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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 nonreversal 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.

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Tailored interventions targeting this deficit may be effective throughout this developmentally turbulent time.

Keywords

bipolar disorder; cognitive flexibility; development; executive function; reversal learning

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; Merikangas et al., 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 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; Pavuluri et al., 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; Weathers et al., 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; Pavuluri et al., 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; Cools et al., 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 versus 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; Dickstein et al., 2007; Dickstein et al., 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 versus adult HCs and associated vPFC and VS alterations (Clark et al., 2001, 2002; Kozicky et al., 2013; Linke et al., 2013; Linke et al., 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).

Methods

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, KKK; $\kappa = 0.85$).

Inclusion criteria for all BD participants were: (1) age between 7–30 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 7–30 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.

CANTAB NEUROPSYCHOLOGICAL PERFORMANCE TASKS

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, with other dimension (white lines) being entirely irrelevant. At the extradimensional (ED) shift stage, this previously irrelevant dimension becomes relevant, and participants must shift their attention from the previously relevant dimension. On any stage, if participants cannot meet the criterion of six consecutive correct responses after 50 trials, the whole task terminates.

Stockings of Cambridge (SOC): Participants’ executive functioning and planning abilities were assessed with the SOC. The task displays two arrangements of three colored balls, one

at the top of the screen and one at the bottom, and participants must move the balls in the bottom set to match the top set. Each trial requires two to five moves for correct completion. If participants make double the necessary moves, the trial terminates. The test ends after three terminations in a row, but all of our participants completed the SOC.

SOC performance is assessed by evaluating (1) total moves, (2) the number of problems solved in minimum moves, (3) thinking time before starting each problem, and (4) thinking time spent after starting. We created a single score for each variable by summing across all problems (weighting by the number of each type).

Spatial Span (SSP): Participants' spatial working memory capacity was assessed with the SSP. Nine squares are displayed on the screen, and change color one by one. Participants are then asked to touch the boxes in the order in which they changed color. The task starts with two boxes changing colors and increases by one box after each successful trial until all nine boxes are changing colors. If participants are not successful on their first try on a level, they receive two more attempts. After three failed attempts on a level, the test terminates. Outcome measures include (1) span length, (2) total errors, and (3) usage errors.

Mood/Functional Ratings

To characterize the BD sample, we evaluated depressive symptoms, manic symptoms, and overall functional impairment. Specifically, the Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski et al., 1985) and the Hamilton Depression Scale (HAM-D) (Hedlund and Vieweg, 1979) were administered to participants under 18 years old and over 18 years old, respectively. The CDRS-R and HAM-D have different scales, so for correlations between depression and task performance, sample-specific Depression Z-scores were created (Wegbreit et al., 2015). Manic symptoms were assessed using the Young Mania Rating Scale (YMRS) (Kaufman et al., 1997). Overall functioning was evaluated using the Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983) for <18 year olds, or the Global Assessment of Functioning (GAF) (Hall, 1995) for those >18. Both the CGAS and the GAF utilize a 1–100 scale with similar, but developmentally appropriate, cut-offs every 10 points (Schorre and Vandvik, 2004).

Analytic strategy

First, we investigated the simple relationship between diagnosis and ID/ED task performance using independent-samples t-tests. Next, we sought to identify which other variables might be of interest when evaluating the relationship between diagnosis and ID/ED task performance, focusing primarily on variables that differed between diagnostic groups. Finally, we ran regression models with diagnosis included along with other variables that could moderate the relationship between diagnosis and ID/ED performance. All statistical tests were conducted in SPSS 22 (IBM Corp., Armonk, NY) and were two-tailed with a 0.05 criterion for statistical significance.

For the ID/ED task, we focused on the intra-dimensional (ID) stages, which measure reversal learning, rather than the extra-dimensional (ED) stages, which measure attention shifting. In prior studies, researchers have summarized participants' ID/ED performance in

several ways, including the (1) number of stages participants completed (Sweeney et al., 2000), (2) number of participants who complete the ED shift stages (Roiser et al., 2009), (3) total errors before the ED shift or overall on the task (Dickstein et al., 2004), and/or (4) total reversal-stage errors (McKirdy et al., 2009). We were primarily interested in increasing task sensitivity versus distinguishing the effects on different types of response reversals, so we took the latter approach and summed errors across pre-ID reversal stages to create a Reversal-Stage Errors score. We were also interested in identifying deficits in general ID/ED performance, so we also summed errors on non-reversal pre-ID stages to create a Total Non-Reversal-Stage Errors score. If participants with BD are generally impaired on the task then they should show more errors on this measure relative to HC in addition to showing more errors on the reversal stages. However, if the impairment is specific to reversal learning then participants with BD should only show an increase in reversal-stage errors relative to HC. In follow up analyses, we also examined errors on each reversal stage (simple, compound, ID-shift compound) separately to compare with prior findings (Dickstein et al., 2007; Dickstein et al., 2004).

Variable selection for regression models

To determine which variables moderate the association between BD and deficits in reversal learning, we first compared the BD and HC groups with *t*-tests for continuous variables (e.g., age, CANTAB scores) and with chi-squared tests for categorical variables (e.g., gender, race) (Table 1). Variables with significant differences between groups were incorporated in our regression models, with two exceptions. We included gender as a variable of *a priori* interest given previous findings of gender differences in cognitive performance in BD samples, including differences in spatial working memory (Barrett et al., 2008; Carrus et al., 2010; Vaskinn et al., 2011). Furthermore, we had relatively few non-White participants, so we did not include race and simply re-ran the models without the non-White participants to assess the potentially confounding effects of race.

Simple comparisons and extended regression analyses

After using *t*-tests to compare the two groups' reversal and non-reversal ID/ED performance, we examined the effect of age, demographic, and neurocognitive variables on the relationship between diagnosis and ID/ED performance. For ID/ED Reversal-Stage Errors and ID/ED Non-Reversal-Stage Errors, we tested two predictive models via multiple linear regressions. The first, "base model" contained four predictors: Diagnosis, Age, the Diagnosis-by-Age interaction, and FSIQ, as in our prior work using a facial emotion recognition task (Wegbreit et al., 2015). The second, "extended model" contained seven predictors: the four base model predictors, plus Gender, SSP Span Length, and SOC Total Moves. We report analyses using SOC Total Moves because these models had the highest adjusted R-squared model fits, but results were unchanged when substituting other SOC variables. For all regression analyses, predictors were standardized to reduce multicollinearity (Cohen et al., 2003).

As an exploratory analysis, we ran the base and extended models for errors on each reversal stage to investigate whether any effects were specific to a particular reversal stage. To investigate potential medication confounds, we conducted *post-hoc* analyses sequentially

excluding participants by the medication class they were taking (e.g., lithium, antidepressants, etc.) (Henin et al., 2009; Pavuluri et al., 2006b). We also conducted additional separate *posthoc* analyses excluding all non-White participants and all non-euthymic participants with BD to preclude any race and mood state confounds, respectively (Wegbreit et al., 2015). Finally, because psychosis could influence clinical course and outcome, we conducted analyses excluding six adults with BD who had current or past psychotic features.

Results

Demographics

Overall, the BD and HC groups as a whole showed a significant difference in FSIQ but not age. For categorical variables, BD and HC groups showed a significantly different distribution of White vs. non-White participants, but their gender distribution did not significantly differ (Table 1). To compare with prior literature that splits youths and adults into groups, we tested for age-by-diagnosis interactions and found no significant effects (Table 2). We also report clinical variables, such as mood state, for BD youths and adults separately (Table 3). Of note, BD youths and adults did not show a significant difference in their approximate age of BD illness onset, $t(70)=0.17$, $p=0.87$.

Between-group differences in CANTAB performance without added variables

In simple comparisons without added variables, participants with BD showed significantly more errors than HC on the ID/ED reversal stages (pooled across the three reversal stages). In contrast, the two groups did not show a significant difference in the number of errors made on the non-reversal stages of the ID/ED task (Table 1, Figure 1).

To test for specific differences across reversal stages, we conducted an omnibus repeated-measures ANOVA with reversal stage as the within-subjects variable and diagnosis as the between-subjects variable. Participants with BD showed significantly more errors overall than HC [$F(1,203)=20.64$, $p<0.001$], the reversal stages showed significant differences in difficulty across participants [$F(2,203)=7.64$, $p<0.001$], but diagnosis did not interact with reversal stage [$F(2,203)=0.85$, $p=0.43$]. Nevertheless, to compare to previous findings of significant differences between BD and HC on simple reversal stages (Dickstein et al., 2007; Dickstein et al., 2004), we evaluated between-group differences at each reversal stage and found that participants with BD showed more errors on each reversal stage than HC (Table 1, Figure 2).

On the SSP task, participants with BD showed significantly shorter spatial span lengths than HC, but the same number of errors and usage errors. On the SOC task, participants with BD needed significantly more moves to complete the task compared to HC and solved significantly fewer problems in the minimum number of moves. On average, participants with BD spent significantly less time thinking before starting each SOC problem than HC, but spent the same amount of time on each problem as HC after starting (Table 1). Thus, participants with BD showed both reduced executive functioning and spatial span relative to their healthy peers.

Reversal-Stage Errors: Base and Extended Models

We examined whether age, FSIQ, or a diagnosis-by-age interaction influenced the effect of diagnosis on ID/ED reversal-stage errors, as in our previous work in facial emotion recognition (Wegbreit et al., 2015). This “base model” showed a significant effect of diagnosis and no significant effects for age, diagnosis-by-age interaction, or FSIQ (Table 4).

Next, we ran the extended model, adding gender, spatial span, and SOC Total Moves, and found that the significant effect of diagnosis on reversal-stage errors remained even after controlling for these extra variables. No other statistically significant effects were found (Table 4).

Non-Reversal-Stage Errors: Base and Extended Models

For non-reversal-stage errors, we tested whether controlling for other variables could reveal a significant difference between diagnostic groups, as this finding could indicate a general ID/ED task impairment. However, the base model showed a non-significant diagnosis effect, no significant age effect, and no significant diagnosis-by-age interaction. Moreover, participants with lower FSIQs, regardless of diagnosis, made significantly more non-reversal-stage errors than those with higher FSIQs (Table 4).

The extended model for non-reversal stages also revealed only a significant effect of FSIQ, and the other effects, including the diagnosis effect, remained non-significant (Table 4). Thus, estimated general intelligence was the best predictor of performance on non-reversal task stages and diagnosis had no predictive power. This finding, along with our analysis of ID/ED reversal-stage errors, suggests a reversal-learning specific deficit in BD on the ID/ED task.

Follow-up analyses: Errors for specific reversal stages

In analyses for each reversal stage, diagnosis showed a significant effect for the base models for compound reversals and a marginal effect for simple reversals (Table S1). For the extended models, compound reversals showed significant effects of diagnosis and FSIQ, whereas the other stages did not show significant effects for any variable.

Post-hoc analyses of potential confounds: medication, psychiatric comorbidity, mood state, race, and psychotic features

In *post-hoc* analyses, we excluded participants affected by confounding variables and re-ran our models. To test for medication effects, we serially excluded participants with BD who were taking each class of medication (e.g., participants taking lithium, participants taking atypical neuroleptics, etc.) and re-ran our analyses. Next, we serially excluded participants with BD who met criteria for abuse/dependence for any substance (N=12) (Table 3). Then, we serially excluded BD participants with comorbid GAD (N=8), comorbid ADHD (N=37), and those *without* ADHD comorbidity (N=38; i.e., comparing BD+ADHD vs. HC) (Table 3). Although none of our participants met criteria for any psychotic disorder, six adults with BD reported a few current or past psychotic features, so we excluded these participants and re-ran the analyses. Across all of these analyses, the findings from our base and extended models were maintained. For reversal-stage errors, we found significant main effects of

diagnosis, no significant diagnosis-by-age interactions, and few other significant effects (Table S2). For non-reversal-stage errors, we only found significant main effects of FSIQ, but no significant effects for diagnosis or any other variable (Table S3). Thus, medications, substances, and psychiatric comorbidities are highly unlikely to have influenced our results.

To examine mood state effects, we excluded 14 non-euthymic participants with BD, with non-euthymia defined as YMRS>12 (youths/adults); and/or CDRS-R>40 (youths) or HAMD>7 (adults) (Zimmerman et al., 2013), and we re-ran our base and extended models with the remaining 61 participants with BD. To be conservative, patients with missing mood ratings data were treated as non-euthymic (Table 3). For reversal-stage errors, we still found significant diagnosis effects while controlling for all other variables. Intriguingly, we also found significant effects of spatial span and SOC Total Moves that were independent of diagnosis (Table S2). These results underscore the notion that these tasks measure processes related to the reversal-learning task, but that BD also has an independent effect. For non-reversal-stage errors, we again found FSIQ effects, no significant effect of diagnosis, and no other significant results (Table S3). Thus, reversal-learning deficits occurred for euthymic participants with BD as well as symptomatic participants and cannot be explained by the BD participants' mood states.

Finally, while we had no *a priori* hypotheses about the effect of participants' race on CANTAB tasks, we re-ran our analyses excluding the 44 non-White BD and HC participants in our sample, because the groups significantly differed in their racial composition (Table 1). When restricting our sample to White participants (N=161), we still found significant effects of diagnosis for errors on reversal stages and no other significant effects (Table S2) and found significant effects of FSIQ for non-reversal stages and no other significant effects (Table S3). Thus, any racial difference between groups is unlikely to have influenced our results.

Post-hoc analyses

To test whether BD participants' mood states influenced their CANTAB performance independently of euthymic status (i.e., dimensionally), we examined correlations between CANTAB performance and Depression, YMRS, and global functioning scores. We found no significant relationships between any clinical variables and CANTAB performance (Table S4), further suggesting that BD participants' mood states did not influence their neuropsychological performance.

In contrast, illness duration did correlate with overall ID/ED errors, but not with reversal-stage errors (Table S4). To investigate this further, we ran versions of our model within the BD participant group with "age" replaced with "illness duration". Illness duration did not significantly predict reversal-stage or non-reversal stage errors (Table S5), further supporting the notion that these reversal-learning deficits are independent of age.

Finally, to address potential concerns about the difference in FSIQ between the BD and HC groups confounding our results, we implemented a stepwise regression model and forced FSIQ into the model as the first step, before diagnosis. Even in this model, we found that diagnosis explained variance in reversal learning errors that FSIQ could not explain. In

contrast, FSIQ was able to explain variance in the non-reversal-learning errors that diagnosis could not (see Table S6).

Discussion

Our study is the first to take a developmental approach to investigate impaired cognitive flexibility in youths and young adults with BD. Our primary findings were: (1) participants with BD made significantly more errors than HC on reversal stages, but not on non-reversal stages; (2) participants with BD showed reduced executive functioning and working memory capacity vs. HC; (3) however, we found a specific reversal-learning deficit for participants with BD even when controlling for working memory, executive functioning, and general intelligence. We did not find our hypothesized diagnosis-by-age interaction in reversal learning. Thus, the age-independent effect on reversal learning contrasts with our prior finding of a developmentally salient impairment in facial emotion recognition in BD youths (Wegbreit et al., 2015). Moreover, our effects generalized across genders, contrasting with prior gender-specific differences in cognitive performance in BD (Barrett et al., 2008; Carrus et al., 2010; Vaskinn et al., 2011). We found no influence of mood state, medication status, comorbid conditions, substance abuse/dependence, race, or psychotic features. Together, these findings suggest that among participants with childhood-onset BD, cognitive flexibility deficits may be integral to the pathophysiology of BD itself, both across development and independent of other cognitive and emotional issues in BD.

Our results showing age-independent reversal learning deficits are interesting in the context of prior work on reversal learning in BD. Specifically, in several studies, BD youths showed impaired cognitive flexibility not just vs. HC but also vs. youth with anxiety, major depression, and severe mood dysregulation (Adleman et al., 2011; Dickstein et al., 2010a; Dickstein et al., 2010b; Dickstein et al., 2007; Dickstein et al., 2004; Gorrindo et al., 2005). However, studies among BD adults are less consistent, as some report differences between BD adults and HC adults (Clark et al., 2001, 2002; Kozicky et al., 2013; Linke et al., 2013; Linke et al., 2012; McKirdy et al., 2009), but others do not (Roiser et al., 2009; Rubinsztein et al., 2000; Sweeney et al., 2000). This inconsistency may exist, in part, because adults in prior studies were in their 30s–50s, whereas our adults were considerably younger. Thus, the cognitive flexibility impairments that our adults exhibited could abate as they age further. However, impaired cognitive flexibility could be phenotypically inherent to childhood-onset BD. Specifically, people with childhood-onset BD could have impaired cognitive flexibility across the lifespan, whereas those with adult-onset BD do not. Answering this important question will require longitudinal studies that enroll participants with childhood-onset and adult-onset BD and study cognitive flexibility longitudinally.

No prior studies of cognitive flexibility in BD have evaluated the effects of age dimensionally in accordance the continuous nature of brain development found in longitudinal studies across the transition from childhood to adolescence (Giedd and Rapoport, 2010). Despite our dimensional approach to age, we did not find any age effect on reversal learning or any diagnosis-by-age interaction, unlike prior developmental work in facial emotion recognition in BD (Wegbreit et al., 2015). As such, individuals with childhood-onset BD may show longer-lasting deficits in reversal learning than in facial

emotion recognition, consistent with the posterior-to-anterior development of the human brain from childhood young adulthood, with perceptual regions maturing years before prefrontal regions involved in cognitive flexibility (Giedd and Rapoport, 2010). Thus, cognitive flexibility training may be appropriate as a specific treatment target for individuals with childhood-onset BD throughout their entire childhood and adolescence, but such training may benefit individuals even if not started until young adulthood. Nevertheless, intervening earlier once a child is diagnosed with BD would be preferable, considering the well-studied links between reduced executive functioning and poor psychosocial outcomes in BD (Andreou and Bozikas, 2013; Buoli et al., 2014; Mora et al., 2013; Pavuluri et al., 2006a; Pavuluri et al., 2009; Peters et al., 2014).

Our results suggest that impaired cognitive flexibility in childhood-onset BD is independent from other executive functioning deficits and from general intelligence, potentially making it a good target for an intervention tailored to individuals with BD (Dickstein et al., 2015b). We found significant deficits for each reversal stage, unlike previous studies that only found effects for some reversal stages (Dickstein et al., 2007; Dickstein et al., 2004). This finding suggests that participants with BD show a rather general deficit in reversal learning relative to HC. Nevertheless, the ID/ED task is not the most sensitive measure of reinforcement learning, as other tasks can separate reward-based vs. punishment-based learning (Linke et al., 2011; van der Schaaf et al., 2011). These more sensitive reversal tasks could delineate the contributions of various brain regions (e.g. sub-regions of the PFC) to each aspect of reversal learning (Linke et al., 2011; Mitchell et al., 2009; van der Schaaf et al., 2011) and help us to better understand the behavioral and neural mechanisms underlying cognitive flexibility impairments in BD.

Limitations

In addition to its strengths, the current study has several limitations. First, to address our focus on developmental alterations in cognitive performance associated with childhood-onset BD, we harnessed cross-sectional data, rather than conducting a prospective longitudinal study. Specifically, our child BD and HC participants were enrolled in a cross-sectional study (K22MH074945). Our young adult BD and HC participants were enrolled in a cross-sectional study (R01MH087513), though the adult BD participants were originally enrolled and prospectively followed for child-onset BD by the longitudinal COBY study (R01MH059929). Thus, while we had a great deal of information about our participants, including age of BD illness onset and assessment for psychopathology, mood, and functioning at the time of CANTAB testing, we did not have prospective information for the child BD participants about number and duration of mood episodes prior to testing. Given that some, but not all studies suggest that clinical course influences cognitive performance, further work is needed using longitudinal studies assessing both psychopathology and cognitive performance (Cardoso et al., 2015; Dickstein et al., 2015a). Our lack of age effects or age-diagnosis interactions could also stem from cohort differences between our younger participants with BD and our older participants with BD. Thus, our youth participants with BD might show normalized reversal-learning performance if followed longitudinally. However, the youths and young adults in our study were very similar in many respects. Furthermore, with some exceptions (e.g., Roiser et al., 2009), studies of adults with BD have

found reversal-learning deficits even into middle adulthood (i.e., 30s–50s) (Clark et al., 2001, 2002; Kozicky et al., 2013; Linke et al., 2013; Linke et al., 2012; McKirdy et al., 2009). Thus, deficits in cognitive flexibility may be an enduring trait in BD.

Second, we did not test for nonlinear age effects because our ID/ED task was not sensitive enough to valence. Cognitive flexibility in healthy individuals exhibits both linear and nonlinear age-related components across childhood, adolescence, and adulthood, with linear effects for valence-dependent reversal learning and nonlinear effects for valence-independent reversal learning (van der Schaaf et al., 2011). Thus, using a reversal-learning task with greater sensitivity to valence effects may be a productive future direction to better understand age-related cognitive flexibility deficits in BD.

Third, because this was not a treatment study, participants with BD remained on their outpatient medications, which could have influenced their performance on the CANTAB tasks (Henin et al., 2009; Pavuluri et al., 2006b). Nevertheless, medication treatment may normalize cognitive deficits rather than exacerbate them (Hafeman et al., 2012), and our post-hoc analyses found no influence of medication usage on reversal learning.

Finally, to obtain a representative sample, we included some participants with BD meeting criteria for other comorbid disorders, such as ADHD or GAD, or for substance abuse/dependence. However, analyses excluding these participants showed the same results. Moreover, prior studies have not shown comorbid ADHD or anxiety to have a significant influence on reversal learning in BD (Dickstein et al., 2010a; Dickstein et al., 2010b; Dickstein et al., 2007). Importantly, our participants' reversal-learning deficits also showed no significant relationship with their mood symptoms, suggesting that these deficits are a trait of BD.

Conclusions

People with childhood-onset BD exhibit a specific deficit in reversal learning, which generalizes across genders and across the developmental transition from late childhood to early adulthood. Further research can build on these findings in two ways. Longitudinal studies following participants with childhood-onset BD could examine the course and functional significance of reversal-learning deficits. Furthermore, targeted cognitive remediation interventions could attempt to ameliorate this specific issue faced by youths and young adults with BD, as has been done for specific issues faced by individuals with schizophrenia or anxiety (Eldar et al., 2012; Wykes et al., 2011). Intervening earlier to reduce or even prevent cognitive issues in BD before they cause negative psychosocial consequences not only could reduce health care costs (Dickstein et al., 2015b), but also could improve outcomes for individuals with BD, their families, and society.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Tested reversal learning in individuals with childhood-onset bipolar disorder (BD)
- Their ages (7–27 yrs.) spanned developmental transition from childhood to adulthood
- BD group showed deficits in reversal learning compared to age-matched healthy peers
- Deficits independent of age, intelligence, and other executive functioning issues
- No confounding influences of gender, race, medications, comorbidity, or mood state

Figure 1.
Mean errors for all reversal and all non-reversal stages of the Intradimensional/
Extradimensional shift task for participants with bipolar disorder (BD) and healthy controls
(HC)

Figure 2.
Mean errors for each reversal stage of the Intradimensional/Extradimensional shift task for participants with bipolar disorder (BD) and healthy controls (HC)

Table 1

Demographics and CANTAB performance data for participants with BD and HC

Characteristic	HC Participants (N=130)				BD vs. HC			
	Participants with BD (N=75)		Mean SD		Mean SD		t (203)	
	Mean	SD	N	%	Mean	SD	t	p
Age (years)	16.5	4.5	17.6	4.9	1.51	0.13		
FSIQ	106.4	9	111.4	3	3.11	0.002		
Male	N	%	N	%	X ² (2)	p		
	45	60.	64	49.	2	2.22	0.14	
Female	30	40.	66	50.	8			
White ^a	64	88.	97	75.	8	5.04	0.03	
Non-white ^a	8	11.	31	24.	2			
Performance Measure	Mean	SD	Mean	SD	t (203)	p		
ID/ED Errors								
All Stages	7.9	3.4	6.5	2.9	3.18	0.002		
Reversal-Stages	5.1	2.3	3.9	1.4	4.54	<0.001		
Non-Reversal-Stages	2.8	2.2	2.6	2.4	0.75	0.45		
Simple-Reversal-Stage	1.9	1.3	1.5	1.1	2.27	0.03		
Compound-Reversal-Stage	1.8	1.3	1.3	0.7	3.69	<0.001		
Intradimensional-Compound-Reversals	1.4	0.9	1.2	0.5	2.66	0.01		
ID/ED Latencies								
All Stages ^b	106.1	51.	105.3	42.	7	0.13	0.90	

Characteristic	HC Participants		BD vs. HC	
	Participants with BD (N=75)	Participants (N=130)		
Reversal-Stages ^b	24. 35.2	22. 30.2	0	1.51 0.13
Non-Reversal-Stages ^b	33. 70.9	28. 75.1	7	0.94 0.35
SSP				
Length	6.0	1.4	7.1	1.4 5.00 1
Errors	13.6	6.3	13.5	7.0 0.17 0.86
Usage Errors	2.2	1.6	1.8	1.6 1.33 0.185
SOC				
Total Moves	71.1	9.5	65.7	8.1 4.31 1
Problems Solved in Minimum Moves	7.7	2.2	9.1	2.0 4.44 1
Total Initial Thinking Time (seconds)	50.6	40. 1	70.2	4 2.95 0.004
Total Subsequent Thinking Time (seconds)	7.5	10. 0	6.3	6.8 1.07 0.29

^aThree participants with BD and two HC did not report their race.

^bOne BD participants' latencies were not recorded.

Legend: BD=Bipolar Disorder; FSIQ=Full-scale IQ; HC=Healthy comparison; ID/ED=Intradimensional/Extradimensional Shift; SD=standard deviation; SOC=Stockings-of-Cambridge; SSP=Spatial span.

Table 2
Sample demographics for participants with BD and HC categorically split by age-group (pediatric vs. adult)

Characteristic	Participants with BD						HC Participants						Diagnosis by Age Interaction
	BD Youths			BD Adults			HC Youths			HC Adults			
	Mea n	SD	%	Mea n	SD	%	Mea n	SD	%	Mea n	SD	%	
	(N=47)			(N=28)			(N=68)			(N=62)			
Age in years	13.8	3.0		21.1	2.4		13.7	2.9		21.9	2.3		<i>F</i> (20 1) <i>p</i>
FSIQ	106. 3	10. 7		106. 6	11. 3		111. 5	10. 9		111. 3	11. 9		1.30 6 0.03 7
Female	19	4	40.	11	3	39.	4	39	57.	27	43.		<i>G</i> ² (4) <i>b</i> <i>p</i>
Non-white ^a	5	9	10.	3	5	11.	4	17	25.	14	23.		8.04 9

^aThree participants with BD and two HC did not report their race

^bLog-linear analyses for A×B×C contingency table (www.vassarstats.net/abc.html)

Legend: BD = Bipolar Disorder; FSIQ = Full-scale IQ; HC = Healthy comparison; SD = standard deviation;

Table 3

Clinical characteristics of participants with BD categorically split by age-group (pediatric vs. adult)

	BD Youths		BD Adults	
	(N=47)		(N=28)	
Clinical Variable	Mean	SD	Mean	SD
YMRS ^a	7.1	4.9	4.4	2.7
Depression Score ^b	5.1	4.3	27.9	9.1
Global Functioning Score ^c	60.7	13.3	65.8	11.8
Illness Onset Age ^d	9.9	3.7	9.8	3.7
Mood Status	<i>N</i>	%	<i>N</i>	%
Euthymic	37	78.7	24	85.7
Hypomanic	4	8.5	3	10.7
Mixed	1	2.1	0	0.0
Depressed	1	2.1	0	0.0
Comorbid Conditions	<i>N</i>	%	<i>N</i>	%
Substance Abuse/Dependence	1	2.1	11	39.3
GAD	4	8.5	4	14.3
ADHD	27	57.4	10	35.7

^aYMRS scores for two youths and one adult were not available.^bCDRS-R for youths, HAM-D for adults; depression scores were not available from two youths and one adult.^cCGAS for youths, GAF for adults; one adult's score was not available.^dIllness onset ages for two youths and one adult were not available.

Legend: ADHD = Attention Deficit Hyperactivity Disorder; BD = Bipolar Disorder; GAD = Generalized Anxiety Disorder; SD = standard deviation; YMRS = Young Mania Rating Scale; CDRS-R = Children's Depression Scale-Revised; HAM-D = Hamilton Depression scale; CGAS = Children's Global Assessment Scale; GAF = Global Assessment of Functioning.

Table 4

Regression analyses of reversal-stage vs. non-reversal-stage errors for individuals with BD or HC participants.

	Reversal-Stage Errors			Non-Reversal-Stage Errors		
	β	$t(201)$	p	β	$t(201)$	p
Base-Model Effects						
Diagnosis	0.29	4.17	<0.001	0.00	0.03	0.98
Age	0.06	-0.86	0.39	0.01	0.18	0.86
Diagnosis-by-Age	0.08	-1.22	0.22	0.02	0.33	0.75
FSIQ	0.02	-0.32	0.75	0.25	-3.58	<0.001
Extended-Model Effects						
Diagnosis	0.23	3.14	0.002	0.03	-0.41	0.69
Age	0.04	0.48	0.63	0.05	0.67	0.50
Diagnosis-by-Age	0.09	-1.31	0.19	0.02	0.25	0.80
FSIQ	0.04	0.54	0.59	0.22	-2.91	0.004
Gender	0.02	-0.22	0.82	0.03	-0.41	0.69
SSP	0.15	-1.88	0.06	0.14	-1.61	0.11
SOC Total Moves	0.11	1.38	0.17	0.01	-0.17	0.86

Legend: BD=Bipolar Disorder; FSIQ=Full-scale IQ; HC=Healthy comparison; SOC=Stockings-of-Cambridge; SSP=Stockings-of-Cambridge; SSP=Stockings-of-Cambridge.