Received: 9 May 2016 | Accepted: 22 July 2016

DOI: 10.1111/bdi.12426

ORIGINAL ARTICLE

WILEY BIPOLAR DISORDERS

# fMRI brain activation changes following treatment of a first bipolar manic episode

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**Objectives:** We tested the hypothesis that, with treatment, functional magnetic resonance imaging (fMRI) regional brain activation in first-episode mania would normalize – i.e., that differences from healthy subjects would diminish over time, and would be associated with clinical remission status, potentially identifying neuroanatomic treatment response markers.

**Methods:** Forty-two participants with bipolar I disorder were recruited during their first manic episode, pseudo-randomized to open-label lithium or quetiapine, and followed for 8 weeks. fMRI scans were obtained at baseline and then after 1 and 8 weeks of treatment, while participants performed a continuous performance task with emotional distracters. Healthy participants received fMRI scans at these same intervals. Specific region-of-interest (ROI) activations within prefrontal emotional networks were assessed as potential measures of treatment response.

**Results:** ROI data were reduced using exploratory factor analysis, which identified five factors that were organizationally consistent with functional anatomic models of human emotion modulation. Half of the participants with bipolar disorder achieved remission by Week 8 and were contrasted with the other half that did not. Analyses demonstrated that, in the bipolar disorder group in general, treatment led to decreases in activation across brain regions toward healthy subject values. However, differences in activation changes were observed between subjects with bipolar disorder who did or did not achieve remission in subcortical and amygdala factors.

**Conclusions:** These findings provide evidence for potential neuroanatomic treatment response markers in first-episode bipolar disorder.

KEYWORDS

amygdala, bipolar disorder, first-episode, fMRI, mania, prefrontal, treatment

Bipolar I disorder is a common psychiatric condition that causes significant morbidity and mortality. Neuroimaging research has steadily improved our understanding of the functional neuroanatomy of bipolar I disorder, thereby providing clues toward its underlying neuropathophysiology. As reviewed recently, although replication across neuroimaging studies, particularly functional magnetic resonance imaging (fMRI), remains an ongoing challenge, the field has consolidated toward a model of bipolar I disorder resulting from disruption

Registered at ClinicalTrials.Gov: Functional and Neurochemical Brain Changes in First-episode Bipolar Mania. NCT00609193.
URL: https://clinicaltrials.gov/ct2/show/NCT00609193?term=strakowski&rank=1

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of healthy ventral prefrontal cortical modulation of other limbic structures, especially the amygdala and striatum.[1,2] However, most studies are limited by primarily being cross-sectional, single assessments, thereby incompletely reflecting the dynamic clinical nature of bipolar I disorder.[1] One approach toward extending these cross-sectional studies is to identify how treatments have an impact on brain function in bipolar I disorder during the course of recovery from acute mood episodes.[1] However, these types of studies, particularly of mania, are relatively rare and have often comprised small samples.[3–8] In the context of an imaging study, mood stabilizers serve as useful neurobiological probes in order to identify brain activation changes during the process of recovery from acute affective episodes (i.e., treatment response) that might further clarify the functional neuroanatomy of bipolar illness.

Although the clinical presentation of bipolar I disorder is dynamic, spanning a wide range of behavioral syndromes and symptoms during the course of illness, in fact it is defined by the occurrence of mania. Among psychiatric syndromes, mania is among the most prognostic, as a single episode of mania predicts a bipolar course of illness in more than 80% of individuals.[9] Moreover, bipolar I disorder, defined by mania, exhibits high heritability (Holzinger heritability index=0.85)[10] and is relatively uniquely responsive to lithium. Additionally, by definition, new cases of bipolar I disorder can only be defined by the occurrence of a first manic episode. Studying first-episode manic patients offers the benefit of controlling for the effects of chronic illness and medication exposure while focusing on the defining syndrome of bipolar I disorder.

With these considerations in mind, we tested an overall hypothesis that regional activation abnormalities in individuals with first-episode manic bipolar I disorder, as compared with healthy participants, would normalize with treatment.[8] Namely, we predicted that baseline differences between groups would diminish over time. Moreover, from previous work, we predicted increases in ventral prefrontal cortex (PFC) activation as bipolar individuals recovered, with corresponding decreases in overactivation of other limbic brain regions (e.g., the amygdale and striatum).[1–5] We used the Continuous Performance Task with Emotional and Neutral Distracters (CPT-END) during fMRI acquisitions because it was designed to evaluate interactions between emotional and attentional brain networks, and because it has been shown in our previous work to distinguish acutely manic and healthy participants in these key prefrontal and subcortical regions of interest.[3,11]

## 1 | MATERIALS/PARTICIPANTS AND METHODS

### 1.1 | Overall design

Participants were recruited as part of the University of Cincinnati Bipolar Disorder Imaging and Treatment Research Center (BITREC; NIMH award P50 MH077138). This protocol was reviewed and approved by the University of Cincinnati and Cincinnati Children's Hospital Medical Center Institutional Review Boards. These participants met DSM-IV criteria for bipolar I disorder, currently experiencing a first manic or mixed episode, and by definition had minimal or no prior psychotropic medication exposure. Participants were treated with either lithium or quetiapine therapy and followed for 8 weeks. Three fMRI scans were obtained, one each at baseline and then after 1 and 8 weeks of treatment. Healthy participants were also recruited and received fMRI scans at the same intervals. Changes in region-of-interest (ROI) activations during the study were then assessed as measures of treatment response.

### 1.2 | Participants

A total of 68 participants with bipolar I disorder experiencing a first manic episode were identified from hospitalizations and, rarely, outpatient assessments at the University of Cincinnati/Cincinnati Children's Hospital Medical Centers, provided informed consent (or assent with parental consent if <18 years old) to participate in the study, and completed a baseline fMRI scan session. As the specific aims of these analyses emphasized within-participant effects, only the 42 participants in the bipolar group who completed all three scans and the entire treatment protocol are included in the present report (62% of the total group). There were no significant differences in age between included and excluded participants ($P$=.90), baseline Young Mania Rating Scale (YMRS)[12] total score ($P$=.65), baseline 17-item Hamilton Depression Rating Scale (HDRS)[13] total scores ($P$=.93), gender ($P$=.28), treatment assignment ($P$=.61), or baseline activation (using standard voxelwise analyses).

Participants with bipolar disorder were included if they: (i) were 13–35 years old, based on the typical age at risk of onset of bipolar disorder; (ii) met DSM-IV criteria for bipolar I disorder, currently manic or mixed with a baseline YMRS total score ≥20; (iii) had no prior episodes of mania and ≤2 prior episodes of depression; (iv) had no previous psychiatric hospitalizations and <3 months of lifetime psychotropic medication exposure other than stimulants in a few cases, including no active psychotropic medication in the 2 weeks prior to the index admission; and (v) could be safely prescribed either lithium or quetiapine.

Demographically similar healthy participants (n=41) were recruited from the same catchment areas as the participants with bipolar disorder and were included if they: (i) were 13–35 years old; (ii) had no history of any Axis I psychiatric disorder; and (iii) had no first-degree relatives with bipolar or psychotic disorders. All healthy subjects completed three scans. Subjects with bipolar disorder and healthy participants were excluded by: (i) a history of substance dependence within 3 months prior to the index assessment; (ii) any medical or neurological disorder that could have an impact on fMRI assessments; (iii) a history of significant developmental delays or estimated full-scale IQ score <85; or (iv) a contraindication to an MRI scan.

### 1.3 | Clinical assessments

Diagnostic assessments were performed using the Structured Clinical Interview for DSM-IV, Patient version (SCID-P)[14] or, for participants under 18-years-old, Washington University's Kiddie

Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (KSADS).[15] Substance use assessments were augmented with the Addiction Severity Index (ASI).[16] Family history information was obtained using the Family Interview for Genetic Studies (FIGS).[17] Manic and depressive symptoms were evaluated using the YMRS and the 17-item HDRS as noted. Symptom ratings were obtained at baseline and then at Weeks 1, 2, 4, 6, and 8. Remission was defined as both YMRS and HDRS total scores ≤10 for at least 1 week at the final Week 8 visit.

### 1.4 | Treatment protocol

Participants with bipolar disorder were pseudo-randomized to open-label treatment with either lithium or quetiapine. Although a randomization schedule was used to assign treatment, participants could refuse either treatment and continue to participate if they agreed to the other medication. Additionally, if a participant had a specific contraindication to one of the treatments, the other was prescribed. These medications were used because they are first-line US Food and Drug Administration-approved treatments for mania in children and adults. Following drug assignment, open-label treatment was initiated during the index hospitalization and then continued following hospital discharge throughout the course of the study. Doses were adjusted by study clinicians based upon serum drug levels for lithium (the target was 0.8–1.2 meq/L) and treatment response and tolerability for both. Adherence was verified by participant report, pill counts, and serum levels when indicated.

### 1.5 | CPT-END

During fMRI sessions, nonferromagnetic goggles were positioned on participants to provide clear visualization of the CPT-END. This task is a visual oddball paradigm in which 70% of cues are colored squares, 10% are colored circles, 10% are emotionally neutral pictures, and 10% are emotionally unpleasant pictures. The neutral and emotional pictures were taken from the International Affective Picture System ([IAPS] University of Florida, Gainesville, FL, USA), based upon the rating criteria developed by Yamasaki et al.[18] Each visual cue required a response; the circles (targets) required a unique response (Button 2), whereas the squares and pictures all required the same response (Button 1). Imaging sessions consisted of two runs of 158 visual cues per run, presented at 3-second intervals for 2.75 seconds each. Emotional and neutral pictures and circles (targets) were presented pseudorandomly. A fixation cross was presented for 250 milliseconds between cues. Previously, we have shown that the emotional cues in this task activate the ventral emotional networks of interest (and that the targets do not) in subjects with bipolar disorder and healthy participants.[11]

### 1.6 | fMRI acquisition

All fMRI scans were obtained at the University of Cincinnati's Center for Imaging Research using a 4.0 Tesla Varian Unity INOVA Whole Body MRI/MRS system (Varian Inc., Palo Alto, CA, USA) following a protocol we previously described.[11,19] Briefly, to provide anatomic localization, a high-resolution, T1-weighted, three-dimensional brain scan was obtained, followed by a multiecho reference scan to correct for ghost and geometric distortions.[20,21] For fMRI, whole-brain images (volumes) were acquired every 3 seconds using a T2*-weighted gradient-echo echoplanar imaging (EPI) pulse sequence (repetition time/echo time [TR/TE]=3000/25 milliseconds, field of view [FOV]=256×256 mm, matrix=64×64 pixels, 35 slices, slice thickness=4 mm, flip angle=90°). Two runs of 174 images were acquired, and the first two images were discarded to account for nonsteady-state magnetization, leaving 172 images for analysis.

### 1.7 | Image processing

Brain imaging data were processed with a combination of in-house image reconstruction software written in IDL and Analysis of Functional NeuroImages (AFNI; http://afni.nimh.nih.gov/afni). EPI data were reconstructed using Hamming filtering, in lieu of later Gaussian smoothing, which introduced a 7-mm blur to the fMRI data. Following reconstruction, structural and functional images were coregistered using scanner coordinates and image coregistration algorithms in AFNI. Functional images were corrected for motion using a six-parameter rigid body transformation. Additionally, each volume was inspected for signal artifacts after coregistration using a semi-automated approach and excluded from further analysis if uncorrectable image artifact affected more than ~30% of voxels in the volume.[22–25]

Anatomic and functional images were transformed into stereotactic Talairach space using the ICBM452 template in AFNI. Motion correction parameters were included as regressors of no interest and low frequency components of the fMRI temporal signal were removed. Event-related responses were calculated for the emotional pictures and circles (targets). Squares provided the baseline against which hemodynamic responses were assessed.

Figure 1A depicts neurophysiologic networks of emotional modulation as presently conceptualized.[1] In these networks, emotional stimuli processed by the amygdala and ventral striatum are modulated by the ventral PFC within iterative feedback prefrontal-striatal-pallidal thalamic feedback loops.[18,26–28] Figure 1B depicts the ROI mask created in AFNI based on these networks. The ROI mask was applied to each individual's fMRI data in order to obtain the average activation within each ROI. The 20 ROIs included the bilateral ventrolateral PFC (VLPFC; Brodmann's area [BA] 45/47), ventromedial PFC (BA 11/12), dorsal anterior cingulate cortex (ACC), superior ACC (BA 32), subgenual ACC, striatum (including the caudate and putamen), globus pallidus, thalamus, and amygdala. The primary variable of interest for analysis of treatment effects was the response to emotional distracters; specifically, the percent signal change within each ROI was calculated by contrasting responses to emotional distracters with responses to baseline colored squares from each participant's event-related fMRI results.

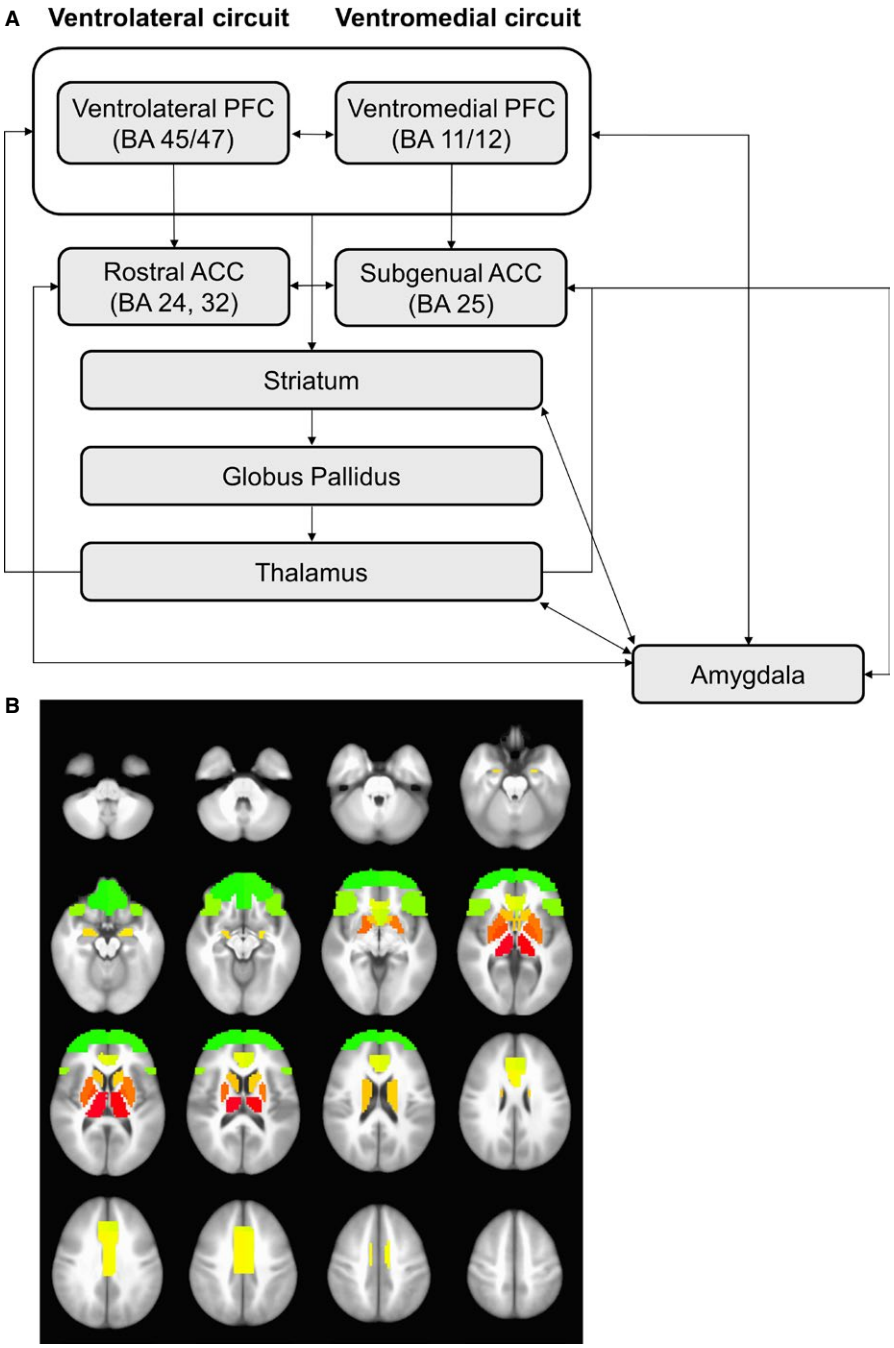


**FIGURE 1** (A) Direct pathways of the ventrolateral and ventromedial prefrontal-subcortical circuits. ACC = anterior cingulate cortex; BA = Brodmann's area; PFC = prefrontal cortex. (B) Regions of an anterior-limbic network mask overlaid on a T1-weighted anatomic image. Colors represent 20 bilateral regions-of-interest (ROI), including the amygdala (yellow), ventromedial PFC (green), ventrolateral PFC (light green), subgenual ACC (yellow/green), dorsal ACC (lime green), superior ACC (light yellow), caudate (rust), putamen (orange), globus pallidus (dark orange), and thalamus (red)

### 1.8 | Statistical analyses

Statistical analyses were performed using the Statistical Analysis System (SAS) v.9.4 (SAS Institute, Cary, NC, USA). Initially, we used exploratory factor analysis (EFA) to assess patterns of covariation among regions without any a priori constraints on the number or composition of latent factors. This approach is useful as a data reduction technique to limit the number of statistical tests required and thereby facilitate interpretation and enhance power. We had applied this approach previously to data from an independent, but similar sample (manic and healthy participants performing the CPT-END task) and obtained a factor structure consistent with the expected functional relationships among regions in the current study.[29] Although these prior results, and the considerable body of evidence supporting the model depicted in Figure 1A,[18,26–28] would justify using confirmatory methods, we elected to use EFA to ensure that a data-driven approach would again produce a factor structure that accords with our hypothesized expectations in this independent dataset. We selected the number of factors based on scree plots of eigenvalues from a principal components analysis, noting the number of eigenvalues that exceeded one,

as no obvious inflection point in the scree plot indicated the maximum number of factors to retain. For each factor solution, we performed varimax and promax rotation to check whether loading patterns were robust to this choice, and noted which regions had the highest loadings on each factor. We verified that a consistent pattern of covariance among regions held across groups and time by running the same factor procedure on the healthy control group at baseline, and then noting the qualitative similarity to the same solution for the bipolar groups and at later weeks. Extremely similar solutions were obtained, indicating that the factor structure was stable (so that, e.g., while the mean activation of shared variance components may differ by group or time as hypothesized, the pattern of correlations that define these components appeared largely invariant).

Principal components analysis revealed five factors with eigenvalues >1, and two rotation methods applied to these factors produced essentially identical loading patterns. Table 1 provides the results of the varimax rotation. ROIs appeared to organize into groups as: (i) subcortical structures, (ii) ACC, (iii) PFC, (iv) amygdala, and (v) subgenual ACC. As expected, bilateral regions consistently loaded on the same factor. The separation of ROIs into these five factors was clear, with almost all regions having a large loading on one factor and small loadings on all others. Notable exceptions to this pattern were ventrolateral prefrontal regions (bilateral BA 45/47), which did not clearly align with one factor but rather exhibited moderate cross-loadings on the subcortical, prefrontal, and amygdala factors. These cross-loadings, as with the remainder of the results, were robust across different factor rotation methods. Additionally, in general, ROI loadings on specific factors were stable in the healthy subjects across time, with minimal variability seen outside anterior cingulate regions (see Table S1). In all cases, bilateral structures loaded on the same factor, and the basic clustering into subcortical, prefrontal, amygdala, and cingulate groups was preserved. Finally, results were based on factor scores computed from the full solution (i.e., with all loadings included), so that each factor contained contributions from each ROI). As the factor structure was generally simple (few cross-loadings), the contributions of ROIs with minor factor loadings had little influence. We verified this by using simplified factor scores based on simple averages of the ROIs with substantial loadings (defined as those >0.40), omitting ROIs with smaller loadings.

Once the factor structure was selected, we extracted factor scores for each observation and analyzed these data using mixed-effects analysis of covariance (ANCOVA) models with group (remitted bipolar,

**TABLE 1** Factor structure of 20 a priori defined regions-of-interest in response to emotional stimuli after varimax rotation in 42 subjects with bipolar I disorder and 41 healthy participants at baseline

| | Factor 1 | Factor 2 | Factor 3 | Factor 4 | Factor 5 |
|---|---|---|---|---|---|
| Region | Subcortical | ACC | PFC | Amygdala | Sub ACC |
| R amygdala | 0.15 | 0.08 | −0.15 | **0.83** | 0.12 |
| L amygdala | 0.29 | 0.04 | 0.24 | **0.79** | 0.04 |
| R vmPFC (BA11/12) | 0.11 | 0.04 | **0.83** | 0.09 | 0.13 |
| L vmPFC (BA11/12) | 0.22 | 0.12 | **0.81** | −0.09 | 0.17 |
| R vlPFC (BA45/47) | 0.43 | 0.28 | 0.48 | 0.39 | 0.05 |
| L vlPFC (BA45/47) | 0.42 | 0.25 | 0.49 | 0.48 | 0.03 |
| R subgenual ACC | 0.14 | 0.07 | 0.17 | −0.10 | **0.82** |
| L subgenual ACC | 0.09 | 0.05 | 0.09 | 0.25 | **0.77** |
| R dorsal ACC | 0.21 | **0.65** | 0.14 | 0.10 | 0.48 |
| L dorsal ACC | 0.22 | **0.72** | 0.15 | 0.12 | 0.39 |
| R superior ACC | 0.28 | **0.88** | 0.02 | 0.04 | −0.09 |
| L superior ACC | 0.27 | **0.89** | 0.13 | 0.06 | −0.01 |
| R caudate | **0.70** | 0.33 | 0.10 | 0.11 | 0.33 |
| L caudate | **0.66** | 0.33 | 0.01 | 0.26 | 0.36 |
| R putamen | **0.86** | 0.13 | 0.21 | 0.01 | 0.00 |
| L putamen | **0.85** | 0.15 | 0.08 | 0.30 | 0.09 |
| R globus pallidus | **0.86** | 0.10 | 0.24 | 0.01 | 0.04 |
| L globus pallidus | **0.87** | 0.18 | 0.10 | 0.17 | 0.16 |
| R thalamus | **0.81** | 0.26 | 0.16 | 0.21 | 0.05 |
| L thalamus | **0.77** | 0.30 | 0.13 | 0.26 | 0.11 |

Bolded font within blue highlighted cells represent factor-specific loadings >0.6. Green highlighted cells represent potentially important cross-loadings across factors.

ACC, anterior cingulate cortex; BA, Brodmann's area; L, left; PFC, prefrontal cortex; R, right; Sub ACC, subgenual anterior cingulate cortex; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex

nonremitted bipolar, healthy control) and time (baseline, Week 1, Week 8) at three levels each. As some ROI activations varied with age, the latter was included as a continuous covariate in the analysis of each factor. Support for our general hypothesis was obtained by finding significant group-by-time interactions that followed a prespecified pattern. As not all possible patterns of interaction were of substantive interest, we required two further conditions (planned contrasts) to be met: at least two of the three groups had to be significantly different from each other at baseline, and the magnitude of this difference also had to be significantly changed at Week 8 (the latter condition is a contrast among means that is sufficient, but not necessary, for a significant overall interaction).

Regions that met these criteria were considered to represent potential predictors of remission. An exploratory analysis conducted as above, but incorporating lithium and quetiapine treatment as the between-subjects' variable, was performed to aid interpretation. Similarly, using mixed models in SAS we completed an exploratory analysis examining correlations among the activation factors and YMRS and HDRS total scores at baseline and Week 8. Furthermore, for completeness, evaluations of brain activation in response to targets (circles) were performed in order to examine activation to purely attentional stimuli. Other comparisons were performed as necessary to aid interpretation. Significance was defined as $\alpha<0.01$ after family-wise Bonferroni correction for the five ANCOVAs conducted (one for each factor identified in EFA). To further protect against possible false positives in the planned contrasts detailed above, each of these additional comparisons was tested at the $\alpha=0.05/3=0.017$ level. Effects between corrected and uncorrected significance levels are reported as "marginal" for completeness. Finally, to extend these results, a standard exploratory whole-brain analysis was performed comparing the bipolar subgroups who did or did not achieve remission by Week 8, using these same processing methods with a minimum voxel cluster of 37 and *P*-value of .005 to give an adjusted *P*=.05.

## 2 | RESULTS

### 2.1 | Participant characteristics and clinical response

Fifty percent of the bipolar sample achieved remission. As illustrated in Table 2, participants with bipolar disorder who achieved remission were significantly younger than those who did not. Additionally, participants with bipolar disorder as a group were younger than healthy participants. Age was also negatively correlated with activation to emotional stimuli in eight ROIs at baseline ($r=-.22$ to $-.32$, $P<.05$ to .003), and was therefore included as a continuous covariate in all subsequent analyses as noted. Gender distributions were similar across groups.

Both remitted and nonremitted participants with bipolar disorder showed improvement in symptom ratings during the study. Both groups exhibited similar YMRS total scores at baseline and Week 1. By Week 8, however, these scores significantly diverged as the remitted group continued to improve whereas the nonremitted group plateaued. A similar pattern of response was seen in HDRS total scores, as changes from baseline to Week 8 in YMRS and HDRS scores were highly correlated ($r=.55$, $P<.0001$). Although participants with bipolar disorder receiving lithium exhibited a numerically greater response rate than those on quetiapine (58% vs 43%), this difference was not significant (Fisher's exact text: $P=.27$). Healthy participants exhibited lower YMRS and HDRS ratings at all time points, by definition.

### 2.2 | Behavioral effects

Proportion correct and reaction time (RT) data from the CPT-END for emotional stimuli were analyzed using 3×3 (group-by-time) repeated measures ANCOVAs, with age as the covariate. There were no significant main effects or interactions in either model; therefore, response profile differences between groups were equivalent and, as such, did not appear to explain brain activation differences.

### 2.3 | Influence of remission status on brain activation

Figure 2 depicts estimated means (age adjusted) for group as a function of time for Factors 1 to 4 (i.e., subcortical structures, ACC, PFC, and amygdala, respectively) (also see Table S2). Factor 5 (subgenual ACC) is not depicted as it did not contribute to any significant main effects or interaction ($P>.05$).

For Factor 1 (subcortical structures; see Fig. 2A), the overall group-by-time interaction was significant [$F(4,160)=4.16$, $P=.003$]. Both remitters and nonremitters overactivated this factor relative to healthy participants at baseline ($P=.002$ and .006, respectively), and these differences were significantly reduced at Week 8 (contrast $P=.006$ and .015, respectively) – i.e., both bipolar disorder groups showed baseline subcortical overactivation that normalized over time.

Factors 2 and 3 did not meet the three a priori defined conditions (i.e., interaction, baseline difference, Week 8 change), supporting of our general hypothesis. Factor 2 (ACC; see Fig. 2B) resulted in a significant main effect of time [$F(2,160)=5.77$, $P<.004$] and Factor 3 (PFC; see Fig. 2C) yielded a marginally significant main effect of group [$F(2, 60)=3.40$, $P=.04$] but the interaction term was not significant ($P>.01$). To extend this specific analysis, as the VLPFC loaded across factors and has been shown previously to be associated with mania,[1,2] we examined this ROI specifically. As seen in Figure 3, bilaterally, the VLPFC exhibited a pattern of activation that differed significantly at baseline and Week 1 from healthy subjects (see also Table S2).

Finally, Factor 4 (the amygdala; see Fig. 2D) demonstrated a significant group-by-time interaction [$F(4,160)=3.82$, $P=.005$], primarily as the result of the nonremitter bipolar subgroup exhibiting a substantially larger decrease from baseline to Weeks 1 and 8, leaving this group to have the lowest level of amygdala activation among all groups at study end. This impression illustrated in Figure 2D was confirmed by a marginal contrast between nonremitters and healthy participants

**TABLE 2** Demographic and clinical characteristics of 42 participants with bipolar disorder experiencing a first manic or mixed episode, divided between those who did and did not achieve remission at 8 weeks of treatment, and 41 healthy comparison participants

| Clinical characteristics | Bipolar disorder | | Total (n=42) | Healthy participants (n=41) |
|---|---|---|---|---|
| | Remitted (n=21) | Nonremitted (n=21) | | |
| Age, years, mean (SD)[a,b] | 16 (2) | 21 (6) | 18 (5) | 22 (6) |
| Gender, male, n (%) | 9 (43) | 8 (38) | 17 (40) | 20 (49) |
| Baseline YMRS, mean (SD)[c] | 25 (5) | 25 (5) | 25 (5) | 1 (1) |
| Week 1 YMRS, mean (SD)[c] | 14 (8) | 14 (6) | 14 (7) | 0 (1) |
| Week 8 YMRS, mean (SD)[c,d] | 5 (3) | 15 (8) | 9 (7) | 1 (1) |
| Baseline HDRS, mean (SD)[c] | 13 (7) | 15 (8) | 14 (8) | 1 (2) |
| Week 1 HDRS, mean (SD)[c,e] | 8 (5) | 11 (5) | 9 (5) | 1 (2) |
| Week 8 HDRS, mean (SD)[c,f] | 4 (2) | 14 (7) | 9 (7) | 1 (2) |
| Treatment assignment, n (%) | | | | |
| Lithium | 11 (52) | 8 (38) | 19 (45) | n/a |
| Quetiapine | 10 (48) | 13 (62) | 23 (55) | n/a |

HDRS, 17-item Hamilton Depression Rating Scale total score; SD, standard deviation; YMRS, Young Mania Rating Scale total score.
[a]Signficant difference: remitted vs non remitted, $t(40)=3.3$, $P=.002$.
[b]Significant difference, bipolar disorder vs healthy participants, $t(81)=3.2$, $P=.002$.
[c]Significant difference, bipolar disorder vs healthy participants (by definition), $t(81)=6.2$, $P<.0001$.
[d]Significant difference, remitted vs non remitted, $t(40)=5.0$, $P<.0001$.
[e]Significant difference, remitted vs non remitted, $t(40)=2.3$, $P=.03$.
[f]Significant difference, remitted vs non remitted, $t(40)=6.8$, $P<.0001$.

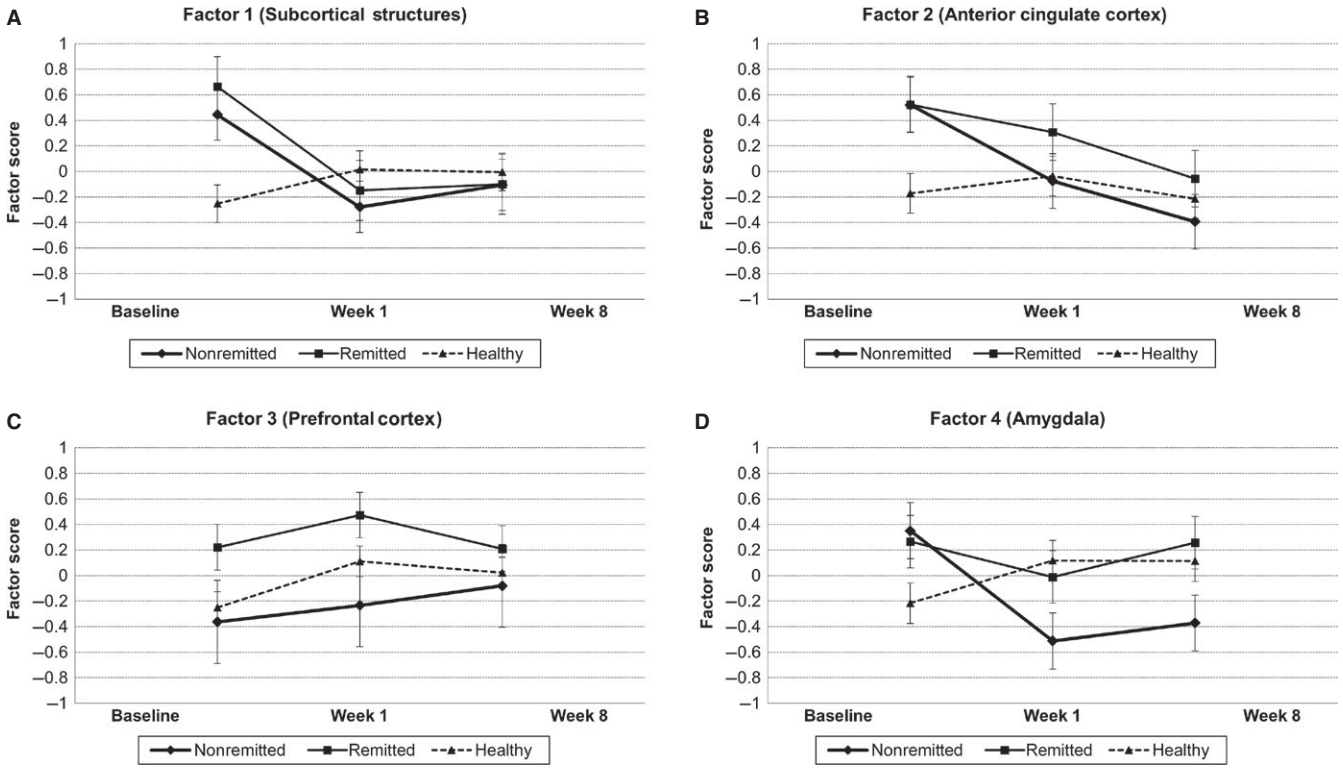


**FIGURE 2** Mean functional magnetic resonance imaging factor scores as a function of time and group for the first four factors within the five-factor solution, including: (A) subcortical structures, (B) anterior cingulate cortex, (C) prefrontal cortex, and (D) the amygdala

at baseline ($P=.04$) and a significant change in the magnitude of this difference at Week 8 ($P=.0025$). In other words, while nonremitters showed a tendency for overactivation of the amygdala at baseline relative to the healthy group, with treatment they underactivated the amygdala at Week 8 relative to remitted subjects with bipolar disorder and healthy participants alike.

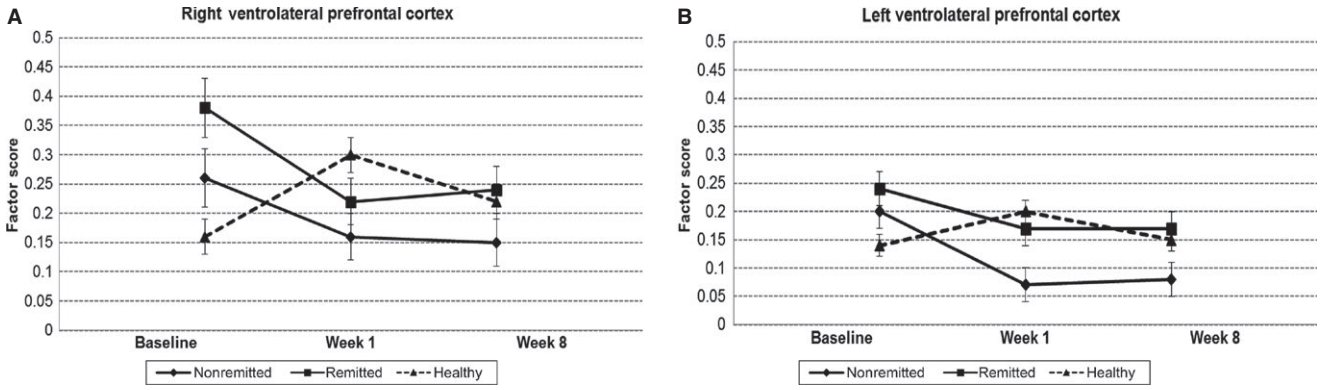


**FIGURE 3** Mean functional magnetic resonance imaging signal change proportion as a function of time and group for (A) the right ventrolateral prefrontal cortex and (B) the left ventrolateral prefrontal cortex

## 2.4 | Associations among symptom ratings and brain activation

In general, correlations among the five factors and baseline and Week 8 YMRS and HDRS total scores were limited. The only significant association at $P<.05$ was between the YMRS total score and Factor 1 (subcortical; $r=.24$, $P=.03$) (Table 3), demonstrating a small to medium effect size.

## 2.5 | Influence of medication type on brain activation

Although not a primary aim of the study, we conducted a post-hoc analysis of medication effects to help interpret the remission status findings. Significant medication type×time interactions were observed for only Factors 1 (subcortical structures) [$F(4,160)=4.64$, $P=.001$] and 4 (the amygdala) [$F(4,160)=4.29$, $P=.003$]; these effects are depicted in Figure 4. Factor 1 demonstrated greater subcortical activation at baseline in both medication groups relative to the healthy group that tended to normalize by Week 8, despite significant relative underactivation in the lithium group at Week 1 (Fig. 4A). Factor 4 showed a crossover effect in the lithium group, with greater amygdala activation at baseline relative to the healthy group, with lithium treatment associated with a relatively underactivated amygdala at Week 1 but not Week 8 (Fig. 4B).

## 2.6 | Brain activation to attentional targets

To aid interpretation, we examined differences between healthy subjects, and remitted and nonremitted participants with bipolar disorder at baseline, Week 1, and Week 8 in response to circles (targets) as the CPT-END was designed to differentiate between emotional and attentional stimuli as noted.[18] The EFA of target stimuli activations resulted in a loading pattern similar to that identified for emotional stimuli except that the ordering of factors changed slightly (i.e., subgenual ACG was Factor 3 rather than Factor 5). No significant group or time main effects or group×time interactions were observed after adjusting for age.

## 2.7 | Exploratory whole-brain voxelwise analysis

The results of the whole-brain voxelwise analysis comparing the bipolar subgroups who did or did not achieve remission are presented in Figure S1 and Table S3. As can be seen, the groups exhibited few differences at baseline, but by Week 1 the subjects with bipolar disorder who achieved remission exhibited increased activation in temporal, medial prefrontal, and posterior accessory cortical areas. At Week 8, the remitted subjects exhibited increased prefrontal, subcortical, and thalamic activation.

# 3 | DISCUSSION

To our knowledge, the present study is the largest prospective fMRI investigation of first-episode bipolar mania generally and, more specifically, of associations of functional imaging changes in response to standard treatments in this unique population. Our findings supported

**TABLE 3** Pearson *r*-values calculated using a mixed model of YMRS and HDRS total scores at baseline and Week 8 with fMRI brain activation factors in 42 first-episode manic subjects with bipolar disorder

| | Subcortical | ACC | Prefrontal | Amygdala | Sub_ACC |
|---|---|---|---|---|---|
| | Factor 1 | Factor 2 | Factor 3 | Factor 4 | Factor 5 |
| HDRS | −0.106 | 0.155 | 0.068 | −0.069 | 0.048 |
| YMRS | 0.239[a] | 0.180 | −0.098 | 0.025 | −0.104 |

ACC, anterior cingulate cortex; fMRI, functional magnetic resonance imaging; HDRS, 17-item Hamilton Depression Rating Scale; Sub ACC, subgenual anterior cingulate cortex; YMRS, Young Mania Rating Scale.
[a]$P<.05$.

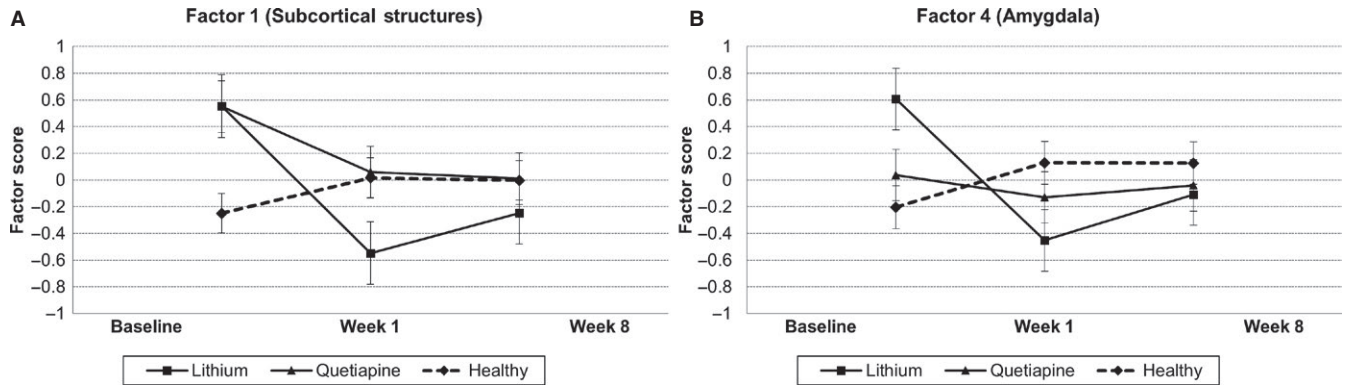


**FIGURE 4** Mean functional magnetic resonance imaging factor scores as a function of time and treatment status for two factors within the five-factor solution including: (A) subcortical structures and (B) the amygdala

our overall hypothesis that treatment of mania leads to normalization of regional brain activation abnormalities – i.e., that increased ROI activation in the bipolar group generally decreased toward healthy subject values, suggesting that in the early course of bipolar disorder, certain brain activation differences between subjects with bipolar disorder and healthy participants resolve with treatment, time, and symptomatic improvement. This finding is consistent with a small study by Passarotti et al.[30] in a combined manic/hypomanic sample (n=17) of pediatric bipolar disorder in whom treatment normalized cortical activation during an affective faces task. Moreover, our observations directly support conclusions from a recent review by Hafeman et al.[8] that suggested that in imaging studies of bipolar individuals, treatment appears to minimize, rather than accentuate, differences from healthy participants. Consistent with the recognized generally good treatment responsiveness of first-episode patients,[31,32] these results also suggest that decreases in regional brain overactivation occur quickly in response to treatment, often within the first week and prior to complete symptom remission. Many of these early changes may reflect the nonspecific treatment impact of hospitalization or simply time after intervention, rather than the specific effects of medications per se.

Beyond these general changes in brain activation, our factor analysis model confirmed that our predefined ROIs exhibited correlations consistent with models of the functional neuroanatomy of human emotional control and of bipolar disorder within the components of the CPT-END task. This analytic approach has the advantage that substantively meaningful patterns can be recovered from the data alone, including the notable cross-loading of VLPFC – e.g., consistent with its complex role in the top-down and bottom-up processing of emotional stimuli within frontosubcortical circuits (Fig. 1A). We believe that this reduced-data (EFA) ROI approach also allowed direct testing of our functional neuroanatomic (ROI-based) hypotheses while reducing comparisons that may not be achievable using standard voxelwise contrast methods.

Our findings indicated that the subcortical structures factor met our predefined criteria of a potential predictor of treatment response by demonstrating a significant group-by-time interaction *and* significant differences in activation between bipolar and healthy groups at baseline but not at Weeks 1 or 8. This factor also demonstrated a significant correlation with dimensional assessment of mania (i.e., the YMRS). The amygdala factor also demonstrated both an interaction and at least marginal baseline overactivation in the nonremitter group but, unlike remitters, nonremitters did not return to healthy activation levels by Week 1 or 8; instead, they showed underactivation at study conclusion. This difference between the bipolar subgroups might reflect functional neuroanatomic changes associated with or necessary for remission. Notably, lithium appeared to induce a more rapid suppression of amygdala overactivation that resembled that of the bipolar group that did not achieve remission, yet also showed a numerically (but not statistically significant) greater treatment response; these observations suggest that clinical improvement, amygdala activation changes and specific medication effects, and the influence of time are complex. The specific molecular mechanisms by which lithium and quetiapine treatment were effective could not be determined in the present study; consequently, it is not possible to presume that these medications are working similarly or differently to lead to somewhat similar endpoints. The few differences observed between the treatments should be interpreted cautiously, given the relatively small numbers of subjects in each treatment cell. Nonetheless, these data also suggest that imaging may provide a useful tool to study functional neuroanatomic effects of different medications with larger cell sizes.

Contrary to our hypothesized predictions, in our sample we did not see significantly decreased ventral prefrontal activation at baseline (i.e., during acute mania) as is commonly (but not always) reported in multiple-episode manic bipolar samples when compared with healthy individuals.[1,2,11,33–35] However, in younger and early-course samples, such as the present one, previous studies have suggested that prefrontal activation may be relatively spared; the current study supports these suggestions.[1,2,36–38] Loss of prefrontal activation in response to emotional cues may therefore develop with duration of illness or recurrence of episodes, perhaps reflecting reports of progressive shortening of euthymic intervals in the early course of bipolar I disorder.[1,2,9] As noted, the VLPFC loaded on several different factors (unlike other ROIs), consistent with it playing a relatively complex role in emotional

network modulation during mania. Additionally, as a separate ROI analysis, outside the factor analysis per se, the VLPFC also exhibited activation differences bilaterally across groups and time. Additionally, the remitted group demonstrated the highest baseline activation, especially on the right, which warrants study to replicate whether this pattern may be a treatment response predictor. Moreover, an exploratory whole-brain analysis of differences over time in activation between the bipolar subgroups who did or did not achieve remission showed differences in brain regions that were largely consistent with the identified factors, although in those analyses medial prefrontal cortical differences were observed. Together, these data continue to suggest that, rather than localizing to specific brain regions, bipolar disorder and its response to treatment are likely to arise from changes in the functions of networks of interconnected emotional brain regions. Unfortunately, to date, there have been few functional imaging studies of first-episode mania in order to provide better context for these current results. Clearly, more longitudinal neuroimaging studies early in the course of bipolar disorder are needed to improve understanding of the brain basis of early disease progression.

The lack of decreased prefrontal activation in bipolar relative to healthy participants at baseline, then, did not support our prediction that increases in ventral prefrontal activation would occur with recovery and be associated with corresponding decreases in amygdala overactivation. In fact, the subgroup of bipolar individuals who remitted demonstrated greater prefrontal activation at all time points (either statistically or numerically), as well as statistically greater amygdala activation after baseline. In the latter case, the remitted group demonstrated amygdala activation similar to that in healthy subjects, which was greater than that in the nonremitted bipolar subgroup at Weeks 1 and 8. In a prior study in a multiple-episode manic bipolar sample using the CPT-END, we observed blunted activation of the amygdala to these emotional cues and suggested that this decreased responsiveness might represent a loss of emotional network flexibility that develops during the course of bipolar I disorder.[11] The current findings might represent an early step in the evolution of bipolar I disorder over time, in that the nonremitted group might be at greater risk for recurrent or recalcitrant illness that would then populate a multiple-episode sample. This speculation would need longitudinal study to understand changes in prefrontal and amygdala responsiveness in bipolar disorder over time; such a study, however, could directly inform models of the progression of bipolar illness from a single manic episode to a recurrent affective disorder.[1,2]

As with any research investigation, limitations must be considered when interpreting results. Although the sample size was relatively large for a functional imaging study in this population with this design, statistical power for subgroup analyses was limited. As noted, most first-episode manic bipolar individuals will remit at some point during the first year, particularly with treatment changes and additions, so that longer treatment duration might lead to alternative changes underlying recovery.[31,32] These findings, then, are limited to an 8-week treatment trial, and the activation difference between groups may more accurately reflect a time to response rather than an absolute response difference. Additionally, the lack of a placebo control group limits the ability to estimate the *true* magnitude of the medication response in the current study, although the use of a well-characterized healthy comparison sample mitigates this concern to some extent. The bipolar group was younger than the healthy comparison group; although controlled statistically, findings might have been different with differently matched samples as prefrontal development in this age range is not strictly linear. Nonetheless, development in many brain areas is complete early in this age range, and most regions did not exhibit significant associations with age, increasing confidence in the general results. Nonetheless, the impact of development requires studies specifically designed to examine these effects. There are also limitations associated with the use of exploratory factor analysis. For example, bilateral regions (e.g., left and right thalamus) display substantial correlation beyond what can be explained by membership in a common subcortical grouping. Regions close in space should also exhibit additional correlation, as the mapping of voxels to true functional structures is imperfect and this measurement error could allow the same functional portion of the brain to be divided among spatially contiguous predefined regions. More elaborate modeling, incorporating substantive knowledge of this type, can be accomplished with confirmatory factor models. These would also allow for hypotheses about which of the latent variables should be correlated to each other, and which might be independent, to be tested. However, we believe that this approach more directly tests our specific ROI-based hypotheses than is possible with voxelwise analyses that contain exploratory components by design. Finally, by limiting the amount of substance use allowed in the sample and recruiting primarily inpatients, these results may not generalize to the larger bipolar I disorder population.

## 4 | CONCLUSIONS

Despite these limitations, the present study is one of the few fMRI examinations of first-episode mania, in general, and to our knowledge the largest (and perhaps only) to examine the impact of treatment on brain activation and symptom remission. The exploratory factor analysis design provided a data reduction strategy that produced results consistent with evolving models of both emotional modulation and bipolar disorder. The differences observed in changes in brain activation in bipolar individuals who did or did not achieve remission offer potential targets for future work using these changes to predict treatment response. Clearly, because the present study was relatively unique, additional similar investigations are needed to replicate and extend these findings. Regardless, these findings add to an evolving model of bipolar I disorder resulting from dysfunction within ventral prefrontal-striatal-thalamic-pallidal networks that underlie the emotional dyscontrol and, specifically, development of the mania that defines this condition.

### ACKNOWLEDGEMENTS

This study was funded by an NIMH CIDAR award P50 MH077138 (SMS). Preliminary results were presented at the ACNP Annual

meeting in December 2014. We thank Ruth Asch for her assistance with data output and in helping to construct the tables for the revised version of this manuscript. As always, we would like to express our gratitude to the many participants who generously gave of their time, without whom none of this work could be possible.

## DISCLOSURES

We do not believe that any of these relationships could influence the reported results but we report them for transparency. SMS serves as DSMB chair for Sunovion and a consultant to Roche and Procter and Gamble. JRS receives research support through the University of Cincinnati from Eli Lilly & Co., Edgemont, Forest Research Laboratories, Lundbeck, Shire, and Assurex (material only); and is a consultant to Neuronetics. MPD receives research support through the University of Cincinnati from Eli Lilly & Co., Otsuka, GlaxoSmithKline, Merck, Martek, Novartis, Lundbeck, Shire, Purdue, Sunovion, and Pfizer; and is a consultant to Pfizer, Lundbeck, Sunovian, Otsuka, Supernus, Forest, Actavis, Jansen, and Neurostar. CMA has received research support through the University of Cincinnati from Johnson & Johnson, Merck, Forest, Otsuka, Purdue, Takeda, Pfizer, Shire, Sunovion, and SyneuRx; and is a consultant to Sunovion. DEF, JW, JCE, MN, MD, RAK, W-JC, WW, JAD, TJB, AS, CK, and J-HL declare no conflicts of interest.

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## SUPPORTING INFORMATION

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**How to cite this article:** Strakowski, S. M., Fleck, D. E., Welge, J., Eliassen, J. C., Norris, M., Durling, M., Komoroski, R. A., Chu, W.-J., Weber, W., Dudley, J. A., Blom, T. J., Stover, A., Klein, C., Strawn, J. R., DelBello, M. P., Lee, J.-H., Adler, C. M. (2016), fMRI brain activation changes following treatment of a first bipolar manic episode. Bipolar Disorders, 18:490–501. doi: 10.1111/bdi.12426