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fMRI brain activation in bipolar mania: Evidence for disruption of the ventrolateral prefrontal-amygdala emotional pathway

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Abstract

Background—Bipolar I disorder is defined by the occurrence of mania. The presence of mania, coupled with a course of illness characterized by waxing and waning of affective symptoms, suggests that bipolar disorder arises from dysfunction of neural systems that maintain emotional arousal and homeostasis. We used functional magnetic resonance imaging (fMRI) to study manic bipolar subjects as they performed a cognitive task designed to examine the ventrolateral prefrontal emotional arousal network.

Methods—We used fMRI to study regional brain activation in 40 DSM-IV manic bipolar I patients and 36 healthy subjects while they performed a continuous performance task with emotional and neutral distracters. Event-related region-of-interest analyses were performed to test the primary hypothesis. Voxelwise analyses were also completed.

Results—Compared with healthy subjects, the manic subjects exhibited blunted activation to emotional and neutral images, but not targets, across most of the predefined regions of interest. Several additional brain regions identified in the voxelwise analysis also exhibited similar differences between groups, including right parahippocampus, right lingual gyrus, and medial thalamus. In addition to these primary findings, the manic subjects also exhibited increased activation in response to targets in number of brain regions that were primarily associated with managing affective stimuli. Group differences did not appear to be secondary to medication exposure or other confounds.

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Conclusions—Bipolar manic subjects exhibit blunted brain fMRI response to emotional cues throughout the ventrolateral prefrontal emotional arousal network. Disruption of this emotional network may contribute to the mood dysregulation of bipolar disorder.

Keywords

Bipolar disorder; mania; fMRI; emotional processing; amygdala; prefrontal cortex Running title: CPT-END in mania

Bipolar disorder is defined by the occurrence of mania, a syndrome characterized by affective lability, neurovegetative disturbances, and cognitive impairments. The features of mania, coupled with a course of illness in which affective symptoms wax and wane among emotional extremes, suggest that bipolar disorder results from dysfunction of brain systems that maintain emotional arousal and homeostasis (1,2). Recent imaging studies support this suggestion by identifying dysfunction within anterior limbic brain networks, namely ventral prefrontal-striatal-thalamic iterative circuits that modulate amygdala and other limbic structures (1–17).

Providing context for these findings, investigators have postulated two parallel networks in which emotional stimuli processed by amygdala are modulated by ventral prefrontal cortex (18–21). The first of these networks involves connections between amygdala and medial ventral prefrontal cortex (BA11) along with rostral insula and subgenual anterior cingulate (BA 25). The second pathway involves connections between amygdala and inferotemporal regions with lateral ventral prefrontal cortex (BA10/47) and rostral anterior cingulate (BA24/32). Although the specific roles of these networks are not completely understood, several lines of evidence suggest that the ventrolateral prefrontal network modulates processing of external emotional cues, whereas the medial network is involved with processing internally referenced emotional states (21).

Yamasaki and colleagues (21,22) developed the continuous performance task with emotional and neutral distracters (CPT-END) in order to discriminate between ventral (emotional) and dorsal (cognitive) neural processing streams during human fMRI studies. In particular, emotional distracters in this task activated the ventrolateral prefrontal network, consistent with the hypothesis that this pathway responds to external emotional stimuli. Consequently, the CPT-END represents a useful cognitive probe to study this network in bipolar disorder. Although previous fMRI studies in bipolar disorder have used either cognitive or emotional tasks, few have employed tasks like the CPT-END that specifically measure emotion regulation processes (15,23,24). These studies each observed abnormalities in ventral-limbic brain areas consistent with dysregulation of emotional processing, although were generally limited by small subject numbers. Wessa et al (15), in euthymic bipolar patients, and Elliott et al (24), in manic subjects, observed increased ventral prefrontal activation during the emotional processing component of an emotional go/no-go task compared with healthy subjects. In contrast, Malhi et al (23) observed the converse in euthymic patients. Consequently, additional studies in bipolar subjects using integrated emotional processing tasks with larger numbers of subjects are warranted (25).

With these considerations in mind, we acquired brain fMRI in bipolar manic and healthy subjects while they performed the CPT-END. We predicted that bipolar subjects would exhibit abnormal activation within the ventrolateral prefrontal-amygdala emotional pathway, including decreased ventrolateral prefrontal activation consistent with prior studies and a model of decreased prefrontal modulation of limbic brain in mania (3,10–14). To test this prediction, we performed a region of interest (ROI) analysis based on this pathway. Additionally, we completed a voxelwise analysis of the brain in order to provide context for

ROI results and to identify other brain areas that may be dysfunctional in mania. Bipolar subjects were studied during mania because it is the defining syndrome of bipolar disorder.

METHODS

Subjects

Subjects with bipolar disorder (N=59) were recruited during a manic or mixed episode from inpatient units at the University of Cincinnati Academic Health Center and Cincinnati Children's Hospital Medical Center (CCHMC). Bipolar subjects met DSM-IV criteria for bipolar I disorder, manic or mixed with a Young Mania Rating Scale (YMRS) score ≥ 20 (26). Demographically matched healthy subjects (N=38) were recruited from the communities served by these hospitals. Healthy subjects had no history of mood or psychotic disorders in themselves or first-degree relatives. All subjects were 16 to 50 years old, were physically and neurologically healthy, and if female, had a negative urine pregnancy test. Potential subjects were excluded by substance dependence within the previous three months, medical or neurological illnesses that might influence brain function, contraindications to receiving an MRI, or an IQ <80 .

Diagnoses were established in bipolar and healthy subjects using the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient version (SCID-I/P) (27) or the WASH-U KDSADS (28) for subjects under 18. Substance use disorders were also assessed with these interviews. Affective symptoms were rated using the YMRS (26) and Montgomery-Asberg Depression Rating Scale (MADRS) (29). Additionally, general measures of premorbid intellectual function (IQ) were obtained using the American Modification of the National Adult Reading Test (ANART) (30) or the Wechsler Abbreviated Scale of Intelligence (WASI) (31). 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 (32).

One healthy and nine bipolar subjects were excluded from analysis because they did not complete scanning (N=6), moved excessively (N=3), or no longer met entry criteria on the day of the scan (N=1). One healthy and ten bipolar subjects were excluded because they correctly responded to less than 40% of targets in the CPT-END, suggesting that they did not understand or could not perform the task. Consequently, 40 bipolar and 36 healthy subjects were analyzed for this report. The 19 excluded bipolar subjects were compared to the remaining 40 bipolar subjects. These subgroups did not significantly differ in age ($p=.45$), sex ($p=.36$), ethnicity ($p=.75$), IQ ($p=.33$), education ($p=.70$), YMRS scores ($p=.34$), MADRS scores ($p=.50$), rates of mixed states ($p=.73$), or rates of lifetime alcohol ($p=.25$) or drug use disorders ($p=.85$).

Thirty-one (78%) of the 40 bipolar subjects were taking medications at the time of the scan, although had been typically non-adherent prior to hospitalization and had often only received a few prescribed doses prior to imaging. Of these, 23 (58%) were taking atypical antipsychotics, 11 (28%) were taking anticonvulsants, and seven (18%) were taking lithium. No medications were discontinued for this study. After study procedures were explained all subjects provided written informed consent or written assent with parental consent for minors. The study was approved by the Institutional Review Boards of the University of Cincinnati and the CCHMC.

CPT-END task

During the fMRI scan, subjects performed the Continuous Performance Task with Emotional and Neutral Distracters (CPT-END) (21). The CPT-END is a visual oddball paradigm. Seventy percent of the cues are simple colored squares, 10% are simple colored

circles, 10% are emotionally neutral pictures, and 10% are emotionally unpleasant pictures. The neutral and emotional (unpleasant) pictures were taken from the International Affective Picture System (IAPS; University of Florida) based upon the rating criteria used by Yamasaki et al (21). Only emotionally negative and neutral images were included to be consistent with the original validated task (21). 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). Each imaging session consisted of two runs of 158 visual cues per run presented at three-second intervals for two seconds each. Emotional and neutral pictures were presented pseudorandomly. A fixation cross was presented for one second between cues.

Image acquisition—Subjects were scanned 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). Visual stimuli were presented using high-resolution video goggles (Resonance Technologies, Inc., Northridge, CA). To provide anatomical localization, a high-resolution, T1-weighted, 3-D brain scan was obtained (33). A midsagittal localizer scan was acquired to place 30 contiguous 5-mm axial slices to encompass the entire brain. Next, a multi-echo reference scan was obtained to correct for ghost and geometric distortions (34). Subjects then completed two fMRI scans in which whole-brain images (volumes) were acquired every three seconds using a T2*-weighted gradient-echo echoplanar imaging (EPI) pulse sequence (TR/TE=3000/29 ms, FOV=20.8 x 20.8 cm, matrix 64 x 64 pixels, slice-thickness=5 mm, flip angle=75 degrees) while performing the CPT-END.

General image processing—The fMRI data were analyzed using AFNI (Analysis of Functional NeuroImages; <http://afni.nimh.nih.gov/afni>). MRI images were reconstructed in order to convert raw scanner data into AFNI format. Structural and EPI (functional) images were co-registered based upon scanner coordinates. Subject motion was determined in six directions of rotation and translation, and the maximum motion of any analyzed subject was <5 mm. The average total displacement for all subjects was <1 mm, with no significant differences between bipolar and healthy groups ($p>.1$). The average displacement between any successive TR pairs was <0.1 mm. Functional images were corrected for motion using a six-parameter rigid body transformation (35). Additionally, each volume was inspected for signal artifacts using a semi-automated algorithm in AFNI and excluded from further analysis if uncorrectable head movement occurred (36). On average less than 16 volumes (10%) were removed from each run.

Anatomical and functional maps were transformed into stereotactic Talairach space using the ICBM452 template. Motion correction parameters were included as regressors of no interest and low frequency components of the signal were removed. A Gaussian blur with a full width at half maximum (FWHM) of 6mm was applied, and signals were converted to percent signal change. Percent signal change was the variable of interest entered into ROI statistical models. Then, individual voxelwise event-related activation maps were created following standard AFNI procedures using an algorithm that compares the actual hemodynamic response to a canonical hemodynamic response function (37,38). Event-related response functions were calculated for the unpleasant pictures, neutral pictures and circles (targets). Squares provided the baseline against which hemodynamic responses were assessed.

ROI analysis—An ROI mask was created for the ventrolateral emotional arousal pathway (Figure 1). This mask was applied to each fMRI activation map in order to obtain activation measurements within ROIs for each cue. The average percent signal change from all of the voxels within each ROI was extracted from each subject's results for each cue (i.e., circles,

neutral pictures, and emotional pictures). We used the automatic anatomical labeling (AAL) atlas in AFNI to create these ROIs (39). Specific ROIs included ventrolateral prefrontal cortex (VLPFC, BA 10/47), rostral anterior cingulate (ACC, BA 24/32), amygdala, and inferior-temporal cortex (fusiform gyrus; BA 37) (Figure 1). The boundaries of these ROIs were based on previous reports (21,40).

We then used multivariate analysis of variance (MANOVA) of percent signal change to identify specific effects of group (bipolar vs. healthy), cue (target, neutral picture, emotional picture) and the interaction (group-by-cue) within the ventrolateral emotional arousal network ROIs, adjusted for differences in task performance (target accuracy which was the primary response variable). Identification of a significant interaction effect (i.e., abnormal pattern of activation in the bipolar subjects) constituted evidence supporting the primary predictions previously described. If a specific significant effect was observed in MANOVA, we used analysis of variance (ANOVA) to identify which ROIs and cues significantly contributed to the overall omnibus effect.

Voxelwise analysis—A voxelwise analysis was also performed to identify other regions besides the defined ROIs that exhibited significant interaction (group-by-cue) effects in order to identify differences between bipolar and healthy subjects in the patterns of responses to the three cues. Based on Monte Carlo simulation using 10,000 iterations, significant activation differences between bipolar and healthy subjects were defined as $p < .001$ with a cluster of 30 voxels that resulted in a corrected threshold of $p < .01$ (41–44). In order to identify the specific group-by-cue differences contributing to the overall interaction effect, we also performed individual group-by-cue voxelwise contrasts using similar methodology ($p < .01$, cluster 37 voxels, corrected $p < .05$). If necessary, ANOVA of percent signal changes from the activated cluster in the interaction map were also calculated to clarify which group-by-cue effects contributed significantly to the interaction term. Other analyses were performed as needed for completeness.

RESULTS

Demographic, clinical and performance variables

Demographic and clinical characteristics for both groups are listed in Table 1. The groups were closely matched for age, sex, ethnicity and IQ. The bipolar subjects had less education, likely reflecting educational disruption due to illness, rather than intellectual ability, given the similar IQ scores. By definition, patients exhibited greater affective ratings scores. Patients were significantly more likely to have met criteria for a past history of an alcohol or drug use disorder. On the CPT-END the bipolar patients responded significantly more slowly to both neutral ($t=2.95$, $df=74$, $p=.004$) and emotional cues ($t=2.16$, $df=74$, $p=.03$). The bipolar group also responded significantly less accurately to targets (circles) ($t=2.50$, $df=74$, $p=.01$).

Ventrolateral Emotional Pathway ROI analysis

MANOVA of the ventrolateral pathway ROIs demonstrated significant group [Wilk's $\lambda=0.91$, $F(8,214)=2.3$, $p=.02$], cue [Wilk's $\lambda=0.43$, $F(16,428)=13.9$, $p<.0001$]; and group-by-cue [Wilk's $\lambda=0.88$, $F(16,428)=1.8$, $p=.02$] effects. Specific ROI differences contributing to these omnibus findings are provided in Table 2 and Figure S1 (see Supplement). As can be seen, the bipolar subjects exhibited decreased activation overall (i.e., across all cues) in left amygdala and bilateral VLPFC. Significant cue effects were observed in all ROIs except right VLPFC. In general, these brain regions exhibited progressively greater activation from target to neutral and then emotional pictures, with the exception of anterior cingulate, consistent with Yamasaki et al (21). Finally, specific group-

by-cue effects were observed in left VLPFC, right ACC, left fusiform, and right amygdala. These group-by-cue effects resulted from blunted responses to emotional and neutral pictures, with similar responses to targets in the bipolar compared with healthy subjects (Table 2; Figure S1 in the Supplement).

Voxelwise analysis results

Regions of activation that exhibited significant group-by-cue effects in the voxelwise analysis are presented in Table 3 and Figure 2. Comparing Figure 2 with Figure 1, many of these regions overlapped with or were included within the ROIs of the ventrolateral prefrontal emotional pathway. Specific group-by-cue effects that contributed to the overall interaction effects are illustrated in Table 3 and Figure S2 (see Supplement). In general the interaction effects observed in Figure 2 result from relatively greater activation in response to circles, but blunted activation in response to emotional and neutral pictures, in the bipolar compared with healthy subjects (Table 3; Figure S2 in the Supplement).

Correlations with affective symptoms

In order to investigate possible associations with affective symptoms, correlations between YMRS and MADRS total scores and percent signal change were calculated for regions of interest from both analyses. In general, few significant associations were observed. However, during emotional images, right amygdala activation was significantly associated with MADRS scores [$r(38)=0.35$, $p=.025$]. During neutral images, MADRS total scores were significantly correlated with right inferior frontal gyrus activation [$r(38)=-0.35$, $p=.025$]. During targets, YMRS total scores were significantly correlated with activation in right amygdala [$r(38)=0.31$, $p=.05$], right inferior frontal gyrus [$r(38)=0.31$, $p=.05$], and right putamen [$r(38)=0.39$, $p=.01$]. MADRS total scores were inversely significantly correlated with right putamen activation [$r(38)=-0.35$, $p=.025$]. No other significant associations were observed. Although these significance values are presented without controlling for multiple comparisons, which is appropriate when examining potential confounds, none of these differences would survive Bonferroni corrections ($p=.05/22$ regions per rating scale=.002). Finally, we compared manic versus mixed subjects and found no significant regional differences.

Medication effects on specific ROI activation

Potential medication effects were examined with two analyses. The first analysis contrasted activation in the nine patients off medications with the 31 receiving medications using ANOVAs of the ROIs. None of the ventrolateral pathway or voxelwise ROIs exhibited significant differences in activation between these two groups [$F(1,118)<2.1$, $p>.15$].

The second analysis used a general linear model (PROC GLM in SAS) to evaluate activation in each ROI as a function of the presence or absence of the three medication classes (lithium, antipsychotics, and anticonvulsants) in order to control for interactions among medications in patients receiving multiple drugs. None of the ROIs from either analysis was significantly associated with antipsychotic use [$F(1,116)<2.85$, $p>.095$] and only one region was associated with lithium use [right inferior frontal gyrus from voxelwise analysis; $F(1,116)=10.0$, $p=.002$]. Several regions exhibited significant associations with anticonvulsant use including left fusiform gyrus [$F(1,116)=4.3$, $p=.04$], left inferior frontal gyrus [$F(1,116)=6.1$, $p=.015$], right putamen [$F(1,116)=4.3$, $p=.04$] and cerebellar vermis [$F(1,116)=15.6$, $p<.0001$]. In order to determine whether these associations with medication exposure impacted group-by-cue findings, activation in right inferior frontal gyrus was contrasted between bipolar and healthy subjects after removing patients on lithium ($N=7$) to see if previously identified significant group and group-by-cue effects persisted. In this re-analysis, the significant interaction effect persisted. Similarly, analyses were repeated

contrasting healthy and bipolar subjects after removing patients on anticonvulsants (N=11). Again, significant group-by-cue differences persisted in all regions. Consequently medications appeared to minimally impact group differences in any region.

Alcohol and drug use history effects

Since the groups demonstrated differences in histories of prior drug and alcohol use disorders, contrasts were re-analyzed covarying for this difference in the individual ANOVAs for each region of interest from both analyses (based on percent signal change). Significant Interaction effects persisted in all regions from both the ROI and voxelwise analyses except for superior frontal gyrus in the latter.

DISCUSSION

Results from this study support our initial prediction that manic bipolar subjects would exhibit abnormalities within the ventrolateral prefrontal emotional arousal network. Specifically, compared with healthy subjects, the manic subjects exhibited blunted activation to emotional and neutral pictures, but not targets, across many of the predefined regions of interest. Several additional brain regions identified in the voxelwise analysis also exhibited similar differences between groups, including right parahippocampus, right lingual gyrus, and medial thalamus. The parahippocampal region is closely integrated with amygdala, and lingual gyrus also contributes to processing emotional stimuli (20,45,46); additionally, medial thalamus comprises part of the iterative prefrontal-striatal-thalamic circuits that modulate anterior limbic structures (1,2,46,47). Together these regions likely represent components of an extended ventral emotional arousal network that is dysfunctional in bipolar disorder.

Similar activation pattern differences to those in the ventral emotional arousal network were also observed in dorsolateral (BA 9,46) and dorsomedial prefrontal areas (BA 9/10), as well as precuneus. Although these dorsal prefrontal regions are commonly associated with attentional processes, group activation differences occurred predominantly during the distracter (pictures) rather than target (circles) components of the task. This finding suggests that attentional components of emotional and neutral image processing are also disrupted in these manic patients, consistent with group differences observed in task performance. Since precuneus is involved with visual processing of emotional and complex stimuli (45), group differences observed in this brain region further support this suggestion.

In addition to these primary findings, manic subjects also exhibited increased activation in response to targets in several brain areas in which healthy subjects had minimal activation. Specifically, exaggerated responses to targets were seen in left fusiform gyrus, right parahippocampus, right amygdala, right inferior frontal gyrus, right putamen, and right superior frontal gyrus (20,21,45). The abnormal response to targets in bipolar subjects suggests that they were recruiting additional accessory brain regions than were the healthy subjects in order to manage the task.

Together, this pattern of findings suggests dysfunction of an extended ventrolateral prefrontal-amygdala emotional network during bipolar mania leading to blunted regional brain responses to negative emotional cues and abnormal attentional processing that is reflected in impaired task performance. A number of other investigators have observed decreased activation in ventral prefrontal cortex, anterior cingulate, and striatum in manic bipolar patients while performing a variety of cognitive tasks (3,10–14), consistent with these findings and the hypothesis that there is a loss of ventral prefrontal modulation of limbic brain during mania (3).

In contrast to our finding of blunted right amygdala responses to emotional and neutral images, Altshuler and colleagues observed increased amygdala activation in mania relative to healthy subjects during affective faces naming and labeling (13). Conversely, Killgore et al (10) observed no differences in amygdala activation, but did observe blunted responses in prefrontal and striatal regions in response to fearful faces in manic compared to healthy subjects. Mazzola-Pomietto et al (11) also observed decreased ventral prefrontal activation, but no differences in amygdala activation, in manic versus healthy subjects during an impulse control task. The reasons for these discrepant findings among studies are not entirely clear, but most likely reflect differences among tasks. Supporting this assertion is a study by Bermpohl and colleagues who found that abnormalities in amygdala activation during mania may be based on the emotional valence of the cues; specifically they observed differences in amygdala activation between manic and healthy subjects when viewing positive, but not negative pictures (14). Consequently, the current study, which included negative emotional images, and that of Killgore et al (10), which included only fearful faces, may not have been designed to elicit excessive amygdala activation in mania. Additional work in mania examining the effects of varying emotional valence on amygdala activation is clearly warranted, as these differential responses may better delineate the nature of emotional network dysfunction in this condition.

In general, there were relatively few significant correlations between symptom ratings and changes in activation from baseline in the bipolar subjects. Associations with manic symptoms were observed only during the attentional (target) component of the task, whereas depressive symptoms were associated with all three components. However, the range of manic symptoms was relatively small, so that power to detect correlations was limited. Similarly, as these were primarily manic patients, the meaningfulness of the associations with depressive measures is less clear. Overall, the relatively few associations suggest that it is the presence of the manic syndrome or bipolar disorder, rather than symptoms *per se* that may be most meaningfully associated with the activation differences observed between bipolar and healthy subjects.

Like all clinical studies, there are limitations to this report. Most of the bipolar patients were receiving medications, whereas none of the healthy subjects were, potentially impacting the findings. However, comparisons between bipolar subjects on and off medications exhibited no relevant effects in any ROI, and the presence or absence of medication classes minimally impacted group-by-cue effects. Additionally, differences between groups occurred in different directions, suggesting that there was no main effect for medications. Together, these observations mitigate against medication effects explaining group differences. We included all voxels in each region for the ROI analysis, which might include voxels that do not meet some *a priori* threshold of activation. Consequently, doing so might weaken the average ROI activation and diminish group differences. However, we chose this approach in order to directly test the ventrolateral-emotional pathway and preserve statistical power by limiting the number of contrasts. Importantly, even with this more conservative approach, group differences were observed throughout the pathway. A number of the originally studied bipolar patients were excluded from the final analysis due to difficulty completing the task or excessive movement. Although these excluded patients did not significantly differ on any of the measured demographic or clinical variables from the remaining sample, it is possible that the excluded patients were more ill than those included in the final analysis. However, if this was true, it would have been expected to increase, not decrease, differences from healthy subjects. One limitation inherent in fMRI is that contrasts involve difference values between two activation states (e.g., baseline squares and emotional pictures) rather than absolute 'activation' (metabolic) changes. Consequently, a blunted response in bipolar subjects in regional activation might reflect either lower overall response with a similar healthy baseline or an elevated baseline compared to healthy subjects with restricted

additional activation. Differentiating between these two possibilities is difficult with fMRI, so that interpreting findings as differences in system flexibility rather than differences in overall activation may be more accurate. However, in this study, in response to different cues bipolar subjects demonstrated both increased and decreased responses, suggesting the differences were not simply due to resting state differences. These limitations are offset by the large number of subjects studied, evaluation of treatment effects, and use of a specific validated task to test a specific hypothesis.

In summary, we observed abnormalities in fMRI activation throughout an extended ventrolateral prefrontal emotional arousal network, as well as in other brain regions that appear to manage emotional function, in a relatively large sample of manic bipolar patients. Additional work to clarify the effects of emotional valence on differences between manic and healthy subjects in regional brain activation is needed to inform future hypothesis and improve interpretation of fMRI results across studies of bipolar disorder. Moreover, since this study was restricted to manic and mixed patients, additional work exploring how dysfunction within these brain networks changes with mood state are needed to clarify the specific underlying neurophysiology of this dynamic condition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Ventrolateral prefrontal emotional arousal pathway regions of interest (ROIs). ROIs include amygdala (green=right, purple=left), inferior temporal (fusiform; olive green=right, brown=left), ventrolateral prefrontal cortex (inferior frontal gyrus; tan=right, light blue=left), and rostral anterior cingulate (aqua=right, mauve=left).

Figure 2. Regional fMRI voxelwise significant group-by-cue effects in 36 bipolar manic and 40 healthy subjects while performing the CPT END. Locations of voxelwise regions of interest for analysis (described in the text): a. cerebellar vermis, b. left fusiform gyrus, c. right parahippocampal gyrus, d. right inferior frontal gyrus, e. left inferior frontal gyrus, f. right amygdala, g. right putamen, h. right lingual gyrus, i. medial thalamus, j. left middle frontal gyrus, k. right middle frontal gyrus, l. right superior frontal gyrus, m. right precentral gyrus and n. right precuneus.

Table 1

Demographic and clinical characteristics of 40 bipolar manic and 36 healthy subjects scanned while performing the CPT-END.

Variable	Healthy Subjects N=36	Bipolar Subjects N=40	p-value
Age, years	30 (9)	30 (10)	.98
Ethnicity, N(%) non-white	6 (17)	9 (23)	.52
Sex, N(%) women	20 (56)	24 (60)	.70
IQ score	111 (9)	108 (11)	.18
Years of Education	15 (2)	14 (3)	.04
YMRS total score	1 (1)	26 (4)	<.0001
MADRS total score	1 (1)	13 (8)	<.0001
Lifetime AUD, N(%)	5 (14)	21 (53)	.0004
Lifetime DUD, N(%)	2 (6)	20 (50)	.0001
Mixed state, N(%)	n/a	15 (38)	n/a
<u>CPT-END performance</u>			
Circles (targets) reaction time, ms	908 (144)	932 (161)	.50
Circles %correct	96 (9)	89 (13)	.01
Squares reaction time, ms	733 (105)	782 (130)	.08
Squares %correct	95 (12)	93 (9)	.44
Emotional distracter reaction time, ms	938 (165)	1025 (185)	.03
Emotional distracter %correct	96 (12)	91 (12)	.12
Neutral distracter reaction time, ms	891 (138)	996 (169)	.004
Neutral distracter %correct	96 (12)	94 (9)	.46

Values are mean (SD) unless otherwise stated. Abbreviations: IQ=intelligence quotient, YMRS=Young Mania Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; AUD=alcohol use disorder; DUD=drug use disorder.

Table 2

Significant specific ROI group, cue and cue-by-group interactions contributing to omnibus effects of significant MANOVA comparison of 40 bipolar manic (BPD) and 36 healthy (H) subjects during performance of the CPT-END (see text for details and Figure S1 in the Supplement). Abbr: HS=healthy subjects, BP=bipolar subjects, NS=not significant, emo=emotional cue, neu=neutral cue, cir=circle (target), VLPFC=ventrolateral prefrontal cortex, ACC=(rostral) anterior cingulate cortex.

ROI	Group effect	Cue Effect	Interaction
Left amygdala	.04	p<.0001 emo>neu>cir	NS (p=.32)
Right amygdala	NS (p=.33)	p<.0001 emo>neu>cir	p=.006 HS emo> BP emo
Left fusiform	NS (p=.09)	p<.0001 emo>neu>cir	p=.02 HS neu>BP neu
Right fusiform	NS (p=.29)	p<.0001 emo,neu>cir	NS (p=.20)
Left VLPFC	p=.004 HS>BP	p<.0001 emo>neu>cir	p=.03 HS emo>BP emo HS neu>BP neu
Right VLPFC	p=.02 HS>BP	NS (p=.87)	NS (p=.21)
Left ACC	NS (p=.27)	p=.0009 emo,cir>neu	NS (p=.06)
Right ACC	NS (p=.22)	p=.003 emo,cir>neu	p=.03 HS neu>BP neu

Table 3

Significant cue-by-group interaction differences observed from voxelwise comparison of 40 bipolar manic (BPD) and 36 healthy (H) subjects during performance of the CPT-END (see text for details and Figure S2 in the Supplement for representative illustrations). Abbr: R=right, L=left, HS=healthy subjects, BP=bipolar subjects, NS=not significant, emo=emotional cue, neu=neutral cue, cir=circle (target).

Region of increased activation	Brodmann Area	Talairach coordinates Center of Mass (X,Y,Z)	Z- Score	Interactions
Cerebellar vermis	n/a	5, -50, -30	4.5	HC neu>BP neu
L. fusiform g.	37	-43, -55, -16	4.6	BP cir>HC cir HC neu>BP neu HC emo>BP emo
R. parahippocampus	35	20, -26, -11	4.1	BP cir>HC cir HC neu>BP neu
R. amygdala	n/a	25, -18, -11	3.6	BP cir > HC cir HC neu>BP neu
R. inferior frontal g.	47	37, 13, -16	4.1	BP cir>HC cir HC emo,neu>BP emo,neu ^a
L. inferior frontal g.	45	-46, 35, 2	3.5	HC emo>BP emo
R. putamen	13	31, -1, -7	4.1	BP cir>HC cir HC neu>BP neu BP emo>BP neu
R. lingual g.	17	8, -94, -4	3.7	HC neu>BP neu HC emo>BP emo ^b
Medial thalamus	n/a	-1, -10, 11	4.5	HC neu>BP neu HC emo>BP emo
L. middle frontal g.	46	-49, 32, 23	3.6	HC neu>BP neu HC emo>BP emo
R. middle frontal g.	9	50, 17, 32	4.1	HC emo>BP emo
R. superior frontal g.	9, 10	5, 54, 33	3.8	BP cir>HC cir HC emo>BP emo
R. precentral g.	3	17, -36, 66	3.3	BP cir>HC cir ^b
R. precuneus	7	29, -64, 53	4.1	HC emo,neu>BP emo,neu ^a

^aSignificance differences between groups observed in voxelwise analysis of combined pictures (emotional plus neutral) processing (image not shown).

^bGroup-by-cue effects identified using ANOVAs of percent signal changes within region identified by overall voxelwise interaction map.