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

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Abstract

Objectives—In this study, we tested the hypothesis that, with treatment, functional magnetic resonance imaging (fMRI) regional brain activation in first-episode mania would normalize, i.e., differences from health 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 eight weeks. fMRI scans were obtained at baseline and then after one and eight 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, replicating previous factor analyses in this population. One-half of the participants with bipolar disorder achieved remission by Week 8 and were contrasted with the other one-half

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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 towards 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 a disruption of healthy ventral prefrontal cortical modulation of other limbic structures, especially 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 impact 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 been comprised of 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 activation as bipolar individuals recovered, with corresponding decreases in over-activation of other limbic brain regions (e.g., amygdala, 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}

Materials/participants and methods

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 eight weeks. Three fMRI scans were obtained, one each at baseline and then after one and eight 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.

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 this study, and completed a baseline fMRI scan session. Because 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 this report (62% of the total group). There were no significant differences between included and excluded participants in age ($p = 0.90$), baseline Young Mania Rating Scale (YMRS)¹² total score ($p = 0.65$), baseline 17-item Hamilton Depression Rating Scale (HDRS)¹³ total scores ($p = 0.93$), sex ($p = 0.28$), treatment assignment ($p = 0.61$), or baseline activation (using standard voxel-wise analyses).

Participants with bipolar disorder were included if they: (i) were 13–35 years old based on the typical age of risk at 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 two 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. Both subjects with bipolar disorder and healthy participants were excluded by: (i) a history of substance dependence within three months prior to the index assessment; (ii) any medical or neurological disorder that could impact fMRI assessments; (iii) a history of significant developmental delays or estimated full scale IQ score < 85; or (iv) an MRI scan was contraindicated.

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, the 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 Weeks 1, 2, 4, 6, and 8. Remission was defined as both YMRS and HDRS total scores ≤ 10 for at least one week at the final Week 8 visit.

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 FDA-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 (target was 0.8 to 1.2 meq/L) and treatment response and tolerability for both. Adherence was verified by participant report, pill counts and serum levels when indicated.

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 three-second intervals for 2.75 seconds each. Emotional and neutral pictures and circles (targets) were presented pseudorandomly. A fixation cross was presented for 250 msec between cues. Previously, we have shown the emotional cues in this task activate the ventral emotional networks of interest (and the targets do not) in subjects with bipolar disorder and healthy participants.¹¹

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 have previously described.^{11, 19} Briefly, to provide anatomic localization, a high-resolution, T1-weighted, 3-D brain scan was obtained followed by a multi-echo reference scan to correct for ghost and geometric distortions.^{20, 21} For fMRI, whole-brain images (volumes) were acquired every three seconds using a T2*-weighted gradient-echo echoplanar imaging (EPI) pulse sequence [repetition time/echo time (TR/TE) = 3000/25 msec, 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 non-steady state magnetization leaving 172 images for analysis.

Image processing

Brain imaging data were processed with a combination of in-house image reconstruction software written in IDL and AFNI [(Analysis of Functional NeuroImages) <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 co-registered using scanner coordinates and image co-registration algorithms in AFNI. Functional images were corrected for motion using a six-parameter rigid body transformation.²² Additionally, each volume was inspected for signal artifacts after co-registration using a semi-automated approach and excluded from further analysis if uncorrectable image artifact affected more than ~30% of voxels in the volume.²³

Anatomical 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 neurophysiological networks of emotional modulation as presently conceptualized.¹ In these networks emotional stimuli processed by amygdala and ventral striatum are modulated by ventral prefrontal cortex 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 bilateral ventrolateral prefrontal cortex [Brodmann's area (BA) 45/47], ventromedial prefrontal cortex (BA 11/12), dorsal anterior cingulate cortex, superior anterior cingulate cortex (BA 32), subgenual anterior cingulate cortex, striatum (including 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, 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.

Statistical analyses

Statistical analyses were performed with 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 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, since 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).

Principle 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) anterior cingulate cortex (ACC), (iii) prefrontal cortex (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 rather 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, like the remainder of the results, were robust across different factor rotation methods. Additionally, in general, ROI loadings on to specific factors were stable in the healthy subjects across time, with minimal variability seen outside anterior cingulate regions (see Supplementary Table S1¹). 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 contains contributions from each ROI). Since the factor structure was generally simple

¹Supplementary Table S1 demonstrates ROI distributions across the five factors over time.

(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 ANCOVA models with Group (remitted bipolar, non-remitted bipolar, healthy control) and Time (baseline, Week 1, Week 8) at three levels each. Since some ROI activations varied with age, it 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 pre-specified 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 $\alpha = 0.05/3 = 0.017$ 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 0.005 to give an adjusted $p = 0.05$.

Results

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 ($r = -0.22$ to -0.32 , $p < 0.05$ to 0.003). Therefore, age was included as a continuous covariate in all subsequent analyses as noted. Sex distributions were similar across groups.

Both remitted and non-remitted participants with bipolar disorder showed improvement in symptom ratings during this 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 non-remitted 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 ($r = 0.55$, $p < 0.0001$). Although participants with bipolar disorder receiving lithium exhibited a numerically greater response rate than those on quetiapine (58% versus 43%, respectively), this difference was not significant (Fisher's exact test: $p = 0.27$). Healthy participants exhibited lower YMRS and HDRS ratings at all time points, by definition.

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, do not appear to explain brain activation differences.

Influence of remission status on brain activation

Figure 2 depicts estimated means (age-adjusted) for Group as a function of Time for Factors 1 through 4 (i.e., subcortical structures, ACC, PFC, and amygdala, respectively) (also see Supplementary Table S2²). Factor 5 (subgenual ACC) is not depicted as it did not contribute to any significant main effects or interaction ($p > 0.05$).

For Factor 1 (subcortical structures; see Fig. 2A), the overall Group-by-Time interaction was significant [$F(4,160) = 4.16$, $p = 0.003$]. Both remitters and non-remitters over-activated this factor relative to healthy participants at baseline ($p = 0.002$ and 0.006 , respectively), and these differences were significantly reduced at Week 8 (contrast $p = 0.006$ and 0.015 , respectively). That is, both bipolar disorder groups showed baseline subcortical over-activation 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 [$F(2,160) = 5.77$, $p < 0.004$] and Factor 3 (PFC; see Fig. 2C) yielded a marginally significant main effect of Group [$F(2, 60) = 3.40$, $p = 0.04$], but the interaction term was not significant ($p > 0.01$). To extend this specific analysis, since 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 Supplementary Table S2).

²Supplementary Table S2 presents the age-adjusted mean fMRI signal change values in each of the 20 *a priori* defined ROIs in response to emotional cues during the CPT-END task. These data are provided to document the individual contribution of each ROI to the larger factor structure, further demonstrate within-factor similarities, and in the interest of documenting the raw data values for potential subsequent research purposes (e.g., meta-analyses).

Finally, Factor 4 (amygdala; see Fig. 2D) demonstrated a significant Group-by-Time interaction [$F(4,160) = 3.82, p = 0.005$], primarily as the result of the non-remitter 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 non-remitters and healthy participants at baseline ($p = 0.04$) and a significant change in the magnitude of this difference at Week 8 ($p = 0.0025$). In other words, while non-remitters showed a tendency for over-activation of amygdala at baseline relative to the healthy group, with treatment they under-activated amygdala at Week 8 relative to both remitted subjects with bipolar disorder and healthy participants.

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 $p < 0.05$ was between the YMRS total score and Factor 1 (subcortical; $r = 0.24, p = 0.03$) (Table 3), demonstrating a small to medium effect size.

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 $\times$ Time interactions were observed for only Factors 1 (subcortical structures) [$F(4,160) = 4.64, p = 0.001$] and 4 (amygdala) [$F(4,160) = 4.29, p = 0.003$]; 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 under-activation 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 relatively under-activated amygdala at Week 1 but not Week 8 (Fig. 4B).

Brain activation to attentional targets

To aid interpretation, we examined differences between healthy subjects, and remitted and non-remitted participants with bipolar disorder at baseline, Week 1, and Week 8 in response to circles (targets) since 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 $\times$ Time interactions were observed after adjusting for age.

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 Supplementary Figure S1³ and Supplementary

³Supplementary Figure S1 provides illustrative maps of the voxelwise analysis.

Table S3⁴. 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.

Discussion

To our knowledge, this 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 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 early course 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 over-activation occurs 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 pre-defined 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 ventrolateral PFC for example, consistent with its complex role in the top-down and bottom-up processing of emotional stimuli within frontosubcortical circuits (Fig. 1A). We believe 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 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

⁴Supplementary Table S3 provides data regarding the ROIs that differed among bipolar subgroups across time in the exploratory voxelwise analysis.

both an interaction and at least marginal baseline over-activation in the non-remitter group, but unlike remitters, non-remitters did not return to healthy activation levels by Week 1 or 8, instead, they showed under-activation 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 over-activation 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 this study; consequently, it is not possible to presume that these medications are working similarly or differently to lead to somewhat similar end points. 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 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, like this one, previous studies suggested that prefrontal activation may be relatively spared; the current study supports those 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 ventrolateral prefrontal cortex 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 ventrolateral prefrontal cortex 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 likely arise from changes in 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

over-activation. 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 an amygdala activation similar to healthy subjects, which was greater than the non-remitted 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 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 non-remitted 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 is 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 eight-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, since 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, since 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 pre-defined 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 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.

Conclusions

Despite these limitations, this study is one of 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 this study is 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 mania that defines this condition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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

Fig. 2.

Mean functional magnetic resonance imaging (fMRI) 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), and amygdala.

Fig. 3.

Mean functional magnetic resonance imaging (fMRI) signal change proportion as a function of Time and Group for (A) right ventrolateral prefrontal cortex and (B) left ventrolateral prefrontal cortex.

Fig. 4.
Mean functional magnetic resonance imaging (fMRI) factor scores as a function of Time and Treatment Status for two factors within the five-factor solution including: **(A)** subcortical structures and **(B)** amygdala.

Table 1

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

Region	Factor 1 Subcortical	Factor 2 ACC	Factor 3 PFC	Factor 4 Amygdala	Factor 5 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
3. 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 vIPFC (BA45/47)	0.43	0.28	0.48	0.39	0.05
L vIPFC (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. PFC = prefrontal cortex; ACC = anterior cingulate cortex; R = right; L = left; BA = Brodmann's area; vmPFC = ventromedial prefrontal cortex; vIPFC = ventrolateral prefrontal cortex; Sub ACC = subgenual anterior cingulate cortex.

Table 2

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

Clinical characteristics	Bipolar disorder		Total (n = 42)	Health participants (n = 41)
	Remitted (n = 21)	Non-remitted (n = 21)		
Age, years, mean (SD) ^{a, b}	16 (2)	21 (6)	18 (5)	22 (6)
Sex, 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

YMRS = Young Mania Rating Scale total score; HDRS = 17-item Hamilton Depression Rating Scale total score; SD = standard deviation.

^aSignificant difference: remitted versus non-remitted, $t(40) = 3.3$, $p = 0.002$.

^bSignificant difference, bipolar disorder versus healthy participants, $t(81) = 3.2$, $p = 0.002$.

^cSignificant difference, bipolar disorder versus healthy participants (by definition), $t(81) = 6.2$, $p < 0.0001$.

^dSignificant difference, remitted versus non-remitted, $t(40) = 5.0$, $p < 0.0001$.

^eSignificant difference, remitted versus non-remitted, $t(40) = 2.3$, $p = 0.03$.

^fSignificant difference, remitted versus non-remitted, $t(40) = 6.8$, $p < 0.0001$.

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

HDRS = 17-item Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale; fMRI = functional magnetic resonance imaging; ACC = anterior cingulate cortex.

^a *p* < 0.05.