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Stress and reward processing in bipolar disorder: an fMRI study

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Abstract

Objectives—A link between negative life stress and the onset of mood episodes in bipolar disorder (BD) has been established, but processes underlying such a link remain unclear. Growing evidence suggests that stress can negatively affect reward processing and related neurobiological substrates, indicating that a dysregulated reward system may provide a partial explanation. The aim of this study was to test the impact of stress on reward-related neural functioning in BD.

Methods—Thirteen euthymic or mildly depressed individuals with BD and 15 controls performed a Monetary Incentive Delay task while undergoing functional magnetic resonance imaging during no-stress and stress (negative psychosocial stressor involving poor performance feedback and threat of monetary deductions) conditions.

Results—In hypothesis-driven region-of- interest-based analyses, a significant group by condition interaction emerged in the amygdala during reward anticipation. Relative to controls, while anticipating a potential reward, subjects with BD were characterized by amygdalar hyperactivation in the no-stress condition but hypoactivation during stress. Moreover, relative to controls, subjects with BD had significantly larger amygdala volumes. After controlling for structural differences, the effects of stress on amygdalar function remained, whereas groups no longer differed during the no-stress condition. During reward consumption, a group by condition interaction emerged in the putamen due to increased putamen activation to rewards in participants with BD during stress, but an opposite pattern in controls.

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Conclusions—Overall, findings highlight possible impairments in using reward-predicting cues to adaptively engage in goal-directed actions in BD, combined with stress-induced hypersensitivity to reward consumption. Potential clinical implications are discussed.

Keywords

amygdale; bipolar disorder; fMRI; MID; putamen; reward; stress

Bipolar disorder (BD) causes marked impairment across social, cognitive, and occupational domains of functioning (1, 2). Although BD is highly heritable, environmental effects such as negative life stress play a significant role in the development and maintenance of mood symptoms, including symptom onset (3), increased time to recovery (4), and higher likelihood of relapse (5). Despite clear links between life stress and BD, these relationships are not well understood. The reward system may be a key substrate in this regard. This system is particularly interesting because individuals with BD often experience anhedonia (e.g., reduced reactivity to pleasurable stimuli) during depressive episodes and hyperhedonia (e.g., increased pleasure-seeking behavior and reactivity to pleasurable stimuli) during manic episodes (6, 7). Various neuroimaging findings suggest that individuals with BD may have an underlying hypersensitivity to rewards [see (8) for review]: euthymic individuals with BD have been found to exhibit hyperactivation of the amygdala in response to rewards and reward reversal contingencies (9), and elevated ventral striatum and orbitofrontal cortex (OFC) activity during reward anticipation (10). In spite of these findings, inconsistencies exist [e.g., (11, 12)], including a recent report of hypoactivation of dorsal striatal regions in unmedicated sub-syndromal individuals with BD during reward anticipation (13), which points more towards blunted reward processing as a vulnerability factor. Mixed findings may partially stem from the fact that structural abnormalities in reward-related regions have also emerged in BD (e.g., 8,14,15), but volumetric findings are rarely controlled for in functional magnetic resonance imaging (fMRI) reports. Such inconsistencies highlight the need for additional research, including the importance of accounting for possible structural abnormalities while probing functional activation.

Convergent lines of evidence suggest that focusing on the reward system in BD in relation to negative stress might be particularly important, since stress often precedes depressive episodes in BD (3). Preclinical and clinical studies have shown that acute stress can reduce reward responsiveness and trigger anhedonic-like behaviors (16–18). Given the behavioral and neurobiological influence of stressors on reward processing in psychiatrically healthy individuals, in combination with the characteristic hyperhedonia and anhedonia seen in BD, it is imperative to investigate the ways in which environmental stressors may disrupt the reward system in BD. To this end, we investigated stress-induced reward dysfunction in euthymic patients with BD utilizing a monetary incentive delay task, an acute psychosocial stress manipulation, and fMRI.

Given previous fMRI studies with the Monetary Incentive Delay Task (MID) task (19, 20), we hypothesized that, relative to controls, euthymic individuals with BD would show reward-related heightened activation in the amygdala [e.g., (9)], but reduced activation in basal ganglia regions [e.g., (25)] during both anticipation and consumption of rewards.

Regarding the impact of negative psychosocial stress, we previously found that controls exposed to acute psychosocial stress exhibited greater activation in the basal ganglia and amygdala during reward anticipation and blunted activation of striatal regions during reward consumption (22). Given the very limited neuroimaging studies reporting on stress-related reward processing in BD (23), we broadly anticipated that individuals with BD would also show dysfunctional reward processing under stress, but could not predict whether the patterns hypothesized above would be blunted or exaggerated by stress.

Methods

Fifteen volunteers with BD (13 bipolar I disorder and two bipolar II disorder) and 18 demographically matched psychiatrically healthy controls (HC) participated in this study. The Committee on the Use of Human Subjects in Research at Harvard University and the Partners Human Research Committee approved this study, and all participants provided written informed consent. Participants were screened using the Structured Clinical Interview for DSM-IV Disorders (SCID) (24) and the attention-deficit hyperactivity disorder (ADHD) section of the Mini-International Neuropsychiatric Interview (MINI) (25). In addition, all participants completed questionnaires probing depressive and anxiety symptoms: Beck Depression Inventory (BDI-II) (26), Mood and Anxiety Symptom Questionnaire (MASQ-short) (27); positive and negative affect: Positive and Negative Affective Schedule (PANAS–Trait) (28); anhedonia: Snaith–Hamilton Pleasure Scale (SHPS) (29); perceived stress levels: Perceived Stress Scale (PSS) (30); and nicotine use: Nicotine Craving Questionnaire (NCQ) (31). Participants with BD also completed a brief interview to assess current mood symptoms: Hamilton Rating Scale for Depression (HAM-D) (32)] and Young-Mania Rating Scale (YMRS) (33). Participants earned $55 for the study session and $10 to $60 in earnings from the MID task. Detailed inclusion and exclusion criteria, as well as medication information are provided in the Supplementary Data. Neuroimaging data from two patients with BD and three HC participants were unusable due to excessive head motion in the scanner (4 mm to 15 mm), leaving 13 BD and 15 HC included in the final analyses.

During the fMRI session, participants completed four runs of a revised version of the MID task (see below); two runs under no-stress and two runs under stress conditions, in the following order: Run #1: no-stress, Run #2: stress, Run #3: stress, and Run #4: no-stress. The stress manipulation involved negative feedback about task performance. More specifically, in order to induce mental stress during the stress runs (Runs #2 and #3), participants were given negative performance feedback immediately before the start of these runs. Participants were told that they were performing worse than prior participants and, as a result, there was a chance they would receive sudden $5 penalty deductions if they continued to perform poorly. In contrast, participants were given positive performance feedback immediately before the start of the two no-stress runs (Runs #1 and #4) with no possibility of receiving $5 penalties (for more details, see Supplementary Data). Immediately after each run, and prior to performance feedback, subjects completed brief computerized affective ratings that included rating the extent to which they experienced 12 different emotions (e.g., tense, anxious, relaxed, in control) on a scale from 1–5 (1 = not at all/very slightly, 5 = extremely).

MID task

The MID task was a variant of a monetarily-reinforced button-press task designed to elicit neural responses during reward anticipation and consumption [e.g., (28, 29)]. Briefly, at the beginning of each trial, participants were presented with a visual cue (1.5 sec) indicating the reinforcer associated with performance ('+$' for reward or '0$' for no-incentive), followed by a visual cue (a red square, 0.2 sec) that indicated they should execute a button press as quickly as possible. Following response execution, participants received visual feedback about their performance (gain or no-gain on reward trials, and no-change on no-incentive trials). Successful performance during reward trials was associated with monetary gain, and occurred if subjects executed the button press within the 66th percentile of their individual reaction times (RT) obtained from the preceding run (for Run #1, the threshold was calculated using the practice block RT). Gains on successful reward trials varied between $0.95 and $1.15 (mean: $1.05); unsuccessful performance of reward trials was associated with no gain. For no-incentive trials, a 'no-change' feedback was presented regardless of the RT. The task was organized into four runs of 33 trials, with 22 reward and 11 no-incentive trials pseudo-randomized in each run. Subjects were instructed that the probability of success was contingent upon how fast they pressed the button after disappearance of the red square. A brief practice run (identical in design but without feedback) was completed immediately prior to the first run.

Imaging data acquisition

The MRI data were acquired on a 1.5-T Symphony/Sonata scanner (Siemens Medical Systems, Iselin, NJ, USA) using a 12-channel head coil. Structural data were collected using a T1-weighted magnetization-prepared rapid acquisition with gradient echo (MPRAGE) imaging sequence with the following parameters: repetition time (TR) = 2730 msec; echo time (TE) = 3.39 msec; field of view (FOV) = 256 mm; voxel dimensions = 1 × 1 × 1.33 mm; 128 slices. fMRI data were acquired using a gradient echo T2*-weighted echoplanar imaging sequence with an optimized pulse sequence from a previous study in our laboratory (34), including the following parameters: TR = 2500 msec; TE = 35 msec; FOV = 200 mm; voxel dimensions = 3.125 × 3.125 × 3 mm; 35 interleaved slices; tilted slice acquisition; and z-shimming to recover signal in regions affected by susceptibility artifacts.

Behavioral data analyses

Demographic and clinical variables—Independent samples *t*-tests were conducted to compare groups on their ratings (BDI-II, MASQ, SHPS, PSS, PANAS-Trait, NCQ).

In-scanner affective ratings—Positive and negative affect were calculated by averaging the scores obtained on five positive (in control, alert, energetic, relaxed, happy) and seven negative (tense, anxious, powerless, defeated, challenged, stressed, out of control) emotions, respectively, after every run. These ratings were analyzed using a 2 × 2 × 2 repeated measures ANOVA with *Valence* (positive, negative) × *Stress* (stress, no-stress) as within-subject factors, and *Group* (HC, BD) as a between-subject factor.

MID task—In line with our previous publication in healthy controls (22), analyses were restricted to Runs #1 and #2 to focus on the acute effects of the stress manipulation without

potentially confounding carry-over effects. Both behavioral and fMRI analyses were, therefore, conducted on Run #1 (No-stress) and Run #2 (Stress) conditions. While positive feedback was given after Run #3 to mitigate potential carryover effects of the stress manipulation, our prior analyses in healthy controls tested with this paradigm indicated that differences between the first two runs more strongly reflected the effects of 'acute' stress (22).

With respect to behavioral performance, groups were compared using unpaired *t*-tests across different variables: % of reward trials in which subjects received successful reward feedback, number of errors and total amount of money won during no-stress and stress blocks. A *Group* (HC, BD) × *Stress* (stress, no-stress) ANOVA was run to assess task performance.

For RT data, outlier responses were removed before analyses. Outliers were defined as responses < 150 msec or > 1000 msec; responses exceeding three standard deviations above or below the individual's mean; and error trials (trials in which subjects pressed the button too soon before the cue or too late after the cue). Next, a 2 × 2 × 2 repeated measures ANOVA of RT with *Incentive* (reward, no-incentive) and *Stress* (stress, no-stress) as within-subject factors, and *Group* (HC, BD) as a between-subject factor was run.

Neuroimaging data analyses

fMRI data processing was completed using FEAT (FMRI Expert Analysis Tool) version 5.98, part of FSL version 4.1.5 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). After removal of non-brain structures using Brain Extraction Tool (BET) (35), the following pre-processing steps were performed: motion correction [using MCFLIRT (36)]; slice-timing correction using Fourier-space time-series phase-shifting; spatial smoothing using a Gaussian kernel with 6.0-mm full-width half-maximum; grand-mean intensity normalization by a single multiplicative factor; high pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 60 sec); in addition, we used the automatic outlier weighing option available in FSL. FLIRT was used to register functional data to the high-resolution structural images, and FSL's Non-linear Image Registration Tool (FNIRT) (36) was used to register structural images to 2-mm Montreal Neurological Institute (MNI) standard space.

At the individual level, statistical analyses of fMRI data were conducted using a general linear model (GLM) with separate regressors for each incentive cue (Reward, No-incentive) and the three types of feedback [successful reward feedback (gain), unsuccessful reward feedback, no-change (on no-incentive trials) feedback]. Each of these events was modeled using a gamma function and constructed as a hemodynamic response function, convolved with the event onset times. The following were included as covariates of no interest: the six rigid-body motion time courses from the motion correction, the target, errors (e.g., responding prior to the target or not responding at all), and penalties (when $5 penalties were presented during the stress runs). Contrast maps were constructed to identify brain regions involved in reward anticipation (reward versus no-incentive cue) and reward consumption (gain versus no-change feedback).

To test a priori hypotheses that bipolar patients would exhibit abnormal reward processing, anatomical masks were created using the Wake Forest University School of Medicine (WFU) PickAtlas for each of the following regions (for the left and right hemispheres separately): caudate, putamen, nucleus accumbens, and amygdala. Next, for each subject and condition (stress, no-stress), the parameter estimates were extracted using featquery from reward anticipation (reward versus no-incentive cue) and consumption (gain versus no-change feedback) contrast maps and entered into SPSS.

Exploratory analyses were conducted to test for the influence of trait affect (measured by the PANAS), depression (as measured by the BDI-II) and perceived stress (measured by the stress scale) on reward processing during the acute stressor, by correlating these scores with the parameter estimates from each significant region (see Supplementary Data).

A repeated measures ANOVA with *Stress* (stress, no-stress) and hemisphere (left, right) as within-subject factors, and *Group* as a between-subjects factor, was run for each region-of-interest (ROI) and *Phase* (anticipation, consumption) individually. A Bonferroni correction was used to correct for the number of ANOVAs performed ($p = 0.05/8 = 0.006265$). In light of the modest sample size, effect sizes (Cohen's *d* for paired and unpaired *t*-tests or η^2_p values for ANOVA effects) were computed to evaluate the robustness of putative findings. A commonly used interpretation is to refer to effect sizes for independent and dependent groups as small ($d = 0.2$), medium ($d = 0.5$), and large ($d = 0.8$). Similarly, for partial eta squared values, effect size are interpreted as small ($\eta^2_p = 0.01$), medium ($\eta^2_p = 0.06$) and large ($\eta^2_p = 0.14$) based on benchmarks suggested by Cohen (37).

Structural analyses

Volumetric segmentation was performed with the FreeSurfer image analysis suite [FreeSurfer Vol. 5.3, (38, 39)]. Freesurfer estimates cortical and subcortical volumes via a whole brain segmentation procedure (39). The brain parcellation and segmentation were run using the standard ‘recon-all’ script using default settings. The post-processing output for each subject was thoroughly inspected for segmentation errors and no manual edits were required. Intracranial volume (ICV) was also calculated to correct for inter-individual differences in total brain size. All volumes measured were exported to IBM, SPSS, Vol. 21 for statistical analyses. Age and gender were also controlled for, as both of these factors are known to influence structural morphology in humans (40).

Results

Participant characteristics

There were no significant differences between groups on any of the following demographic variables: gender, age, ethnicity, years of education, current/past smoker, tobacco dependency, or current caffeine consumption ($p > 0.10$) (Table 1). Relative to controls, participants with BD had a wider range of depressive symptoms as measured by the BDI-II (range: 0–16), but groups did not differ ($p > 0.30$). On the BDI-II, 12 of the 13 subjects with BD were in the ‘minimal’ range (0–13) and only one subject was in the ‘mild’ range (14–19, score: 16). Similarly, groups did not differ in their PANAS-Trait Positive Affect, MASQ-

AD, or PSS [all p > 0.10]. Relative to controls, subjects with BD reported higher scores on the PANAS-Trait Negative Affect [$t(26) = -2.41$, p = 0.024] and the MASQ [general distress anxious subscale only; missing data on one control subject; HC: $t(25) = -2.49$, p = 0.020]. On the day of the scan, YMRS ratings indicated that all BD participants were below the cut-off for hypomania (< 12). HAM-D ratings on the day of the scan indicated that 8 BD participants were in the 'normal range' (0–7) and five participants were in the 'mildly depressed' (8–15) range.

Behavioral results

Affective ratings—As hypothesized, a significant *Valence* × *Stress* interaction emerged [$F(1,26) = 55.85$, $p < 0.001$] but this effect did not interact with group (p > 0.10). Post-hoc *t*-tests revealed that the stress manipulation significantly increased negative affect and decreased positive affect across all participants (p < 0.003) (Figs. 1A and 1B).

MID performance—Overall, there were no behavioral differences between groups and stress runs in terms of the amount of reward feedback received, number of error trials, total number of errors, and total amount of money won during the task (all p > 0.50) (see Supplementary Data). On average, across all runs and participants, approximately 65% of reward trials (~14 trials) were successful (i.e., participants were faster than the set threshold of 66%) and 35% (~8 trials) were not successful (i.e., participants were slower than the 66% threshold).

RT—When examining RT to the target in Runs #1 and #2, the *Cue* (reward, no-incentive) × *Stress* (stress, no-stress) × *Group* (HC, BD) ANOVA yielded significant main effects of both *Cue* [$F(1,26) = 28.12$, p < 0.01] and *Condition* [$F(1,26) = 5.82$, p = 0.02]; all other p > 0.43. As evident from Figures 1C and 1D, RT was shorter for reward than no-incentive trials (confirming motivated responding) and shorter during the stress (Run #2) than no-stress (Run #1) block (in line with the stress manipulation).

Neuroimaging results

Parameter estimates from our ROIs were normal and satisfied the homogeneity of variance assumption.

Putamen—A *Group* × *Stress* × *Hemisphere* ANOVA on beta weights extracted for reward anticipation (Reward cue minus No-incentive cue) revealed no significant effects (Fig. 2A). An analogous ANOVA for the reward consumption phase (gain minus no-gain) highlighted a significant three-way interaction [$F(1,26) = 4.80$, p = 0.04, $\eta^2_p = 0.16$]. Separate *Group* × *Stress* ANOVAs run for each hemisphere individually clarified that this interaction was driven by the left putamen [$F(1,26) = 4.83$, p = 0.04, $\eta^2_p = 0.16$] (Fig. 2B]. Post-hoc *t*-tests revealed, however, no differences between HC and BD in Run #1 [$t(26) = 1.58$, p = 0.13, $d_s = 0.60$] or Run #2 [$t(26) = -1.38$, p = 0.18, $d_s = 0.52$], indicating that groups differed only in their relative activation in the no-stress versus stress condition.

Caudate and nucleus accumbens—No effects involving *Stress* or *Group* were observed in the caudate or nucleus accumbens during reward anticipation or consumption.

Amygdala—Two significant outliers (1 BD, 1 HC), as listed by SPSS, were identified in the left amygdala during reward anticipation, so these participants were removed from analyses. For reward anticipation, the *Group* × *Stress* × *Hemisphere* ANOVA revealed a significant main effect of *Stress* [$F(1,24) = 6.49$, $p = 0.018$, $\eta^2_p = 0.21$], which significantly interacted with *Group* [$F(1,24) = 27.52$, $p < 0.001$, $\eta^2_p = 0.53$]. Irrespective of the hemisphere, stress increased amygdalar activation in controls, whereas subjects with BD had a stress-induced reduction in amygdala activation. Given that *Hemisphere* did not interact with *Group* × *Stress*, activation from the left and right amygdala were averaged in subsequent analyses. Within Run #1 (no-stress), control subjects demonstrated lower activation than subjects with BD during reward anticipation [$t(24) = -2.75$, $p = 0.01$, $d_s = 1.08$]; conversely, HCs demonstrated higher activation than subjects with BD [$t(24) = 3.51$, $p = 0.002$, $d_s = 1.38$] during reward anticipation in Run #2 (stress) (Fig. 2C). In addition, within the BD group, there was a significant reduction in the amygdalar activation with stress [$t(11) = 4.35$, $p = 0.001$, $d_s = 1.25$], whereas HCs had a significant stress-induced increase in amygdalar activation during reward anticipation [$t(13) = -2.59$, $p = 0.02$, $d_s = 0.69$]. No significant findings emerged in the amygdala during reward consumption in the stress condition (Fig. 2D).

Structural Freesurfer analyses—While controlling for age, gender, and ICV, no significant group differences emerged in the basal ganglia. However, the left and right amygdala were both found to be structurally larger in bipolar subjects as compared to controls [left: $t(26) = -2.83$, $p = 0.009$, $d_s = 1.07$; right: $t(26) = -2.65$, $p = 0.020$, $d_s = 1.00$] (Fig. 3A). No other significant structural group differences emerged. Unstandardized residuals of averaged left and right amygdala controlling for age, gender, and ICV, were calculated and the aforementioned functional analyses for the amygdala were repeated controlling for these residuals. Results did not change in the basal ganglia after controlling for structural volume. Specifically, Group × Stress interaction in the left putamen remained after controlling for volume [$F(1,25) = 4.75$, $p = 0.039$, $\eta_p = 0.16$]. Similar to above results, post-hoc *t*-tests revealed no group differences in Run #1 or Run #2 ($p > 0.10$), indicating that groups differed only in their relative activation in the no-stress versus stress condition with no influence from structural variability. Similarly, significant *Group* × *Stress* interaction for the amygdala was confirmed when taking into account the structural differences [$F(1,23) = 15.17$, $p = 0.001$, $\eta^2_p = 0.39$]. More specifically, under stress (Run #2), HC subjects continued to demonstrate higher amygdalar activation during reward anticipation than subjects with BD ($p = 0.003$, $\eta^2_p = 0.32$) (Fig. 3C). When considering the no-stress condition (Run #1), the group difference in amygdalar activation during reward anticipation was no longer significant ($p = 0.21$)[1]. Finally, across the entire sample, amygdala volume correlated positively with amygdalar activation while anticipating potential rewards during Run #1 ($r = 0.59$, $p = 0.001$) (Fig. 3B); this effect was mainly driven by the BD group (BD: $r = 0.58$, $p = 0.046$; HC: $r = 0.21$, $p = 0.47$), but the groups did not differ in their correlations ($z = 1.04$, $p > 0.05$).

[1]Even though there were no group differences in depressive symptoms (as measured by BDI-II score), there was a greater variability of depressive symptomology in the BD group. Accordingly, we repeated all neuroimaging analyses controlling for BDI-II score and found that stress-induced reward dysfunction in participants with BD remained significant.

Discussion

Using fMRI in conjunction with the MID task and a negative psychosocial stress manipulation, the current study examined the impact of an acute stressor on reward processing in individuals with BD and HCs. The main finding emerging from the fMRI analyses was a stress-dependent effect in the amygdala: relative to controls, individuals with BD showed significantly higher amygdalar activation during reward anticipation under no-stress, whereas the opposite pattern was seen under stress conditions (BD < HC). Notably, groups did not differ in terms of behavioral performance or any of the pre-scan baseline 'in-the-moment' affective questionnaires, suggesting that fMRI findings were not confounded by group differences in task difficulty or mood state on the day of the scan.

Interestingly, structural analyses revealed that both the left and right amygdala were larger in subjects with BD than HC. These findings are in line with some prior studies that have reported similar structural abnormalities in amygdala volume in BD [e.g., (40, 14, 25, 43)], although opposite patterns have also been described (8). A recent meta-analysis reported overall reduced amygdala volumes in BD (43), although these conclusions were driven by studies of children and adolescents with BD, who may show meaningful structural brain differences from adults with BD (44). Medication history may contribute to inconsistencies in amygdala volume differences, since certain BD medications may increase amygdala volumes (14, 45) making it more likely to find larger amygdala volumes in adults with BD as compared to controls and youth with BD. Of note, in the current study, amygdala volume correlated positively with amygdala activation suggesting that prior reports of amygdalar hyperactivation in response to reward anticipation under no-stress [e.g., (9, 44)] might be partially confounded by structural abnormalities in this region.

The amygdala is involved in appetitive motivated learning (47) and plays an important role in reward-related DA release in order to generate 'approach' behaviors (48). Thus, in the face of stress, increased amygdalar activation during reward anticipation may reflect that controls have increased appetitive motivation to engage in actions to cope with the stressor, gain rewards, and avoid punishments. In contrast, among individuals with BD, blunted amygdalar activation while anticipating a potential reward may indicate an impaired ability to use reward-predicting cues to appropriately engage in goal-directed actions when under stress.

During reward consumption, ROI analyses revealed a significant *Group* × *Stress* interaction in the left putamen. Although post-hoc tests did not reveal significant group differences within any run, the overall significant interaction showed that bipolar subjects had a stress-induced increase in putamen activation in response to reward feedback, whereas controls showed the opposite pattern. Decreased striatal activation in controls fits prior reports that acute stressors blunt reward responsiveness or 'liking' of positive stimuli (17, 18, 22, 49), and lead to reduced striatal activation to rewards (50, 51). Conversely, the pattern of increased striatal activation in BD suggests this group may experience stress-induced heightened reward responsiveness, which is consistent with models of hypersensitivity to rewards in BD (52), and findings of reward-related dorsal striatal hyperactivation in BD [e.g., (50)]. Interestingly, participants with BD baseline (under no-stress) putamen activation

during reward consumption correlated with their trait positive affect (see Supplementary Data).

Limitations and future directions

Several limitations should be acknowledged. First, the sample size was small and the BD group was heterogeneous with regard to BD subtype. Second, individuals in the BD group were taking psychotropic medications, as maintenance drugs are often necessary to control symptoms, but sample size was too small to allow sub-analyses evaluating the potential effects of different classes of medication. Third, although affective self-report ratings indicated that the psychosocial stress manipulation was successful, there were no physiological data to confirm the effectiveness of the stress manipulation (or to parse those participants with strong vs. weak physiological stress responses during the experiment). When a Bonferroni correction for multiple comparisons was applied, the *Group* × *Stress* interaction in the amygdala survived ($p = 0.001$) correction, whereas the *Group* × *Stress* interaction in the putamen ($p = 0.04$) becomes insignificant. However, our effect sizes show a large effect (0.16–0.39).

Conclusions

Despite these limitations, findings from the present study extend previous lines of research by highlighting potential atypical patterns of neural functioning—e.g., dysregulated stress-related activation of the amygdala and putamen—that may underlie the relationship between a dysfunctional reward-processing system and BD, at least among predominantly euthymic (and medicated) individuals. Given the euthymic status of the BD group, atypical functioning of these neural regions may represent trait markers of the illness. However, future research is necessary to determine if these neural findings are more appropriately conceptualized as vulnerability factors to BD or effects of the illness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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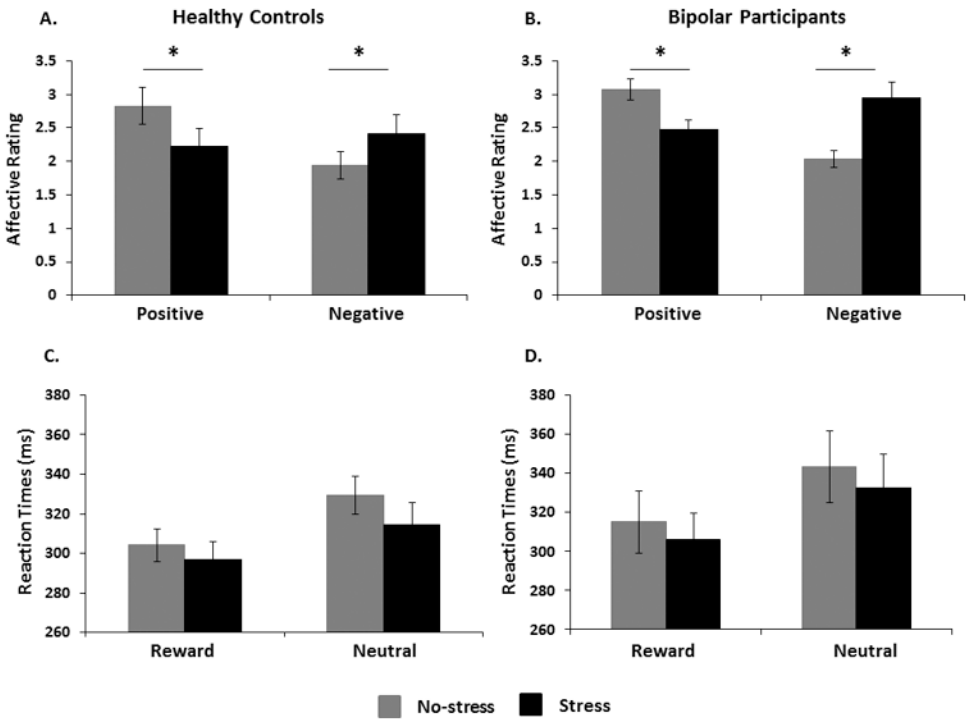

Fig. 1.

Affective ratings (**A** and **B**) and Reaction times (**C** and **D**) across no-stress (Run #1) and stress (Run #2) runs in healthy controls and participants with bipolar disorder. Error bars indicate standard errors.

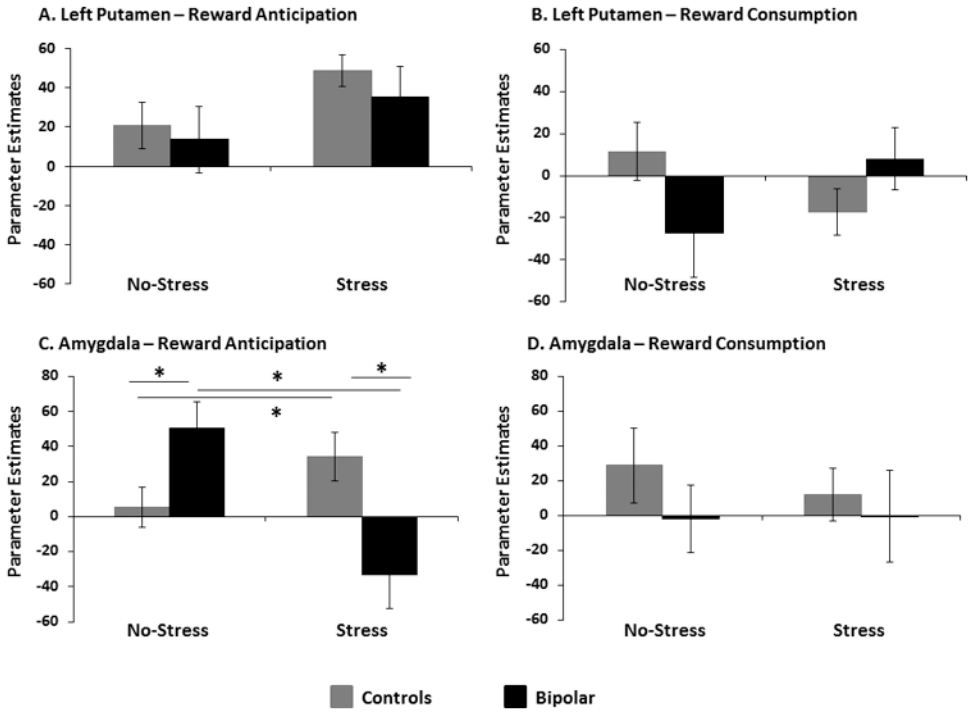

Fig. 2.

Parameter estimates extracted from functional region-of-interest (ROIs) during anticipation and consumption in the putamen (**A** and **B**) and amygdala (**C** and **D**) during stress (Run #1) and no-stress (Run #2) conditions in healthy controls and bipolar participants with bipolar disorder. Error bars indicate standard errors.

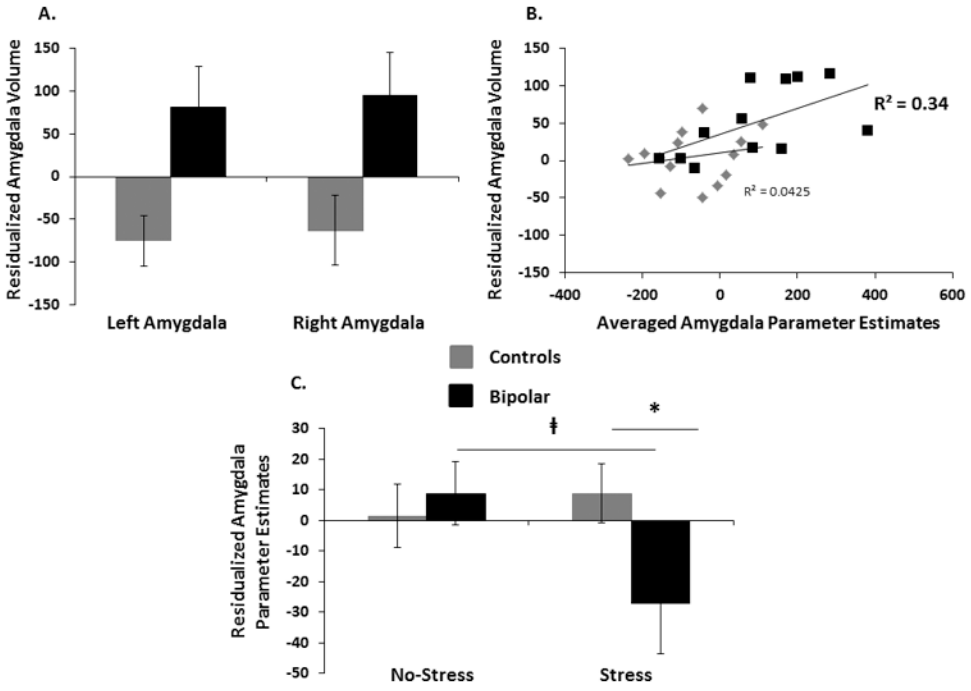

Fig. 3.

Gray matter (corrected for age, gender, and intracranial volume) differences between healthy controls and participants with bipolar disorder (**A**). Association between structural volume and function activation to reward anticipation in the amygdala under no-stress in both groups (**B**). Parameter estimates from the amygdala during reward anticipation after controlling for structural volume in healthy controls and participants with bipolar disorder (**C**). Error bars indicate standard errors.

Table 1
Characteristics of participants by groups

	Controls (n = 15)	Bipolar disorder (n = 13)	p-value
Gender, % female	67% (n = 10)	62% (n = 8)	0.89
Age, years	31.73 (12.35)	27.01 (6.25)	0.21
Ethnicity, % Caucasian	64% (n = 9)	77% (n = 10)	0.92
Education, years	16.86 (2.03)	15.73 (2.02)	0.16
BDI-II score[a]	3.21 (4.61)	5.15 (5.01)	0.31
Anhedonia (MASQ)[a]	52.64 (11.18)	55.69 (11.18)	0.48
General distress anxious (MASQ)[a]	14.17 (3.85)	19.00 (6.25)	0.02
PANAS NA (trait)	12.53 (2.50)	15.38 (3.73)	0.02
PANAS PA (trait)	35.20 (6.82)	34.23 (8.01)	0.73
PSS[a]	18.21 (7.94)	20.77 (5.45)	0.34
HAM-D score	N/A	5.62 (3.62)	N/A
YMRS score	N/A	3.08 (2.84)	N/A

Values are expressed as mean (standard deviation) unless indicated otherwise. BDI-II = Beck Depression Inventory; MASQ = Mood and Anxiety Symptom Questionnaire; PANAS = Positive (PA) and Negative Affect (NA) Schedule; PSS = Perceived Stress Scale; HAM-D = Hamilton Rating Scale for Depression; YMRS = Young Mania Rating Scale.

[a]Data was missing for one healthy control.