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Within- and Between-Session Changes in Neural Activity During Emotion Processing in Unipolar and Bipolar Depression

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Abstract

Background—Bipolar disorder (BD) and unipolar depression (UD) can be difficult to distinguish clinically, particularly during episodes of depression. In this study we test for differences between BD, UD, and healthy control (HC) adults regarding within- and between-session changes in BOLD response during implicit emotional processing.

Methods—During fMRI, HC adults (N=19) and depressed adults with UD (N=19) and BD (N=16) performed an implicit emotion-processing task. Each participant was scanned twice, separated by 6-months, resulting in 108 scans. BOLD response and linear change in BOLD response were examined within and between sessions.

Results—We observed within-session linear decreases in BOLD signal (irrespective of group, condition, or session) in the left amygdala, a right-sided temporo-parietal region, and a right-sided fronto-insular region. Furthermore, we observed group differences in within-session BOLD signal change ($p < 0.05$, FWE corrected) in a left-sided striatal-insular-thalamic region. Individuals with BD demonstrated a linear decrease in BOLD signal compared to HC ($p < 0.008$, FWE corrected) across this region and compared to UD in the posterior insula portion of the region ($p < 0.008$, FWE corrected). Finally, we observed main effects of emotional valence in bilateral visuo-spatial processing regions as well as in the left and right amygdala.

Conclusions—Individuals with BD demonstrated linear attenuation of BOLD response to emotional stimuli within left-sided striatal-insular-thalamic regions. Individuals with BD may either have experienced abnormal habituation in this region or disengaged quickly from processing the emotional stimuli, despite comparable task performance. This pattern may represent an underlying pathophysiological process associated with BD that differs from UD.

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Keywords

Emotion processing; Bipolar Disorder; Major Depressive Disorder; fMRI; BOLD attenuation; Whole brain analysis

Introduction

Bipolar disorder can be difficult to diagnose correctly, particularly during depressive episodes. The delay between initial treatment-seeking and correct diagnosis can span more than a decade (1,2). Even when a bipolar disorder diagnosis is made, as many as 17%–27% of individuals will go on to be misdiagnosed by other treatment providers later in the course of their illnesses (3,4). The potential value of identifying biologically based markers that could help differentiate bipolar and unipolar illness is clear (e.g., 5,6), and there has been a recent increase in the number of functional neuroimaging studies aimed at helping to identify such differences (6,7). The majority of this work, however, has examined neural activity as a function of average Blood Oxygen Level Dependent (BOLD) response during a single scanning session. In the current work, we test for differences between bipolar depressed (BD), unipolar depressed (UD), and healthy control (HC) individuals regarding the temporal dynamics of the BOLD response during emotion processing within and between neuroimaging sessions. We argue that examining the dynamics of neural regions involved in emotion processing may provide important information about the pathophysiology of the illness.

Prior neuroimaging work has revealed abnormalities in several key circuits among individuals with BD compared to healthy individuals. In a recent review, Phillips and Swartz (6) identified that individuals with BD demonstrate dysfunction in cortico-limbic regions during emotion regulation coupled with hypersensitivity to positive and rewarding stimuli in striatal and frontal reward systems. Abnormalities that can help to differentiate individuals with BD from those with UD have been more challenging to identify (7).

Across a small number of studies, differences between UD and BD to positive and negatively valenced emotional faces have been observed in limbic (8–11), subcortical (12), visuospatial (11), and prefrontal regions (10,12). Different BOLD activity patterns have emerged across studies, however. For example, in one study from our research group, we (9) observed increased activity in the amygdala to faces displaying a mild sad emotion in BD relative to UD, HC, and individuals with BD who were in remission. In another study from our group, using a subsample of the Session 1 data analyzed below (11), we likewise observed increased activity to dynamically emerging facial displays of sadness in BD relative to UD, but this time in several temporo-parietal regions involved in visuo-spatial processing. By contrast, in a set of studies using pattern classification techniques, Grotgard and colleagues (10,13) observed the opposite pattern. That is, they found that increased amygdala activation to negative (10) and sad (13) faces was key to accurately classifying individuals with UD, whereas increased amygdala activity to happy faces was more important in classifying individuals with BD.

One way to begin to account for the varied emotional valence effects in neural response between unipolar and bipolar disorder is suggested by Grotegord and colleagues (13) who note that emotion processing is a dynamic mechanism that unfolds over time. They suggest that different findings may obtain depending on when in that time course the system is probed (also see, 14). We agree that examining the temporal dynamics of emotion processing is an important next step in the search to identify biomarkers that may differ between UD and BD.

In the current work, we examine differences among BD, UD, and HC individuals regarding mean BOLD activity as well as changes in the BOLD signal that occur between scanning sessions, separated by a six-month interval, and changes that occur over time within scanning sessions in response to dynamically emerging positive and negative facial displays. The six-month interval was chosen to be representative of the durations of typical major depressive episodes (see, 15) and, therefore, to allow sufficient time for symptom reductions. Following our approach in prior work (9,11,12), and given the findings noted above, we focused the analyses on between group differences in the amygdala and across the whole-brain. Based on our prior work (9,11), we hypothesized increased mean BOLD response to negative emotions among adults with bipolar relative to unipolar depression across sessions. Whereas we expected to observe attenuation of the BOLD signal across groups and conditions in regions involved in emotional processing, including the amygdala (potentially representing habituation effects over time), based on related findings from previous work (13), we expected to observe greater attenuation of BOLD signal to happy faces among the adults with unipolar versus bipolar depression, both within- and between-sessions. Finally, an exploratory aim of the project was to examine the degree to which changes in brain activity across sessions tracked with changes in symptoms. We expected that normalization of brain function in patient groups would be associated with symptom reduction.

Materials and Methods

Participants

The 57 participants for the current study were a subset of individuals who participated in a larger examination of neural differences between bipolar and unipolar depression (R01-MH076971, PI:MLP). The current sample represents those who were scanned at an initial visit (Session 1) and who were scanned again six months later (Session 2): 21 currently depressed adults diagnosed with UD, 17 currently depressed adults diagnosed with BD, and 19 HC participants. All participants were right handed, all were native English speakers, and all were screened with the Structured Clinical Interview for Psychiatric Disorders (16). In all diagnostic groups, participants were excluded if they had a history of head injury, systemic medical illness known to interfere with blood flow or brain function, cognitive impairment (score < 24 Mini-Mental State Examination, 17), color-blindness, premorbid IQ estimate < 85 (18), psychosis (including any psychotic mood symptoms), borderline personality disorder (19), and standard MRI exclusion criteria (e.g. metallic objects in the body). Participants in the UD and BD groups were also excluded if they met criteria for an alcohol/substance use disorder within 2 months prior to the scan. For the HC group, additional exclusion criteria included any current or prior alcohol or substance use disorder and any

personal or immediate-family history of an Axis I disorder. All participants in all groups were required to pass urine drug screens and breath alcohol tests prior to both scanning sessions. In the original project from which these data originated, participant groups were age- and gender-matched. Because the current sample consisted of the subset of participants who returned for a second scan, rigid gender matching was not possible, but rather will be addressed statistically (see below). Three participants, one from the BD group and two from the UD group, were excluded due to behavioral performance of <75% correct during the scan. Thus, the final sample included 19 adults with UD, 16 adults with BD, and 19 HC adults (Table 1), each of whom were scanned twice, six months apart, resulting in a total of 108 scans. All participants were followed naturalistically during the six-month assessment window. No specific intervention was administered, and participants were free to receive, augment, or terminate treatment as needed. The study protocol was approved by the University of Pittsburgh Institutional Review Board. After hearing a complete description of the study, participants provided written informed consent.

Clinical Measures

Demographic, family history, medication, and clinical information were collected through self-report questionnaires and clinical interviews. Depressive symptoms were assessed using the 25-item Hamilton Rating Scale for Depression (HRSD, 20), and manic symptoms were assessed using the Young Mania Rating Scale (YMRS, 21). Current and trait anxiety was assessed using the Spielberger State-Trait Anxiety Inventory (22). IQ was estimated with the National Adult Reading Test (NART, 18).

Paradigm

Participants completed a 12.5-minute emotional dynamic faces task during fMRI. Stimuli comprised faces from the NimStim set (23) that were morphed in 5% increments, from neutral (0% emotion) to 100% emotion for 4 emotions: happy, sad, angry and fear (24–27). Morphed faces were collated into 1s movies progressing from 0% to 100% emotional display. In control trials, movies comprised a simple shape (dark oval) superimposed on a light-grey oval, with similar structural characteristics to the face stimuli, which subsequently morphed into a larger shape, approximating the movement of the morphed faces. Participants were asked to use one of three fingers to press a button indicating the color of a semi-transparent foreground color flash (orange, blue, or yellow) that appeared during the mid 200ms–650ms of the 1s presentation. The emotional faces were task-irrelevant and, thus, were processed implicitly. Each condition consisted of 36 total trials (see Supplement for additional details).

Data Analyses

Neuroimaging data acquisition—Structural and functional fMRI data were collected using a 3-Tesla Siemens Trio MRI scanner. See Supplement for detailed acquisition parameters.

Functional neuroimaging data preprocessing—Data were preprocessed with statistical parametric mapping software version 12b (SPM12b; <http://www.fil.ion.ucl.ac.uk/spm>). During preprocessing, data were motion corrected, co-registered, segmented and

normalized into Montreal Neurological Institute [MNI] space, resampled to $3 \times 3 \times 3 \text{ mm}^3$, and smoothed with an 8-mm full-width at half maximum (FWHM) Gaussian kernel. AFNI 3dDespike was used to reconstruct scans with abnormal spikes in signal intensity.

Functional neuroimaging data analyses—Each of the four emotion conditions (anger, fear, sad, happy) was entered as separate conditions in the design matrix, as was the shape condition, which served as the baseline. The experiment was treated as a mixed block/event-related design at the first level, and events were convolved to the canonical hemodynamic response function. Standard first-level, within-subject general linear models were fit. The six movement parameters from the preprocessing procedure, along with their first-order derivatives, were entered as covariates of no interest. We also included an additional nuisance regressor to capture potential physiological confounds in the global signal (calculated as the average signal from voxels located within a white matter and CSF mask and described in detail in an earlier methodological examination of first-level model specification using some of the data reported below, 28). Finally, changes in BOLD signal within each scanning session were modeled by the addition of orthogonal first- and second-order polynomial terms corresponding to each event type. In order to examine our hypotheses regarding BOLD response to negative emotions, the anger-, fear-, and sad- minus shape contrasts were pooled to form one negative-emotion-versus-shape contrast. The decision to pool these contrasts was made a-priori, given statistical power constraints, the absence of any specific hypotheses regarding differential group effects of BOLD attenuation to different negative facial expressions, and previous studies using this approach in other patient samples (e.g., 29). First-level models were calculated separately for each testing occasion, resulting in separate contrast estimates for each.

Whole brain analyses—Across the whole brain, we examined one between-subjects factor (group) and two within-subjects factors (session and emotion-valence), resulting in a $3(\text{group}) \times 2(\text{session}) \times 2(\text{emotion-valence})$ repeated measures ANOVA. We utilized the partitioned-errors approach (30), implemented in the GLM Flex suite of tools (http://mrtools.mgh.harvard.edu/index.php/Main_Page) to ensure that the proper error terms were used for each contrast. Outliers, calculated separately for each voxel on the basis of Cook's D, were removed. Separate second level models were estimated to examine mean BOLD signal and linear changes in BOLD signal within sessions.

Inference and multiple comparison correction—Inferences were made on the basis of cluster level statistics (cluster forming threshold $p < 0.005$, uncorrected, extent threshold $p < 0.05$ corrected). AFNI 3dClusterSim software was used to implement Monte Carlo simulations to determine the familywise error corrected cluster extent thresholds, using the smoothness values for each error term estimated separately from the second level models above. The required cluster extents for mean BOLD activity were: a) $k > 100$ for group, b) $k > 101$ for session, c) $k > 89$ for emotion-valence, and d) $k > 92$ for session-by-emotion-valence interaction effects. The corresponding values for linear within-session changes in BOLD signal were $k > 102$, $k > 97$, $k > 84$, and $k > 90$, respectively. We computed all post-hoc tests of main- and interaction-effects using the same whole-brain cluster correction techniques. The omnibus FWE alpha levels of these tests were Bonferroni corrected for the

number of tests performed. Only those portions of the significant (whole-brain cluster-corrected) post-hoc clusters that overlapped with the initial main or interaction effects are discussed below. Furthermore, only statistically significant results are discussed (see Supplement for discussion non-significant trends, $p < 0.10$, in the data).

Clinical and demographic data analyses—Because voxelwise repeated measures ANCOVAs are not possible using standard neuroimaging software, in order to examine the effects of demographic and clinical variables, we extracted beta values representing the contrasts of interest from those regions identified in the analyses described above. We next examined whether demographic or clinical variables could account for any observed group differences. To examine differences that emerged among all three groups (UD, BD, and HC), we examined the effects of sex, age, and IQ. To examine differences between the two clinical groups, we examined: illness duration, current antidepressant medication (y/n), current antipsychotic medication (y/n), current mood stabilizer medication (y/n), current benzodiazepine (y/n), number of prior mood disorder episodes, total 25-item HRSD score, total YMRS score, total state-anxiety score, and total trait-anxiety score. Repeated measures maximum likelihood models, estimated with SAS version 9.4 statistical software (SAS Institute Inc., Cary, NC), were constructed in order to incorporate changes in these variables between testing occasions. Because these analyses were intended to identify potential confounds, we first employed a liberal p-value threshold of $p < 0.10$ to identify those variables that exhibited at least a trend-level significant bivariate relationship with the extracted data. Next, we added all of the variables that crossed this threshold to a model that included group membership.

Region of interest analysis (ROI)—To examine activity in the right and left amygdala we extracted data from anatomical amygdala masks, as defined in the Wake Forest Toolbox PickAtlas Talairach Daemon template(31). We used SAS 9.4 to estimate repeated measures maximum likelihood models to examine the effects of group, emotional-valence, session and relevant covariates (described above).

Results

Demographic and behavioral data are presented in Table 1. The ratio of males to females differed as a function of group membership. Post-hoc contrasts revealed that the ratio was more balanced in HC compared to BD groups. Overall, task accuracy was high, and there were no significant effects of group regarding behavioral performance. Clinical characteristics are displayed in Table 2. The two patient groups differed on three baseline clinical variables. Participants with BD experienced a greater number of previous episodes of illness, and a higher proportion were taking antipsychotic and mood stabilizing medications. On average, symptoms of depression ($t(34) = -4.31$, $p < .001$) and sub-threshold mania ($t(33) = -3.55$, $p = 0.001$) were significantly reduced between sessions. No differences in symptom change were observed between BD and UD (Table 2).

Mean BOLD Response

Whole brain analyses—In the examination of average BOLD activity, we observed a significant main effect of emotional-valence in six clusters (Figure 1, Table 3). Two clusters demonstrated increased BOLD response to positive emotional stimuli across groups and sessions. These left- and right-sided clusters included portions of bilateral thalamus and the hippocampus. Four clusters demonstrated increased activity to negative stimuli. These included bilateral visual regions, portions of Lobules I–V of the cerebellum, and a cluster in the frontal pole.

Amygdala ROI—In the analysis of data extracted from the left and right amygdala, we observed significant main effects of emotional-valence regarding average BOLD response ($F(1,51)=7.85, p=0.007$ on the left; $F(1,51)=9.91, p=0.003$ on the right). For both sides, average BOLD response was higher for negative compared to positive faces.

Linear BOLD Attenuation within Sessions

Whole brain analyses—We observed general within-session attenuation (linear decreases) of the BOLD signal to the emotional stimuli over time during the task in two clusters, one in a right-sided fronto-insular region and one in a right-sided temporo-parietal region (Figure 2a, Table 3). Further, we observed a significant effect of emotional valence in a large medial occipital cluster and a cluster in bilateral posterior precuneus (Figure 2b, Table 3). Both clusters evidenced linear increases in within-session BOLD response over time to negative emotional stimuli relative to positive stimuli.

We observed a significant main effect of group on within-session BOLD attenuation in a large cluster in left insular-striato-thalamic regions (Figure 3a). Independent, whole-brain cluster-corrected (FWE $p<0.0083$) post-hoc analyses revealed that the effect was driven primarily by a greater within-session linear attenuation in BOLD signal for the BD group compared to the UD group in the posterior insula portion of the region, and compared to the HC group across the region (Figure 3b. See Supplement for further information). No HC versus UD comparisons were significant (all $k_s < 21$).

Potential confounds—We examined whether clinical, demographic, or behavioral effects could account for the group difference in attenuation of BOLD signal in the left insular-striato-thalamic region. Neither sex, age, or IQ was associated with attenuation of activity in this region across the full sample (all $F_s(1,52)<2.24, p>0.14$). Regarding possible clinical confounds among those in the two depressed groups (UD and BD), two variables crossed the initial $p<0.10$ threshold: antipsychotic and mood stabilizing medications, however neither remained significant when added to the model containing group and session (both $F_s<0.23, p_s>0.66$). Moreover, within the BD group, neither medication was associated with estimates of BOLD signal attenuation in this region (both $F_s<0.05, p_s>0.87$). See the Supplement for secondary analyses regarding effects of the gender of the facial images.

Although behavior on the task (i.e., color matching), was not directly related to the emotional content of the images, behavioral performance might serve as a proxy for task engagement. In order to determine whether the group differences in attenuation could be

explained by differences in behavioral performance, we computed linear mixed-effects models of the trajectories of reaction times (using SAS PROC MIXED) and accuracy (using SAS PROC GLIMMIX). We observed no evidence that individuals with bipolar disorder differed from the other groups with respect to the trajectories of reaction times or accuracies over the task ($F(1, 54) < 1.55$, $p > 0.21$).

Amygdala ROI—We observed significant general within-session BOLD attenuation in the left amygdala, irrespective of group, condition, or session ($t(53) = -3.14$, $p = 0.003$). On the right, we also observed a main effect of emotional valence whereby greater within-session attenuation occurred for the negative emotional faces compared to the positive faces ($F(1, 51) = 5.14$, $p = 0.03$).

Discussion

Contrary to our hypotheses, we did not observe greater average BOLD activity in the BD group compared to the UD group during the negative emotional faces condition, nor did we observe attenuation of BOLD signal to positive faces either within- or between-sessions among members of the UD group. Rather, the primary finding of this study was that in a large area that spanned portions of the left thalamus, striatum, and posterior insula, individuals with BD displayed abnormal BOLD signal attenuation, relative to UD in the posterior insula and to HC individuals in all three regions, during an implicit emotion processing task. These effects were observed despite the fact that no corresponding decrements were observed in behavioral performance. That is, the individuals with BD did not seem to be disengaging from the task *per se*, but rather, they showed a linear decline in BOLD signal in response to the emotional information contained in the task. Furthermore, we did not observe any evidence that the group differences regarding attenuation varied across the two sessions.

In addition, we observed general within-session attenuation of BOLD signal in the left amygdala and in right fronto-insular and temporo-parietal regions. This attenuation was observed irrespective of group, condition or session. Activity in these regions has been associated with social-affective processing (32–34), and these findings suggest that over time, these regions became generally less activated to the emotional facial stimuli. Given that no differences were observed between the patient and HC samples in these regions, such attenuation is likely normative.

By contrast, our primary findings regarding abnormal attenuation of an insular-striato-thalamic system among BD compared to the other two groups suggests that part of the pathophysiology of BD could involve the additional, and abnormal, habituation of this system, potentially subserving attention, sustained arousal, and behavioral responses to emotional stimuli as function of the perceived salience of those stimuli (35–40). Our previous findings indicated elevated left-sided striatal and ventrolateral prefrontal cortical activity during uncertain reward anticipation in individuals with BD relative to HC and UD (41–43). The uncertainty of the outcomes in these studies may have increased the perceived salience of task stimuli to individuals with BD and led to increases in BOLD response in these regions. We have interpreted this pattern of abnormally elevated activity as a neural

mechanism underlying greater encoding of future reward potential, which may be evident in individuals with higher levels of impulsive sensation seeking and risky decision-making, characteristics of BD. By contrast, the pattern of abnormally increased attenuation in the left-sided thalamo-striatal-insula cluster in individuals with BD in the present study may reflect the relative similarity and predictability of the stimuli within each emotional block, and the absence of any uncertainty regarding task outcomes. Future research will be needed to investigate further the interplay between salience and emotion processing in bipolar disorder, as well as the real-world consequences of altered functioning in these systems.

In addition to the group differences in BOLD attenuation, we also observed main effects of emotional valence in average BOLD response in several brain regions that have been implicated more generally in emotional face processing, including the left and right amygdala (e.g., 44,45,46). Furthermore we observed a pattern of within-session changes in BOLD response whereby response in the right amygdala attenuated to a greater degree for negative than to positive faces – a pattern of findings similar to those of Phillips and colleagues (47) who observed a more rapidly decreasing BOLD response in the right amygdala to fearful faces. We also observed a pattern of within-session strengthening of BOLD response to negative faces in occipital and posterior parietal regions, potentially representing increased activity in portions of the dorsal visual stream over time to the negative emotional images. These results are in line with those of Goldberg and colleagues (48) who reported preferential activity in areas of the dorsal visual stream to dynamic, naturalistic movie clips depicting emotional scenes. Finally, it is not immediately clear why we did not observe emotional-valence-by-group interaction effects or significant changes in BOLD signal across sessions. One possibility is that although the sample size of the current study is the largest to date to compare the longitudinal functioning of the emotion processing system among bipolar and unipolar depression, it was too small to examine more fine-grained distinctions in the functioning of the system for different discrete emotions.

Limitations

The results of the current study must be understood in the context of several limitations. First, given the naturalistic follow-up design, the groups were unbalanced with respect to gender. Gender was not a significant predictor of BOLD activity, but future work will be needed to verify that the observed BOLD attenuation effects replicate in both men and women. Second, we did not have access to data from a sufficiently large group of remitted UD or BD participants to examine their data separately. We did examine whether symptom changes were correlated with the observed effects and found no evidence of any such association. Finally, many of the UD and BD adults were taking psychotropic medications, and the two groups differed in the proportion of participants taking antipsychotic and mood stabilizing medications. None of the effects of medications remained significant when examined in statistical models that also contained a term representing group membership. Due to the sample sizes and the naturalistic design, it is not possible strictly to parcel out the unique effects of medications and group membership. Although we cannot rule out the possibility that medication affected BOLD response, the most likely explanation of the pattern of results that we observed is that the medications were associated with BOLD

activity in bivariate models because of their correlation with group membership, rather than the reverse (see 49,50).

Conclusion

The findings from this study highlight the importance of examining changes in the BOLD signal over time for understanding the pathophysiology of bipolar disorder. Specifically, they suggest that individuals with bipolar disorder differ both from healthy control participants and from individuals with unipolar depression in the degree to which left-sided striato-insular-thalamic activity is sustained during emotion processing. This may represent an important pathophysiological process in bipolar disorder, which if replicated in independent samples, could represent a core deficit associated with the illness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Main Effect of Emotional Valence (Mean BOLD Signal). Clusters represent significant effects of emotional valence (negative vs positive facial displays of emotion) for average BOLD activity, across groups and across sessions. Plotted values represent t statistics. Green-blue clusters represent regions wherein the negative-emotion-minus-shape-contrast was significantly larger than the positive-emotion-minus-shape contrast. Red-orange clusters represent the reverse. All effects are familywise error cluster-corrected at $p < 0.05$, using an initial cluster-forming threshold of $p < 0.005$ and Monte-Carlo methods to determine minimum cluster extents.

Figure 2.

Within Session BOLD Attenuation. A) The clusters represent significant BOLD signal attenuation across groups, emotional-valence conditions, and sessions during an implicit emotion-processing task (whole-brain, Monte-Carlo cluster-corrected FWE $p < 0.05$). Plotted values represent t statistics. B) The clusters represent significant effects of emotional-valence (positive vs negative emotional faces) regarding within-session linear change in BOLD response. Plotted values represent F statistics. The bar graph is provided for descriptive purposes only. It depicts extracted beta estimates from the regions depicted. Bars represent the slope of the linear change in BOLD signal. Negative values represent decreases in BOLD activity over time; positive values represent increases in BOLD activity. Error bars represent ± 1 standard error.

Figure 3.

Main Effect of Group (Within Session BOLD Attenuation). A) The cluster represents a significant effect of group (bipolar depressed [BD] vs healthy control [HC] vs unipolar depressed [UD]) regarding within-session linear change in BOLD response in a left striatal-insular-thalamic region during the implicit emotion-processing task (whole-brain, Monte-Carlo cluster-corrected FWE $p < 0.05$). Plotted values represent F statistics. B) The clusters represent whole-brain, cluster-corrected (FWE $p < 0.0083$) post-hoc comparisons of BP versus HC (yellow) and BP versus UD (Green). Plotted clusters represent the overlap between the significant clusters identified in the whole-brain post-hoc analysis and the main-effect of group (panel A). Full whole-brain post-hoc results are presented in the Supplement. Plotted values represent t-statistics. C) The bar graph is provided for descriptive purposes only, it depicts extracted beta estimates from the region depicted in Panel A. Bars represent the slope of the linear change in BOLD signal. Negative values represent decreases in BOLD activity over time; positive values represent increases in BOLD activity. Error bars represent ± 1 standard error.

Table 1

Demographics and Behavior.

Variable	UD(N=19)	BD(N=16)	HC(N=19)	Effect of Group	Post-hoc
Demographics:					
%Female	78.95%	93.75%	57.89%	$\chi^2(2)=6.26^*$	BD > HC [*]
Age, <i>M(SD)</i>	32.53 (7.24)	35.22 (8.91)	32.17 (6.28)	$F(2,51)=0.84$	
IQ (NART Estimate), <i>M(SD)</i>	111.34 (10.29)	114.10 (8.84)	113.19 (7.68)	$F(2,51)=0.43$	
Behavior (Session 1):					
Accuracy, <i>M(SD)</i>	95.32% (4.94%)	92.84% (7.01%)	96.86% (3.00%)	$\chi^2(2)=4.14^a$	
Reaction Time, <i>M(SD)</i>	959.72 (145.96)	997.57 (154.16)	948.70 (185.44)	$\chi^2(2)=1.63^a$	
Behavior (Session 2):					
Accuracy, <i>M(SD)</i>	94.48% (5.78%)	93.97% (7.64%)	92.03% (7.76%)	$\chi^2(2)=1.07^a$	
Reaction Time, <i>M(SD)</i>	961.04 (161.06)	985.65 (184.55)	941.66 (106.96)	$\chi^2(2)=0.15^a$	

Note. UD = Unipolar Depressed, BD = Bipolar Depression, HC = Healthy Control.

^aDue to non-normality, the non-parametric Kruskal-Wallis test was used for comparisons. HRSD–Hamilton Rating Scale for Depression, YMRS–Young Mania Rating Scale,

* p<0.05

Table 2

Clinical Characteristics.

Variable	UD(M=19)	BD(N=16)	Effect of Group
Session 1			
# Episodes, $M(SD)$	2.58 (0.69)	5.06 (1.95)	$F(1,33)=26.96^{***}$
HRSD, $M(SD)$	26.53 (4.86)	24.50 (8.25)	$F(1,33)=0.81$
YMRS, $M(SD)$	3.95 (2.37)	3.94 (2.57)	$F(1,33)<0.01$
State Anxiety, $M(SD)$	57.42 (8.14)	54.81 (11.46)	$F(1,33)=0.62$
Trait Anxiety, $M(SD)$	58.47 (10.32)	58.33 (8.79) ^a	$F(1,32)<0.01$
Duration(years), $M(SD)$	14.11 (8.31)	17.78 (8.50)	$F(1,33)=0.20$
Diagnostic Comorbidities (%):			
Current Anxiety	63.16%	37.50%	$\chi^2(1)=2.29$
Current Somatoform	0.00%	6.25%	<i>Fisher's Exact: NS</i>
Current Eating	0.00%	0.00%	–
Lifetime Drug/Alcohol	31.58%	50.00%	$\chi^2(1)=1.23$
Medication (% Prescribed):			
Antidepressant	63.16%	43.75%	$\chi^2(1)=1.32$
Antipsychotic	0.00%	50.00%	$\chi^2(1)=12.31^{***}$
Mood Stabilizer	10.53%	62.50%	$\chi^2(1)=10.41^{***}$
Benzodiazepine	15.79%	18.75%	$\chi^2(1)=0.05$
Change (Session 2 – Session 1)			
Additional Episodes	10.53%	0.00%	<i>Fisher's Exact: NS</i>
HRSD Change, $M(SD)$	–7.16 (6.85)	–7.56 (13.17)	$F(1,33)=0.01$
YMRS Change, $M(SD)$	–2.5 (3.29) ^a	–1.63 (3.63)	$F(1,32)=0.54$
State Anxiety Change, $M(SD)$	–8.17 (11.27) ^a	–1.60 (17.66) ^a	$F(1,31)=0.21$
Primary Diagnosis Change (%) ^b			
Partial Remission	0.00%	12.50%	<i>Fisher's Exact: NS</i>
Remission	15.79%	31.25%	
Medication (% Prescribed):			
Antidepressant			<i>Fisher's Exact: NS</i>
% Increase	10.53%	6.25%	
% Decrease	0.00%	6.25%	
Antipsychotic			<i>Fisher's Exact: NS</i>
% Increase	5.26%	6.25%	
% Decrease	0.00%	6.25%	
Mood Stabilizer			<i>Fisher's Exact: NS</i>
% Increase	5.26%	6.25%	
% Decrease	5.26%	6.25%	
Benzodiazepine			<i>Fisher's Exact: NS</i>

Variable	UD(M=19)	BD(N=16)	Effect of Group
% Increase	5.26%	0.00%	
% Decrease	0.00%	0.00%	

Note. UD = Unipolar Depressed, BD = Bipolar Depression, HC = Healthy Control, NS = Non-Significant.

^aData from one participant was missing.

^bPercentages concern changes to the primary diagnoses corresponding to group membership. No UD individuals experienced episodes of mania or hypomania or converted to bipolar disorder spectrum diagnosis. HRSD=Hamilton Rating Scale for Depression, YMRS=Young Mania Rating Scale,

p<0.001

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Table 3

Coordinates of Clusters Showing Significant Activations.

Contrast Region	K	x	y	z
Mean BOLD Response				
Main effect of condition (negative > positive)				
R. Inf./Mid. Occipital Gyrus, Fusiform Gyrus	527	45	-76	-5
L. Inf. Occipital Gyrus, Fusiform Gyrus	274	-36	-82	-11
Cerebellar Lobules I-IV, V	125	9	-31	-11
Frontal pole	120	-12	56	28
Main effect of condition (positive > negative)				
R. Hippocampus, Thalamus	228	12	-34	16
L. Hippocampus, Thalamus	155	-9	-34	16
Linear BOLD Attenuation				
General attenuation				
R. Sup. Temporal Gyrus, Mid. Temporal Gyrus,	116	57	-55	10
Inf. Parietal Lobule, Supramarginal Gyrus				
R. Anterior Insula, Inf. Frontal Gyrus, BA 47	114	45	26	-8
Main effect of condition (negative > positive)				
Cuneus, L./R. Calcarine, L./R. Lingual	485	-12	-88	1
L./R. Precuneus	108	6	-61	61
Main effect of group				
L. Thalamus, Post. Insula, Caudate, Putamen	201	-33	-10	-8

Note. R. = Right, L. = Left, Inf. = Inferior, Mid. = Middle, Sup. = Superior, Post. = Posterior