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Neurochemical Alterations in Adolescent Bipolar Depression: A Proton Magnetic Resonance Spectroscopy Pilot Study of the Prefrontal Cortex

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Abstract

Objective: Identifying neurochemical alterations in adolescent bipolar depression may enhance our understanding of the neurophysiology of bipolar disorder across the age spectrum. The objective of this study was to compare *in vivo* neurometabolite concentrations in bipolar adolescents with a depressed episode and healthy adolescents using proton magnetic resonance spectroscopy (^{1}H MRS).
Method: Bipolar adolescents with a depressed episode ($n = 28$) and healthy adolescents ($n = 10$) underwent a ^{1}H MRS scan. Anterior cingulate (ACC) and left and right ventral lateral prefrontal (LVLPFC, RVLPFC) metabolite concentrations were calculated and compared between groups using analysis of covariance (ANCOVA).
Results: ANCOVA showed significant group differences in ACC *N*-acetyl-aspartate (NAA) ($F_{1,33} = 17.8$, $p = 0.0002$), LVLPFC choline (Cho) ($F_{1,32} = 13.1$, $p = 0.001$), creatine/phosphocreatine (Cr) ($F_{1,32} = 18.5$, $p = 0.0002$), and NAA ($F_{1,32} = 13.6$, $p = 0.0008$), and RVLPFC Cr ($F_{1,32} = 9.6$, $p = 0.004$), mI ($F_{1,32} = 11.1$, $p = 0.002$), and NAA ($F_{1,32} = 11.4$, $p = 0.002$) concentrations. In general, the bipolar depressed group had higher neurometabolite concentrations than the healthy group.
Conclusions: There may be localized alterations in brain neurometabolites in adolescents with bipolar depression. Limitations include lack of bipolar adolescents in other mood states and potential confounding effects of prior psychotropic medication use. Confirmatory ^{1}H MRS studies in larger samples of youths with bipolar depression are needed.

Introduction

The pathophysiology of bipolar disorder is not well understood, and it is unclear whether brain neurochemical abnormalities observed with proton magnetic resonance spectroscopy (^{1}H MRS) are consistent across the age spectrum. Because adolescents are closer to their illness onset compared with adults, ^{1}H MRS investigations of adolescents with bipolar disorder are typically free of confounding variables often seen in adults, such as illness duration and repeated affective episodes (DelBello et al. 2006a), and this may allow for a better understanding of the developmental neurophysiology of bipolar disorder. Several studies have characterized neurochemical abnormalities in youths with mania (Davanzo et al. 2001; Davanzo et al. 2003; DelBello et al. 2006b; Moore et al. 2007), but to our knowledge, there are no published ^{1}H MRS studies exclusively studying youths with bipolar depression. Understanding neurochemical alterations in this phase of the illness may provide the identification of biomarkers specific for bipolar depression, thereby

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helping to clarify whether such abnormalities correspond with specific symptom clusters (state-dependent), or with an underlying disease process (trait-dependent). Furthermore, knowledge about neurochemical profiles across the mood spectrum in bipolar disorder may provide for the development of targeted, more effective treatments.

Studies have shown that abnormalities in emotion, attention, and behavioral regulation are associated with the ventral prefrontal cortex (Blumberg et al. 2004), implicating a role for this region of the brain in bipolar disorder. With these considerations in mind, we conducted an exploratory *post hoc* analysis of prefrontal neurometabolite concentrations in groups of adolescents with bipolar I disorder presenting with depressive episodes and healthy adolescents.

Methods

This study was approved by the University of Cincinnati and the Cincinnati Children's Hospital Medical Center Institutional Review Boards. Adolescent subjects provided written assent and their legal guardians provided written informed consent for study participation after study procedures were fully explained.

Adolescents, ages 12–18 years, with bipolar I disorder, currently depressed ($n = 28$) were eligible. Trained interviewers with established good interrater reliability conducted diagnostic interviews using the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH U K-SADS) (Geller et al. 2001; Patel et al. 2006). All bipolar depressed patients were medication-free at the time of the ^{1}H MRS scan (Patel et al. 2006). The mean ($\pm$[SD]) duration of time off psychotropic medications prior to the start of the study was 18.0 $\pm$ 31.4 days. In the 6 months prior to the study, 61% ($n = 17$) received antidepressants (selective serotonin reuptake inhibitors [$n = 14$], bupropion [$n = 5$], venlafaxine [$n = 2$], mirtazapine [$n = 1$], amitriptyline [$n = 1$]), 25% ($n = 7$) atypical antipsychotics (quetiapine [$n = 4$], olanzapine [$n = 2$], risperidone [$n = 2$]), 14% ($n = 4$) anticonvulsants (valproate [$n = 3$], oxcarbazepine [$n = 1$]), 14% ($n = 4$) psychostimulants (atomoxetine [$n = 2$], dextroamphetamine [$n = 1$], methylphenidate [$n = 1$]), 4% ($n = 1$) lithium, and 4% ($n = 1$) clonidine. Furthermore, bipolar patients were excluded by a mood episode secondary to drug or alcohol intoxication or withdrawal, history of substance use disorder, mental retardation, or clinically significant medical conditions or laboratory abnormalities (Patel et al. 2006). Healthy subjects ($n = 11$), ages 12–18 years, were excluded by a history of psychiatric illness in themselves or a first-degree relative, or current treatment with any psychotropic medications (DelBello et al. 2006b). Subjects were excluded by any contraindication to having a ^{1}H MRS scan (DelBello et al. 2006b; Patel et al. 2006).

After meeting inclusion/exclusion criteria, subjects underwent a ^{1}H MRS scan. For bipolar depressed patients, the scan was conducted prior to administration of medication; healthy subjects did not receive medications (DelBello et al. 2006b; Patel et al. 2006). ^{1}H MRS was acquired on a 1.5 T Signa LX General Electric Magnetic Resonance scanner; data were acquired for all groups using the same MRS scanner and occurred over the same calendar period. An axial three-dimensional, inversion recovery prepped, fast spoiled gradient echo was acquired (echo time [TE] = 5.4 msec, repetition time [TR] = 12.5 msec, inversion time [TI] = 300 msec, field of view [FOV] = 24 cm, 1.5-mm thick with contiguous slices] to provide an anatomic template for voxel (8 cc) placement. An experienced spectroscopist (K.M.C.) positioned the voxels in the anterior cingulate cortex (ACC; predominantly gray matter), and the left and right ventral lateral prefrontal cortices (LVLPFC and RVLPFC; predominantly white matter) using anatomical landmarks to ensure consistent placement and to avoid signal artifacts from the orbits as described elsewhere (DelBello et al. 2006b; Patel et al. 2006). Spectra were acquired from these voxels with proton brain examination (PROBE) software using a point-resolved spectroscopy acquisition mode (PRESS) sequence (TE = 35 msec, TR = 2 seconds with 64 averages). Data were processed using the Linear Combination Model program (LCModel; Provencher 1993). Concentrations of glutamine/glutamate/γ-aminobutyric acid (Glx), choline (Cho), creatine/phosphocreatine (Cr), myo-inositol (mI), and *N*-acetyl-aspartate (NAA) were determined in each spectrum (DelBello et al. 2006b; Patel et al. 2006). A K-means segmentation algorithm applied to the three-dimensional high-resolution imaging sequence for each voxel location was used to determine gray, white, and cerebrospinal fluid (CSF) contributions to each voxel for each subject for the scan. Each neurometabolite concentration was adjusted by a scale factor that was based upon the ratio of volume of CSF to total volume, and adjusted neurometabolite concentrations are reported in international units (IU) (DelBello et al. 2006b; Patel et al. 2006).

Analysis of covariance (ANCOVA) was used to compare neurometabolite concentrations in each voxel between groups. Demographic variables were compared between groups to identify potential confounds, using a liberal p value of 0.2 for inclusion. Neurometabolite data that were not normally distributed were log-transformed for their respective analysis. Significance for the ANCOVAs was defined as a $p \leq 0.01$ (Bonferroni correction was applied for multiple comparisons). Effect sizes were calculated as Cohen $f = \sqrt{[(SS_{Between}/SS_{Total})/(1 - (SS_{Between}/SS_{Total})]}$ and an $f = 0.10$ represents a small-effect size, 0.25 a medium-effect size, and 0.40 a large-effect size (Cohen 1988). Pearson correlation (r) coefficients were computed to identify relationships between severity of depressive symptoms, as indicated by Children's Depression Rating Scale–Revised (CDRS-R; Poznanski and Mokros 1995) total scores (CDRS-R was administered by trained interviewers), and neurometabolite concentrations in each voxel. Significance for the correlation analyses was defined as a $p \leq 0.01$, correcting for multiple comparisons.

Results

Table 1 provides demographic and clinical variables for the groups, and adjusted mean neurometabolite concentrations and 99% confidence intervals for the groups in each voxel. Age in years and sex were included as covariates. ANCOVA showed significant group differences in ACC NAA; LVLPFC Cho, Cr, and NAA; and, RVLPFC Cr, mI, and NAA concentrations (Table 1). For these differences, the bipolar depressed group had significantly higher neurometabolite concentrations than the healthy group. CDRS-R total scores did not significantly correlate with neurometabolite concentrations in any voxel ($p \leq 0.04$).

Table 1. Demographic and Clinical Variables, and Adjusted Prefrontal Neurometabolite Concentrations (IU) in Bipolar Depressed Adolescents and Healthy Adolescents

Variable	Group: DEP (n = 28)	Group: HA (n = 10)	Statistical tests
Age (years)	15.5 ± 1.5	14.6 ± 1.8	$t = 1.7$, df = 36, $p = 0.1$
% Female	82%	60%	$\chi^2 = 2.0$, df = 1, $p = 0.2$
% White	79%	80%	$\chi^2 = 0.01$, df = 1, $p = 0.9$
YMRS	15.0 ± 6.9	—	
CDRS-R	63.2 ± 12.6	—	
% ADHD	25%	—	
% Any other DBD	50%	—	
% Any anxiety disorder	44%	—	

Voxel	Metabolite	p value for normality[a]	p value for equality of variances[b]	ANCOVA	Group (mean, 99% CI): DEP (n = 27)	Group (mean, 99% CI): HA (n = 10)	Cohen f
ACC					DEP (n = 27)	HA (n = 10)	
	Cho	>0.15	0.2	$F_{1,33} = 0.6$, $p = 0.4$	1.7 (1.5–1.8)	1.6 (1.4–1.8)	0.1
	Cr	>0.15	0.3	$F_{1,33} = 3.6$, $p = 0.07$	6.8 (6.5–7.2)	6.4 (5.9–6.9)	0.3
	Glx	>0.15	0.4	$F_{1,33} = 4.5$, $p = 0.04$	15.0 (14.3–15.8)	14.0 (13.0–15.1)	0.4
	mI	>0.15	0.9	$F_{1,33} = 5.3$, $p = 0.03$	6.0 (5.6–6.4)	5.5 (4.9–6.0)	0.4
	NAA	>0.15	0.8	$F_{1,33} = 17.8$, $p = 0.0002$	9.0 (8.6–9.5)	7.9 (7.3–8.5)	0.7
LVLFC					DEP (n = 27)	HA (n = 9)	
	Cho	>0.15	1.0	$F_{1,32} = 13.1$, $p = 0.001$	1.9 (1.7–2.0)	1.5 (1.2–1.7)	0.6
	Cr (log)	0.02	0.03	$F_{1,32} = 18.5$, $p = 0.0002$	5.2 (4.8–5.7)	4.1 (3.7–4.7)	0.7
	Glx	>0.15	0.1	$F_{1,32} = 6.1$, $p = 0.02$	10.3 (9.3–11.2)	8.7 (7.3–10.1)	0.4
	mI	>0.15	0.1	$F_{1,32} = 5.1$, $p = 0.03$	5.0 (4.4–5.8)	4.1 (3.4–5.1)	0.4
	NAA	>0.15	0.02	$F_{1,32} = 13.6$, $p = 0.0008$	8.5 (8.0–9.1)	7.2 (6.4–8.0)	0.6
RVLPFC					DEP (n = 26)	HA (n = 8)	
	Cho	>0.15	0.1	$F_{1,32} = 7.0$, $p = 0.01$	1.8 (1.7–2.0)	1.5 (1.3–1.8)	0.5
	Cr (log)	0.02	0.06	$F_{1,32} = 9.6$, $p = 0.004$	5.3 (4.8–5.7)	4.4 (3.8–5.1)	0.5
	Glx	>0.15	0.8	$F_{1,30} = 6.4$, $p = 0.02$	11.1 (10.1–12.0)	9.4 (7.8–11.0)	0.4
	mI	>0.15	0.7	$F_{1,32} = 11.1$, $p = 0.002$	4.9 (4.5–5.4)	4.0 (3.4–4.7)	0.6
	NAA	>0.15	0.2	$F_{1,32} = 11.4$, $p = 0.002$	8.6 (7.9–9.4)	7.1 (5.9–8.2)	0.5

[a]Kolmogorov-Smirnov test for normality.
[b]Levene's test for equality of variances.
IU = international units; DEP = depressed; HA = healthy adolescent; y = years; YMRS = Young Mania Rating Scale; CDRS-R = Children's Depression Rating Scale-Revised; ADHD = attention-deficit hyperactivity disorder; DBD = disruptive behavior disorder; Glx = glutamate/glutamine/γ-aminobutyric acid; Cho = choline; Cr = creatine/phosphocreatine; mI = myo-inositol; NAA = *N*-acetyl-aspartate; ACC = anterior cingulate cortex; LVLPFC = left ventral lateral prefrontal cortex; RVLPFC = right ventral lateral prefrontal cortex; ANCOVA = analysis of covariance; CI = confidence interval.

Discussion

Our findings suggest that there may be localized alterations in brain neurometabolites in adolescents with bipolar depression. Decreased prefrontal metabolism may explain observed differences in ACC and VLPFC NAA concentrations between the two groups that were associated with large effect sizes. Specifically, with decreased prefrontal metabolism, sufficient energy sources may be available to synthesize NAA, leading to increased concentrations (Stork and Renshaw 2005).

This finding of higher ACC and VLPFC NAA concentrations in the bipolar depressed group compared with the healthy group is in contrast with ^{1}H MRS studies of adults with bipolar depression (Dager et al. 2004; Frye et al. 2007). One explanation for our discrepant finding may be variability in the previous use of psychotropic medications shown to affect NAA (i.e., lithium and antidepressants) between the adolescent and adult samples (Moore et al. 2000a; DelBello and Strakowski 2004; Stork and Renshaw 2005; Gonul et al. 2006). Other possible explanations include age- and/or illness duration-dependent decreases in brain NAA concentrations (Winsberg et al. 2000; Brooks et al. 2001).

The bipolar depressed group had significantly higher Cho concentrations in the VLPFC than the healthy group. Cho abnormalities are believed to contribute to the neuropathophysiology of bipolar disorder (Kato et al. 1996; Hamakawa et al. 1998; Moore et al. 2000b; Dager et al. 2004; Frye et al. 2007). Elevated Cho concentrations may reflect impaired phospholipid metabolism, secondary to mitochondrial dysfunction (Farber et al. 2000; Stork and Renshaw 2005). Alternatively, increased Cho concentration may be associated

with decreased prefrontal metabolism, as observed in the bipolar depressed group (Mielke et al. 2001; Bustillo et al. 2002).

Bipolar depressed adolescents also showed increased VLPFC Cr concentrations as compared to the healthy group. The Cr peak is assumed to be stable and thus is often used as an internal reference in ^{1}H MRS studies. In euthymic and manic bipolar youths, no significant alterations in Cr concentrations have been observed in the medial prefrontal cortex (Cecil et al. 2003; Davanzo et al. 2003), cerebellar vermis (Cecil et al. 2003), or dorsolateral prefrontal cortex (Sassi et al. 2005). In contrast, our results, which are in accordance with those from a recent study in adult bipolar depression (Frye et al. 2007), suggest that alterations in Cr concentrations may reflect abnormal energy metabolism and may suggest that the Cr peak may not be appropriate as an internal standard in ^{1}H MRS studies of bipolar disorder. Further investigation of the stability of the Cr peak in bipolar disorder is warranted.

Several ^{1}H MRS studies in manic children and adolescents have reported elevated mI concentrations compared to healthy subjects (Davanzo et al. 2001; Cecil et al. 2002; Davanzo et al. 2003), which is consistent with our observed increase in RVLPFC mI concentrations in the bipolar depressed group. However, spectroscopy research in adults with bipolar disorder does not support abnormal brain mI concentrations (Moore et al. 2000b; Cecil et al. 2002; Dager et al. 2004; Frye et al. 2007). This suggests that alterations in mI, like NAA, may be influenced by psychotropic medication exposure and age and/or illness duration.

There are several limitations to this study. First, we did not evaluate neurochemical profiles of bipolar adolescents in other mood states, and thus we were unable to assess how neurochemical concentrations may be related to severity of mood symptoms across the spectrum in bipolar disorder. Second, we were unable to examine systematically the potential confounding effects of previous psychotropic medication use due to considerable variation in agents used and their respective doses and durations. Third, generalizability of the results may be limited given the small sample from a single site. Fourth, statistical analyses of unbalanced samples are at risk for reduced statistical power, nonnormality, and violations in the assumption of equality of variances. LVLPFC Cr and mI data were not normally distributed and thus, these data were log transformed. Despite the log transformation, LVLPFC Cr data remained a nonnormal distribution. LVLPFC Cr and NAA data violated the assumption of equality of variances. The Kruskal–Wallis Test (nonparametric) of LVLPFC Cr ($\chi^2 = 12.9$, df = 1, $p = 0.0003$) and NAA ($\chi^2 = 13.4$, df = 1, $p = 0.0003$) concentrations showed group differences. Fifth, technical factors such as T2 relaxation effects and tissue contamination could influence each group differentially such that the higher metabolite concentrations arise in the patients. We did not specifically correct for each of these factors on individual metabolite concentrations. Finally, other regions in which neurochemical abnormalities have been observed in bipolar patients, such as the dorsolateral prefrontal cortex, were not examined.

Conclusion

There may be localized alterations in brain neurometabolites in adolescents with bipolar depression. Confirmatory ^{1}H MRS studies in larger samples of youths with bipolar depression, preferably treatment naïve, are needed to gain a better understanding of the neurophysiology of bipolar depression.

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