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A longitudinal functional connectivity analysis of the amygdala in bipolar I disorder across mood states

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Abstract

Objective—Bipolar I disorder is characterized by affective symptoms varying between depression and mania. The specific neurophysiology responsible for depression in bipolar I disorder is unknown, but prior neuroimaging studies suggest impairments in corticolimbic regions that are responsible for regulating emotion. The amygdala seems to play a central role in this network and is responsible for appraisal of emotional stimuli. To further understand the role of the amygdala in the generation of mood symptoms, we used functional magnetic resonance imaging (fMRI) to examine a group of patients with bipolar I disorder longitudinally.

Methods—fMRI was used to study regional brain activation in 15 bipolar I disorder patients followed for up to one year. Patients received an fMRI scan during an initial manic episode and a subsequent depressive episode. During the scans, patients performed an attentional task that incorporated emotional pictures. Fifteen healthy comparison subjects were also scanned at baseline and then at four months. Wholebrain functional connectivity analysis was performed using the left and right amygdala as seed regions.

Results—Significant changes in amygdala functional connectivity were found between the manic and depressed phases of illness. The right amygdala was significantly more positively correlated with the left inferior frontal gyrus during mania and with the right insula during depression. There were no significant differences in left amygdala correlations across mood states in the bipolar I disorder group.

Conclusions—In the transition from a manic/mixed episode to a depressive episode, subjects with bipolar I disorder showed unique changes in cortical–amygdala functional connectivity. Increased connectivity between the insula and right amygdala may generate excessive positive feedback, in that both of these regions are involved in the appraisal of emotional stimuli. Increased correlation between the right amygdala and the inferior frontal gyrus in mania is consistent with prior findings of decreased prefrontal modulation of limbic regions in mania. These differences in connectivity may represent neurofunctional markers of mood state, as they occurred in the same individuals across manic and depressive episodes.

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Disclosures

The authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this manuscript. MPD, CMA, and SMS have disclosed all potential conflicts of interest; however, these are not relevant to the current manuscript.

Keywords

bipolar disorder; functional connectivity; functional magnetic resonance imaging; fMRI

Bipolar I disorder is defined by the occurrence of mania and exhibits a dynamic course of symptoms that alternate among affective extremes. The specific neurophysiological basis of bipolar disorder is unknown, but neuroimaging studies suggest impairments in corticolimbic regions responsible for regulating emotion that have been termed the anterior limbic network (1–5). In subjects with bipolar I disorder, abnormal brain activation has been shown in the amygdala, anterior cingulate gyrus (ACC), ventrolateral prefrontal cortex (VLPFC), insula, and medial prefrontal cortex (1, 3). The amygdala seems to play a central role in this network and is responsible for the appraisal of emotional stimuli (6–8). Other regions in the anterior limbic network, including the VLPFC and insula, interact with the amygdala to provide cortical modulation of the appraisal process (3).

Patients with bipolar I disorder spend significantly more time in depression than mania (9). Yet few studies have specifically examined the neurophysiology of the depressed phase of bipolar I disorder, and it is not clear which corticolimbic regions are involved in the generation of the syndrome of depression or involved in the switch from mania to depression. One approach to answer these questions is to use imaging to examine patients with bipolar I disorder across different mood states. However, there are few longitudinal imaging studies of bipolar I disorder across mood states (3). Comparing the same patients across manic and depressive episodes may lead to a better understanding of the how corticolimbic networks generate mood states (10).

The current study was designed to understand the role of the amygdala during the course of bipolar I disorder. Using amygdala as the primary seed region in a functional connectivity analysis allowed us to identify altered connections with other brain regions in mania and depression. Subjects with bipolar I disorder were assessed during an initial manic or mixed episode and then followed for up to one year and re-assessed if they developed a depressive episode. Subjects received an fMRI scan at each assessment while performing a modified continuous performance task with emotional distracters (5). The task was designed to discriminate between ventral emotional and dorsal cognitive brain networks and their interaction and requires effective regulation of emotion to complete successfully (5). We predicted that subjects with bipolar I disorder would show different patterns of amygdala connectivity in mania versus depression. Given previous findings of decreased prefrontal modulation of limbic regions in mania, we predicted that when subjects no longer had manic symptoms (i.e., they switched to being in a depressive episode) activation in these brain regions would normalize to more closely resemble healthy comparison subjects (HC) (5, 11–13). Therefore we predicted that during depression subjects would show increased amygdala connectivity with ventral and dorsal prefrontal regions.

Methods

Subjects

Subjects with bipolar I disorder ($n = 72$) were initially identified and recruited during a manic or mixed episode from the inpatient units at the University of Cincinnati Academic Health Center and the Cincinnati Children's Hospital Medical Center (CCHMC). These subjects were then prospectively evaluated for up to one year in order to identify subjects who developed a depressive episode ($n = 23$). Subjects received an MRI scan during the index manic/mixed episode and then a second scan during a depressive episode (on average 14 weeks after the initial scan). The diagnosis of bipolar I disorder was made using the

Structured Clinical Interview for DSM-IV Axis I Disorders–Patient version (SCID-I/P) (14), or the Washington University in St. Louis Kiddie and Young Adult Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) (15) for subjects under 18. Manic and depressive symptoms were rated at each time point using the Young Mania Rating Scale (YMRS) (16) and Montgomery-Åsberg Depression Rating Scale (MADRS) (17).

Potential subjects were excluded by a substance use disorder within the previous three months, medical or neurological illnesses that might influence brain function, any contraindications to receiving an MRI, and an IQ <80. Additionally, general measures of premorbid intellectual function (IQ) were obtained using the American Modification of the National Adult Reading Test (ANART) (18) or the Wechsler Abbreviated Scale of Intelligence (WASI) (19). The ANART provides an estimate of premorbid IQ that is strongly correlated with the Verbal (VIQ) WASI score and is resilient to the influence of affective symptoms in bipolar disorder (20).

Demographically matched HC (n = 15) were recruited from the communities served by these hospitals and had no history of Axis I psychiatric disorders in themselves or first-degree relatives. HC were scanned at an initial visit and again approximately four months latter. All subjects were 16 to 50 years old, were physically and neurologically healthy, and if female, had a negative urine pregnancy test. Out of the 23 initial subjects with bipolar disorder, data from eight subjects were not usable because five subjects were not able to complete that scan or task and three subjects had excessive motion (in either the manic or depressed scan). The eight subjects excluded did not differ from the remaining 15 in gender, age, or medication status, but did differ in race ($\chi^2 = 9.1$, $p < 0.001$) with more African American subjects in the excluded scans. Seven of the remaining 15 subjects were diagnosed with a mixed episode at baseline while the other eight were diagnosed with a manic episode. Only one of the 15 subjects with bipolar I disorder was under 18 (this subject was 16 years old).

There was little psychiatric comorbidity among the 15 subjects with bipolar I disorder. The mood disorders, psychosis, impulse control disorders, substance use disorders, and attention-deficit hyperactivity disorder (ADHD) sections of the SCID were completed to access for comorbidity. Subjects with mood disorders other than bipolar disorder or any psychotic disorder were excluded from participation. Two subjects had comorbid ADHD, combined type (with one of these subjects also being diagnosed with binge eating disorder) and one subject was diagnosed with kleptomania. All subjects were taking a mood stabilizer (valproate or lithium), an atypical antipsychotic, or a combination of these. By the time of the second scan, seven subjects had medication changes from the initial scan. In four of these cases, this change included the addition of an atypical antipsychotic to the existing regimen, two cases involved switching from monotherapy with a mood stabilizer or atypical antipsychotic to another single agent, and in one subject sertraline was added to an atypical antipsychotic and a mood stabilizer. All subjects provided written informed consent or written assent with legal guardian consent for minors, after study procedures were fully explained. The study was approved by the Institutional Review Boards of the University of Cincinnati and the CCHMC.

Image acquisition and analysis

All fMRI scans were performed 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). Non-ferromagnetic high-resolution visual goggles (Resonance Technologies, Inc., Northridge, CA, USA) were used to present the video stimuli in the MRI scanner. Anatomical localization was obtained using a high-resolution, T1-weighted, 3-D brain scan (21). To encompass the entire brain a midsagittal localizer scan was acquired to place 35 contiguous 5-mm axial slices. Next, to correct for ghost and geometric distortions,

a multi-echo reference scan was obtained (22). The subjects completed the Continuous Performance Task with Emotional and Neutral Distractors (CPT-END) task in an fMRI session. The CPT-END task is based on a task by Yamasaki et al (23) and is a visual oddball paradigm with the addition of neutral and emotional (unpleasant) distractor pictures taken from the International Affective Picture System (IAPS) (University of Florida, Gainesville, FL, USA). Each imaging session consisted of two runs of 158 visual cues per run presented at three-second intervals for two seconds each with a fixation cross presented for one second between cues. Wholebrain images (volumes) were acquired every three seconds using a T2*-weighted gradient-echo echoplanar imaging (EPI) pulse sequence [repetition time/echo time (TR/TE) = 3000/30 msec, field of view (FOV) = 20.8 × 20.8 cm, matrix = 64 × 64 pixels, slice thickness = 5 mm, flip angle = 75°].

All analyses of the fMRI data were conducted using AFNI (Analysis of Functional NeuroImages; <http://afni.nimh.nih.gov/afni>). Before the analysis the raw MRI images were reconstructed in order to convert the raw scanner data into AFNI format. Preprocessing steps performed in AFNI included co-registration based upon scanner coordinates for both structural and EPI (functional) images and motion correction. Motion for each subject was determined for the six directions of rotation and translation and was corrected using a six-parameter rigid body transformation (24). Subjects were excluded from analysis if the maximum motion was > 5 mm. The average total displacement for all subjects was < 1 mm and the average displacement between any successive TR pair was < 0.1 mm. In addition to standard motion correction, each volume was inspected for signal artifacts using a semi-automated algorithm in AFNI and excluded from further analysis if visual inspection indicated uncorrectable head movement. Less than 16 volumes (10%) on average were removed from each run. Five subjects could not be used because of excessive motion during one of the fMRI scans. Finally, anatomical and functional maps were transformed into stereotactic Talairach space using the ICBM452 template (25).

Functional connectivity analysis

A functional connectivity analysis (26, 27) was performed using the left and right amygdala as seed regions of interest (ROIs). Given that the functional connectivity analysis was not conducted using brain activation in response to any of the specific stimulus types comprising the CPT-END, but rather on activation across all stimulus types combined, the design is considered *steady state* as opposed to *resting state* in which no task is performed. The effects of head movement on EPI signal was removed from the fMRI data through regression of the motion correction parameters against the original time series. Then these signals were subtracted from the original EPI time series using a combination of the AFNI program 3dsynthesize and 3dcalc. After these parameters were removed the individual EPI time series were run through a low-pass filter to remove all frequencies above 0.1 Hertz in order to remove aliasing effects from respiration and heart rate (28, 29). To create the seed regions, a mean time series for left and right amygdala were calculated by averaging the time series for all voxels within the respective ROI. The anatomic ROIs were created using the predefined region of the amygdala from an anatomic parcellation of the Montreal Neurological Institute (MNI) brain (30). A mean times series for the entire brain was also calculated for each subject for use in global mean correction in the final regression (31–33). Regression analysis was then performed in AFNI between the mean amygdala time series and the time series for all other individual voxels in the brain, resulting in activation maps for each participant. Global activation was included as a regressor in this analysis in order to remove any spurious brain wide correlations. The *r*-values were calculated from the regression results and then converted to *z*-scores using Fisher's *Z*-transformation in order to reduce skewness and normalize the values (34, 35). The individual activation maps of *z*-scores were combined across participants in a 2 × 2 ANOVA to produce wholebrain

composite maps. The ANOVA was performed using the GroupAna tool set in AFNI with group (HC and bipolar I disorder subjects) and time (baseline and repeat scan) as the two factors. All reported regions were significant at $p < 0.05$ corrected with a voxelwise threshold of 0.005 and a cluster threshold of 20 or more contiguous voxels which gives a false discovery rate of < 0.05 (36).

Results

Demographic, clinical, and performance variables

As seen in Table 1, there were no significant differences in demographics between the bipolar I disorder and HC groups. As expected, the bipolar manic group had significantly higher average YMRS scores (25 ± 3 versus 8 ± 6) relative to the bipolar depressed group [$F(1,25) = 98$, $p < 0.001$]. However, there was no significant difference between baseline and follow-up MADRS scores [17 ± 8 versus 19 ± 4 ; $F(1,25) = 0.91$, $p = 0.34$].

A mixed ANOVA revealed no significant effects of group, time, or group-by-time interaction on the CPT-END task for either the error rate or reaction time (see Table 2). This finding suggests not only that the groups performed the CPT-END similarly, but that no appreciable behavioral practice effects were apparent across time.

Functional connectivity analysis

There were no significant interaction effects in the ANOVA. There were no significant differences in connectivity in the left amygdala between depressed and manic patients. The group comparison results of right amygdala connectivity are listed below. The direction of correlation for each cluster can be determined by examining the absolute direction of correlation in each group. These correlation values are included in Tables 1–4.

HC baseline versus HC follow-up—Three brain regions showed a significant change in connectivity with right amygdala at follow-up relative to baseline. Figure 1 graphically depicts each of these regions which included the right middle temporal gyrus, right parahippocampal gyrus and right precuneus. Table 1 shows the direction of change in the correlation values across time, hemisphere, Talairach coordinates for the center of mass, and volume for each region depicted in Figure 1. As seen in Table 3 (columns two and three), group differences in amygdala connectivity derived from negative coupling in the middle temporal gyrus and precuneus, and increasing positive coupling in the parahippocampal gyrus at follow-up. For each ROI the magnitude of effect was greater at follow-up.

HC baseline versus bipolar manic—As depicted in Figure 2, seven brain regions showed a significant change in connectivity with right amygdala between the bipolar manic and HC groups at baseline. As seen in Table 4 (columns two and three), in each instance group differences in amygdala connectivity derived from negative functional coupling in the HC group and positive coupling in the bipolar manic group.

HC follow-up versus bipolar depressed—As displayed in Figure 3, six brain regions showed a significant change in connectivity with right amygdala between the bipolar depressed and HC groups at follow-up. As seen in Table 5 (columns two and three), group differences in amygdala connectivity derived from differences in the direction of connectivity between the study groups. In the bipolar depressed group there was positive coupling in the right middle temporal gyrus, right medial frontal gyrus, right middle frontal gyrus, and right fusiform gyrus. By contrast, connectivity differences derived from negative coupling in right putamen and left cuneus in the bipolar depressed group.

Bipolar manic (baseline) versus bipolar depressed (follow-up)—As displayed in Figure 4, six brain regions showed a significant change in connectivity with right amygdala between the bipolar depressed and bipolar manic groups. As seen in Table 6 (columns two and three), group differences in amygdala connectivity derived from differences in the direction of connectivity between the study groups. In the bipolar depressed group there was a change to positive coupling in the right insula, left middle frontal gyrus, and right superior frontal gyrus. By contrast, connectivity differences derived from a change to negative coupling in left inferior frontal gyrus, right cerebellar tonsil, and right middle frontal gyrus in the bipolar depressed group.

Discussion

In the current study differences in amygdala connectivity were found between a cohort of subjects with bipolar I disorder in a depressed versus a manic/mixed state. These subjects had similar depression ratings during both scans. Consequently, differences in the two time points represent the presence versus absence of mania in the context of similar depressive symptoms rather than a contrast between manic and depressive syndromes per se; i.e., the activation changes seem to reflect changes in manic symptoms specifically. In fact, although the lack of differences in depression severity was not anticipated, it does control for depressive symptoms across the two time points.

The analysis of HC at baseline and four months showed increased negative correlation in the middle temporal gyrus and precuneus, both of which are part of posterior attentional networks. As the only difference in the HC group between time points was the familiarity of the task at the second scan; therefore, these activation changes may reflect the possibility that subjects were less distracted by the emotional images during the follow-up scan and therefore needed less modulation of posterior attentional regions by the amygdala. The right parahippocampal gyrus showed increased correlation with amygdala in the second scan and this could be related to anticipating emotional images. The differences in connectivity in the subjects with bipolar I disorder time did not include these regions and were therefore more likely related to changes in manic symptoms rather than familiarity with the task.

Without mania the subjects with bipolar I disorder showed greater functional connectivity between the right amygdala and right insula than during mania. The insula has been shown to be involved in the anticipation of emotional stimuli, the generation of empathy, and to activate in response to disgust (37–39). Many of the IAPS photos involved mutilation or injury, and so would be expected to generate both disgust and empathy in subjects. Depression causes a heightened sensitivity to negative stimuli (40–43) that may have caused these subjects to show a greater emotional response to negative emotions. This suggestion may partially explain the increased functional connection of these two regions during depression. One of the few prior neuroimaging studies of bipolar depression found increased activation in the insula compared with HC (44). Given the overlapping role of insula and amygdala in the appraisal of emotions, a potential hypothesis is that they form a positive feedback loop that increases the negative valence of stimuli and contributes to the symptoms of depression. Increased connectivity with the insula was also observed in manic compared to HC subjects at baseline, suggesting that this region may play a role in bipolar I disorder across mood states. However the altered connectivity was found in the opposite hemisphere (left) and this activation difference was no longer found in the comparison between HC subjects and bipolar depressed subjects.

Subjects with bipolar I disorder also showed several changes in prefrontal regions across mood states. Bipolar manic subjects showed increased connectivity with the right middle frontal gyrus compared to HC, whereas bipolar depressed subjects showed increased

connectivity with the right medial frontal gyrus and left middle frontal gyrus compared to HC subjects. Altered activation in ventral frontal regions has been found in prior neuroimaging studies of bipolar mania (1, 5). Using the larger sample that included the manic subjects used in the current study, Strakowski et al. (5) found decreased activation in the left VLPFC compared to HC subjects. In addition, two prior functional connectivity studies of subjects with bipolar I disorder during mania found reduced connectivity between the amygdala and VLPFC (45, 46). These prior studies are consistent with the current findings of reduced connectivity between the right amygdala and VLPFC in manic patients. Previously, we hypothesized that dysfunction in connections between these anterior limbic network regions may disrupt emotional homeostasis (1–5). The differences in connectivity of the right amygdala and VLPFC across mood states suggest that there may be different network dysfunction during mania and depression. Manic subjects showed increased connectivity with the left inferior frontal gyrus and decreased connectivity in the left and right middle frontal compared to depressed subjects. Further knowledge of network dysfunction during depression and mania could allow the development of neurofunctional markers of mood state.

There are several limitations to the current study. One significant limitation of functional connectivity is that it does not allow the determination of causal connections between regions. If activation between two brain regions, *A* and *B*, is correlated, then there are three possible explanations: (i) region *A* causes the simultaneous activation (or deactivation) in region *B*; (ii) region *B* causes the simultaneous activation in region *A*; (iii) or the correlated activation in region *A* and *B* is caused by a third region of the brain. Functional connectivity cannot distinguish among these possibilities. Although physiological artifacts were controlled using low-pass filtering and global correction, it would have been ideal to directly measure physiological parameters during the scans to more accurately control for these potential artifacts. While less than half of subjects had medication changes made between scans and there was no systematic pattern to these changes, it is still possible these had some effect on the results.

Another limitation to the current study is the relatively small number of subjects. Due to the many challenges in following patients with bipolar disorder, the study had may have been underpowered. Repetition effects are another potential limitation of this study. However, in order to assess the stability of this task over time, HC participants with a baseline and four-month follow-up scan were included in this analysis. None of the regions that showed changes across time in controls overlapped with those observed in the change from mania to depression.

Despite the limitations, the current results provide evidence for changes in cortical-amygdala functional connectivity across mood states during an emotional regulation process in bipolar I disorder. In that these connectivity differences occurred in the same individuals across manic and depressive episodes, they are likely to represent neurofunctional markers of mood state. Further longitudinal studies are needed to further clarify the role these regions play in the generation of mood symptoms in bipolar I disorder.

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Fig. 1. Clusters showing significant differences in right amygdala connectivity in healthy comparison subjects (HC) at baseline compared to four months. Blue regions represent greater absolute amygdala connectivity in HC at baseline and orange regions represent greater absolute amygdala connectivity in HC at four months. All comparisons are shown at $p < 0.05$, corrected with a voxelwise threshold of 0.005, and a cluster threshold of 20 or more contiguous voxels.

Fig. 2.

Clusters showing significant differences in right amygdala connectivity in healthy comparison subjects (HC) at baseline compared to bipolar manic subjects. Blue regions represent greater absolute amygdala connectivity in the manic subjects. All comparisons are shown at $p < 0.05$, corrected with a voxelwise threshold of 0.005, and a cluster threshold of 20 or more contiguous voxels.

Fig. 3. Clusters showing significant differences in right amygdala connectivity in healthy comparison subjects (HC) at four months compared to bipolar depressed subjects. Blue regions represent greater absolute amygdala connectivity in the depressed subjects and orange regions represent greater absolute connectivity in HC. All comparisons are shown at $p < 0.05$, corrected with a voxelwise threshold of 0.005, and a cluster threshold of 20 or more contiguous voxels.

Fig. 4. Clusters showing significant differences in right amygdala connectivity in bipolar manic/mixed subjects compared to bipolar depressed subjects. Blue regions represent greater absolute amygdala connectivity in mania and orange regions represent greater absolute connectivity during depression. All comparisons are shown at $p < 0.05$, corrected with a voxelwise threshold of 0.005, and a cluster threshold of 20 or more contiguous voxels.

Table 1

Demographics of the patients and healthy comparison (HC) subjects

	Bipolar I disorder (n = 15)		HC (n = 15)	Bipolar I disorder versus HC
Mood state	Manic	Depressed		
Age, years, mean (SD)	30.0 (9.8)	–	30 (8.7)	p = 0.95
Ethnicity, non-white, %	0	–	7	p = 0.31 ^a
Sex, female, %	33	–	60	p = 0.14 ^a
Education, years, mean (SD)	14.0 (2.4)	–	14.0 (1.6)	p = 0.62 ^b
YMRS total score, mean (SD)	25.0 (2.9)	8.0 (5.6)	0 (0.8)	
MADRS total score, mean (SD)	17.0 (7.5)	19.0 (4.3)	1.0 (1.1)	

YMRS = Young Mania Rating Scale; MADRS = Montgomery-Åsberg Depression Rating Scale.

^aChi-square test.^bANOVA.

Table 2

Behavioral performance data for all groups

Performance	Bipolar I disorder		HC (baseline)	HC (four months)	Significance
	Manic	Depressed			
Average RT, msec	834	836	800	833	$F = 1.03$ $p = 0.32^a$
Average ACC, %	85	93	91	90	$F = 0.61$ $p = 0.42^a$

HC = healthy comparison subjects; RT = reaction time; ACC = accuracy.

^aMixed-model ANOVA.

Table 3

Three clusters showing significant differences in right amygdala connectivity in healthy comparison subjects (HC) at baseline and at four months

ROI correlated with right amygdala	Correlation		Laterality	Center of mass (Talairach coordinates)			Volume ^a
	HC baseline	HC follow-up		x	y	z	
Middle temporal gyrus	0.03	-0.15	Right	-37.5	58.5	11.5	72
Parahippocampal gyrus	0.09	0.38	Right	-31.5	4.5	-18.5	71
Precuneus	0.01	-0.16	Right	-22.5	55.5	29.5	69

The average correlation values for each cluster are shown for the two groups to allow determination of directionality in the group comparison. All comparisons are shown at $p < 0.05$, corrected with a voxelwise threshold of 0.005, and a cluster threshold of 20 or more contiguous voxels. ROI = region of interest.

^a 3-mm³ voxels.

Table 4

Seven clusters showing significant differences in right amygdala connectivity in healthy comparison subjects (HC) at baseline compared to subjects with bipolar I disorder when manic/mixed

ROI correlated with right amygdala	Correlation		Laterality	Center of mass (Talairach coordinates)			Volume ^a
	HC baseline	Manic		x	y	z	
Middle frontal gyrus	-0.06	0.14	Right	-49.5	-16.5	26.5	236
Insula	-0.06	0.11	Left	34.5	-19.5	8.5	62
Cerebellar tonsil	-0.03	0.16	Right	-31.5	46.5	-24.5	57
Declive (Cerebellum)	-0.12	0.05	Left	25.5	73.5	-21.5	36
Superior frontal gyrus	-0.12	0.06	Left	10.5	-55.5	23.5	36
Insula	-0.04	0.12	Left	37.5	28.5	23.5	33
Declive (Cerebellum)	-0.03	0.13	Left	4.5	82.5	-15.5	32

The average correlation values for each cluster are shown for the two groups to allow determination of directionality in the group comparison. All comparisons are shown at $p < 0.05$, corrected with a voxelwise threshold of 0.005, and a cluster threshold of 20 or more contiguous voxels. ROI = region of interest.

^a 3-mm³ voxels.

Table 5

Six clusters showing significant differences in right amygdala connectivity in healthy comparison subjects (HC) at four months compared to bipolar depressed subjects

ROI correlated with right amygdala	Correlation		Laterality	Center of mass (Talairach coordinates)			Volume ^a
	HC follow-up	Depressed		x	y	z	
Middle temporal gyrus	-0.14	0.03	Right	-40.5	58.5	11.5	71
Medial frontal gyrus	-0.02	0.17	Right	-16.5	-31.5	29.5	29
Putamen	0.02	-0.13	Right	-22.5	4.5	20.5	28
Middle frontal gyrus	-0.13	0.03	Left	28.5	-22.5	56.5	24
Fusiform gyrus	-0.06	0.12	Right	-40.5	40.5	-15.5	22
Cuneus	-0.01	-0.20	Left	1.5	85.5	38.5	21

The average correlation values for each cluster are shown for the two groups to allow determination of directionality in the group comparison. All comparisons are shown at $p < 0.05$, corrected with a voxelwise threshold of 0.005, and a cluster threshold of 20 or more contiguous voxels. ROI = region of interest.

^a 3-mm³ voxels.

Table 6

Six clusters showing significant differences in right amygdala connectivity in bipolar manic/mixed subjects compared to bipolar depressed subjects

ROI correlated with right amygdala	Correlation		Laterality	Center of mass (Talairach coordinates)			Volume ^a
	Manic	Depressed		x	y	z	
Insula	-0.01	0.19	Right	-31.5	7.5	17.5	64
Inferior frontal gyrus	0.11	-0.06	Left	37.5	-22.5	8.5	31
Middle frontal gyrus	-0.06	0.12	Left	37.5	-10.5	59.5	25
Cerebellar tonsil	0.14	-0.03	Right	-28.5	46.5	-24.5	23
Middle frontal gyrus	0.06	-0.10	Right	-37.5	-19.5	38.5	21
Superior frontal gyrus	-0.02	0.16	Right	-16.5	-70.5	2.5	20

The average correlation values for each cluster are shown for the two groups to allow determination of directionality in the group comparison. All comparisons are shown at $p < 0.05$, corrected with a voxelwise threshold of 0.005, and a cluster threshold of 20 or more contiguous voxels. ROI = region of interest.

^a 3-mm³ voxels.