ORIGINAL ARTICLE

Brain Magnetic Resonance Imaging of Structural Abnormalities in Bipolar Disorder

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Background: The neuropathogenesis of bipolar disorder remains poorly described. Previous work suggests that patients with bipolar disorder may have abnormalities in neural pathways that are hypothesized to modulate human mood states. We examined differences in brain structural volumes associated with these pathways between patients with bipolar disorder hospitalized with mania and healthy community volunteers.

Methods: Twenty-four patients with bipolar disorder and mania were recruited from hospital admission records. Twenty-two healthy volunteers were recruited from the community who were similar to the patients in age, sex, race, height, handedness, and education. All subjects were scanned using a 3-dimensional radiofrequency–spoiled Fourier acquired steady state acquisition sequence on a 1.5-T magnetic resonance imaging scanner. Scans were analyzed using commercial software. Prefrontal, thalamic, hippocampal, amygdala, pallidal, and striatal volumetric measurements were compared between the 2 groups.

Results: Patients with bipolar disorder demonstrated a significant ($\Lambda = 0.64$; $F_{6,37} = 3.4$; $P = .009$) overall difference in structural volumes in these regions compared with controls. In particular, the amygdala was enlarged in the patients. Brain structural volumes were not significantly associated with duration of illness, prior medication exposure, number of previous hospital admissions, or duration of substance abuse. Separating patients into first-episode (n = 12) and multiple-episode (n = 12) subgroups revealed no significant differences in any structure ($P > .10$).

Conclusion: Patients with bipolar disorder exhibit structural abnormalities in neural pathways thought to modulate human mood.

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ALTHOUGH BIPOLAR disorder is a common psychiatric illness that causes considerable morbidity and mortality,[1-3] its neuropathogenesis is poorly understood. Because mood dysregulation is the defining symptom of bipolar disorder, the neuroanatomic substrates of this illness likely include neural pathways that modulate emotional function. Indeed, numerous cases have been reported[4-7] of affective syndromes developing following focal brain injuries. Specifically, lesions involving left prefrontal cortical or basal ganglial regions are associated with secondary depression, whereas secondary mania is more commonly associated with lesions of the orbitofrontal and basotemporal cortices, the head of the caudate, and the thalamus.[4-7] Recent studies[8-10] of healthy volunteers found activation in these same brain regions in response to induced mood states. Other brain regions, such as the amygdala-hippocampal complex, were also implicated[8-10] in controlling induced emotion in these studies. Integrating human studies with studies of animals, investigators[11-14] have proposed a neuroanatomic model of mood regulation involving 2 interconnected brain circuits: a limbic (amygdala)-thalamic-prefrontal cortical circuit and a limbic-striatal-pallidal-thalamic circuit. Disruptions in these pathways may contribute to the pathological mood states and neurovegetative symptoms of bipolar disorder.

Few magnetic resonance imaging (MRI) studies[15-25] of bipolar disorder have specifically examined these brain structures implicated in mood regulation, and results have varied. For example, amygdala volumes in patients with bipolar disorder have been found to be larger than,[21] smaller than,[16] and equal to[17] those of normal controls. Similar mixed results have been observed for the hippocampus,[17,21,23] the caudate,[17-20] the thalamus,[19,20] and the prefrontal cortex.[20,22,24] To our knowledge, however, no study has examined the network of structures proposed to underlie mood regulation using a single multivariate analy-

SUBJECTS AND METHODS

SUBJECTS

For this study, 24 patients with bipolar disorder according to criteria of *DSM-III-R*,[26] manic (n = 14) or mixed (n = 10), 20 (83%) of whom currently had psychosis, were recruited from admissions to the University of Cincinnati Hospital, Cincinnati, Ohio. Healthy volunteers with no history of major psychiatric disorders in themselves or first-degree relatives were recruited from surrounding neighborhoods and were paid for their participation. Additional inclusion criteria for all subjects were an age of 18 to 45 years, no history of major neurological or medical illness, a negative finding from the pregnancy test in women, no contraindication to an MRI scan, no evidence of mental retardation, no substance use disorder during the previous 3 months as confirmed by negative results on a toxicology screen, and the provision of informed consent.

Subjects were evaluated using the Structured Clinical Interview for *DSM-III-R*,[27] completed by experienced psychiatrists ($\kappa = 0.94$).[1-3] Patients received medical evaluations during their hospital stay. Healthy volunteers were medically screened using a review-of-systems interview. Family histories of psychiatric illness were identified by asking the healthy volunteers screening questions drawn from the Family History–Research Diagnostic Criteria.[28]

CLINICAL VARIABLES

As listed in **Table 1**, several demographic and clinical variables were obtained. The duration of illness was calculated as the current age minus the age at the first affective episode.[1,2] Substance abuse was defined as any *DSM-III-R* substance use disorder, and the duration of substance abuse was calculated as the current age minus the age when the abuse began.[1-3] Patients with no previous treatment were considered to be in a first episode.[1]

IMAGE ACQUISITION AND ANALYSIS

We used a 3-dimensional, radio-frequency–spoiled Fourier acquired steady state acquisition sequence (repetition time, 22 milliseconds; echo time, 7 milliseconds; and flip angle, 25°) on a 1.5-T MRI machine (Picker International, Cleveland, Ohio) to obtain whole-brain T_1-weighted images with an in-plane field of view of 24 cm^2 and a 128×256-pixel matrix. The third (z) dimension of the acquisition was defined so that 1-mm-thick coronal slices covered the entire brain (about 190 per subject). The data matrix was interpolated to a $256 \times 256 \times 256$-pixel matrix on reconstruction to provide a 1-mm isotropic image data set.

Image sets were reformatted and analyzed using commercial software (Brain Image, Version 2.3.3)[29] that provides interactive semiautomatic region-of-interest (ROI) measurement by direct manual tracing (used for measures of small structures, eg, amygdala) and by brain thresholding and segmentation (used for larger ROIs, eg, prefrontal cortex). It also provides concurrent visualization of the orthogonal sagittal, coronal, and axial views for any ROI. Each image set was reformatted into the same coronal plane before ROI measurements, which were obtained blind to the subject's identity. To do this, the midsagittal plane was identified as the plane that bisected the left and right cerebral hemispheres in both axial and coronal views and in which the cerebral aqueduct and the posterior commissure were most clearly visualized. Next, an orthogonal axial plane was identified that intersected both the anterior and posterior commissures. Finally, 1-mm-thick coronal images orthogonal to the midsagittal and anterior commissure–posterior commissure planes were obtained. A different orientation was used for measurements of the amygdala and hippocampus to improve measurement reliability.[21,30] Specifically, after the midsagittal plane was identified, an orthogonal plane parallel to the long axis of the left anterior hippocampus was identified. Then, coronal images orthogonal to those 2 planes were obtained.

Regions of interest were identified using atlases[31,32] in conjunction with an ongoing review of scans by experienced investigators (S.M.S. and K.W.S.).[20,25,33] For all ROIs except the cerebrum, areas were measured in every slice in which the structures were visualized, and volumes were calculated by multiplying by slice thickness (1 mm). For the cerebrum, every fifth slice was measured and the volume calculated by multiplying by 5 mm.

Each person completing volumetric assessments was extensively trained by comparing ROI measurements from at least 10 non–study subjects with an experienced rater, in which the 2 raters' measurements were obtained blind to each other. If high interrater reliability was not achieved (ie, intraclass correlation coefficient = 0.90), then this process was repeated until the person was successfully trained. Reliability assessments were also obtained from measurements by trained raters on study subjects. Using these methods, high interrater and intrarater reliability for each ROI in this study was established (intraclass correlation coefficient >0.90 for all measurements). The specific ROIs follow.

Cerebrum

The total cerebral volume was measured semiautomatically from about 40 slices using thresholding and segmentation. Cerebral volume was significantly ($P<.05$) associated with height ($r = 0.31$) and sex ($r = 0.36$) but not age ($r = -0.04$; $P>.70$), reflecting the limited age range of the subjects. It did not differ between groups (Table 1; $t_{44} = 0.65$; $P>.50$), so was covaried in analyses to control for head-size differences among subjects.

Prefrontal Lobe

The prefrontal lobe volume included all cerebral tissue anterior to the coronal plane at the most anterior point of the

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sis to control for intercorrelations among brain regions. Furthermore, many of the differences among previous studies may reflect the relatively thick image slices used, which can confound measurements of small brain structures by obscuring subtle group differences.

With these considerations in mind and using multivariate analyses, we studied brain structures in the hypothesized mood-regulatory pathways of 24 patients with bipolar disorder and 22 healthy volunteers. Measurements were made from thinly sliced (1-mm) high-resolution MRI scans. We hypothesized that the patients would demonstrate abnormalities in the putative mood-regulatory pathways compared with healthy volunteers.

genu of the corpus callosum.[34] It was measured semiautomatically (mean, 32 slices).

Thalamus

The thalamic nuclei were manually traced in their entirety (mean, 27 slices). The medial boundary was the lateral ventricle, and the lateral boundary was the posterior limb of the internal capsule. When the lateral boundary was difficult to visualize, raters relied on the continuation of boundaries from previous and subsequent slices and the concurrent views of the structure in the orthogonal axial and sagittal planes to make measurements.[20,34] This approach was used for other ROIs as well.

Striatum

The striatum included the sum of the caudate and putamen volumes (**Figure 1**), which were combined to decrease the number of dependent variables because individually they did not differ significantly between groups. The head and body of the caudate were traced in each slice until the tail turned inferolaterally (mean, 45 slices).[20,34,35] To separate the caudate from the rest of the striatum where it merges with the nucleus accumbens, a line was drawn extending from the most inferior point of the ipsilateral lateral ventricle to the most inferomedial point of the internal capsule. The putamen was traced in its entirety (mean, 40 slices). It was bounded laterally and anteriorly by the external capsule and separated from the rest of the striatum by a line extending inferiorly from the anterior limb of the internal capsule.[34,35] It was separated from the globus pallidus by the lateral medullary lamina.[34,35]

Globus Pallidus

The globus pallidus was traced in its entirety (mean, 20 slices) and was separated from the putamen as described (Figure 1). It was bounded superiorly and medially by the internal capsule and inferiorly by the substantia innominata and anterior commissure.[34,35]

Hippocampus

The anterior hippocampus was separated from the amygdala by identifying the most anterior coronal image in which the alveus was clearly visualized (**Figure 2**).[21,30] From that point, the hippocampus was measured posteriorly (mean, 28 slices) to the image where right and left inferior and superior colliculi were jointly visualized.[21,30] The remaining boundaries were defined by the temporal white matter.

Amygdala

The amygdala was measured in its entirety (mean, 25 slices) using published methods.[21,30] It was distinguished from the superior border of the hippocampus by the alveus (Figure 2). The lateral and superior boundaries were defined by the temporal lobe white matter. The endorhinal sulcus was identified and followed laterally to separate the amygdala from the lateral geniculate.[30] The anterior pole of the amygdala was defined as the image in which its width was approximately 2.5 times the thickness of the adjacent entorhinal cortex located inferiorly. From that point, the amygdala was traced posteriorly until it joined the tail of the caudate. Medially this measurement included small parts of the overlying cortical gray matter (entorhinal cortex, ambiens gyrus, and semilunar gyrus).[21,30]

Finally, at the reviewers' request, ventricular measurements are reported. Lateral ventricles were measured in their entirety using thresholding and segmentation (mean, 100 slices). The third ventricle was measured using a combination of thresholding and manual tracing (mean, 32 slices). Its anterior boundary was the slice in which the optic chiasm was first visualized. It was bounded posteriorly by the pineal gland.

STATISTICAL ANALYSIS

Clinical and demographic variables (Table 1) were examined as possible covariates, but none demonstrated differences between the groups, even at $P<.30$. No ROI-laterality differences were observed between groups using Student *t* tests, so for subsequent analysis, these measurements were combined.

To test our primary hypothesis, a multivariate analysis of covariance (MANCOVA) was performed. Group assignment (ie, patient or healthy volunteer) served as the independent variable, and the 6 ROIs were the dependent variables. As noted, the duration of substance abuse and total cerebral volume were covaried a priori. Following MANCOVA, effect sizes ($\hat{f}$) for group differences were calculated to identify structures that most contributed to the overall difference.[36] A multivariate profile analysis was then performed in which the original ROI variables were transformed to successive differences between variables to examine whether the configural pattern of ROIs differed between groups. Finally, repeated-measures analyses of covariance (ANCOVAs) were performed for selected structures to identify group-by-ROI interactions.

In healthy volunteers, no ROI measurements exhibited distributions significantly different from normal (Shapiro-Wilks statistic, $W>0.93$; $P>.10$). In patients, the amygdala and hippocampal distributions, but no other structures, exhibited small but significant deviations from normal ($W=0.85$ and $W=0.83$, respectively; $P<.05$). To determine whether this violated the normality assumption of MANCOVA, ROI variables were rank-transformed, and MANCOVAs of the ranked and unranked variables were compared.[28] The results of these 2 analyses were essentially identical, supporting the original MANCOVA.

RESULTS

The 2 groups demonstrated significantly different overall ROI volumes as hypothesized (Λ [Wilks lambda] $=0.64$, $F_{6,37}=3.4$; $P=.009$) (**Table 2**). The differences between groups in amygdala volumes contributed the only large effect ($\hat{f}>0.40$) to the overall differences, although the differences in volumes of the thalamus, globus pallidus, and striatum contributed medium effect sizes ($\hat{f}>0.25$; Table 2). These structures were larger in patients than in healthy volunteers. The profile analysis suggested between-group differences among ROIs ($\Lambda=0.76$, $F_{5,38}=2.3$; $P<.06$). When the ROI with the lowest effect size (hippocampus) was compared with that with

Table 1. Demographic and Diagnostic Characteristics of 24 Patients With Bipolar Disorder (BD) Hospitalized for Treatment of Mania and 22 Normal Comparison Subjects*

Characteristic	Patients With BD	Healthy Volunteers
Age, y	27 (6)	28 (6)
Sex, No. (%) male	17 (71)	13 (59)
Race, No. (%) white	19 (79)	15 (68)
Education, y	13 (2)	14 (2)
Height, cm	173 (8)	175 (10)
Right-handed, No. (%)	22 (92)	21 (95)
History of any substance use disorder, No. (%)†	10 (42)	3 (14)
Alcohol dependence	4 (17)	0 (0)
Drug dependence	5 (21)	0 (0)
Substance use disorder duration, y‡	1.7 (2.5)	0.4 (1.0)
Duration of affective disorder, y	6 (6)	. . .
Previous depressive episodes	3 (5)	0 (0)
Previous manic episodes	2 (4)	0 (0)
No. of previous hospitalizations	2 (3)	. . .
Medications before index episode, No. (%)		
Antipsychotic	8 (33)	. . .
Mood stabilizer	12 (50)	. . .
None (first-episode)	12 (50)	. . .
Medications during index episode, No. (%)		
Antipsychotic	17 (71)	. . .
Mood stabilizer	24 (100)	. . .

*Data are given as mean (SD) except where noted. Ellipses indicate not applicable.
†Significant difference between groups: $\chi^2 = 4.4$; P = .04.
‡Significant difference between groups: $t_{44} = 2.4$; P = .02.

the highest (amygdala) using repeated-measures ANCOVA, a significant group-by-ROI interaction was observed ($F_{1,42} = 5.1$; $P = .03$). Similar comparisons with the hippocampus were performed for the next 2 structures in descending order of effect size, and significant group-by-ROI interactions were not observed (for thalamus: $F_{1,42} = 3.4$, $P = .07$; for pallidum: $F_{1,42} = 0.64$, $P > .40$; no other comparisons were performed). When subjects with a history of substance abuse were excluded, the MANCOVA demonstrated a similar overall test statistic that remained significantly different between the 2 groups, even with the smaller number of subjects ($\Lambda = 0.58$, $F_{6,25} = 3.0$; $P = .02$). The profile analysis results also remained similar when subjects with substance abuse were excluded ($\Lambda = 0.70$, $F_{5,26} = 2.3$; $P = .08$).

In the patients, none of the ROIs exhibited significant correlations with the duration of illness, the number of previous hospital admissions, the duration of substance abuse, antipsychotic or mood stabilizer medication exposure, or number of previous affective episodes. Univariate ANCOVAs between patients with a first episode and those with multiple episodes also showed no significant differences for these ROIs. Finally, because the groups were not perfectly balanced in sex distribution, this was covaried in another MANCOVA and elicited little change ($\Lambda = 0.65$, $F_{6,36} = 3.2$; $P = .01$). Because these secondary analyses involved small numbers of subjects in some groups, they should be considered preliminary and interpreted cautiously.

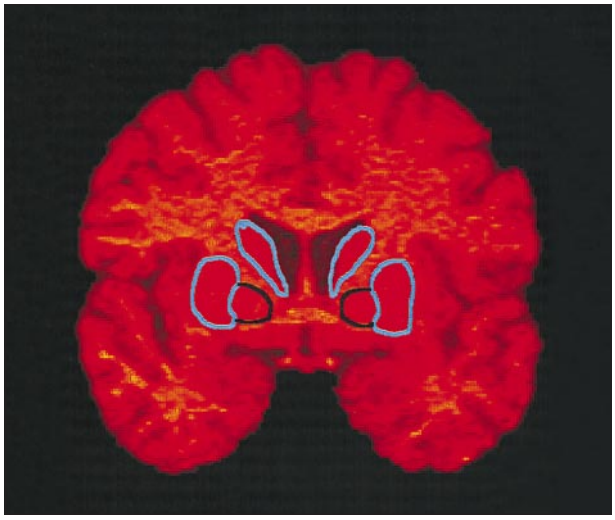

Figure 1. *Examples of manual tracings of the striatum (blue line; the caudate is located superiorly, the putamen inferiorly) and the globus pallidus (black line) from a reformatted coronal magnetic resonance image.*

Finally, we used univariate ANCOVAs to compare ventricular measurements between groups, which revealed that the left lateral ventricle was significantly larger in the patients ($F_{1,42} = 4.4$; $P = .04$).

COMMENT

We observed a significant difference between patients with bipolar disorder and healthy volunteers in the volumes of structures in brain pathways hypothesized to modulate mood. Although differences in amygdala volumes contributed the only large effect to this difference, other structures (thalamus, pallidum, and striatum) contributed medium to large effects. In contrast, the prefrontal cortex and hippocampus contributed little to the overall group differences. These results suggest that in bipolar disorder, abnormalities may exist in the network of structures that putatively modulate human mood, although these abnormalities may be confined to only a few specific structures, ie, the amygdala and possibly the globus pallidus and thalamus.

Indeed, the amygdala exhibited the only significant region-by-group interaction. The amygdala—or amygdaloid complex because it is actually a collection of structurally, histochemically, and functionally diverse nuclei—has long been recognized as an important component of the neural circuitry underlying human emotion.[32,37-39] Amygdala injuries disrupt emotional expression and stimulus-reward associations, which can resemble the symptoms of bipolar disorder.[37-39] Complete bilateral amygdala ablation leads to a state of hypoemotionality.[37,38] In contrast, we found the amygdala to be enlarged in patients with bipolar disorder, suggesting possible hypertrophy of this brain region that might reflect dysfunction underlying the mood lability of bipolar disorder. In the absence of neuropathological and functional studies of this structure in patients with bipolar disorder, this remains speculative.

Other investigators have observed enlargement in the amygdala,[21] as well as the thalamus[17] and caudate,[19]

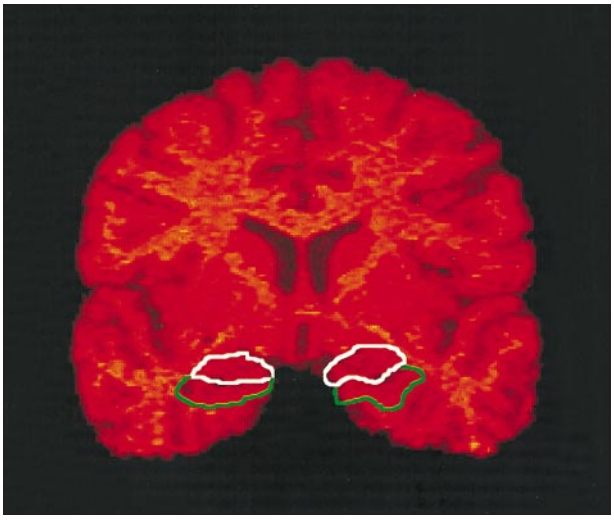

Figure 2. *Examples of manual tracings of the hippocampus (green line) and the amygdala (white line) from a reformatted coronal magnetic resonance image.*

in patients with bipolar disorder. Altshuler et al[21] recently reported amygdala enlargement in patients with bipolar disorder compared with patients with schizophrenia, whereas the latter group demonstrated volume reduction of the hippocampus. The investigators suggested that these relative volume differences between the patient groups in hippocampus and amygdala may have some diagnostic specificity. Unfortunately, we did not include a psychiatric comparison group, so we cannot specifically address this possibility. Nonetheless, volume reduction in medial temporal structures is commonly the rule in patients with schizophrenia.[40]

Aylward et al[18] have also reported striatal enlargement in bipolar disorder, and several investigators[41] have reported similar increases in patients with schizophrenia. Caudate enlargement in schizophrenia has been associated with exposure to neuroleptic medication, suggesting that medication effects may account for at least some of the observed regional volume increase. In contrast, we found that previous treatment with antipsychotic and mood stabilizer medications was not significantly associated with any of the structural volumes we measured. Because we did not obtain specific quantitative assessments of exposure to neuroleptic and mood stabilizer medications, this lack of association should be considered preliminary.

As has been reported by others,[13,15] we observed lateral ventricular enlargement in the patients with bipolar disorder, specifically on the left. This enlargement, however, does not appear to be due to tissue loss or underdevelopment in the striatum or thalamus, similar to what we reported previously.[20] The specific cause of ventricular enlargement in bipolar disorder remains unknown.[13,15]

We could not determine whether volumetric abnormalities preceded the bipolar syndrome or, alternatively, developed during the bipolar disorder. The lack of associations between brain regional volumes and the duration of illness and the lack of differences between patients with a first episode and those with multiple episodes support the former suggestion. The onset of affective illness, however, was defined in this study as the age at which a first full affective episode developed. It is possible that some patients had periods of subsyndromal affective illness before this age that, if identified, might be associated with changes in neuroanatomic structure. Longitudinal studies and studies of at-risk persons in whom bipolar illness has not yet developed are needed to identify specific relationships between structural abnormalities and the course of bipolar illness.

Table 2. Magnetic Resonance Imaging Morphometric Brain Structural Measurements in 24 Patients With Bipolar Disorder (BD) With Mania and 22 Normal Comparison Subjects*

Brain Structure†	Patients With BD	Healthy Volunteers	Effect Size, $\hat{f}$‡
Total cerebrum	1132 (130)	1110 (98)	0.10
Prefrontal cortex, total	129.6 (14.7)	133.1 (24.4)	
Right	66.2 (8.1)	66.9 (11.9)	0.17
Left	63.4 (7.8)	66.2 (13.1)	
Thalamus, total	15.1 (2.2)	13.5 (1.7)	
Right	7.4 (1.0)	6.6 (0.8)	0.32
Left	7.7 (1.2)	6.9 (0.9)	
Hippocampus, total	8.6 (1.2)	8.4 (0.8)	
Right	4.3 (0.6)	4.2 (0.4)	0.03
Left	4.3 (0.6)	4.2 (0.4)	
Amygdala, total§	7.1 (1.1)	6.3 (0.8)	
Right	3.6 (0.5)	3.2 (0.4)	0.46
Left	3.5 (0.6)	3.1 (0.4)	
Striatum, total	24.2 (2.8)	22.6 (1.8)	
Right	14.2 (1.4)	11.4 (1.0)	0.28
Left	12.0 (1.5)	11.2 (0.9)	
Globus pallidus, total	3.6 (0.5)	3.2 (0.6)	
Right	1.8 (0.3)	1.6 (0.3)	0.31
Left	1.8 (0.2)	1.6 (0.3)	
Left lateral ventricle‖	5.9 (3.4)	4.6 (2.4)	0.31
Right lateral ventricle	5.4 (2.8)	4.7 (2.1)	0.17
Third ventricle	1.0 (0.3)	0.9 (0.3)	0.05

**Data, in cubic centimeters, are given as mean (SD).*

†Overall multivariate analysis of covariance of bipolar patients vs healthy volunteers: $\Lambda = 0.64$, $F_{6,37} = 3.4$, $P = .009$; test of parallelism: $\Lambda = 0.76$, $F_{5,38} = 2.3$, $P < .06$.

‡$\hat{f} = 0.10$ indicates a small effect size; $\hat{f} = 0.25$, a medium effect size; and $\hat{f} > 0.40$, a large effect size.

§Significant group-by-region-of-interest interaction: $F_{1,42} = 5.1$, $P = .03$.

‖Significant difference between groups: $F_{1,42} = 4.4$, $P = .04$.

Several limitations should be considered when interpreting these results. First, abnormalities of structure do not necessarily mean abnormalities of function. In the absence of associations between a brain structure's function and clinical symptoms, it is not possible to directly demonstrate that the structure is involved in the expression of bipolar disorder. Second, we chose to include patients and healthy volunteers with past histories of substance abuse or dependence, which may be viewed as controversial. As many as 60% of patients with bipolar disorder abuse psychoactive substances, so excluding all patients with histories of substance abuse produces an unrepresentative sample.[1-3,7,42] Nonetheless, because substance abuse, particularly alcohol dependence, is associated with structural brain changes, its influence must be examined.[43-46] To address this, we excluded subjects with substance abuse during the 3 months before the index assessment because brain atrophy associated

with chronic alcohol abuse appears to improve after 1 to 3 months of sobriety.[43-46] In addition, the lack of significant associations between substance abuse duration and any of the structures measured and the continued significant difference between patients and controls after all the subjects with past histories of substance abuse were removed support our approach to this problem. Third, the methods for delineating the frontal lobe, although based on previous research,[34] do not identify specific regions within the prefrontal cortex and, therefore, may not identify abnormalities in the bipolar group that would be apparent with a different approach. Finally, the anterior pole of the amygdala was determined by its thickness relative to the thickness of the nearby medial temporal cortex. It was also not possible to separate entirely the amygdala measurement from medial temporal cortex, as noted previously. Thus, differences between groups in medial temporal cortical thickness may have contributed to differences in amygdala volume.

CONCLUSIONS

We found significant volumetric differences between patients with bipolar disorder and healthy volunteers in the network of structures hypothesized to modulate human mood. Specifically, the patients exhibited enlargement of the amygdala and possibly the thalamus and globus pallidus. Although we found no significant associations of these volumetric abnormalities with a variety of clinical measures, whether these findings are primary to bipolar disorder or secondary to some other factor remains to be determined.

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