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Age associations with neural processing of reward anticipation in adolescents with bipolar disorders

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ABSTRACT

Reward/behavioral approach system hypersensitivity is implicated in bipolar disorders (BD) and in normative development during adolescence. Pediatric onset of BD is associated with a more severe illness course. However, little is known about neural processing of rewards in adolescents with BD or developmental (i.e., age) associations with activation of these neural systems. The present study aims to address this knowledge gap. The present sample included 21 adolescents with BD and 26 healthy adolescents, ages 13 to 19. Participants completed a functional magnetic resonance imaging (fMRI) protocol using the Monetary Incentive Delay (MID) task. Behavioral performance was similar between groups. Group differences in BOLD activation during target anticipation and feedback anticipation periods of the task were examined using whole-brain analyses, as were group differences in age effects. During both target anticipation and feedback anticipation, adolescents with BD, compared to adolescents without psychopathology, exhibited decreased engagement of frontal regions involved in cognitive control (i.e., dorsolateral prefrontal cortex). Healthy adolescents exhibited age-related decreases, while adolescents with BD exhibited age-related increases, in activity of other cognitive control frontal areas (i.e., right inferior frontal gyrus), suggesting altered development in the BD group. Longitudinal research is needed to examine potentially abnormal development of cognitive control during reward pursuit in adolescent BD and whether early therapeutic interventions can prevent these potential deviations from normative development.

1. Introduction

Bipolar disorders (BD) often emerge in youth (Beesdo et al., 2009). Some estimates suggest that 65% of patients with BD experience onset before age 18 (Perlis et al., 2004). Pediatric BD onset is a risk factor for more frequent episodes, greater comorbidity, suicidality, and poorer treatment adherence (Leclerc et al., 2013; Perlis et al., 2004; Tozzi et al., 2011). Regardless of age of onset, adolescents with BD experience poor functioning (Goldstein et al., 2009). The links between early onset and worse prognosis/functioning are concerning given the high suicide risk and the significant impairment experienced by many individuals with BD (Goodwin and Jamison, 2007).

Investigating BD in adolescence is important since the neural systems proposed to be dysregulated in BD undergo significant changes during this time. Specifically, theoretical models of BD hypothesize dysregulated responses to rewards/incentives, i.e., behavioral approach system (BAS) dysregulation (Depue and Iacono, 1989; Johnson et al., 2012; Urošević et al., 2008), or dysregulation of positive emotions overall (Gruber, 2011). According to the BAS dysregulation model (Urošević et al., 2008), individuals with BD experience extreme responses to reward-relevant cues, reflecting hypersensitivity of the underlying neurobehavioral reward system, i.e., BAS. Moreover, the model proposes that BAS hyperactivation leads to mania/hypomania and BAS hypoactivity leads to depression (Urošević et al., 2008). The neural system involved in these processes includes dopaminergic pathways from the ventral tegmental area to the striatum (nucleus accumbens [Nacc], specifically) and frontal cortical areas, such as orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), and the cingulate gyrus (Depue and Iacono, 1989; Urošević et al., 2008). *Adult* studies support BAS/reward dysregulation in BD (Johnson et al., 2012; Urošević et al., 2008). Developmental studies find normative adolescence to be characterized by BAS/reward hypersensitivity (Urošević et al., 2012).

Abbreviations: ACC, anterior cingulate cortex; ADHD, attention-deficit/hyperactivity disorder; BAS, behavioral approach system; BD, bipolar disorders; DLPFC, dorsolateral prefrontal cortex; MID, monetary incentive delay task; Nacc, nucleus accumbens; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; SUD, substance use disorders.

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Neuroimaging studies of healthy adolescents support structural changes in the Nacc (Urošević et al., 2012) and relatively increased responses in the ventral striatum to incentives (Ernst et al., 2005; Galvan et al., 2006; Somerville et al., 2011). The examination of neural aspects of reward/BAS dysregulation in adolescent BD is presently underexplored.

Several functional neuroimaging studies have examined neural responses to rewards in *adult* BD. During reward anticipation, adults in acute mania exhibited greater activation of posterior cingulate cortex (PCC), and increased OFC activity with increasing reward magnitude, compared to controls (Bermpohl et al., 2010). Also during reward anticipation, adults with bipolar II disorder exhibited greater ventral striatal, caudate and left DLPFC activity compared to controls (Caseras et al., 2013). During reward feedback anticipation, acutely depressed adults with BD showed decreased activation of the anterior cingulate cortex (ACC; Chase et al., 2013), whereas, in another study, euthymic adults with BD exhibited increased OFC and ventral striatal activity (Nusslock et al., 2012). Overall, these studies support dysregulated patterns of reward processing in adult BD, as well as current clinical state (e.g., acute mania) and clinical-state independent (e.g., during euthymia) effects on neural responses to rewards. However, an examination of differences in neural responses during different phases (e.g., anticipation of response execution, reward feedback anticipation) of reward processing within the same study is needed.

Knowledge is limited about reward processing in *adolescents* with BD, partly because many studies combine children and adolescents (e.g., Bebko et al., 2014; Ernst et al., 2004; Gorrindo et al., 2005), precluding an examination of adolescent-specific processes. For example, unlike healthy controls, children and adolescents with BD failed to improve performance on an incentive-guided antisaccade task during and exhibited worse performance compared to healthy controls (Mueller et al., 2010). There is an increased effect of incentives on antisaccade performance with older age in healthy adolescents (Jazbec et al., 2006). It is unclear whether adolescents with BD deviate from this normative developmental pattern.

Still, a behavioral high-risk study showed prospectively that adolescents with high BAS/reward sensitivity were at heightened risk of developing BD (Alloy et al., 2012). To date, there is only one neuroimaging study that has investigated regional brain activation during a reward paradigm in adolescent BD (Singh et al., 2013). BOLD responses were examined during a monetary incentive delay (MID) task (Knutson et al., 2001) following an affective priming task (Singh et al., 2013). During reward anticipation following positive affect priming, adolescents with BD exhibited decreased thalamic and inferior temporal gyrus activation compared with controls. Regardless of the affective priming manipulation, adolescents with BD exhibited greater medial OFC activity during reward anticipation (Singh et al., 2013).

The present study further addresses gaps in the literature by examining neural responses during the MID task, a well-validated reward anticipation paradigm (Knutson et al., 2001), in adolescents with BD versus those without psychopathology. Based on the BAS dysregulation model (Depue and Iacono, 1989), we hypothesize group differences in activation of striatal and frontal cortical regions (e.g., DLPFC, OFC, ACC), during both the *target anticipation period* (i.e., as one prepares to make a response to gain a reward) and during *feedback anticipation* (i.e., after response execution). Most prior studies fail to report on both processes and focus on either feedback anticipation (e.g., Nusslock et al., 2012) or anticipation of a response execution, i.e., target anticipation (e.g., Singh et al., 2013). Based on prior research (Bermpohl et al., 2010; Nusslock et al., 2012; Singh et al., 2013), we predict that adolescents with BD will exhibit greater OFC activation during both target anticipation and feedback anticipation periods compared to healthy adolescents. Still, given the vast developmental changes in reward-relevant prefrontal cortical areas during adolescence and paucity of data focusing on adolescents with BD, it is not clear whether the same group differences in OFC activity will be observed. For analyses examining sensitivity to reward magnitude (i.e., small versus large rewards), we hypothesize that adolescents with BD will show greater striatal responses to increasing reward magnitude than healthy adolescents. Finally, we hypothesize that group by age interactions will demonstrate potential deviations from normative development in BD.

2. Material and methods

2.1. Participants

Participants (ages 13 to 19) were recruited from university-affiliated clinics, a database of community research volunteers, and community flyers. Inclusion criteria were: meeting DSM-IV criteria for bipolar I disorder, bipolar II disorder, or bipolar disorder Not Otherwise Specified (NOS) for the BD group, and no psychopathology for the control group; no neurological disorders or severe head injury; no current major/chronic physical conditions; IQ ≥ 70; no learning disabilities/developmental problems; normal/corrected-to-normal vision/hearing; native English speaker/bilingual since early age; right-handedness, and no imaging contraindications.

A phone screening and an in-person semi-structured diagnostic interview, Kiddie-Sads-Present and Lifetime Version 2009 (K-SADS-PL, 2009; Axelson et al., 2009) assessed eligibility. For minors, different interviewers conducted a parent interview versus the participant interview. Participants age ≥ 18 provided all information themselves. A two-tiered consensus procedure was employed: 1) a clinical psychologist (SU) conducted the adolescent or parent interview for every participant and supervised consensus meetings to derive summary ratings based on these interviews; and 2) a psychologist with expertise in pediatric BD assessment (EAY) reviewed 57% of the BD interviews. Consistent with Axelson et al. (2009), only bipolar symptoms that started within mood episodes, or chronic symptoms (e.g., difficulty concentrating) that clearly worsened during mood episodes, counted towards bipolar symptomatology. Inter-rater reliability for K-SADS-PL symptom assessments was excellent (weighted kappa = .87).

This procedure yielded a sample of 47 adolescents (21 BD, 26 controls). Consistent with prior studies (Singh et al., 2013), participants remained on their psychotropic medications. BD diagnoses varied within that group with most participants meeting criteria for Bipolar I or Bipolar II disorders. Five participants with DSM-IV BD NOS diagnoses were included in the BD group, which is consistent with recommendations about pediatric bipolar diagnoses. All five participants met criteria for at least one hypomanic episode except for duration (i.e., hypomanic mood of duration <4 days with 3 symptoms present [4 for irritable mood], change in functioning observable by others). All five had histories of major depressive episodes, psychiatric hospitalizations, and were currently prescribed mood stabilizers and/or lithium. All five fit the criteria for BD Otherwise Specified by DSM-5 (2013). Their BD presentation is well above the minimal criteria for BD NOS established by previous studies (Arnold et al., 2011; Birmaher et al., 2006), which has shown comparable functional impairment, symptom severity, and psychiatric family history to bipolar I disorder (Hafeman et al., 2013). Four of five participants with BD NOS also had first-degree relatives with mood disorder diagnoses. The inclusion of BD NOS is also consistent with empirical reviews concluding that BD NOS is an impairing disorder on a continuum with Bipolar I Disorder (Youngstrom et al., 2008).

To assess current clinical state, BD group participants were administered the K-SADS depression rating (KDRS) and K-SADS mania rating scales (KMRS; Ladoucer et al., 2011) examining BD symptoms in the week before the testing day. Based on prior established cut-offs (Ladoucer et al., 2011), 11 BD participants were euthymic (KDRS ≤ 10 and KMRS ≤ 12), 5 participants exhibited depressive and hypomanic symptoms (KDRS > 10 and KMRS > 12), 3 participants exhibited hypomanic symptoms only (KDRS ≤ 10 and KMRS > 12), and 1 participant exhibited depressive symptoms (KDRS > 10 and KMRS ≤ 12). Prior studies of adults with BD have found similar neural activation (e.g., increased OFC activity) to reward in euthymia (e.g., Nusslock et al., 2012) and acute mania (e.g., Bermpohl et al., 2010), as well as significant presence

of bipolar symptoms outside of bipolar episodes (e.g., Judd et al., 2003). Periods of bipolar symptoms that do not reach episode criteria are common in pediatric BD (Axelson et al., 2006). For these reasons, analyses included all BD participants with symptom severities on the day of testing as predictors (see Supplemental Materials for analyses of current symptom effects).

In the BD group, the most common lifetime comorbidities were anxiety disorders (57.1%), attention deficit/hyperactivity disorder (ADHD; 42.9%), and substance use disorders (SUD; 38.1%). Five BD participants met current SUD criteria for cannabis and/or alcohol; of these, four were in DSM-IV-defined early full remission and one was symptomatic but denied use in the week before testing. All participants were asked to abstain from substance use for 24 h prior to testing.

2.2. Procedures

After complete description of the study to the participant and a parent/legal guardian, informed assents/consents were obtained. The University of Minnesota's Institutional Review Board approved the study protocol, which was in accordance with the Helsinki Declaration of 1975. Participants completed two visits: 1) a semi-structured diagnostic interview, self-report questionnaires, and intelligence testing; and 2) a neurobehavioral task battery, neuroimaging, and psychophysiological assessments. The present analyses include age, current symptom assessments, intelligence as assessed by Vocabulary and Matrix Reasoning subtests (Wechsler's Abbreviated Scale of Intelligence 2nd Edition; Wechsler, 2011), and the MID task's behavioral and functional magnetic resonance imaging (fMRI) measures.

2.3. Measures

2.3.1. Internal State Scale (ISS; Bauer et al., 1991)

The ISS is a self-report measure of current bipolar symptoms (across the previous 24 h) with four subscales (Activation, Well-being, Perceived Conflict, and Depression). ISS Activation and Depression scores correlate highly with interview-based ratings of mania and depression, respectively (Bauer et al., 1991).

2.3.2. Monetary Incentive Delay (MID) task (Knutson et al., 2001)

The task includes three runs (each 6 min, 12 s) of 60 randomly ordered trials. In each run, 24 were *gain* trials with an opportunity to win money by fast and accurate responding, 24 were *loss* trials with an opportunity to avoid losing money by fast and accurate responding, and 12 were *no-incentive trials* in which there were no gains or losses. For gain and loss trials, there were 6 trials for each magnitude: small ($0.25), medium ($1), large ($5), or random (i.e., randomly chosen magnitude of $0.25, $1, or $5). Fig. 1 depicts a typical trial sequence. The inter-trial interval was 100 ms. The present analysis focused on neural responses during target anticipation (i.e., delay before target presentation and response) and feedback anticipation (i.e., delay before feedback) for gain and no-incentive trials

Participants completed an in-scanner practice run during a structural imaging sequence. The duration of target presentation was adjusted for each participant to achieve approximately 70% accuracy, i.e., successfully pressing the button during the target presentation. The adjustment algorithm rank ordered the prior run's RTs (for 1st run, practice trials' RTs were used) from the fastest to slowest and then chose RT at the 70th percentile as the target duration for the current run. At the end of the task, participants were informed that a portion (~10%) of their total winnings ($M = \$8.64$, $SD = \$2.52$) would be added to their compensation.

2.3.3. MRI acquisition and processing

Images were acquired on two 3-Tesla Siemens Tim Trio (Siemens Medical Systems, Erlangen, Germany) scanners at the University of Minnesota's Center for Magnetic Resonance Research. Forty-three

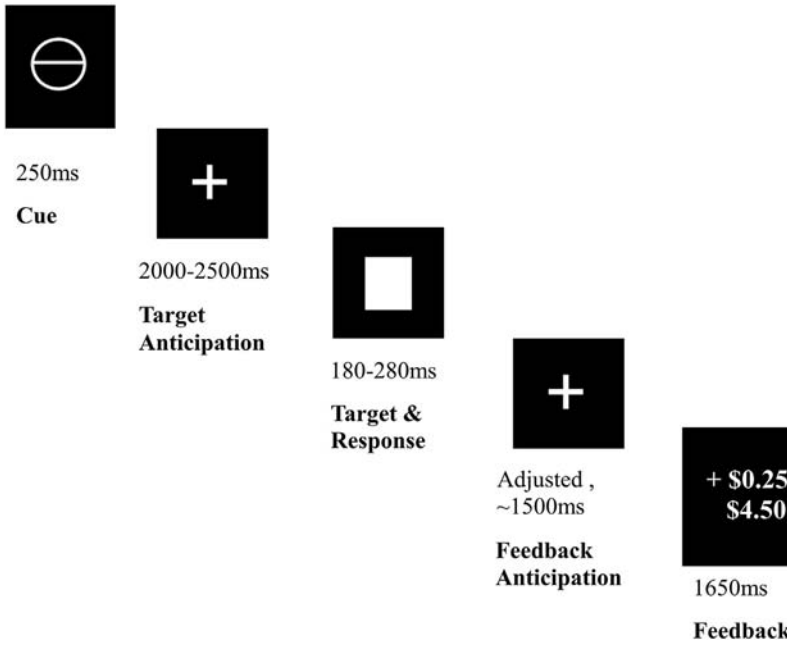

Fig. 1. Monetary Incentive Delay (MID) task. The figure illustrates the timing for a single behavioral trial. In this example, the circle cue with a single line indicates a small gain trial. The feedback screen indicates that the participant responded fast enough in

participants were scanned on one scanner; two participants per group were scanned on the other. The scanner was entered as a predictor of no interest, but given that equivalent numbers of BD and control participants of similar ages were scanned on the second scanner, this is unlikely to affect contrasts of interest. Structural three-dimensional images were obtained with a coronal T_1-weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence (TR = 2530 ms, TE = 3.65 ms, TI = 1100 ms, 240 slices, voxel size = 1.0 mm^3, flip angle = 7°, FOV = 256 mm). Next, functional images were acquired using T2*-weighted echo planar imaging with 34 interleaved transaxial slices (TR = 2000 ms, TE = 28 ms, flip angle = 80°, FOV = 200 mm, and 64 × 64 matrix; voxel size 3.1 × 3.1 × 4.0 mm). The first 2 TRs of each run were discarded to allow for longitudinal magnetization stabilization

All processing and analyses of MRI data were conducted using *FMRIB's Software Library* (*fsl*) 4.1.9 software (http://fsl.fmrib.ox.ac.uk/fsl/; Jenkinson et al., 2012). Non-brain tissue was removed using *fsl*'s brain extraction tool. Functional image preprocessing included high pass temporal filtering (60 s), slice timing correction, FILM prewhitening, and spatial smoothing using an 8 mm full-width half-maximum Gaussian filter. Motion artifacts were examined using MCFLIRT. Motion spikes were identified by absolute displacement >3 mm and/or relative displacement >1.5625 mm. The maximum percentage of TRs per individual participant containing motion spikes was 6.5%. There were no significant group differences in the amount of motion displacement. Images were transformed to Montreal Neurological Institute (MNI)-152 2 mm template space using linear alignment with 6 degrees of freedom.

2.4. Statistical approach

A series of univariate/multivariate ANCOVAs were conducted to examine group differences in MID task performance, controlling for current bipolar symptoms and age.

General Linear Models (GLM) were conducted on MRI data using *fsl* 4.1.9's FEAT tool, with separate analyses for target anticipation and feedback anticipation. At the first level, BOLD responses in each run for each participant were modeled using motion confounds, a motion spikes covariate, task predictors representing 9 trial types (i.e., small, medium,

large and random gains; small, medium, large and random losses; and no-incentive), and their temporal derivatives. Predictors were convolved with a canonical hemodynamic response function. In the case of feedback anticipation analyses, both anticipation of correct and incorrect feedback for each trial type was modeled, but only correct trials were included in the contrasts of interest. The contrasts of interest for both sets of analyses were gain > no-incentive trials and large gain > small gain trials, although all contrasts originally proposed by Knutson et al. (2001) were modeled (e.g., loss > no-incentive). First-level analyses at the individual subject level were conducted with a voxelwise threshold of $p < .05$, uncorrected. In second-level GLM analyses with fixed effects, the three runs for each participant were combined to generate the mean signal for each contrast at threshold of $p < .05$.

Group-level GLM analyses (mixed-effects, FLAME 1) used the following predictors: diagnostic group, current hypomanic/manic symptoms, current depressive symptoms, age, scanner, and the diagnostic group by age interaction. Contrasts of interest included group effects and group by age interactions. The voxel-wise p threshold was <.005. For significant group by age interactions, follow-up analyses involved extracting % BOLD signal change for each significant cluster and correlating these values with age *separately for each group*.

For multiple-comparisons correction, we used the 3dStimClust program (http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html) to derive a cluster size with a family-wise $\alpha = .05$. For each contrast of interest, 10,000 iterations of Monte Carlo simulations were run with a voxel-wise p threshold of .005 and FWHM estimates derived from the individual participant's level-two residual files (ranging from 8.77 to 9.19). This procedure yielded the following cluster size thresholds: 212 MNI 2-mm standard voxels (i.e., ~1696 mm^3) for gain > no incentive during target anticipation, 201 MNI 2-mm standard voxels (i.e., ~1608 mm^3) for large gain > small gain during target anticipation, 197 MNI 2-mm standard voxels (i.e., ~1576 mm^3) for gain > no incentive during feedback anticipation, and 193 MNI 2-mm standard voxels (i.e., ~1544 mm^3) for large gain > small gain during the feedback presentation. We present all clusters surviving this multiple comparison correction threshold from the whole-brain analyses.

Table 1
Descriptive statistics for adolescents in the bipolar disorders (BD) and control groups.

	BD ($n = 21$)	Control ($n = 26$)
Age range in years	13.41–19.39	13.03–18.39
Age, *M* (*SD*)	16.33 (1.66)	15.9 (1.32)
Puberty Tanner stage	4.14 (0.57)	4.15 (0.75)
Male gender, *n* (%)	13 (61.9%)	16 (61.5%)
Caucasian, *n* (%)	13 (61.9%)	19 (73.1%)
SES, *M* (*SD*)	44.86 (12.47)	45.44 (11.24)
IQ, *M* (*SD*)	105.19 (12.04)*	112.35 (12.09)*
BD I Dx, *n* (%)	8 (38.1%)	–
BD II Dx, *n* (%)	8 (38.1%)	–
BD NOS Dx, *n* (%)	5 (23.8%)	–
BD Age of Onset	7.81 (3.72)	–
Number of comorbid axis I diagnoses, *M* (*SD*)	2.38 (1.96)	–[a]
Family Hx of BP, *n* (%)	10 (47.6%)	0 (0%)
Current psychotropic medications, *n* (%)	19 (90.5%)	–
Number of psychotropic medications, *M* (*SD*)	2.62 (1.60)	–
Antipsychotics, *n* (%)	14 (66.7%)	–
Anticonvulsants/mood stabilizers, *n* (%)	4 (19%)	–
Lithium, *n* (%)	5 (23.8%)	–
Antidepressants, *n* (%)	7 (33.3%)	–
ADHD medications, *n* (%)	9 (42.9%)	–
Anxiolytics, *n* (%)	5 (23.8%)	–
Other (e.g., *sleep*), *n* (%)	7 (33.3%)	–
ISS activation, *M* (*SD*)	187.62 (119.83)*	66.54 (63.87)*
ISS depression, *M* (*SD*)	35.24 (35.02)*	7.31 (22.01)*

Note: ADHD = attention deficit/hyperactivity disorder; BD NOS = bipolar disorder not otherwise specified; ISS = Internal State Scale; IQ = WASI-II 2-subtest *t*-score estimating overall intelligence; SES = socio-economic status. Puberty Tanner stage was determined by averaging ratings of sex-appropriate Tanner drawings (Taylor et al., 2001); SES assessed based on parental education and family income (40); IQ was estimated using Vocabulary and Matrix Reasoning subscales of the WASI-II; family history of BD was determined using a semi-structured interview with a parent or adult participant.

* Denotes significant group differences at $p < .05$.

[a] One control participant had a history of enuresis in full remission.

3. Results

3.1. Sample characteristics

Table 1 summarizes demographic and clinical characteristics of the sample. There were no group differences in age, pubertal stage, sex distribution, ethnicity, or socio-economic status as assessed by parental education and occupation (Hollingshead, 1975). Based on the two WASI-II subtests, the BD group exhibited significantly lower estimated IQ scores than controls, $t\ (45) = -2.02$, $p = .049$, but there were no group difference in *t*-scores, $t\ (45) = -1.97$, $p = .055$. In the BD group, age of onset was determined by K-SADS-PL interview and defined as onset of first BD symptoms. There was no significant relationship between current age and age of onset, $r = .13$, $p = .574$.

3.2. Group differences in MID task performance

Consistent with the task's adjustment of target duration to optimize each participant's performance, there were no significant group differences in overall MID task accuracy, $F\ (1, 42) = 1.06$, $p = .31$, *partial* $\eta^2 = .03$, or group by age interactions. The BD group's and the control group's respective mean accuracies were 72.2% ($SD = 0.08\%$) and 74.9% ($SD = 0.07\%$). There were no significant group differences in correct-trial RTs, *multivariate* $F\ (9, 34) = 0.68$, $p = .726$, *partial* $\eta^2 = 0.15$, or group by age interactions. There were also no significant group differences in total winnings participants received, $t\ (45) = -0.51$, $p = .614$. The pattern of results remains the same when IQ is included as a covariate. MRI findings cannot be explained by group differences in performance.

3.3. Group differences in BOLD activation during target anticipation

3.3.1. Gain > no-incentive

Table 2 summarizes clusters with significant group differences in BOLD activity. Controls exhibited increased activation in the right DLPFC and no change in left precuneus for gain > no incentive cues, while the BD group exhibited decreased activation (Fig. 2). There were no significant clusters with greater activity for the BD group versus controls and no significant age by group interaction effects.

3.3.2. Large gain > small gain

As shown in Table 2, controls exhibited relatively greater activity in the right frontal pole cluster, which expanded into the right Superior

Table 2
Group differences in BOLD activation during the target anticipation period.

Region	Cluster size	Maximum Z MNI coordinates			Maximum Z
		x	y	z	
BP > control comparison for gain > no-incentive					
None					
Control > BP comparison for gain > no-incentive					
R DLPFC	641	54	22	36	4.21
L precuneus	257	−2	−70	36	3.2
BP > control comparison for large gain > small gain					
None					
Control > BP comparison for large gain > small gain					
R frontal pole area	389	30	38	48	3.88

Note: DLPFC = dorsolateral prefrontal cortex; BP = bipolar spectrum participants. Cluster sizes are presented in standard 2 mm voxels.

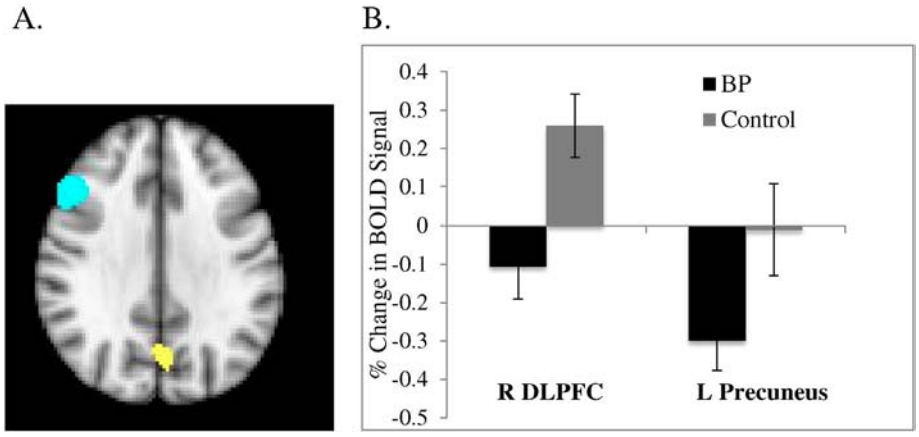

Fig. 2. Group differences in activity for reward processing (gain > no incentive) during target anticipation. (A) This figure depicts locations of clusters with greater activation in controls than bipolar group; right dorsolateral prefrontal cortex (DLPFC) cluster is depicted in light blue and left precuneus in yellow. (B) Means and standard deviations of percent change in BOLD activity from no incentives to gains for bipolar (BD) and control groups. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

frontal gyrus and middle frontal gyrus. As illustrated in Fig. 3, there was a positive BOLD signal change with greater reward magnitude for the control group and a decrease in signal for the BD group (Fig. 3). There were no significant clusters with greater activity for the BD group compared to controls.

Table 3 describes clusters with significant group by age interaction effects for reward magnitude. Follow-up analyses (presented in Table 3) revealed that, with maturation, healthy adolescents, but not those with BD, exhibited increased activation with increasing reward magnitude in brain regions involved in attention and visual processing.

3.4. Group differences in BOLD activation during feedback anticipation

3.4.1. Gain > no-incentive

As summarized in Table 4, the control group exhibited relatively greater activity in the right DLPFC, the right inferior parietal region, right OFC, and left precuneus. Controls exhibited either a BOLD signal increase (e.g., right DLPFC, right OFC) or no signal change (e.g., left precuneus) for these significant clusters, whereas the BD group exhibited a relative decrease in signal (Fig. 4).

Table 5 describes the significant age by group interaction effect in the right inferior frontal gyrus (IFG), a region involved in response inhibition, during reward feedback anticipation. As illustrated in Fig. 5, in the control group, the right IFG signal change during the reward > no-incentive feedback anticipation was inversely correlated with age. In the BD group, associations between signal change in r IFG and older age was positive.

3.4.2. Large gain > small gain

As summarized in Table 4, the BD group exhibited increased activity in the right OFC and temporal pole region while anticipating receipt of increased magnitude of reward, whereas the control group exhibited a decrease in signal change in the same cluster (see Supplemental Fig. 5 for additional analyses). In a left brainstem cluster, the control group exhibited increases in signal change, whereas the BD group exhibited no change with increased magnitude of reward feedback.

As summarized in Table 5, when examining group by age interaction effects, there were multiple significant clusters, which are involved in attention, motor, somatosensoty, and visual processing. The control group exhibited positive and significant associations between age and signal change for these clusters, whereas the BD group showed negative and non-significant correlations between age and signal change.

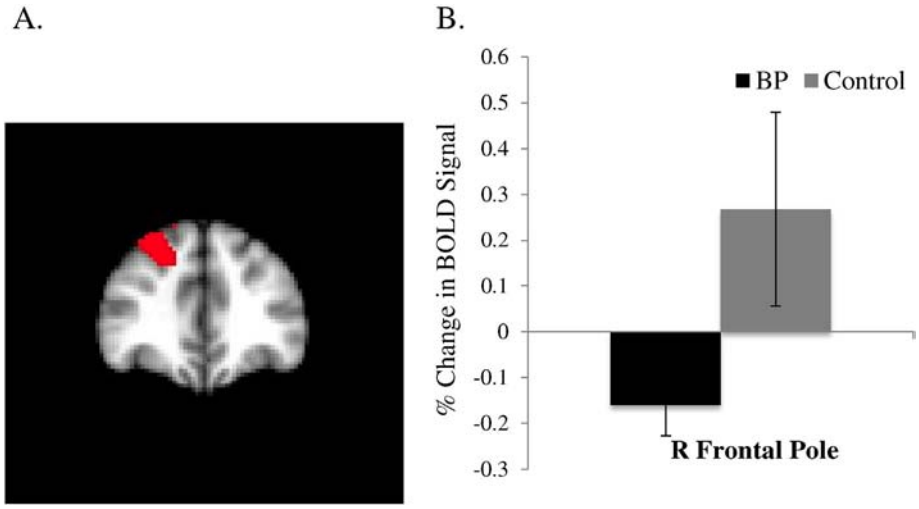

Fig. 3. Greater effect of reward magnitude (large gain > small gain) in frontal pole area for control vs. BD group during target anticipation. (A) This figure depicts locations of frontal pole cluster with greater activation in controls than bipolar group. (B) Means and standard deviations of percent change in BOLD signal for large gain trials relative to small gain trials for bipolar (BD) versus control groups separately.

Table 3
Age by group interaction effects for reward magnitude (large gain > small gain) during the target anticipation period.

Region	Cluster size	Maximum Z MNI coordinates				Pearson *r* between age & BOLD % signal change	
		x	y	z	MaxZ	BP group	Control group
Precuneus, L & R	1650	−4	−66	20	4.05	−.331	.545**
Temporal/occipital fusiform cortex, R	829	36	−54	−6	3.84	−.205	.572**
Lateral occipital cortex, L	458	−42	−62	24	3.4	−.046	.689**
Angular gyrus, R	352	54	−44	14	3.47	−.367	.569**
Lateral occipital cortex, R	237	40	−70	22	3.57	−.220	.595**

Note: BP = bipolar spectrum participants. Cluster sizes are presented in standard 2 mm voxels.
** Denotes $p < .005$.

3.5. Functional MRI MID main effect and additional analyses

Supplemental Materials present main effects of the MID task (gain > no-incentive, large gain > small gain) in the full sample (Supplemental Figs.1–4), which were consistent with expected findings given prior studies using the task. For example, as expected, gain > no incentive yielded greater activation in the striatum. Supplemental Materials also include group-difference analyses excluding BD participants with comorbid ADHD or SUD, which yielded largely similar patterns of group differences in BOLD responses (Supplemental Tables 1–4), with a few exceptions. For example, certain clusters exhibited greater activity in BD versus control group only when BD participants with comorbid disorders were excluded (e.g., insula cluster for gain > no incentive during feedback anticipation after excluding BD participants with comorbid ADHD). Supplemental Materials present BOLD activity associations with current bipolar symptoms in the BD group (Supplemental Tables 5–6). Supplemental Tables 7–8 present findings of the repeated analyses with IQ added as a covariate.

4. Discussion

In the present study, adolescents with BD exhibited lower activity, as compared to healthy adolescents, in cognitive control brain regions (e.g., DLPFC; Miller and Cohen, 2001) when anticipating response execution for a monetary reward (i.e., target anticipation). Similarly, adolescents with BD exhibited lower activity in this cognitive control region after response execution while anticipating reward feedback. Moreover, there were differential associations between maturation and activity within a cognitive control frontal area (i.e., right IFG) during reward feedback anticipation. As illustrated in Fig. 5, older healthy adolescents, compared to younger healthy adolescents, showed *less* engagement of right IFG, a brain region implicated in response inhibition (Hwang et al., 2010), after response execution and while anticipating reward feedback. In contrast, among adolescents with BD during reward feedback anticipation, activity of this response inhibition brain region was positively associated with age. These group differences and differences in age associations with activity in cognitive control brain regions were not explained by the presence of psychiatric comorbidity among adolescents with BD or by group differences in general intelligence (see Supplemental Materials). Consequently, the current findings provide evidence for disrupted maturation of the cognitive control network and its function within reward contexts in adolescent BD.

These deviations from normative development are important because cognitive control systems continue to mature from adolescence to adulthood (Hwang et al., 2010). Stronger connectivity between frontal cortical regions (e.g., right inferior frontal gyrus, right middle frontal gyrus), thalamus, and sensorimotor regions is observed in healthy adults versus adolescents during an inhibitory control task (Hwang et al., 2010). Moreover, successful recruitment of cognitive control in reward contexts is associated with adult-like connectivity between the right IFG and the striatum (Somerville et al., 2011).

Recruitment of control mechanisms during high-stakes reward contexts allows behavior to be adaptively modulated in pursuit of short-term and longer-range goals. Within the MID task, which stimulates incentive motivation, participants must engage control mechanisms to closely attend to cue stimuli, link those stimuli with reward outcomes, prepare fast responses that will lead to gains/loss avoidance, and incorporate feedback to adjust the speed of responding. In the present study, adolescents with BD relied on different neural processes to successfully perform this reward task. Specifically, adolescents with BD appeared to exert less effort to update reward valuations and adjust responding

Table 4
Group differences in BOLD activation during the feedback anticipation period.

Region	Cluster size	Maximum Z MNI coordinates			Maximum Z
		x	y	z	
BP > control comparison for gain > no-incentive					
None					
Control > BP comparison for gain > no-incentive					
R DLPFC	501	56	22	38	4.85
R inferior parietal lobule	387	50	−54	44	3.84
R OFC	362	40	58	−14	3.92
L precuneus	219	−2	−72	36	3.18
BP > control comparison for large gain > small gain					
R OFC and temporal pole	235	24	6	−28	4.50
Control > BP comparison for large gain > small gain					
Brain stem	226	−10	−22	−14	3.86

Note: DLPFC = dorsolateral prefrontal cortex; OFC = orbitofrontal cortex; BP = bipolar spectrum participants. Cluster sizes are presented in standard 2 mm voxels.

Table 5
Age by group interaction effects during the feedback anticipation period.

Region	Cluster size	Maximum Z MNI coordinates				Pearson *r* between age & BOLD % signal change	
		x	y	z	MaxZ	BP group	Control group
Gain > no-incentive contrast							
R inferior frontal gyrus	264	52	28	6	3.83	.576*	−.520*
Large gain > small gain contrast							
L lateral occipital cortex	522	−50	−64	10	3.39	−.100	.682**
L precentral gyrus	355	−26	4	38	3.58	−.402	.570**
R postcentral gyrus	322	16	−32	68	3.44	−.363	.625**
L precuneus	309	−4	−60	4	3.35	−.392	.426*
L posterior cingulate cortex	304	−8	−44	38	3.34	−.380	.568**
R lateral occipital cortex	280	48	−62	−2	3.35	−.256	.471*
L paracingulate gyrus	234	−2	52	−6	3.27	−.201	.464*
L postcentral gyrus	225	−10	−36	76	3.45	−.261	.577**

Note: BP = bipolar spectrum participants; OFC = orbitofrontal cortex. Cluster sizes are presented in standard 2 mm voxels.
* Denotes $p < .05$.
** Denotes $p \leq .005$.

based on feedback about successful reward attainment, but with older age they may have exerted greater efforts to cease responding to target stimuli. Future longitudinal studies will need to examine whether these abnormalities in development of cognitive control persist into adulthood in BD or are developmentally limited to BD during adolescence.

A growing literature supports dysregulated goal-striving in adults with BD. They are at increased risk for mania/hypomania following goal-attainment (Johnson et al., 2000) and during goal-striving life events (Nusslock et al., 2007). Unlike healthy controls, they sustain high approach motivation while pursuing hard to obtain rewards (Harmon-Jones et al., 2008) and are less likely to reduce their efforts even after unexpected positive feedback (Fulford et al., 2010). The present study provides a potential neural mechanism for these prior observations, i.e., deficiencies in cognitive control activation in the context of heightened incentive motivation during both response preparation and periods when action strategies are adapted based on feedback. Still, there were no group differences in behavioral performance on the MID task in the present study, and examination of goal-striving in adolescent BD is scarce. Future studies will need to examine behavioral performance using additional reward paradigms, particularly those that tax cognitive control network during reward pursuit.

The findings related to OFC activity were mixed. Adolescents with BD versus controls exhibited diminished OFC activity for gain versus no-incentive trials during feedback anticipation, but greater increases in activity to larger magnitude of the reward feedback in the non-overlapping cluster encompassing OFC and temporal pole. This patterning is inconsistent with prior findings of increased OFC activation in adults with BD versus controls during reward anticipation (Nusslock et al., 2012). There could be different neural abnormalities in the context of reward paradigms characterizing adolescents (e.g., lower activation of DLPFC) versus adults with BD (e.g., greater OFC activation, Nusslock et al., 2012). Additional research is needed before firm conclusions can be established.

The present study yielded group differences and group by age interaction effects in brain regions involved in attentional processes (e.g., precuneus, parietal areas). Healthy adolescents exhibited greater activity than adolescents with BD during both target and reward feedback anticipation. Importantly, group difference in precuneus activity during target anticipation remained in a repeated analysis excluding adolescents with BD and comorbid ADHD (Supplemental Materials). Additionally, older healthy adolescents versus younger healthy adolescents exhibited greater precuneus activity in response to increases in reward magnitude during target and feedback anticipation, whereas adolescents with BD showed no such relationship with age. Recent research implicates precuneus' involvement in reinforcement learning, particularly learning about multidimensional stimuli (e.g., differences in

shape and pattern of cues in the MID task) where attentional networks may play a key role in honing in on the reward-relevant aspects of the stimuli (Niv et al., 2015). In a previous study of reward processing during adolescence, functional connectivity between the striatum and precuneus was linked to greater severity of unipolar depression (Gabbay et al., 2013) and it mediates the relationship between sensation-seeking and alcohol use among young adults (Weiland et al., 2013). Moreover, prior studies support increases in precuneus activity with maturation, i.e., greater activity among healthy adults versus healthy adolescents, during reward receipt (Jarcho et al., 2012). Consequently, the present findings suggest a disrupted development of the attentional network within reward contexts in adolescent BD. Future longitudinal studies will need to further examine whether these abnormalities persist into adulthood for BD.

There were also group by age interaction effects in brain regions involved in visual processing (e.g., lateral occipital cortex) for contrasts examining effects of the increasing reward magnitude during target anticipation and during feedback anticipation. Older healthy adolescents exhibited greater activation of these regions in response to larger reward magnitudes, while there were no significant associations with age among adolescents with BD. These maturational differences are intriguing given a recent study suggesting abnormalities in visual processing of faces in pediatric BD (Perlman et al., 2013). Additional research is needed to fully understand the clinical significance of these developmental differences in visual processing streams for BD.

The present findings are also consistent with prior research in adolescent BD (Singh et al., 2013), in so far as no group differences in striatal activation were observed. Normative development during adolescence is characterized by increased reward sensitivity (Urošević et al., 2012), structural changes in the striatum (Urošević et al., 2012), and increased striatal activation in response to rewards (Ernst et al., 2005; Galvan et al., 2006; Silverman et al., 2015; Somerville et al., 2011; but see Bjork et al., 2010). Adolescents with BD may not demonstrate hyperactive striatal function compared to normative adolescent developmental trends. However, there are also several differences between Singh and colleagues' findings and the present study, including differences in experimental design (i.e., the lack versus absence of an affective priming task prior to the MID task). Future research will need to further investigate neural reactivity to rewards in adolescent BD using different reward paradigms, as well as investigate potential longitudinal changes in striatal reactivity as adolescents age into adulthood.

The present study has several strengths, including the examination of differential associations of reward-relevant activity with maturation in adolescent BD versus healthy adolescents and during different points of reward processing. The BD sample had psychiatric comorbidities typical of a pediatric onset BD (Perlis et al., 2004), implying generalizability of the findings to clinical populations. Additional analyses (Supplemental Materials) excluding BD participants with highly prevalent comorbidities ensure that the findings are not driven by other psychopathological conditions.

Limitations are similar to those commonly reported in other studies of individuals with BD. Participants in the BD group were not asked to withdraw/alter their psychopharmacological treatment due to ethical considerations. Incomplete information precluded analyses of dosage effects. fMRI studies investigating responses to emotional stimuli in BD either report no effects or a normalizing effect of psychotropic medications (Hafeman et al., 2012). This implies that our observed group differences may, if anything, be attenuated. In addition, participants with BD were not required to be euthymic. Significant bipolar symptoms are common during remission/euthymia in BD (Judd et al., 2003). In pediatric BD, symptomatic periods meeting all DSM-IV criteria except episode duration are also common (Axelson et al., 2006). Some adult BD studies also find similarities in brain regions activated by rewards (e.g., OFC) in euthymia (e.g., Nusslock et al., 2012) and acute episodes (e.g., Bermpohl et al., 2010). Consequently, we modeled the current bipolar symptoms effects in our analyses rather than exclude participants based on their symptom presentation, and all group differences were observed after controlling for these current-state effects. Finally, the present sample is relatively small, although consistent with prior pediatric BD studies (e.g., Mueller et al., 2010). The small sample size precluded a more thorough examination of effects of current clinical state, differences among adolescents with different BD diagnoses, or differences among the BD adolescents with and without various psychiatric comorbidities.

5. Conclusions

Theoretical models of *adult* BD implicate abnormalities in reward processing as a core dysfunction (e.g., Depue and Iacono, 1989; Johnson et al., 2012; Urošević et al., 2008). Additionally, patients with BD often experience illness onset before age 18 (e.g., Perlis et al., 2004), i.e., during a developmental period with both structural (e.g., Urošević et al., 2012) and functional (e.g., Somerville et al., 2011) changes in reward-relevant neural systems. The present study is important as it extends the current literature by suggesting that adolescent BD may be associated with deviations in normative, age-related changes in activation of PFC regions involved in cognitive control during reward anticipation. Adolescents with BD engaged frontal cortical regions involved in cognitive control to a lesser extent than healthy adolescents when approaching rewards or anticipating reward feedback. Moreover, adolescents with BD did not recruit response inhibition regions as expected with increasing age. In addition, the present study supports disruption in functional development of brain regions (e.g., precuneus) implicated in attentional network relevant for reinforcement learning. Longitudinal studies investigating adolescents with BD into adulthood are needed to clarify the significance of these cross-sectional differences in age associations and their significance for the achievement of adult levels of executive control over behavior.

In real world settings, the lack of greater PFC recruitment with older age could impact inhibitory control in risk-taking contexts. Similarly, the lack of greater attentional network recruitment with older age may impact reward contingency learning and could explain pursuit of rewards with disregard for consequences seen in mania/hypomania. Future studies should investigate whether therapeutic interventions (e.g., atypical antipsychotics, cognitive skills training) targeting these cognitive control and attentional processes during adolescence can improve long-term outcomes, such as prospective BD course (e.g., prolong euthymic periods).

Author disclosures

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Appendix A. Supplementary data

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