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Original Article

Waiting to win: elevated striatal and orbitofrontal cortical activity during reward anticipation in euthymic bipolar disorder adults

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Objective: Bipolar disorder may be characterized by a hypersensitivity to reward-relevant stimuli, potentially underlying the emotional lability and dysregulation that characterizes the illness. In parallel, research highlights the predominant role of striatal and orbitofrontal cortical (OFC) regions in reward-processing and approach-related affect. We aimed to examine whether bipolar disorder, relative to healthy, participants displayed elevated activity in these regions during reward processing.

Methods: Twenty-one euthymic bipolar I disorder and 20 healthy control participants with no lifetime history of psychiatric disorder underwent functional magnetic resonance imaging (fMRI) scanning during a card-guessing paradigm designed to examine reward-related brain function to anticipation and receipt of monetary reward and loss. Data were collected using a 3T Siemens Trio scanner.

Results: Region-of-interest analyses revealed that bipolar disorder participants displayed greater ventral striatal and right-sided orbitofrontal [Brodmann area (BA) 11] activity during anticipation, but not outcome, of monetary reward relative to healthy controls ($p < 0.05$, corrected). Whole-brain analyses indicated that bipolar disorder, relative to healthy, participants also displayed elevated left-lateral OFC (BA 47) activity during reward anticipation ($p < 0.05$, corrected).

Conclusions: Elevated ventral striatal and OFC activity during reward anticipation may represent a neural mechanism for predisposition to expansive mood and hypo/mania in response to reward-relevant cues that characterizes bipolar disorder. Our findings contrast with research reporting blunted activity in the ventral striatum during reward processing in unipolar depressed individuals, relative to healthy controls. Examination of reward-related neural activity in bipolar disorder is a promising research focus to facilitate identification of biological markers of the illness.

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Bipolar disorder is a severe and recurrent illness involving significant impairment, including erratic work performance, high rates of divorce and suicide, and high rates of alcohol and substance abuse (1, 2). Yet, bipolar disorder is often diagnosed late in illness course, or misdiagnosed as other illnesses such as unipolar depression (3). Examination of underlying pathophysiological

processes of bipolar disorder with neuroimaging techniques such as functional magnetic resonance imaging (fMRI) is a step forward not only toward understanding the neural basis of bipolar disorder, but also toward identifying biological markers to facilitate earlier and more accurate diagnosis and treatment of the illness (4).

Research suggests that bipolar disorder may be characterized by a hypersensitivity to reward-relevant stimuli which may be a key component of the emotional lability and dysregulation that characterize the illness (5). A hypersensitivity to potential future rewards may lead to an excessive increase in approach or goal-related affect in the presence of reward-relevant life events, which may be reflected in a vulnerability to hypo/manic symptoms (5). Support for this perspective comes from psychosocial research indicating that, compared to relevant control groups, individuals with bipolar disorder display elevated scores on self-report measures of sensitivity to reward-relevant stimuli (6, 7), and that among bipolar disorder individuals, a heightened sensitivity to reward-relevant stimuli is associated with a more severe course (8). Furthermore, both reward-striving and reward-attainment-relevant life events have been demonstrated to trigger hypo/manic episodes among individuals with bipolar disorder (9, 10).

The ventral striatum is a core component of the neural circuitry of reward processing and is involved in processing both primary (pleasant tastes/smells/sights) and secondary (monetary) rewards (11–14). The ventral striatum is part of a larger cortico-limbic circuit subserving reward-related processing, and a subregion of the prefrontal cortex, specifically the orbitofrontal cortex (OFC), has also been implicated in reward processing (14, 15). Bermpohl and colleagues (16) recently reported that, compared to healthy controls, bipolar manic patients displayed increased lateral OFC activity [Brodmann area (BA) 11, BA47] during anticipation of reward-relevant cues. Using electroencephalography (EEG), we also have reported that individuals with bipolar disorder displayed abnormally elevated left-lateral prefrontal cortical activity during reward anticipation, supporting a reward hypersensitivity model of bipolar disorder (17).

No neuroimaging studies have yet examined neural activity during reward processing in bipolar euthymic individuals. Accordingly, the goal of the present study was to examine neural activity during reward processing in bipolar euthymic, relative to age and gender ratio-matched healthy control, participants using a well-validated card-guessing paradigm designed to examine neural activity during both anticipation and receipt of monetary reward and loss (12, 18, 19). We focused on examination of euthymic bipolar disorder adults to examine whether abnormalities in reward-related brain function may represent a persistent, rather than mood state-dependent, feature of bipolar disorder. Using region-of-interest analyses, we hypothesized that bipolar euthymic, relative to healthy control, participants would show elevated ventral striatal and OFC activity to reward but not loss-relevant cues. Previous research indicating that (i) the ventral striatum is involved in monitoring the anticipation of reward (15, 20), and (ii) individuals with bipolar disorder are particularly affected by anticipatory or goal striving-based life events/stimuli (10, 21) also allowed us to hypothesize that bipolar disorder, relative to healthy control, participants would show elevated reward-related brain activity during anticipation, rather than receipt, of reward. Exploratory whole-brain analyses were also conducted to examine group differences in other reward-related brain regions.

Materials and methods

Participants

Twenty-one remitted adults with bipolar I disorder [mean age = 31.53, standard deviation (SD) = 8.66; male/female: 9/12] participated in the study. Bipolar disorder was diagnosed according to DSM-IV criteria using the Structured Clinical Interview for DSM-IV-research version (SCID-P) (22). All bipolar disorder participants had been in remission, as determined by SCID-P criteria, for at least two months at the time of scanning. Current mood state was confirmed by having a 25-item Hamilton Rating Scale for Depression (HRSD-25) score ≤ 7 and a Young Mania Rating Scale (YMRS) score ≤ 10 on the day of the scan. Bipolar disorder participants had been in remission for an average of 24 months and 85% had had a depressive episode as their most recent episode. Sixteen bipolar disorder participants had at least one lifetime comorbid psychiatric disorder. This rate of lifetime comorbidity is consistent with existing epidemiological research on lifetime comorbidity rates in bipolar disorder (23, 24). Importantly, participants with bipolar disorder were free from alcohol/substance abuse or dependence for a minimum of seven months (range: 7 to 269 months). Comorbid diagnoses, including alcohol/substance abuse or dependence, were diagnosed according to DSM-IV criteria using the SCID-P. Twenty bipolar disorder participants were taking at least one psychotropic medication, representative of the bipolar disorder population,

most of whom require psychotropic medication (25) (Table 1).

Twenty healthy adult control participants (mean age = 31.56, SD = 6.87; male/female: 8/12) with no previous personal or family history of psychiatric illness in first-degree relatives participated in the study. We used the Family History Questionnaire (Nimgaonkar, personal communication) to assess the psychiatric illness of first-degree relatives of participants. Healthy control participants were gender ratio matched [$\chi^2(1) = 0.03$, $p = 0.85$] and age-matched [$t(39) = -0.01$, $p = 0.99$) with bipolar disorder participants. All participants were right handed and native English speaking.

Exclusion criteria for all participants included: a history of head injury (from medical records and participant report), systemic medical illness, cognitive impairment [score < 24 on the Mini-Mental State Examination (26)], premorbid IQ estimate < 85 on the National Adult Reading Test (27), Axis-II borderline personality disorder, and general exclusion criteria for MRI. Further exclusion criteria for bipolar disorder participants included rapid cycling disorder, and for control participants included previous or current alcohol/illicit substance abuse (determined by SCID-P, saliva, and urine screen).

The participant population reflected the demographics of Pittsburgh and the surrounding area. The study protocol was approved by the University of Pittsburgh Institutional Review Board. After giving a complete description of the study to the participants, written informed consent was obtained.

Paradigm

We employed a slow event-related fMRI card-guessing paradigm (Fig. 1) designed to examine reward-related brain function to anticipation and receipt of monetary reward and loss. Each trial included an anticipation period and outcome period, where participants received win, loss, or no-change feedback for each trial.

Trials were presented in a pseudorandom order with predetermined outcomes. During each 20-sec trial, participants had 4 sec to guess, via button press, whether the value of a visually presented card with a possible value of 1–9 was higher or lower than five. After a choice was made, the trial type was presented visually for 6 sec, indicating whether the trial was a reward-anticipation (presentation of an upward arrow) or loss-anticipation (presentation of a downward arrow) type. In reward-anticipation trials participants would win money if their guess was correct and there would be no change in earnings if their guess was incorrect. In loss-anticipation trials participants would lose money if their guess was incorrect and there would be no change in

Table 1. Demographic and clinical variables

	Bipolar disorder (n = 21)		Healthy controls (n = 20)			
	Mean or proportion	SD	Mean or proportion	SD	Statistic	p-value
Age at scan	31.53	8.66	31.56	6.87	$t(39) = -0.01$	0.99
Females	12/21		12/20		$\chi^2(1) = 0.03$	0.85
Daily nicotine consumption	7/21		2/20		$\chi^2(1) = 2.03$	0.15
Daily caffeine consumption	16/21		7/20		$\chi^2(1) = 5.48$	0.02
Age of illness onset	18.14	6.33				
Illness duration	13.39	8.07				
HRSD-25	6.43	4.20				
YMRS	2.29	2.51				
No. of psychotropic drugs	2.14	1.01				
Total medication load	3.00	1.64				
Antipsychotic medication load (chlorpromazine equivalent)	1.57	0.51				
Mood stabilizers	15/21					
Antipsychotic agents	12/21					
Antidepressants	8/21					
Benzodiazepines	3/21					
Dopaminergic antidepressants (buproprion)	3/21					
Lifetime presence of anxiety disorder	9/21					
Lifetime presence of eating disorder	0/21					
Lifetime presence of somatoform disorder	0/21					
Prior history of alcohol/drug abuse or dependence	13/21[a]					

SD = standard deviation; HRSD-25 = Hamilton Rating Scale for Depression (25-item); YMRS = Young Mania Rating Scale.
[a]Bipolar disorder participants were free from alcohol/drug abuse or dependence for a minimum of seven months prior to the present study (range: 7–269 months).

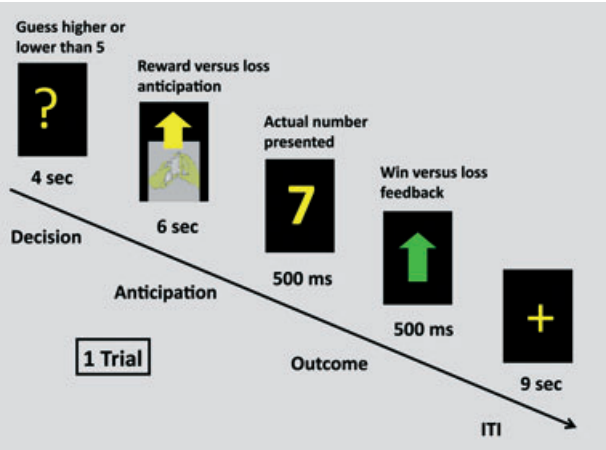

Fig. 1. Functional magnetic resonance imaging (fMRI) monetary reward paradigm. The anticipation period involved either reward-anticipation (presentation of an upward arrow) or loss-anticipation (presentation of a downward arrow). Analyses for the outcome period focused on win-outcome-after-reward-anticipation (presentation of an upward green arrow) and loss-outcome-after-loss-anticipation (presentation of a downward red arrow). ITI = inter-trial interval.

earnings if their guess was correct. The anticipation period was immediately followed by the outcome period, where participants were presented with the *actual* numerical value of the card (500 msec) and received outcome feedback (additional 500 msec): a green upward-facing arrow for win, a red downward-facing arrow for loss, or a yellow circle for no-change feedback. A crosshair was then presented for 9 sec [inter-trial interval (ITI)]. The outcome period was defined as a 7-sec period starting at the point when participants were presented with the actual numerical value of the card, and the baseline period comprised the last 3 sec of the ITI. Twenty-four trials were presented in one run, with 12 reward-anticipation and 12 loss-anticipation trials. Within reward-anticipation trials there were six win-outcome-after-reward-anticipation trials and six no-change-outcome-after-reward-anticipation trials. Within the loss-anticipation trials there were six loss-outcome-after-loss-anticipation trials and six no-change-outcome-after-loss-anticipation trials. Previous findings have indicated that one run of 24 trials (12 trials for each of the two possible anticipation trial types and six trials for each of the four possible outcome trial types) is effective for assessing reward-related brain function and minimizing fatigue and habituation (18, 19).

Participants were told that they would receive $1 for each win, lose 50 cents for each loss, and obtain no earnings change for no-change outcomes. Outcome probabilities were, in fact, fixed such that each participant received $3 in earnings. Participants were unaware of the fixed outcome probabilities in the paradigm and were led to believe that their performance would determine net monetary gain.

The version of the card-guessing task employed in the present study was designed to examine reward-related brain activity while equating behavior across groups. In line with existing research that utilized the current version of the card-guessing task (18, 19), we predicted no differences in reaction time between individuals with bipolar disorder and healthy control participants.

Medication

To examine the possible effects of psychotropic medication on neuroimaging measures in bipolar disorder participants, we computed: (i) a medication load, an index that reflects the number and dose of different medications, as in our previous neuroimaging studies on bipolar disorder (28, 29) (see *Supplementary materials*); (ii) total antipsychotic medication load (in chlorpromazine equivalents); (iii) the total number of psychotropic medications; and (iv) the identified medication status [taking versus not taking each of five main psychotropic medication subclasses: mood stabilizers, antipsychotic agents, antidepressants, anxiolytics, and dopaminergic antidepressants (e.g., bupropion)]. Given the possible role that dopamine plays in ventral striatal-centered reward processing (14), we also re-ran ventral striatal region-of-interest (ROI) analyses after excluding three bipolar disorder participants taking dopaminergic antidepressants.

Neuroimaging data acquisition

Neuroimaging data were collected using a 3.0 Tesla Siemens Trio MRI scanner (Erlangen, Germany) at the University of Pittsburgh. Structural three-dimensional axial MPRAGE images were acquired in the same session [echo time (TE) = 3.29 msec; repetition time (TR) = 2200 msec; flip angle = 9°; field of view (FOV) = 256 × 192 mm; slice thickness = 1 mm; matrix = 256 × 256; 192 continuous slices]. Mean blood oxygen level-dependent (BOLD) images were then acquired with a gradient echo EPI sequence during 8 min covering 39 axial slices (3.1 mm thick; TR/TE = 2000/28 msec; FOV = 205 × 205 mm; matrix 64 × 64; flip angle = 90°).

Neuroimaging data analysis

Data were preprocessed and analyzed using Statistical Parametric Mapping (SPM) software, version 5

(London, UK) (http://www.fil.ion.ucl.ac.uk/spm). Data for each participant were realigned to the first volume in the time series to correct for head motion. Realigned images were then coregistered with the subject's anatomical image, segmented, normalized to the standard Montreal Neurological Institute (MNI) template, and spatially smoothed with a Gaussian kernel of 8 mm full width at half maximum (FWHM).

A first-level fixed-effect model was constructed for each participant and scan, and predetermined condition effects at each voxel were calculated using a *t*-statistic, producing a statistical image for six contrasts: reward-anticipation-minus-baseline, loss-anticipation-minus-baseline, win-outcome-after-reward-anticipation-minus-baseline, no-change-outcome-after-reward-anticipation-minus-baseline, loss-outcome-after-loss-anticipation-minus-baseline, and no-change-outcome-after-loss-anticipation-minus-baseline. Movement parameters from the realignment stage were entered as covariates of no interest to control for participant movement. No participant displayed greater than 4 mm of movement. Trials were modeled using the canonical hemodynamic response function.

Two general linear models (GLMs) were conducted on the *t*-contrast images generated in the previous single-subject analyses to examine the BOLD signal during the anticipation period and the outcome period, as there were different numbers of variables for anticipation (two: reward versus loss-anticipation) and outcome (four: win-outcome-after-reward-anticipation, no-change-outcome-after-reward-anticipation, loss-outcome-after-loss-anticipation, and no-change-outcome-after-loss-anticipation). In the GLM for the anticipation-period, a second-level random-effects within-group and between-group analysis was therefore conducted as a 2 (diagnostic group) × 2 (anticipation type) repeated-measures analysis of variance (ANOVA). In the GLM for the outcome period, a second-level random-effects within-group and between-group analysis was conducted as a 2 (diagnostic group) × 4 (outcome type) repeated-measures ANOVA. Both GLMs were conducted on an *a priori* bilateral ventral striatal ROI mask, an *a priori* bilateral OFC ROI, and additionally on whole-brain data. The bilateral ventral striatal ROI was defined as two 8 mm spheres based on MNI coordinates (right: x = 9, y = 9, z = –8; left: x = –9, y = 9, z = –8) from previous meta-analyses (30, 31). The OFC ROI was defined as bilateral BA11 and BA47 [Wake Forest Toolbox PickAtlas Talairach Daemon template (32)], given Bermpohl and colleagues' (16) finding that manic bipolar disorder patients displayed elevated activity in these OFC regions during reward expectation. To control for multiple statistical testing in ROI analyses we maintained a family-wise error (FWE) rate at $p < 0.05$. Given the conservative nature of the FWE correction for whole-brain analyses, we used the AlphaSim method to control for multiple voxelwise statistical testing in whole-brain analyses. This provided an empirically driven clusterwise threshold of $p < 0.05$ across the whole brain. For whole-brain analyses, we therefore used a voxelwise threshold of $p < 0.005$ and a cluster (k) extent, determined by Monte Carlo simulations at the whole-brain level implemented in AlphaSim, of 58 voxels. This accounted for spatial correlations between BOLD signal changes in neighboring voxels. Post-hoc analyses with pairwise and independent *t*-tests were performed within SPM in ROI and whole-brain clusters showing a significant (corrected) group × condition interaction in each ANOVA. Beta values were extracted for graphical purposes only.

To control for multiple post-hoc tests we used a Bonferroni-corrected voxelwise threshold to correct for the four *a priori* post-hoc comparisons in the anticipation-period GLM: (i) bipolar-reward-anticipation versus control-reward-anticipation; (ii) bipolar-loss-anticipation versus control-loss-anticipation; (iii) bipolar-reward-anticipation versus bipolar-loss-anticipation; (iv) control-reward-anticipation versus control-loss anticipation; $p < 0.05/4 = 0.013$. We similarly controlled for four main *a priori* post-hoc comparisons of interest focusing on actual win or actual loss in the outcome period GLM: (i) bipolar-win-outcome-after-reward-anticipation versus control-win-outcome-after-reward-anticipation; (ii) bipolar-loss-outcome-after-loss-anticipation versus control-loss-outcome-after-loss-anticipation; (iii) bipolar-win-outcome-after-reward-anticipation versus bipolar-loss-outcome-after-loss-anticipation; (iv) control-win-outcome-after-reward-anticipation versus control-loss-outcome-after-loss-anticipation; $p < 0.05/4 = 0.013$.

Exploratory analyses

We explored possible relationships between activity in regions from ROI and whole-brain analyses showing a significant main effect of group or a group × condition interaction and demographic, clinical, daily caffeine and nicotine consumption, and medication variables, as well as medication load (total and antipsychotic), total number of psychotropic medications, and taking versus not taking each of five main psychotropic medication subclasses: mood stabilizers, antipsychotic agents, antidepressants, anxiolytics, dopaminergic antidepressants (bupropion).

Results

Behavioral analyses

In line with prediction and existing research that employed the current version of the card-guessing task (18, 19), bipolar disorder and healthy control participants did not differ in reaction time during the card-guessing task, $t(35) = 1.10$, $p = 0.29$.

Ventral striatal activity during anticipation period

There was a main effect of anticipation condition on activity in both the right and left ventral striatal ROI mask ($p < 0.05$, FWE corrected), such that all participants had greater bilateral ventral striatal activity during reward, as opposed to loss, anticipation trials (Table 2). There was a significant group × anticipation condition interaction on activity in both the right and left ventral striatum ($p < 0.05$, FWE corrected) (Table 2, Fig. 2). This effect was maintained after removing three bipolar disorder participants taking dopaminergic antidepressants ($p < 0.05$, FWE corrected). Post-hoc analyses revealed that bipolar disorder participants displayed significantly greater right, but not left, ventral striatal activity during reward anticipation relative to healthy controls ($p < 0.007$, Bonferroni corrected) (Table 2). No difference in ventral striatal activity was observed between individuals with bipolar disorder and healthy control participants during loss anticipation. Post-hoc analyses also indicated that bipolar disorder, but not healthy control, participants showed significantly greater bilateral ventral striatal activity during reward anticipation than loss anticipation ($p < 0.001$, Bonferroni corrected) (Table 2).

Orbitofrontal cortical activity during anticipation period

There was a significant group × anticipation condition interaction on activity in the right OFC [(BA11) $p < 0.05$, FWE corrected] (Table 2, Fig. 3). Post-hoc analyses revealed that bipolar disorder participants displayed significantly greater right-sided OFC activity during reward anticipation relative to healthy controls ($p < 0.004$, Bonferroni corrected) (Table 2). Bipolar disorder participants also displayed significantly greater right OFC activity during reward versus loss anticipation ($p < 0.001$, Bonferroni corrected) (Table 2). No difference in right OFC activity was observed between bipolar disorder and healthy control participants during loss anticipation, or in healthy control participants between reward and loss anticipation. The group × anticipation condition interaction on activity in the left lateral OFC (BA47) (Table 2) failed to meet FWE correction. Exploratory post-hoc analyses, however, revealed that left-lateral OFC activity during the anticipation period displayed a similar pattern as right-sided OFC activity (see *Supplementary materials*).

Whole-brain activity during anticipation period

There was a main effect of anticipation condition on activity in the right middle occipital gyrus and in a number of neural regions supporting reward processing and affect that surpassed our cluster extent threshold of 58 voxels. In all cases, these regions were characterized by greater activity during reward, as opposed to loss, anticipation trials. There was a significant group × anticipation condition interaction on whole-brain activity in the left-lateral OFC (BA47) that surpassed our AlphaSim-corrected cluster extent threshold of 58 voxels (Table 3, Fig. 4). Post-hoc analyses on the left-lateral OFC revealed that bipolar disorder, relative to healthy control, participants displayed significantly greater left-lateral OFC activity during reward anticipation ($p = 0.007$, Bonferroni corrected) (Table 3). No difference in left-lateral OFC activity was observed between bipolar disorder and control participants during loss anticipation. Post-hoc analyses also indicated that bipolar disorder, but not healthy control, participants showed significantly greater left-lateral OFC activity during reward anticipation than loss anticipation ($p < 0.001$, Bonferroni corrected) (Table 3).

Outcome period

There was no significant main effect of group, or group × condition interaction, within the ventral striatal or OFC ROI mask (see *Supplementary Table 1*), or for whole-brain activity, for the four contrasts of interest in the outcome period.

Correlational analyses with ventral striatal and OFC activity

There were no relationships between ventral striatal or OFC activity during reward processing and demographic variables, comorbid anxiety diagnosis, daily caffeine and nicotine consumption, total medication load, medication load for antipsychotic medications, total number of psychotropic medications, and taking versus not taking each of the five main psychotropic medication subclasses: mood stabilizers, antipsychotic medications, antidepressants, anxiolytics, and dopaminergic antidepressants (see *Supplementary Table 2*). There was also no relationship between ventral striatal

Table 2. ROI analyses on ventral striatal and orbitofrontal cortical BOLD signal during anticipation period

Condition	Hemisphere	Cluster size	*F*/*t*	df	Corrected for multiple tests
Main effect of anticipation type (reward > loss)	Right VS	48	11.51[a]	39	Yes ($p < 0.05$, FWE)
	Left VS	66	18.49[a]	39	Yes ($p < 0.05$, FWE)
	Right OFC	15	7.59[a]	39	No
	Left OFC	4	11.68[a]	39	No
Main effect of group	Right VS	2	4.68[a]	39	No
	Left VS	0	2.17[a]	39	No
	Right OFC	3	5.01[a]	39	No
	Left OFC	4	5.26[a]	39	No
Group × anticipation interaction	Right VS	42	10.91[a]	39	Yes ($p < 0.05$, FWE)
	Left VS	28	8.34[a]	39	Yes ($p < 0.05$, FWE)
	Right OFC	41	15.21[a]	39	Yes ($p < 0.05$, FWE)
	Left OFC	92	10.22[a]	39	No
Between-group post-hoc effects					
BD > HC: reward anticipation	Right VS	36	2.50[b]	39	Yes ($p < 0.013$, Bonferroni)
	Left VS	4	1.88[b]	39	No
	Right OFC	27	2.75[b]	39	Yes ($p < 0.013$, Bonferroni)
BD > HC: loss anticipation	Right VS	1	1.67[b]	39	No
	Left VS	0	0.64[b]	39	No
	Right OFC	1	1.83[b]	39	No
Within-group post-hoc effects					
BD reward anticipation >	Right VS	80	4.14[b]	20	Yes ($p < 0.013$, Bonferroni)
BD loss anticipation	Left VS	78	5.15[b]	20	Yes ($p < 0.013$, Bonferroni)
	Right OFC	56	3.14[b]	20	Yes ($p < 0.013$, Bonferroni)
HC reward anticipation >	Right VS	0	1.33[b]	19	No
HC loss anticipation	Left VS	3	1.80[b]	19	No
	Right OFC	2	1.42[b]	19	No

Analyses were conducted on an *a priori* bilateral ventral striatal region of interest (ROI) defined as two 8 mm spheres based on Montreal Neurological Institute (MNI) coordinates (right: x = 9, y = 9, z = –8; left: x = –9, y = 9, z = –8) from previous meta-analyses (30, 31) and an *a priori* bilateral OFC ROI (BA11, BA47). Main effect, interaction, and post-hoc analyses were conducted on the blood oxygen level-dependent (BOLD) signal for the anticipation period minus the baseline period. To control for multiple statistical tests for ROI main effect and interaction analyses, we maintained a family-wise error (FWE) rate at $p < 0.05$. We used a Bonferroni-corrected voxelwise cut-off to correct for four multiple *a priori* post-hoc comparisons ($p < 0.05/4 = 0.013$). BD = bipolar disorder; HC = healthy controls; VS = ventral striatum; OFC = orbitofrontal cortex.
[a]*F*-value
[b]*t*-value.

and OFC activity during reward processing and a lifetime history of alcohol/substance abuse or dependence (see *Supplementary Table 2*) [as noted, participants with bipolar disorder were free from alcohol/substance abuse or dependence for a minimum of seven months (range: 7–269 months)].

Discussion

The present study was the first to examine reward-related brain activity in bipolar euthymic participants and healthy controls during reward processing. Consistent with hypotheses, ROI analyses indicated that bipolar disorder participants showed greater ventral striatal activity and right-sided OFC activity during anticipation, but not outcome, of monetary reward, relative to healthy controls. Whole-brain analyses indicated elevated left-lateral OFC activity among bipolar disorder participants during reward anticipation, relative to healthy controls. No difference in ventral striatal activity and OFC activity was observed between bipolar disorder and healthy control participants during loss anticipation. All main findings were specific to the anticipation period.

The ventral striatum is implicated in reward processing (11–14) and there is growing evidence that dopamine plays an important role in ventral striatal-centered reward processing (14). Dopaminergic abnormalities may therefore serve as the neurochemical basis for elevated ventral striatal activity in bipolar disorder. Elevated OFC activity has also been linked to reward processing, and Bermpohl and colleagues (16) recently reported that bipolar manic patients displayed greater OFC activity during reward anticipation relative to healthy controls. We have now shown abnormally elevated OFC and ventral striatal activity during reward anticipation in bipolar disorder euthymic adults, and suggest that this may represent a neural mechanism for the elevated self-report and neurophysiological indices of reward sensitivity

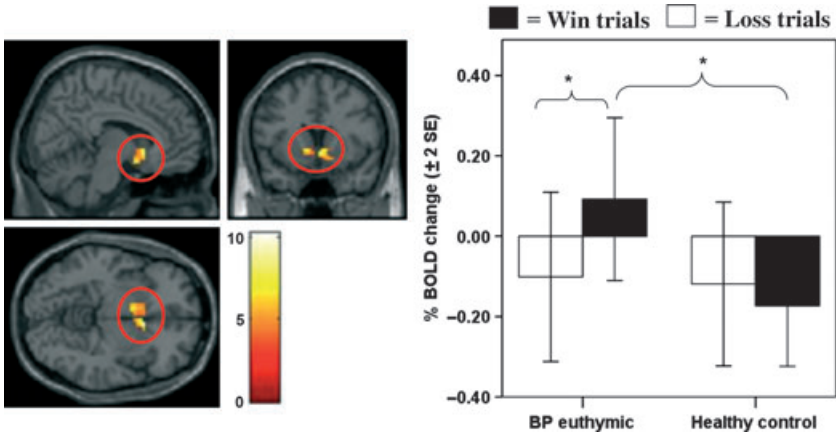

Fig. 2. Bilateral ventral striatal activity during anticipation period [region of interest (ROI)]. The left panel displays the anatomical location of the significant group × anticipation condition interaction on the bilateral ventral striatal ROI mask, defined as 8 mm spheres based on the Montreal Neurologic Institute coordinates system (right: x = 9, y = 9, z = –8; left: x = –9, y = 9, z = –8) from previous meta-analytic research (30, 31) [right: $F(1,39) = 10.91$, $p < 0.05$, family-wise error (FWE) corrected, $k = 42$ voxels; left: $F(1,39) = 8.34$, $p < 0.05$, FWE corrected, $k = 28$ voxels]. The right panel displays a histogram of the mean bilateral ventral striatal activity depicting the group x anticipation condition interaction. Color bars reflect beta values, and significant clusters were overlaid on sagittal, coronal, and axial brain slices. Statistical tests were performed within Statistical Parametric Mapping software and beta values were extracted for graphical purposes only. BOLD = blood oxygen level dependent; SE = standard error; BP euthymic = bipolar disorder patients in a euthymic state (n = 21); healthy controls (n = 20). *significant post-hoc comparison at $p < 0.013$ (Bonferroni corrected).

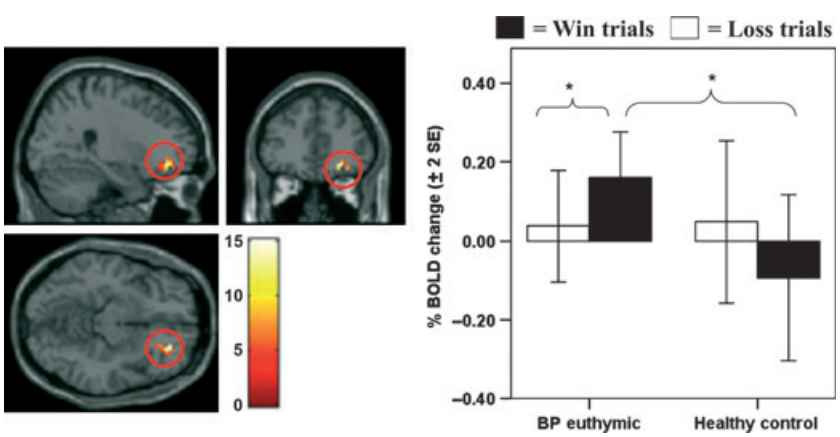

Fig. 3. Right orbitofrontal cortical (OFC) activity during the anticipation period [region of interest (ROI)]. The left panel displays the anatomical location of the significant group × anticipation condition interaction on right-sided OFC activity (BA11) from the bilateral OFC ROI mask [$F(1,39) = 15.21$, $p < 0.05$, family-wise error (FWE) corrected, $k = 41$ voxels]. The right panel displays a histogram of mean right-sided OFC activity depicting the group × anticipation condition interaction. Color bars reflect beta values, and significant clusters were overlaid on sagittal, coronal, and axial brain slices. Statistical tests were performed within Statistical Parametric Mapping software and beta values were extracted for graphical purposes only. BOLD = blood oxygen level dependent; SE = standard error; BP euthymic = bipolar disorder patients in a euthymic state (n = 21); healthy controls (n = 20). *significant post-hoc comparison at $p < 0.013$ (Bonferroni corrected).

(6–8, 17) and approach-related behavior (5) underlying vulnerability for hypo/mania in bipolar illness.

While control participants did not recruit the ventral striatum, they did recruit the left-lateral OFC during both reward and loss anticipation. Rodent studies suggest that the ventral striatum may encode both the value (or magnitude) and identity (or quality) of rewarding stimuli, while the OFC may be necessary for encoding the identity, but not the value, of reward (33). This suggests that bipolar disorder and control participants may have employed different strategies during the encoding of potential future reward during the anticipation period and that, unlike participants with bipolar disorder, control participants may have focused on encoding the identity rather than value of potential future reward.

Table 3. Whole-brain analyses for the anticipation period

Group × anticipation period interaction on whole-brain BOLD signal							
			Talairach coordinates				
Multiple tests	Brodmann area	Cluster size	x	y	z	*F*-value	Corrected for multiple tests
Left-lateral orbitofrontal cortex	47	60	−45	27	−3	12.10	Yes (AlphaSim)

Post-hoc effects on left-lateral orbitofrontal cortex (BA47) BOLD signal during anticipation period					
Condition	Region	Cluster size	*t*-value	df	Corrected for multiple tests
Between-group post-hoc effects					
BD > HC: reward anticipation	Left OFC	24	2.53	39	Yes ($p < 0.013$, Bonferroni)
BD > HC: loss anticipation	Left OFC	0	0.95	39	No
Within-group post-hoc effects					
BD reward anticipation > BD loss anticipation	Left OFC	60	3.45	20	Yes ($p < 0.013$, Bonferroni)
HC reward anticipation > HC loss anticipation	Left OFC	0	−0.84	19	No

To control for multiple statistical testing for whole-brain analyses, we used a cluster (*k*) extent determined by Monte Carlo simulations at the whole-brain level implemented in AlphaSim, of 58 voxels. Post-hoc analyses were conducted on the cluster in the left-lateral orbitofrontal cortex [Montreal Neurological Institute (MNI) coordinates: x = −45, y = 27, z = −3] that was significant in the group x anticipation-period interaction. Main effect, interaction, and post-hoc analyses were conducted on the blood oxygen level-dependent (BOLD) signal for the anticipation period minus the baseline period. To control for multiple post-hoc tests, we used a Bonferroni-corrected voxelwise cut-off to correct for four multiple *a priori* post-hoc comparisons ($p < 0.05/4 = 0.013$). BD = bipolar disorder; HC = healthy controls; OFC = orbitofrontal cortex.

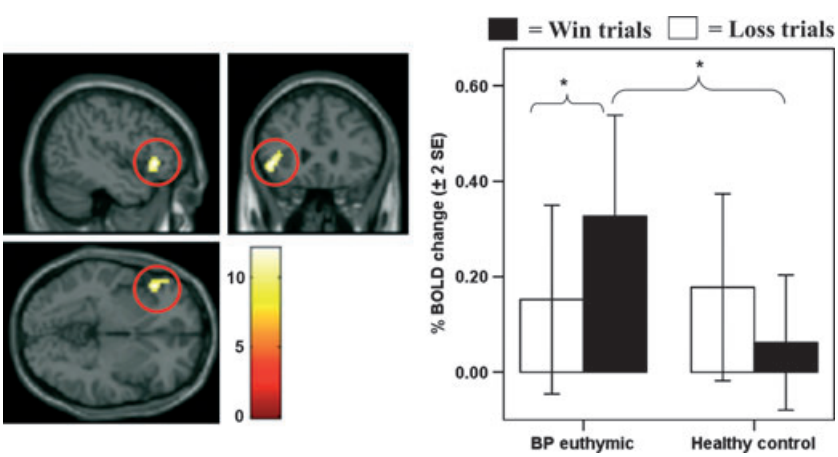

Fig. 4. Left-lateral orbitofrontal cortical (OFC) activity during the anticipation period (whole brain). The left panel displays the anatomical location of the significant group × anticipation condition interaction on left-lateral OFC activity (BA47) from whole-brain analyses [$F(1,39) = 12.10$, $p = 0.001$, $k = 60$ voxels, AlphaSim corrected]. The right panel displays a histogram of mean left-lateral OFC activity from whole-brain analyses depicting the group × anticipation condition interaction. Color bars reflect beta values, and significant clusters were overlaid on sagittal, coronal, and axial brain slices. Statistical tests were performed within Statistical Parametric Mapping software and beta values were extracted for graphical purposes only. BOLD = blood oxygen level dependent; SE = standard error; BP euthymic = bipolar disorder patients in a euthymic state (n = 21); healthy controls (n = 20). *significant post-hoc comparison at $p < 0.013$ (Bonferroni corrected).

Accordingly, previous and present data suggest that ventral striatal hypersensitivity, together with elevated OFC activity to anticipation of reward-relevant cues, may be a key biological marker of bipolar disorder, potentially reflecting an underlying neural mechanism for abnormal processing of potential future reward that in turn may predispose a person to hypo/mania. These patterns of abnormal neural activity may be a useful future biological target for novel interventions to help individuals with bipolar disorder develop strategies for effectively regulating their behavior in response to reward-relevant environmental events (34).

Neuroimaging studies in unipolar depression reported abnormally reduced, as opposed to elevated, ventral striatal activity versus healthy controls during reward-related laboratory tasks (18, 35, 36) and to positive emotional stimuli (37, 38). Together with our present findings, these findings suggest that unipolar depression and bipolar disorder may be characterized by differential patterns of abnormal ventral striatal activity during reward anticipation and receipt. It is important to note, however, that research on ventral striatal activity to reward cues in unipolar depression has typically examined participants in a depressive episode at the time of fMRI scanning. Future research is needed which directly compares euthymic bipolar with euthymic unipolar depressed individuals to determine whether ventral striatal activity during reward processing may yield state-independent biological markers to help to distinguish between the two disorders.

Rates of lifetime comorbidity reported in the present study were consistent with existing epidemiological research on lifetime comorbidity rates in bipolar disorder (23, 24). Importantly, bipolar disorder participants were free from alcohol/substance abuse or dependence for a minimum of seven months (range: 7–269 months), and we did not observe any significant relationships between a prior history of substance or alcohol abuse and ventral striatal or OFC activity during reward anticipation in participants with bipolar disorder. Further, individuals with substance use disorders have previously been shown to display decreased, rather than increased, ventral striatal activity during anticipation of non-drug-related cues, such as monetary reward (39). Thus, the elevated ventral striatal and OFC activity observed in the present study among bipolar disorder participants during reward anticipation is likely not attributable to alcohol/substance abuse or dependence.

There were limitations to the present study. First, future studies are needed to examine mood state-independent versus mood state-dependent components of abnormally elevated neural activity during reward anticipation and receipt in bipolar disorder by comparing euthymic bipolar disorder to manic and/or depressed bipolar disorder participants. It will be important for this research to employ fMRI reward paradigms examining both the anticipation and receipt of reward, as well as omission of reward. This is particularly relevant given the research suggesting that bipolar manic patients fail to show the previously reported pattern of decreased ventral striatal activation when an expected reward is omitted (40). Second, further research is needed to examine whether elevated neural activity to reward cues is specific to bipolar disorder or indicative of more general motivational and/or regulatory deficits observed across multiple psychiatric disorders. Third, bipolar disorder participants were medicated at the time of study. We did not, however, observe any significant relationships between psychotropic or antipsychotic medication load, total number of psychotropic medications, or between any specific class of psychotropic medication, including dopaminergic antidepressants or antipsychotic medications, and neural activity during reward anticipation in participants with bipolar disorder. Furthermore, removing individuals on dopaminergic antidepressants did not alter the critical interaction in the ventral striatal ROI. Given that 12 out of 21 bipolar disorder participants were taking antipsychotic medications at fMRI scanning, we did not have the statistical power to examine our *a priori* hypotheses excluding participants taking antipsychotic medications. Future studies may wish to examine this issue. Lastly, we used one run of 24 trials for the fMRI reward paradigm, on the basis of previous research indicating that this configuration is effective for assessing reward-related brain function and minimizing fatigue and habituation (18, 19). However, we cannot rule out the possibility that a larger number of trials could have produced group differences to other conditions or in other neural regions. Future research may wish to address this issue.

Abnormally elevated ventral striatal and OFC activity during reward anticipation is a potential neural basis for the observed hypersensitivity to reward-relevant stimuli in bipolar disorder. The possible dopaminergic basis of elevated ventral striatal activity in bipolar disorder has important implications for treatment choices and new treatment development for the illness. Future studies should aim to replicate our findings and examine the extent to which abnormally elevated ventral striatal and OFC activity during reward processing may serve as a potential biological marker of bipolar disorder. It will be important for this subsequent research to examine reward-related brain activity in individuals at heightened risk for bipolar disorder, but who have not yet developed the disorder. This will help to determine whether abnormally elevated ventral striatal and OFC activity during reward processing represents a pre-existing vulnerability for bipolar disorder or is a consequence of having a bipolar episode.

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Disclosures

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Supporting information

Additional supporting information may be found in the online version of this article:

Table S1. ROI analyses on ventral striatal (VS) and orbitofrontal cortical (OFC) BOLD signal during the outcome period

Table S2. Exploratory relationships between demographic variables, clinical variables, medication variables, ventral striatal (VS) activity, and orbitofrontal cortical (OFC) activity during the anticipation period

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