The Effects of Ziprasidone on Prefrontal and Amygdalar Activation in Manic Youth with Bipolar Disorder

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ABSTRACT

Background: Prior research has found that manic adolescents with bipolar disorder exhibit neuro-functional changes in the amygdala and prefrontal cortex following treatment with some pharmacological agents. We examined the neurofunctional effects of ziprasidone in manic adolescents.

Method: Manic adolescents with bipolar disorder (n=23) participated in a placebo-controlled study of ziprasidone and underwent a functional magnetic resonance imaging scanning session while performing a task of sustained attention at baseline, prior to treatment as well as on days 7 and 28 (or early termination) of treatment. A comparison group of healthy adolescents (n=10) participated in a single scanning session. Region of interest analyses were performed to assess activation changes associated with treatment in Brodmann Areas (BA) 10, 11 and 47 and in the amygdala.

Results: Compared with placebo, treatment with ziprasidone was associated with greater increases over time in right BA 11 and 47 activation. These effects were not associated with differences in symptom improvement between the treatment groups. Patients who subsequently responded to ziprasidone showed significantly greater deactivation in the right Brodmann area 47 at baseline than those who did not respond to ziprasidone. Similarly, among the bipolar adolescents who were treated with ziprasidone, baseline activation in right BA 47 was negatively correlated with improvement in Young Mania Rating Scale (YMRS) score.

Limitations: The small sample size limits the ability to detect significant group differences in other regions of interest. Healthy comparison subjects were scanned only at a single timepoint, which limits the interpretation of the results. Ziprasidone is not currently approved by the United States Food and Drug Administration for the treatment of adolescents with mania, and, therefore, the clinical relevance of these results is limited.

Conclusions: The increases in right BA 11 and 47 activation observed during sustained attention tasks following ziprasidone treatment and the association identified between lower baseline BA 47 activation and ziprasidone treatment response suggests that ziprasidone may correct prefrontal dysfunction in manic adolescents with bipolar disorder.

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INTRODUCTION

Bipolar disorder is a serious psychiatric disorder that often presents during adolescence (1). Several investigators hypothesize that alterations in ventral prefrontal and amygdala structure and function underlie the symptoms of bipolar disorder (2, 3). Indeed, structural imaging studies of youth with bipolar disorder consistently report decreased amygdala volumes relative to healthy subjects (4-8). Moreover, findings from functional imaging studies identify increased amygdala activation in children and adolescents with bipolar disorder during cognitive and emotional tasks (9-13). In addition to amygdala abnormalities, several studies identify decreased orbitofrontal cortex gray matter (Brodman areas 11/47) in children and adolescents with bipolar disorder (14, 15). Furthermore, findings from functional MRI studies of adolescents with bipolar disorder indicate ventral prefrontal dysfunction during performance of both emotional and cognitive tasks. Together, these studies suggest that prefrontal and amygdala abnormalities are involved in the neuropathology of bipolar disorder.

Pharmacological intervention is the primary treatment for children and adolescents with bipolar disorder. In recent years, second generation antipsychotics (SGAs) have increasingly been used as first-line treatments for mania in adolescents (16). However, the specific mechanisms of action of SGAs that lead to the reduction of manic symptoms remain unknown. Neuroimaging studies examining functional changes associated with pharmacological treatment and response may help to identify these mechanisms. However, to date, there have been few reports prospectively examining neurofunctional changes associated with pharmacological interventions in youth with bipolar disorder (13, 17-20). A majority of these studies focus on the neurofunctional effects of the mood stabilizer lamotrigine (10, 13, 18, 20), although in some of these reports manic patients were initially stabilized with SGAs. Several studies report decreases in amygdala activation following treatment with lamotrigine (14, 20), which is correlated with symptom reduction (14). However, even after treatment, youth with bipolar disorder continue to demonstrate amygdala overactivation relative to healthy subjects (20). In contrast, these studies reported baseline underactivation and treatment related increases in ventral prefrontal activation of manic bipolar youth who were treated with lamotrigine (18, 20). To our knowledge, there is only one report examining the neurofunctional effects of monotherapy with an SGA in children and adolescents (19). In this study, bipolar youth were randomized to monotherapy with either risperidone or divalproex. In contrast to the results seen with lamotrigine, as well as those observed in the divalproex treated group, risperidone was associated with decreased activation in several areas of prefrontal cortex, including dorsolateral, ventrolateral and medial regions. Taken together, these results suggest that specific pharmacological treatments may be associated with distinct patterns of prefrontal activation changes. However, prior studies have not included a placebo control group, making it difficult to distinguish between medication effects and mood state changes.

Ziprasidone is a SGA that is approved by the United States Food and Drug Administration (FDA) for the treatment of manic or mixed episodes in adults with bipolar disorder. Preliminary research supports its safety and efficacy in children and adolescents with bipolar disorder (21, 22). When compared to other SGAs, ziprasidone may have a more benign metabolic side-effect profile (21-23) and, therefore, may represent an important treatment option for youth with manic or mixed episodes associated with bipolar disorder.

With these considerations in mind, we used functional magnetic resonance imaging (fMRI) during a task of sustained attention to examine the neurofunctional correlates of treatment and response in a placebo-controlled study of ziprasidone for mania in adolescents with bipolar disorder. Prior research has shown that patients with bipolar disorder exhibit deficits in sustained attention (24, 25) as well as abnormal activation in emotional networks during the performance of purely attentional tasks (12, 26). This abnormal functional pattern and the observed deficits in attention may be due to a primary abnormality of limbic networks, which are normally inhibited in the face of attentional demands. Therefore, tasks of sustained attention serve as effective probes for dysfunction in limbic brain networks. Based on prior studies, we hypothesized that treatment with ziprasidone would be associated with increases in ventral prefrontal activation which would lead to greater inhibition of amygdala overactivation. As an exploratory aim, we also examined baseline patterns of neuronal activity that are associated with subsequent clinical improvement to identify potential predictors of ziprasidone response. To our knowledge, this is the first study to explore the neurofunctional effects of ziprasidone and the first placebo-controlled study to examine the neurofunctional correlates of pharmacological treatment for youth with bipolar disorder.
METHODS

STUDY PARTICIPANTS
This study was conducted in conjunction with a multi-site placebo-controlled registration clinical trial of ziprasidone for the treatment of adolescent mania. Patients from 10 and 17 years old with bipolar I disorder, current episode manic or mixed, according to the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR) criteria, were recruited (n=23). Diagnoses were confirmed using the Kiddie Schedule of Affective Disorders and Schizophrenia for School Aged Children – Present and Lifetime Version (K-SADS-PL). Patients were included if they had a Young Mania Rating Scale (YMRS) total score ≥ 16 at both screening and baseline visits. Patients were excluded for a diagnosis of substance abuse or dependence in the previous month for any substances other than nicotine or caffeine, being clinically stable on a well-tolerated treatment regimen, prior treatment with ziprasidone, a known allergy to ziprasidone, or a serious suicidal risk. Patients were also excluded if they had any history of head injury resulting in loss of consciousness for > 10 minutes, or any unstable medical or neurological disorder.

Healthy adolescents (n=10), who were demographically matched to the study participants, were recruited from the community. The healthy adolescents were included in order to interpret the changes in the patient group (i.e., whether activation normalized with treatment). All healthy adolescents were free of DSM-IV-TR Axis I disorders, as confirmed by a K-SADS-PL interview. Both healthy adolescents and adolescents with bipolar disorder were included only if they had an estimated IQ > 80 and were free of any contraindications to undergoing an MRI scan (e.g., braces or claustrophobia). A negative urine pregnancy test was required prior to each scan for girls.

Written informed consent from the participant’s legal guardian and written informed assent from the child were obtained prior to study procedures. This protocol was approved by the University of Cincinnati and Cincinnati Children’s Hospital Medical Center Institutional Review Boards.

ZIPRASIDONE TREATMENT
Study participants with mania entered a washout period of exclusionary medications, including antipsychotics, mood stabilizers, stimulants, and antidepressants. None of the patients were taken off medications for the purpose of the study. Patients were only eligible to participate if their non-study related treatment team had determined that their symptoms warranted discontinuation of their current medication regimen prior to enrollment. Eleven of the participants had been treated with medication in the month prior to study participation. Seven patients had no history of prior treatment with any psychotropic agent.

Patients were randomized to receive either ziprasidone (n=14) or placebo (n=9) twice daily for four weeks as part of a large multi-center study. The dose was titrated over a 1-2 week period from an initial dose of 20mg/day to a target dose of 120-160 mg/day for subjects weighing ≥45 kg and 60-80 mg/day for subjects weighing < 45 kg. Participants who had an insufficient clinical response at 1 week following titration and had reached a maximum tolerated dose were discontinued from participation in the double-blind phase of the study, and were eligible to enroll in a 6-month open-label extension trial. Healthy adolescents received no medication.

RATINGS AND ASSESSMENTS
Patients with bipolar disorder were assessed at baseline, and then weekly during the 4 weeks of ziprasidone treatment. At each visit, study participants were evaluated using the YMRS, the Children’s Depression Ration Scale – Revised (CDRS-R), and the Clinical Global Impression Scale-Severity (CGI-S). Additionally, the Clinical Global Impression Scale-Improvement (CGI-I) score was administered at each visit beginning at week one. All ratings were performed by trained raters with established reliability (ICC > 0.8 for each rating scale), and when possible, the same rater performed all ratings for an individual patient. IQ score estimates were obtained at baseline for all study participants using the Wechsler Abbreviated Scale of Intelligence (WASI)(27) or the Kaufman Brief Intelligence Test, 2nd edition (K-BIT) (28). Handedness was assessed for all study participants using the Crovitz Handedness Questionnaire (29).

BEHAVIORAL TASK
During each scanning session, all study participants completed a single-digit version of the Continuous Performance Task – Identical Pairs Version (CPT-IP), a sustained attention task. The task was administered using E-Prime (Psychology Software Tools, Inc.) on a dedicated PC. In this task, study participants were presented with series of single-digit numbers, and were asked to respond via button press using the thumb
of their dominant hand each time the same number was presented twice in a row. During each 30 second epoch, numbers were presented for 700ms at 750ms intervals, for a total of 40 stimuli/epoch. There were 5 target stimuli in each active task epoch. This active task was presented in an alternating block design with a control task that consisted of the number ‘1' presented repeatedly with the same rate and intervals used in the active task. To control for activation associated with the motor response, subjects were asked to press the button 5 times at the onset of each control epoch, and then to simply view the remaining numbers without responding. Responses were recorded electronically, and response parameters, including discriminability and mean reaction time for target responses were calculated for all subjects. Discriminability is the ability to discriminate signal and noise, and incorporates both target and false positive responses; it is calculated as \( A' = 0.5 + (y-x)(1+y-x)/4y(1-x), \) where \( x \) is the probability of a false alarm and \( y \) is the probability of a hit.

**Functional MRI Scanning Protocol**

Study participants with bipolar disorder were scanned at baseline, prior to the initiation of treatment, as well as on days 7 and 28 (or at early termination for those who did not complete all four weeks of the trial). Healthy adolescents underwent a single scan, which served a basis for the interpretation of treatment-associated changes seen in the bipolar youth. All scans were performed at the University of Cincinnati Center for Imaging Research (CIR) using a 4.0 Tesla (4T) Varian Unity INOVA MRI. A radio-frequency coil was placed over the subject’s head and padding was placed between the head and the coil to minimize movement during the scanning session. Following a scout scan for alignment and brain localization, a shimming procedure was used to generate a homogeneous magnetic field. A high resolution T1-weighted, 3D scan of the brain was obtained to provide anatomic localization for functional imaging data using a modified driven equilibrium Fourier transform (MDEFT) sequence [\( T_{MD} = 1.1s, TR=13ms, TE=6ms, FOV=25.6 \times 19.2 \times 19.2 \text{ cm}, \text{matrix} = 256 \times 192 \times 96 \text{ pixels, flip angle} = 20^\circ \)]. A midsagittal localized scan was used to place 30 contiguous 5mm coronal slices, covering the entire brain. Subjects then completed the fMRI session by performing the CPT-IP task. Functional images were acquired using a T2*-weighted gradient echo EPI pulse sequence (TR/TE = 3000/30ms, FOV = 4 X 4 X 5mm, matrix = 256 X 256 pixels, slice thickness =5mm, flip angle = 75°). Data from the first acquisition of each run were discarded in post-processing to avoid non-equilibrium intensity modulation effects.

**Functional MRI Processing**

MRI images were reconstructed using in-house software to convert the raw data into AFNI format, and all subsequent analysis was performed using AFNI (30) (Analysis of Functional NeuroImages: http://afni.nimh.nih.gov/afni). Specifically, MDEFT (structural) and EPI (functional) images were co-registered using scanner coordinates, and EPI data were then corrected for motion. Data was normalized to Talairach space, and binary masking was applied to remove voxels outside the brain. Individual activation maps were created using a deconvolution algorithm that compares the actual hemodynamic response to a canonical hemodynamic response function. AFNI was then used to generate an estimate of the “fit coefficient” describing the magnitude of the hemodynamic response during the active task relative to the control task. Final activation maps consisted of these fit coefficients divided by the average signal intensity, to create a percentage change score associated with task performance. For our primary analysis, the following regions of interest (ROIs) were defined using AFNI; left and right Brodmann Areas 10, 11, and 47 in the ventral prefrontal cortex, and left and right amygdala. The location of these regions of interest is illustrated in Figure 1. The average percent change in activation during performance of the active CPT-IP task for these regions was extracted using the 3dROI program in AFNI and a mask created using AFNI Talairach coordinates. These numerical percent change results were used for all subsequent analysis.

**Statistics and Imaging Analyses**

All statistical analyses were performed using SAS Version 9.2 (SAS Institute, Inc.). Comparisons for baseline demographic, clinical and task performance variables were performed using Wilcoxon Signed Rank tests for continuous variables and Fisher Exact tests for categorical variables. Analysis of the task performance variables over time for the treatment groups was performed using a repeated measures mixed effects model, with treatment group as a between subject factor and time-point as a within subject factor. Primary analysis focused on treatment related changes in activation patterns in the eight pre-selected ROIs. Therefore, Bonferroni correction for multiple comparisons was applied for all primary analyses, yielding a cor-
rected threshold for significance of \( p < 0.006 \). Although the groups did not differ on task performance, discriminability was initially considered as a potential covariate because prior work using a similar task demonstrated activation changes are associated with task performance in individuals with bipolar disorder (12, 26). However, when analyses were repeated including this variable, results did not differ from those reported here.

Activation in a priori selected ROIs was compared between treatment (ziprasidone vs. placebo) groups using a repeated-measures mixed effects model, controlling for sex and days of treatment. Significant main effects were further explored using pair-wise t-tests on least squares means and the Tukey-Kramer adjustment for multiple comparisons. This mixed model analysis was then repeated also controlling for change in YMRS score (endpoint-baseline) to determine if differences between the groups were due to differences in symptom improvement or medication effects.

We also explored whether baseline activation patterns were associated with subsequent treatment response. For this purpose, patients were classified as treatment responders if at study endpoint (day 28 assessment or early termination visit) they demonstrated \( \geq 50\% \) reduction in YMRS from baseline and a CGI-I score \( \leq 2 \). Baseline activation in each ROI was compared between responders and non-responders within the ziprasidone-treated group using a general linear model. The placebo group was too small to allow for a separate responder analysis. We also performed correlation analyses to assess whether baseline activation or activation change in any of the ROIs was correlated with reduction in symptom severity as measured by change in YMRS scores.

Secondary exploratory analyses were conducted comparing the activation between healthy and bipolar Table 1. Baseline demographic and clinical characteristics of study participants with bipolar disorder (n=23) who were treated with either ziprasidone (n=14) or placebo (n=9) and healthy comparison adolescents (n=10)

<table>
<thead>
<tr>
<th></th>
<th>Healthy adolescents (n=10)</th>
<th>Adolescents with bipolar disorder (n=23)</th>
<th>Ziprasidone (n=14)</th>
<th>Placebo (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>15.0 (1.8)</td>
<td>14.6 (2.2)</td>
<td>14.7 (2.3)</td>
<td>14.5 (2.2)</td>
</tr>
<tr>
<td>Sex, N(%), boys</td>
<td>6 (60)</td>
<td>11 (48)</td>
<td>9 (64)a</td>
<td>2 (22)a</td>
</tr>
<tr>
<td>Race, N (%), White</td>
<td>7 (70)</td>
<td>20 (87)</td>
<td>12 (86)</td>
<td>8 (89)</td>
</tr>
<tr>
<td>IQ, mean (SD)</td>
<td>111 (9)</td>
<td>104 (12)b</td>
<td>106 (14)b</td>
<td>103 (10)</td>
</tr>
<tr>
<td>Attention Deficit Hyperactivity Disorder, N(%)</td>
<td>0(0)</td>
<td>10(43)</td>
<td>3(33)</td>
<td>7 (50)</td>
</tr>
<tr>
<td>YMRS</td>
<td>n/a</td>
<td>27(6)</td>
<td>27(6)</td>
<td>27(7)</td>
</tr>
<tr>
<td>CDRS-R</td>
<td>n/a</td>
<td>37(10)</td>
<td>37 (9)</td>
<td>39 (10)</td>
</tr>
<tr>
<td>Age of Onset, mean (SD)</td>
<td>n/a</td>
<td>121 (3.0)</td>
<td>11.6 (3.6)</td>
<td>12.6 (1.8)</td>
</tr>
<tr>
<td>Current Episode, N(%), Mixed</td>
<td>n/a</td>
<td>18 (76)</td>
<td>9 (64)</td>
<td>9 (100)</td>
</tr>
</tbody>
</table>

*p < 0.1

IQ data was not available for three study participants with bipolar disorder who were in the ziprasidone group.

YMRS = Young Mania Rating Scale
CDRS-R = Children's Depression Rating Scale- Revised
adolescents. The goal of these analyses was to provide a basis for the interpretation of the results of the primary analyses of treatment effects.

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Table 1 illustrates the demographic information and baseline clinical characteristics for all study participants. There were no significant differences in demographic characteristics between healthy youth (n= 10) and youth with bipolar disorder (n=23), nor between bipolar youth randomized to placebo (n=9) and those randomized to ziprasidone (n=14), with the exception that more boys were assigned to ziprasidone than placebo (using a liberal criteria of p< 0.1 for consideration of potential covariates). There were also no significant differences between the treatment groups in baseline symptom rating scale scores, age of onset of bipolar disorder, percentage of patients with co-morbid ADHD, or current episode type.

Table 2 provides a summary of the scans completed for participants with bipolar disorder. At baseline, a participant from the ziprasidone group was too ill to complete the scan, and a participant from the placebo group had unusable scan data. At day 7, scan data was not available for 4 patients treated with ziprasidone for the following reasons: termination from the study (n=1), refusal to participate in the scan (n=1), unusable data (n=1), and not receiving medication during the 48 hours prior to day 7 scan (n=1). A participant in the placebo group had unusable day 7 scan data. Four participants in the ziprasidone group and a participant in the placebo group terminated participation prior to their final scanning session. A participant in the placebo group had unusable endpoint scan data.

Table 3 provides a summary of the number of responders and non-responders in each treatment group, and the mean change in YMRS score for each subgroup. There was no significant difference in the dose of ziprasidone at day 7 between responders (mean = 74 mg) and non-responders (mean = 80mg). There was also no significant difference in the dose of ziprasidone received at study endpoint between responders (mean = 90 mg) and non-responders (mean = 120 mg).

There was a significant difference between the treatment groups in the number of days between their baseline and endpoint scans (p=0.03). Participants randomized to placebo remained in the study for fewer days (mean= 20) than those treated with ziprasidone (mean = 28), likely due to the fact that participants were allowed to discontinue for non-efficacy. Therefore, number of days of treatment was included as a covariate in analyses comparing the treatment groups.

CPT-IP PERFORMANCE

Table 4 illustrates the mean CPT-IP performance measures at each time-point for study participants with bipolar disorder by treatment group. Healthy adolescents and adolescents with bipolar disorder performed similarly on the CPT-IP, and there were no significant differences on task performance measures at baseline. There were also no statistically significant treatment group by time differences in performance measures, nor were there differences in performance measures between treatment groups at each time point or within each treatment group over time.

ACTIVATION CHANGES ASSOCIATED WITH TREATMENT

Mixed model analyses revealed a treatment (ziprasidone vs. placebo) by time interaction for right BA 11 and right BA 47 (F_{2,20}=27.1, p<0.0001 and F_{2,20}=16.2, p<0.0001, respectively) indicating that the change
over time in these regions differed between treatment groups. Specifically, the ziprasidone group exhibited greater increases in activation over time compared with the placebo group in both right BA 11 and 47.

Furthermore, there was a significant main effect for time (i.e., change over time among the entire patient group) for both right BA 11 and 47 ($F_{2,20}=15.3$, $p<0.0001$ and $F_{2,20}=8.4$, $p=0.002$, respectively). Pair-wise comparisons revealed that independent of treatment group, study participants had deactivation in right BA 11 at baseline and increased activation over time such that by study endpoint, participants activated this region during task performance. At endpoint right BA 11 activation across both treatment groups was significantly greater than at baseline ($p<0.0001$) and at day 7 ($p=0.0002$). There were no significant differences between the treatment groups at any time in right BA11 activation. Similarly, pair-wise comparisons also revealed that independent of treatment group, study participants exhibited deactivation in right BA 47 at baseline and increased activation over time such that by endpoint, participants activated this region during task performance. Right BA 47 activation at endpoint was significantly higher than at baseline ($p=0.0002$) and at day 7 ($p=0.003$). The mixed model analyses were repeated to include change in YMRS score as a covariate in effort to distinguish the group differences that were related to ziprasidone treatment vs. those related to symptom improvement. Activation patterns were similar to those described above adjusting for group differences in change in YMRS scores, indicating that the group by treatment effects are likely due to ziprasidone treatment rather than group differences in symptom improvement.

**BASELINE ACTIVATION PATTERNS ASSOCIATED WITH SUBSEQUENT RESPONSE TO ZIPRASIDONE**

Within the ziprasidone group there were 13 participants who completed a baseline scan. Of these individuals, seven were classified as responders and six were classified as non-responders.

To examine whether baseline activation in each of the ROIs is associated with subsequent treatment response to ziprasidone, we compared baseline activation in each of the ROIs between ziprasidone responders and non-responders. Baseline activation in right BA 47 was significantly different between subsequent responders and non-responders to ziprasidone ($F=11.6$, $p=0.006$). Specifically, responders exhibited decreased activation in right BA 47 (mean = -0.40), while non-responders showed little task related activation change in this ROI (mean = 0.04).

Similarly, among the patients treated with ziprasidone, baseline activation in right BA 47 (Figure 2) was negatively correlated with improvement in YMRS score ($r=-0.78$, $p=0.002$), i.e., larger decreases in activation of right BA 47 at baseline were associated with greater symptom reduction within the ziprasidone group.

Since there were too few responders in the placebo group, we did not examine baseline predictors of symptom improvement in this group. However, among all bipolar study participants there were no statistically significant associations between change in activation and change in YMRS score for any of the ROIs.

**COMPARISONS BETWEEN BIPOLAR ADOLESCENTS AND HEALTHY CONTROLS**

Exploratory analyses were conducted to compare activation in the ROIs between healthy adolescents and adolescents with bipolar disorder, in order to provide a basis for interpreting treatment-related activation changes. At baseline, there were significant differences in right BA 10 and left amygdala between bipolar and healthy youth. Specifically, bipolar youth exhibited deactivation in right BA 10 during task performance, whereas healthy youth exhibited increased activation in this region during task performance ($F=5.5$, $p=0.03$). Both healthy study participants and those with bipolar disorder showed deactivation in the left amygdala during task performance. However, healthy youth exhibited a significantly larger decrease in left amygdala activation during task performance as compared to youth with bipolar disorder ($F=4.6$, $p=0.04$).

There were no statistically significant differences in activation of any of the ROIs between healthy adolescents and adolescents with bipolar disorder at day 7, nor at endpoint.
EFFECTS OF ZIPRASIDONE IN ADOLESCENTS

DISCUSSION

In the present study, we found that treatment with ziprasidone was associated with increased activation during a task of sustained attention in several areas of the ventral prefrontal cortex, including right BA 11 and right BA 47, but not with detectable changes in amygdala activation. These changes appear to be associated with ziprasidone treatment, rather than symptomatic improvement. Additionally, study participants with bipolar disorder who subsequently responded to ziprasidone had less baseline BA 47 activation during CPT-IP performance than those who did not respond. Similarly, lower baseline activation in this region was also associated with greater improvement in manic symptoms following treatment with ziprasidone, suggesting that a subgroup of patients with lower activation in these regions may be more susceptible to the anti-manic effects of ziprasidone. These findings also indicate that ziprasidone's anti-manic effects may be related to increasing prefrontal modulation of emotional regulation.

These findings provide the first placebo-controlled evidence for neurofunctional effects of pharmacological treatment in manic adolescents with bipolar disorder. Our results are consistent with a neuropathological disease model in which patients with bipolar disorder show inappropriate limbic activation in the face of non-emotional tasks due to a failure to properly engage regions of the ventral prefrontal cortex to modulate activity in limbic regions, including the amygdala. This may represent a failure of the reciprocal inhibition of emotional and attentional networks that has been demonstrated in healthy individuals. Moreover, our findings suggest that treatment with ziprasidone is associated

Figure 2. Improvement in YMRS (baseline-endpoint) score over the study period vs. baseline right BA 47 activation in manic adolescents with bipolar disorder (n= 13) treated with ziprasidone
with increased functional activation in regions of the ventral prefrontal cortex, and indeed that patients with the lowest levels of activation in these regions may experience the most robust response to treatment with this medication. Although we did not detect changes in amygdala activation associated with ziprasidone treatment, there was a difference in amygdala activation between healthy controls and bipolar patients at baseline, which was no longer present at endpoint. Our small sample size and short duration of treatment may have limited our ability to detect statistically significant changes in amygdala activation following treatment.

Our results are consistent, in part, with those reported by Passarotti and colleagues (18), who found a pattern of increased amygdala activation and decreased prefrontal activation in manic youth relative to healthy youth during a combined emotion-attention task. Following treatment the increases in amygdala activation persisted, while prefrontal cortex activity increased over time, normalizing relative to healthy subjects. Consistent with this, in a study of euthymic adults with bipolar disorder, both amygdala and ventrolateral prefrontal cortex activation were found to be increased compared to healthy controls during a sustained attention task (12), indicating that such increased prefrontal modulation may be related to symptomatic improvement.

The fact that the treatment groups were not balanced with regard to gender is an important potential confound in the current study. Prior research has suggested that there may be differences between boys and girls in timing of developmental progress (31, 32) and on the performance of emotional tasks (33). However, no published studies described significant gender differences in response to ziprasidone. We included gender as a covariate in the models comparing the treatment groups. The gender term was not significant for either of the regions in which we report significant findings (p=0.89 for Right BA 11, p=0.72 for Right BA47), suggesting that the difference in gender ratio between the groups did not contribute significantly to the findings that we describe. Further research may be needed to explore gender differences in response to treatments for bipolar disorder.

There are several additional limitations to consider when interpreting the results of this study. First, despite the fact that deficits in sustained attention are well-documented in individuals with bipolar disorder, we were not able to detect performance differences between adolescents with bipolar disorder and healthy adolescents, nor were there any performance alterations associated with the changes in activation pattern seen with ziprasidone treatment. This is likely due to ceiling effects of task performance. Nonetheless, we identified differences in activation of prefrontal and amygdala regions between patients and healthy controls. Additionally, the small sample size of this study limits our ability to explore activation patterns seen in specific subgroups of our sample, (e.g., placebo responders, manic vs. mixed patients) and also prevents us from assessing the potential influences of comorbid psychiatric disorders. Also, although we included a comparison group of healthy youth, they underwent fMRI scans at a single time point, making it difficult to control for differences in activation that are related to practice effects.

Finally, this study was conducted as an add-on to the multi-site clinical trial of ziprasidone for adolescents with mania. Ziprasidone is not currently approved by the FDA for the treatment of mania in patients younger than 18 years, and there are ethical considerations that must be addressed whenever medications are being used “off-label.” We believe that the prior research (21, 22) provided sufficient justification for a clinical trial of ziprasidone in this population, and ziprasidone has been approved for the treatment of adolescent mania in the European Union. Still, the clinical relevance of these results is limited by the fact that ziprasidone is not approved for the population described. However, several other SGAs are approved for the treatment of mania in adolescents with bipolar disorder, and these results contribute to our understanding of the mechanisms of action which may be common to other members of this frequently-used class.

Despite the limitations, the findings of this study contribute to our understanding of the neurofunctional effects of pharmacological treatment for mania in adolescents with bipolar disorder. Further research is needed to determine whether treatment related increases in ventral prefrontal activation are associated with improvements in sustained attention and other executive function domains, if there are differences in patterns of change patients experiencing manic versus mixed episodes, as well as to investigate whether functional alterations in specific regions of ventral prefrontal cortex may be useful as specific biomarkers of ziprasidone response in patients with mania.
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References