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Archival Report

Reward-Related Striatal Responses Following Stress in Healthy Individuals and Patients With Bipolar Disorder

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ABSTRACT

BACKGROUND: Stress has a major impact on the onset and recurrence of mood episodes in bipolar disorder (BD), but the underlying mechanisms remain unknown. Previous studies have shown distinct time-dependent effects of stress on reward processing in healthy individuals. Impaired reward processing is a core characteristic of BD, and altered reward processing during recovery from stress could influence the development and course of bipolar disorder.

METHODS: We investigated brain responses during reward processing 50 minutes after stress using functional magnetic resonance imaging in 40 healthy control subjects and 40 patients with euthymic BD assigned to either an acute stress test (Trier Social Stress Test) or a no-stress condition.

RESULTS: Acute stress increased cortisol levels in both healthy control subjects and patients with BD. Ventral striatal responses to reward outcome were increased in healthy control subjects during stress recovery but not in patients with BD. For anticipation, no differences were found between the groups following stress.

CONCLUSIONS: For the first time, we show altered reward processing in patients with BD during the recovery phase of stress. These data suggest reduced neural flexibility of hedonic signaling in response to environmental challenges. This may increase the susceptibility to stressful life events in the future and play a role in the development of further psychopathology in the longer term.

Keywords: Bipolar disorder, Cortisol, Imaging, Reward, Stress, Trier Social Stress Test

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Stress susceptibility plays an important role in the course of bipolar I disorder (BD). For example, early life trauma is more prevalent in patients with BD (1), and stressful life events often precede the recurrence of both depressive and (hypo)manic episodes (2,3). In contrast to individuals without BD, who often maintain mental health after stressful experiences (4), individuals with BD appear to be more susceptible to the detrimental consequences of stress. To improve treatment of BD, it is important to understand what is causing mood symptoms in this patient group. However, the exact underlying neurobiological mechanism is still unclear.

One important line of research in this area is the relation between stress and reward processing. The neural circuitry underlying reward processing, consisting of the ventral striatum and the orbitofrontal cortex (OFC), is highly sensitive to the effects of stress. More specifically, acute stress reduces OFC and ventral striatal responses during the receipt of a reward (i.e., reward outcome/consumption/feedback) in the healthy brain (5,6). Because of its association with anhedonia in the absence of stress (7,8), reduced neural responses to reward outcome suggest that acute stress reduces the ability to experience pleasure, at least temporarily. However, stress initiates the release of neuromodulators that affect the brain and body in a time-dependent manner. Acute stress induces a state of hypervigilance induced by (nor)adrenaline and the acute effects of cortisol. However, after stress has subsided, cortisol is one of the players in the recovery and cognitive reappraisal of the stressful experience [for a review, see Hermans *et al.* (9)]. Stress-induced reward processing effects are time dependent as well, as shown by increased OFC and striatal responses to reward during stress recovery, suggesting an upregulation in the subjective pleasantness of a reward after stress has subsided (10). Therefore, abnormalities in the brain's adaptation after stress may ultimately have detrimental consequences for resilience and result in the development of symptoms in patients with BD. However, to date, no studies have investigated the neural responses to reward during stress recovery in BD.

Therefore, we investigated ventral striatal and OFC responses during a reward processing task in the aftermath of stress in patients with euthymic BD and healthy control (HC) subjects. As the use of antipsychotics is associated with an attenuated stress-induced cortisol response (11), we decided to exclude patients that were currently using antipsychotics.

Participants were randomly assigned to either the psychosocial stress condition or no-stress condition of the Trier Social Stress Test (TSST) and subjected to the functional magnetic resonance imaging (fMRI) reward task 50 minutes later. We hypothesized that in HC subjects, ventral striatal and OFC responses to reward outcome would be increased in HC subjects, whereas we would find a lack of upregulation of activity in these areas in patients with BD.

METHODS AND MATERIALS

Participants

All procedures were checked and approved by the University Medical Center Utrecht ethical review board. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Because of the difference between men and women on both stress-induced cortisol levels and reward responses (12,13), we decided to only include male participants. All participants gave written informed consent and received a financial reimbursement. A total of 40 male HC subjects and 40 euthymic male patients were included in this study. The diagnosis of BD was established in a previous study at University Medical Center Utrecht (14) using the Structured Clinical Interview for DSM Disorders (15) [the reliability of which is moderate to excellent (16)]. To reduce patient burden, we did not do the interview again. All patients with BD and 16 HC subjects were recruited from this previous study, and an additional 24 control subjects were recruited via advertisements. HC subjects were matched to BD subjects on age, education, smoking, and body mass index. Participants were randomly assigned to the validated stress or no-stress condition of the TSST (see below for a detailed description). Three subjects were excluded owing to MRI scanner artifacts, missing task data, or failed coregistration during preprocessing (HC-no stress group = 1, BD-no stress group = 1, BD-stress group = 1). These participants' data were not excluded from the cortisol and demographics data analyses. All patients were required to be euthymic for at least 2 weeks and antipsychotic free and to have unchanged drug treatment for 4 weeks (for a list of medication, see Table 1). A euthymic state was defined as the absence of a current episode of depression or mania based on a clinical interview: the Inventory of Depressive Symptomatology, Clinician Rating (17) for depression, cutoff score >24, and Young Mania Rating Scale (18), for mania, cutoff score >12, as previously published (11). Based on these criteria, 1 patient was rescheduled to participate on a different day. Exclusion criteria for all participants were the use of corticosteroids, the use of recreational drugs in the week preceding participation (based on a urine multidrug screening device), heavy exercise 2 hours prior to participation, and caffeine intake 4 hours prior to participation. Additional exclusion criteria for HC subjects were a psychiatric disorder (as assessed with a semistructured interview by a trained researcher (the Mini-International Neuropsychiatric Interview) (19) or a self-reported first-degree family member with a psychiatric disorder. Participants were instructed not to consume any heavy meals or brush their teeth in the 2 hours preceding participation, and we ensured that they did not eat, drink, or chew gum in the 20 minutes before each saliva sample. Each participant had a small snack 30 minutes after the start of the experiment. To reduce variability between participants in effects of eating on cortisol levels, participants were not allowed to eat after this snack until the end of the experiment.

General Procedure and Stress Induction

We carried out an adapted version of the TSST to induce psychosocial stress (20). The reward task was carried out in the MRI scanner 50 minutes after TSST onset. A full description of the TSST and the experimental day can be found in the Supplement.

Reward Task

The reward task included the anticipation and consumption of rewarding and nonrewarding outcomes. In short, each trial started with a cue, followed by fixation point, the target, and the outcome screen (Figure 1). Participants were instructed to press a button during target presentation as fast as possible, irrespective of cue type. If the button was pressed within the time limit (duration of target presentation), the trial was categorized as a hit. A full description of the task can be found in the Supplement.

Salivary Cortisol and Alpha-amylase

From each participant, we obtained 7 saliva samples using salivettes (Sarstedt, Nümbrecht, Germany) (time = −10, +5, +15, +30, + 45, +95 and +115 minutes relative to TSST onset). The first sample was taken 115 minutes after the start of the experiment. Samples were temporarily stored at 4°C and subsequently stored at −20°C. Cortisol and alpha-amylase levels were analyzed as previously described (21).

Questionnaires

To investigate whether the experience of stressful life events was associated with reward-related neural responses following stress, participants completed the Life Stressor Checklist-Revised (LSC-R) (22). Given the previously reported association between the number of life events and BD symptomatology, we calculated an overall life stressor score for all participants, giving 1 point to every positively endorsed stressor (LSC-R number of life events). Additionally, we assigned weights to the life stressors, reflecting the participant's subjective rating of how the stressor affected the participant's life in the past year (LSC-R severity). Questionnaires were missing for 3 participants (HC group = 1, BD group = 2). Subjective stress levels during the test day were assessed using a 100-mm visual analog scale, which was completed before, during, and after the stress or control test (−10, +5, and +15 minutes after onset).

Functional MRI

All imaging was performed on a Philips 3T whole-body MRI scanner (Philips Medical Systems, Bothell, WA). First, a whole-brain 3-dimensional T1-weighted structural image was acquired with the following scan parameters: voxel size = 0.8 mm

Table 1. Demographics

	HC-No Stress Group (n = 19)	HC-Stress Group (n = 20)	BD-No Stress Group (n = 19)	BD-Stress Group (n = 19)	p[a]
Age, Years	41.5 ± 1.7	39.0 ± 1.8	42.9 ± 1.8	39.8 ± 2.0	.420
Stressful Life Events (LSC-R Events)[b]	3.5 ± 0.6	3.3 ± 0.5	5.3 ± 0.5	5.0 ± 0.5	.015[c]
Severity of Stressful Life Events (LSC-R Severity)	6.53 ± 1.27	7.74 ± 1.57	10.72 ± 1.66	10.89 ± 1.39	.098
Handedness (Right/Left)	17/2	19/1	16/3	16/3	.680
Education[d]	4.6 ± 0.3	4.3 ± 0.3	4.4 ± 0.3	4.8 ± 0.3	.513
Smoking (Yes/No)	3/16	3/17	4/15	4/15	.936
Body Mass Index, kg/m^2	25.7 ± 0.9	25.6 ± 0.8	26.1 ± 0.8	25.4 ± 0.8	.948
Duration of Illness, Years	–	–	16.5 ± 2.2	17.2 ± 1.6	.782
Manic Episodes	–	–	4.7 ± 1.2	6.4 ± 2.9	.582
Depressive Episodes	–	–	8.8 ± 2.9	10.8 ± 5.8	.760
IDS-C Score	–	–	4.9 ± 0.9	3.5 ± 0.6	.204
YMRS Score	–	–	1.0 ± 0.4	0.3 ± 0.2	.114
Medications	–	–	1.3 ± 0.2	1.2 ± 0.2	.706
Lithium (Yes/No)	–	–	14/5	13/6	.721
Benzodiazepine (Yes/No)	–	–	2/17	1/18	.547
Anticonvulsants (Yes/No)	–	–	6/13	1/18	.036[c]
Antidepressants (Yes/No)	–	–	3/16	5/14	.426
General Medication Load[e]	–	–	2.5 ± 0.2	3.1 ± 0.3	.172

Values are mean ± SD or n/n.

BD, bipolar disorder; HC, healthy control; IDS-C, Inventory of Depressive Symptomatology, clinician-rated; LSC-R, Life Stressor Checklist-Revised; YMRS, Young Mania Rating Scale.

[a]Values represent comparisons between BD-no stress and BD-stress groups if data were not available for HC subjects; otherwise, comparisons were made among the 4 groups. All measures were normally distributed as indicated by a Kolmogorov-Smirnov test.

[b]Data from 3 participants were missing for the questionnaires (1 HC subject, 2 patients with BD).

[c]$p < .05$.

[d]Evaluated on a scale ranging from 1 (low education) to 6 (master or Ph.D. degree).

[e]Calculated as described in Sackeim (43).

isotropic, repetition time = 10 ms, echo time = 4.6 ms, slices = 200, flip angle = 8°. Functional images were obtained using a 2-dimensional echo-planar imaging sensitivity encoding sequence with the following parameters: repetition time = 1600 ms, echo time = 23 ms, voxel size = 4 × 4 × 3.6 mm, gap = 0.4 mm, dynamics = 366, slices = 30, scan duration = 10 minutes. A full description of the preprocessing steps can be found in the Supplement.

Statistical Analyses

Demographics and Behavior. Differences in demographics were analyzed using 2-sample t tests or chi-square tests. The percentage hits and reaction times for rewarding and nonrewarding trials were calculated and analyzed using two 2 × 2 analyses of variance (ANOVAs) with group (HC/BD) and stress (stress/no stress) as between-subjects factors.

Functional MRI. Imaging data were analyzed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm). The effects of reward (reward/nonreward) on brain activity during the anticipation and outcome phases were estimated during individual first-level analyses. The design matrix consisted of 6 regressors modeling the onsets and duration of the anticipation (time between cue presentation and target presentation) and outcome phases (time from target presentation to end outcome) of each trial. The regressors were as follows: reward anticipation, nonreward anticipation, reward hit, reward miss, nonreward hit, and nonreward miss. These factors were convolved with a canonical hemodynamic response function. The movement parameters (3 translations and 3 rotations) obtained from realignment were added as factors to correct for head movement. A high-pass filter with a cutoff period of 128 seconds was applied to correct for signal drift.

We selected the ventral striatal and OFC regions of interest (ROIs), as previously described (23), using the automatic anatomical labeling atlas (24) and the WFU PickAtlas Toolbox implemented in SPM. The mean regression coefficient over all voxels within each ROI (combining the left and right hemispheres) was extracted for each subject for the 6 regressors. These values were subsequently analyzed using two 2 × 2 × 2 ANOVAs (for anticipation and outcome), with group (HC/BD) and stress (stress/no stress) as between-subjects factors, and reward (reward/nonreward) as within-subjects factor. Interaction effects were defined significant if they survived multiple-comparison correction of $p < .025$ ($p < .05/2$ comparisons: anticipation and outcome). Given the clear predefined hypothesis of increased neural responses after stress in HC subjects only, we employed Fisher's least significant difference test for follow-up pairwise comparisons among the 4 groups. Participants were removed from the analysis if the parameter estimates exceeded ±2 SDs from the group mean on more than one ROI and all phases, as previously described (10). Based on this criterion, we found one outlier (HC-no stress).

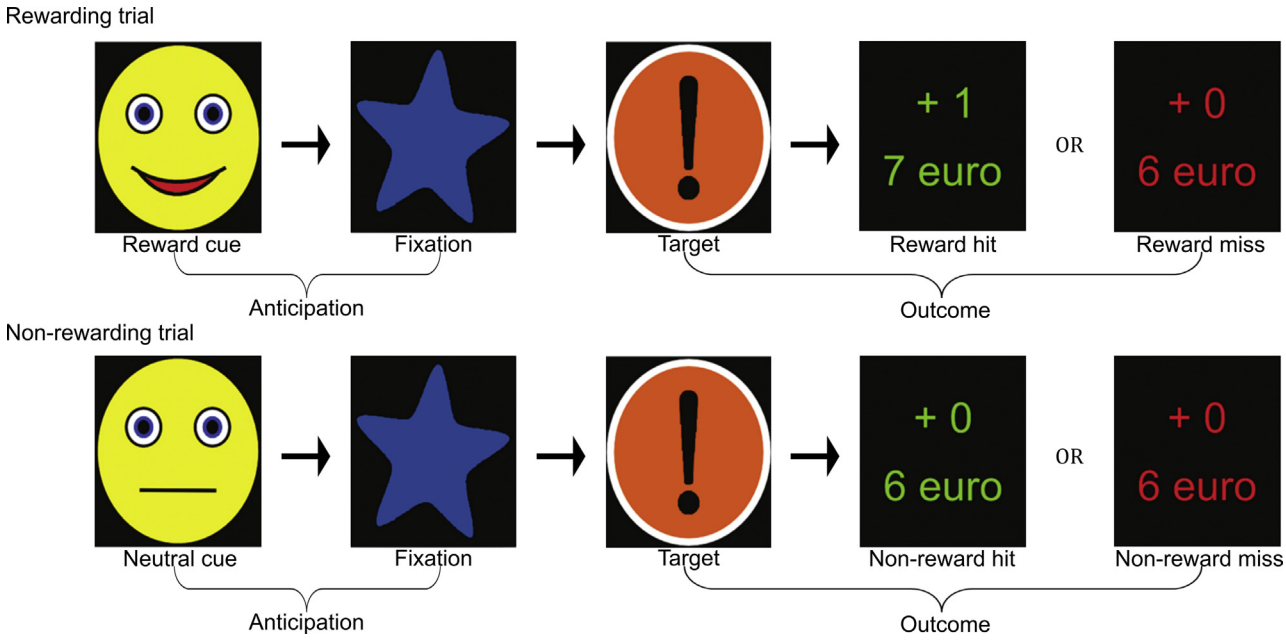


Figure 1. Reward task. The task consisted of two phases: reward anticipation and reward outcome/feedback. Participants were instructed to press a button as fast as possible during target presentation. There were two types of anticipation: reward anticipation and neutral (nonrewarding) anticipation. Depending on whether the button was pressed within time limit, there were four possible types of feedback: reward hit, reward miss, nonreward hit, and nonreward miss.

This resulted in the following samples sizes for the fMRI analyses: HC-no stress (n = 18), HC-stress (n = 20), BD-no stress (n = 19), and BD-stress (n = 19). The outlier was not excluded from the other analyses.

Cortisol, Alpha-amylase, and Subjective Stress. The effects of stress, group, and their interaction on cortisol and alpha-amylase over time were analyzed using two 7 × 2 × 2 repeated-measures ANOVAs with time as within-subjects factor and group (HC/BD) and stress (stress/no-stress) as between-subjects factors. To check whether patients show more blunting of the cortisol response, we calculated the number of responders and nonresponders. Responders were defined as those with a minimum increase of 2.5 nmol/L in response to the TSST (25). Subjective stress over time was analyzed using a 3 × 2 × 2 repeated-measures ANOVA with time as within-subjects factor and group and stress as between-subjects factors. Significant interaction effects were followed up by Bonferroni-corrected post hoc comparisons, correcting for 7 time points for cortisol and alpha-amylase and cortisol, and 3 time points for subjective stress.

Correlation Analyses. Differences between patients with BD and HC subjects in number of stressful life events were analyzed using a 2-sample t test. We used Pearson's correlation to examine the association between ROI activity (mean parameter estimate within the ventral striatum and OFC during reward/nonreward anticipation and outcome) and the number of stressful life events (LSC-R score), cortisol (directly after reward task), and alpha-amylase (during TSST) within the stress groups. Fisher's Z tests were used to test for significant differences between correlations. Correlations were defined significant if $p < .0083$ ($p < .05/6$ comparisons).

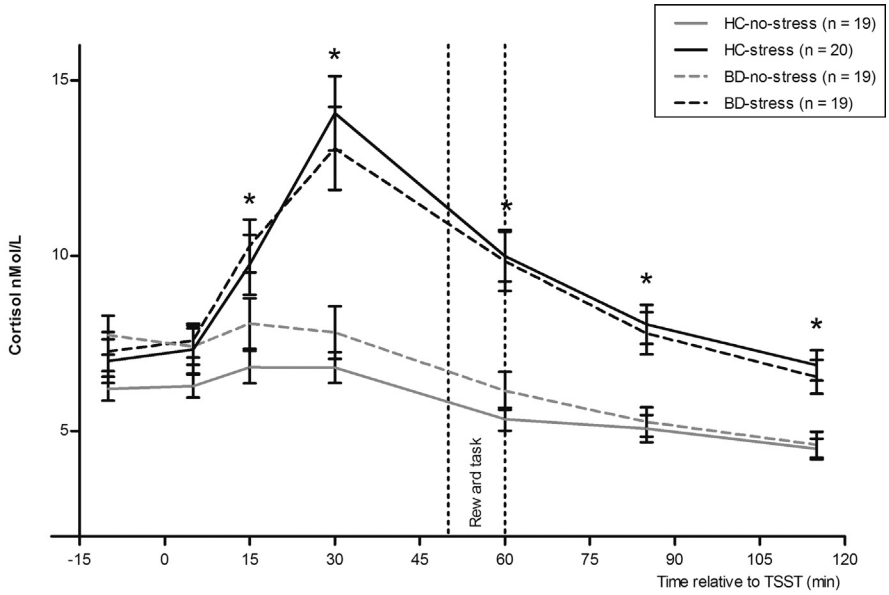
RESULTS

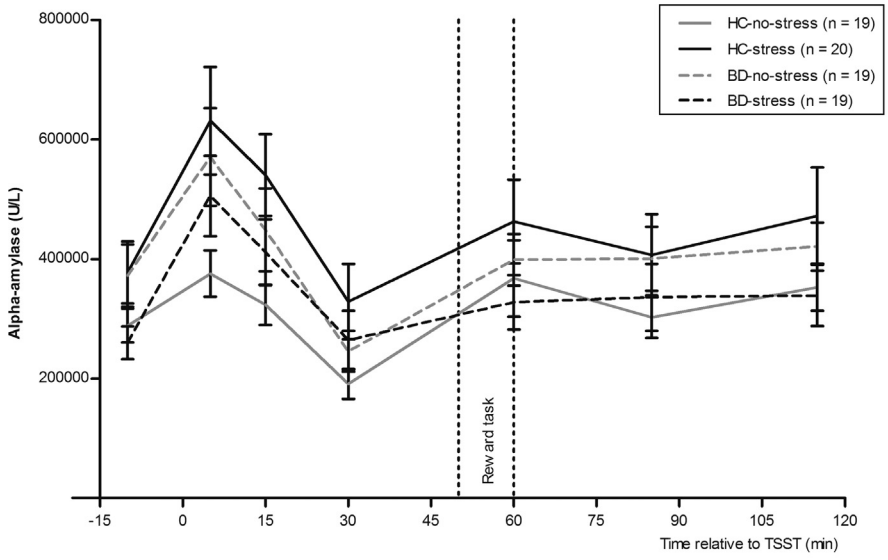
Demographics

There were no significant differences among the 4 groups in age, handedness, education, smoking, or body mass index. Moreover, there were no significant differences between the BD-no stress and BD-stress groups in terms of duration of illness; Inventory of Depressive Symptomatology, Clinician Rating score; Young Mania Rating Scale score; number of medications used; and general medication load (Table 1). Patients with BD scored higher on the number of stressful life events as measured by the LSC-R compared with control subjects ($F_{3,70}$ = 3.730, p = .015). There was a significant difference in use of anticonvulsants between the BD-no stress and BD-stress groups (6 of 19 in the BD-no stress group and 1 of 19 in the BD-stress group were using anticonvulsants [χ^2_1 = 4.4, p = .036]).

Cortisol, Alpha-amylase, and Subjective Stress

Cortisol increased over time in the stressed groups (time × stress interaction [$F_{6,68}$ = 9.635, p = 1.169 × 10^{-7}, η_p^2 = .460, power = 1.000]) (Figure 2) and peaked at +30 minutes. Cortisol remained elevated in the stress groups up until the final sample (main stress effect $p < .05$ on cortisol levels from third to final sample). We found no main effect of group, group × stress interaction, or time × group × stress interaction on all measures (all p values >.05). There was no significant difference in the number of cortisol responders in patients compared with control subjects (numbers of responders in each group: 17





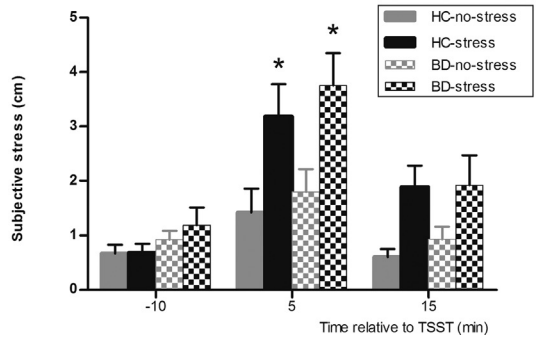


Figure 2. Subjective stress, salivary cortisol, and alpha-amylase response to the Trier Social Stress Test (TSST). There was a time × stress interaction in cortisol levels, subjective stress, and alpha-amylase. Times are relative to TSST onset. Brain responses to reward were measured between +50 and +60 minutes. Error bars represent SEM. *$p < .05$. BD, bipolar disorder; HC, healthy control.

Table 2. Performance During Reward Task

	Reward vs. Nonreward	HC-No Stress Group	HC-Stress Group	BD-No Stress Group	BD-Stress Group
Reaction Time, ms, Mean ± SEM	Reward	272.2 ± 5.5	281.9 ± 6.4	269.0 ± 7.4	281.4 ± 14.2
	Nonreward	297.2 ± 8.6	301.1 ± 5.9	302.0 ± 7.5	303.6 ± 14.2
Hits, %, Mean ± SEM	Reward	49.5 ± 1.1	49.3 ± 1.7	49.6 ± 2.6	48.2 ± 1.2
	Nonreward	44.0 ± 1.2	45.3 ± 1.5	44.0 ± 3.2	43.5 ± 1.5

Values are averaged over reward hit and nonreward hit.
BD, bipolar disorder; HC, healthy control.

control subjects, 13 patients; $t_{37} = 1.212$, $p = .234$). Brain responses during reward processing were measured between +50 and +60 minutes.

Stress increased subjective stress (time × stress interaction [$F_{2,72} = 8.364$, $p = .001$, $\eta_p^2 = .191$, power = 0.941]) and alpha-amylase levels (time × stress interaction [$F_{6,68} = 4.520$, $p = .001$, $\eta_p^2 = .277$, power = 0.978]). There was a trend toward a significant difference between patients and control subjects in the no-stress condition on alpha-amylase levels, implying slightly higher alpha-amylase levels in the BD-no stress group over all samples (group × stress interaction [$F_{1,73} = 3.528$, $p = .064$, $\eta_p^2 = .046$, power = 0.458]) (Figure 2). There was no main effect of group or stress, or time × stress × group interaction.

Behavior

There was a main effect of reward on reaction times and percentage correct trials, showing faster reaction times ($F_{1,73} = 78.800$, $p = 3.169 \times 10^{-13}$, $\eta_p^2 = .519$) and more hits ($F_{1,73} = 34.344$, $p = 1.237 \times 10^{-7}$, $\eta_p^2 = .320$) during rewarding trials. The four groups did not differ in reaction time to rewarding or nonrewarding trials or percentage correct trials (Table 2).

Functional MRI

Reward Outcome. We first investigated ventral striatal and OFC responses during reward outcome using a mixed-model 2 × 2 × 2 (group × stress × reward) ANOVA, expecting increased responses in HC subjects in the aftermath of stress. In general, rewarding outcomes elicited higher OFC responses than nonrewarding outcomes (main effect of reward [$F_{1,72} = 47.124$, $p = 1.962 \times 10^{-9}$, $\eta_p^2 = .396$, power = 1.000]) (Table 3). We found that the effects of stress on ventral striatal responses significantly differed between HC subjects and patients (group × stress interaction [$F_{1,72} = 5.759$; $p = .019$, $\eta_p^2 = .074$, power = 0.658]) (Figure 3), which did not differ between reward and nonreward outcome (group × stress × reward interaction $p > .05$). Post hoc comparisons revealed that ventral striatal responses were higher in stressed control subjects than in nonstressed control subjects ($p = .014$), while there was no difference between patients in the stress and no-stress conditions ($p = .392$), between control subjects and patients in the no-stress conditioning condition ($p = .079$), and between control subjects and patients in the stress condition ($p = .112$). These results indeed reveal increased ventral striatal responses in the aftermath of stress to both reward and nonreward outcomes in HC subjects only.

In contrast to our expectations, we found no difference between HC subjects and patients in OFC responses following stress (group × stress [$F_{1,72} = 1.341$; $p = .251$, $\eta_p^2 = .018$], group × stress × reward [$F_{1,72} = 0.460$ $p = .500$, $\eta_p^2 = .006$]).

Owing to the nonnormal distribution of anticonvulsant users in the BD groups, we performed the analyses again with the use of anticonvulsant as a covariate. We found similar results in the ventral striatum (group × stress interaction [$F_{1,71} = 5.660$, $p = .020$, $\eta_p^2 = .074$]) and the OFC (group × stress interaction [$F_{1,71} = 1.497$, $p = .225$, $\eta_p^2 = .021$]).

Reward Anticipation. Overall, striatal responses were higher during the anticipation of rewarding versus nonrewarding outcomes (main effect of reward [$F_{1,72} = 23.867$, $p = 6.044 \times 10^{-6}$, $\eta_p^2 = .249$]). There were no effects of stress on ventral striatal responses during reward anticipation (group × stress interaction [$F_{1,72} = 0.127$, $p = .723$, $\eta_p^2 = .002$], reward × group × stress interaction [$F_{1,72} = 0.009$, $p = .924$, $\eta_p^2 = 1.261 \times 10^{-4}$]) (Supplemental Figure S1).

Correlational Analyses. We did not find any significant correlations between striatal or OFC responses during each phase (anticipation/outcome) and the number of stressful life events, salivary cortisol, and salivary alpha-amylase that survived correction of multiple comparisons ($p < .0083$ [.05/6 comparisons]). See Supplemental Table S1 for a list of all p values.

DISCUSSION

This study investigated reward processing during the recovery phase of acute stress in patients with euthymic BD and HC subjects. We found that ventral striatal responses during

Table 3. Statistics From the Group (Control/Patient) × Stress (Stress/No Stress) × Reward (Reward/Nonreward) Analysis of Variance on Blood Oxygen Level–Dependent Responses During the Outcome Phase

	p	F	η_p^2
Ventral Striatum			
Reward	.435	0.615	.008
Group × stress	.019[a]	5.759	.074
Group × stress × reward	.172	1.905	.026
Orbitofrontal Cortex			
Reward	1.962×10^{-9}	47.124	.396
Group × stress	.251	1.341	.018
Group × stress × reward	.500	0.460	.006

[a]Significant after multiple-comparison correction of $p < .025$ ($p < .05/2$ comparisons: anticipation and outcome).

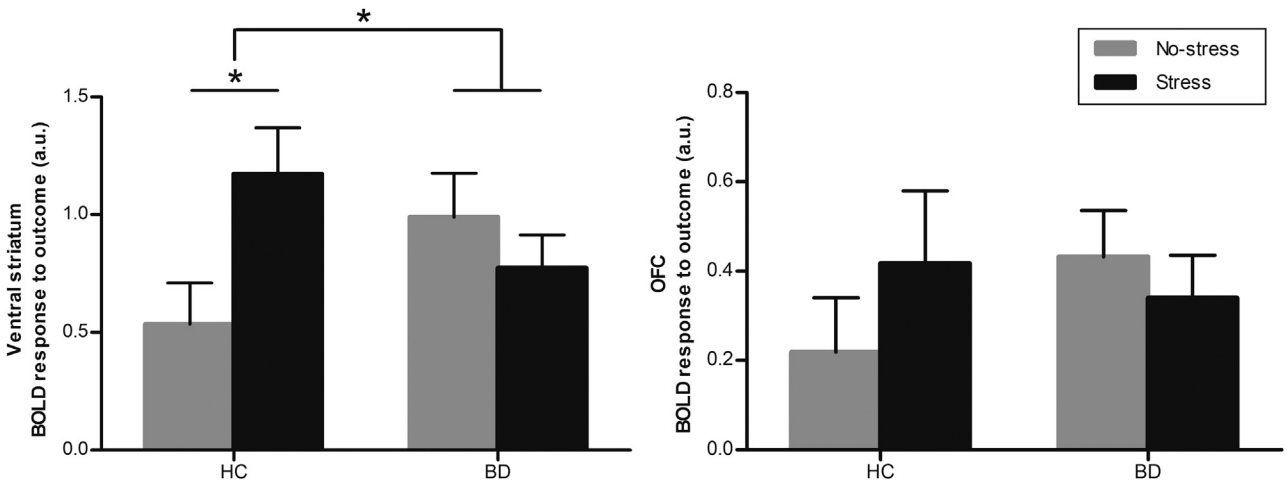


Figure 3. Ventral striatal and orbitofrontal cortex (OFC) blood oxygen level–dependent (BOLD) responses during the outcome phase in the contrast outcome > rest. A 2-way analysis of variance revealed a significant group (healthy control [HC]/bipolar disorder [BD]) × stress (stress/no stress) interaction in the ventral striatum. There was no interaction with reward, and BOLD responses were therefore averaged across reward and nonreward outcomes. Error bars represent SEM. a.u., arbitrary units. *$p < .05$

reward outcome were increased during the recovery phase of stress in the healthy brain but not in patients with BD. We found no effects on OFC responses. These results show altered recovery from stress in patients with BD regarding striatal reward processing. This reduction of stress-related dynamics in reward processing may at least partially explain an increased sensitivity for (recurrent) mood episodes following stressful experiences.

Given 1) altered reward processing across mood states (26–33), 2) the relation between stress and the onset and recurrence of bipolar disorder (2), and 3) the profound effects of stress on reward processing (5,6,34), we hypothesized that reward processing in association with stress would be altered in euthymic BD patients. Indeed, a previous study found that patients with BD display altered reward processing during stress (35), but the neural response to stress is complex and time dependent. Acute stress induces a state of hypervigilance whereas the aftermath of stress is characterized by recovery and cognitive reappraisal, (at least partially) driven by increased cortisol levels (9). Because these factors are important for resilience in the longer term, we investigated reward processing during the recovery from stress. We previously reported an absence of ventral striatal and OFC upregulation in the aftermath of stress in a different set susceptible individuals, namely siblings of patients with schizophrenia (10). For the first time, we now show that patients with BD show reduced striatal responses to reward outcome during the recovery phase of stress. In HC subjects, an increase in reward-related responses following stress may be related to an increase in the hedonic value of rewards after stress termination. In patients with BD, a lack of this increase in reward-related responses following stress suggests reduced neural flexibility in association with stress and impaired recovery of reward-related processes, which could ultimately lead to mood symptoms.

Our findings in HC subjects are in line with our previously published findings in an independent study. In that study, using the same reward task, we found increased ventral striatal and OFC responses to reward and nonreward hits following stress in a different set of HC subjects (10). In the current study, we replicated our finding of increased ventral striatal activity following stress in HC subjects but failed to replicate the OFC finding. Although many variables were similar across these two studies (gender, education, handedness, body mass index), a couple of explanations for this discrepancy are possible. First, the two studies made use of different imaging acquisition settings. Given the fact that the OFC is specifically vulnerable to image distortion and signal losses, there may have been differences in data quality. Second, age could have played a role. OFC activity is known to decrease with age (36), and the mean age in the HC subjects in the current study was higher than the previous study (40.3 years vs. 33.9 years). An additional similarity between the current study and our previous study is that our effects were independent of monetary reward. Regarding this, two explanations are possible: 1) the sample size may have been too small to detect significant effects of reward in a 3-way ANOVA; and 2) receiving feedback from a rewarding correct trial without monetary value may be rewarding in itself, as presented previously during verbal feedback (37). Therefore, it should be noted that our design may possibly not include an actual neutral, nonrewarding cue, which should be included in future versions of the task.

A strength is that we excluded the use of corticosteroids and antipsychotics. A portion of patients with BD in the general population use antipsychotics, which affect stress-induced cortisol levels (11) and striatal responses to reward (38,39). The use of antidepressants, anticonvulsants, and/or lithium has not been reported to influence the stress-induced cortisol response (11,40,41). Moreover, clinical characteristics between patient groups that are and are not on antipsychotics were previously found to be comparable (11), indicating that by selecting this subgroup of patients with BD, we do not reduce the generalizability of our results to patients

that do take antipsychotics. An important limitation of our study is that we restricted our sample to male patients, which complicates the generalizability of the results to female patients. Another limitation is that we investigated reward processing only, as opposed to brain responses to anticipating/avoiding losses. It has been suggested that successfully achieving/anticipating a reward is the same as avoiding/anticipating a loss (42), but this has only been found in HC subjects. Therefore, it is important that future studies explore the effects of stress on loss avoidance/anticipation in psychiatric populations in relation to stress. Another limitation is that our design does not include a behavioral measure of reward outcome (reward likeability or reward learning). The only behavioral outcome was reaction time, which is more likely related to reward anticipation. It remains unclear whether our findings of increased neural responses to reward outcome are mirrored by increased reward learning; therefore, this measure should be included in future versions of the task. Another limitation is that we investigated neural responses to one type of reward outcome, as opposed to brain responses to anticipating/avoiding losses and/or to varying amounts of reward. Therefore, it is possible that stress affected responsiveness to stimuli in general, instead of responses to positive task performance specifically. It is therefore important that future studies include punishment trials and varying amount of rewards in relation to stress. Furthermore, given the limited sample size, this study is in need of replication in a new sample to confirm the observed effects.

In summary, our findings demonstrate that patients with euthymic BD display altered stress recovery in striatal responses to neutral and rewarding outcomes. Specifically, HC subjects showed an increase in ventral striatal activity during reward outcome 50 minutes after stress, while this was absent in patients with BD. Together, these data suggest altered neural flexibility and reduced stress-related dynamics in striatal reward reactivity, which in turn may increase the risk of relapse in BD.

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