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Research paper

Reversal-learning deficits in childhood-onset bipolar disorder across the transition from childhood to young adulthood

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ABSTRACT

Background: Bipolar disorder (BD) is a severe mental illness that can have high costs for youths (< 18 years old) and adults. Relative to healthy controls (HC), individuals with BD often show impaired attention, working memory, executive function, and cognitive flexibility (the ability to adapt to changing reward/punishment contingencies). In our study of youths and young adults with BD, we investigated 1) how cognitive flexibility varies developmentally in BD, and 2) whether it is independent of other executive function deficits associated with BD.

Methods: We measured errors on a reversal-learning task, as well as spatial working memory and other executive function, among participants with BD (N = 75) and HC (N = 130), 7–27 years old. Regression analyses focused on the effects of diagnosis on reversal-learning errors, controlling for age, gender, IQ, spatial span, and executive function. Similar analyses examined non-reversal errors to rule out general task impairment.

Results: Participants with BD, regardless of age, gender, or cognitive ability, showed more errors than HC on the response reversal stages of the cognitive flexibility task. However, participants with BD did not show more errors on non-reversal stages, even when controlling for other variables.

Limitations: Study limitations include the cross-sectional, rather than longitudinal, design; inability to measure non-linear age effects; and inclusion of medicated participants and those with psychiatric comorbidity.

Conclusions: Individuals with BD show a specific impairment in reversing a previously rewarded response, which persists across the transition from childhood to young adulthood. Tailored interventions targeting this deficit may be effective throughout this developmentally turbulent time.

1. Introduction

Bipolar disorder (BD) is a highly impairing psychiatric illness, with health care costs estimated to be twice those of depression (Keck et al., 2008; Kleinman et al., 2003) and a prevalence of 1–4% in the general population (Merikangas et al., 2007, 2012). BD often leads to serious health and psychosocial problems, and tragically even suicide (Holma et al., 2014; Keck et al., 2008; Kleinman et al., 2003). While many assume BD solely affects adults, ample research especially during the past two decades demonstrates that BD may also affect children and adolescents (hereafter "youths" age < 18 years old). As in adults, BD in youths can be a devastating illness associated with high health care costs, poor psychosocial outcomes, and suicide (Dusetzina et al., 2012; Hauser et al., 2013; Leverich et al., 2007; Romero et al., 2009). Increasing numbers of youths are being diagnosed with and treated for BD – a 40% increase in one study - as evidenced by both inpatient and outpatient clinical data from the US and abroad (Blader and Carlson, 2007; Holtmann et al., 2010; Moreno et al., 2007). Furthermore, while BD symptoms may start in childhood (Leboyer et al., 2005), many patients are not formally diagnosed with BD until adulthood, potentially creating substantial delays in receiving BD-specific treatments (Leverich et al., 2007). Altogether, a critical need exists for more studies to include both children and young adults with BD so as to examine how the phenomenology and

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pathophysiology of BD change across the lifespan.

In studies involving either youths (Dickstein et al., 2004; Joseph et al., 2008; Kyte et al., 2006; Pavuluri et al., 2006a, 2006b) or adults with BD (Badcock et al., 2005; Green, 2006; Jabben et al., 2010; Roiser et al., 2009; Sweeney et al., 2000), but not both groups in the same study, BD is associated with cognitive deficits, including impaired attention, working memory, executive function, and response inhibition—all compared to healthy controls (HC) without psychopathology. Although several functional magnetic resonance imaging (fMRI) studies have compared youths and adults with BD on facial emotion recognition tasks (e.g., Brotman et al., 2013), fewer studies have directly compared cognitive deficits between youths and adults with BD (Wegbreit et al., 2014). Two such fMRI studies involving response inhibition tasks found that youths with BD showed more neural alterations than adults with BD in the inferior frontal gyrus and the anterior cingulate cortex, which are involved in cognitive control (Weathers et al., 2013, 2012). Moreover, in an fMRI meta-analysis, youths with BD showed more consistently decreased anterior cingulate activation during cognitive tasks than adults with BD (Wegbreit et al., 2014). These cognitive problems are important to study because many are associated with reduced psychosocial functioning and do not remit during euthymia (Andreou and Bozikas, 2013; Buoli et al., 2014; Mora et al., 2013; Pavuluri et al., 2006a, 2009; Peters et al., 2014). Better knowledge of their pathophysiology could provide a cost-effective way to improve the lives of individuals with BD by spurring the development of novel pharmacological agents (Miskowiak et al., 2014) and cognitive remediation treatments (Dickstein et al., 2015b).

Another cognitive construct that has been investigated in separate studies of BD adults or BD youths is *cognitive flexibility*, defined as adapting to changes in rewards and punishments (Cools et al., 2002, 2004). Reversal-learning tasks are one laboratory measure of cognitive flexibility, whereby participants use trial-and-error learning to determine which of two objects is rewarded vs. punished. Then, without warning, the stimulus/reward association reverses, so that the previously rewarded stimulus is now punished, and vice versa. During reversal learning, youths with BD make more errors than HC youths (Dickstein et al., 2010a, 2007, 2004; Gorrindo et al., 2005) and show specific alterations in regions involved in cognitive control, including ventral prefrontal cortex (vPFC) and ventral striatum (VS) (Adleman et al., 2011; Dickstein et al., 2010b). Adults with BD are less consistent, as some studies revealed behavioral deficits in reversal learning vs. adult HCs and associated vPFC and VS alterations (Clark et al., 2001, 2002; Kozicky et al., 2013; Linke et al., 2013, 2012; McKirdy et al., 2009), but others have not (Roiser et al., 2009; Rubinsztein et al., 2000; Sweeney et al., 2000). To the best of our knowledge, no study has examined altered response reversal in BD using a developmental framework including both youths and adults with BD.

Consequently, we examine response reversal in participants with childhood-onset BD, including both young adults (those ≥ 18) and youths (those < 18). Specifically, we enrolled adults who had been followed for BD since childhood by the Brown University site of the Course and Outcome of Bipolar Youth (COBY) study to ensure that retrospective recall bias did not affect these participants' BD diagnosis (Birmaher et al., 2009; Leboyer et al., 2005). This strategy also eliminates another potential confound because all participants had early-onset BD, rather than comparing youths with childhood-onset BD to adults with adult-onset BD. We employed age as a continuous variable to search for specific diagnosis-by-age interactions, as our prior work suggests that younger people with BD show delayed development in their facial emotion recognition ability (Wegbreit et al., 2015). Thus, we hypothesized that younger participants with BD would also show worse reversal-learning performance than expected for their age relative to older participants with BD (Jarcho et al., 2012; Wegbreit et al., 2015). Moreover, we conducted additional analyses to determine how cognitive flexibility deficits relate to broader deficits in executive function, given that spatial span predicts planning ability in participants with BD (Badcock et al., 2005). These extended analyses investigated whether cognitive flexibility deficits in BD are independent of other executive functioning deficits, including mental storage capacity (spatial span) and planning ability (tested by the Stockings of Cambridge task).

2. Methods

2.1. Participants

All participants were enrolled in Institutional Review Board-approved research studies conducted at Bradley Hospital and Brown University. After written informed consent and assent were obtained, participants' psychiatric symptoms and history were assessed using the Child Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997) administered to participants under 18 years old and their parents separately, or the Structured Clinical Interview for DSM-IV (SCID) (First et al., 2002) for participants 18 years and older. All interviews were conducted by either a board-certified child/adolescent psychiatrist or a licensed clinical psychologist with established inter-rater reliability (DPD, KLK; $\kappa \geq 0.85$).

Inclusion criteria for all BD participants were: (1) age between 7 and 30 years, (2) English fluency, and (3) meeting DSM-IV-TR criteria for BD type-I. More specifically, participants needed to have at least one manic episode (≥ 7 days) with abnormally elevated/expansive and/or irritable mood and ≥ 3 DSM-IV criterion "B" mania symptoms (≥ 4 if predominantly irritable mood). All adults with BD were originally enrolled as youths in the Brown University site of the aforementioned COBY study (Birmaher et al., 2009). Therefore, all participants were diagnosed with child onset type-I BD. No participants were biologically related.

Inclusion criteria for all HC were: (1) age between 7 and 30 years, (2) no current or lifetime psychiatric illness or substance abuse/dependence in themselves or any first-degree relatives, and (3) English fluency.

Exclusion criteria for participants with BD were: (1) Autism spectrum disorder or primary psychosis, (2) Full Scale IQ (FSIQ) < 80 on the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 2005), (3) medical/neurological conditions potentially mimicking BD.

Exclusion criteria for HC were: (1) WASI FSIQ < 80, (2) serious non-psychiatric medical disorders (e.g., epilepsy), and (3) learning disorders or pervasive developmental disorders.

2.2. CANTAB neuropsychological performance tasks:

2.2.1. Intra-dimensional/extra-dimensional shift (ID/ED)

Reversal learning was assessed using the ID/ED task of the Cambridge Neuropsychological Testing Automated Battery (CANTAB) (Cambridge Cognition Limited, 2012). The task has nine stages— including four reversal stages (simple, compound, intradimensional, and extra-dimensional). Depending on the stage, each trial displays two simple shapes (lone, color-filled shapes) or two compound shapes (white lines overlying color-filled shapes), and participants must identify the "correct" stimulus. On-screen feedback establishes an underlying rule, and participants move onto the next stage after completing six consecutive correct trials. The previously correct stimulus then becomes incorrect, and participants must reverse their responses. The first seven stages are intradimensional (ID) stages only involving the colored shapes,