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Brain gamma-aminobutyric acid (GABA) abnormalities in bipolar disorder

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Abstract

Objectives—Gamma-aminobutyric acid (GABA) abnormalities have been implicated in bipolar disorder. However, due to discrepant studies measuring postmortem, cerebrospinal fluid, plasma, and *in vivo* brain levels of GABA, the nature of these abnormalities is unclear. Using proton magnetic resonance spectroscopy, we investigated tissue levels of GABA in the anterior cingulate cortex and parieto-occipital cortex of participants with bipolar disorder and healthy controls.

Methods—Fourteen stably medicated euthymic outpatients with bipolar disorder type I (mean age 32.6 years, eight male) and 14 healthy control participants (mean age 36.9 years, 10 male) completed a proton magnetic resonance spectroscopy scan at 4-Tesla after providing informed consent. We collected data from two 16.7-mL voxels using MEGAPRESS, and they were analyzed using LCModel.

Results—GABA/creatine ratios were elevated in bipolar disorder participants compared to healthy controls [$F_{(1,21)}$ = 4.4, p = 0.048] in the anterior cingulate cortex (25.1% elevation) and the parieto-occipital cortex (14.6% elevation). Bipolar disorder participants not taking GABA-modulating medications demonstrated greater GABA/creatine elevations than patients taking GABA-modulating medications.

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Conclusions—We found higher GABA/creatine levels in euthymic bipolar disorder outpatients compared to healthy controls, and the extent of this elevation may be affected by the use of GABA-modulating medications. Our findings suggest that elevated brain GABA levels in bipolar disorder may be associated with GABAergic dysfunction and that GABA-modulating medications reduce GABA levels in this condition.

Keywords

anterior cingulate cortex; bipolar disorder; GABA; magnetic resonance spectroscopy; MEGAPRESS

Several lines of research indicate that gamma-aminobutyric acid (GABA) system abnormalities may play a role in mediating severe psychotic and mood disorders (1–3). As an inhibitory neurotransmitter, GABA facilitates the coordination of cortical activity, which may influence overall cognitive processing abilities (4). Thus, alterations in the GABAergic system may contribute to cognitive deficits seen in patients with schizophrenia and bipolar disorder (5, 6).

GABAergic abnormalities implicated in bipolar disorder include polymorphisms of GABA receptor genes (7–9) and, in postmortem studies, abnormalities in expression of multiple GABA-related proteins (9–11). Several studies report reduced GABA levels in the plasma (12–14) and cerebrospinal fluid (CSF) of bipolar disorder patients (15), but not all studies agree. Elevated GABA levels have also been reported in plasma (16, 17) and, using magnetic resonance spectroscopy (MRS), in the brain (1), as have decreased (18) and normal GABA levels in the brain (19) and CSF (20–23). Differences in patient population, clinical state (mania, euthymia, or depression), and treatment status likely contribute to these discrepant findings. In studies whose subjects include medicated, euthymic bipolar disorder patients, results indicate higher plasma GABA levels (17), but normal CSF (23) and brain GABA levels (19) when compared to controls. In addition, there are methodological differences among the MRS studies, and few MRS studies have examined brain regions specifically implicated in the pathophysiology of bipolar disorder. As a result of these issues, the field is still lacking insight into the exact nature of GABAergic abnormalities in this condition.

In the present study, we used MRS to investigate brain parenchymal GABA levels in the anterior cingulate cortex (ACC) and the parieto-occipital cortex (POC) of stably medicated outpatients with bipolar disorder using creatine (Cr) as an internal reference and the GABA/Cr ratio as an outcome measure. The contradictions in the current literature did not allow us to generate a specific hypothesis about the level of GABA/Cr ratios in the brains of bipolar disorder patients relative to controls, but we expected that there would be abnormalities in this measure. One potential confound in the interpretation of our findings is the impact of GABA-modulating medications on brain GABA levels. Based on prior literature (3, 24, 25), we posed a secondary hypothesis that GABA/Cr ratios would be altered in bipolar disorder patients taking GABA-modulating medications relative to those who were not.

Participants and methods

Participants

Following approval by McLean Hospital Institutional Review Board, 15 healthy control subjects and 15 participants diagnosed with bipolar disorder type I provided informed consent. All but two bipolar disorder participants were taking psychiatric medications including mood stabilizers, antidepressants, antipsychotics, and benzodiazepines (see Table 1). Participants with significant neurological or medical problems, current substance abuse, or history of substance dependence (except tobacco smoking) were excluded. All participants had negative urine toxicology screens. Participants with bipolar disorder were assessed using the Structured Clinical Interview for DSM-IV (SCID), Young Mania Rating Scale (YMRS), Montgomery- Åsberg Depression Rating Scale (MADRS), and Positive and Negative Syndrome Scale (PANSS). All patients were euthymic on the day of their scan and none met criteria for either mania or depression within the prior month as determined by SCID. Healthy control subjects were assessed using the SCID to rule out Axis I disorders. Demographic and clinical variables are presented in Table 1.

Magnetic resonance imaging (MRI)/MRS procedures

Proton MRS acquisitions were conducted on a 4-Tesla MR scanner (Varian/UnityInova; Varian, Palo Alto, CA, USA), using a 16-rung, single-tuned, volumetric-birdcage coil (XLR Imaging, London, ON, Canada; http://www.xlrimaging.com). Voxels measuring 23 × 22 × 33 mm (16.7 mL) were placed on the ACC or POC. The ACC voxels were placed anterior to genu of the corpus callosum, with the ventral edge obliqued and aligned with the dorsal corner of the genu, and positioned on the midline on axial images. The POC voxels were placed on midsagittal images, aligning the ventral edge of the voxel with the dorsal boundary of the splenium of the corpus callosum, covering posterior cingulate and retrosplenial cortices, and positioned on the midline in axial images. MEGAPRESS (26) was implemented for GABA editing. Total time in the scanner was less than 75 min.

MRS processing was blinded to diagnosis. For each voxel, the *off* scans that are part of the MEGAPRESS sequence were subtracted from the *on* scans to yield a difference-edited MEGAPRESS spectrum. In addition, the *off* scans were averaged to yield a standard PRESS (TE = 68 msec) proton MRS spectrum. We used LCModel (version 6.0–1) (27) with a MEGAPRESS-specific phantom-acquired basis set. Usable data were acquired from 14 out of 15 bipolar disorder participants and 14 out of 15 control participants. Out of 60 possible voxels, 54 usable data sets were obtained (15 bipolar disorder ACC voxels, 12 bipolar disorder POC voxels, 15 control ACC voxels, and 12 control POC voxels). Inability to tolerate the scanning environment was the cause of missing POC voxels.

LCModel provides Cramer Rao Lower Bounds (CRLBs), an estimate of the variance associated with fitting. The CRLBs for GABA in this study were 26 ± 9% and 21 ± 7% for healthy controls, and 19 ± 9% and 21 ± 8% for bipolar disorder participants (ACC and POC, respectively). GABA data from five voxels were excluded from this analysis on the basis of CRLBs >50% (two POC voxels and one ACC voxel from the bipolar disorder group, and one ACC voxel and one POC voxel from the healthy comparison group). In our experience,

using this CRLB cutoff was associated with good test–retest reliability [see *Supplemental Materials* of (3)]. We also performed a secondary analysis using a more stringent CRLB cutoff of 20%. This secondary analysis included nine ACC and five POC voxels from the bipolar disorder group and six ACC and six POC voxels from the healthy control group. The results of LCModel fitting for each metabolite are reported as arbitrary units (AU), not absolute cerebral concentrations. Concentrations of GABA are expressed as ratios of the GABA AU/CR-phosphocreatine AU. There were no group differences in Cr levels (mean 200.37, SD ± 56.78 AU for the healthy control group and mean 219.51, SD ± 68.54 AU for the bipolar disorder group, $p = 0.291$), and Cr was used as an internal reference to reduce subject-specific sources of variance in the MRS signal. Prior literature demonstrates similar Cr levels in healthy controls and subjects with bipolar disorder (28).

Image segmentation

Tissue segmentation of T1-weighted images into gray matter (GM), white matter (WM), and CSF used FMRIB's Automated Segmentation Tool (Oxford, UK). The percentage of GM in ACC and POC was 55.1% ± 10.8% and 52.3% ± 5.4% (bipolar disorder group), and 58.7% ± 4.95% and 52.7% ± 4.26% (healthy control group), respectively, while that of WM was 26.8% ± 11% and 29.2% ± 6.1% (bipolar disorder group), and 23.1% ± 1.9% and 32.7% ± 4.36% (healthy control group), respectively. There was no statistically significant difference in GM percentage between the bipolar disorder patients and healthy controls in the ACC ($p = 0.289$) or POC ($p = 0.889$). Nor was there any statistically significant difference in WM between the bipolar disorder patients and healthy control participants in the ACC ($p = 0.250$) or POC ($p = 0.178$).

Statistical analysis

Given our *a priori* hypothesis, and the specialized MEGAPRESS sequence used to measure GABA, we considered the GABA/Cr ratio as our primary outcome measure. We used a general linear model analysis fit using the Mixed routine in SPSS statistical software (SPSS Inc., Chicago, IL, USA) to assess the effect of diagnosis and voxel location (ACC versus POC) on GABA/Cr measures using age, gender, and GM percentage as covariates. Main diagnosis effects and voxel location by diagnosis interaction were also explored using SPSS. Significance was fixed at $\alpha = 0.05$. We examined the effects of gender and medication (i.e., status for benzodiazepines, lithium, antidepressants, and anticonvulsants) on metabolite ratios using oneway ANOVAs. We calculated correlation coefficients for the relationships between age, voxel GM percentage, and chlorpromazine (CPZ) equivalents with GABA/Cr values. Finally, we examined age of disease onset and MADRS, YMRS, and PANSS score correlations with GABA/Cr values. All p-values are two-tailed.

Given existing literature on the effects of benzodiazepine and anticonvulsants on GABAergic neurotransmission (3, 24, 25), we considered these to be GABA-modulating medications. In order to examine their effect on GABA levels, we performed a secondary analysis in which we assigned participants to one of three groups: healthy controls (n = 14), bipolar disorder participants on a GABA-modulating medication (n = 10), or bipolar disorder participants whose regimen did not include these medications (n = 4). We assessed

the effect of group membership and voxel location on GABA/Cr measures using a linear mixed model analysis with age, gender, and GM percentage as covariates.

Patients not taking a GABA-modulating medication were either taking no psychotropic medications (n = 2), taking an antipsychotic (n = 1), or were taking an antipsychotic plus an antidepressant (n = 1).

Results

Adjusting for age, gender, and GM percentage, GABA/Cr levels showed a significant main effect of diagnosis [$F_{(1,21)}$ = 4.40, p = 0.048] and a trend toward a significant effect of voxel location [$F_{(1,22)}$ = 2.961, p = 0.099] but no voxel location × diagnosis interaction [$F_{(1,22)}$ = 0.108, p = 0.746]. GABA/Cr was elevated by 25.1% (ACC) and 14.6% (POC) in bipolar disorder participants compared to healthy controls (see Table 2).

Using a more stringent CRLB cutoff of 20%, GABA/Cr levels showed a trend toward a significant main effect of diagnosis [$F_{(1,12)}$ = 3.851, p =0.074] and a trend toward a significant effect of voxel location [$F_{(1,16)}$ = 3.672, p = 0.073] but no voxel location × diagnosis interaction [$F_{(1,16)}$ = 0.115, p = 0.738]. GABA/Cr was elevated by 16% (ACC) and 27.3% (POC) in bipolar disorder participants compared to healthy controls.

In our secondary analysis, GABA/Cr levels showed a significant main effect of group [$F_{(1,6)}$ = 6.263, p = 0.016] and voxel location [$F_{(1,18)}$ = 10.074, p = 0.005]. GABA/Cr was lowest in healthy control participants, higher in bipolar disorder participants taking a GABA-modulating medication, and highest in bipolar disorder participants not taking these medications. GABA/Cr was elevated by 21.9% in ACC and lowered by 5.4% in POC in patients with bipolar disorder prescribed these medications compared to healthy controls. GABA/Cr was elevated by 32.2% in ACC and 34.2% in POC in patients with bipolar disorder who were not prescribed these medications compared to healthy controls.

There were no significant relationships between GABA/Cr and age (Pearson's $r = -0.164$), CPZ equivalents (r = 0.101), or GM percentage (r = 0.092). In a series of one-way ANOVAs, GABA/ Cr levels were not different between participants who were and were not taking second-generation antipsychotics [$F_{(1,22)}$ = 0.400, p = 0.534], first-generation antipsychotics [$F_{(1,22)}$ = 0.004, p = 0.950], lithium [$F_{(1,22)}$ = 2.530, p = 0.126], antidepressants [$F_{(1,22)}$ = 0.298, p = 0.592], or benzodiazepines [$F_{(1,22)}$ = 0.021, p = 0.886]. A trend toward significance was observed for anticonvulsants [$F_{(1,22)}$ = 3.37, p = 0.0797]. No effect of gender on GABA/Cr levels was observed [$F_{(1,47)}$ = 1.91, p = 0.173].

No significant relationships were observed between GABA/Cr levels and age at disease onset (r = −0.068), or scores on the MADRS (r = 0.108), YMRS (r = −0.075), or PANSS (r = 0.114).

Given the observed main effect of diagnosis and the trend toward a significant effect of voxel location, we performed post hoc *t*-tests examining the effect of diagnosis within the ACC (p = 0.171) and POC (p = 0.450).

Discussion

Using a dedicated ^{1}H-MRS sequence at 4-Tesla, we observed elevated GABA/Cr levels in a group of euthymic patients with bipolar disorder. This elevation was observed in both the ACC and the POC. A similar broadly distributed elevation in GABA has been previously seen in a population of chronically ill subjects with schizophrenia who were scanned in the same manner (3).

Given the previous literature regarding the effects of medications on GABA, we performed a secondary analysis in which we compared patients with a bipolar disorder diagnosis whose regimen included GABA-modulating agents such as benzodiazepines or anticonvulsants. This analysis revealed an even more pronounced effect of bipolar disorder diagnosis itself on GABA/Cr levels. This effect of diagnosis was partially (but not fully) corrected toward healthy control levels when patient medication regimens included a benzodiazepine or anticonvulsant (or both). A recent study (29) observed that antipsychotic medications were also associated with normalization of the elevated GABA levels seen in schizophrenia. Of note, our data were consistent with prior work (3) demonstrating an association between anticonvulsant use and reductions in cerebral GABA concentration in a population of subjects with chronic psychiatric illness. Another study has observed an increase in cerebral GABA in a population of healthy control subjects prescribed certain anticonvulsants (25). A potential explanation for these findings could be that a subset of chronically ill patients with abnormally low GABA have responded clinically to anti-convulsants because of a partial correction of this deficit. Testing this hypothesis is unfortunately beyond the scope of this study.

Strengths of this study include high magnetic field, metabolite-selective data acquisition and analysis, the focus on two distinct brain regions, and the inclusion of a three-way comparison between controls and two patient groups differentiated on the basis of their medication regimen. A limitation of this study is that the total number of bipolar disorder participants does not allow for large subgroups differentiated on the basis of medication regimen or menstrual cycle phase, which is known to affect cerebral GABA levels (30). In our sample, only four bipolar disorder subjects were not prescribed medications from classes thought to affect cerebral GABA levels. An important feature of a follow-up study will be to recruit sufficient numbers of bipolar disorder participants whose medication regimens allow for more precise determination of medication effects on GABA. This study demonstrates increased GABA concentration in bipolar disorder subjects as an increase in the ratio of GABA/Cr, where Cr was shown not to differ significantly between bipolar disorder and healthy control subject groups. Future studies could include a determination of absolute cerebral GABA concentration in each subject group. Of note, a previous study did not detect GABA abnormalities in bipolar disorder (19). This discrepancy might be explained by the smaller sample size and MRS sequence, which was not GABA-dedicated.

Although multiple lines of evidence have suggested that GABAergic neurotransmission is abnormal in bipolar disorder [e.g., (31)], there is little information on the exact GABAergic brain abnormalities in this condition. Our findings suggest that GABAergic dysfunction is associated with elevated brain GABA levels in bipolar disorder and that GABA-modulating

medications reduce GABA levels in this condition. Our findings in bipolar disorder parallel those that we (3) and some others (29) have reported in schizophrenia [but not all reports in that condition (32, 33)]. This observation suggests that GABAergic dysfunction may be one shared feature of pathophysiology in these two conditions. Notably, studies of unipolar depression have revealed decreased brain GABA concentration in patients in a depressed state (34). The abnormalities we observed may be trait related since we studied stable euthymic outpatients with bipolar disorder. How GABA levels vary in mania and depression remains to be studied in future work and may provide additional insights into GABAergic abnormalities in bipolar disorder.

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Table 1
Subject demographic and clinical information

	Healthy controls (n = 14)	Bipolar disorder (n = 14)
Age, years, mean ± SD	36.9 ± 10.4	32.6 ± 13.6
Gender	10M, 4F	8M, 6F
Age of onset, years, mean ± SD	–	23.9 ± 5.4
MADRS score, mean ± SD	–	5.5 ± 5.8
YMRS score, mean ± SD	–	2.4 ± 3.7
PANSS score, mean ± SD	–	35.0 ± 12.4
Lithium	–	4
Anticonvulsants[a]	–	5
SGAs	–	9
FGAs	–	2
Antidepressants	–	7
CPZ equivalents, mean ± SD	–	312 ± 293
Benzodiazepines	–	6

The values in the medication rows are the number of subjects whose regimen included that class of psychotropic medication. CPZ = chlorpromazine; F = female; FGA = first-generation antipsychotic; MADRS = Montgomery-Åsberg Depression Rating Scale; M = male; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; SGA = second-generation antipsychotic; YMRS = Young Mania Rating Scale.

[a]In this sample, five subjects were prescribed anticonvulsants, which included lamotrigine (three patients), topiramate, oxcarbazepine, and valproic acid (three patients). Three subjects were prescribed a combination of two anticonvulsants. Two participants were taking no psychotropic medications.

Table 2

Metabolite levels

	GABA/Cr
Anterior cingulate cortex	
Healthy controls	0.155 ± 0.053
Bipolar disorder	0.194 ± 0.087
BD/GABA meds	0.189 ± 0.058
BD/No GABA meds	0.205 ± 0.151
Parieto-occipital cortex	
Healthy controls	0.130 ± 0.045
Bipolar disorder	0.149 ± 0.067
BD/GABA meds	0.123 ± 0.051
BD/No GABA meds	0.208 ± 0.069

Values are given as mean ± standard deviation. BD = bipolar disorder; Cr = creatinine; GABA = gamma-aminobutyric acid; GABA meds = GABA-modulating medications.