cortex (IFC) and striatum in the healthy and bipolar I disorder groups. (**A**) Healthy subjects (n = 30). (**B**) Euthymic bipolar I disorder subjects (n = 32). R = right.

Table 1. Within-group results show areas of significant activation in control and euthymic bipolar disorder groups during the Go/NoGo contrast

		Controls (n = 30)				Bipolar euthymic (n = 32)			
		x	y	z	*Z*-statistic	x	y	z	*Z*-statistic
Frontal lobe									
L MFG	BA9	−36	38	36	5.41[a]	−34	36	30	3.41
R MFG	BA9/46					24	44	16	5.35
L MFG	BA10	−36	48	20	4.92[a]	−36	46	20	4.32
R MFG	BA10	32	58	16	5.11	34	58	14	5.81
L PreCG	BA6[a]	−28	−4	48	4.27				
L IFG	BA47	−34	20	2	5.37	−44	16	−10	5.16
						−32	24	−6	4.13
R IFG	BA47	36	20	2	5.77[a]	40	20	0	5.20
L insula		−42	14	2	5.76	−34	16	4	5.24
R cingulate	BA32	2	16	38	5.54	14	12	34	5.44
Temporal lobe									
L STG	BA22	−58	−46	20	4.08				
R MTG	BA21					52	−32	−6	4.72[a]
Parietal lobe									
L IPL	BA40	−58	−40	42	4.02				
L IPL	BA40	−36	−46	44	3.97				
R IPL	BA40	46	−44	38	4.60	44	−50	40	4.59
R SPL	BA7					26	−70	50	4.38
L SupmargG	BA40	−58	−48	28	4.06				
R SupmargG	BA40	62	−44	30	5.29	60	−48	28	5.11
Occipital lobe									
L IOG	BA18/19	−36	−90	−6	4.39	−30	−94	−6	3.74
L MOG	BA19					−38	−78	−8	3.87
R MOG	BA19					38	−62	−10	3.67
R OG	BA18/19	30	−60	36	4.53	24	−94	0	3.88
R cuneus	BA17					8	−88	4	3.54
Subcortical									
L caudate		−16	10	8	3.50				
R caudate		24	10	14	3.51	16	−4	20	4.07
L putamen		−22	10	8	4.36				
R putamen		20	10	0	4.60	16	6	8	3.88
L thalamus		−14	−10	8	3.58				
R thalamus		16	−10	8	4.68				
L STN		−8	−16	−8	2.90				
R STN		10	−14	−10	2.52				

L = left; R = right; MFG = middle frontal gyrus; PreCG = precingulate gyrus; IFG = inferior frontal gyrus; STG = superior temporal gyrus; MTG = middle temporal gyrus; IPL = inferior parietal lobe; SPL = superior parietal lobe; SupmargG = supramarginal gyrus; IOG = inferior occipital gyrus; MOG = middle occipital gyrus; OG = occipital gyrus; STN = subthalamic nucleus.
[a]Indicates there is more than one local maxima cluster within a 10-mm radius.

IFC, including in bilateral BA47, left BA44, and left BA45. (See Table 2 for complete between-group results.)

Between-group results (see Table 2 and Fig. 2A) revealed significantly reduced activation for euthymic bipolar disorder compared to healthy subjects in the bilateral putamen, bilateral caudate, bilateral globus pallidus, right thalamus, and right STN. In the reverse comparison, no areas of greater activation were seen in the bipolar disorder subjects compared with healthy subjects.

Contribution of medications: a subanalysis

To evaluate whether medications contributed to the significant attenuation observed in the between-group results, two analyses were performed. We contrasted the entire healthy group with unmedicated euthymic patients; in this analysis we found significant results similar to those in the original healthy versus all euthymic patients analyses ($Z > 1.7$, $p = 0.05$ corrected). To ensure that these between-group differences were not biased by the larger number of healthy subjects, we next identified a subset of age- and gender-matched healthy subjects to contrast with the smaller group of unmedicated euthymic bipolar disorder patients and repeated the between-group analysis at the same statistical threshold. Results were unchanged (Fig. 2B); healthy subjects showed significantly greater activation in left BA44/45 and left BA47. Subcortical regions of greater activation

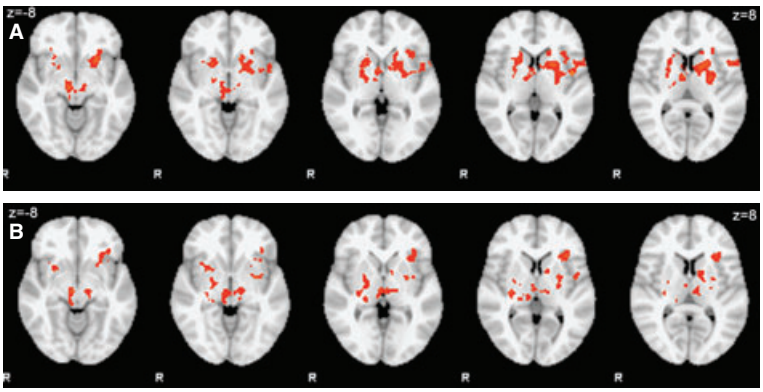

Fig. 2. Between-group results show areas of significantly greater activation in healthy subjects compared to euthymic patients with bipolar disorder. (**A**) Between-group results of healthy subjects (n = 30) > euthymic bipolar I disorder patients (n = 32) in inferior frontal cortex (IFC) and subcortical regions. (**B**) Remarkably similar between-group results of age- and gender-matched healthy subjects (n = 9) > unmedicated euthymic bipolar I disorder patients (n = 9) with significantly greater activation in IFC and subcortical regions. R = right.

Table 2. Between-group results show areas of significantly greater activation in control compared to euthymic patients with bipolar disorder

	BA region	x	y	z	*Z*-statistic
Frontal lobe					
L IFG	44	−44	−2	4	4.20
	44	−50	10	8	2.87[a]
	45	−36	24	2	2.41
	47	−28	22	−10	2.17
R IFG	47	30	16	−14	2.45
L medial FG	6	−4	2	50	3.79[a]
Parietal lobe					
L IPL/SupmargG	40	−60	−42	44	3.46[a]
L SPL	40	−50	−54	50	3.17
Subcortical					
L putamen		−22	−6	12	3.78
		−24	12	−8	3.49[a]
R putamen		20	10	−2	3.50[a]
L globus pallidus		−16	6	−2	2.46
R globus pallidus		20	4	−10	2.84
L caudate		−16	4	10	3.22
R caudate		4	2	2	3.42
R thalamus		22	−18	12	2.72
R subthalamic nucleus		10	−14	−6	2.39

BA = Brodmann's area; L = left; R = right; IFG = inferior frontal gyrus; FG = frontal gyrus; IPL = inferior parietal lobe; SupmargG = supramarginal gyrus; SPL = superior parietal lobe.
[a]Indicates there is more than one local maxima cluster within a 10-mm radius.

in healthy compared to unmedicated euthymic bipolar disorder subjects also included similar regions as found in the larger analysis [left caudate, bilateral globus pallidus, bilateral putamen, right STN, and right thalamus (Fig. 2B and Table 3)]. An exploratory whole-brain analysis comparing the 23 medicated and nine unmedicated patients found no significant differences in any brain regions ($Z > 1.7$, $p = 0.05$ corrected).

Discussion

This study replicates prior studies in healthy subjects reporting activation of motor, attention, and inhibitory brain regions while performing a response inhibition task. Specifically, IFC, cingulate, and striatal structures were activated in our control sample, consistent with previous fMRI inhibition studies of healthy subjects (5, 20). Many of these same regions were activated in the euthymic patients with bipolar disorder, but to a significantly lesser degree.

Prior fMRI studies using response inhibition paradigms in healthy subjects have shown activation primarily in the right IFC, STN, and the pre-supplementary motor area (pre-SMA) (21). Results of such studies and more recent connectivity studies (22) have led to the proposal that the response inhibition results from interactions between the IFC, STN, and pre-SMA. Anatomical connectivity between the IFC and STN, and between pre-SMA/SMA and the STN and striatum have been shown to be predictors of response inhibition performance (6). That is, activation of this fronto-basal-ganglia circuitry acts to facilitate inhibition of responses that have already been initiated, such as in the NoGo condition. Specifically, the right IFC has been posited to block execution of a *Go* response via the basal ganglia. Activation of the STN activates the globus pallidus. One potential mechanism of this inhibition is that activation of the basal ganglia leads to response suppression, through increasing the globus pallidus' GABAergic (inhibitory) effect of pallidal neurons on the thalamus. Suppression of thalamic response, in turn, leads to a suppression (or lack of stimulation) of the motor cortex, which

Table 3. Results of a subanalysis show significantly greater activation in healthy subjects (age- and gender-matched) compared to unmedicated euthymic patients with bipolar disorder in frontal and striatal regions

	BA region	x	y	z	*Z*-statistic
Frontal lobe					
L IFG	44/45	−34	24	4	3.76
	47	−36	28	−8	2.60
Subcortical					
L putamen		−28	−2	−4	3.11
R putamen		30	−18	2	2.98
L globus pallidus		−26	−10	2	2.70
R globus pallidus		24	−6	−2	3.08
L caudate		−8	22	14	2.23
R thalamus		16	−22	4	2.20
R subthalamic nucleus		8	−18	−8	3.27

BA = Brodmann's area; L = left; R = right; IFG = inferior frontal gyrus.

is necessary to block the *Go* response (22). However, the direct parallels between BOLD signal changes and the specific alterations in neurotransmitter release have yet to be determined, as reduced regional BOLD signal may be the result of either less presynaptic input or more inhibitory presynaptic input from other regions.

Several studies have shown blunted IFC activation in bipolar disorder patients when manic (7–9, 23). Unlike a prior study from our group, in which manic patients failed to significantly activate the IFC during an identical Go/NoGo task (9), euthymic patients in the current study did demonstrate significant (within-group) bilateral IFC activation. The extent of the activation, however, remained significantly less than the activation in the healthy sample. This finding held true even in the smaller unmedicated euthymic group. The only other study using the Go/NoGo paradigm examined medicated euthymic patients with bipolar disorder (15) and found reduced left frontal activation in euthymic patients with bipolar disorder, albeit in a more polar anterior region (BA10). That study and the current study suggest that a functional deficit in the IFC persists during euthymia. This attenuation may reflect less activity of neurons involved in the inhibitory motor response, and may help to explain the continued impulsivity behavioral symptoms reported in euthymic patients (11).

In another study of response inhibition in medicated euthymic patients with bipolar disorder, Wessa et al. (14) used an emotional version of the Go/NoGo task to probe orbitofrontal–limbic circuit functions. They found significant group differences of increased activation in euthymic bipolar disorder patients versus healthy subjects in a range of regions when assessing emotional NoGo trials, but none when all NoGo trials (emotional and non-emotional) were compared with the baseline rest condition. As the investigators did not present data of the non-emotional NoGo minus Go tasks—the contrast that has been shown to specifically engage the IFC, and thus the contrast used in our study—it is difficult to compare these results directly to the current study.

Additionally, our results revealed reduced striatal activation with euthymic bipolar disorder patients versus healthy subjects. This finding is consistent with prior reports of patients with bipolar disorder in the literature. Decreased left putamen activation in euthymic patients with bipolar disorder compared to normal controls has been demonstrated in other studies using the Stroop test (24, 25). Strakowski and colleagues (26) found this same attenuation of left subcortical activation in manic patients with bipolar disorder when compared to healthy subjects, suggesting that subcortical dysfunction may exist in both mania and euthymia. Reduced striatal (caudate and putamen) activation results in attenuated globus pallidus inhibition and thus less thalamic inhibition projected to the SMA. It is possible that decreased activation of the fronto-basal ganglia–thalamic pathway represents dysfunction that may begin with reduced activation of the IFC that cascades down to subcortical regions. This possibility may leave a patient vulnerable to demands on this network. Hypofunction in these brain regions may explain some of the disinhibition (e.g., impulsivity) characteristics that are observed in patients with bipolar disorder even while euthymic (11).

The underlying etiology of a persistent reduction in IFC activation during euthymia remains to be further understood. Reduction in gray matter in the left IFC has been reported in several studies (27, 28), including a recent study from our group (29). These findings of reduced frontal gray matter density might provide an explanation for the functional abnormalities seen in patients with bipolar disorder even during euthymia. Alternatively, deficits in white matter tracts (30, 31) or white matter volume (32) could result in a disruption of normal activation in this brain region. The clinical significance of IFC hypofunction also remains to be understood, and disruption may occur not only in the inhibitory network, but also in *affective* brain regions. Primate studies have shown reciprocal connections between the lateral edge of the OFC and the medial prefrontal emotion-regulatory network (33). These brain regions share extensive reciprocal connections with the amygdala, anterior temporal, and anterior cingulate cortex (34), and functional neuroimaging studies have demonstrated a role for the medial

and lateral sectors of the IFC in mood regulation (35, 36) and in associative emotional memory functions (20). It has been speculated that the IFC is involved in the highest level of behavioral regulation, especially in relation to emotion, through pathways between the IFC and autonomic systems that govern visceral responses associated with affective stimuli (37). Chronic hypofunction of a brain region that may have an inhibitory effect on multiple limbic regions in the brain could result in chronic limbic hyperactivation, which has been reported in other studies of euthymic bipolar disorder patients (14).

One limitation of the current study is that while the number of euthymic patients is the largest yet to be reported for an fMRI study, the proportion of patients who were unmedicated was relatively small (~1/3). Interestingly, exploratory analyses comparing the unmedicated euthymic patients and matched control subjects showed similar findings to those comparing the larger groups. Prior studies by our group using different cognitive tasks performed in patients with bipolar disorder taking similar medications have demonstrated hyperactivation in certain brain regions despite being medicated (10, 38). Thus, medication exposure *per se* may not be driving the primary findings. Future studies involving larger numbers of unmedicated patients will help disentangle medication effects versus enduring trait deficits (illness effects). A second limitation of the current study is the use of a block design, in which blocks of Go-only events were contrasted against blocks composed of both Go and NoGo events presented randomly. We specifically chose this block design to match the paradigm we had previously used in manic patients with bipolar disorder (9). A block design lacks a *pure* response-withholding condition as would be seen in an event-related design; consequently, the signal magnitude during the inhibition blocks might have been reduced or there may have been less power to see activity in some regions. Despite these potential limitations, we observed robust IFC activation in both groups during this task and thus did not find the block design to be disadvantageous in activating response inhibition networks. It is also possible that in the current design, a control block in which participants are certain that every trial will involve a *Go* response provides a more striking contrast condition to that where any trial could potentially involve response inhibition. Future studies should examine potential differences in activation patterns during an event-related Go/NoGo design. A final limitation is that, while our analyses revealed deficits in the basal ganglia and IFC, the exact nature of the relationship of the regional changes to each other cannot be determined. Future functional and effective connectivity analyses will provide insight into the nature of the connections between these regions and whether the findings in the basal ganglia are primary or secondary to changes in the IFC in patients with bipolar disorder.

To conclude, during a response inhibition task, euthymic patients with bipolar disorder activated IFC and striatal regions significantly less than healthy subjects. Our results suggest that reduced activation in the orbitofrontal cortex and striatum is not solely related to the state of mania. The relationship of our findings to the vulnerability for future episodes remains to be explored.

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