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The effects of carbamazepine on prefrontal activation in manic youth with bipolar disorder

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Abstract

This preliminary study investigated the neurofunctional effects of carbamazepine-extended release (XR) treatment in 11 manic youth with bipolar disorder during performance of a sustained attention task, the Continuous Performance Task – Identical Pairs version, during functional magnetic resonance imaging (fMRI). All patients underwent baseline fMRI, and 10 patients were scanned again at endpoint. Nine demographically matched normal youth, who were scanned once, served as controls. Carbamazepine-XR treatment was associated with normalization of activation in right Brodmann Area 10. These results suggest that carbamazepine-XR treatment may correct prefrontal dysfunction in adolescent mania.

Keywords

Functional magnetic resonance imaging (fMRI); mania; adolescents

1. Introduction

Bipolar disorder typically presents during adolescence. However, short-term studies find that only 50% of youth treated for mania respond to a given medication (Correll et al., 2010). Therefore, additional treatment options are needed. Carbamazepine is an anticonvulsant approved by the U.S. Food and Drug Administration for the treatment of

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bipolar manic or mixed episodes in adults. Several open-label studies support the safety and tolerability of carbamazepine in youth with bipolar disorder (Ginsberg, 2006). Functional imaging studies suggest increased amygdala activation and abnormalities in ventral prefrontal function are found in youth with bipolar disorder during the performance of a task of sustained attention, and that treatment with second generation antipsychotics may correct the prefrontal alterations (Schneider et al., 2012). To our knowledge, however, there are no published data examining the *in vivo* effects of extended release carbamazepine on neurofunctional activation patterns. We hypothesized that manic bipolar youth treated with carbamazepine-extended release (XR) would exhibit normalization of prefrontal and amygdala activation during a task of sustained attention.

2. Methods

Patients ($n=11$) were included in this study if they (1) were 10-17 years old; (2) were diagnosed with DSM-IV-TR bipolar I disorder, current manic or mixed episode; (3) had a Young Mania Rating Scale (YMRS) score ≥ 16 ; (4) had a Clinical Global Impressions-Severity (CGI-S) score ≥ 4 ; and (5) had no prior treatment with carbamazepine. Diagnoses were confirmed using the Kiddie Schedule of Schizophrenia and Affective Disorders for School-Aged Children – Present and Lifetime Version (KSADS-PL).

Demographically matched healthy subjects ($n=9$) were recruited from the community. Healthy subjects were free of DSM-IV-TR Axis I disorders, as confirmed by a K-SADS-PL. Subjects were eligible for participation if they had an estimated IQ > 80 , were free of contraindications to magnetic resonance imaging (MRI) such as braces or claustrophobia, had no major medical problems, and had no history of head trauma resulting in loss of consciousness for more than 10 min. A negative urine pregnancy test was required for girls. Before the study began and after study procedures had been explained, all study participants and their legal guardians signed written informed assent and consent, respectively. The University of Cincinnati Institutional Review Board approved this protocol.

Bipolar patients received treatment with carbamazepine-XR as part of a multi-center, 8-week, open-label study. Only patients participating at the University of Cincinnati site were eligible for the functional imaging portion of the study. Patients were initiated on a dose of 200 mg BID and titrated to a maximum tolerated dose over 5 weeks, up to 1200 mg/day. Patients underwent a washout period for any previous medications before they began the study treatment; they were taking no psychoactive medications at baseline, and no psychoactive medications other than carbamazepine-XR at endpoint. Healthy adolescents received no medication.

Patients were assessed by trained raters with established reliability at baseline and weekly visits throughout the study using the YMRS. Functional MRI (fMRI) during a single-digit version of the Continuous Performance Task – Identical Pairs version (CPT-IP) was conducted on a 4.0 Tesla (4T) Varian Unity INOVA MRI instrument at the University of Cincinnati Center for Imaging Research using methods identical to those previously published by our group (Schneider et al., 2012). Patients underwent fMRI before they began the study medication and at week 8 (or early termination). Healthy subjects were scanned

once. MR images were reconstructed using in-house software to convert the raw data into AFNI format, and all analysis was performed using a previously published region of interest approach. Analysis focused on Brodmann areas (BA) 10, 11, and 47 and the amygdala, which have been previously shown to exhibit abnormal activation patterns during sustained attention in both adults (Strakowski et al., 2004) and youth with bipolar disorder (Schneider et al., 2012). Statistical analyses were performed using SAS. Behavioral measures included reaction time and discriminability, a signal detection measure that takes into account both correct hits and false positive responses, 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. Behavioral and demographic comparisons were conducted using the Wilcoxon signed rank for continuous variables and Fisher's Exact Test for categorical variables. General linear models were used to look for group effects, and linear mixed models were used to explore longitudinal effects of carbamazepine treatment. In exploratory analysis, the endpoint scans for bipolar individuals were also compared with the baseline healthy control data to explore potential normalizing effects.

3. Results

One bipolar subject did not complete the final scan due to an adverse skin reaction and thrombocytopenia. Two other bipolar subjects terminated the study and underwent endpoint scans early due to lack of efficacy (days 25 and 29). Baseline data from one patient were excluded due to poor task performance (defined as less than 50% correct).

There were no significant differences between the bipolar and healthy participants in age, sex, score on the Crovitz handedness scale (Crovitz and Zener, 1962), or race (Table 1). Bipolar youth had significantly lower IQs than healthy youth ($p=0.01$). As both bipolar and healthy youth scored within the normal range, this difference was not considered clinically significant. Six (55%) of participants with bipolar disorder and none of the healthy controls met diagnostic criteria for attention-deficit/hyperactivity disorder (ADHD). Bipolar youth had significantly lower discriminability than healthy controls at both baseline and endpoint (Table 1). Therefore, discriminability was included as a covariate in all comparisons between bipolar and healthy youth. There were no significant differences in reaction times between groups at either baseline or endpoint, and no differences in either reaction time or discriminability between baseline and endpoint in bipolar participants.

Bipolar subjects showed significant improvements in the YMRS with treatment; scores improved by an average of 11 points ($p<0.001$) from baseline to endpoint. The mean dose of carbamazepine-XR at endpoint was 1120 mg (mode=1200 mg).

Analysis comparing baseline and endpoint data for bipolar youth treated with carbamazepine-XR revealed a significant effect in right BA 10 ($P=0.02$). Activation in this region increased with treatment such that while bipolar subjects showed deactivation associated with the CPT-IP task at baseline, they showed little task-related activation change at endpoint. Change in activation over time in this region was not significantly correlated with change in YMRS score. At baseline, there was significantly greater activation during task performance in right BA 10 in healthy youth compared with youth with bipolar disorder

($p=0.03$). When healthy youth at baseline were compared with bipolar youth at endpoint, the group difference in activation in this region was no longer statistically significant.

There was also a significant time effect in the left amygdala ($p=0.05$). Bipolar individuals showed deactivation associated with the task at baseline and increased activation over time, such that they showed task-related activation in this region at endpoint. There was no significant difference in left amygdala activation when healthy subjects at baseline were compared with bipolar youth at baseline or endpoint. We did not detect significant differences in activation in BA 11 or 47 between bipolar and healthy youth, or changes in activation in these regions associated with carbamazepine treatment. A summary of the results for all regions of interest considered can be found in Supplementary Table 2.

4. Discussion

While preliminary, the present study suggests that carbamazepine-XR treatment improves mood symptoms in adolescents with bipolar disorder and is associated with normalization of activation in the ventral prefrontal cortex. Given the high response rate in this study and the absence of a placebo-treated group, it is possible that the changes in activation detected are associated with symptom resolution rather than carbamazepine-XR treatment itself. However, changes in YMRS ratings were not significantly correlated with the activation changes in BA 10, which would be expected if the activation change were directly related to symptomatic resolution. Alternatively, the activation changes may be directly related to carbamazepine-XR treatment, and system resolution may occur through a more complex or indirect mechanism. In manic youth with bipolar disorder treated with ziprasidone and tested using the same behavioral task, treatment was associated with changes in other areas of the prefrontal cortex, right BA 11 and 47, whereas treatment effects in BA 10 were not detected (Schneider et al., 2012). In contrast to previous studies (Schneider et al., 2012), we found no significant correlations between baseline activation in any region and subsequent changes in YMRS scores in response to carbamazepine-XR treatment, although failure to find this association may simply reflect insufficient power due to the small number of subjects. Further research using larger sample sizes and directly comparing the effects of different medications is needed to determine if there are general neurofunctional mechanisms of symptomatic improvement in bipolar disorder, or if different medications or medication classes lead to symptomatic resolution accompanied by distinct neurofunctional effects. If the latter proves to be true, it is possible that baseline activation patterns could one day be used in medication selection or to predict treatment response.

These findings provide evidence for neurofunctional effects of treatment with carbamazepine-XR in manic youth. Our results are consistent with a previous study wherein treatment of manic youth with the anticonvulsant lamotrigine was also associated with normalization of prefrontal cortex activation patterns (Passarotti et al., 2011).

In light of the very small sample size, the results reported here, both positive and negative, should be interpreted with caution (Button et al., 2013). The power of this study limits our ability to correct for multiple comparisons and examine the effects of potential confounding factors, such as rates of comorbid ADHD. While 55% of the participants with bipolar

disorder in this study also met criteria for ADHD diagnosis, analysis comparing performance or activation between those with and without ADHD comorbidity was not possible in this small sample. Youth with bipolar disorder did have lower discriminability than healthy youth. However, both groups performed near ceiling on this relatively easy behavioral task, and we do not believe that ADHD was a significant factor. In addition, while patients were compared with healthy subjects, healthy youth only completed one fMRI scan, not allowing for analyses of practice effects on the CPT-IP. Finally, with no placebo arm, we cannot determine whether changes in activation were due to treatment effects or simply the passage of time. In an earlier study, however, placebo-treated patients were tested twice on the same behavioral task and did not show the pattern of neurofunctional changes reported here (Schneider et al., 2012). Further research is needed to determine the longer term effects of treatment with carbamazepine XR.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Demographic and behavioral performance data

<i>Demographics</i>		
	Healthy adolescents (n=9)	Bipolar adolescents (n=11)
Age, mean (SD)	14.7 (1.6)	13.0 (2.2)
Sex, n (% male)	4 (44%)	5 (45%)
Race, n (% white)	9 (100%)	11 (100%)
Crovitz Handedness Scale, mean (SD)	9 (33.5)	11 (33.5)
IQ, mean (SD)	111 (9)	100 (10) ^a
<i>Behavioral task performance</i>		
Discriminability at baseline, mean (SD)	0.97 (0.03)	0.92 (0.05) ^a
Discriminability at endpoint, mean (SD)	N/A	0.91(0.06) ^a
RT at baseline (ms)	631 (62)	664 (87)
RT at endpoint (ms)	N/A	696 (132)
<i>Clinical characteristics of bipolar participants</i>		
	Baseline	Endpoint
YMRS, mean (SD)	28 (5)	18 (7) ^b

^a $p < 0.05$ vs. healthy controls,

^b $p < 0.05$ vs. baseline. RT, reaction time; YMRS, Young Mania Rating Scale.