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A Developmental Study of the Neural Circuitry Mediating Motor Inhibition in Bipolar Disorder

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Abstract

Objective—Despite increased interest in the developmental trajectory of the pathophysiology mediating bipolar disorder (BD), few studies compare adults and youths with BD. Deficits in motor inhibition are thought to play an important role in the pathophysiology of BD across the age spectrum. Here we compare neural circuitry mediating this process in youths vs. adults with BD and healthy volunteers.

Method—fMRI data from 89 subjects (16 BD youth, 23 BD adults, 21 healthy children, 29 healthy adults) were acquired while subjects performed the stop-signal task.

Results—During failed inhibition, an age group x diagnosis interaction manifested in the anterior cingulate cortex (ACC), with child BD participants showing hypoactivation relative to healthy children and adult BD, and adult BD showing hyperactivation relative to healthy adults. During successful inhibition, a main effect of diagnosis emerged in the right nucleus accumbens and left ventral prefrontal cortex, with bipolar individuals, irrespective of age, showing less activation than healthy participants.

Conclusions—Child BD and adult BD both show ACC dysfunction during failed motor inhibition, although the nature of that dysfunction differs between groups. Adults and youth with BD show similar deficits in nucleus accumbens and ventral prefrontal cortex activation during

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successful inhibition. Therefore, while subcortical and VPFC hypoactivation is present in BD across the lifespan, ACC dysfunction varies developmentally, with reduced ACC activation in child BD and increased activation in adult BD during failed inhibition. Longitudinal fMRI studies on the developmental trajectory of the neural circuitry mediating motor inhibition in BD are warranted.

Introduction

There is increased interest in the developmental trajectory of bipolar disorder (BD), since a developmental perspective can lead to better prevention and treatment (1). While considerable research on development uses family-history or longitudinal designs (2), few studies utilize neuroscience approaches. The current study uses functional magnetic resonance imaging (fMRI) and the stop-signal task (3) to map the neural correlates of motor inhibition in pediatric and adult BD.

Motor inhibition impairments have been demonstrated in adult and pediatric BD. Studies clearly implicate deficient motor inhibition in adult BD (4), whereas data in pediatric BD are less definitive (5). In adult BD, motor-inhibition deficits (4) have been linked to impulsivity during mania (6). In healthy adults, stop cues activate the ventral prefrontal cortex (VPFC), enabling pre-supplementary motor area (pre-SMA) mediated inhibition (7) via striatal circuits (8). Response conflict from these cues is detected by the anterior cingulate cortex (ACC) (9). Data comparing neural correlates of motor inhibition in healthy youth and adults is inconsistent, with some studies reporting increased PFC involvement in youth (10, 11) and others reporting the reverse (8).

Response inhibition in pediatric BD has been associated with decreased striatal, VPFC, and ACC activation compared to healthy volunteers (HV) (12). However, interpretation of these findings was complicated by comorbid ADHD in BD, as both diagnoses are characterized by impulsivity. Differences in VPFC and ACC activation have been reported in manic BP vs. HV youth during a task requiring motor inhibition (13). Finally, during response inhibition, adults with mania show decreased VPFC (14) and ACC (15) activation compared HV.

Overall, this literature generates three conclusions: motor inhibition deficits exist in BD and are related to impulsivity; motor inhibition is mediated by frontostriatal circuitry that is dysfunctional during inhibition in BD; and functional circuitry mediating inhibition varies developmentally in healthy individuals. However, no study directly contrasts the neural correlates of motor inhibition in adult and pediatric BD. Using event-related fMRI, we tested for age-group-by-diagnosis interactions during successful and unsuccessful inhibition on the stop-signal task. We excluded patients with ADHD because comorbid ADHD complicates the interpretation of neuroimaging findings (12). Available data reviewed above generates three regions of interest (ROI): ACC, VPFC, and striatum. Based on this literature, we hypothesized that BD patients, compared to HV, would exhibit reduced levels of activity in these regions during failed inhibition (12-14) and, given evidence of increasing inhibitory ability through adolescence (16), this effect would be most pronounced in youth.

Methods

Subjects

Participants were part of an ongoing IRB approved study at the National Institute of Mental Health. Adult subjects and parents/guardians of child subjects provided informed consent, while children provided informed assent.

Patient recruitment was through advertisements to support groups and clinicians. Comparison subjects, (21 healthy children, 29 healthy adults) were recruited from the community through advertisements; they had no lifetime psychiatric diagnoses or first-degree relatives with a mood or anxiety disorder. Exclusions for all participants included: IQ<80, substance abuse within the past three months, major medical illnesses, neurological damage/disorder, comorbid ADHD, and pervasive developmental disorders. No participants were related.

Children were assessed for Axis-I disorders, including ADHD, with the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL) (17). Child BD participants ($n=16$) met criteria for “narrow phenotype” BD, with at least one hypomanic (4 days) or manic (7 days) episode with abnormally elevated mood or grandiosity and at least three criterion “B” mania symptoms (18). Thirteen children (81.3%) were BD-I and three (18.8%) BD-II. Adults were assessed for Axis-I disorders using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders-Patient Edition (SCID-I/P) (19) or the Diagnostic Interview for Genetic Studies (DIGS)(20). For all adults, ADHD was assessed using the DIGS ADHD module. The adult BD group ($n=23$) consisted of fourteen (60.9%) BD-I and nine (39.1%) BD-II patients. Interviewers were masters or doctoral level clinicians with excellent interrater reliability ($\kappa>0.9$ for all diagnoses).

In patients, mood was assessed within 48 hours of scanning using the Children’s Depression Rating Scale (CDRS) (21) and the Young Mania Rating Scale (YMRS) (22) for children, and the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders Version (SIGH-SAD) (23) and YMRS for adults.

Of the 153 individuals scanned, data were excluded for 64 (41.8 %), specifically, for excessive movement (19.6%), poor performance i.e., <55% accuracy on go trials (13.1%), equipment failure or poor scan quality (7.2%), or abnormal clinical findings (2.0%). More children than adults ($t=6.17$, $p<.013$) were excluded for movement. The final sample ($n=89$) includes 16 child BD and 21 healthy children reported previously (12)

Stop Signal Task (3)

A white cross appeared at the screen center for 500 ms at the start of each trial. This was replaced by an “X” or “O” “go-signal” for 1000 ms. Using a button-box, subjects were instructed to press “1” for “X” and “2” for “O”. Participants were told to respond within 1000 ms, unless the stop signal appeared (i.e., background changed to red). This occurred on 25% of trials i.e., “stop” trials. Subjects were to refrain from button pressing if the stop signal appeared.

On the first stop trial, the stop signal appeared 250 ms after the go-signal. Subsequent stop-signal timing was adjusted trial-by-trial based on subject performance. When subjects inhibited successfully, the next stop signal appeared 50 ms later than on the last stop trial; when subjects failed, the signal appeared 50 ms earlier than on the last stop trial. Trials were separated by 750 ms.

Before scanning, subjects were trained to a mean reaction time (RT) less than 1000 ms on “go” trials. During scanning, participants completed 4 runs, each consisting of randomly presented go ($n=32$), stop ($n=16$; 8 correct and 8 incorrect), and fixation ($n=16$) trials. This resulted in 32 correct and 32 incorrect stop trials per participant.

Scanning acquisition

Scans were conducted in a General Electric Signal 3T magnet. Participants viewed stimuli through Avotec Silent Vision Glasses (Stuart, FL). A high-resolution T1 weighted anatomical image following standardized magnetization prepared gradient echo sequence was collected (180 1 mm sagittal slices; FOV=256; NEX=1; TR=11.4 ms; TE=4.4 ms; matrix=256 × 256; TI=300 ms; bandwidth=130 Hz/pixel, 33kHz/256 pixels). Gradient echo planar images (23 contiguous 5 mm axial slices/brain volume; parallel to anterior commissure posterior line; single shot gradient echo T2* weighting [matrix 64×64; TR=2000 ms; TE=40ms; FOV=240mm; voxels were 3.75 × 3.75 × 5mm]) were collected following manual shim and sagittal localization.

Analyses

Behavior—For each group, we computed means for accuracy on go and stop trials; response time on go trials (GoRT); and, on stop trials, the time between the go and stop signal onsets, or ‘inhibit delay’. Stop signal reaction time (SSRT) was calculated by subtracting mean GoRT from inhibit delay at the point when the participant’s accuracy on stop trials was 50% (3) (if accuracy was not 50%, the mean inhibit delay was subtracted from the RT at the X^{th} percentile of go trials, where X was the participant’s stop trial accuracy).

Differences in mean stop and go accuracy, RT, inhibit delay, and SSRT were tested independently using separate 2 (Age group: children and adult) × 2 (Diagnosis: BD and HV) factorial univariate analysis of variance (ANOVA). Post-hoc contrasts between groups were done using the Tukey’s test.

Imaging—SPM8 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>) and Matlab 7 (The MathWorks, Natick, MA) were used. Preprocessing included slice timing correction, motion correction, spatial normalization to Montreal Neurological Institute (MNI) space, and smoothing (kernel FWHM=8). At the subject level, event-related response amplitudes were estimated using the General Linear Model (GLM). Event types included unsuccessful stop (“stop incorrect”), “go” (only *correct* go trials included) and successful stop (“stop correct”) trials. Three contrasts were used for primary analysis: stop correct versus go; stop correct versus stop incorrect; and stop incorrect versus go. These contrasts controlled for response accuracy, task demand, and presence of a motor response, respectively. Individual contrast images were created using pair-wise comparisons of event-related response amplitudes, and then entered into second-level random-effects group analyses. A high pass filter (0.0078 Hz) was used.

Motivated by previous findings (12-15), we used small volume corrected (SVC) ROI analyses to test our hypotheses. Since adult groups differed in age, age was a covariate of adult data in our analysis. We used a factorial design to test for a 2 (age group: children and adult) × 2 (diagnosis: BD and HV) interaction in each ROI (bilateral putamen, caudate, nucleus accumbens, ACC, and VPFC) using anatomical templates applied to individual participant’s data. For each contrast, we: (1) identified clusters whose peak surpassed the $p < .05$ threshold, using the SVC procedure in SPM8; (2) averaged the estimated contrast values across these clusters for each participant; (3) conducted univariate ANOVAs and Tukey post-hoc tests in SPSS to clarify group activation differences in the clusters. We report the p values from these ROI analyses, as well as Bonferroni-corrected p values that correct for the fact that we examined activation in five ROIs.

To decompose the interactions from primary contrasts, we compared group differences on stop incorrect vs. fixation, stop correct vs. fixation, and go vs. fixation, separately, in clusters identified by the primary analysis. In addition an exploratory whole-brain analysis was conducted for each primary contrast using a statistical threshold of $p=.005$ and spatial extent of 20 contiguous voxels (24).

Separate exploratory post-hoc analyses examined the impact of mood state, medication status, and comorbid oppositional defiant disorder (ODD) as child and adult BD differed on these variables. To test whether primary effects remained significant when controlling for these differences, we stratified the BD sample into euthymic vs. non-euthymic, and + medication vs. – medication groups. Similar techniques were used to test the effect of ODD.

Results

Demographic and clinical characteristics

BD subtype (I vs. II) did not differ between child and adult BD (Table 1). There were no between-group differences in I.Q. or gender. Adult BD's ($M=40.85$, $\pm = 11.81$) were older than healthy adults ($M=35.18$, $\pm = 8.06$), $t(50) = -2.05$, $p<.046$.

Twelve (75.0%) child BD were euthymic (YMRS ≤ 12 and CDRS ≤ 40), and four (25.0%) hypomanic (YMRS=12-24 and CDRS ≤ 40). Eleven (47.8%) adult BD were euthymic (YMRS ≤ 12 and SIGH-SAD ≤ 20), eight depressed (34.8%) (YMRS ≤ 12 and SIGH-SAD ≥ 20), one (4.3%) hypomanic (YMRS=12-24 and SIGH-SAD ≤ 20), and one (4.3%) in a mixed state (YMRS ≥ 12 and SIGH-SAD ≥ 20). BD groups did not differ in percentage of euthymic patients. Mean YMRS was higher in child BD ($M=7.75 \pm 5.98$) than adult BD ($M=3.90 \pm 4.90$), $t(35)=2.15$, $p<.039$, and more adult BD than child BD were depressed ($p<.006$, Fisher's Exact Test). More child than adult BD met criteria for ODD, and more child BD than adult BD were unmedicated ($N=22$ (95.7%) adult BD vs. $N=19$ (56.2%) child BD were medicated; $p<.002$, Fisher's Exact Test). Mean age (in years) at mania onset differed between patient groups (children: $M=11.7 \pm 3.64$; adults: $M=21.8 \pm 10.7$; $t(34)=3.41$, $p<.002$).

Behavioral findings

No age group x diagnosis interactions emerged on any measure (Table 2). There was a main effect of diagnosis on stop accuracy, with HV having higher accuracy than BD ($F(3,85)=4.30$, $p<.042$). There was also a main effect of age on stop accuracy ($F(3,85)=13.41$, $p<.001$), GoRT ($F(3,85)=17.83$, $p<.001$), and mean inhibit delay ($F(3,85)=14.60$, $p<.001$). No group differences emerged for SSRT.

Imaging Data

ROI Analysis

Stop-incorrect versus go: On stop-incorrect versus go, there was an age group x diagnosis interaction in the left ACC (L-ACC) ($F(3,85)=12.98$, $p<.001$ (uncorrected), $p<.005$ (corrected)) and right ACC (R-ACC) ($F(3,85)=13.80$, $p<.001$ (uncorrected), $p<.005$ (corrected)) (Figure 1; Table 3A). In L-ACC and R-ACC, child BD had decreased activation relative to both healthy children (L: $p<.008$; R: $p<.001$) and adult BD (L: $p<.001$; R: $p<.002$). Activation in L-ACC was higher in adult BD compared to healthy adults ($p<.013$). In R-ACC, activation in healthy children was higher than healthy adults ($p<.037$).

Post-hoc analyses of the stop incorrect vs. fix contrast revealed decreased activation in L-ACC and R-ACC in child BD compared to healthy children (L: $t(35)=2.08$, $p<.045$; R:

$t(35)=2.42, p<.021$) and adult BD (L: $t(37)=2.63, p<.013$; R: $t(37)=2.91, p<.006$). No group differences emerged on go vs. fix.

Stop-correct versus go: There was a main effect of diagnosis in the right nucleus accumbens (R-NAc), with healthy subjects having greater activation than BD ($F(1,87)=6.58, p<.012$ (uncorrected), $p=.060$ (corrected)) (Figure 2). Post-hoc analysis of the stop-correct vs. fix contrast showed this was due to increased activity in the R-NAc in HV vs. BD during stop-correct trials ($t(87)=2.58, p<.012$).

There was a main effect of diagnosis in the left ventral prefrontal cortex (L-VPFC), with HV showing increased activation vs. BD ($F(1,87)=9.39, p<.003$ (uncorrected), $p<.015$ (corrected)) (Figure 2). Post-hoc analysis of the stop-correct vs. fix contrast showed that this was driven by increased activity in HV vs. BD during stop-correct trials ($t(87)=3.00, p<.004$).

Stop-correct versus stop-incorrect: There were no age group x diagnosis, age group, or diagnosis effects.

Whole-Brain Analysis—No effects were found on the three primary contrasts.

Associations of Clinical Variables with Brain Activation

Mood: The age group x diagnosis interaction for the stop incorrect versus go contrast remained significant when only euthymic BD participants (child BD (N=12); adult BD (N=11)) were included (L-ACC: $F(3,69)=6.40, p<.014$; R-ACC: $F(3,69)=7.22, p<.009$). The main effect of diagnosis (BD vs. HV) in the stop correct versus go contrast, in both R-NAc and L-VPFC, remained significant when only euthymic patients were included ($F(1,71)=4.47, p<.038$) and ($F(1,71)=8.21, p<.005$), respectively).

Medication status: The age group x diagnosis interaction for the stop incorrect versus go contrast remained significant when only medicated patients were included (child BD (N=9); adult BD (N=22); L-ACC $F(3,77)=6.23, p<.015$, R-ACC $F(3,77)=6.23, p<.015$). On the stop correct versus go contrast, the main effect of diagnosis in the R-NAc ($F(1,79)=5.35, p<.023$) and L-VPFC ($F(1,79)=7.42, p<.008$) remained significant.

Comorbid ODD: The age group x diagnosis interaction for the stop incorrect versus go contrast remained significant when child BD with comorbid ODD (N=4) were excluded (L-ACC ($F(3,81)=9.44, p<.003$); R-ACC ($F(3,81)=9.20, p<.003$). On the stop-correct versus go contrast, the main effects of diagnosis in the R-NAc ($F(1,83)=7.47, p<.008$) and L-VPFC ($F(1,83)=9.18, p<.003$) remained significant.

Discussion

Recent reports emphasize the importance of studying neurodevelopment in BD (1, 25). Using fMRI during response inhibition in adult and child BD vs. healthy subjects, we confirmed our hypothesis that BD patients without ADHD show frontostriatal dysregulation during unsuccessful response inhibition, and this is most pronounced in youth. Specifically, during unsuccessful inhibition, there was an age group x diagnosis interaction, with BD youth showing reduced activity in L-ACC and R-ACC compared to both age-matched HV and adult BD, and adult BD showing increased activation in L-ACC compared to healthy adults. During successful inhibition there was a main effect of diagnosis, with HV showing greater activity in L-VPFC and R-NAc compared to BD. VPFC, NAc, and ACC dysregulation during response inhibition exists across development in BD, and suggests

their dysfunction is central to the pathophysiology of BD. Further analyses suggested that these findings were not due to differences between pediatric and adult patients on mood, comorbid ODD, and medication status.

The ACC mediates conflict monitoring and error detection during choice tasks (9). Here we found HV youth showed increased ACC activation compared to HV adults when making errors, consistent with literature indicating that error detection develops from childhood into adulthood (26). Few investigations in BD focus on ACC activation during motor inhibition; none directly compare adult and pediatric BD. Data comparing motor inhibition in children with mania vs. healthy comparisons found decreased ACC activity (13), while in a prior study adults with BD didn't differ from healthy comparisons (27). In the present study, child BD had *decreased* ACC activation during failed motor inhibition compared to age-matched HV and adult BD, whereas adult BD had *increased* ACC activation relative to adult HV. This indicates that error detection during motor inhibition may develop abnormally in BD compared to HV. Our data support existing evidence that cortical dysfunction is already present in children with BD and does not arise first in adulthood (13, 24). The ACC hypoactivation during unsuccessful inhibition is similar to that found in BD youth during response inhibition (13). However, the ACC hyperactivation that we observed in adult BD is different from hypoactivation reported previously during response inhibition (15) in adult BD. Therefore our results should be considered preliminary.

Here, BD youth do not engage the ACC appropriately during response conflict, which could diminish their ability to inhibit inappropriate responses to external cues in real-world environments, such as when children interact with teachers, parents, and friends. Also, BD adults showed ACC hyperactivation during response conflict relative to adult HV to produce comparable performance. The hyperactivation in adults with BD may result from functional *compensation* for the hypoactivation that is present and impairing in childhood. This compensatory hyperactivation in patients with BD may emerge as the ACC continues to develop throughout adolescence and adulthood (28, 29). Alternatively, pediatric-onset BD may differ from adult-onset BD in certain pathophysiological and clinical features, including ACC hypoactivation during unsuccessful motor inhibition, mode of inheritance (30) and increased heritability (31). These possibilities can be dissociated only by longitudinal studies.

Compared to healthy volunteers (HV), children with BD with co-occurring ADHD showed decreased striatal, VPFC, and ACC activation during unsuccessful inhibition (12), while adults with BD showed decreased VPFC (14) and ACC (15) activation during response inhibition. These findings, as well as findings in the current study in BD youth without ADHD, resemble those in some studies of ADHD. Specifically, ACC hypoactivation has been reported in ADHD youth during unsuccessful inhibition (32, 33), while VPFC hypoactivation has been reported in ADHD adults during successful inhibition (34). This suggests that similar neural dysfunction may be present across diagnoses in patients with motor inhibition deficits.

During successful inhibition, HV subjects showed increased activation in the L-VPFC and R-NAc compared to patients. The VPFC supports inhibition by suppressing basal ganglia output (35), while the NAc receives input from the brainstem important in conditioned learning (36). Our findings are consistent with published literature showing abnormalities in these regions, particularly in adults with BD (24, 37, 38). The finding of VPFC and NAc dysfunction in BD across the developmental spectrum suggests impaired inhibitory signals to the basal ganglia and aberrant associative learning mechanisms arise early in BD and persist throughout its course. Longitudinal studies are necessary to confirm this hypothesis.

Our behavioral analysis revealed a main effect of age on GoRT and stop accuracy. Compared to adults, youth showed faster responses on “go” trials and decreased accuracy during motor inhibition. Thus, youth use a strategy that sacrifices accuracy for speed, while adults sacrifice speed for accuracy. The age x diagnosis ACC findings in BD may reflect patient versus control differences when youth and adults employ these different strategies. Specifically, BD youth differ from HV youth in hypoactivating the ACC during their ‘speed-driven’ strategy, while adult BD differ from adult HV in hyperactivating the ACC during their ‘accuracy-driven’ strategy. Patients and HVs did not differ on SSRT or other behavioral measures, consistent with the observation that fMRI measures can be more sensitive than behavioral measures in detecting between-group differences, especially with small sample sizes (39).

Two important limitations should be noted. We eliminated 42% of scanned subjects for excessive movement, poor performance, technical problems, and abnormal brain findings. The exclusion of these subjects, and the fact that more children than adults were excluded for movement, potentially limits the generalizability of our findings. However, we note that this percentage of child exclusions is not unusual (40). Additionally, the effect of medication on imaging results could not be investigated thoroughly, since only one adult BD patient was unmedicated. However, ethical considerations complicate the recruitment of medication-free patients, and data, including some from the youth in this study, suggest that medication increases the probability of Type II, but not Type I, errors (12).

Cross-sectional comparisons represent a first step in developmental-imaging, which ultimately should involve prospective collection of imaging and clinical data. History suggests that cross-sectional comparisons of pathophysiology among children and adults with similar clinical presentations represent a vital “first step” in the formation of developmentally informed models. No prior fMRI study has compared pediatric and adult BD using any cognitive task; here we examine motor inhibition, a psychological construct implicated with some consistency in both pediatric and adult BD. Hence, these results might initiate a new phase of developmentally-informed longitudinal imaging.

This study provides evidence of developmental differences in frontostriatal activation between BD patients and healthy subjects. Understanding how brain activation and behavior progresses in BD can only be addressed with longitudinal fMRI studies. Doing so would help with accurate diagnosis of child BD, understanding age-specific deficits in BD, and applying intervention strategies appropriate for developmental stage in BD.

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Figure 1. Mean activation in left and right anterior cingulate cortex (ACC) during stop-incorrect vs. go contrast

(A) Anterior cingulate cortex (ACC) activation in stop-incorrect vs. go contrast. (B) Mean activation in right ACC (MNI coordinates $x = 4, y = 42, z = 6$). (C) Mean activation in left ACC (MNI coordinates $x = 4, y = 42, z = 6$). HV = healthy volunteers; BD = bipolar disorder

Figure 2. Mean activation in left ventral prefrontal cortex (VPFC) and right nucleus accumbens (NAc) during stop-correct vs. go contrast

(A) Ventral prefrontal cortex (VPFC) and nucleus accumbens (NAc) activation in stop-correct vs. go contrast. (B) Mean activation in left VPFC (MNI coordinates $x = -26$, $y = 26$, $z = 8$). (C) Mean activation in right NAc (MNI coordinates $x = 16$, $y = 4$, $z = -6$). HV= healthy volunteers; BD= bipolar disorder

Table 1

Subject Characteristics

Characteristic	Child BD (N = 16)		Adult BD (N = 23)		Child HV (N = 21)		Adult HV (N = 29)	
	Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD	
Age ^a	14.65 ± 2.19		40.85 ± 11.81		13.79 ± 1.97		35.18 ± 8.06	
WASI Full-scale IQ ^b	107.81 ± 11.88		114.80 ± 10.35		114.00 ± 13.95		115.57 ± 9.37	
* YMRS ^c	7.75 ± 5.98		3.90 ± 4.90					
CDRS ^d	24.81 ± 5.43		NA					
SIGH-SAD ^e	NA		16.62 ± 11.40					
* Age of onset: Mania ^f	11.71 ± 3.65		21.82 ± 10.66					
Number of medications	1.57 ± 1.65		2.48 ± 1.53					
	N (%)		N (%)		N (%)		N (%)	
Male	8 (50.0)		7 (30.4)		12 (57.1)		11 (37.9)	
Euthymic	12 (75.0)		11 (47.8)					
** Depressed	0 (0)		8 (34.8)					
Hypomanic	4 (25.0)		1 (4.3)					
Mixed State	0 (0)		1 (4.3)					
Bipolar I	13 (81.3)		14 (60.9)					
Bipolar II	3 (18.7)		9 (39.1)					
Any Comorbidity	13 (81.3)		15 (60.0)					
Any Anxiety Disorder	7 (43.8)		6 (26.1)					
* ODD	4 (25.0)		0 (0)					
CD	1 (6.25)		0 (0)					
Any Substance Abuse/Dependence	0 (0)		2 (8.7)					
** Unmedicated	7 (43.8)		1 (4.3)					
Atypical Antipsychotic	4 (25.0)		10 (43.8)					
Lithium	3 (18.8)		5 (21.7)					
Antiepileptic	6 (37.5)		15 (65.2)					
Antidepressant	5 (31.3)		9 (39.1)					

Characteristic	Child BD (N = 16)	Adult BD (N = 23)	Child HV (N = 21)	Adult HV (N = 29)
Stimulants	2 (12.5)	1 (4.3)		

^aNote, significant difference between adult groups ($t=2.05^*$), but not pediatric groups ($t=1.26$).

^bMissing data from 2 adults with BD and 1 adult control.

^cYoung Mania Rating Score; Missing data from 2 adults with BD.

^dChildren's Depression Rating Scale.

^eThe Structured Clinical Interview Guide for the Hamilton Rating Scale, Seasonal Affective Disorders Version. Missing data from 2 adult BD patients.

^fData missing from 2 children with BD and 1 adult with BD.

* $p<0.05$,

** $p<0.01$,

*** $p<0.001$ for between group differences in patients

HV= healthy volunteers; BD= bipolar disorder

Table 2

Performance of subjects on the stop signal task during scanning, presented by group.

Variable	Child Healthy volunteer N=21		Children with Bipolar Disorder N=16		Adult Healthy volunteer N=29		Adults with Bipolar Disorder N=23		Age by Diagnosis Factorial <i>F</i> statistic		Planned post hoc's (Tukey's test)
	Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Interaction	Diagnosis	Age
Accuracy Go (%)	83.9 (11.4)		83.0 (12.5)		85.8 (10.5)		82.2 (11.1)		0.3	0.8	0.0
Accuracy Stop (%)	53.4 (10.8)		48.4 (8.5)		59.0 (7.7)		56.3 (7.2)		0.4	4.3*	13.4*** Adult BD>Child BD***; Adult HV>Child BD***
Go Reaction Time (msec)	696.8 (109.4)		656.3 (80.7)		763.9 (94.9)		757.0 (75.1)		0.7	1.4	17.8*** Adult BD>Child BD***; Adult HV>Child BD***
Inhibit Delay ^a (msec)	504.6 (127.6)		431.8 (110.5)		562.1 (119.0)		558.9 (82.7)		2.0	2.5	14.6*** Adult BD>Child BD***; Adult HV>Child BD***
Stop signal reaction time ^b (msec)	198.6 (41.3)		210.3 (39.3)		235.3 (84.2)		218.4 (43.4)		1.2	0.04	3.0

^a Inhibit Delay=interval between onset of go and onset of stop signals.

^b See text for method of calculation.

* $p<0.05$,

**

$p<0.01$,

$p<0.001$

HV = healthy volunteers; BD = bipolar disorder

Table 3

Between group differences in brain activation

Table 3A									
Primary Contrast	Effect	Area of Activation (secondary contrast)	Side	cluster size [†]	MNI coordinates			F	p <
					x	y	z		
Stop Incorrect vs Go Correct	Interaction of Diagnosis and Age	ACC (stop incorrect vs. fixation)	R	777	4	42	6	$F_{(3,85)}=13.80$	.00
									Child HV>Child BD ^{***} ; Child HV>Adult HV ^{**} ; Adult BD>Child BD ^{**}
	ACC (stop incorrect vs. fixation)		L	869	4	42	6	$F_{(3,85)}=12.98$	.00
									Adult BD>Child BD ^{**} ; Child HV>Child BD ^{**}
									Child HV>Child BD ^{**} ; Adult BD>Child BD ^{***} ; Adult BD>Adult HV ^{**}
									Adult BD> Child BD ^{**} ; Child HV>Child BD ^{**}
Table 3B									
Primary Contrast	Effect	Area of Activation (secondary contrast)	Side	cluster size [†]	MNI coordinates			F	p
					x	y	z		
Stop Correct vs Go Correct	Main Effect of Diagnosis	NAc (stop correct vs. fixation)	R	24	16	4	-6	$F_{(1,87)}=6.58$	.01
									HV>BD ^{**}
	VPFC (stop correct vs. fixation)		L	405	-26	26	-8	$F_{(1,87)}=9.39$	.00
									HV>BD ^{**}
									HV>BD ^{**}
									HV>BD ^{**}

*
 $p < .10$,

**

 $p < .05$,

 $p < .001$.

BD = bipolar disorder, HV= healthy volunteers, ACC= anterior cingulate cortex, VPFC= ventral prefrontal cortex, NAc= nucleus accumbens. x,y, and z coordinates refer to the voxel with maximum signal intensity.

[†] determined using a significance threshold of $p < .05$ and corrected for the number of voxels in each region. Secondary contrasts were conducted in regions identified by the primary contrasts (e.g., stop incorrect vs. go correct) to be significantly different between groups