ARCHIVAL REPORT

Frontal-Amygdala Connectivity Alterations During Emotion Downregulation in Bipolar I Disorder

Jennifer D. Townsend, Salvatore J. Torrisi, Matthew D. Lieberman, Catherine A. Sugar, Susan Y. Bookheimer, and Lori L. Altshuler

Background: The symptoms of bipolar disorder suggest dysfunction of emotion regulatory networks. In healthy control populations, downregulation of emotional responses activates the ventral lateral prefrontal cortex (vlPFC) and dampens amygdala activation. This study investigated frontal and limbic function and connectivity during emotion downregulation in euthymic subjects with bipolar I disorder (BPI) and healthy control subjects.

Methods: Thirty BPI and 26 control subjects underwent functional magnetic resonance imaging scanning while performing an emotion processing task with passive viewing and emotion downregulation conditions. Contrasts were made for each group comparing the downregulation and passive viewing conditions, and these were entered into a between-group random effects analysis to assess group differences in activation. Psychophysiological interaction analyses were conducted to test for significant group differences in functional connectivity between the amygdala and inhibitory frontal regions (i.e., vlPFC).

Results: Control subjects showed the expected robust bilateral activation of frontal and limbic regions during passive viewing and emotion downregulation tasks. Between-group analyses revealed similar activation of BPI and control subjects during passive viewing but significantly decreased activation in bilateral vlPFC, bilateral anterior and posterior cingulate, medial frontal gyrus, and bilateral dorsal lateral prefrontal cortex during emotion downregulation in subjects with BPI. Connectivity analysis demonstrated that control subjects had significantly greater negative functional connectivity between the left amygdala and bilateral vlPFC compared with subjects with BPI.

Conclusions: This study provides evidence that dysfunction in the neural networks responsible for emotion regulation, including the prefrontal cortex, cingulate, and subcortical structures, are present in BPI subjects, even while euthymic.

Key Words: Amygdala, bipolar disorder, emotion regulation, functional connectivity, functional neuroimaging, vlPFC

Emotion processing involves detection and evaluation of salient stimuli, as well as regulation of affective response to these stimuli (1). Dysregulated emotional responses can lead to pathological mood states (2,3). This is exemplified by bipolar disorder, a mood disorder characterized by symptoms of dysregulated emotional states that include mania and depression. This mood instability suggests possible dysfunction of neural networks involved in emotion regulation. Despite the fact that emotion dysregulation is its defining criteria, neural network connectivity remains understudied in bipolar disorder.

The amygdala, insula, anterior cingulate cortex (ACC), medial prefrontal cortex (mPFC), and ventral lateral prefrontal cortex (vlPFC) are considered key neural substrates of an emotion processing and regulation circuit (1). Neuroimaging studies have demonstrated a role for the amygdala and insula in normal emotion processing and for the medial and lateral regions of the vlPFC in mood regulation (4,5) and associative emotional memory functions (6,7).

From the Department of Psychiatry and Biobehavioral Sciences (JDT, SJT, SYB, LLA), David Geffen School of Medicine at University of California, Los Angeles, and Semel Institute for Neuroscience and Human Behavior, Los Angeles; Department of Psychology (MDL), Jane and Terry Semel Institute of Neuroscience and Human Behavior (CAS), and Department of Biostatistics (CAS), School of Public Health, University of California, Los Angeles; and Department of Psychiatry (LLA), Veterans Affairs Greater Los Angeles Healthcare System, West Los Angeles, California.

Address correspondence to Lori L. Altshuler, M.D., David Geffen School of Medicine at UCLA, Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, 300 UCLA Medical Plaza, Suite 1544, Box 957057, Los Angeles, CA 90095-7057; E-mail: laltshuler@mednet.ucla.edu.

Received Sep 1, 2011; revised Jun 13, 2012; accepted Jun 14, 2012.

Functional neuroimaging studies involving the simple viewing of emotion stimuli in healthy subjects demonstrate reliable amygdala and vlPFC activation (8–10). Functional magnetic resonance imaging (fMRI) studies requiring subjects to modify their emotions by downregulating their normal emotional responses typically show activation of the vlPFC and other frontal regions and reduced amygdala activation (8–11). The vlPFC plays a role in integrating emotional information and regulating the intensity of emotional responses (12,13) and regulating emotion through pathways between itself and autonomic systems governing visceral responses associated with affective stimuli (14). Ventral lateral prefrontal cortex dysfunction may explain the failure to modulate regions underlying affect, such as the amygdala, and may correlate with the mood shifts characteristic of bipolar disorder.

In cognitive reappraisal, one emotion regulation technique, subjects attempt to consciously reframe the context of disturbing emotional stimuli to reduce (downregulate) their emotional effect. In behavioral studies, downregulation of emotion via cognitive reappraisal has been shown to decrease physiological arousal (15–17) and subjective reports of distress (18). Emotion downregulation studies in healthy subjects demonstrate reliable activation in the vlPFC and presupplementary motor area (SMA), and less frequently in the ACC (18–23). These studies demonstrate reduced amygdala activity during cognitive reappraisal, consistent with the putative role of the vlPFC in inhibiting limbic activity. The amygdala has extensive reciprocal connections with the frontal lobe, including direct connections to the medial and vlPFC (24).

Several neuroimaging studies have demonstrated attenuated vlPFC function and ⁄or heightened amygdala activation in manic compared with healthy subjects (25–28). Functional magnetic resonance imaging studies during mania specifically probing emotion processing demonstrate hypoactivation of the vlPFC during processing of negative faces (27), fear perception (29), and negatively captioned pictures (30). Furthermore, hypoactivation of frontal re-

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2012.06.030

gions, including dorsal lateral prefrontal cortex and mPFC, have been reported during mania (29,31). Few network connectivity studies have been performed during mania. Reports of decreased negative connectivity between vlPFC and amygdala (32) and between amygdala and anterior cingulate (33) suggest deficient prefrontal modulation over limbic structures during mania.

Most bipolar disorder neuroimaging studies have evaluated subjects during acute mood states. To date, no studies have investigated emotion downregulation and functional connectivity in subjects with bipolar disorder during euthymia, which could elucidate trait-level dysfunction in key neural circuitry. One recent study demonstrated that euthymic bipolar disorder subjects did not differ in amygdala activation during emotion processing compared with control subjects but had vlPFC hypoactivation during an emotion labeling condition (34). Persistent dysfunction in prefrontal regions involved in emotion regulation during euthymia might contribute to an abnormal inhibitory vlPFC-amygdala network and might contribute to the vulnerability of patients with bipolar disorder to shift into acute mood states. The primary aim of this fMRI study was to assess regional activation and functional connectivity between the amygdala and frontal lobe in healthy control and euthymic bipolar I subjects. We hypothesized that during emotion regulation, euthymic bipolar I disorder subjects would show vlPFC hypoactivation and reduced functional connectivity in the frontolimbic network (specifically vlPFC-amygdala) compared with healthy subjects.

Methods and Materials

The study protocol was approved by the Institutional Review Board at the University of California, Los Angeles (UCLA); each participant gave written consent before initiating the study. Subjects with a DSM-IV diagnosis of bipolar I disorder, currently euthymic, were recruited through the UCLA Outpatient Clinic, local advertising, or other research projects of the UCLA Mood Disorders Research Program. Control subjects were recruited by advertisement. All subjects were interviewed using the Structured Clinical Interview for DSM-IV (35) to confirm a bipolar diagnosis or absence thereof. Subjects with bipolar I disorder were excluded if they met criteria for any other current Axis I disorder. Twenty subjects with bipolar I disorder met criteria for past history of substance abuse or dependency, with a minimum of 3 months free from substance abuse (mean = 4.2 years ± 5.9 years). Control subjects were medication-free and excluded for current or past psychiatric diagnoses. Exclusions for all subjects included left-handedness, hypertension, neurological illness, metal implants, and history of head trauma with loss of consciousness >5 minutes.

Mood symptoms were evaluated on the day of the scan using the Young Mania Rating Scale and the 21-item Hamilton Depression Rating Scale. Bipolar I disorder subjects were eligible if they had been euthymic by self-report and Structured Clinical Interview for DSM-IV for > 1 month before scanning (Young Mania Rating Scale score <7 and Hamilton Depression Rating Scale score <7).

fMRI Procedure

Subjects underwent fMRI scanning on a 3-Tesla Siemens Allegra (Siemens AG, Munich, Germany). Blood oxygen level-dependent contrast was evaluated using a T2-weighted echo planar image gradient-echo pulse sequence (repetition time = 2500 msec, echo time = 35 msec, flip angle = 90°, matrix 64 × 64, field of view = 24 cm, 28 axial slices, in-plane voxel size 3.75 mm × 3.75 mm, slice thickness = 3 mm, 1 mm gap). Echo planar image high-resolution structural images (spin-echo; repetition time = 5000 msec, echo time = 33 msec, matrix 128 × 128; field of view = 24 cm, 28 axial slices, 3 mm thick, 1 mm gap) were obtained co-planar to functional scans.

Activation Task

Subjects performed a validated emotion reactivity and regulation task that required viewing neutral or negative images and either reacting normally or reducing their emotional response through cognitive reappraisal. Images were taken from the International Affective Picture System set (36). Images were chosen (negative: 0–3 and neutral: 4–5) based on a valence rating (0–8 scale with 0 the most negative). Image types (animal, faces, scene), valence (mean = 2.8; analysis of variance [ANOVA]: $F = .10$, $df = 45,2$, $p = .91$), and arousal (mean = 6.5; ANOVA: $F = .17$, $df = 45,2$, $p = .84$) ratings were balanced across blocks.

Subjects passively viewed neutral (observe neutral) or negative (observe negative) images. For these two blocks, subjects were instructed to attend to and naturally experience the emotional state elicited by the images. During the emotion downregulation block (decrease emotion), subjects were instructed to cognitively re-evaluate the image. (Sample instructions: "If you see an image of a snake you might think, 'That snake isn't poisonous—it can't hurt me' "). All subjects were trained to ensure they could perform this cognitive reappraisal in the given time. Finally, to ensure participation and attention, in a final block, subjects selected the word that best described the image using a button box (scene description) (e.g., with an image of a snake, subjects selected between venom and wreck). Images were presented for 4 seconds, with instructions (3 seconds) beginning each block. Each experimentation block (observe negative, decrease negative, and scene description) contained eight images and was repeated twice (35 seconds per block). Experimental blocks were interleaved with control blocks (observe neutral), containing three neutral images (15 seconds per block). Experimental conditions were counter-balanced across subjects.

Behavioral Data Analysis

To assess group differences in response times and accuracy, performance data from the scene description condition were analyzed using a mixed effects analysis of variance model (unconstrained covariance matrix) with diagnosis as a grouping variable and task as a repeated measure. Two subjects (one from each group) were missing behavioral data.

fMRI Analysis

Functional images were examined for severe motion or spike artifacts, and scans with >1.5 mm of motion were excluded. Functional magnetic resonance imaging data were processed using FEAT (FMRI Expert Analysis Tool), part of FSL 4.0 (FMRIB Software Library, www.fmrib.ox.ac.uk/fsl). Preprocessing steps included motion correction, nonbrain removal using Brain Extraction Tool (BET) (37,38), spatial smoothing using a 5 mm Gaussian kernel, grand-mean intensity normalization; and high-pass temporal filtering (Gaussian-weighted least-squares fitting, sigma = 65 seconds). Time-series statistical analysis used FMRIB Improved Linear Model (FILM) with local autocorrelation correction (38). Registration to standard space was performed with a two-step transformation of registering subjects' functional images to their structural image and then to a standard space template.

First, contrasts were made for observe negative versus observe neutral, as this has been shown to robustly activate amygdalae (22). This contrast enables the comparison of simple passive viewing and emotion reactivity between bipolar and control groups. Next, decrease versus observe negative contrasts were created to investigate regions involved in emotion downregulation. This process has

been shown to activate lateral and medial prefrontal cortices and decrease amygdala activation in healthy subjects (20–23). These outputs were entered into second-level analyses, with subject as a random factor, to determine regions that were significantly different between groups (cluster threshold $Z > 2.0$, $p = .05$ corrected).

Region of Interest Analysis

For task validation, region of interest (ROI) analyses were conducted in the bilateral amygdala, using Pick Atlas structural masks (fMRI Laboratory, Wake Forest University School of Medicine, http://www.fmri.wfubmc.edu). We used structural amygdala ROIs to avoid issues of bias inherent with using functionally based ROIs in nonindependent tasks ([39] for review of this issue). The time course from each ROI was extracted and used to calculate the mean percent signal change per subject. We fit a $2 \times 2 \times 2$ repeated measure ANOVA with group (control and bipolar) as the between-subjects factor and condition (observe and decrease) and hemisphere (left and right) as within-subject factors, along with all possible interactions, to investigate patterns of amygdala activation during these conditions.

Psychophysiological Analysis

To assess functional connectivity, we performed a psychophysiological interaction (PPI) analysis (40) with SPM8 (www.fil.ion.ucl.ac.uk/spm) using the preprocessing steps described above. Psychophysiological interaction analyses use regionally specific activation to identify statistical interactions between brain activity and a psychological process (40), reporting differential correlations between regions in one task compared with another. Context-specific changes in functional connectivity are generally interpreted as contributory when the correlation in activity between two regions is either positive or negative (i.e., activity in X suppresses activation in Y). It should be noted that PPI cannot determine the causal direction of connectivity.

Our PPI procedure was adapted from previous studies (32,41–43). Three time series were used: 1) the physiological variable represents the time series activity taken from the seed region (left/right amygdala structural ROIs), with the first principal component adjusted for effects of interest (i.e., despiked and denoised); 2) the psychological regressor represents task condition and is used to determine condition-specific changes in functional connectivity between regions; and 3) the PPI variable is formed by deconvolving the blood oxygen level-dependent physiological time series to represent the interaction at the neuronal level, computing the element by element product of the first two variables and reconvolving this time series to create a regressor for the PPI analysis (44).

To determine which areas reflected this PPI, a general linear model was formed that incorporated these interaction terms. Applying a t contrast of -1 for the PPI regressor and 0 elsewhere produced statistical images revealing voxels having a significant negative regression slope with activity in the left or right amygdalae during emotion downregulation versus passive viewing conditions. Subject-specific PPI statistical images were taken to a second-level random effects analysis to evaluate within-group and between-group differences using one-sample and two-sample t tests, respectively. Given our a priori hypothesis, PPIs between amygdala seed regions and vlPFC were identified (using an uncorrected statistical threshold of $p = .005$ and an extent threshold of $k = 5$). For other regions, we used a more conservative threshold ($p = .005$, $k = 20$).

Results

Subjects

Table 1 provides demographic information. Thirty-six subjects with bipolar I disorder and 32 control subjects met inclusion criteria, while data from 6 subjects in each group were excluded due to excessive motion. Thus, the final analysis included 30 euthymic bipolar disorder and 26 control subjects. There were no significant differences between groups in gender ($\chi^2 = .19$, $p = .66$) or age ($T = .72$, $p = .47$). Nine (30%) bipolar disorder subjects were medication-free when scanned. The rest were on a range of medications to treat bipolar disorder, including anticonvulsants ($n = 14$) (valproic acid, lamotrigine, carbamazepine, or oxcarbazepine), antipsychotics ($n = 13$) (aripiprazole, olanzapine, quetiapine, ziprasidone, or risperidone), or antidepressants ($n = 9$) (bupropion, trazodone, or selective serotonin reuptake inhibitors).

Behavioral Data

Behavioral data analyses revealed no significant differences between bipolar and control groups in accuracy ($T = .63$, $p = .53$) or reaction time ($T = .57$, $p = .57$) during the scene description condition, indicating subjects were attentive during the task.

fMRI Results

Amygdala ROI: Emotion Reactivity Versus Emotion Regulation. Amygdala ROI results showed a significant main effect of condition (ANOVA: $F = 5.77$, $df = 1,54$, $p = .02$), with a significant

Table 1. Demographic Information for Healthy Control and Euthymic Subjects with Bipolar I Disorder

Demographics	Control Subjects	Bipolar I Disorder
n	26	30
Age (Mean ± SD)	35.5 ± 12.4 years	37.9 ± 12.6 years
Gender (M/F)	15/11	19/11
YMRS Score (Mean ± SD)	—	1.7 ± 2.2
HAM-D Score (Mean ± SD)	—	3.8 ± 1.9
Duration of Euthymia (Mean ± SD)	—	15.4 ± 19.9 months
Duration of Illness (Mean ± SD)	—	20.7 ± 13.6 years
Number Prior Manic Episodes (Median)		4
Number Prior Depressive Episodes (Median)		4
Medication	—	
Unmedicated		9
Anticonvulsants		14
Antipsychotics		13
Antidepressants		9

F, female; HAM-D, Hamilton Depression Rating Scale; M, male; YMRS, Young Mania Rating Scale.

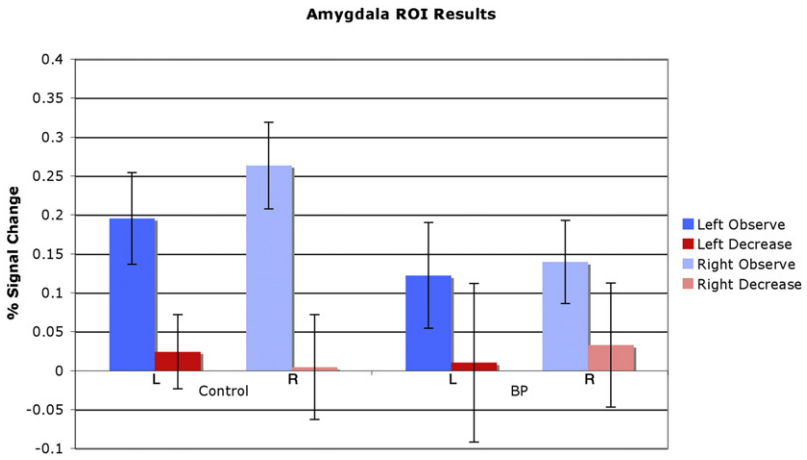

Figure 1. Region of interest (ROI) results show significant decreased activation in left (L) and right (R) amygdala during emotion downregulation (decrease negative compared to observe negative) in control and euthymic subjects with bipolar I disorder. Analysis of variance results show significant main effects of condition ($F = 5.77$, $df = 1,54$, $p = .02$). There were no significant main effects of group ($F = 1.34$, $df = 1,54$, $p = .25$) or hemisphere ($F = .63$, $df = 1,54$, $p = .43$), nor were there any significant interactions (all $p > .44$). BP, bipolar disorder.

decrease in amygdala activation during the decrease versus observe conditions. There were no other significant main effects of either group (ANOVA: $F = 1.34$, $df = 1,54$, $p = .25$) or hemisphere (ANOVA: $F = .63$, $df = 1,54$, $p = .43$), nor were there any significant interactions (all $p > .44$) (Figure 1). In addition, there were no significant correlations between ROI results and any clinical variable.

Emotion Reactivity. In our reactivity contrast (observe negative vs. observe neutral), bipolar disorder and control subjects extensively activated frontolimbic regions, including bilateral vlPFC (Brodmann area [BA] 44/45 and 47), bilateral insula, mPFC, ACC, and bilateral amygdala (Figure 2). There were no significant differences between bipolar disorder and control subjects ($Z > 2.0$, $p = .05$ corrected) in any frontal or limbic regions of interest.

Emotion Downregulation. In the emotion downregulation contrast (decrease negative vs. observe negative), control subjects activated frontolimbic regions reported in previous reappraisal studies, including bilateral vlPFC (BA 44/45 and 47), insula, dorsomedial prefrontal cortex (BA 8), and ACC (BA 32/24). Thus, there was significantly greater activation in the vlPFC during emotion downregulation than during passive viewing. Additional regions of activation included bilateral insula, bilateral superior frontal gyrus (BA 9/10), bilateral pre-SMA, bilateral hippocampal gyrus (BA 28/36), bilateral inferior parietal lobule (BA 40), left middle temporal gyrus (MTG), bilateral superior temporal gyrus, occipital regions (BA 17/18/19), and cerebellum (Figure 3A).

Bipolar disorder subjects also activated frontolimbic regions, including left vlPFC (BA 45/47), dorsomedial prefrontal cortex (BA8), and ACC (BA 32/24). Other regions of significant activation included bilateral insula, bilateral superior frontal gyrus (BA 9/10), left pre-SMA, left MTG (BA 20/21), and left cerebellum (Figure 3B).

Between-group analysis revealed significantly greater activation in control compared with bipolar disorder subjects in the frontal lobe, including bilateral vlPFC (BA 47/44/45), insula, bilateral middle frontal gyrus (BA 46/9), bilateral cingulate (BA 24 and BA 23), and pre-SMA (BA 6). Other regions of greater activation in the control subjects were seen in the right inferior parietal lobule (BA 40), bilateral MTG (BA 18), bilateral lingual gyri, bilateral caudate, and right thalamus (Figure 4, Table 2). There were no areas of significantly greater activation in bipolar versus control subjects. An exploratory analysis of unmedicated bipolar disorder subjects ($n = 9$) showed a similar trend of reduced bilateral vlPFC activation compared with control subjects but did not reach significance as the sample size was small and underpowered.

PPI: Emotion Downregulation. In the within-group analysis, control subjects showed significant negative functional connectivity between left amygdala and left vlPFC (BA 44/45). Control subjects showed significant negative functional connectivity between right amygdala and right vlPFC (BA 44/47), left fusiform gyri (BA 18), and left occipital gyrus (BA 18/19).

Bipolar disorder subjects showed significant negative functional connectivity between left amygdala and right vlPFC (BA 47), as well as significant negative functional connectivity between right amygdala and left vlPFC (BA 44).

Between-group analyses using the left amygdala as a seed region revealed significantly greater negative functional connectivity in control > bipolar disorder in left vlPFC (BA 44/45), left occipital gyrus (BA 19), and right posterior cingulate (BA 23/31) (Figure 5, Table 3). The bipolar disorder > control comparison showed no significantly greater negative connectivity between the left amygdala and any regions. For confirmation, we ran additional connectivity analyses using main effect of task to functionally define amygdala seeds; the main results did not change significantly.

Using the right amygdala as a seed region, there were no regions of significantly greater connectivity between control > bipolar dis-

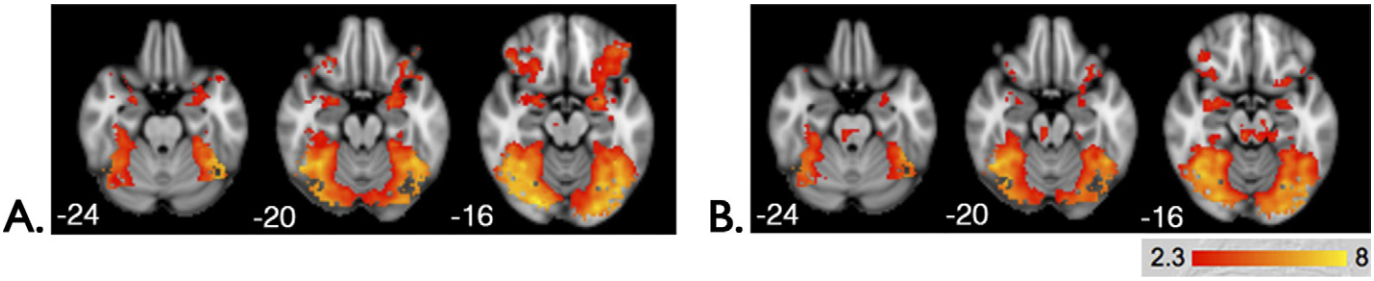

Figure 2. Within-group results during emotion reactivity (observe negative vs. observe neutral) show robust bilateral amygdala activation in both **(A)** control and **(B)** euthymic subjects with bipolar I disorder (left = left).

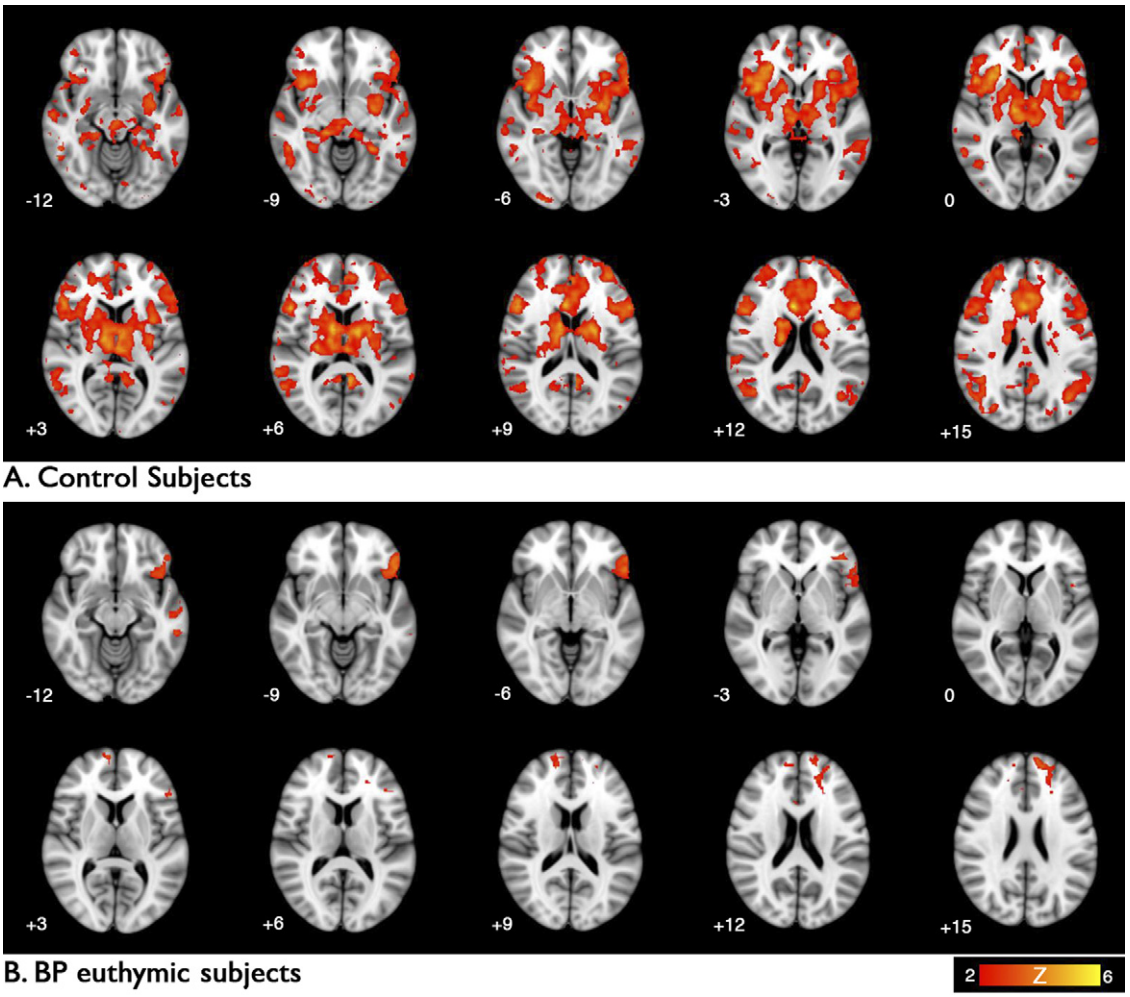

Figure 3. Within-group results show activation in control **(A)** and bipolar I euthymic **(B)** subjects during emotion downregulation (decrease negative vs. observe negative). BP, bipolar disorder.

order. The bipolar disorder > control comparison showed significantly greater negative connectivity between right amygdala and right middle frontal gyrus (BA 9).

Discussion

This is the first functional connectivity study exploring neural network functioning during emotion downregulation in euthymic subjects with bipolar I disorder. During emotion regulation using cognitive reappraisal, which recruits vlPFC, significant group differences emerged. Consistent with our hypothesis, control subjects showed significantly greater engagement of prefrontal structures, including bilateral vlPFC, compared with bipolar disorder subjects. Psychophysiological interaction analysis revealed subjects with bipolar disorder had significantly less negative functional connectivity between left amygdala and bilateral vlPFC during downregulation. These findings support our second hypothesis that during emotion regulation, there are specific neural network frontal-amygdala functional connectivity differences in bipolar disorder.

During passive viewing of emotional images, both groups demonstrated significant bilateral amygdala activation consistent with prior studies (10,45) of control subjects. No differences in frontolimbic functioning were present between euthymic bipolar and control groups during passive viewing, consistent with some (34,46), but not all (47), prior studies. Differences in the type of emotional stimuli used (valence and salience), as well as sample size, may explain some of these inconsistencies. However, tasks requiring simple emotion reactivity (bottom-up processing, as in passive viewing) consistently show greater amygdala activation than tasks requiring emotion regulation (top-down, as in cognitive reappraisal) (10,32,48); we replicate these findings in both groups. Similar amygdala activation between control and bipolar groups suggests no amygdala dysfunction during euthymia, at least with these stimuli, while persistent vlPFC hypoactivation in euthymic subjects may suggest a trait abnormality.

Our results are consistent with prior emotion regulation studies demonstrating healthy control subjects engage frontal regions, including vlPFC and anterior cingulate (32,49,50), significantly more during regulation than passive emotion conditions and downregulate limbic regions via vlPFC activation (10,45). During emotion downregulation, control subjects show increased activation in vlPFC, mPFC, and anterior cingulate (18,51). These regions have extensive anatomical connectivity to the amygdala (13,14,52). Human (53) and nonhuman (54) primate anatomical studies show reciprocal connections between amygdalae and prefrontal cortex (PFC), and neurochemical studies in animals suggest an inhibitory amygdala-PFC connection (55,56). Studies of control subjects re-

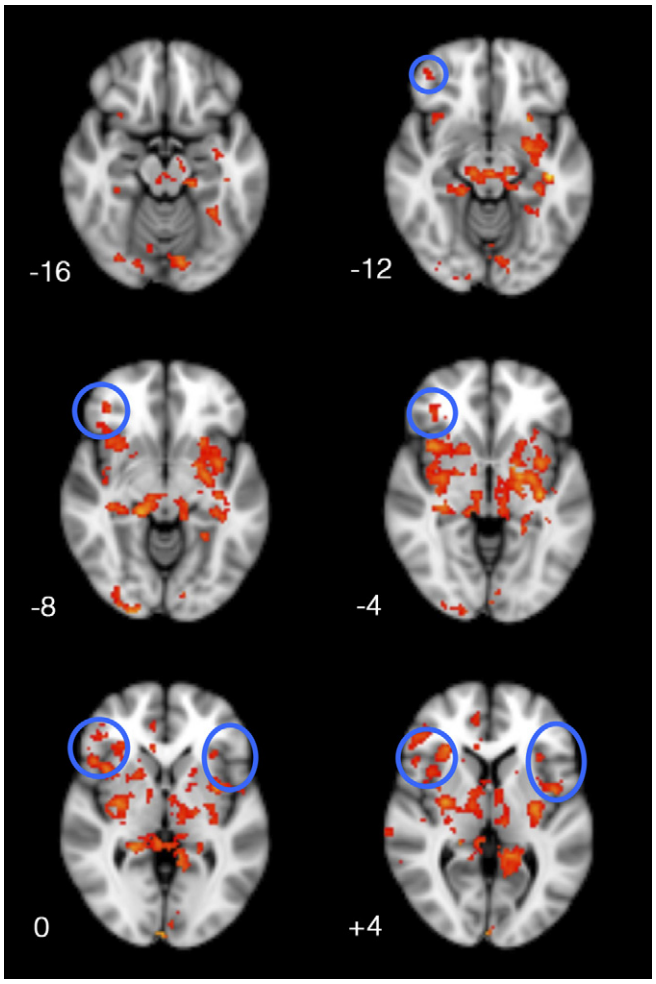

Figure 4. Between-group results show areas of significantly increased activation in control versus euthymic subjects with bipolar I disorder during emotion downregulation (decrease negative vs. observe negative) in the bilateral ventral lateral prefrontal cortex (circled), bilateral insula (circled), striatum, medial prefrontal cortex, and posterior cingulate (left = left).

port significant effective connectivity between amygdala, vlPFC, insula, and anterior cingulate (57) and significant negative functional connectivity between amygdala and frontal regions during emotion regulation (10,32). These latter findings of significant negative connectivity between limbic and frontal regions are consistent with our results of control subjects.

Studies of mania report amygdala hyperactivation (27,58) and bilateral vlPFC hypoactivation (27,29,59). Manic subjects have shown significantly reduced negative functional connectivity between left amygdala and bilateral vlPFC and anterior cingulate (32), suggesting neural network differences of emotion downregulation in bipolar disorder subjects during mania. Such results are consistent with the present study and suggest these connectivity differences persist in euthymia. A recent effective connectivity study of euthymic subjects implicated a dysfunctional ventromedial neural system in automatic emotion regulation (60). While amygdala function may vary as a function of mood state (27,58), vlPFC hypoactivation has been reported in euthymia (29,61,62), mania, and depression (63,64). Lesion studies support the role of vlPFC in emotion regulation, as impairment here is associated with manic and depressive symptoms (65,66). In the present study, vlPFC hypoactivation in bipolar disorder subjects was more prominent in the left hemisphere, perhaps due to the verbal nature of this cognitive reappraisal paradigm. Most emotion studies in euthymia found hypoactivation of bilateral vlPFC or left vlPFC, depending on paradigm specifics (32,62,67). The current functional connectivity results are consistent with another study of bipolar euthymia that reported abnormal frontolimbic connectivity while viewing emotional faces (68). Furthermore, resting state studies support decreased corticolimbic functional connectivity in unmedicated subjects with bipolar disorder (69). A second resting state study found reduced negative functional connectivity specifically in vPFC-amygdala activity between bipolar disorder versus control groups (70). These studies, using bipolar disorder subjects in acute and euthymic mood states, are consistent with the present study's results in bipolar disorder euthymia. Thus, vlPFC hypoactivation may represent a trait neural marker of bipolar disorder that endures across mood states (71).

Neuropsychological studies suggest bipolar disorder patients continue to display mood instability and increased mood reactivity in the absence of an acute episode (72,73). Chronic vlPFC hypoactivation and/or reduced modulatory control of limbic structures may explain these findings. The vlPFC may act as a brake on extreme emotion through its inhibitory connections with limbic structures. It is possible that abnormal PFC function and the resultant frontolimbic circuit alterations may create dysregulation of emotional reactions and increase the vulnerability of patients to lapse into mood episodes ([74] for review).

Although our hypothesis focused on amygdala and vlPFC activation, other areas showed significant group differences. Control subjects showed significantly increased activation in bilateral insula and bilateral anterior cingulate and increased negative connectiv-

Table 2. Between-Group Results Show Areas of Significantly Increased Activation in Healthy Control vs. Euthymic Subjects with Bipolar I Disorder During Emotion Downregulation (Decrease Negative vs. Observe Negative Contrast)

	BA	x	y	z	*Z* Statistic	*k* (Voxels)
Frontal						
Left IFG (vlPFC)	47/45	−32	26	−2	2.15[a]	41
Right IFG (vlPFC)	47/45	38	38	−8	2.77[a]	65
Left MFG	46	−44	38	20	2.06	39
Right MFG	46	50	38	8	3.47	7
Left pre-SMA	6	−48	−6	12	2.52	3
Right pre-SMA	6	26	−18	60	3.05	24
Cingulate						
Anterior	24	−12	8	34	4.46[a]	75
Posterior	23/30	−6	−50	12	4.39	58
Parietal						
Left IPL	40	64	−20	24	3.56[a]	95
	40	44	−36	52	3.14	6
Temporal						
Left MTG	20/21	−40	−24	−12	4.22	19
Right MTG	21	58	−56	10	3.38[a]	4
Occipital						
Left LG	18	−4	−86	−4	2.53[a]	6
Right LG	18	2	−96	2	4.25[a]	13
Subcortical						
Left caudate		−22	10	26	2.62	3
Right caudate		10	14	8	2.58	9
Right thalamus		10	−4	12	4.42	148

BA, Brodmann area; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; LG, lingual gyrus; MFG, middle frontal gyrus; MTG, middle temporal gyrus; SMA, supplementary motor area; vlPFC, ventral lateral prefrontal cortex.
[a]Indicates more than one local maxima within a 10 mm radius.

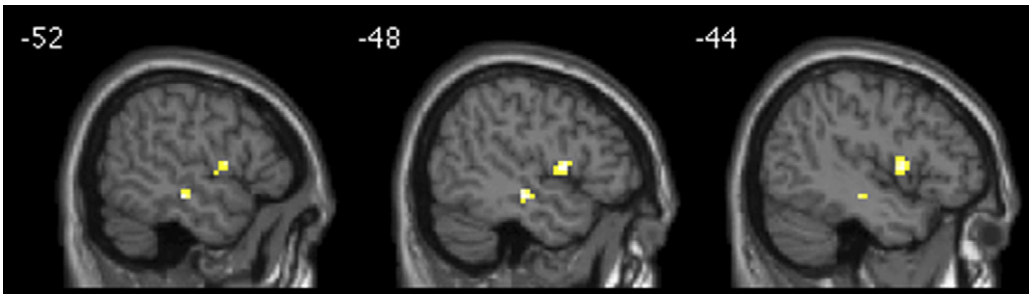

Figure 5. Psychophysiological interaction between-group results reveal significantly greater negative functional connectivity between the left amygdala and left ventral lateral prefrontal cortex in control compared with euthymic subjects with bipolar I disorder during emotion downregulation (decrease negative vs. observe negative).

ity between left amygdala and posterior cingulate compared with bipolar disorder subjects. The anterior insula is part of the salience-emotion network (75) and is integral in introspection (76). Extensive reciprocal connections exist between the insula and amygdala (77), and decreased amygdala-insula connectivity in bipolar euthymia suggests another emotion network difference that may contribute to the presentation of bipolar disorder. The ACC, particularly the rostral portion that shows hypoactivation in bipolar disorder subjects during downregulation, is also part of the emotional salience network and has extensive frontal and limbic connections (78). The posterior cingulate is important for internal awareness, processing spontaneous thought, and is part of the default mode network (79), engaged in the absence of task-specific challenges and suppressed during task demands (80). In primates, the posterior cingulate receives direct efferent connections from the amygdala (81). The amygdala and posterior cingulate may be part of two functionally distinct networks that are on and off at different times (i.e., have significant anticorrelations) (82). The decreased negative (or equivalently, increased positive) connectivity between these regions in bipolar disorder suggests less functional segregation between networks, findings reported in other psychiatric populations (83,84). We are currently conducting studies investigating these networks in bipolar disorder.

While this is the first study of emotion regulation in euthymic subjects with bipolar I disorder and has the largest sample size of a functional connectivity study in this population, this study has several limitations. First, while ~30% bipolar disorder subjects were unmedicated, this sample remained underpowered to provide meaningful subanalyses into medication effects on frontolimbic functioning. However, an exploratory analysis suggested similar patterns of vlPFC hypoactivation in unmedicated and medicated subjects. Also, as bipolar and control groups showed similar activation of many structures (e.g., amygdala) during passive emotion reactivity, it is doubtful that medication per se caused selective vlPFC hypoactivation during emotion regulation in the bipolar group. A review study (85) found medication either had no significant or ameliorative effects on abnormal functional neuroimaging results, suggesting medication alone likely does not explain the current findings. Second, this study utilized a paradigm previously used in healthy control subjects but not used in subjects with bipolar disorder. As such, these results require replication. Future studies may determine whether amygdala differences emerge between bipolar and control subjects as demands for emotion regulation increase beyond the relatively simple condition used in this study. Finally, as subjective ratings were not collected at the time of scanning, we were unable to make direct conclusions regarding neural responses and subjective affective experiences. However, we spent considerable time training subjects to complete cognitive reappraisal of images during the time frame. Future studies that collect subjective and physiological measures simultaneously during fMRI can provide a more complete picture of the success of emotion regulation strategies used in bipolar disorder and control subjects.

This study provides evidence of decreased vlPFC activation, decreased vlPFC-amygdala connectivity, and amygdala-posterior cingulate abnormalities during emotion downregulation in bipolar I disorder. Ventral lateral prefrontal cortex hypoactivation in bipolar I disorder is consistent with several studies in this population and suggests that these abnormalities persist in the absence of acute mood episodes. Reduced frontolimbic connectivity in euthymia may underlie the decreased ability of bipolar disorder subjects to regulate emotions and the proclivity to relapse into acute mood states. Ventral lateral prefrontal cortex inhibitory inputs to the amygdalae may be abnormal in bipolar disorder due to local alterations (e.g., neuronal) and/or disrupted connections (e.g., white matter tracts) between regions. Follow-up studies tracking subjects longitudinally across mood states may help determine whether the degree of vlPFC hypoactivation and decreased frontolimbic connectivity can help predict future mood episodes.

Table 3. Between-Group Psychophysiological Interaction Results Show Significantly Greater Negative Functional Connectivity between the Left Amygdala and Left vlPFC in Healthy Control vs. Euthymic Subjects with Bipolar I Disorder During Emotion Downregulation (Decrease Negative vs. Observe Negative)

	BA	x	y	z	*Z* Statistic	*k* (Voxels)
Frontal						
Left vlPFC	44/45	−48	2	5	3.72	29
Right vlPFC	47	27	35	−1	3.05	6
Cingulate						
Posterior	23/31	21	−67	14	3.88[a]	51
Occipital						
Left MOG	19	−18	−67	17	3.48	23

BA, Brodmann area; MOG, middle occipital gyrus; vlPFC, ventral lateral prefrontal cortex.

[a]More than one local maxima within a 10 mm radius.

For financial support of this study, we gratefully acknowledge the Furlotti Family Foundation, the Swift Family Foundation, and the following two components of the National Institutes of Health: the National Institute of Mental Health (R01 MH084955 [LLA], K24 MH001848 [LLA], R21 MH075944 [LLA]) and the National Center for Research Resources (RR012169, RR013642, and RR00865). Contents of this report are solely the responsibility of the authors and do not necessarily rep-

resent the official views of any sponsoring organization. For generous support, we also thank the Brain Mapping Medical Research Organization, Brain Mapping Support Foundation, Pierson-Lovelace Foundation, The Ahmanson Foundation, William M. and Linda R. Dietel Philanthropic Fund at the Northern Piedmont Community Foundation, Tamkin Foundation, Jennifer Jones-Simon Foundation, Capital Group Companies Charitable Foundation, Robson Family, and Northstar Fund. The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. Dr. Altshuler, Dr. Bookheimer, Dr. Lieberman, Mr. Torrisi, Dr. Sugar, and Ms. Townsend had full access to all study data and take responsibility for its integrity and the accuracy of data analysis.

Dr. Altshuler has received past (and potential future) funding from Abbott Laboratories (research support and consulting honoraria); Forest Laboratories (consulting and speakers bureau honoraria); Glaxo-SmithKline (speakers bureau honoraria); and no past, but potential future honoraria from Astra-Zeneca (speakers bureau) and Merck and Co. (consulting). Ms. Townsend, Mr. Torrisi, Dr. Lieberman, Dr. Sugar, and Dr. Bookheimer report no biomedical financial interests or potential conflicts of interest.

1. Phillips ML, Drevets WC, Rauch SL, Lane R (2003): Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biol Psychiatry* 54:504–514.
2. Phillips ML, Drevets WC, Rauch SL, Lane R (2003): Neurobiology of emotion perception II: Implications for major psychiatric disorders. *Biol Psychiatry* 54:515–528.
3. Critchley H (2003): Emotion and its disorders. *Br Med Bull* 65:35–47.
4. Baker SC, Frith CD, Dolan RJ (1997): The interaction between mood and cognitive function studied with PET. *Psychol Med* 27:565–578.
5. Northoff G, Richter A, Gessner M, Schlagenhauf F, Fell J, Baumgart F, *et al.* (2000): Functional dissociation between medial and lateral prefrontal cortical spatiotemporal activation in negative and positive emotions: A combined fMRI/MEG study. *Cereb Cortex* 10:93–107.
6. Price JL (2003): Comparative aspects of amygdala connectivity. *Ann N Y Acad Sci* 985:50–58.
7. Bookheimer S (2002): Functional MRI of language: New approaches to understanding the cortical organization of semantic processing. *Annu Rev Neurosci* 25:151–188.
8. Adolphs R (2008): Fear, faces, and the human amygdala. *Curr Opin Neurobiol* 18:166–172.
9. Breiter HC, Etcoff NL, Whalen PJ, Kennedy WA, Rauch SL, Buckner RL, *et al.* (1996): Response and habituation of the human amygdala during visual processing of facial expression. *Neuron* 17:875–887.
10. Hariri AR, Bookheimer SY, Mazziotta JC (2000): Modulating emotional responses: Effects of a neocortical network on the limbic system. *Neuroreport* 11:43–48.
11. Lieberman MD, Eisenberger NI, Crockett MJ, Tom SM, Pfeifer JH, Way BM (2007): Putting feelings into words: Affect labeling disrupts amygdala activity in response to affective stimuli. *Psychol Sci* 18:421–428.
12. Cabeza R, Nyberg L (2000): Imaging cognition II: An empirical review of 275 PET and fMRI studies. *J Cogn Neurosci* 12:1–47.
13. Fuster JM (2001): The prefrontal cortex–an update: Time is of the essence. *Neuron* 30:319–333.
14. Morris JS, Dolan RJ (2004): Dissociable amygdala and orbitofrontal responses during reversal fear conditioning. *Neuroimage* 22:372–380.
15. Gross JJ (2002): Emotion regulation: Affective, cognitive, and social consequences. *Psychophysiology* 39:281–291.
16. Jackson DC, Malmstadt JR, Larson CL, Davidson RJ (2000): Suppression and enhancement of emotional responses to unpleasant pictures. *Psychophysiology* 37:515–522.
17. Driscoll D, Tranel D, Anderson SW (2009): The effects of voluntary regulation of positive and negative emotion on psychophysiological responsiveness. *Int J Psychophysiol* 72:61–66.
18. Ochsner KN, Bunge SA, Gross JJ, Gabrieli JD (2002): Rethinking feelings: An fMRI study of the cognitive regulation of emotion. *J Cogn Neurosci* 14:1215–1229.
19. Levesque J, Eugene F, Joanette Y, Paquette V, Mensour B, Beaudoin G, *et al.* (2003): Neural circuitry underlying voluntary suppression of sadness. *Biol Psychiatry* 53:502–510.
20. Phan KL, Fitzgerald DA, Nathan PJ, Moore GJ, Uhde TW, Tancer ME (2005): Neural substrates for voluntary suppression of negative affect: A functional magnetic resonance imaging study. *Biol Psychiatry* 57:210–219.
21. McRae K, Hughes B, Chopra S, Gabrieli JD, Gross JJ, Ochsner KN (2010): The neural bases of distraction and reappraisal. *J Cogn Neurosci* 22:248–262.
22. Koenigsberg HW, Fan J, Ochsner KN, Liu X, Guise K, Pizzarello S, *et al.* (2010): Neural correlates of using distancing to regulate emotional responses to social situations. *Neuropsychologia* 48:1813–1822.
23. Kanske P, Heissler J, Schonfelder S, Bongers A, Wessa M (2011): How to regulate emotion? Neural networks for reappraisal and distraction. *Cereb Cortex* 21:1379–1388.
24. Van Hoesen GW, Pandya DN, Butters N (1972): Cortical afferents to the entorhinal cortex of the Rhesus monkey. *Science* 175:1471–1473.
25. Chen CH, Lennox B, Jacob R, Calder A, Lupson V, Bisbrown-Chippendale R, *et al.* (2006): Explicit and implicit facial affect recognition in manic and depressed states of bipolar disorder: A functional magnetic resonance imaging study. *Biol Psychiatry* 59:31–39.
26. Elliott R, Ogilvie A, Rubinsztein JS, Calderon G, Dolan RJ, Sahakian BJ (2004): Abnormal ventral frontal response during performance of an affective go/no go task in patients with mania. *Biol Psychiatry* 55:1163–1170.
27. Altshuler L, Bookheimer S, Proenza MA, Townsend J, Sabb F, Firestine A, *et al.* (2005): Increased amygdala activation during mania: A functional magnetic resonance imaging study. *Am J Psychiatry* 162:1211–1213.
28. Rubinsztein JS, Fletcher PC, Rogers RD, Ho LW, Aigbirhio FI, Paykel ES, *et al.* (2001): Decision-making in mania: A PET study. *Brain* 124:2550–2563.
29. Killgore WD, Gruber SA, Yurgelun-Todd DA (2008): Abnormal corticostriatal activity during fear perception in bipolar disorder. *Neuroreport* 19:1523–1527.
30. Malhi GS, Lagopoulos J, Ward PB, Kumari V, Mitchell PB, Parker GB, *et al.* (2004): Cognitive generation of affect in bipolar depression: An fMRI study. *Eur J Neurosci* 19:741–754.
31. Yurgelun-Todd DA, Gruber SA, Kanayama G, Killgore WD, Baird AA, Young AD (2000): fMRI during affect discrimination in bipolar affective disorder. *Bipolar Disord* 2:237–248.
32. Foland LC, Altshuler LL, Bookheimer SY, Eisenberger N, Townsend J, Thompson PM (2008): Evidence for deficient modulation of amygdala response by prefrontal cortex in bipolar mania. *Psychiatry Res* 162:27–37.
33. Wang F, Kalmar JH, He Y, Jackowski M, Chepenik LG, Edmiston EE, *et al.* (2009): Functional and structural connectivity between the perigenual anterior cingulate and amygdala in bipolar disorder. *Biol Psychiatry* 66:516–521.
34. Foland-Ross LC, Bookheimer SY, Lieberman MD, Sugar CA, Townsend JD, Fischer J, *et al.* (2012): Normal amygdala activation but deficient ventrolateral prefrontal activation in adults with bipolar disorder during euthymia. *Neuroimage* 59:738–744.
35. First MB SR, Gibbon M, Williams JBW (2002): *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. (SCID-I/P)*. New York: Biometrics Research, New York State Psychiatric Institute.
36. Lang PJ BM, Cuthbert BN (1997): *International Affective Picture System (IAPS): Technical Manual and Affective Ratings*. Gainesville, FL: The Center for Research in Psychophysiology, University of Florida.
37. Smith SM (2002): Fast robust automated brain extraction. *Hum Brain Mapp* 17:143–155.
38. Woolrich MW, Ripley BD, Brady M, Smith SM (2001): Temporal autocorrelation in univariate linear modeling of fMRI data. *Neuroimage* 14:1370–1386.
39. Kriegeskorte N, Simmons WK, Bellgowan PS, Baker CI (2009): Circular analysis in systems neuroscience: The dangers of double dipping. *Nat Neurosci* 12:535–540.
40. Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ (1997): Psychophysiological and modulatory interactions in neuroimaging. *Neuroimage* 6:218–229.
41. Williams LM, Das P, Liddell BJ, Kemp AH, Rennie CJ, Gordon E (2006): Mode of functional connectivity in amygdala pathways dissociates level of awareness for signals of fear. *J Neurosci* 26:9264–9271.

42. Egner T, Hirsch J (2005): The neural correlates and functional integration of cognitive control in a Stroop task. *Neuroimage* 24:539–547.
43. Stephan KE, Marshall JC, Friston KJ, Rowe JB, Ritzl A, Zilles K, Fink GR (2003): Lateralized cognitive processes and lateralized task control in the human brain. *Science* 301:384–386.
44. Gitelman DR, Penny WD, Ashburner J, Friston KJ (2003): Modeling regional and psychophysiologic interactions in fMRI: The importance of hemodynamic deconvolution. *Neuroimage* 19:200–207.
45. Ochsner KN, Ray RR, Hughes B, McRae K, Cooper JC, Weber J, *et al.* (2009): Bottom-up and top-down processes in emotion generation: Common and distinct neural mechanisms. *Psychol Sci* 20:1322–1331.
46. Hassel S, Almeida JR, Frank E, Versace A, Nau SA, Klein CR, *et al.* (2009): Prefrontal cortical and striatal activity to happy and fear faces in bipolar disorder is associated with comorbid substance abuse and eating disorder. *J Affect Disord* 118:19–27.
47. Chen CH, Suckling J, Ooi C, Jacob R, Lupson V, Bullmore ET, Lennox BR (2010): A longitudinal fMRI study of the manic and euthymic states of bipolar disorder. *Bipolar Disord* 12:344–347.
48. Hariri AR, Tessitore A, Mattay VS, Fera F, Weinberger DR (2002): The amygdala response to emotional stimuli: A comparison of faces and scenes. *Neuroimage* 17:317–323.
49. Ochsner KN, Gross JJ (2005): The cognitive control of emotion. *Trends Cogn Sci* 9:242–249.
50. Goldin PR, McRae K, Ramel W, Gross JJ (2008): The neural bases of emotion regulation: Reappraisal and suppression of negative emotion. *Biol Psychiatry* 63:577–586.
51. Schaefer SM, Jackson DC, Davidson RJ, Aguirre GK, Kimberg DY, Thompson-Schill SL (2002): Modulation of amygdalar activity by the conscious regulation of negative emotion. *J Cogn Neurosci* 14:913–921.
52. Price JL, Carmichael ST, Drevets WC (1996): Networks related to the orbital and medial prefrontal cortex; a substrate for emotional behavior? *Prog Brain Res* 107:523–536.
53. Ben-Ari Y (1981): *The Amygdaloid Complex: Proceedings of the International Symposium on the Amygdaloid Complex Held in the Château de Fillerval, Senlis (France), 1–4 September, 1981*. Amsterdam; New York: Elsevier/North-Holland Biomedical Press.
54. Roberts AC, Tomic DL, Parkinson CH, Roeling TA, Cutter DJ, Robbins TW, Everitt BJ (2007): Forebrain connectivity of the prefrontal cortex in the marmoset monkey (Callithrix jacchus): An anterograde and retrograde tract-tracing study. *J Comp Neurol* 502:86–112.
55. Cunningham MG, Bhattacharyya S, Benes FM (2002): Amygdalo-cortical sprouting continues into early adulthood: Implications for the development of normal and abnormal function during adolescence. *J Comp Neurol* 453:116–130.
56. Perez-Jaranay JM, Vives F (1991): Electrophysiological study of the response of medial prefrontal cortex neurons to stimulation of the basolateral nucleus of the amygdala in the rat. *Brain Res* 564:97–101.
57. Stein JL, Wiedholz LM, Bassett DS, Weinberger DR, Zink CF, Mattay VS, Meyer-Lindenberg A (2007): A validated network of effective amygdala connectivity. *Neuroimage* 36:736–745.
58. Bermpohl F, Dalanay U, Kahnt T, Sajonz B, Heimann H, Ricken R, *et al.* (2009): A preliminary study of increased amygdala activation to positive affective stimuli in mania. *Bipolar Disord* 11:70–75.
59. Blumberg HP, Leung HC, Skudlarski P, Lacadie CM, Fredericks CA, Harris BC, *et al.* (2003): A functional magnetic resonance imaging study of bipolar disorder: State- and trait-related dysfunction in ventral prefrontal cortices. *Arch Gen Psychiatry* 60:601–609.
60. Almeida JR, Mechelli A, Hassel S, Versace A, Kupfer DJ, Phillips ML (2009): Abnormally increased effective connectivity between parahippocampal gyrus and ventromedial prefrontal regions during emotion labeling in bipolar disorder. *Psychiatry Res* 174:195–201.
61. Kruger S, Seminowicz D, Goldapple K, Kennedy SH, Mayberg HS (2003): State and trait influences on mood regulation in bipolar disorder: Blood flow differences with an acute mood challenge. *Biol Psychiatry* 54:1274–1283.
62. Malhi GS, Lagopoulos J, Sachdev PS, Ivanovski B, Shnier R (2005): An emotional Stroop functional MRI study of euthymic bipolar disorder. *Bipolar Disord* 7(suppl 5):58–69.
63. Altshuler L, Bookheimer SY, Townsend J, Proenza MA, Eisenberger N, Sabb F, *et al.* (2005): Blunted activation in orbitofrontal cortex during mania: A functional magnetic resonance imaging study. *Biol Psychiatry* 58:763–769.
64. Altshuler L, Bookheimer S, Townsend J, Proenza MA, Sabb F, Mintz J, Cohen MS (2008): Regional brain changes in bipolar I depression: A functional magnetic resonance imaging study. *Bipolar Disord* 10: 708–717.
65. Angrilli A, Palomba D, Cantagallo A, Maietti A, Stegagno L (1999): Emotional impairment after right orbitofrontal lesion in a patient without cognitive deficits. *Neuroreport* 10:1741–1746.
66. Grafman J, Vance SC, Weingartner H, Salazar AM, Amin D (1986): The effects of lateralized frontal lesions on mood regulation. *Brain* 109: 1127–1148.
67. Van der Schot A, Kahn R, Ramsey N, Nolen W, Vink M (2010): Trait and state dependent functional impairments in bipolar disorder. *Psychiatry Res* 184:135–142.
68. Versace A, Thompson WK, Zhou D, Almeida JR, Hassel S, Klein CR, *et al.* (2010): Abnormal left and right amygdala-orbitofrontal cortical functional connectivity to emotional faces: State versus trait vulnerability markers of depression in bipolar disorder. *Biol Psychiatry* 67:422–431.
69. Anand A, Li Y, Wang Y, Lowe MJ, Dzemidzic M (2009): Resting state corticolimbic connectivity abnormalities in unmedicated bipolar disorder and unipolar depression. *Psychiatry Res* 171:189–198.
70. Chepenik LG, Raffo M, Hampson M, Lacadie C, Wang F, Jones MM, *et al.* (2010): Functional connectivity between ventral prefrontal cortex and amygdala at low frequency in the resting state in bipolar disorder. *Psychiatry Res* 182:207–210.
71. Chen CH, Suckling J, Lennox BR, Ooi C, Bullmore ET (2011): A quantitative meta-analysis of fMRI studies in bipolar disorder. *Bipolar Disord* 13:1–15.
72. Judd LL, Akiskal HS, Schettler PJ, Endicott J, Leon AC, Solomon DA, *et al.* (2005): Psychosocial disability in the course of bipolar I and II disorders: A prospective, comparative, longitudinal study. *Arch Gen Psychiatry* 62: 1322–1330.
73. Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, *et al.* (2002): The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry* 59:530–537.
74. Altman S, Haeri S, Cohen LJ, Ten A, Barron E, Galynker II, Duhamel KN (2006): Predictors of relapse in bipolar disorder: A review. *J Psychiatr Pract* 12:269–282.
75. Cauda F, D'Agata F, Sacco K, Duca S, Geminiani G, Vercelli A (2011): Functional connectivity of the insula in the resting brain. *Neuroimage* 55:8–23.
76. Craig AD (2009): How do you feel–now? The anterior insula and human awareness. *Nat Rev Neurosci* 10:5970.
77. Augustine JR (1996): Circuitry and functional aspects of the insular lobe in primates including humans. *Brain Res Brain Res Rev* 22:229–244.
78. Bush G, Luu P, Posner MI (2000): Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci* 4:215–222.
79. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001): A default mode of brain function. *Proc Natl Acad Sci U S A* 98:676–682.
80. Greicius MD, Krasnow B, Reiss AL, Menon V (2003): Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *Proc Natl Acad Sci U S A* 100:253–258.
81. Buckwalter JA, Schumann CM, Van Hoesen GW (2008): Evidence for direct projections from the basal nucleus of the amygdala to retrosplenial cortex in the Macaque monkey. *Exp Brain Res* 186:47–57.
82. Tomasi D, Volkow ND (2011): Association between functional connectivity hubs and brain networks. *Cereb Cortex* 21:2003–2013.
83. Veer IM, Beckmann CF, van Tol MJ, Ferrarini L, Milles J, Veltman DJ, *et al.* (2010): Whole brain resting-state analysis reveals decreased functional connectivity in major depression. *Front Syst Neurosci* 4:41.
84. Johnstone T, van Reekum CM, Urry HL, Kalin NH, Davidson RJ (2007): Failure to regulate: Counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. *J Neurosci* 27:8877–8884.
85. Phillips ML, Travis MJ, Fagiolini A, Kupfer DJ (2008): Medication effects in neuroimaging studies of bipolar disorder. *Am J Psychiatry* 165:313–320.