NeuroImage: Clinical 11 (2016) 476–485

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

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

Snežana Urošević[a,b,*], Monica Luciana[a,b], Jonathan B. Jensen[c], Eric A. Youngstrom[d], Kathleen M. Thomas[b,e]

[a] Department of Psychology, University of Minnesota—Twin Cities, United States
[b] Center for Neurobehavioral Development, University of Minnesota—Twin Cities, United States
[c] Department of Psychiatry, University of Minnesota—Twin Cities, United States
[d] Department of Psychology, University of North Carolina—Chapel Hill, United States
[e] Institute of Child Development, University of Minnesota—Twin Cities, United States

ARTICLE INFO

Article history:
Received 23 November 2015
Received in revised form 4 February 2016
Accepted 17 March 2016
Available online 18 March 2016

Keywords:
Bipolar disorder
Adolescence
Reward
BAS dysregulation
fMRI

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.

* Corresponding author at: Department of Psychology, University of Minnesota, N218 Elliott Hall, 75 East River Parkway, Minneapolis, MN 55455, United States.
E-mail address: snezana.urosevic@gmail.com (S. Urošević).

http://dx.doi.org/10.1016/j.nicl.2016.03.013

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