Enhanced Prefrontal Function With Pharmacotherapy on a Response Inhibition Task in Adolescent Bipolar Disorder

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Objective: The aim of the current study is to determine whether pharmacotherapy normalizes cognitive circuitry function supporting voluntary behavioral inhibition in adolescent bipolar disorder.

Method: Healthy controls and unmedicated patients with *DSM-IV* adolescent bipolar disorder in manic, mixed, or hypomanic episodes were matched on demographics and IQ (n = 13 per group; mean age = 14.4 ± 2.4 years). Functional magnetic resonance imaging studies were performed at baseline and after 14 weeks, during which time patients with adolescent bipolar disorder were treated initially with second-generation antipsychotics (SGAs) followed by lamotrigine monotherapy. The primary outcome measure was a Response Inhibition Task, which involved a planned motor response, already "on the way" to execution, that had to be voluntarily inhibited by the subjects in the trials in which a stop signal was presented. There were 6 blocks, each with a predominant rate of either "go" or "stop" trials. The study was conducted from June 2006 through July 2009.

Results: All patients showed significant improvement ($P < .001$) in both the manic and depressive symptoms from baseline. Behavioral data showed that accuracy improved over 14 weeks in patients and healthy controls. Significant time by group interaction effects ($F_{1,24} = 5.34$, $P < .03$) for the difference between stop versus go blocks showed greater increases of activation in prefrontal (left inferior and middle frontal gyri and medial frontal gyrus bilaterally) and temporal (left superior temporal gyrus and right middle temporal gyrus) regions and greater decreases in activation in right putamen and bilateral thalamus at follow-up in the adolescent bipolar disorder group than in healthy controls. Increased ventrolateral prefrontal cortex function was related to clinical treatment response.

Conclusions: Treatment with SGAs followed by lamotrigine monotherapy enhanced prefrontal and temporal lobe activity during a Response Inhibition Task demonstrating the reversal of disorder-relevant neural circuitry dysfunction in patients with adolescent bipolar disorder. Patient performance was not slowed down with this treatment regimen.

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In adolescent bipolar disorder, inattention, impulsivity, and behavioral disinhibition are prominent and persist even after achieving mood stability.[1] The frontostriatal circuitry that supports motor response inhibition has been shown to be affected in adolescent bipolar disorder.[2] Appropriate goals of treatment, therefore, are to aim for mood stabilization, reduce motor response inhibition problems, and reverse the related frontostriatal deficits in adolescent bipolar disorder. Lamotrigine is one such medication that is used to stabilize mood in adolescent bipolar disorder[3] and adult bipolar disorder[4,5] due to its glutamatergic attenuating function that is believed to have the potential to improve cognitive function related to motor response inhibition problems.[6–8]

There is preliminary evidence from 2 functional magnetic resonance imaging (fMRI) studies indicating that lamotrigine may enhance brain circuitry function in bipolar disorder.[3,9] In a study of patients with adolescent bipolar disorder performing an affective task requiring the rating of emotions in pictures, reduction in depressive symptoms was correlated with decreased right amygdala activation over an 8-week period.[3] In an adult study of euthymic bipolar patients performing an N-back working memory task, greater activation in the left medial prefrontal cortex and bilateral pregenual anterior cingulate cortex was observed after 6 weeks of treatment with lamotrigine.[9] Methodological limitations in these studies include a short treatment period and lack of demonstration of greater improvement in brain function after treatment in patients relative to matched healthy controls retested over a similar time period. This control group is essential for interpreting change over time as representing a drug treatment effect rather than a benefit from practice effects with the task or the scanning experience. Further, meta-analysis of studies of response inhibition in healthy controls has demonstrated increased activity in the right prefrontal cortex.[10]

The task of response inhibition is complex and multifactorial with attention, perceptual discrimination, and motor executive control. Response suppression involves a situation that is highly stereotyped, requiring repetitive responses with little deliberation, except when an unusual event occurs in the midst of this routine task with clear stimulus-response requirements. This effort is shown to deploy dorsal, ventral, and medial prefrontal cortex regions in healthy controls.[10–12] It was also shown that in adolescent bipolar disorder poor performance on voluntary motor response inhibition tasks is related to the high degree of impulsivity and inattention[2] with underlying frontostriatal disturbances.[2,13,14] Patients

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with adult bipolar disorder, relative to healthy controls, have also shown decreased activation in the orbitofrontal cortex during response suppression.[15]

Therefore, the primary aim of the current study is to evaluate the differences between adolescent bipolar disorder and healthy controls in the domain of neurobehavioral deficits in frontostriatal circuitry that support the ability to voluntarily suppress behavioral responses. Our aim is to see if pharmacotherapy can reverse the frontostriatal circuitry dysfunction in adolescent bipolar disorder. Our pharmacotherapy consists of second-generation antipsychotics (SGAs) for acute mania followed by lamotrigine for continued mood stabilization. We did not use SGAs for maintenance treatment due to high risk for metabolic side effects if prescribed for long-term treatment[16] and because of our interest in determining the beneficiary effects of lamotrigine for optimal symptomatic recovery and cognitive function. We designed a Response Inhibition Task to probe the neural circuitry supporting "stopping process and motor inhibition." We administered this task at baseline and after 14 weeks to healthy controls and to adolescent patients with bipolar disorder, who were acutely ill and unmedicated at baseline and at 14 weeks after mood stabilization with pharmacotherapy.

The concept underlying this task is to compare the process of motor response inhibition to motor execution in adolescent patients with bipolar disorder compared to healthy controls, rather than examining response inhibition in the context of a prepotent tendency to respond.[17] This is an important first step in clarifying the basic neural circuits for motor inhibition versus execution in these patients. To this end, we contrasted blocks of trials that mainly required motor inhibition (stop trials) to blocks of trials that mainly required motor action (go trials). We predicted that there would be differences in prefrontal activation between the adolescent bipolar disorder subjects and healthy controls at baseline. We hypothesized that lamotrigine, by virtue of pharmacologic effects on prefrontal and striatal systems, would reverse the dysfunction in these regions that are believed to contribute to behavioral control deficits in adolescent bipolar disorder.

METHOD

This study represents a prospective outpatient open-label trial of SGAs for acute mania/hypomania followed by lamotrigine monotherapy for 13 adolescents with bipolar disorder type I (n = 8) and II (n = 5). The fMRI Response Inhibition Task was administered at baseline and at the end of 14 weeks, and the blood oxygenation level–dependent (BOLD) signal activation based on this paradigm was used as the primary outcome. The total duration of the trial was 14 weeks. All patients received an initial 4 weeks of prospective treatment with SGAs, which were discontinued in weeks 4–6. During the 14 weeks of the trial, lamotrigine was prospectively titrated up alongside SGAs over the first 8 weeks, followed by 6 weeks of full-dose treatment with lamotrigine alone. The SGAs served the role of rescue medication for acute symptoms of mania while lamotrigine was still being titrated up to full dose. Healthy controls and patients with adolescent bipolar disorder who were matched demographically and by IQ (n = 13 per group; mean age = 14.4 ± 2.4 years) had fMRI studies performed at baseline and again at 14 weeks. Healthy controls did not receive treatment but were retested to control for potential changes at retest due to familiarity with the behavioral paradigm or magnetic resonance imaging (MRI) scanning procedure. The study was conducted from June 2006 through July 2009. It was approved by the University of Illinois at Chicago Institutional Review Board. Parents gave written consent and children gave assent to participate in this trial.

Inclusion criteria for patients with adolescent bipolar disorder were a *DSM-IV*[18] diagnosis of bipolar disorder type, mixed or manic episode or hypomanic episode, 10 to 18 years of age, and a baseline score of > 12 on the Young Mania Rating Scale (YMRS).[19] Patients were already medication free, not requiring a washout at study entry, or were sufficiently unstable on prior medications to justify discontinuation of an ineffective treatment prior to beginning treatment with lamotrigine with the consent of parents and assent of patients. The washout period consisted of tapering previous medications over 1 week prior to study entry except for those who received aripiprazole who required a 4-week washout period. All patients were medication free for at least 4–7 days prior to scanning. None of the patients were taking fluoxetine, which would have required a longer washout period.

Inclusion criteria for healthy controls were subjects who did not meet *DSM-IV* criteria for an Axis I disorder, did not have a family history of affective illness, were 10 to 18 years of age, and had a baseline score of ≤ 12 on the YMRS. The adolescent bipolar disorder group and the healthy controls group did not differ significantly in age (14.4 ± 2.4 years), gender, race, parental socioeconomic status, IQ, or word-reading ability (Table 1).

Exclusion criteria for all subjects included active substance abuse; comorbid psychiatric diagnosis requiring pharmacotherapy including attention-deficit/hyperactivity disorder; serious medical problems; previous exposure to lamotrigine; IQ < 80; and contraindications to MRI studies including metallic implants, retractors or braces, and claustrophobia. IQ was estimated using the Wechsler Abbreviated Scale of Intelligence.[22]

Assessment Procedures

A board-certified child psychiatrist (M.N.P.) completed the Washington University Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS)[23] with all subjects. Subsequently, all available clinical information was reviewed to make a consensus clinical diagnosis. Live diagnostic interviews of 10 cases were independently coded by 2 researchers to establish interrater diagnostic reliability, which by Cohen κ was 0.94.[24] The primary clinical treatment

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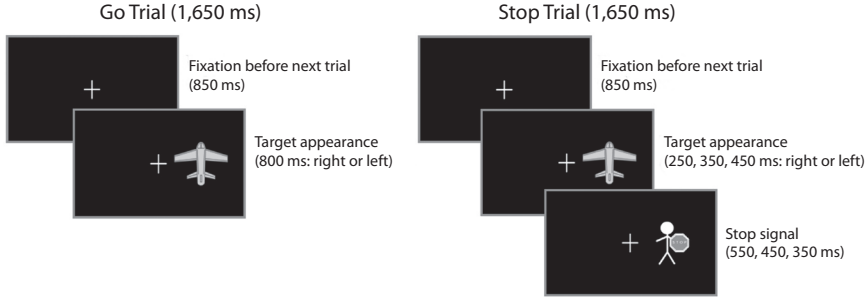
Table 1. Demographic Variables and Clinical Characteristics

Variable	Healthy Controls	Adolescent Bipolar Disorder	*P* Value
Age, mean (SD), y	14.4 (2.8)	14.4 (2.2)	.97
Sex, n (%)			.99
Adolescent boys	4 (30)	10 (77)	
Adolescent girls	9 (70)	3 (23)	
Race, n (%)			.71
White	7 (54)	8 (62)	
Other	6 (66)	5 (38)	
WASI-IQ,[a] mean (SD)	109.7 (4.8)	106.2 (6.8)	.09
WRAT-3, reading subtest[20] score, mean (SD)	45 (3.7)	42.6 (5.5)	.10
Socioeconomic status			
Four-Factor Index of Social Position[21] score, mean (SD)	2.5 (0.52)	2 (1.0)	.27
YMRS score, mean (SD)			
Pre YMRS	1.2 (1.6)	17.1 (6.4)	.00002
Post YMRS	1.5 (2.1)	4.77 (6.9)	.11
CDRS-R score, mean (SD)			
Pre CDRS-R	19.5 (2.4)	52.12 (11.5)	.00001
Post CDRS-R	19.08 (1.6)	25.4 (6.6)	.003

[a]Matrix reasoning and vocabulary subtests.
Abbreviations: CDRS-R = Child Depression Rating Scale-Revised; NS = not significant; WASI IQ = Wechsler Abbreviated Scale of Intelligence, Intelligence Quotient; WRAT-3 = Wide Range Achievement Test-Third Edition; YMRS = Young Mania Rating Scale.

Figure 1. Stop and Go Trials in Response Inhibition Task[a]



[a]Appearance of an airplane must be followed by immediate response by the subject in a go trial, and the subject must stop from responding when the airplane is replaced by a man with the stop sign in a stop trial.

efficacy measures were the YMRS and the Child Depression Rating Scale-Revised (CDRS-R).[25]

SGAs During the First 4 Weeks

Manic and hypomanic symptoms were treated in the acute phase of illness by using SGAs given that we recruited acutely ill unmedicated patients to this study and it takes at least 8 weeks to titrate up the dose of lamotrigine. The order of preference for SGAs given for the first 4 weeks of acute illness was risperidone, aripiprazole, quetiapine, and ziprasidone. The order was modified according to reported previous ill effects of any SGA. For example, if a patient did not respond to risperidone and was agitated while taking aripiprazole, they received quetiapine. The SGA was slowly withdrawn over 2–4 weeks as tolerated (ie, between the fourth to eighth week period). An overall guideline for withdrawal of SGAs was followed, with reduction at 0.25 mg of risperidone, 2.5–5 mg of aripiprazole, 25–50 mg of quetiapine, or 20–40 mg of ziprasidone every other day until the patients were off of the SGA. Benztropine was allowed on as-needed basis for extrapyramidal symptoms if patients were taking SGAs, but only during the first 4-week period.

Lamotrigine Dosing Over 14 Weeks

Lamotrigine starting dose was 12.5 mg during the first week. It was increased by 12.5 mg per week during the first 4 weeks, by 25 mg per week during the next 2 weeks, and was titrated to 200 mg per week by 8 weeks. All patients remained on this fixed dose of 200 mg for the last 6 weeks of treatment prior to being scanned at week 14.

Response Inhibition Task

The fMRI behavioral paradigm was a block design task in which a motor response, already "on the way" from planning to execution, had to be voluntarily inhibited when a cue instructing subjects to stop an impending response was presented on some trials (Figure 1). Prior to the fMRI scanning session, subjects were trained to perform the task in a mock scanner. At the beginning of each trial a fixation cross appeared for 850 ms. On go trials, a target stimulus (a green airplane) was presented for 800 ms with equal probability of being to either the left or right of a center crosshair. Subjects pressed a button with their right hand if the green plane appeared on the right side of the screen or with their left hand if the plane appeared on the left. On stop trials, a stop signal (a man holding a stop signal in his hands) replaced the airplane with equal probability 250, 350, or 450 ms after the airplane appeared, and subjects had to inhibit their response. Button press response latencies in paradigms of this nature are approximately 650 ms in pediatric studies, which led us to choose the 250–450 ms range of stop signal delays.[26] Varying the stop signal delays also ensured that subjects paid attention on each trial and did not habituate or learn fixed-trial conditions. The task lasted 6.11 minutes and consisted of 6 experimental blocks, 3 of which were go blocks and 3 of which were stop blocks, and there were 7 fixation blocks of 10-sec fixation each. Each experimental block had 30 trials and lasted 49.5 sec. The experimental and fixation blocks were pseudorandomly interspersed as follows: fixation, go, fixation, stop, fixation, stop, fixation, go, fixation, stop, fixation, go, fixation. In go blocks, 70% of the trials were go trials, and 30% were stop trials. Conversely, in stop blocks, 70% of the trials were stop trials and 30% were go trials. We adopted this 70/30 proportion of trials in go and stop blocks

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so that subjects would not habituate to fixed-trial presentation within a certain block. Within each block, go and stop trials were pseudorandomly presented.

MRI Protocol

Magnetic resonance imaging studies were performed using a 3.0 Tesla whole-body scanner (Signa, General Electric Medical System, Milwaukee, Wisconsin). Functional images were acquired using echo-planar imaging, which is sensitive to regional alterations in blood flow via BOLD contrast effects. Twenty-five axial slices were acquired. Parameters for functional scans were TE = 25 ms; flip angle = 90°; field of view = 20 × 20 cm^2; acquisition matrix = 64 × 64; TR = 2.5 s; 5-mm slice thickness with 1-mm gap. Anatomic images were acquired in the axial plane (3-dimensional spoiled gradient recalled [SPGR], 1.5-mm thick contiguous axial slices) to coregister and normalize the functional data.

Image Processing and Data Analysis

We conducted whole-brain analyses. For functional imaging data, Functional Imaging Analysis Software-Computational Olio[27] was used to implement 3D motion estimation and correction and to remove slow signal drift. Individual volumes were excluded from analysis if, relative to median head position, head displacement was greater than 1.5 mm or head rotation was greater than 0.5 degrees. The number of volumes retained after discarding those with motion artifact did not significantly differ across groups. To evaluate subject-wise activation effects for statistical analyses, voxel-wise effect size (*r*) maps were calculated for each subject by contrasting activation for stop and go blocks, go and fixation blocks, and stop and fixation blocks. For the purposes of this article, our analyses focused on the stop versus go contrast, to examine the impact of stop versus go signal processing. A Fisher *z* transform was applied to the *r* values so they would more closely approximate a normal distribution (*zr*).[28] Subjects' *zr* maps (effect size) and SPGR anatomic images were warped into Talairach space using Analysis of Functional NeuroImages' (AFNIs') automated procedure.[29] Functional maps were resampled to an isotropic 3 × 3 × 3 mm grid to provide a voxel dimension similar to that of the in-plane resolution of the acquired data prior to statistical analysis.

The primary analysis of the fMRI data was a whole-brain, voxel-wise analysis of variance (ANOVA) in AFNI, with the between-subjects factor of group (adolescent bipolar disorder, healthy controls) and the within-subject factor of time (baseline, 14 weeks) carried out voxel-wise on the *zr* maps representing the difference in activation between the stop and go conditions. Significant clusters of activation were identified using a contiguity threshold (minimum cluster volume of 270 mm^3) that maintained an experiment-wise Type I error rate of $P < .025$, based on AFNIs' AlphaSim Monte Carlo simulations. A significant group by time interaction ($F_{1,24} = 5.34$, $P < .03$) was followed by step-down comparisons (see Tables 3 and 4) to clarify findings.

Table 2. Response Time and Percentage Accuracy Measures for Go and Stop Trials at Baseline and Follow-Up in the Adolescent Bipolar Disorder and Healthy Controls Groups

Variable	Adolescent Bipolar Disorder	Healthy Controls	*P* Value
Response time, median (SD), ms[a]			
Go trials at baseline	530 (114.5)	567 (112.7)	.36
Go trials at follow-up	570 (85.3)	617 (69.3)	.14
Trial average	581 (118.9)	614 (100.8)	.20
Accuracy, % (SD)[b]			
Go trials at baseline	88 (8)	92 (8)	.24
Go trials at follow-up	86 (10)	88 (12)	.63
Stop trials at baseline	72 (16)	82 (13)	.12
Stop trials at follow-up	76 (17)	87 (8)	.06
Trial average	81 (12.8)	87 (10.3)	.01

[a]For go trials response time, the interaction of group by testing time was not significant ($P = .77$).
[b]The interaction of group by trial type by testing time was not significant ($P = .70$).

RESULTS

Clinical and demographic data are summarized in Table 1. Symptom control on mania (YMRS score < 12) was achieved in 92% (n = 12) of the patients. At week 14, the patients did not differ significantly from healthy controls in YMRS scores, though they still differed on CDRS scores (Table 1). There were 3 subjects (23%) with comorbid diagnosis of generalized anxiety disorder in the adolescent bipolar disorder group. Within the adolescent bipolar disorder group, the daily mean ± SD doses of SGAs received at the end point of first 4 weeks of acute symptom stabilization were risperidone 1.2 ± 0.35 mg (n = 5), aripiprazole 13.5 ± 2 mg (n = 5), and quetiapine 385 ± 75 mg (n = 3). Benztropine was required in 4 cases with a mean dose of 1.2 ± 0.6 mg per day at the end of first 4 weeks of SGA therapy, and it was tapered off subsequently, along with the SGAs. None of the subjects were on SGAs or any other psychotropic medications during the 6-week trial of fixed-dose lamotrigine 200 mg.

Treatment Effects Using Response Inhibition Task

Behavioral data. Response time and accuracy data are summarized in Table 2. Separate repeated-measures ANOVAs were conducted on response accuracy and response time data for the Response Inhibition Task. For response accuracy, group (adolescent bipolar disorder, healthy controls) was the between-subjects factor and testing time (baseline and follow-up), trial type (go trials in go blocks and stop trials in stop blocks), and trial block (first, second, and third) were within-subjects factors. Our ANOVA on response time had the same factors, except that we included only mean response time for correct go trials (because correct stop trials had no key press).

Accuracy for go and stop trials. The main effect of group was significant ($F_{1,24} = 7.01$, $P = .01$) in that, overall, on stop trials, more accurate performance was yielded by the healthy controls group (87%) than the adolescent bipolar disorder group (81%). Nevertheless, there was no significant interaction of group by testing time ($P = .91$), or group by testing

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time by trial type ($P = .70$), indicating that there were no group differences in accuracy performance from baseline to follow-up. The significant interaction of testing time by trial type ($F_{1,24} = 6.67$, $P = .02$) revealed that, overall, both groups had improved performance accuracy on stop trials at follow-up (82%) relative to baseline (77%) ($F_{1,24} = 4.54$, $P = .04$).

Response time for go trials. There was a significant effect of testing time in that response time was faster at baseline than follow-up across groups (548 ms vs 593 ms) ($F_{1,24} = 8.32$, $P = .008$). The main effect of block was also significant ($F_{1,48} = 9.20$, $P = .0004$), but there was no main effect of group ($P = .20$) and the interaction of group by testing time was not significant ($P = .77$).

fMRI data. Group differences at baseline and follow-up.

- *Adolescent bipolar disorder versus healthy controls at baseline*. For the stop- versus go-condition comparison at baseline, the adolescent bipolar disorder group showed greater activation than the healthy controls group in bilateral motor cingulate, right ventral premotor cortex, and striatum but less activation in right and left prefrontal cortex as specified in Table 3.
- *Adolescent bipolar disorder versus healthy controls at follow-up*. The adolescent bipolar disorder group exhibited greater activation than the healthy controls group in left motor cortex (M1), but less activation in bilateral thalamus and putamen. No group differences were found in prefrontal cortex activation at follow-up.
- *Baseline vs follow-up in adolescent bipolar disorder and healthy controls*. Within the adolescent bipolar disorder group, significantly greater activation was found at follow-up in bilateral medial frontal gyri, pregenual anterior cingulate cortex, posterior cingulate and ventral striatum, and right subgenual anterior cingulate cortex and left superior temporal gyrus. There were no regions of greater activation at baseline relative to follow-up (Figure 2, panel I: pictures A, B, and C). The healthy controls group exhibited greater activation at baseline compared to follow-up in left middle frontal gyrus/dorsolateral prefrontal cortex and bilateral medial frontal gyri, and greater activation at follow-up in bilateral motor cingulate gyri and dorsal striatum. These results are presented in eTable 1.

Degree of change in activation over the duration of trial period in adolescent bipolar disorder versus healthy controls group. The adolescent bipolar disorder group exhibited greater increases in activation than the healthy controls group from baseline to follow-up in left prefrontal cortex (medial, inferior, and middle frontal gyri) and right prefrontal cortex (medial frontal gyri) (Figure 2, panel II: picture D), as well as in temporal cortex (left superior temporal and right middle temporal gyri) (Table 4). The healthy controls showed a larger increase in activation at follow-up than the adolescent bipolar disorder group in right putamen (Figure 2, panel II: picture E) and bilateral thalamus.

Table 3. Significant Group Differences at Baseline and at Follow-Up[a]

Brain Region	Talairach Coordinates for Peak Activation	Brodmann Area	Volume (mm^3)	*t* Value for Peak Activation
Baseline				
Adolescent bipolar disorder > healthy controls				
R motor cingulate	14, −17, 30	31	729	4.37
L motor cingulate	−12, −10, 29	31	675	3.87
R ventral premotor cortex	50, −17, 18	43	513	2.85
L striatum	−17, 2, 12	9	1,107	4.14
Healthy controls > adolescent bipolar disorder				
R medial frontal gyrus	17, 68, 17	11	1,512	2.33
L medial frontal gyrus	−11, 68, 18	11	405	3.28
R middle frontal gyrus	8, 53, 18	9	1,080	2.64
L inferior frontal gyrus	−53, 26, 12	46	648	3.42
Follow-up				
Adolescent bipolar disorder > healthy controls				
L primary motor cortex (M1)	−7, −34, 47	5,7	324	2.89
Healthy controls > adolescent bipolar disorder				
R putamen	26, −22, 1	…	513	2.67
L putamen	−23, −20, −4	…	297	2.76
R thalamus	26, −23, 9	…	459	3.02
L thalamus	−2, −17, 6	…	324	3.37

[a]This table shows Talairach coordinates and *t* values for peak activation representing significant group differences in activation at baseline and follow-up for the Response Inhibition Task (clusters with $P < .025$ using a contiguity threshold).
Abbreviations: L = left, R = right.

Correlation between symptom response and brain activation. We performed hypothesis-driven Pearson correlation analyses (2-tailed) to examine the relationship between improvement in YMRS and Child Depression Rating Scale-Revised scores over the 14-week trial and change in activation from baseline to follow-up in selected regions of interest (medial, inferior, middle frontal gyri, cingulate cortex [subgenual, pregenual, dorsal and posterior cingulate], striatum [caudate and putamen], and temporal cortex [middle and superior temporal gyri]) in adolescent bipolar disorder. After correcting for multiple comparisons, we found positive correlation between the degree of improvement in YMRS scores and increase in activation from baseline to follow-up in right ($r = 0.57$, $P < .01$, corrected) and left ($r = 0.54$, $P < .01$, corrected) inferior frontal gyri/ventrolateral prefrontal cortex (VLPFC). No other significant correlations were found.

DISCUSSION

This study is the first to examine treatment effects on brain circuitry function underlying response inhibition in manic, mixed, and hypomanic patients with adolescent bipolar disorder. Our aim was to study the treatment effects on the ability to inhibit motor response in contrast to executive

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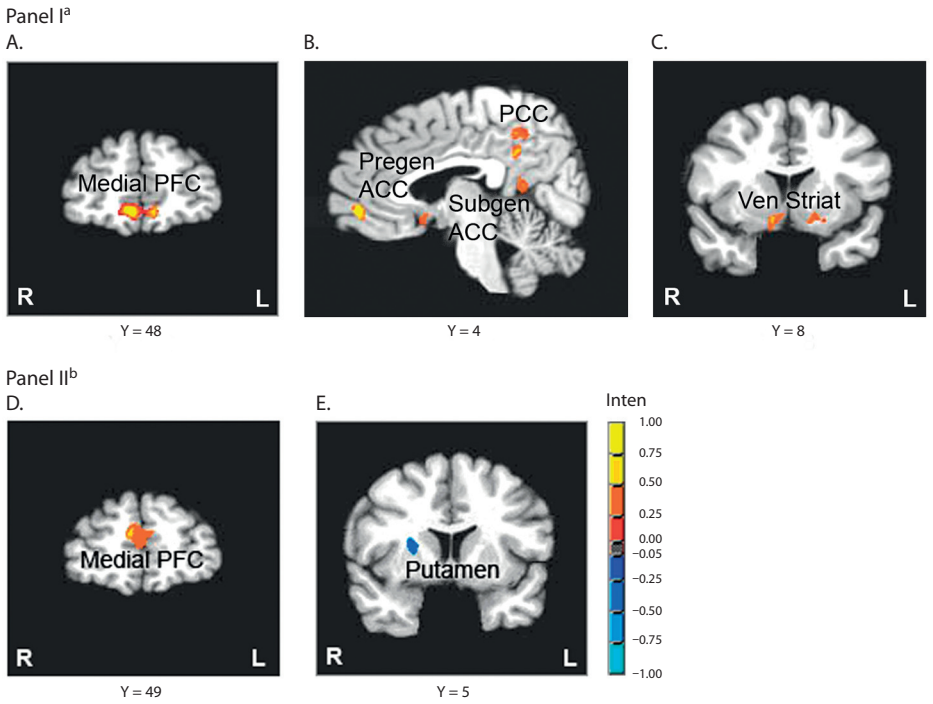
Figure 2. Lamotrigine Treatment Effects



[a]Panel I: pictures A, B, and C show posttreatment activation relative to pretreatment for stop vs go condition in patients with adolescent bipolar disorder. Red indicates increased activation posttreatment relative to pretreatment, and blue indicates increased activation pretreatment relative to posttreatment (not shown here).
[b]Panel II: pictures D and E show lamotrigine treatment effects over time on brain function in patients with adolescent bipolar disorder vs healthy controls. Red indicates increased activation in patients with adolescent bipolar disorder relative to healthy controls, and blue indicates increased activation in healthy controls relative to patients with adolescent bipolar disorder for stop vs go condition over the 14-week period.
Abbreviations: L = left, PCC = posterior cingulate cortex, PFC = prefrontal cortex, Pregen ACC = pregenual anterior cingulate cortex, R = right, Subgen ACC = subgenual anterior cingulated cortex, Ven Striat = ventral striatum.

Table 4. Regions With Significantly Different Change in Activation From Baseline to Follow-Up Testing in Patients With Adolescent Bipolar Disorder Relative to the Healthy Controls Group[a]

Brain Region	Talairach Coordinates for Peak Activation	Brodmann Area	Volume (mm^3)	*t* Value for Peak Activation
Adolescent bipolar disorder > healthy controls				
L medial frontal gyrus	−10, 65, 14	11	594	3.24
L inferior frontal gyrus	−31, 2, −10	45	270	2.46
L middle frontal gyrus	−43, 47, 8	46	270	3.10
R medial frontal gyrus	5, 50, 17	11	297	3.03
L superior temporal gyrus	−43, 20, −25	22	567	2.77
R middle temporal gyrus	47, −70, 26	39	432	4.28
Healthy controls > adolescent bipolar disorder				
R putamen	20, 5, 6	…	621	2.56
R thalamus	23, −19, 11	…	459	3.74
L thalamus	−19, −22, −1	…	270	2.48

[a]This table shows Talairach coordinates and *t* values for peak activation in significant clusters ($P < .025$ with contiguity threshold) representing group differences in change from baseline to follow-up.
Abbreviations: L = left, R = right.

response function, instead of inhibiting a prepotent tendency to respond. The block design paradigm of Response Inhibition Task is utilized to measure the net behavioral inhibition and executive control by contrasting BOLD signal activity during stop versus go blocks in adolescent bipolar disorder patients relative to healthy controls over a 14-week time period. Our aim was to understand the ability of patients with adolescent bipolar disorder to predominantly stop the context-inappropriate behavior on treatment, rather than just the prepotent response generated by an occasional stop cue. The central finding is increased cortical activation in prefrontal and temporal regions after lamotrigine monotherapy in adolescent bipolar disorder relative to healthy controls during performance of a Response Inhibition Task. The absence of significant group differences between adolescent bipolar disorder and healthy controls groups in the 14-week data in prefrontal and temporal cortex suggests that these changes represent a normalization of function in these

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regions with lamotrigine therapy in patients. Further, within the adolescent bipolar disorder group, increased VLPFC activation with lamotrigine treatment is significantly correlated with reduction in manic and hypomanic symptoms. This association highlights the clinical significance of our findings, as VLPFC is believed to be a higher cortical center associated with impaired affect regulation and cognitive-affective integration in pediatric bipolar disorder.[2,30,31] With regard to behavioral data, both groups showed slowed response time and improved performance accuracy at follow-up relative to baseline, where there was no differential change in time by group. This suggests practice effects with the paradigms in both the groups, but no differential change in task performance that could account for the improvement in brain function in patients. However, it is important to note that patients were not slowed down by this medication regimen, and treatment did not lead to deterioration.

Understanding Circuitry Changes Over 14 Weeks of Lamotrigine Therapy in Adolescent Bipolar Disorder

Reduced frontal function at baseline in patients with adolescent bipolar disorder. Brain function abnormality in untreated patients with adolescent bipolar disorder relative to healthy controls suggests pathophysiology associated with the illness and therefore constitutes a target of treatment. In patients with adolescent bipolar disorder at baseline, relative to healthy controls, greater activation was observed during stop trials in the "dorsal motor circuit" described by Alexander et al[32] including motor cingulate and striatum. Greater activation in this system is consistent with reduced modulation by stop signal commands in motor circuitry.[33] In parallel with this finding, patients with adolescent bipolar disorder showed a reduced engagement of prefrontal cortex during stop trials that provides executive control to support voluntary motor response inhibition.[34–36] This pattern of findings suggests that behavioral disinhibition seen in patients with adolescent bipolar disorder may in part be explained by dysregulation of motor circuitry secondary to reduced top-down control from prefrontal systems.

Our pretreatment findings are similar to those reported by Blumberg et al,[13] who used a block design Stroop paradigm to probe executive control and response inhibition. They showed increased striatal and thalamic activation and decreased prefrontal activation in adolescent bipolar disorder. A study of adolescent bipolar disorder by Leibenluft et al[2] employed an event-related stop signal task that showed decreased VLPFC and striatal activation in patients relative to healthy controls during failed inhibition trials. Our findings are consistent with these results in demonstrating abnormal VLPFC function in PBD and underscore the significance of treatment-related improvements in VLPFC. However, increased striatal activation at baseline, shown in our study, that decreases with treatment relative to healthy controls during motor response inhibition is not comparable to the decreased striatal activation in failed trials reported by Leibenluft et al.[2] These disparities need to be resolved in future studies comparing effects in successfully and unsuccessfully performed stop trials across a range of stop signal delays, in addition to comparing the ability to inhibit with varying degrees of prepotent response. While there are no directly comparable fMRI treatment studies similar to our current study, our results are similar to that in euthymic adult patients with bipolar disorder treated with lamotrigine showing an increase in left prefrontal activation while performing an N-back working memory task.[9] It is possible, however, that these changes of decreased BOLD signal in frontotemporal regions may be specific to manic or hypomanic symptoms, and normalization may be due to stabilization of mood. Conversely, the changes in BOLD signal in patient group may not be specific to SGA and/or lamotrigine regimen.

Development of automaticity in healthy controls. There was a greater increase in putamen and thalamic activity over time in healthy controls relative to patients during the Response Inhibition Task. Within-group change analyses suggest that this group difference is primarily due to increased activation in striatum in controls at follow-up. This might reflect differential practice effects[37] in healthy controls, with more automatic task performance in healthy controls supported by striatal function based on experience and skills gained from prior task performance.

The positive correlation between maintenance of symptom control and increased activation in bilateral VLPFC from baseline to follow-up suggests that 1 mechanism of action of pharmacologic treatment may involve normalization of function in VLPFC. In cross-sectional studies, we previously showed reduced VLPFC activation in patients with adolescent bipolar disorder relative to healthy controls while they viewed angry faces compared to neutral faces[31] and also during cognitive processing under emotional challenge.[30] As mentioned above, Leibenluft et al[2] previously reported reduced VLPFC activation during a stop signal task condition in patients with adolescent bipolar disorder. The parallel changes in adolescent bipolar disorder symptoms and VLPFC activation during a cognitive paradigm indicate the critical role of VLPFC in relation to both emotional control and response inhibition deficits in adolescent bipolar disorder. Thus, enhanced function in VLPFC observed in the present study might facilitate positive clinical outcomes via modulation of downstream affective and motor system function. Given the glutamatergic projections that extend from VLPFC to amygdala, medial prefrontal cortex, and striatum,[38] lamotrigine may exert effects on this circuitry to enhance behavioral self-control and affect modulation. It is important to note here that the study was specifically designed to allow SGAs for acute-phase treatment and did not entirely rely on lamotrigine, although patients received lamotrigine as monotherapy in the 6-week stabilization phase. We do not suggest that lamotrigine is effective in acute mania as monotherapy especially given the long titration period. It was shown to be effective in maintenance in adult bipolar disorder[4,5] as opposed to negative trials in acute mania.[39] In

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line with the experience in adult studies, we utilized it only for symptom control after initial mood stabilization.

Limitations of the study are using a block design as opposed to an event-related design, which would enable us to look at correct versus incorrect trials, and not being able to implement a placebo-controlled trial. Given the acutely vulnerable and seriously ill patients, we considered it unethical to use placebo. Although the healthy controls group does not replace the value of a placebo-controlled group of patients, it accounts at least partially for practice effects. This is a preliminary study, leading to our future studies that are rapid event–related fMRI designs, which will parametrically vary and contrast the degrees of response inhibition across trials. Also, though not a limitation, it is important to note that the findings in this study are relevant to the treatment of manic, hypomanic, or mixed episodes of bipolar illness. Our patient findings may differ from those subjects in depressive episode or euthymic state receiving medications other than lamotrigine.

CONCLUSION

This "proof of concept" study uses a block design fMRI paradigm to examine the pharmacologic effects of initial SGAs followed by lamotrigine maintenance treatment on brain function in adolescent bipolar disorder. Strengths of this study include studying unmedicated patients at baseline; prospective use of initial SGAs followed by lamotrigine monotherapy for 6 weeks prior to scanning; use of a healthy controls group to account, at least in part, for practice effects in fMRI data; and the whole brain analyses adapting a neuroscience systems approach to study treatment effects on frontostriatal systems and their relation to clinical outcome. The study findings suggest that improved VLPFC function may be a promising treatment target, and thus provide a biomarker of clinical response in adolescent bipolar disorder to pharmacotherapy that may serve to normalize frontostriatal and frontolimbic systems to improve behavioral response inhibition and affect modulation, respectively.

Drug names: aripiprazole (Abilify), lamotrigine (Lamictal and others), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

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Potential conflicts of interest: **Dr Pavuluri** is an employee of the University of Illinois; has received grant/research support for work unrelated to this article from the National Institute of Mental Health, National Institute of Child Health and Human Development, Dana Foundation, American Foundation of Suicide Prevention, Abbott (study medication), and Johnson & Johnson (study medication); and has been a speaker for Bristol-Myers Squibb. **Dr Sweeney** is an employee of the University of Illinois and has received grant/research support for work unrelated to this article from National Institutes of Health, GlaxoSmithKline, and Johnson & Johnson. **Dr Passarotti** and **Ms Harral** are employees of the University of Illinois.

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Supplementary material: Available at PSYCHIATRIST.COM.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.

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Supplementary Material

Article Title: Enhanced Prefrontal Function With Pharmacotherapy on a Response Inhibition Task in Adolescent Bipolar Disorder

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List of Supplementary Material for the article

1. eTable 1 Within-Group Differences at Baseline vs. Follow-up

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eTable 1. Within-Group Differences at Baseline vs. Follow-up

Brain region	Talairach coordinates for peak activation	BA Area	*Volume (mm3)*	t value for peak activation
ABD: Baseline > Follow-up				
None				
ABD: Follow-up > Baseline				
L Medial Frontal Gyrus	-6, 49, -4	11	1080	3.14
R Medial Frontal Gyrus	11, 50, -4	11	1647	3
L Pregenual ACC	-8, 41, -1	32	270	2.92
R Pregenual ACC	2, 51, -2	32	270	4.35
R Subgenual ACC	6, 10, -9	25	540	4.1
R Posterior Cingulate Cortex	5, -50, 12	29	540	3.82
L Posterior Cingulate Cortex	-5, -59, 18	30	459	3.17
L Superior Temporal Gyrus	-58, -28, 17	22	405	3.9
R Ventral Striatum	11, 8, -10	-	351	3.14
L Ventral Striatum	-16, 6, -10	-	351	3.04
HC: Baseline > Follow-up				
L Middle Frontal Gyrus	-44, 47, 6	46	1323	4.28
R Medial Frontal Gyrus	23, 62, 3	11	621	3.49
L Medial Frontal Gyrus	-2, 29, 51	11	621	3.3
HC: Follow-up > Baseline				
R Motor Cingulate Cortex	14, -2, 45	24	297	2.92
L Motor Cingulate Cortex	-11, -8, 45	24	324	2.79
R Putamen	26, -20, 9	-	486	3.26
L Putamen	-23, -11, 12	-	3078	4.7
R Caudate	11, 14, 9	-	594	2.93
L Caudate	-13, 14, 6	-	540	4.05

Table shows Talairach coordinates and t values for peak activation in significant clusters ($p<0.025$ with contiguity threshold) representing, for each group, the difference in activation between baseline and follow-up; HC: healthy controls; ABD: Adolescent bipolar disorder; BA: Brodmann's Area; L: Left; R: Right; ACC=anterior cingulate cortex.

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