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Relationship Between Cognitive Flexibility and Subsequent Course of Mood Symptoms and Suicidal Ideation in Young Adults with Childhood-Onset Bipolar Disorder

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Abstract

Neurocognitive deficits, such as cognitive flexibility impairments, are common in bipolar disorder (BD) and predict poor academic, occupational, and functional outcomes. However, the association between neurocognition and illness trajectory is not well understood, especially across developmental transitions. This study examined cognitive flexibility and subsequent mood symptom and suicidal ideation (SI) course in young adults with childhood-onset BD-I (with distinct mood episodes) vs. BD-Not Otherwise Specified (BD-NOS) vs. Typically-Developing Controls (TDCs). Sample included 93 young adults (ages 18-30) with prospectively verified childhood-onset *DSM-IV* BD-I (n=34) or BD-NOS (n=15) and TDCs (n=44). Participants completed cross-sectional neuropsychological tasks and clinical measures. Then, participants with BD completed longitudinal assessments of mood symptoms and SI at 6-month intervals (M=39.18±16.57 months of follow-up data). Analyses included ANOVAs, independent-samples

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Ethical approval

Written informed consent was obtained from all participants prior to study inclusion. Procedures were approved and overseen by the Institutional Review Boards of Bradley Hospital and Brown University, and therefore, the described research has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

t-tests, chi-square analyses, and multiple linear regressions. Participants with BD-I had significant deficits in cognitive flexibility and executive functioning vs. BD-NOS and TDCs, and impaired spatial working memory vs. TDCs only. Two significant BD subtype-by-cognitive flexibility interactions revealed that cognitive flexibility deficits were associated with subsequent percentage of time depressed and with SI in BD-I but not BD-NOS, regardless of other neurocognitive factors (full-scale IQ, executive functioning, spatial working memory) and clinical factors (current and prior mood and SI symptoms, age of BD onset, global functioning, psychiatric medications, comorbidity). Thus, cognitive flexibility may be an important etiological brain/behavior mechanism, prognostic indicator, and intervention target for childhood-onset BD-I, as this deficit appears to endure into young adulthood and is associated with worse prognosis for subsequent depression and SI.

Keywords

bipolar disorder; cognitive flexibility; depression; suicidal ideation; child; course

Introduction

Childhood-onset bipolar disorder (BD) is an unfortunately common and devastating illness that has been documented across international samples [1,2] and is characterized by recurrent mood symptoms, psychiatric comorbidity, psychosocial dysfunction, and suicidality [3-6]. Neurocognitive deficits are also common in BD (e.g., impaired attention, working memory, executive functioning, response inhibition, cognitive flexibility) [7,8] and have been linked to academic difficulties in youth [9], occupational underachievement in adults [10], and functional impairment across the lifespan [11]. However, the association between neurocognition and mood symptom trajectory is not well understood, especially across the developmental transition from childhood to young adulthood [7,12]. Enhanced understanding of this relationship can identify potential neurocognitive mechanisms involved in the etiology of BD, thereby informing diagnostic efforts, novel treatment targets, and strategies for tailoring extant interventions to address the unique cognitive impairments present in BD across the lifespan.

Longitudinal studies examining the association between neurocognition and mood symptom course have largely focused on older adolescent/young adulthood-onset BD and concurrent/simultaneous changes in neurocognition and symptoms. For instance, in adults with BD experiencing their first manic episode, those with recurrence (experiencing at least one mood episode over one-year follow-up) showed worsening in neurocognitive performance compared to those who maintained remission (no mood episodes over follow-up) and typically-developing controls (TDCs), particularly for those with more days manic and/or hypomanic [13]. Similarly, adults with BD *without* recurrence (no mood episodes over one-year follow-up) demonstrated neurocognitive improvements and better global and occupational functioning compared to those with recurrence (experiencing at least one mood episode over one-year follow-up) and TDCs [14]. In another study, both greater number of manic and/or hypomanic episodes and more time spent with such symptoms were associated with worse verbal memory and executive functioning after M=72 months

[15]. One investigation specifically examining the temporal relationship between cognitive deficits and subsequent illness course in adults with BD found a significant association between longer time to recovery (number of days required to return to baseline functioning) and more impaired executive functioning (and trend for verbal fluency) over one year [16]. However, no studies have examined the relationship between *specific* neurocognitive deficits and *subsequent* symptom trajectory in young adults with *childhood-onset* BD, despite the potential for such data to inform etiology, mechanisms of illness progression, and areas for intervention.

Cognitive flexibility, defined as the ability to adapt one's thinking and behavior in response to changing environmental conditions (e.g., rewards, punishments) [17,18], is a *specific* neurocognitive construct salient to *childhood-onset* BD [19-26]. Adaptation to rewards and cognitive flexibility are relevant to BD and could be related to symptom course because clinical features of the illness (manic and depressive symptoms) may reflect altered reward processing and an inability to respond or adapt effectively to emotional stimuli [19,27]. Increased reward responsivity during manic episodes may result in excessive involvement in activities with high potential for painful consequences, increased goal-directed activity, and inflated self-esteem/grandiosity. In contrast, decreased reward responsivity during depressive episodes may result in diminished interest and pleasure in daily activities, anhedonia, and feelings of worthlessness. In a laboratory setting, cognitive flexibility can be measured via reversal learning tasks, whereby participants use trial-and-error learning to determine which of two stimuli is rewarded vs. punished. Subsequently the association reverses, so that the initially rewarded stimulus is now punished, and vice versa.

Cognitive flexibility deficits have been well-documented in both youth and adults with affective disorders. For instance, cognitive flexibility deficits are a well-known risk factor for depression [28], and have been found to predict first onset of major depressive episodes in adolescents [29]. In the adult literature, cognitive flexibility deficits have been consistently found in BD compared to TDCs [30-32]. In addition, impaired cognitive flexibility appears to be a trait (vs. state-dependent) marker of BD in adults [33]. Some research with adults suggests that clinical characteristics of BD, such as duration of illness, psychosis, number of mood episodes, and depressive symptoms contribute to declining cognitive functioning and cognitive flexibility deficits [30,32]. However, no research has examined whether cognitive flexibility predicts subsequent symptom trajectory in young adults with childhood-onset BD. Cognitive flexibility deficits have also been found to predict subsequent suicidal ideation (SI) in transdiagnostic clinical samples [34,35], though this has not been examined in childhood-onset BD. Given high rates of suicidality in childhood-onset BD [6], objective predictors of subsequent SI are important to identify.

In the child literature, youth meeting Leibenluft et al.'s definition of narrow phenotype BD (with distinct hypomanic, manic, and/or depressive episodes characteristic of BD-I and BD-II) [36] show impairments in cognitive flexibility compared to: 1) TDCs when youth with BD are euthymic [19-25]; 2) youth with chronic and non-episodic irritability, characteristic of *DSM-5* disruptive mood dysregulation disorder (DMDD) [19,26]; and 3) youth with BD-Not Otherwise Specified (BD-NOS, without distinct mood episodes, intermediate phenotype BD) [24]. In addition, youth with narrow phenotype BD demonstrate distinct functional

magnetic resonance imaging (fMRI) neural activation patterns during reversal learning tasks compared to TDCs [25] and DMDD [26]. The current study expanded upon these findings by comparing cognitive flexibility deficits in young adults with childhood-onset BD-I (narrow phenotype BD) vs. BD-NOS (intermediate phenotype BD) vs. TDCs.

To go beyond cross-sectional data and address gaps in the literature, the current study also examined cognitive flexibility and both mood symptom and SI course in young adults with prospectively verified childhood-onset BD [via their participation in the Brown University site of the Course and Outcome of Bipolar Youth (COBY) study] [37]. Findings arising from the COBY study demonstrate impaired clinical trajectory and poor functional outcomes across youth with different subtypes of BD [3,5,37]. The COBY study also used latent class growth analysis to identify four longitudinal mood trajectories using about 8 years of follow-up data: 1) predominantly euthymic (84.4% time euthymic); 2) moderately euthymic (47.3% time euthymic); 3) ill with improving course (42.8% time euthymic); and 4) predominantly ill (11.5% time euthymic) [4], thereby demonstrating the impaired yet variable nature of symptoms in these youth.

Prior work with the COBY sample also yielded findings directly relevant to the current study. In an investigation of concurrent longitudinal changes in neurocognition and mood symptoms, youth with persistently low cognitive functioning spent a significantly greater percentage of time with overall, manic, and depressive symptoms than youth with persistently high and/or moderate cognitive functioning over two and a half years [12]. These youth also had significantly poorer global, academic, and social functioning than those with persistently high cognitive functioning [12]. In addition, youth with BD-I and BD-II demonstrated greater impairment in cognitive flexibility compared to both those with BD-NOS and TDCs; impairments across other cognitive domains were similar across BD subtypes and exacerbated compared to TDCs [24]. Finally, prior research using a subset of the COBY sample demonstrated that cognitive flexibility deficits were apparent in BD-I vs. TDCs across children and adults in cross-sectional analyses [20]. Thus, presence of distinct hypomanic, manic, and/or depressive episodes may confer exacerbated cognitive impairment in those with narrow phenotype BD-I vs. BD-NOS, particularly for cognitive flexibility [24], which could have implications for symptom course. However, no studies have examined whether this neurocognitive deficit predicts subsequent mood symptoms and SI in BD-I vs. BD-NOS, especially across the transition from childhood to adulthood.

The current study will build on these prior COBY findings by: 1) examining cognitive flexibility deficits in COBY participants as *young adults* with BD-I vs. BD-NOS vs. newly enrolled, young adult TDCs (to determine if impairments observed in childhood are apparent in young adulthood); and 2) incorporating subsequent, prospective longitudinal measures to examine the relationship between cognitive flexibility deficits and symptom course. Based on literature documenting neuropsychological deficits in BD (any subtype) vs. TDCs [7,8], and specific deficits for cognitive flexibility in BD-I vs. BD-NOS and/or TDCs [19-26], we hypothesized that: 1) young adults with childhood-onset BD-I will display greater impairments in cognitive flexibility compared to those with BD-NOS and TDCs; 2) across other indices of neuropsychological performance young adults with childhood-onset BD-I and BD-NOS will display greater impairments compared to TDCs, though there will not

be significant differences across BD subtypes; and 3) impaired cognitive flexibility will be associated with greater percentage of time symptomatic (subthreshold/threshold mood symptoms) and with SI during follow-up among young adults with childhood-onset BD-I but not BD-NOS. To examine whether cognitive flexibility deficits as young adults predicted greater percentage of time symptomatic and with SI above and beyond prior mood trajectory as children, we controlled for both current symptoms and prior mood trajectory latent class per COBY [4].

Method

Participants

Study procedures were approved by the Institutional Review Boards of Bradley Hospital and Brown University. Participants (N=93) were young adults (ages 18-30) with childhood-onset BD-I or BD-NOS (n=49) and TDCs (n=44). Participants with BD were originally enrolled in the Brown University site of the COBY study as children (ages 7-17 years), and later enrolled in the current study as young adults (ages 18-30) [37]. TDCs were newly enrolled as young adults in the current study only.

Inclusion criteria for participants with BD were: 1) ages 18-30; 2) English fluency; 3) childhood-onset BD diagnosis per COBY (prior to the age of 18); and 4) at least one year of COBY follow-up data as young adults. Participants met *DSM-IV's* definition of BD-I (n=34, requiring at least one manic episode) or the COBY study's definition of BD-NOS (n=15), operationalized as either elation plus two associated symptoms or irritability plus three associated symptoms, change in functioning, ≥ 4 hours within a 24-hour period, ≥ 4 cumulative lifetime days [3,37].

Inclusion criteria for TDCs were: 1) ages 18-30; 2) English fluency; and 3) no current/lifetime psychiatric illness or substance abuse/dependence in participants or first-degree relatives.

Exclusion criteria for BD and TDCs were: 1) full-scale intelligent quotient (FSIQ) < 70 on the Wechsler Abbreviated Scale of Intelligence (WASI) [38]; 2) autism spectrum disorder, learning disorders, or primary psychosis; and 3) medical/neurological conditions potentially mimicking/confounding psychiatric illness and BD diagnosis.

Procedures

After written informed consent, young adult participants with BD and TDCs completed a battery of cross-sectional neuropsychological tasks and clinical measures via their participation in the current study. Thus, participants with BD (and TDCs) completed neuropsychological tasks as young adults in the current study, not as children in the COBY study. For those with BD who continued to participate in the COBY study as young adults, we leveraged prospective longitudinal assessments of mood symptoms and SI at 6-month intervals (M=8.7±5.2 months) following neuropsychological tasks completed in the current study. Participants had 39.18±16.57 months of follow-up data on average and completed 6.53±2.76 assessments on average, as young adults.

Measures

Cross-sectional neuropsychological tasks—The following tasks from the Cambridge Neuropsychological Testing Automated Battery (CANTAB, Cambridge UK) [39] were administered.

Cognitive flexibility: Participants' cognitive flexibility was assessed using the Intra-Dimensional/Extra-Dimensional (ID/ED) shift task [39], which is a set-shifting task modeled after the Wisconsin Card Sorting Task. This task has nine stages (Table 1). Depending on the stage, each trial displays two simple shapes or two compound shapes with overlaid white lines. Participants use feedback during trial-and-error learning to determine which of two stimuli is rewarded (earning points) and move onto the next stage after completing six consecutive correct trials (maximum 50 attempts). During reversal stages (stages 2, 5, 7, 9) the stimulus/reward association switches, such that the previously rewarded stimulus becomes punished, and vice versa.

Based on prior research documenting cognitive flexibility deficits in childhood-onset BD using the ID/ED task, two variables of interest included: 1) simple reversal (stage 2) trials, errors, latency; and 2) ID reversal errors (stages 2, 5, 7). Simple reversal (stage 2) trials, errors, and latency represent the *first time* participants are required to adapt to the reversal of the prior stage 1 stimulus/reward relationship [19,21,24]. Focus on ID reversal errors (stages 2, 5, 7) enhances task sensitivity, as ID stages primarily measure reversal learning (akin to cognitive flexibility), while ED stages measure attention shifting [20]. For simple reversal (stage 2) trials, errors, and latency, and ID reversal errors, higher scores indicate more impaired cognitive flexibility.

Executive functioning: Participants' executive functioning (spatial planning and problem solving domains) were assessed with the Stockings of Cambridge (SOC) task [39]. The task displays two arrangements of three colored balls, and participants must move the balls in the bottom set to match the top set. Each trial requires two to five moves. If participants make double the necessary moves, the trial terminates. The task ends after three consecutive terminations. Performance is assessed via total moves, number of problems solved with minimum moves, thinking time before starting each problem, and thinking time after starting. In this study, a single score for each variable was created by summing across problems (weighting by number of each type). For total moves, thinking time before starting each problem, and thinking time after starting each problem, higher scores indicate more impaired executive functioning. For number of problems solved with minimum moves, lower scores indicate more impaired executive functioning.

Spatial working memory: Participants' spatial working memory was assessed with the Spatial Span (SSP) task [39]. Participants watch nine squares displayed on a screen sequentially change colors and then are asked to touch the squares in the order in which they changed color. The number of squares increases from two to nine across trials. If participants are unsuccessful on their first try on a level, they receive two more attempts. After three failed attempts on a level, the task terminates. Outcome measures in this study include span length (with lower scores indicating more impaired spatial working memory)

and total errors and usage errors (with higher scores indicating more impaired spatial working memory).

Cross-sectional measures

Demographic information: Participants reported on their age, race, psychiatric medications, and socioeconomic status (SES), categorized according to the Hollingshead Index [40]. They were also administered the WASI [38] by trained research assistants to measure FSIQ.

Psychiatric diagnoses: Participants' current and lifetime BD subtypes (BD-I, BD-NOS) and other psychiatric diagnoses (number of comorbid conditions, ADHD, Any Anxiety Disorder, Substance Use Disorder) were evaluated using the Structured Clinical Interview for *DSM-IV* [41] for adults. Interviews were conducted by a board-certified child/adolescent psychiatrist or a licensed clinical psychologist with established inter-rater reliability (κ>.85). For those with BD who participated in the COBY study, in childhood BD diagnoses were determined via the Schedule for Affective Disorders and Schizophrenia for School Age Children, Present and Lifetime Version [42], with good inter-rater reliability (κ>.8). Given participants' initial participation in the COBY study, young adults' diagnoses of childhood-onset BD were prospectively confirmed (i.e. assessed/determined when participants were children, rather than recalling symptoms that occurred during childhood as adults, providing more accurate diagnoses assessed closer to initial onset incorporating both parent and child report).

Mood symptoms and global functioning: To characterize current mood and functioning during baseline neuropsychological tasks, participants were assessed via the clinician-administered Young Mania Rating Scale (YMRS) [43] and the Hamilton Rating Scale for Depression (HAM-D) [44]. These scales have well established reliability and validity [43,45]. Higher scores indicate greater severity. Functional impairment was assessed via the clinician-rated Global Assessment Scale of Functioning [46] (scores range from 1-100; 100 indicates superior functioning).

Longitudinal measures

Mood symptoms and suicidal ideation: Weekly change in mood symptoms and SI following neuropsychological tasks and measures was assessed using the clinician-administered Psychiatric Status Rating (PSR) scales from the semi-structured adolescent version of the Longitudinal Interval Follow-up Evaluation (A-LIFE), administered via the COBY study [47,48]. Participants had 200.84±71.85 weeks of follow-up data on average following completion of neuropsychological tasks and measures. The A-LIFE PSR evaluates symptom course by identifying change points, anchored by memorable dates (e.g., holidays, start of summer). Participants are queried regarding mood symptoms and SI since the last interview; subsequently, this information is translated into weekly ratings during the interim period. Thus, each 6-month follow-up assesses mood symptoms and SI weekly since the last interview. Mood rating values are operationally linked to *DSM-IV* criteria and indicate symptom severity and impairment. The A-LIFE PSR scores for mood symptoms range from: 1=no symptoms; 2-4=increasing symptom severity and impairment not meeting *DSM-IV*

episode criteria (subthreshold symptoms); 5-6=increasing severity or impairment meeting *DSM-IV* criteria (threshold symptoms). The A-LIFE PSR scores for SI range from: 1=none; 2=slight (thoughts of death); 3=mild (occasional thoughts of suicide); 4=moderate (frequent thoughts of suicide with method); 5=severe (frequent thoughts of suicide with mentally rehearsed plan or suicidal gesture); 6=extreme (preparations for serious attempt). For current analyses, the percentage of time symptomatic (subthreshold and/or threshold mania and depression) and with SI (mild, moderate, severe, and/or extreme) during follow-up (defined as A-LIFE PSR scores ≥ 3) were the primary longitudinal dependent variables of interest. A prior publication used A-LIFE PSR data to determine four latent classes of mood trajectory (predominantly euthymic, moderately euthymic, ill with improving course, predominantly ill) [4]. In the current study, young adult participants' prior mood trajectory (as children in the COBY study) in the prior analyses/publication [4] were: 6.1% (n=3) predominantly euthymic; 34.7% (n=17) moderately euthymic; 32.7% (n=16) ill with improving course; 26.5% (n=13) predominantly ill (n=13).

Analytic Strategy

Analyses were implemented in SPSS 25 with two-tailed comparisons. First, descriptive statistics were calculated to characterize the sample, using one-way ANOVAs (followed by Tukey post-hoc tests and Cohen's d effect sizes for significant values) to compare BD-I vs. BD-NOS vs. TDCs on demographic and neuropsychological variables. For clinical variables (data available for BD-I and BD-NOS only), independent-samples t-tests and chi-square analyses were used.

Primary analyses involved multiple linear regressions to examine the association between cognitive flexibility (measured via ID/ED variables) and percentage of time symptomatic (subthreshold and/or threshold mania and depression) and with SI (mild, moderate, severe, and/or extreme) during follow-up among participants with BD, defined as A-LIFE PSR scores ≥ 3. Independent variables of interest included BD subtype (BD-I vs. BD-NOS), ID/ED cognitive flexibility variables [simple reversal (stage 2) trials, errors, and latency; ID reversal errors (stages 2, 5, 7)], and the BD subtype-by-ID/ED cognitive flexibility variable interaction. Dependent variables of depression, mania, and SI were analyzed in separate models. Prior mood trajectory latent class (during COBY as children; predominantly ill vs. not) [4] and continuous measures of baseline mood and SI symptoms (in the current study as young adults) were included in models as covariates. To be conservative, only analyses with a significant interaction were decomposed via separate univariate regressions for each BD subtype, as recommended by statistical experts [49]. All independent variables were standardized to reduce multi-collinearity, and standardized beta-weights were reported to facilitate interpretable and direct comparisons between regressions [49].

Lastly, to examine the robustness of findings post-hoc analyses: 1) statistically controlled for additional neurocognitive variables (FSIQ, executive functioning, spatial working memory), clinical variables (age of onset of BD, other COBY mood trajectory latent classes, baseline global functioning, psychiatric medications, comorbidity), and amount of follow-up data available; and 2) examined whether neurocognitive variables that were significantly different

in BD-I vs. BD-NOS cross-sectionally predicted subsequent percentage of time symptomatic and with SI.

Results

Demographics

The sample was composed of young adults with childhood-onset BD-I (n=34) or childhood-onset BD-NOS (n=15) and TDCs (n=44). There were no significant differences between participants with BD-I vs. BD-NOS vs. TDCs in terms of age, sex, race, FSIQ, and SES (Table 2). Similarly, there were no significant between-group differences on clinical variables in BD-I vs. BD-NOS, including: 1) age of onset of BD; 2) prior mood trajectory latent class per COBY as children (predominantly ill vs. not); 3) baseline mania, depression, and global functioning as young adults; 4) baseline psychiatric medication status as young adults; 5) number of lifetime comorbid conditions; and 6) lifetime presence of ADHD, any anxiety disorder, and substance use disorder (Table 2). There were also no significant differences when comparing BD-I vs. BD-NOS across all four COBY mood trajectory latent classes as children [$\chi^2(3)=4.39$, p=.22].

Between-Group Differences in CANTAB Neuropsychological Performance

In one-way ANOVAs of CANTAB tasks there were significant between-group effects for: 1) cognitive flexibility indices of ID/ED simple reversal (stage 2) trials, errors, and ID reversal errors (stages 2, 5, 7); 2) executive functioning indices of SOC total moves and problems solved in minimum moves; and 3) spatial working memory indices of SSP length and usage errors (Table 3).

Cognitive flexibility—Post-hoc pairwise Tukey tests for cognitive flexibility indices indicated that participants with BD-I required significantly more ID/ED simple reversal (stage 2) trials than participants with BD-NOS and TDCs; there was no significant difference for BD-NOS < TDCs. In addition, participants with BD-I made significantly more ID reversal errors (stages 2, 5, 7) than TDCs; there were no significant differences for BD-I > BD-NOS and BD-NOS > TDCs. Post-hoc comparisons for ID/ED simple reversal (stage 2) errors were not significant, despite the overall ANOVA between-group effect being significant: BD-I > BD-NOS, BD-I > TDCs, and BD-NOS < TDCs (Table 3).

Executive functioning—Post-hoc pairwise Tukey tests for executive functioning indices indicated that participants with BD-I required significantly more SOC total moves than participants with BD-NOS and TDCs; there was no significant difference for BD-NOS < TDCs. In addition, participants with BD-I solved significantly less SOC problems in the minimum number of moves than participants with BD-NOS and TDCs; there was no significant difference for BD-NOS > TDCs (Table 3).

Spatial working memory—Finally, post-hoc pairwise Tukey tests for spatial working memory indices indicated that participants with BD-I had significantly shorter SSP length than TDCs; there were no significant differences for BD-I < BD-NOS and BD-NOS < TDCs. Similarly, participants with BD-I made significantly more SSP usage errors than

TDCs; there were no significant differences for BD-I > BD-NOS and BD-NOS > TDCs (Table 3).

Primary Analyses: Relationship between Cognitive Flexibility and Subsequent Percentage of Time Symptomatic

Cognitive flexibility and depression—In multiple linear regression analyses of the PSR depression scale, there was a significant interactive effect of BD subtype-by-ID reversal errors (stages 2, 5, 7) [β=0.36, p=.02 (Table 4). Follow-up regressions for BD-I and BD-NOS separately revealed that more ID reversal errors significantly predicted greater percentage of time with subthreshold/threshold depressive symptoms (A-LIFE PSR scores ≥ 3) during follow-up for those with BD-I [β=0.49, p<.01], but not BD-NOS [β=−0.25, p=.39] (Figure 1). There was also a significant main effect for the "predominantly ill" COBY mood trajectory latent class, which significantly predicted greater percentage of time with subthreshold/threshold depressive symptoms during follow-up [β=0.41, p<.01]. No significant main or interactive effects were found for BD subtype, baseline depression, and simple reversal (stage 2) trials, errors, and latency.

Cognitive flexibility and suicidal ideation—In regression analyses of the PSR SI scale, there was a significant main effect for simple reversal latency [β=0.42, p<.01] and significant interactive effect of BD subtype-by-simple reversal latency [β=0.32, p=.03] (Table 4). Follow-up regressions for BD-I and BD-NOS separately revealed that greater simple reversal latency significantly predicted greater percentage of time with SI (A-LIFE PSR scores ≥ 3) during follow-up for those with BD-I [β=0.57, p<.01], but not BD-NOS [β=0.30, p=.39] (Figure 2). There was also a significant main effect for ID reversal errors, such that more ID reversal errors predicted greater percentage of time with SI during follow-up [β=0.49, p<.01]; the interaction was not significant (Table 4). No significant main or interactive effects were found for BD subtype, baseline depression or SI, COBY mood trajectory latent class, and simple reversal trials and errors.

Cognitive flexibility and mania—In regressions of the PSR mania scale, there were no significant main or interactive effects for BD subtype, baseline mania, COBY mood trajectory latent class, and ID/ED (Table 4).

Post-Hoc Analyses: Effect of Additional Neurocognitive and Clinical Variables

Cognitive flexibility ID/ED interactive and main effects were maintained when controlling for additional neurocognitive variables (FSIQ, executive functioning, spatial working memory), clinical variables (age of BD onset, other COBY mood trajectory latent classes, baseline global functioning, psychiatric medications, comorbidity), and amount of follow-up data, demonstrating the robustness of findings. In addition, there were no significant main or interactive effects for executive functioning and spatial working memory variables on subsequent percentage of time symptomatic and with SI (A-LIFE PSR scores ≥ 3).

Discussion

To our knowledge, this is the first study to examine the relationship between cognitive flexibility and subsequent mood symptoms and SI in young adults with prospectively verified childhood-onset BD. Results suggest that young adults with childhood-onset BD-I (meeting diagnostic criteria for distinct manic, hypomanic, and/or depressive episodes) experience greater cognitive flexibility deficits vs. BD-NOS and TDCs. In addition, those with BD-I demonstrated impaired executive functioning compared to BD-NOS and TDCs, and impaired spatial working memory compared to TDCs only. Importantly, cognitive flexibility deficits were associated with subsequent percentage of time with subthreshold/threshold depressive symptoms and SI in those with BD-I but not BD-NOS, regardless of other neurocognitive factors (FSIQ, executive functioning, spatial working memory) and clinical factors (current and prior mood and SI symptoms, age of BD onset, global functioning, psychiatric medications, comorbidity). Findings suggest that cognitive flexibility may be an important brain/behavior mechanism, prognostic indicator, and intervention target for those with childhood-onset BD-I, as this deficit appears to endure into young adulthood and is associated with worse prognosis for depressive symptoms and SI.

Results advance the literature on cognitive impairments [7,8] and cognitive flexibility deficits [19-26,30-33] in BD. Consistent with hypotheses, participants with childhood-onset BD-I displayed significantly greater impairments in cognitive flexibility compared to BD-NOS and TDCs on ID/ED simple reversal (stage 2) trials; for ID/ED reversal errors (stages 2, 5, 7) there was a significant difference between BD-I and TDCs only. Results replicate cognitive flexibility impairments documented in other samples of childhood-onset BD [19-26] and extend prior work in the COBY study [12,20,24] by demonstrating that cognitive flexibility deficits in children with BD-I vs. BD-NOS and TDCs seem to persist into young adulthood, thereby indicating a marker of BD-I (with distinct manic, hypomanic, and/or depressive episodes) vs. BD-NOS.

Though we expected other neuropsychological domains to be equally impaired in BD-I and BD-NOS (and both more so than TDCs), results indicated that participants with BD-I were significantly more impaired in executive functioning than both BD-NOS and TDCs, and those with BD-I were significantly more impaired in spatial working memory than TDCs only. Thus, individuals with childhood-onset BD-I as young adults may be more impaired across cognitive domains than BD-NOS and TDCs. Though inconsistent with prior analyses in the COBY sample, which found similar impairment in other neurocognitive domains across BD subtypes in childhood [12,24], results align with the broader adult literature suggesting that clinical characteristics of BD, including number of mood episodes, contribute to declining cognitive functioning over time [30,32]. Thus, while cognitive flexibility impairments in childhood-onset BD-I vs. BD-NOS and TDCs may be identifiable at a young age and enduring across development, subsequent clinical course and mood episodes may contribute to deterioration in other cognitive domains (executive functioning, spatial working memory) over time, leading to greater cognitive impairments in BD-I vs. BD-NOS and TDCs in young adulthood.

Importantly, cognitive flexibility impairments (ID reversal errors—stages 2, 5, 7) predicted subsequent percentage of time with depressive symptoms in BD-I vs. BD-NOS regardless of other neurocognitive and clinical factors. Findings are in line with previous research documenting: 1) associations between clinical characteristics of BD (illness duration, psychosis, mood episodes, depression) and cognitive flexibility deficits [30,32]; 2) concurrent [13-15] and directional/temporal [16] changes in neurocognition and mood symptoms in adults with BD; and 3) concurrent changes in neurocognition and mood symptoms in youth with BD [12]. Current results extend prior work by examining the relationship between a *specific* neurocognitive deficit (cognitive flexibility) and *subsequent* symptom trajectory in young adults with *childhood-onset* BD. Based on this prior research identifying cognitive flexibility deficits in childhood-onset BD-I [19-26] and documenting longitudinal associations between neurocognition and course [12-16,30,32], cognitive flexibility may be an etiological brain/behavior mechanism of childhood-onset BD-I that persists into young adulthood and yields important clinical implications by predicting subsequent depression above and beyond other neurocognitive and clinical factors.

As such, and in line with current recommendations based on the extant literature [50], consideration of cognitive flexibility deficits could be useful in treatment planning for BD-I. Greater cognitive flexibility impairment (defined as a deficit in adaptation to changing rewards and punishments) [17,18] predicting subsequent subthreshold/threshold depressive symptoms may be related to aberrant reward processing (reward hyposensitivity) and reinforcement characterized by anhedonia [27]. Thus, patients with BD-I and impaired cognitive flexibility may benefit from therapeutic strategies specifically targeting reward processing and positive reinforcement, such as behavioral activation and problem solving. As these are strategies common in existing psychotherapies for childhood-onset BD [51], adjunctive interventions may be necessary to target ongoing cognitive flexibility impairments to enhance learning/uptake of these skills, such as cognitive remediation [50] and specialized psychosocial treatments that have been found to improve cognitive functioning in BD, like Mindfulness-Based Cognitive Therapy [52]. Importantly, research in adults with BD suggests that impaired cognitive flexibility is a trait feature of BD that may worsen over time [33] and influence illness progression. Thus, early identification and intervention is crucial to prevent decline in cognitive functioning and symptoms.

Another novel aspect of this study is the focus on the relationship between cognitive flexibility and subsequent SI, which has been documented in transdiagnostic clinical samples [34,35], though not specifically in childhood-onset BD, despite high rates of suicidality in this population [6]. While one index of cognitive flexibility (ID reversal errors—stages 2, 5, 7) predicted increased SI across BD subtypes, another measure of cognitive flexibility (simple reversal stage 2 latency) predicted subsequent percentage of time with SI in BD-I vs. BD-NOS, regardless of other neurocognitive and clinical variables. Thus, consideration of cognitive flexibility impairments could be useful when selecting interventions and determining prognosis. For instance, adaptations to specialized interventions for suicidality, like Dialectical Behavior Therapy (DBT), may be necessary to enhance their efficacy for individuals with BD, especially BD-I (e.g., addition of new therapeutic skills or cognitive remediation [50] to directly target cognitive flexibility, which if left unaddressed may hinder learning/implementation of strategies taught in DBT).

Greater cognitive flexibility impairment predicting greater percentage of time with SI is also consistent with problem solving difficulties observed in suicidality. When individuals are unable to effectively manage stressors, they may experience hopelessness, thereby leading to increased SI [35]. In addition, those with a history of suicide attempts tend to generate fewer solutions to problems vs. those without an attempt, and their solutions are often less effective [53]. Although additional research is needed to clarify the relationship between cognitive flexibility, problem solving, and suicidality, problem solving skills may be especially relevant in treatment of BD-I.

Results should be interpreted within the context of other findings arising from the COBY study. Specifically, COBY study results demonstrate impaired clinical trajectory, poor functional outcomes, and neurocognitive deficits across childhood BD subtypes [3,5,12,37]. Current study findings suggest that the presence of distinct mood episodes may confer exacerbated cognitive impairment in those with BD-I vs. BD-NOS for cognitive flexibility (previously documented in the sample as children) [24], executive functioning, and spatial working memory in young adulthood. Cognitive flexibility impairment has clinical relevance across the developmental transition from childhood to adulthood, as it is associated with subsequent time depressed and with SI in BD-I, but not BD-NOS. Thus, cognitive flexibility may be important in the etiology and treatment of BD-I.

Limitations

First, the sample size and small number of individuals with BD-NOS limited power to detect significant between-group differences. Similarly, given the small number of participants with BD-II in the sample (n=3), we chose not to include these individuals in analyses. Second, all possible demographic, clinical, and neurocognitive variables were not assessed, and therefore could not be controlled for in analyses. Third, as only one cross-sectional assessment of cognitive flexibility was administered, followed by assessment of mood symptoms and SI, the relationship between course of cognitive flexibility and illness progression is unknown. Fourth, although we were able to examine whether psychiatric medication usage was related to outcomes, we did not have detailed information on other interventions. Future research should address shortcomings by: 1) replicating findings in a larger sample with longer follow-up; 2) measuring and accounting for additional demographic, clinical, and neurocognitive variables; 3) assessing cognitive flexibility, mood, and SI concurrently over time; and 4) determining how pharmacotherapy and/or psychotherapy may impact the relationship between cognitive flexibility and symptom course.

Conclusions

Cognitive flexibility may be an enduring brain/behavior mechanism in childhood-onset BD-I with implications for prognosis. Thus, consideration of cognitive flexibility impairments may be helpful in treatment planning for those with BD-I, and important to target via cognitive remediation [50] or novel psychosocial strategies, to augment and/or enhance the efficacy of existing evidence-based treatments for this population [51].

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Conflict of interest

Dr Dickstein receives research support from the NIMH and the Brain and Behavior Research Foundation (NARSAD). Dr. Thomas is partially supported by Institutional Development Award Number U54GM115677 from the National Institute of General Medical Sciences of the NIH, which funds Advance Clinical and Translational Research. Dr. Yen receives research support from the NIMH, NICCH, and AFSP and had served as a consultant at Janssen Global Services. Ms. Hower receives honorarium from the U.S. Department of Defense and research support from the NIMH. Dr. Hunt receives honoraria from Wiley Publishers and Lifespan Physician Group, and research support from the NIMH. Dr. Keller receives research support from the NIMH and donor gifts from The John J. McDonnell and Margaret T. O'Brien Foundation. Drs. MacPherson, Kudinova, Kim, Radoeva, and Babcock Fenerci, and Ms. Schettini, Jenkins, and Gilbert, declare that they have no conflict of interest to disclose.

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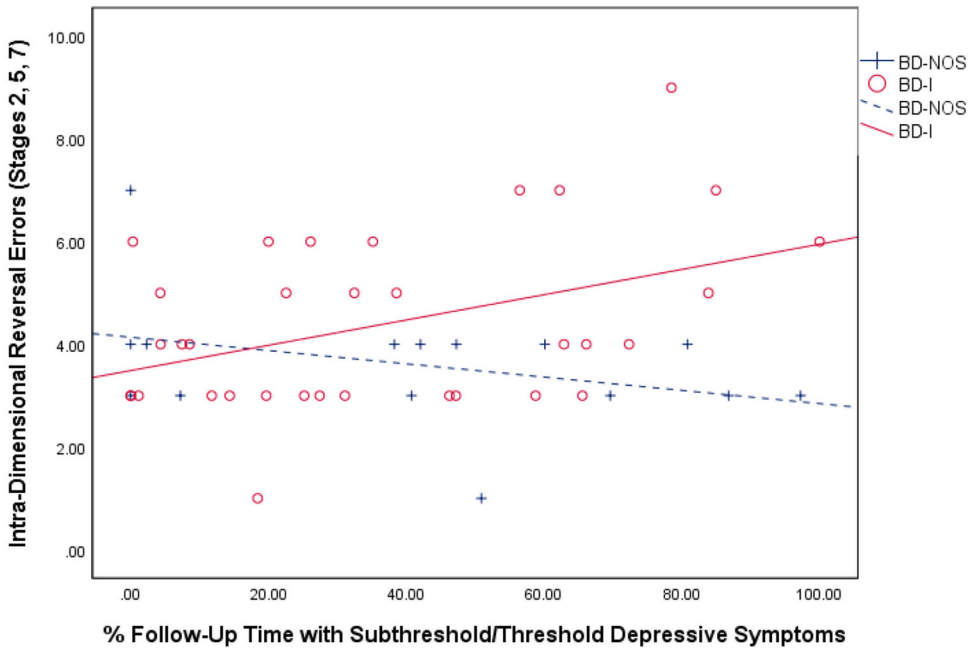

Fig. 1.

Relationship between cognitive flexibility deficits [intra-dimensional reversal errors (stages 2, 5, 7)] and subsequent percentage of follow-up time with subthreshold/threshold depressive symptoms in participants with bipolar disorder I vs. bipolar disorder not otherwise specified. *BD* Bipolar Disorder, *NOS* Not Otherwise Specified

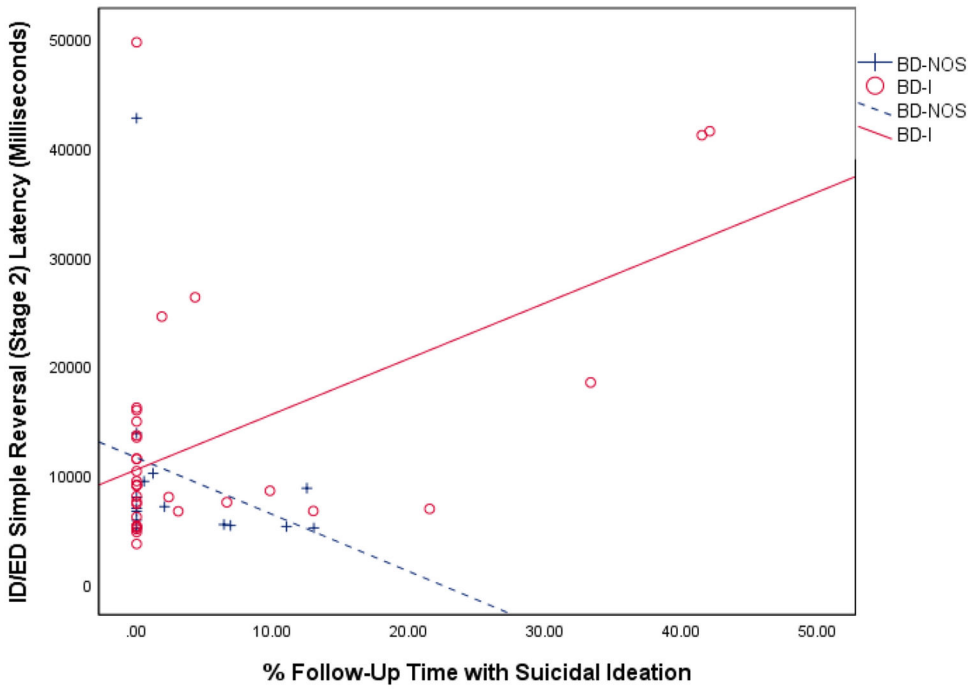

Fig. 2.

Relationship between cognitive flexibility deficits [ID/ED simple reversal (stage 2) latency] and subsequent percentage of follow-up time with suicidal ideation in participants with bipolar disorder I vs. bipolar disorder not otherwise specified. *BD* Bipolar Disorder, *NOS* Not Otherwise Specified, *ID/ED* Intra-Dimensional/Extra-Dimensional

Table 1

Intra-Dimensional/Extra-Dimensional (ID/ED) Shift Task of the Cambridge Neuropsychological Testing Automated Battery (CANTAB, Cambridge UK) assessing Cognitive Flexibility

ID/ED Stage	Description
1	Simple Discrimination
2	Simple Reversal (previously non-rewarded stimulus is now rewarded)
3	Compound Discrimination 1 (white line designs added; shape still rewarded)
4	Compound Discrimination 2
5	Compound Reversal (previously non-rewarded shape is now rewarded)
6	ID Shift (novel exemplars; shape still rewarded)
7	ID Reversal
8	ED Shift (novel exemplars; line now rewarded rather than shape)
9	ED Reversal

Stages 1-7 are ID, with only colored shapes determining reward and the other dimension (white lines) being irrelevant. At ED shift stage 8, the previously irrelevant dimension (white line) becomes relevant (and the colored shape becomes irrelevant)

Table 2

Between-Group Demographic and Clinical Characteristics in Participants with Bipolar Disorder I vs. Bipolar Disorder Not Otherwise Specified vs. Typically-Developing Controls

Variables	BD-I (*n*=34)	BD-NOS (*n*=15)	TDC (*n*=44)	Statistic $\chi^2/F/t$	*p*
Demographics					
Age, *M*(*SD*)	20.52(2.34)	20.53(2.71)	21.10(2.16)	0.72	0.49
Sex (Male), *n*(%)	21(61.76%)	8(53.33%)	25(56.82%)	0.36	0.84
Race (Caucasian), *n*(%)	28(84.85%)	12(85.71%)	34(80.95%)	0.28	0.87
Full-Scale IQ, *M*(*SD*)	104.24(12.88)	111.60(13.37)	109.50(11.85)	2.49	0.09
Socioeconomic Status, *M*(*SD*)	25.45(10.28)	21.86(6.02)	22.38(7.02)	1.54	0.22
Clinical Characteristics					
Age of Onset of Bipolar Disorder, *M*(*SD*)	9.48(3.23)	7.94(2.10)	--	1.59	0.12
COBY Prior Mood Trajectory (Predominantly Ill), *n*(%)	11(32.35%)	2(13.33%)	--	1.93	0.17
Baseline Mania, *M*(*SD*)	4.52(3.40)	2.73(2.28)	--	1.61	0.12
Baseline Depression, *M*(*SD*)	5.30(4.40)	5.27(5.14)	--	0.02	0.99
Baseline Global Functioning, *M*(*SD*)	66.00(12.14)	65.04(9.96)	--	0.24	0.81
Baseline Psychiatric Medications (Yes), *n*(%)	15(44.12%)	5(35.71%)	--	0.29	0.59
Lifetime Comorbid Conditions, *M*(*SD*)	3.65(3.54)	4.00(4.88)	--	−0.29	0.78
Lifetime ADHD (Yes), *n*(%)	20(58.82%)	7(46.67%)	--	0.62	0.43
Lifetime Anxiety Disorder (Yes), *n*(%)	14(41.18%)	9(60.00%)	--	1.48	0.22
Lifetime Substance Use Disorder (Yes), *n*(%)	13(38.24%)	7(46.67%)	--	0.31	0.58

BD Bipolar Disorder, *NOS* Not Otherwise Specified, *TDC* Typically-Developing Control, *COBY* Course and Outcome of Bipolar Youth Study, *ADHD* Attention/Deficit-Hyperactivity Disorder

There were no significant differences between groups.

Table 3

Between-Group Neuropsychological Characteristics of Participants with Bipolar Disorder I vs. Bipolar Disorder Not Otherwise Specified vs. Typically-Developing Controls

Variables	BD-I (*n*=34)	BD-NOS (*n*=15)	TDC (*n*=44)	Statistic *F*(2,90)	*p*	Significant Post-hoc Tests	Cohen's *d*
Cognitive Flexibility (ID/ED Task)							
Simple Reversal (Stage 2) Trials	9.09(3.60)	7.07(0.26)	7.43(1.17)	6.24	<.01	BD-I > BD-NOS, *p*=.02 BD-I > TDC, *p*<.01	0.67 0.66
Simple Reversal (Stage 2) Errors	1.59(1.02)	1.07(0.26)	1.23(0.57)	3.47	.04	*NS*	
Simple Reversal (Stage 2) Latency (*ms*)	13198.47 (11143.67)	9736.47 (9430.69)	10758.70 (8895.81)	0.87	.42		
ID Reversal Errors (Stages 2, 5, 7)	4.38(1.69)	3.60(1.24)	3.55(1.13)	3.86	.03	BD-I > TDC, *p*=.03	0.59
Executive Functioning (SOC Task)							
Total Moves	17.64(2.55)	15.57(1.51)	16.36(2.11)	5.57	<.01	BD-I > BD-NOS, *p*<.01 BD-I > TDC, *p*=.04	0.90 0.55
Problems Solved in Minimum Moves	8.71(2.13)	10.27(1.22)	9.77(1.88)	4.67	.01	BD-I < BD-NOS, *p*=.03 BD-I < TDC, *p*=.04	0.82 0.53
Total Initial Thinking Time (*ms*)	16235.85 (10213.11)	20651.87 (10603.75)	20300.23 (12513.53)	1.43	.25		
Total Subsequent Thinking Time (*ms*)	1872.61 (2272.65)	618.91 (735.39)	1209.83 (1507.58)	2.96	.06		
Spatial Working Memory (SSP Task)							
Length	6.24(1.35)	6.87(2.30)	7.36(1.20)	5.61	<.01	BD-I < TDC, *p*<.01	0.88
Errors	13.44(6.20)	13.87(5.81)	12.07(7.08)	0.63	.54		
Usage Errors	2.35(1.76)	1.67(1.88)	1.32(1.12)	4.55	.01	BD-I > TDC, *p*=.01	0.72

BD Bipolar Disorder, *NOS* Not Otherwise Specified, *TDC* Typically-Developing Control, *NS* Not Significant, *ID/ED* Intra-Dimensional/Extra-Dimensional, *SOC* Stockings of Cambridge, *SSP* Spatial Span

Table 4

Regression Analyses Examining Association between Cognitive Flexibility (measured via the ID/ED Task) and Subsequent Percentage of Time Symptomatic in Participants with Bipolar Disorder I vs. Bipolar Disorder Not Otherwise Specified

Effects	Mania		Depression		Suicidal Ideation	
	β	*t*	β	*t*	β	*t*
BD Subtype (BD-I vs. BD-NOS)	0.23	0.33	0.57	0.92	0.21	0.31
COBY Prior Mood Trajectory (Predominantly Ill)	0.01	0.08	0.40	2.64*	0.18	1.10
Baseline Mania	0.05	0.27	--	--	--	--
Baseline Depression	--	--	0.04	0.26	−0.11	−0.69
Baseline Suicidal Ideation	--	--	--	--	−0.04	−0.23
Simple Reversal (Stage 2) Trials	−0.25	−0.24	−0.82	−0.87	−0.04	−0.04
BD Subtype x Simple Reversal (Stage 2) Trials	−0.02	−0.02	1.13	1.19	0.47	0.46
Effects	**Mania**		**Depression**		**Suicidal Ideation**	
	β	*t*	β	*t*	β	*t*
BD Subtype (BD-I vs. BD-NOS)	0.20	0.83	0.05	0.27	0.03	0.16
COBY Prior Mood Trajectory (Predominantly Ill)	0.00	0.02	0.41	2.82**	0.21	1.32
Baseline Mania	0.08	0.44	--	--	--	--
Baseline Depression	--	--	0.05	0.34	−0.11	−0.65
Baseline Suicidal Ideation	--	--	--	--	−0.00	−0.02
Simple Reversal (Stage 2) Errors	−0.22	−0.67	−0.02	−0.07	0.28	0.98
BD Subtype x Simple Reversal (Stage 2) Errors	−0.07	−0.22	0.43	1.54	0.26	0.88
Effects	**Mania**		**Depression**		**Suicidal Ideation**	
	β	*t*	β	*t*	β	*t*
BD Subtype (BD-I vs. BD-NOS)	0.19	1.05	−0.05	−0.34	0.04	0.26
COBY Prior Mood Trajectory (Predominantly Ill)	0.04	0.24	0.35	2.20*	0.07	0.48
Baseline Mania	−0.04	−0.23	--	--	--	--
Baseline Depression	--	--	0.10	0.64	−0.03	−0.19
Baseline Suicidal Ideation	--	--	--	--	−0.01	−0.07
Simple Reversal (Stage 2) Latency	−0.03	−0.14	0.12	0.79	0.42	2.89**
BD Subtype x Simple Reversal (Stage 2) Latency	−0.00	−0.01	0.21	1.38	0.32	2.23*
Effects	**Mania**		**Depression**		**Suicidal Ideation**	
	β	*t*	β	*t*	β	*t*
BD Subtype (BD-I vs. BD-NOS)	0.20	1.07	−0.03	−0.21	−0.01	−0.06
COBY Prior Mood Trajectory (Predominantly Ill)	0.04	0.22	0.41	2.88**	0.21	1.45
Baseline Mania	−0.05	−0.29	--	--	--	--
Baseline Depression	--	--	0.07	0.51	−0.09	−0.54
Baseline Suicidal Ideation	--	--	--	--	−0.02	−0.13
ID Reversal Errors (Stages 2, 5, 7)	0.00	0.00	0.21	1.50	0.49	3.55**

Effects	Mania		Depression		Suicidal Ideation	
	β	*t*	β	*t*	β	*t*
BD Subtype x ID Reversal Errors (Stages 2, 5, 7)	0.06	0.31	0.36	2.56*	0.27	1.92

ID/ED Intra-Dimensional/Extra-Dimensional, *BD* Bipolar Disorder, *NOS* Not Otherwise Specified, *COBY* Course and Outcome of Bipolar Youth Study

*$p<.05$

**$p<.01$