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TEMPORAL LOBE VOLUME IN BIPOLAR DISORDER: RELATIONSHIP WITH DIAGNOSIS AND ANTIPSYCHOTIC MEDICATION USE

Lindsay D. Jones, BA, BSc^d, Martha E. Payne, MPH, PhD^{a,c}, Denise F. Messer, MA^{a,c}, John L. Beyer, MD^{a,c}, James R. MacFall, PhD^{b,c}, K. Ranga R Krishnan, MD^{a,c,e}, and Warren D. Taylor, MD^{a,c,*}

a The Department of Psychiatry, Duke University, Durham, North Carolina, United States

b The Department of Radiology, Duke University, Durham, North Carolina, United States

c The Neuropsychiatric Imaging Research Laboratory, Duke University, Durham, North Carolina, United States

d The School of Medicine, Duke University, Durham, North Carolina, United States

e The Duke-NUS Graduate Medical School, Singapore

Abstract

Background—We tested for differences in temporal lobe volume in bipolar disorder and the relationship between these volumes and psychotropic medication use.

Methods—125 subjects with bipolar disorder and 87 comparison subjects with no psychiatric illness completed clinical interviews and 1.5T MRI brain scans. Temporal lobe volumes were manually traced and segmented into gray matter and white matter volumes using an automated process. General linear models examined the relationship between these volumes and diagnosis as the primary predictor with age, sex, education, and race as copredictors. Secondary analyses incorporated the use of psychotropic medication into the linear models, and parsimonious models developed through backwards regression.

Results—In initial models, subjects with bipolar disorder exhibited larger temporal lobe white matter bilaterally (left: $F_{1,211} = 2.86, p = 0.0047$; right: $F_{1,211} = 3.25, p = 0.0014$). Current antipsychotic use was significantly associated with larger bilateral temporal lobe white matter volumes (left: $F_{2,211} = 9.45, p = 0.0001$; right: $F_{2,211} = 10.79, p < 0.0001$), wherein bipolar subjects taking antipsychotics had larger volumes than bipolar subjects not taking antipsychotics or healthy comparison subjects. Temporal lobe gray matter volume was not significantly associated with diagnosis or medication use.

Limitations—Excluding subjects with substance use disorders may limit the study's generalizability.

Conclusions—These findings indicate that differences in temporal lobe white matter are associated with bipolar disorder and use of antipsychotic medications.

*Corresponding author: Warren D. Taylor, MD, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, DUMC Box 3903, Durham, NC 27710, P: (919) 668-7887, F: (919) 681-7668, Taylo066@mc.duke.edu.

INTRODUCTION

Bipolar disorder is characterized by alternating episodes of mania and depression. The etiology of bipolar disorder and its characteristic mood episodes may be due to both functional and structural brain changes detectable with magnetic resonance imaging (MRI). Although many brain regions have been examined in previous structural MRI studies of bipolar disorder, the temporal lobe may be of particular importance given its role in perception and processing of environmental stimuli. However, previous studies of the temporal lobe in bipolar disorder have reached conflicting conclusions, reporting that bipolar subjects exhibit either smaller (Altshuler et al., 1991; El-Badri et al., 2006) or larger (Harvey et al., 1994) volumes, or finding no significant difference between subject groups (Johnstone et al., 1989; Swayze et al., 1992; Pearlson et al., 1997; Hauser et al., 2000). When distinct temporal lobe structures have been examined, reports have demonstrated no difference in hippocampus volume (Pearlson et al., 1997; Altshuler et al., 1998; Sax et al., 1999; Strakowski et al., 1999), while studies examining the amygdala have had mixed conclusions (Swayze et al., 1992; Pearlson et al., 1997; Altshuler et al., 1998; Strakowski et al., 1999; Brambilla et al., 2003).

These apparently contradictory findings may reflect the underlying heterogeneity of the clinical diagnosis of bipolar disorder or methodological differences in image acquisition and analysis across studies. One factor that may contribute to this heterogeneity is that few studies have included medication data in the final statistical analyses. Those studies that examined medication data frequently limited their analyses to medicated versus unmedicated subjects (Sax et al., 1999) or lithium-treated versus drug-free subjects (Brambilla et al., 2003), and in each case have found no significant difference between treated and untreated subjects in the regions of interest examined. However, several studies demonstrate that psychotropic medications may be related to changes in regional brain volumes (Moore et al., 2000; Sassi et al., 2002). It is possible that differences in psychotropic medication use across study populations may have contributed to the differences in conclusions.

We examined temporal lobe volumes in a cohort of bipolar and comparison subjects, hypothesizing that bipolar subjects would exhibit differences in temporal lobe volumes. We also examined the effect of concurrent psychotropic medication use on temporal lobe volumes.

METHODS

Sample and Clinical Evaluation

Subjects with bipolar disorder were recruited from outpatient clinics at Duke University Medical Center in Durham, NC. Comparison subjects were recruited through community advertisements. The study was approved by the Duke University Health System Institutional Review Board. After complete description of the study to the subjects, written informed consent was obtained.

All subjects completed the SCID (Structured Clinical Interview for DSM-IV) to assess for psychiatric diagnoses. Bipolar subjects met DSM-IV criteria (American Psychiatric Association, 1994) for Bipolar I disorder. Comparison subjects did not meet diagnostic criteria for any psychiatric diagnosis. All subjects had to be age 18 years or older to participate. Exclusion criteria included meeting DSM-IV diagnostic criteria for another Axis I psychiatric illnesses, a current manic episode, and active substance abuse or dependence. Exclusion criteria further included any neurological illness, evidence of cognitive impairment (as suggested by a score of ≤ 23 on the Mini Mental Status Exam (MMSE) (Folstein et al., 1975), or contraindications to MRI.

Demographic data were gathered through the clinical evaluation, including a list of current medications and self-report of the number of previous mood episodes. When subjects could not provide documentation of their medication regimen, it was confirmed with the prescribing physician. Current depressive symptoms were assessed using the Center for Epidemiological Studies – Depression (CES-D) scale (Radloff, 1977).

MRI Acquisition and Processing

MR imaging of the brain was performed on a 1.5T system (Signa, GE Medical Systems, Milwaukee, WI) using the standard head volumetric radiofrequency coil. The scanner alignment light was used to adjust the head tilt and rotation so that the axial plane lights passed across the cantho-meatal line and the sagittal lights were aligned with the center of the nose. A rapid sagittal localizer scan was acquired to confirm the alignment.

A dual-echo fast spin-echo (FSE) acquisition producing proton-density weighted and T2-weighted images was obtained in the axial plane for morphometry of whole brain and cerebrum. Pulse sequence parameters were: TR = 4000 ms, TE = 30, 135 ms, bandwidth=32 KHz (+/-16 KHz) full imaging bandwidth, echo train length = 16, 256 × 256 matrix, 3 mm section thickness, 1 excitation, and a 20 cm field of view. The images were obtained with two separate acquisitions each of 55 slices with a 3 mm gap between sections for each acquisition. The second acquisition was offset by 3 mm from the first, so that the resulting data set consisted of contiguous sections. An axial IR prepped 3D series producing a T1-weighted image was used for measuring the temporal lobe. Pulse sequence parameters were TR=12ms, TE = minimum full echo, TI = 300 ms, flip angle = 20 degrees, 32 KHz (+/- 16 KHz) full imaging bandwidth, a 256 × 256 matrix, 1.5 mm section thickness, 124 slices, 1 excitation and a 24 cm field of view.

The images were processed at the Neuropsychiatric Imaging Research Laboratory (NIRL) by blinded analysts. A NIRL-modified version of MrX, initially created by GE Corporate Research and Development (Schenectady, NY) and originally modified by Brigham and Women's Hospital (Boston, MA) for image segmentation (Payne et al., 2002), was used to measure both cerebral white matter volume and total cerebral volume (composed of total cerebral gray matter, white matter, and CSF); in statistical analyses, total cerebral volume was used to control for head size. This measure did not include the brainstem or cerebellum.

Temporal lobe tracing was performed on the T1-weighted 3D image set with the NIRL-developed GRID program which is based on a point-counting method (MacFall et al., 1994). Before tracing began, two alignments were performed: a standard realignment procedure which aligned the images to a plane bisecting the brain into right and left cerebral hemispheres, and a sagittal realignment for each temporal lobe such that the temporal lobe axis was defined as the horizontal. The temporal lobe was traced based on anatomically defined boundaries, moving anteriorly in the coronal view, starting at the most posterior slice where the crus fornix is full and visible. The anterior boundary was the anterior pole of the temporal lobe, and the medial boundary was the medial temporal gray matter in all slices except those involving the temporal stem, which was crossed at its shortest distance. This boundary avoided the thalamus, putamen, and other non-temporal structures. After tracing was complete, the tracing was used as a mask to define the temporal lobe region on a segmentation image which was obtained using a previously described automated method (Van Leemput et al., 1999) in order to obtain both gray and white matter tissue volume estimates. The automated method was used to identify gray matter, white matter, and CSF voxels due to its lower variance for this small region of the brain.

Reliability was established for all regions of interest by repeated measures on multiple scans before raters were approved to process the study data. Intraclass correlation coefficients (ICCs) attained were: total cerebrum = 0.997, left total temporal lobe = 0.99, left temporal lobe gray

matter = 0.99, left temporal lobe white matter = 0.95, right total temporal lobe = 0.98, right temporal lobe gray matter = 0.99, and right temporal lobe white matter = 0.95.

Analytic plan

All statistical analyses were performed using SAS version 9.1 and Enterprise Guide version 4.0 (Cary, NC). Temporal lobe volumes were adjusted to account for differences in brain size by dividing the regional volume by the total cerebral volume, which was defined as the sum of cerebral gray matter, white matter, and CSF. These mean adjusted volume ratios were used as the primary measures for each region. This approach was used instead of using the unadjusted temporal lobe measures to make univariate analyses more informative, while reducing the number of independent variables required for the planned general linear models. We tested the alternate approach of including cerebral volume as an independent variable, and it did not significantly change our results.

Two-tailed pooled *t*-tests examined for group differences in continuous variables, while chi-squared tests examined categorical variables, where race was dichotomized to Caucasian versus non-Caucasian. For continuous variables, distributions were assessed by graphical means and equality of variance was verified by a folded *F* test. Multivariate analyses were conducted using general linear models (the GLM procedure) for each adjusted temporal lobe measure, where adjusted regional volume was the dependent variable and diagnosis, age, and sex were independent variables, along with any demographic measures different between the diagnostic groups. Graphical analysis of standardized residual plots was performed to verify the normality of distribution of residual values. A Bonferroni correction for multiple comparisons was performed to adjust for the six planned comparisons; this resulted in $\alpha = 0.0083$. We subsequently examined a similar model with total cerebral white matter as the dependent variable; this was done to determine if our finding was specific to the temporal lobe, or if our temporal lobe findings were merely reflective of a more widespread difference.

For the medication analysis, *t*-tests initially examined for differences in adjusted regional volumes between subjects who were and were not taking each class of medication: lithium, antipsychotics, anticonvulsants, antidepressants, and benzodiazepines. As there were five drug classes, each including six variables (white matter, gray matter, and total volume, each in two hemispheres), this resulted in thirty comparisons and a Bonferroni-adjusted alpha of 0.0017.

These univariate analyses were followed by backwards regression, wherein the GLM procedure described above was repeated, replacing the original subject diagnosis grouping with a trichotomous variable: comparison subjects, bipolar subjects not taking that class of medication, and bipolar subjects currently using that class of medication. Thus each model initially included age, sex, education, race, and five medication variables. Medication variables but not demographic variables were removed through backwards regression. When this procedure was complete, for any medication variable that was statistically significant, a least squares means analysis was used to isolate the effect of medication in the model and the Tukey-Kramer procedure used to adjust for multiple comparisons. Finally, as post-hoc analyses, for those drug classes which were related to temporal lobe volume, we tested for demographic and clinical differences between those who were and were not taking that medication class.

RESULTS

The sample consisted of 212 individuals, 125 bipolar subjects and 87 comparison subjects with no psychiatric disorders (Table 1). Sex representation and mean age were not significantly different between groups (age range 18 – 77 years). Bipolar subjects overall exhibited higher CES-D scores, fewer years of education, and there were more minority subjects in the comparison cohort. Non-Caucasian subjects were primarily African-American, with a small

number of Native American and mixed-ethnicity subjects. The bipolar group reported a mean number of 6.6 (SD=13.9) previous mood episodes (mean 3.7 depressed, SD = 9.8; mean 2.9 manic, SD = 7.2).

Adjusted mean temporal lobe volumes are shown on Table 2. After correcting for multiple comparisons, temporal lobe white matter volumes were significantly larger bilaterally in bipolar subjects as compared with comparison subjects. There were no significant differences after this correction in temporal lobe gray matter bilaterally, total temporal lobe volume bilaterally, or total cerebral white matter between the two groups.

The relationship between medication use and temporal lobe volumes was next analyzed. *T*-tests were used to test for temporal lobe volume differences between those taking or not taking each of the five drug classes. These analyses included both bipolar and comparison subjects, although no comparison subjects were taking any psychotropic medications. After corrections for multiple comparisons, medication use was not significantly associated with either temporal lobe gray matter volume or total temporal lobe volume (data not shown), although right temporal lobe total volume was significantly different between subjects who were and were not taking antipsychotics at an unadjusted *p* value (not taking: 0.0711, SD = 0.005; taking: 0.0732, SD = 0.005; *t* = 2.33, 210 *df*, *p* = 0.0210). The only association reaching the Bonferroni-corrected level of statistical significance appeared between antipsychotic use and temporal lobe white matter bilaterally (Table 3).

New models were created, replacing the previous dichotomous diagnosis variable with the trichotomous diagnosis variables for each of the five drug classes. After backwards regression, only use of antipsychotic medication was significantly associated with temporal lobe volume, and then only with temporal lobe white matter (left: $F_{2,211} = 9.63$, *p* = 0.0001; right: $F_{2,211} = 11.14$, *p* < 0.0001) and right total temporal lobe volume ($F_{2,211} = 4.22$, *p* = 0.0160). In least square means analyses (Table 4), left hemisphere temporal lobe white matter was significantly greater in bipolar subjects on antipsychotics when compared with the other two groups, however the difference between comparison subjects and bipolar subjects not on antipsychotic medications was not significantly different. Right temporal lobe white matter was significantly different between all three groups. Bipolar subjects on antipsychotics also exhibited a larger right hemisphere total temporal lobe volume than did comparison subjects, but the other group comparisons were not statistically significant.

As typical and atypical antipsychotics have differences in their mechanism of action and may have different effects on brain structure, we examined what specific medications subjects were taking. Seventeen subjects were on olanzapine (mean dose [MD] = 14.8mg, SD = 8.2mg, range = 2.5–30mg daily), six on quetiapine (MD = 145.8mg, SD = 60.0mg, range = 75–200mg), ten on risperidone (MD = 2mg, SD = 1mg, range = 1–3mg), and one on clozapine (100mg daily). Two were on oral haloperidol (2mg and 10mg daily), one on haloperidol decanoate, and two on thiothixene 10mg daily. Removing the five subjects on typical antipsychotics from the sample did not alter the differences observed between groups in Table 4.

In post-hoc analyses, we tested for demographic and clinical differences between bipolar subjects who were and were not taking antipsychotic medications. There was no significant difference between groups in age (not taking: 43.7y, SD = 14.5y; taking: 44.1y, SD = 13.9y; *t* = 0.12, 121 *df*, *p* = 0.9024), sex (not taking: 65.5% or 55/84 female; taking: 61.0% or 25/41 female; $\chi^2 = 0.24$, 1 *df*, *p* = 0.6226) or minority representation (not taking: 14.3% or 12/84 minority; taking: 28.1% or 9/41 minority; $\chi^2 = 1.16$, 1 *df*, *p* = 0.2822). There were also no significant differences in depression severity by CES-D (not taking: 33.9, SD = 38.2; taking: 44.7, SD = 42.4; *t* = 1.43, 121 *df*, *p* = 0.1543), or for the bipolar cohort, in number of previous depressive (not taking: 4.2, SD = 10.0; taking: 2.4, SD = 4.2; *t* = 1.10, 121 *df*, *p* = 0.2753) or

manic mood episodes (not taking: 3.5, SD = 8.0; taking: 3.9, SD = 9.5; $t = 0.25$, 121 df , $p = 0.8178$).

DISCUSSION

The primary finding of this study is that individuals with bipolar disorder exhibit significantly larger temporal lobe white matter volumes bilaterally. Furthermore, bipolar subjects on antipsychotic medications exhibit significantly larger temporal lobe white matter volumes bilaterally than either bipolar subjects not taking antipsychotics or comparison subjects, while comparison subjects had smaller volumes than antipsychotic-free bipolar subjects only in the right hemisphere.

This study suggests that bipolar disorder is related to temporal lobe white matter pathology. Diffusion tensor imaging has also identified white matter differences in bipolar disorder (Regenold et al., 2006). Interestingly, a recent report used diffusion tensor tractography in a cohort of euthymic subjects with and without bipolar disorder, and found that bipolar disorder was associated with an increased number of reconstructed frontotemporal fibers between the subgenual cingulate cortex and the amygdalo-hippocampal complex, with no difference in anisotropy in those fiber tracts (Houenou et al., 2007). The authors interpreted these data to suggest that this fiber tract may have an increased volume with no change in fiber density. This would support our findings of increased temporal lobe white matter volumes, and may represent a structural finding that is related to the observed hyperactivity of anterior limbic structures in euthymic individuals with bipolar disorder (Strakowski et al., 2004).

Given the limitations inherent in any cross-sectional study, we cannot definitively explain the observed relationship between antipsychotic use and the MRI findings. Potential hypotheses for this relationship include an effect of the antipsychotics on temporal lobe structure or a relationship between greater temporal lobe white matter volume and clinical symptoms more often requiring antipsychotic medications, although in post-hoc analyses we found no association with clinical factors. The effects of antipsychotic medications on brain structure have not been well studied in bipolar disorder, but have been examined in schizophrenia. Antipsychotic use in schizophrenia has been associated with widespread changes in white matter and gray matter (Christensen et al., 2004; Girgis et al., 2006), including recent reports demonstrating increased volumes of frontal and basal ganglia white matter in subjects with schizophrenia who were treated with atypical antipsychotics (Bartzokis et al., 2007; Okugawa et al., 2007). Such studies support a role of atypical antipsychotic medications on brain myelination, a theory supported by animal studies demonstrating that atypical antipsychotics increase the genesis of glial cells (Kodama et al., 2004). It is not clear if these theories would explain our current findings; this would need to be tested using a longitudinal study design.

To our knowledge, no previous studies have reported a difference in temporal lobe white matter volumes between bipolar and comparison subjects, although a computational morphometric mapping study identified a white matter deficit in the left temporoparietal region in subjects with bipolar disorder when compared with unaffected relatives (McDonald et al., 2004). Although a few studies have reported hemispheric or cerebral white matter reductions in bipolar subjects (Davis et al., 2004), most have not found a significant difference from comparison subjects (Strakowski et al., 1993; Lim et al., 1999; Sassi et al., 2002). Our inability to identify a significant difference between groups in total cerebral white matter volume supports that our findings are specific to the temporal lobe, and not reflective of more widespread white matter differences.

We found no significant difference between subject groups in temporal lobe gray matter volumes or total cerebral white matter supporting previous reports finding no significant

difference in bipolar disorder of total temporal lobe volume (Johnstone et al., 1989; Swayze et al., 1992; Hauser et al., 2000), temporal lobe gray matter volume (Pearlson et al., 1997), or the superior temporal gyrus (Schlaepfer et al., 1994; Kasai et al., 2003). However, it should be recognized that some studies have identified significant differences in temporal lobe measures related to bipolar disorder (Altshuler et al., 1991; Wilke et al., 2004; El-Badri et al., 2006).

The principal limitation of this study is its cross-sectional design which limits our ability to make conclusions of causal relationships. Further, the samples were different in minority representation and education, which has the potential to bias the results despite controlling for these factors in multivariate analyses. Another is the lack of data on length of illness or length of treatment with current medications. Although current medication use provides some information, past medication use and compliance may also affect brain volume measures. Such data would have helped elucidate if our finding is related to a drug effect, and should be gathered in future studies. A longitudinal study design with prospective monitoring of medications and mood episodes, and more than one MRI measure would provide more clarity when examining the relationship between diagnosis, course of illness, medication use and temporal lobe volumes. It could also better elucidate potential interactions between drug classes which cannot be thoroughly addressed in a cross-sectional study.

Our findings are also generalizable only to clinically euthymic and depressed subjects with bipolar disorder; it is unclear if similar findings would be seen in a cohort in the midst of a manic episode. It could also be argued that our entry criteria, which excluded individuals with comorbid Axis I disorders or active substance abuse created a sample that is not fully representative of more severely affected individuals with bipolar disorder. However, had we included such individuals, it would have created a significant confounding factor in interpretation of our imaging data, as one could not clearly state any findings were related to bipolar disorder, and not another psychiatric diagnosis.

We have identified cross-sectional associations between a diagnosis of bipolar disorder, use of antipsychotic medications, and temporal lobe white matter volume. Volumetric studies, while helpful in observing group differences, tell us little about the intrinsic quality or integrity of the white matter. Future studies may include diffusion tensor imaging or magnetization transfer ratio imaging to further examine our findings. When used alongside volumetric techniques in a prospective longitudinal study, such a design may allow for a more clear understanding of the relationships identified in this report.

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Table 1

Sample Characteristics

Demographic / MRI measure	Bipolar subjects N = 125	Comparison subjects N = 87	Test statistic	p-value
Age (years)	43.8 (14.3)	40.8 (14.8)	$t = -1.27$	0.2057
Sex (% Female)	64.0% (80/125)	72.4% (63/87)	$\chi^2 = 1.94$	0.1835
Race (% Caucasian)	83.2% (104/125)	58.6% (51/87)	$\chi^2 = 14.9$	0.0001
Education (years)	14.5 (2.11)	15.1 (1.81)	$t = 2.33$	0.0209
CES-D score	24.8 (16.7)	3.6 (3.6)	$t = 13.01$	< 0.0001
Cerebrum (mL)	1171.8 (132)	1160 (136)	$t = -0.64$	0.5253

Data for continuous variables presented as mean (standard deviation). Analysis of continuous variables used pooled, two-tailed *t*-tests with 211 degrees of freedom, except for the CES-D comparison which used the Satterthwaite *t*-test with 126 *df* due to unequal variances. Analysis of categorical variables used the chi-square test with 1 degree of freedom.

Table 2
Relationship between diagnosis and temporal lobe volume adjusted for cerebral volume

Temporal lobe measure	Mean adjusted volume ratio (SD)		F value	p-value
	Bipolar subjects	Control subjects		
Left hemisphere				
Gray matter	0.0506 (0.0042)	0.0513 (0.0037)	0.66	0.4188
White matter	0.0202 (0.0023)	0.0193 (0.0022)	11.88	0.0007
Total (Gray + White)	0.0708 (0.0049)	0.0706 (0.0048)	1.37	0.2428
Right hemisphere				
Gray matter	0.0515 (0.0040)	0.0515 (0.0039)	0.43	0.5113
White matter	0.0205 (0.0025)	0.0193 (0.0024)	15.19	0.0001
Total (Gray + White)	0.0720 (0.0051)	0.0708 (0.0052)	5.15	0.0243
Total cerebral white matter	0.3446 (0.0485)	0.3492 (0.0428)	0.02	0.8992

Models examined for the effect of diagnosis on adjusted temporal lobe volumes while controlling for age, sex, education, and race. The diagnosis variable had 1, 211 degrees of freedom. Only white matter measures remained statistically significant after correcting for multiple comparisons.

Table 3

Psychotropic medication use and temporal lobe white matter volumes

	On Drug	Off Drug	t value	P value
Lithium	N = 39	N = 173		
Left temporal WM	0.0202 (0.0020)	0.0197 (0.0024)	1.01	0.3119
Right temporal WM	0.0204 (0.0022)	0.0200 (0.0026)	0.95	0.3408
Antipsychotics	N = 41	N = 171		
Left temporal WM	0.0210 (0.0025)	0.0195 (0.0022)	3.70	0.0003
Right temporal WM	0.0214 (0.0024)	0.0193 (0.0024)	3.92	0.0001
Anticonvulsants	N = 65	N = 147		
Left temporal WM	0.0202 (0.0024)	0.0196 (0.0022)	1.68	0.0949
Right temporal WM	0.0206 (0.0026)	0.0198 (0.0024)	2.17	0.0322
Antidepressants	N = 55	N = 157		
Left temporal WM	0.0199 (0.0021)	0.0198 (0.0024)	0.21	0.8341
Right temporal WM	0.0201 (0.0022)	0.0200 (0.0026)	0.08	0.9340
Benzodiazepines	N = 44	N = 168		
Left temporal WM	0.0202 (0.0024)	0.0197 (0.0023)	1.28	0.2032
Right temporal WM	0.0202 (0.0025)	0.0200 (0.0025)	0.51	0.6129

Results of two-tailed *t*-tests examining associations between adjusted regional volumes and psychotropic medication use, with 210 degrees of freedom. Only white matter results are shown. $\alpha = 0.00125$ after Bonferroni correction for multiple comparisons (standard $\alpha = 0.05$ divided by 40 separate comparisons).

Table 4
Adjusted temporal lobe white matter volume differences: relationship with diagnosis and antipsychotic medication use

Least squares mean adjusted volume			p-value between groups		
Bipolar subjects on antipsychotics (Group 1) N = 41	Bipolar subjects not on antipsychotics (Group 2) N = 84	Control subjects (Group 3) N = 87	1-2	1-3	2-3
Left hemisphere temporal lobe white matter, adjusted for cerebrum					
0.0214	0.0202	0.0195	0.0212	<0.0001	0.0888
Right hemisphere temporal lobe white matter, adjusted for cerebrum					
0.0217	0.0205	0.0196	0.0211	<0.0001	0.0358
Right hemisphere temporal lobe total volume, adjusted for cerebrum					
0.0731	0.0713	0.0703	0.4026	0.0114	0.1518

Temporal lobe white matter volumes are adjusted for cerebral volume, resulting from models also controlling for age, sex, education, and race. P-values determined using the least square means procedure, adjusted for multiple comparisons using the Tukey-Kramer procedure.