Reward Processing in Adolescents With Bipolar I Disorder

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Objective: Bipolar disorder (BD) is a debilitating psychiatric condition that commonly begins in adolescence, a developmental period that has been associated with increased reward seeking. Because youth with BD are especially vulnerable to negative risk-taking behaviors, understanding the neural mechanisms by which dysregulated affect interacts with the neurobehavioral processing of reward is clearly important. One way to clarify how manic symptoms evolve in BD is to "prime" the affect before presenting rewarding stimuli. The objective of this study was to investigate the neural effects of an affective priming task designed to positively induce mood before reward processing in adolescents with and without BD. **Method:** Neural activity and behaviors during the anticipation of and response to monetary reward and loss after an affective prime were compared using functional magnetic resonance imaging in 13- to 18-year-old adolescents with a recent onset of BD-I (n = 24) and demographically matched healthy comparison youth (n = 24). **Results:** Compared with the healthy control youth, youth with BD had speeded reaction times and showed decreased activation in the thalamus and inferior temporal gyrus while anticipating gains after priming but increased activations in the middle frontal gyrus and parietal cortices while anticipating losses after priming. Youth with BD also showed less activation in the inferior parietal lobule, thalamus, and superior frontal gyrus while receiving losses after priming. **Conclusions:** Aberrant prefrontal and subcortical activations during reward processing suggest mechanisms that may underlie disordered self-awareness during goal pursuit and motivation in BD. Longitudinal studies are needed to examine whether this pattern of neural activation predicts a poorer long-term outcome. J. Am. Acad. Child Adolesc. Psychiatry; 2012;52(1):68–83. **Key Words:** reward processing, functional magnetic resonance imaging, adolescent, bipolar disorder, affective prime

Bipolar disorder (BD) is a debilitating, recurrent psychiatric condition with an onset typically during adolescence,[1] a developmental period that has been associated with increased risk-taking and reward-seeking.[2] Clinically, BD is characterized by aberrations in emotion and motivation that may lead to risk-taking behaviors that have maladaptive consequences. Specifically, individuals with BD experience hyperhedonia (e.g., excessive pleasure-seeking and goal-directed activity) during manic states and anhedonia (i.e., decreased pleasure in response to hedonic stimuli or experiences) during depressive episodes.[3] These disturbances in core emotional and motivational functions may provide a basis for understanding the origins of symptom manifestations associated with BD. Surprisingly, however, few studies have examined the precise nature of, and neural aspects associated with, these aberrations, particularly in adolescents with BD who are temporally close to the onset of illness and, consequently, are likely to be symptomatic at the time of assessment and to have minimal lifetime exposure to psychotropic medications or many previous mood episodes.

Studies to date have examined different aspects of reward processing in individuals with BD, including responses to various types of positive stimuli (e.g., money, faces), affective responses to rewards, and aspects of decision making

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(e.g., reversal learning) or judgments, which target similar regions of the brain. These studies have found that adults[4] and youth[5,6] with BD have decreased reward learning, even when they are euthymic.[4] However, happy mood states can be induced in euthymic adults with BD while they are engaging in a reward paradigm, suggesting potentially important interactions between cognitive and emotional responses to rewarding stimuli.[7] Other investigators have found that youth with BD compared with typically developing controls report increased reward reactivity and greater arousal in reward conditions[8] and greater satisfaction with winning.[9] The first of four neuroimaging studies examining reward processing in BD used a monetary incentive delay (MID) task in acutely manic and medicated adults with BD.[10] In this study, adults with BD did not activate the ventral tegmentum as did healthy and schizophrenic comparison adults while anticipating high versus no reward outcomes and had a lower differential signal in the nucleus accumbens (NAcc) upon receipt of rewards compared with healthy control subjects. In the second study, adults with mania did not differ from healthy controls in the ventral striatal response to cued incentives.[11] However, adults with mania did show significant increases in activation in the left lateral orbitofrontal cortex (Brodmann areas [BAs] 11 and 47) while anticipating increasing gains and decreased activation in this region during an expectation of increasing loss, whereas healthy subjects tended to show the opposite effect. In a third study that used a card-guessing paradigm, whole-brain analyses found adults with BD to have increased left-sided lateral orbitofrontal activation during reward anticipation. Region-of-interest (ROI) analyses in this study showed that adults with BD compared with healthy controls exhibited greater ventral striatal and right-sided orbitofrontal (BA 11) activity during the anticipation, but not during the outcome, of monetary reward.[12] A recent study related increased activity in the amygdala and the orbitofrontal cortex to heightened sensitivity in response to reward and reward reversal and to deficient prediction error signaling in individuals with BD and their relatives.[13] These studies highlight the aberrant neural functioning in BD that may be related to an increased motivation for seeking rewards and to an underestimation of associated risks and potential punishments.

It is not clear, however, whether these patterns of behavioral and neural functioning reflect a developmental process typical of adolescents versus adults, play an etiologic role in BD, or are a consequence of chronic exposure to multiple mood episodes or psychotropic medications. Moreover, neither the specific neural features that are associated with aberrant reward processing in adolescents nor the mechanisms by which reward processing interacts with mood state are currently known. In addition, findings across studies are inconsistent, showing different regions and opposite directions of activations during gain and loss conditions, possibly due to type I error or small samples. Therefore, to gain a better understanding of the precise nature and origins of the aberrant emotion and motivation associated with BD, it is important to compare neural correlates of reward processing in a large sample of typically developing adolescents and youth who are close to the onset of their first manic episode, to experimentally manipulate mood state while participants are processing rewards by priming their affect before the presentation of rewarding stimuli, and to model analyses to explore the regions and directions of neural activations associated with reward (gain) versus risk (loss). Such an approach would advance researchers' understanding of the neural basis of how dysregulated mood might lead to the intensification of goal pursuit and motivation in BD.

The first aim of the present study was to examine neural activations associated with reward processing after an affective prime by scanning adolescents with BD-I who experienced only a single episode of mania in their lifetime. Because the authors were interested in the interaction of cognitive and emotional processes in BD, they predicted that compared with healthy control (HC) youth, youth with BD would exhibit significant aberrations in frontostriatal activation associated with the MID task that would be more pronounced when the task was preceded by an affective prime, which the authors posited would intensify emotional and neural responses to rewarding stimuli (similar to the effects of a positive mood induction[7]) than when it was preceded by a nonaffective control task. Drawing on previous reports showing differential brain function and behavior during anticipation and receipt of rewards versus punishments in adults with BD,[10–13] the second aim was to explore neural activations as a function of the interaction of group and prime within gain and loss conditions separately. In these secondary analyses, the authors predicted that

compared with HC participants, adolescents with BD would exhibit increased activation in the ventral striatum (i.e., NAcc) and orbitofrontal cortex (inclusive of BA 10, 11, or 47) while anticipating gains on the MID task and increased activation in the amygdala while receiving gains. They also predicted that while anticipating and receiving losses, youth with BD would show decreased activation in the ventral striatum and orbitofrontal cortex but not in the amygdala. Third, given the likely relation between symptoms of dysregulated motivation in mania and reward processing, the authors predicted that the manic mood state would intensify emotional and neural responses such that those participants with higher levels of mania on the day of scanning would show relatively greater activations in the orbitofrontal and striatal regions during reward anticipation and receipt and lower orbitofrontal and striatal activations during the anticipation and receipt of losses.

METHOD

Participants

The university panel of medical research in human subjects approved this research protocol. After hearing a complete description of the study, parents and youth younger than 18 years gave written informed consent and assent, respectively. Adolescents (13–18 years old) with BD-I (n = 24) diagnosed as having their first manic episode within the previous 12 months (mean interval from the onset of mania to the scan = 5 months) were recruited by referral to a pediatric BD clinic or from the surrounding community. HC adolescents (n = 24) without any personal or family history of psychiatric diagnoses or psychotropic medication exposure were recruited through local community advertisements. A telephone screening with a parent established that all participants had English fluency and did not have any metal in their body, a history of head injury (with loss of consciousness >5 minutes), seizures, or developmental disorders. Youth with BD who were prescribed stimulants did not take them 24 hours before neuroimaging and were required to not have used recreational drugs for at least 30 days before the magnetic resonance imaging (MRI) scan. To avoid the risk of mood destabilization, subjects with BD were allowed to continue any other psychotropic medications, including mood stabilizers, atypical antipsychotics, or antidepressants.

Diagnostic and Clinical Assessments

All participants were evaluated for current and lifetime psychiatric disorders using the Washington University in St. Louis Schedule for Affective Disorders and Schizophrenia[14] for affective disorders and the Schedule for Affective Disorders and Schizophrenia Present and Lifetime version[15] for other psychopathology, which were administered separately to parents and children by the interviewers, with established symptom and diagnostic inter-rater reliability ($\kappa > 0.9$). A manic episode was defined by *DSM-IV-TR* criteria, lasted at least 1 week, and could not have been precipitated by exposure to recreational drugs, antidepressants, psychostimulants, or other medications or medical conditions. Symptom severity was assessed on the day of scan using the Young Mania Rating Scale (YMRS),[16] the Children's Depression Rating Scale–Revised Version,[17] and the Childhood Global Assessment Scale[18] by raters with established reliabilities (intra-rater intercorrelation coefficients >0.9). Active symptoms on the day of scanning were summarized for the imaging analyses using the following cutoffs: a YMRS score higher than 20 for active manic symptoms and a Children's Depression Rating Scale score higher than 40 for active depression. All participants completed the Barratt Impulsiveness Scale 11, which yielded subscale scores on the dimensions of attentional, motor, and nonplanning trait impulsivity.[19] Age, sex, socioeconomic status (Hollingshead Four Factor Index),[20] pubertal stage (Pubertal Development Scale),[21] IQ (Wechsler Abbreviated Scale of Intelligence),[22] and handedness (Crovitz Handedness Questionnaire)[23] were also assessed.

MID Task

All participants practiced and were tested for their comprehension of explicit cues presented in the MID task.[24] They were shown cash that they could win during the task before entering the scanner. The MID task was designed to probe neural responses to the anticipation and receipt of gain and loss outcomes by using a set of cues to indicate whether the participants could win or avoid losing money if they responded quickly enough to a target (represented by a triangle) that followed a cue and anticipation period. In each trial the participants were presented with a cue indicating that they had a chance to win or lose $0, $1, or $2. Circle cues indicated trials with the opportunity to win money, square cues indicated trials when money could be lost, and lines within those shapes defined the amount of money presented for that trial. Immediately after each trial, the participants were shown feedback (how much money they won or lost on that trial and a running total).

Each of these six trial types appeared nine times for 6 seconds and was pseudorandomly distributed, for a total of 54 trials per run (approximately 6 minutes × 2 runs). Cues were displayed for 250 ms, followed by a jittered anticipatory period (2,000–2,500 ms). The target was displayed for different durations (250–350 ms) determined from reaction times collected during a practice session before scanning and set such that the participants would succeed on approximately 66% of their target responses. A jittered delay period separated

the offset of the target stimulus from the onset of the feedback stimulus, so that the length of the entire trial was exactly 6 seconds. After the scan, participants were retested on their comprehension of the cues.

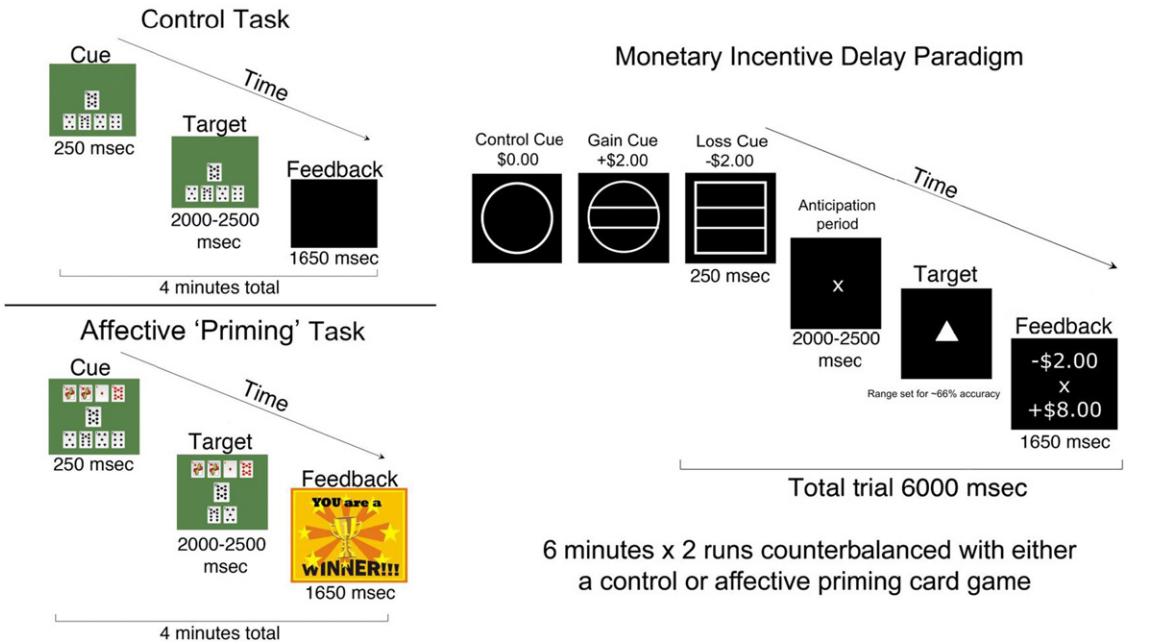
Affective Priming Task

To examine the interaction between emotion and motivation, and because participants with BD were in different mood states on the day of their scan, a new functional MRI (fMRI) task was designed to experimentally induce an elevated state of arousal in all participants. Positive mood inductions during reward processing have been described previously in adults with BD[7] and provide a relevant context for this approach; however, in the present study, the mood induction could yield a positive or negative affect. Two runs of the MID task, with each run preceded by card games using a traditional 52-card deck, were designed to enhance engagement, motivation, confidence, and drive to perform in the MID task. Using a button box, the participants were instructed to press a button corresponding to one of four card piles that would move a card of adjacent value to a deposit pile, creating a sequence. Two versions of the card game were presented to the participants in each group in counterbalanced order: in one version (affective priming), they played against the computer and, during the last minute of the game, were given feedback that they had won the game; in the other version (control task), the participants played by themselves without any feedback (Figure 1). The participants rated their levels of happiness, distraction, excitement, anxiety, and confidence about winning money in the subsequent MID task (1 = not at all, 2 = somewhat, 3 = very, 4 = extremely) at the beginning and end of each card game.

MRI Data Collection and Preprocessing

After being trained on the fMRI tasks and desensitized to the scanning environment by an MRI simulator, imaging-related procedures were performed using a 3-T Signa Excite scanner (GE Medical Systems, Milwaukee WI) equipped with echo-speed gradients using a standard whole-head coil (General Electric, Milwaukee, WI) and high-resolution, T1-weighted, spoiled Gradient Recall Acquisition in Steady State (GRASS) images. Functional images were collected with a T2*-weighted spiral pulse sequence with a recovery time of 2,000 ms, an echo time of 30 ms, a flip angle of 80°, a field of view of 22 cm, a matrix of 64 × 64, a voxel size of 3.4375 × 3.4375 mm, and a slice thickness of 4 mm with 1-mm spacing. An automated high-order shimming method was used before acquiring fMRI data to decrease field inhomogeneities. Structural images were collected to aid in the localization of the functional data using high-resolution, T1-weighted, spoiled gradient-recalled acquisition, three-dimensional MRI sequences with a recovery time of 6.4 ms, an echo time of 2.0 ms, an inversion recovery preparation pulse of 300 ms, a flip angle of 15°, a field of view of 22 cm, a matrix of 256 × 256, three excitations, 124 slices in the coronal plane, and 1.5-mm slice thickness. Seven participants (six with BD and one HC youth)

FIGURE 1 Experimental paradigm of tasks presented during functional magnetic resonance imaging. Note: The control task or the affective priming task was counterbalanced to precede two runs of the monetary incentive delay paradigm.



originally recruited were excluded from analysis owing to motion artifacts or poor behavioral performance, resulting in a sample size of 24 per group.

Functional images were processed with SPM 8 (Wellcome Department of Cognitive Neurology, London, United Kingdom), including realignment, slice time correction, coregistration, normalization into Montreal Neurological Institute (MNI) space with 2-mm voxel resampling, and spatial smoothing. Images were repaired by interpolation from the nearest unaffected volumes using the ArtRepair software toolbox for SPM (http://cibsr.stanford.edu/tools/methods/artrepair-software.html) if the motion exceeded a 0.5-mm/recovery time threshold or if the global signal was greater than 3% from the mean global signal of all images. Data were coregistered and spatially normalized into standard stereotactic space using an adolescent template (https://irc.cchmc.org/software/pedbrain.php). Normalized images were then smoothed with a 7-mm full-width half-maximum Gaussian filter.

Statistical Analysis

Reaction time and accuracy were recorded for each trial of the MID task. Three-way (group [BD, HC] repeated over priming condition [prime, control] and valence [gain, loss]) analyses of variance (ANOVAs) were conducted on individual hit rates, mean reaction times, and total money gained across anticipation and feedback conditions. These were followed by two-way ANOVAs to examine the behavioral differences occurring during the gain and loss conditions.

Statistical contrasts were conducted separately from anticipation and feedback event onsets. Because reaction times did not differ as a function of incentive level, trials presenting anticipation of gain cues (i.e., $1 and $2) were combined to increase statistical power, as were trials presenting anticipation of loss cues. For the anticipation phase, trials with gain or loss cues were compared with their corresponding nongain and nonloss trials. For the feedback phase, trials in which participants gained money were compared with nongain feedback trials, and trials in which participants lost money were compared with nonloss trials. Statistics conducted at the individual level used a fixed effects model to define experimental (anticipation gain and loss, gain and loss outcomes) and control (nongain and nonloss outcomes) conditions using SPM 8. A high-pass filter of 120 seconds was applied and six motion regressor nuisance covariates were included in the model.

To investigate group differences in reward processing after an affective prime, a three-way (group [BD, HC] by prime [affective priming, control] by valence [gain, loss]) ANOVA was conducted as the primary analysis. In a secondary analysis, a two-way (group [BD, HC] by prime [affective priming, control]) ANOVA was conducted for each MID condition (gain, loss). Significant activations associated with the main effect of group, the main effect of priming, and the interaction of these terms were identified for the comparison of anticipated and received gains versus nongains and of anticipated and received losses versus nonlosses. Activation foci were superimposed on high-resolution, T1-weighted images in MNI space, and their locations were interpreted using the Talairach atlas and known neuroanatomic landmarks. The voxel level significance ($p = .01$) and cluster size ($k = 194$) criteria used to hold the family-wise error at a p value equal to .05 were calculated with AlphaSim (AFNI, Bethesda, MD)[25] based on parameters for a matrix size of $91 \times 109 \times 91$, voxel dimensions of 2 mm^3, 7-mm full-width half-maximum smoothing kernel, and 10,000 Monte Carlo simulations. This program generates null hypothesis distributions and corresponding statistical criterion values through the use of Monte Carlo simulation. Parameters known to affect the shape of null hypothesis distributions of fMRI data, such as the number of voxels compared and their effective size, the per-voxel statistical criterion, and the definition of voxel clustering used, are modeled in these Monte Carlo simulations.[26]

Exploratory ROI analyses were conducted within the BD group to examine the effects of priming on the reward processing associated with the presence of high versus low manic symptoms on scan day. ROIs were defined by the Automated Anatomical Labeling atlas[27] and were selected based on findings from the present whole-brain analysis and from the extant reward literature[12,28–30]: anterior cingulate cortex (ACC), amygdala, insula, and portions of the striatum including the caudate, putamen, NAcc, and globus pallidus. Mean Z-score values were extracted using MarsBar (http://marsbar.sourceforge.net/) and imported into SPSS 18 (http://www.spss.com/) for analysis. ROI significance levels were corrected for multiple comparisons using a Bonferroni correction (0.05/n ROIs = 0.007).

RESULTS

Participant Characteristics

Demographic and clinical characteristics of the two participant groups are presented in Table 1. The BD and HC groups did not differ significantly with respect to age ($t_{46} = 1.51$), gender (n = 48, $\chi^2 = 1.34$), handedness (n = 48, $\chi^2 = 2.10$), Wechsler Abbreviated Scale of Intelligence IQ scores ($t_{46} = 1.73$), socioeconomic status ($t_{46} = 0.32$), Tanner stage ($t_{46} = 1.08$), or ethnicity (n = 48, $\chi^2 = 8.74$, $p > .05$ for all comparisons). Adolescents with BD reported significantly higher YMRS ($t_{46} = 10.7$, $p < .0001$), Children's Depression Rating Scale ($t_{46} = 8.6$, $p < .0001$), and Trait Impulsivity subscale scores in attention ($t_{41} =$

TABLE 1 Participant Demographic and Clinical Variables

Variable	BD (n = 24)	HC (n = 24)
Age (y), mean (SD)	15.7 (1.7)	15.0 (1.4)
Female, n (%)	11 (46)	15 (63)
Caucasian, n (%)	13 (54)	14 (58)
Right handedness, n (%)	19 (79)	21 (88)
Tanner stage, mean (SD)	3.30 (0.40)	3.16 (0.53)
Socioeconomic status, mean (SD)	4.7 (0.56)	4.61 (0.65)
Full-Scale IQ, mean (SD)	107 (10.2)	113 (10.8)
YMRS, mean (SD)*	17.8 (8.1)	0.13 (0.34)
CDRS, mean (SD)*	44.0 (14.8)	17.9 (1.4)
CGAS, mean (SD)*	58.3 (11.0)	93.7 (3.2)
BIS—attentional impulsivity, mean (SD)*	20.8 (4.9)	14.0 (3.3)
BIS—motor impulsivity, mean (SD)*	25.1 (3.9)	20.4 (3.4)
BIS—nonplanning impulsivity, mean (SD)*	28.9 (6.2)	24.1 (4.2)
Mood state on day of scan, n (%)*		
Manic	6 (25)	0 (0)
Mixed (manic + depressed)	5 (21)	0 (0)
Depressed	9 (38)	0 (0)
Euthymic	4 (17)	24 (100)
Other lifetime psychiatric diagnoses, n (%)*		
ADHD	9 (38)	0 (0)
Any anxiety disorder	5 (21)	0 (0)
Oppositional-defiant disorder	4 (17)	0 (0)
Conduct disorder	1 (4)	0 (0)
Marijuana abuse	9 (38)	0 (0)
Lifetime medication exposure, n (%)	20 (83)	0 (0)
Weeks on medication on scan day, mean (SD)	15.5 (25)	0 (0)
Depressive episode before mania, n (%)	14 (58)	0 (0)
Months to scan after manic episode, mean (SD)	5.57 (3.4)	0 (0)
Lifetime medication exposure, n (mean exposure in wk)*		
Lithium	8 (1.25)	0 (0)
Atypical antipsychotics	17 (4.6)	0 (0)
Antidepressants	12 (4.2)	0 (0)
Psychostimulants	7 (5)	0 (0)
Any medication	20 (16)	0 (0)

Note: ADHD = attention-deficit/hyperactivity disorder; BD = adolescents with bipolar I disorder; BIS = Barratt Impulsiveness Scale; CGAS = Clinical Global Assessment Scale; CDRS = Childhood Depression Rating Scale; HC = healthy control adolescents; YMRS = Young Mania Rating Scale.
*$p < .05$.

5.4, $p < .0001$), motor ($t_{41} = 4.2$, $p < .0001$), and nonplanning ($t_{41} = 3.1$, $p < .004$) compared with the HC group. The BD group had lower scores on the Childhood Global Assessment Scale ($t_{46} = 14.8$, $p < .0001$) compared with the HC group, indicating greater functional impairment.

Behavioral Results

A three-way (group by prime by valence) ANOVA conducted on reaction times yielded a significant interaction of group and valence ($F_{1,48} = 3.99$, $p = .05$). Subsequent two-way (group by prime) ANOVAs indicated that adolescents with BD had significantly faster reaction times than did HC adolescents for anticipation of gain and gain control trials during the MID task after the affective prime ($F_{1,48} = 5.734$, $p = .021$); analyses of hit rates and reaction times for anticipation of loss trials yielded no significant main effects or interactions, indicating comparable performance of the two groups on the task. Three-way (group by prime by order [i.e., pre-/post-task rating]) ANOVAs conducted on self-report measurements yielded significant interactions of prime and order for positive affect ($F = 34.71$, $p < .001$),

TABLE 2 Behavioral Results and Mean Affective Ratings Before and After Prime and Control Tasks

Variable	Third Factor	Bipolar Group		Control Group		ANOVA significant interactions
		Prime	Control	Prime	Control	
MID RT	gain	193.11 (54.60)	205.60 (38.56)	224.65 (36.22)	222.53 (31.11)	group × valence, $F = 3.99$, $p = .05$
	loss	203.84 (39.77)	207.36 (46.09)	223.90 (30.19)	225.96 (26.71)	
MID accuracy	gain	0.71 (0.16)	0.72 (0.16)	0.69 (0.16)	0.69 (0.11)	no significant interactions
	loss	0.66 (0.14)	0.69 (0.14)	0.68 (0.15)	0.66 (0.11)	
Happiness	before	2.18 (0.50)	2.21 (0.58)	1.96 (0.69)	2.13 (0.74)	prime × order, $F = 34.71$, $p < .001$
	after	2.79 (0.50)	2.33 (0.56)	2.38 (0.82)	2.04 (0.55)	
Excitement	before	2.04 (0.35)	2.13 (0.45)	1.87 (0.95)	1.92 (0.77)	prime × order, $F = 5.35$, $p = .025$
	after	2.46 (0.65)	2.08 (0.50)	1.92 (0.78)	1.79 (0.83)	
Anxiety	before	1.62 (0.64)	1.58 (0.58)	2.08 (1.06)	2.00 (0.97)	group × order, $F = 4.51$, $p = .039$
	after	2.46 (0.65)	2.08 (0.50)	1.92 (0.78)	1.79 (0.83)	
Confidence	before	2.42 (0.65)	2.50 (0.72)	2.21 (0.83)	2.42 (0.92)	prime × order, $F = 6.69$, $p = .013$
	after	2.71 (0.62)	2.46 (0.72)	2.54 (0.83)	2.21 (0.83)	
Distraction	before	1.74 (0.61)	1.78 (0.73)	2.09 (0.95)	1.96 (0.80)	no significant interactions
	after	1.62 (0.71)	1.71 (0.69)	1.96 (0.86)	2.09 (0.95)	

Note: First factor of analysis of variance (ANOVA) = group; second factor of ANOVA = prime task; third factor of ANOVA = valence of monetary incentive delay (MID) task behavioral performance condition or order of self-report scores. BD = adolescents with bipolar I disorder; HC = healthy comparison adolescents; RT = reaction time.

excitability ($F = 5.35$, $p = .025$), and confidence ($F = 6.686$, $p = .013$). Subsequent paired t tests showed significant increases across the priming task from before to after the priming task for positive affect ($t = 5.38$, $p < .001$), excitability ($t = 2.12$, $p = .04$), and confidence ($t = 4.23$, $p < .001$); there were no significant pre-/post-task differences across the control task for these measurements ($p > .05$ for all comparisons; Table 2).

Neuroimaging Results

Primary Three-Way ANOVA Results With Post Hoc Analyses. A three-way (group by prime by valence) ANOVA during the anticipation condition yielded a significant three-way interaction; activations in this interaction included the left middle frontal gyrus (BA 10), left and right inferior parietal lobules (BA 40), right inferior temporal gyrus (BA 20), and left thalamus (Table 3, Figure 2). Post hoc tests in these regions indicated that, compared with the HC group, the BD group showed decreased activation in the thalamus and inferior temporal gyrus while anticipating gains after priming but increased activations in the middle frontal gyrus and parietal cortices while anticipating losses after priming.

During the feedback phase of the task, the three-way ANOVA also yielded a significant three-way interaction, with activations in the right inferior parietal lobule (BA 40), thalamus, and right superior frontal gyrus (BA 8; Table 3). Post hoc t tests showed that, compared with the HC group, the BD group showed less activation in these three regions while receiving losses after priming.

Secondary Whole-Brain Two-Way ANOVA Results. A significant main effect of valence from the three-way ANOVA showed that the ventral striatum was significantly more activated during the anticipation of gain than during the anticipation of loss. To pursue the hypotheses about differential prefrontal and subcortical dysfunctions during gain and loss conditions as shown in previous studies using the MID task,[24,26,29] the authors conducted exploratory two-way whole-brain ANOVAs comparing the BD with HC group in gain and loss conditions. These secondary analyses were not derived from the three-way ANOVA and thus should be viewed with caution as exploratory and yielded the following results ($p = .05$, family-wise error -corrected; Table 4, Figure 3).

TABLE 3 Significant Clusters of Activation Using Three-Way Analysis of Variance (ANOVA)

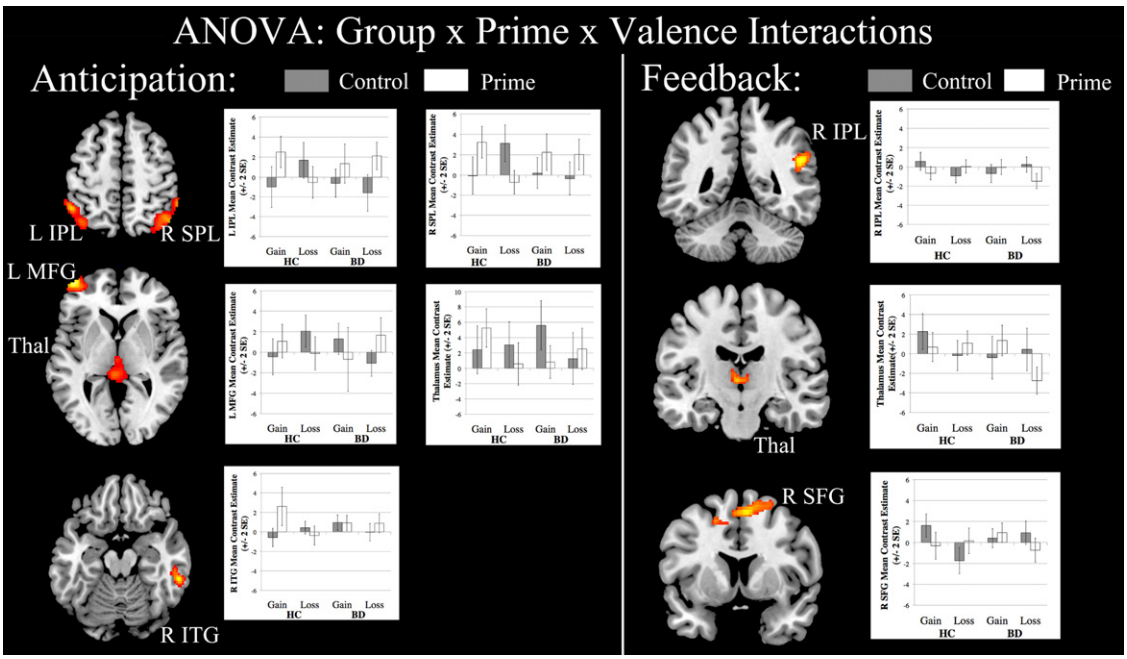
ANOVA	Cluster Location	BA	Extent	*F*	Primary Peak (*x, y, z*)	Direction of Significant Post Hoc Analyses
Anticipation: group × prime × valence 3-way ANOVA						
Group × prime × valence	right superior parietal lobule	7	632	11.38	56, −42, 50	group × prime, $F_{46} = 4.17$, $p = .047$; prime × valence, $F_{46} = 9.49$, $p = .003$ group differences: loss after prime, BD > HC, $p = .006$; loss after control, HC > BD, $p = .006$ prime differences: HC, gain, prime > control, $p = .021$; HC, loss, control > prime, $p = .001$; BD, loss, prime > control, $p = .013$ valence differences: HC, prime, gain > loss, $p = .001$; HC, control, loss > gain, $p = .015$
	left inferior parietal lobule	40	445	9.28	−50, −48, 56	main effect of prime: prime > control, $F_{46} = 8.76$, $p = .005$ group differences: loss after prime, BD > HC, $p = .016$; loss after control, HC > BD, $p = .014$ prime differences: HC, gain, prime > control, $p = .005$; BD, loss, prime > control, $p = .006$ valence differences: HC, prime, gain > loss, $p = .009$; HC, control, loss > gain, $p = .022$
	left middle frontal gyrus	10	617	12.01	−43, 56, −3	group differences: loss after control, HC > BD, $p = .003$ prime differences: HC, loss, control > prime, $p = .039$; BD, loss, prime > control, $p = .015$ valence differences: HC, control, loss > gain, $p = .002$; BD, control, gain > loss, $p = .013$
	thalamus		226	11.46	−3, 31, 2	main effect of valence, prime > control, $F_{46} = 5.04$, $p = .030$ group differences: gain after prime, HC > BD, $p = .009$ prime differences: BD, gain, control > prime, $p = .012$ valence differences: HC, control, gain > loss, $p = .004$; BD, control, gain > loss, $p = .010$
	right inferior temporal gyrus	20	197	10.26	58, −36, −15	main effect of prime: prime > control, $F_{46} = 4.17$, $p = .048$; main effect of valence: gain > loss, $F_{46} = 4.43$, $p = .041$; prime × valence, $F_{46} = 3.87$, $p = .055$ group differences: gain after control, BD > HC, $p = 0.016$ prime differences: HC, gain, prime > control, $p = .013$ valence differences: HC, prime, gain > loss, $p = .019$; BD, control, gain > loss, $p = .050$

TABLE 3 Continued

ANOVA	Cluster Location	BA	Extent	*F*	Primary Peak (*x*, *y*, *z*)	Direction of Significant Post Hoc Analyses
Feedback: group × prime × valence 3-way ANOVA						
Group × prime × valence	right inferior parietal lobule	40	409	17.52	49, −43, 28	group differences: loss after prime, HC > BD, $p = .006$; loss after control, HC > BD, $p = .035$ prime differences: HC, gain, prime > control, $p = .035$; BD, loss, control > prime, $p = .008$ valence differences: HC, control, gain > loss, $p = .012$; BD, prime, gain > loss, $p = .008$
	right superior frontal gyrus	8	1,101	13.79	7, 24, 49	main effect of valence: gain > loss, $F_{46} = 8.75$, $p = .005$ group differences: loss after control, BD > HC, $p = .003$ prime differences: HC, gain, control > prime, $p = .024$; HC, loss, prime > control, $p = .035$ valence differences: HC, control, gain > loss, $p < .001$; BD, prime, gain > loss, $p = .028$
	thalamus		377	11.75	−3, −13, 4	main effect of group: HC > BD, $F_{46} = 4.10$, $p = .049$; main effect of valence: gain > loss, $F_{46} = 4.48$, $p = .04$ group differences: loss after prime, HC > BD, $p > .001$ prime differences: BD, loss, control > prime, $p = .019$ valence differences: BD, prime, gain > loss, $p = .001$

Note: BA = Brodmann area; BD = adolescents with bipolar I disorder; HC = healthy controls.

FIGURE 2 Significant neural activations from whole-brain three-way analysis of variance (ANOVA; threshold of $p = .05$, $k \geq 194$ voxels). Note: IPL = inferior parietal lobule; ITG = inferior temporal gyrus; L = left; MFG = middle frontal gyrus; R = right; SFG = superior frontal gyrus; SPL = superior parietal lobule; Thal = thalamus.



Anticipation of Gain Minus Nongain. The main effect of group showed that the BD group had increased orbitomedial frontal cortex (OMFC) activation compared with the controls, whereas the HC group had increased bilateral angular gyrus activation compared with the BD group during this contrast. The main effect of priming while anticipating gains showed significant activations throughout the brain compared with the control condition (Table 3). In the two-way interaction of group and prime, the HC group had significantly greater activation in the subgenual ACC than did the BD group after affective priming.

Anticipation of Loss Minus Nonloss. The main effect of group yielded no significant clusters of activation during this contrast. The main effect of priming during the anticipation of loss showed significant activations in the right posterior cingulate, inferior parietal lobe, and caudate compared with the control condition. In the interaction of group and prime, the BD group showed greater activation than the HC group in the bilateral inferior parietal lobules, bilateral middle frontal gyrus, and left middle temporal gyrus, whereas the HC group showed greater activation in the left parahippocampal gyrus compared with the BD group after affective priming.

Gain Minus Nongain Outcomes. This contrast yielded no significant main effects or interactions.

Loss Minus Nonloss Outcomes. The main effect of group showed that the BD group had greater activation than the HC group in the right superior and orbitofrontal gyri. The main effect of priming showed significant activations in the left parahippocampal gyrus compared with the control condition. In the interaction of group and prime, the HC group had greater activation in the right superior frontal gyrus than did the BD group after affective priming.

Exploratory ROI analysis from the two-way ANOVAs showed that during the anticipation of gain after affective priming, youth with BD with high levels of mania at the scan (YMRS score >20, n = 11) exhibited less activation in the NAcc bilaterally than did youth with BD and low levels of mania (YMRS score ≤ 20, n = 13, $p = .003$, uncorrected). Levels of depression were not associated with a priming effect.

DISCUSSION

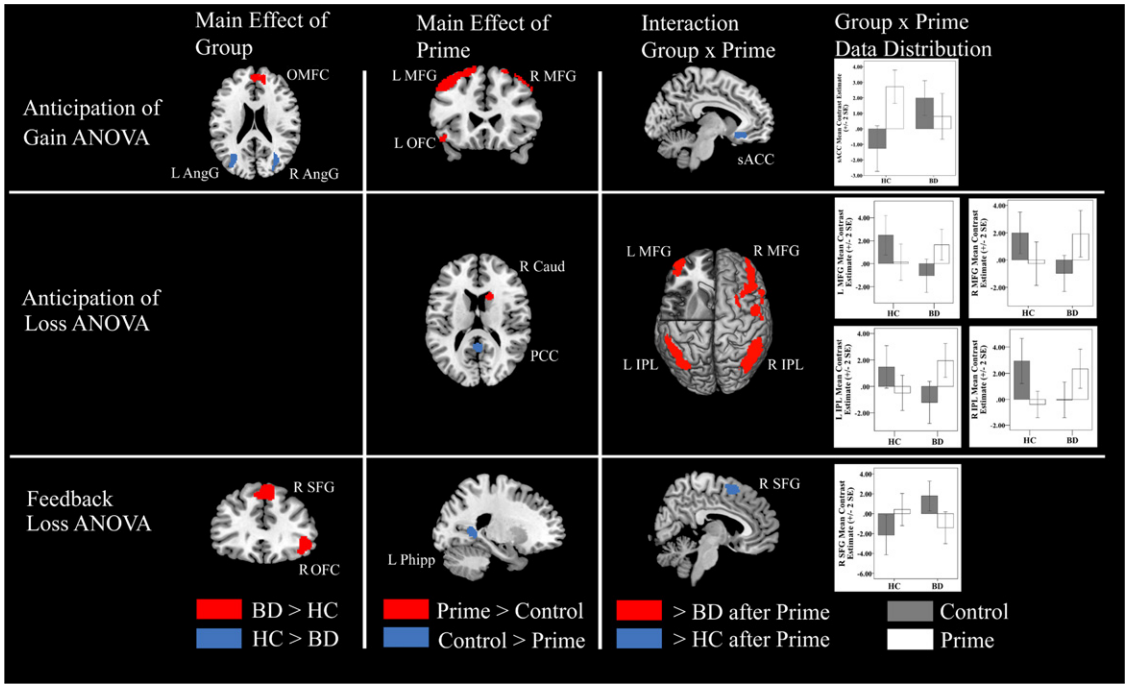
The present study is the first to compare neural activation during reward processing after affective priming in adolescents with BD and healthy adolescents. Youth with BD were found to show

TABLE 4 Significant Clusters of Activation Using Two-Way Analysis of Variance (ANOVA)

ANOVA	Cluster Location	BA	Extent	Direction of Post Hoc t-Test	Post Hoc t-Test (*p*)	*F*	Primary Peak		
							x	*y*	*z*
Anticipation gain ANOVA									
Main effect of group	right orbitomedial frontal cortex	10	403	BD > HC	.003	9.94	11	55	14
	right angular gyrus	39	202	HC > BD	.001	11.88	31	−65	27
				prime > control	.02	5.53			
	left angular gyrus	39	233	HC > BD	.005	8.92	−31	−63	18
				prime > control	.013	6.73			
Main effect of prime	left middle frontal gyrus	6	1,363	prime > control	<.001	20.45	−37	11	57
	left inferior parietal lobule	40	1,271	prime > control	<.001	14.67	−52	−44	43
	right superior parietal lobule	7	808	prime > control	.002	10.44	29	−69	55
	right superior frontal gyrus	8	454	prime > control	.001	12.93	41	24	49
	right middle temporal gyrus	21	371	prime > control	.001	12.02	66	−28	−14
	left inferior occipital gyrus	18	223	prime > control	.001	12.39	−43	−84	−3
	right parahippocampal gyrus	30	207	prime > control	.002	10.45	29	−54	58
	right precentral gyrus	6	205	prime > control	.001	11.98	60	5	31
	left orbitofrontal gyrus	11	203	prime > control	.001	12.53	−29	34	−17
Group × prime	subgenual cingulate	25	213	HC > BD	<.001	14.97	−13	22	−14
Anticipation loss ANOVA									
Main effect of group	no significant clusters identified				>.05				
Main effect of prime	right posterior cingulate	31	408	control > prime	.002	10.34	1	−39	31
	right inferior parietal lobule	40	491	prime > control	<.001	14.38	62	−29	46
	right caudate		249	prime > control	.002	11.19	15	16	16
Group × prime	right inferior parietal lobule	40	1,083	BD > HC	<.001	17.30	54	−42	52
	right middle frontal gyrus	10	894	BD > HC	<.001	15.54	41	44	16
	left inferior parietal lobule	40	823	BD > HC	.001	11.98	−49	−50	56
	left parahippocampal gyrus	19	381	HC > BD	<.001	18.47	−35	−43	−3
	left middle frontal gyrus	46	372	BD > HC	.001	13.71	−43	42	15
	right middle frontal gyrus	6	223	BD > HC	.002	10.40	50	1	52
	left middle temporal gyrus	20	195	BD > HC	.002	11.38	−60	−45	−11
Feedback gain ANOVA									
Main effects and interactions	no significant clusters identified				>.05				
Feedback loss ANOVA									
Main effect of group	right superior frontal gyrus	6	446	BD > HC	<.001	15.08	7	30	55
				prime > control	.042	4.39			
	right orbitofrontal gyrus	47	355	BD > HC	<.001	17.81	43	28	−7
Main effect of prime	left parahippocampal gyrus	30	211	control > prime	<.001	27.11	−21	−48	6
Group × prime	right superior frontal gyrus	6	214	HC > BD	.001	11.95	5	12	53

Note: BA = Brodmann area; BD = adolescents with bipolar I disorder; HC = healthy controls.

FIGURE 3 Significant neural activations from secondary two-way whole-brain analysis of variance (ANOVA; threshold of $p = .05$, ≥ 194 voxels) depicted in red and blue. Note: No significant activations during the feedback gain ANOVA were identified. AngG = angular gyrus; BD = bipolar disorder; Caud = caudate; HC = healthy controls; L = left; MFG = middle frontal gyrus; OFC = orbitofrontal cortex; OMFC = orbitomedial frontal cortex; PCC = posterior cingulate cortex; Phipp = parahippocampal gyrus; R = right; sACC = subgenual anterior cingulate cortex; SFG = superior frontal gyrus.



aberrant neurobehavioral responses during anticipation and receipt of reward and loss with affective priming. The present results point to anomalous mechanisms of reward processing in youth with BD that may be related to aberrant goal pursuit and motivation. Specifically, compared with their HC peers, youth with BD showed decreased activation in the thalamus and inferior temporal gyrus while anticipating gains after priming, but increased activations in the middle frontal gyrus and parietal cortices while anticipating losses after priming. Youth with BD also showed less activation in the inferior parietal lobule, thalamus, and superior frontal gyrus while receiving losses after priming. Given the significant effect of valence, the authors conducted an exploratory examination of gain and loss conditions separately in a secondary analysis. This analysis yielded increased activation in prefrontal and subcortical regions that has been documented to subserve functions related to reward processing, such as motivation, goal pursuit (caudate, OMFC), and emotion regulation (OMFC, ACC). The increased orbitomedial frontal activation (BA 10) in the BD compared with the HC group during reward anticipation was consistent with the authors' prediction. It is noteworthy, however, that the BD group also showed decreases in subgenual ACC activation after affective priming, suggesting interference in cognitive control over reward processing during primed reward anticipation. In addition, compared with HC adolescents, youth with BD showed speeded reaction times and decreases in activation in the parahippocampal gyrus during loss anticipation after affective priming. In summary, the profile of aberrant activation observed in the present adolescent BD sample provides an initial picture of developmental brain dysfunction that may underlie disordered goal pursuit and motivation in individuals at the earliest stages of this serious neuropsychiatric disorder.

The present study showed that, in BD youth, the processing of reward after affective priming results in aberrant activations in regions important in information relay to the prefrontal cortex (thalamus), visuospatial processing (parietal cortex, inferior temporal gyrus), and uncertainty and self-awareness (superior frontal and middle frontal gyrus). These regions have been previously implicated in individuals with BD while they are performing tasks assessing visuospatial

emotion processing and reactivity,[31] working memory,[32] sustained attention with emotional and neutral distracters,[33–35] response inhibition,[36] and reversal learning.[37] Most relevant to bipolar symptomatology, however, particularly in the context of hedonic drive, grandiosity, and poor insight, were the findings of prefrontal activation in the middle and superior frontal gyri. Contrary to the authors' prediction, increased activation was observed in the middle frontal gyrus in the BD group during the primed loss compared with the primed gain condition, suggesting that priming has differential effects on gain and loss conditions in pediatric BD. It is noteworthy, however, that decreased activation in the superior frontal gyrus after primed loss receipt is consistent with prior studies that have associated this region with aberrant attention to negative emotional information[38] and decreased top-down control of emotional reactivity[31] in youth with bipolar symptoms. The present results point to potential neural mechanisms that may underlie disordered self-awareness or insight during goal pursuit and motivation in BD.[39] That similar activation patterns have been observed in youth with BD across different cognitive tasks[40] suggests that these candidate neural regions are likely involved in the pathophysiology of BD.

Although exploratory and not derived from the primary three-way analysis, the findings from the secondary two-way whole-brain ANOVAs examining activations within each condition, combined with the literature on reward processing, provide a relevant context within which to understand the role of the medial prefrontal cortex in the processing of rewarding stimuli in youth with BD.[13] Prior research has suggested that mesocorticolimbic brain regions subserve a hierarchical model of reward processing that may be relevant to several possible pathways leading to dysregulated goal pursuit and motivation in BD. Although striatal regions represent an affective component expressed as arousal and action, cortical regions represent a probabilistic component that may be related to confidence in goal attainment and may manifest in BD as grandiosity and dysregulated goal pursuit.[28] In the secondary two-way ANOVA, the main effect of group suggests that the typical mechanisms of reward processing are altered in BD. Although youth with BD showed increased OMFC activation, HC youth exhibited activation of the angular gyrus bilaterally during reward anticipation. OMFC activation may be related to the perceived likelihood of attaining a reward,[26] whereas the angular gyrus has been found to be involved in calculations concerning arithmetic fact retrieval.[41] Although the probability of reward in the MID task is titrated individually to be held constant across all participants,[28] the subjective perception of a higher probability of reward outcomes may underlie illness-associated characteristics such as unrealistic outcome expectations[3,42] and impaired decision making[43] that may make individuals with BD particularly vulnerable to increased reward reactivity during reward anticipation. For example, when youth with BD received feedback about losing money after priming, the primary and secondary analyses yielded deficits in the recruitment of superior frontal regions compared with the HC group, putatively indicating a lack of self-awareness that would otherwise strengthen executive control to improve performance. Importantly, the BD and HC groups did not differ in ventrostriatal activation during reward anticipation in the primary or secondary analysis, suggesting a lack of differential regard for reward magnitude during this condition.[10,11,28] Together, these findings suggest that reward magnitude is less salient for youth with BD than is OMFC-mediated reward probability, and that youth with BD have aberrant prefrontal executive control when primed to process rewards.

This study was also a proof-of-concept investigation to examine whether an affective prime has neurobehavioral effects. Behaviorally, the authors found that affective priming resulted in increased reaction times in the BD compared with the HC group, particularly during reward anticipation followed by affective priming. Self-report ratings of increased happiness, excitability, and confidence were observed after priming across all participants, permitting neural comparisons without the confound of heterogeneous mood states within the BD group. Regarding the neural activation effects associated with priming, which have not previously been studied, the authors obtained the main effects of priming that included increased frontostriatal activation during anticipation of reward and loss. Decreases in activation after priming were found in the thalamus and inferior temporal gyrus during gain anticipation and in the thalamus, inferior parietal lobule, and superior frontal gyrus during loss feedback, suggesting task condition-specific effects that might aid in understanding how different mood states (versus traits) influence reward processing.

In a previous study using positive mood inductions to examine mood state and trait factors that mediate cognitive changes associated with emotional processing in BD, the investigators reported that positive mood inductions were more effective in individuals with BD than in controls.[44] In that study, individuals with BD showed a positive emotional bias on an affective go/no-go task and performed more slowly than did controls on a Cambridge Gambling Task, especially while making more difficult decisions. That study was limited, however, by the lack of a neutral control condition, so latency differences on the Cambridge Gambling Task could not be explained as being due to state or trait effects in BD. Together, these data underscore the strengths of the present experimental design.

In the present study, speeded reaction times and neural interactions of group and priming support the notion that an affective prime interferes with the typical processing of reward stimuli. The fact that the interaction of group and prime in self-report ratings was not significant suggests that neural differences between the BD and HC groups are unlikely to be explained by any state-related positive affect that was induced with priming. Significant decreases in thalamic and inferior temporal activations after affective priming in the BD versus HC group during reward anticipation and greater NAcc deactivation during reward anticipation after affective priming in youth with BD with higher levels of manic symptoms provide supporting evidence that errors in reward prediction signaling may be due to desensitization or downregulation of the NAcc during reward activation.[10] Thus, deficits in thalamic, temporal, and striatal activation may be due to the interference of typical reward processing by trait affective symptoms or may reflect abnormal top-down modulation of these regions by higher cortical regions, a phenomenon that has been documented with other emotion-processing[31,32,45–47] and reversal-learning[48] tasks in youth with BD.

Some limitations of this study should be noted. First, to minimize motion artifact and limit the strain of scanning teenagers with significant mood symptoms, in the MID task, only nine replications of each trial type were administered, which may have decreased power to obtain significant effects. Second, the cross-sectional design does not permit a separation of mania- versus depression-dependent contributions to these findings that may center on state-dependent enhanced arousal to reward during mania and on the avoidance of punishment or loss during depressed and euthymic states. Indeed, although the affective priming task influenced self-reported affect and neural activation, it did not intensify activation in reward- or emotion-related regions across conditions. Importantly, however, an advantage of adding an affective prime is that it may have neutralized any confound of heterogeneity of opposing mood states on the day of scanning by inducing a comparable affective state in all participants; moreover, a control condition that counterbalanced the affective prime permitted the authors to make inferences about the trait versus state features of BD. Third, although the authors attempted to minimize heterogeneity in this sample, variations remained in the levels of medication and substance exposure and in the time elapsed since the first episode of mania. Although group differences in neural responses may have been due to a differential exposure to medications, this is unlikely in the present sample in which participants had an average of only 16 weeks of lifetime medication exposure and in which the length of lifetime exposure to atypical antipsychotics, lithium, antidepressants, or psychostimulants did not correlate with any significant activations within the BD group. Fourth, although not within the scope or goals of the present study, further investigation is needed to relate these findings to the true trait features of BD that could be evaluated in adolescents at risk for BD preceding the onset of illness, to examine the specificity of these findings to adolescent-onset BD as opposed to other psychiatric disorders in this age group, and to determine whether these characteristics predict long-term clinical outcome. Nevertheless, the authors found group differences in key brain regions involved in cognition, self-awareness, motivation, and affect in adolescents with and without mania, providing an initial step in understanding the role of reward processing in the neurophysiology of pediatric BD.

In summary, mania affects the neural mechanisms underlying the anticipation and receipt of reward. This study presents evidence that early after the onset of mania, adolescents with BD exhibit anomalies in prefrontal and subcortical regions during reward processing. These regions may be promising candidates for biological markers for the development and progression of BD into adulthood. Future research is needed to examine

the longitudinal trajectories of these characteristics and their ability to predict the clinical progression of this disorder over time. &

CG Clinical Guidance

- Youth with BD showed aberrant neurobehavioral responses during the anticipation and receipt of reward and loss with affective priming.
- Compared with typically developing adolescents, youth with BD had speeded reaction times while anticipating primed rewards and showed aberrant patterns of activation in regions important for information relay to the prefrontal cortex (thalamus), visuospatial processing (parietal cortex, inferior temporal gyrus), and self-awareness (superior frontal and middle frontal gyrus).
- Youth with BD who had higher levels of manic symptoms showed decreases in NAcc activation compared with those with lower levels of manic symptoms.
- Together, these patterns of activation may clinically manifest in BD as grandiosity and dysregulated goal pursuit and distinguish psychopathology from the processes associated with typical adolescence.

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Drs. Singh, Chang, Cui, Gotlib, and Reiss, Mr. Kelley, Ms. Sherdell, and Ms. Howe are with Stanford University School of Medicine, Stanford, CA.

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