

Amygdala and Hippocampal Volumes in Adolescents and Adults With Bipolar Disorder

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Background: The purported functions of medial temporal lobe structures suggest their involvement in the pathophysiology of bipolar disorder (BD). Previous reports of abnormalities in the volume of the amygdala and hippocampus in patients with BD have been inconsistent in their findings and limited to adult samples. Appreciation of whether volumetric abnormalities are early features of BD or whether the abnormalities represent neurodegenerative changes associated with illness duration is limited by the paucity of data in juvenile samples.

Objective: To investigate amygdala and hippocampal volume in adults and adolescents with BD.

Setting and Participants: Subjects included 36 individuals (14 adolescents and 22 adults) in outpatient treatment for BD type I at a university hospital or Veterans Affairs medical center or in the surrounding community, and 56 healthy comparison subjects (23 adolescents and 33 adults).

Design and Main Outcome Measures: Amygdala and hippocampal volumes were defined and measured on high-resolution anatomic magnetic resonance imaging scans. We

used a mixed-model, repeated-measures statistical analysis to compare amygdala and hippocampal volumes across groups while covarying for total brain volume, age, and sex. Potential effects of illness features were explored, including rapid cycling, medication, alcohol or other substance dependence, duration, and mood state.

Results: For both the amygdala and hippocampal regions, we found an overall significant volume reduction in the BD compared with the control group ($P < .0001$). Amygdala volume reductions (15.6%) were highly significant ($P < .0001$). We observed a nonsignificant trend ($P = .054$) toward reductions in hippocampal volumes of lesser magnitude (5.3%). Effects of illness features were not detected.

Conclusions: These results suggest that BD is associated with decreased volumes of medial temporal lobe structures, with greater effect sizes in the amygdala than in the hippocampus. These abnormalities are likely manifested early in the course of illness, as they affected adolescent and adult subjects similarly in this sample.

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THE NEUROBIOLOGY of adolescent and adult bipolar disorder (BD) has received little study, although the identification of brain abnormalities associated with early onset and age-related disease progression could help to inform prevention and treatment strategies. Medial temporal lobe abnormalities have been implicated in the pathophysiology of BD by studies of localized lesions, seizure disorders, and neuropsychological test performance. Lesions in this brain region, especially those that produce seizure foci, are associated with episodic symptoms that range from inappropriate elation, grandiosity, distractibility, and hypersexuality to depression, excessive guilt, circumstantiality, and paranoia.¹⁻⁴ Preclinical observation of the

vulnerability of medial temporal structures to sensitization spawned a valuable heuristic model to conceptualize the increased rate of BD cycling as a consequence of the increasing accumulation of multiple, untreated affective episodes.⁵ The reduction of sensitization by anticonvulsants led to their successful implementation in the treatment of BD.^{5,6} In adult BD, the impaired recognition of facial affects and the inappropriate emotional biasing of cognitive functions have implicated disturbances in amygdala functioning.⁷⁻¹⁰ Verbal learning deficits during times of mania and euthymia in adults with BD,¹¹⁻¹³ discordant monozygotic twins, and non-twin siblings^{14,15} implicate a trait deficit in hippocampal functioning.

Functional and structural neuroimaging studies in adult BD further support

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Table 1. Features of the BD and Healthy Control Groups*

	BD Group (n = 36)	Healthy Control Group (n = 56)	P Value†
Sex			
Male	16 (44)	29 (52)	.49
Female	20 (56)	27 (48)	
Age, mean (SD), y	31.0 (14.1)	28.3 (13.7)	.23
Age group‡			
Adolescent	14 (39)	23 (41)	.83
Adult	22 (61)	33 (59)	
TBV, mean (SD), mm ³	1 165 475 (138 447)	1 195 615 (124 817)	.28

Abbreviations: BD, bipolar disorder; TBV, total brain volume.

*Unless otherwise indicated, data are expressed as number (percentage) of subjects.

†Calculated for comparison between the healthy control and BD groups.

‡For purposes of this study, adults are aged 23 to 57 years; adolescents, 10 to 22 years.

amygdala and hippocampal involvement in the illness. Reports of functional abnormalities in the temporal lobe in adult subjects with BD¹⁶⁻¹⁹ include recent observations of increased amygdala activity in depressed subjects with BD at rest^{20,21} and during performance of a facial emotion recognition task.⁷ Reports of abnormal amygdala volumes in adult BD have been highly variable and include negative findings, increases and decreases in volume, and findings that have been unilateral and bilateral.²²⁻²⁵ Studies of hippocampal volumes in adult BD have also yielded variable findings that include no group differences, as well as unilateral decreases in subjects with BD, and in ill members of monozygotic twin pairs who are discordant for BD.²²⁻²⁸ Data conflict as to whether volume abnormalities in medial temporal lobe structures are present at the time of the first episode or increase in magnitude with the duration of illness.^{23,24,27,29}

We are unaware of previous imaging studies of the anatomic or functional integrity of the amygdala or hippocampus in juveniles with BD. In one study of juvenile BD, clinical interpretation of magnetic resonance imaging scans was suggestive of an increased incidence of abnormal asymmetry of the temporal horn of the lateral ventricles. Amygdala and hippocampal measurements, however, were not reported.³⁰ We report herein a study of amygdala and hippocampal volumes in adolescents and adults with BD compared with healthy control subjects.

METHODS

SUBJECTS

Patients (**Table 1**) included 22 adult outpatients with BD I (aged 23-54 years; 12 [55%] female; 8 [36%] free of medication) treated at the Connecticut Veterans Affairs Medical Center, West Haven, or the Yale University School of Medicine Medical Center, New Haven, Conn, or by practitioners in the community, and 14 adolescent outpatients with BD I (aged 10-22 years; 8 [57%] female; 6 [43%] free of medication) treated at the Yale Child Study Center, New Haven, or in the local community. The control group consisted of 33 healthy adults (aged, 24-57

years; 17 females [52%]) and 23 healthy adolescents (aged 10-22 years; 10 females [43%]).

Healthy adult controls were recruited by word of mouth and advertisement in the surrounding community. Healthy adolescent controls were selected randomly from a list of 10 000 names purchased from a telemarketing company of potential subjects living in the same range of neighborhoods as the patients in an attempt to draw from similar socioeconomic backgrounds. Introductory letters were followed by screening telephone calls. Of the eligible control families contacted, approximately 10% participated. After complete description of the study, written informed consent was provided by all study subjects 18 years and older. For the younger subjects, written informed consent was provided by a guardian and written informed assent was provided by the subject.

Structured clinical interviews confirmed the presence or absence of DSM-IV Axis I disorders. The Structured Clinical Interview for DSM-IV Axis I & II Disorders, Version 2.0,³¹ for the adults was performed by a board-certified adult psychiatrist (H.P.B.), and the revised Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version³² for subjects 18 years and younger (juvenile subjects) was performed by a board-certified child psychiatrist and a psychologist expert in childhood mood disorders (A.M. and J.K., respectively). For the juvenile subjects, interviews were administered separately to the subject and a parent (or maternal grandmother for 1 patient). Final DSM-IV diagnoses were established by the consensus diagnosis of clinical and structured interviews. All patients met criteria for BD I. All patients also reported at least 1 first- or second-degree relative with a mood-spectrum disorder that included BD, major depressive disorder, or alcohol abuse, although a positive family history was not required for study entry.

Nine adults and 7 adolescents (44% of the patients) met criteria for rapid cycling (this and other clinical features are summarized in **Table 2**). Eleven (31%) of the BD subjects had a history of alcohol dependence (9 adults and 2 adolescents). History of dependence or abuse of other substances included marijuana abuse/dependence (8 adults and 3 adolescents [31%]), cocaine dependence (2 adults), polysubstance dependence (1 adult), stimulant abuse (1 adult), and hallucinogen abuse (1 adult). Duration of alcohol and substance dependence remission was longer than 5 years, with the exception of 2 subjects who were in remission for only 1 year. Other comorbidities were present only in the adolescents and included 2 subjects each with attention-deficit/hyperactivity disorder, oppositional defiant disorder, and a learning disorder not otherwise specified, and 1 subject each with posttraumatic stress disorder, obsessive-compulsive disorder, avoidant disorder of childhood, and developmental coordination disorder. At the time of scanning, 10 adults (45%) were euthymic, 7 (32%) were in a manic/mixed or hypomanic state, and 5 (23%) were depressed. All adolescents were symptomatic at the time of scanning and reported varying degrees of depressive and manic symptoms consistent with the characteristic clinical presentation in adolescents with BD.³³⁻³⁶ One adolescent had mood symptoms but did not meet DSM-IV criteria for an acute mood episode.

According to the retrospective reporting by BD subjects or by the guardians of juvenile subjects, mean ± SD age of illness onset was 17.4 ± 8.0 years, and mean ± SD illness duration was 13.1 ± 9.5 years. Twenty-two (61%) of all BD subjects had a history of psychiatric hospitalization. Nine adults and 2 adolescents had had 1 hospitalization; 4 adults and 2 adolescents, 2 to 4 hospitalizations; and 4 adults and 1 adolescent, more than 5 hospitalizations.

All subjects had no history of other neurological disorders, loss of consciousness for longer than 5 minutes, or significant medical illness, with the exception of 1 subject each

in the adult and the adolescent BD samples with hypothyroidism. Healthy controls had no history of Axis I disorder in themselves or their first-degree family members. No subject drank alcohol or used street drugs for a minimum of 24 hours before scanning. Medications used by BD subjects included lithium carbonate in 7 adults (32%) and 3 adolescents (21%), anticonvulsants in 7 adults (32%) and 5 adolescents (36%), antidepressants in 10 adults (45%) and 3 adolescents (21%), antipsychotics in 3 adults (14%) and 2 adolescents (14%), benzodiazepines in 1 adult (5%), stimulants in 1 adolescent (7%), clonidine hydrochloride in 1 adolescent (7%), and levothyroxine sodium (Synthroid) in 1 adult (5%) and 1 adolescent (7%).

MAGNETIC RESONANCE IMAGE ACQUISITION AND PROCESSING

Magnetic resonance imaging scans were obtained using a single 1.5-T scanner (GE Signa; General Electric, Milwaukee, Wis). Head positioning was standardized using canthomeatal landmarks. Images were obtained using a 3-dimensional sagittal spoiled gradient echo sequence (repetition time, 24 milliseconds; echo time, 5 milliseconds; flip angle, 45°; frequency encoding superior/inferior; no wrap; 256 × 192 matrix; field of view, 30 cm; 2 excitations; slice thickness, 1.2 mm; and 124 contiguous slices).

Morphometric analyses were performed on Sun Ultra 10 workstations using ANALYZE 7.5 software (Biomedical Imaging Resource, Mayo Foundation, Rochester, Minn) by operators blinded to subject characteristics and hemisphere (images were flipped in the transverse plane randomly before region definition). Large-scale variations in image intensity were removed, and images were reformatted to standardized head flexion/extension, rotation, and tilt using the anterior commissure-posterior commissure and standard midline landmarks. An isointensity contour function was used in conjunction with manual editing to isolate the cerebrum. Total brain volume measures (TBV) (cerebral gray and white matter volume excluding cerebrospinal fluid) were used as covariates in the statistical analyses to control for general scaling effects. In addition, data were analyzed separately using intracranial volume measures (cerebral volume including sulcal cerebrospinal fluid) as covariates in place of TBV to minimize potential effects of atrophy due to neurodegenerative processes.³⁷ The amygdala and hippocampus were defined by means of manual tracing. Initial tracings in the coronal plane were confirmed in orthogonal views. If corrections were made, their accuracy was corroborated in the orthogonal imaging planes. Amygdala and hippocampal delineations were performed in accordance with methods described previously.^{37,38}

Interrater intraclass reliability coefficients, assessed on 10 scans obtained at times spaced equally throughout the study, were 0.89 for amygdala delineations and 0.94 for hippocampal delineations. An expert in these procedures (B.S.P.) reviewed all of the tracings used for this study for spatial accuracy. Spatial agreement for these procedures are approximately 75%.³⁸ Differences in spatial agreement were resolved by the consensus of 2 trained investigators expert in the delineations (R.W. and B.S.P.).

STATISTICAL ANALYSES

We performed all statistics analyses using SAS software, version 8.2 (SAS Institute Inc, Cary, NC). A *P* value of .05 (2-sided) was used as the level of significance for all tests.

Primary Hypothesis Testing

The primary statistical model tested whether the BD and healthy control groups differed in regional volume. The model in-

Table 2. Clinical Features of the BD Group*

	All With BD (n = 36)	Adolescents With BD (n = 14)	Adults With BD (n = 22)
Rapid cycling			
Yes	16 (44)	7 (50)	9 (41)
No	20 (56)	7 (50)	13 (59)
Medication at scan			
Yes	22 (61)	8 (57)	14 (64)
No	14 (39)	6 (43)	8 (36)
Lithium carbonate at scan			
Yes	10 (28)	3 (21)	7 (32)
No	26 (72)	11 (79)	15 (68)
Anticonvulsant at scan			
Yes	12 (33)	5 (36)	7 (32)
No	24 (67)	9 (64)	15 (68)
Antidepressant at scan			
Yes	13 (36)	3 (21)	10 (45)
No	23 (64)	11 (79)	12 (55)
History of alcohol dependence			
Yes	11 (31)	2 (14)	9 (41)
No	25 (69)	12 (86)	13 (59)
History of marijuana abuse/dependence			
Yes	11 (31)	3 (21)	8 (36)
No	25 (69)	11 (79)	14 (64)
Illness duration, mean (SD), y	13.1 (9.5)	5.4 (3.1)	18.0 (9.0)
Age at first episode, mean (SD), y	17.4 (8.0)	10.1 (4.0)	22.1 (6.2)
Mean (SD) No. of hospitalizations	1.9 (2.7)	1.1 (2.0)	2.5 (3.0)
Mood state at scan†			
Euthymic			10 (45)
Elevated			7 (32)
Depressed			5 (23)

Abbreviation: BD, bipolar disorder.

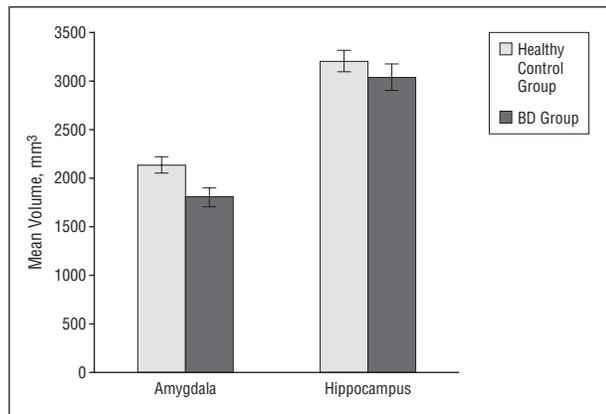
*Unless otherwise indicated, data are expressed as number (percentage) of patients.

†Adolescents with BD had varying degrees of mixed symptoms.

cluded data from all subjects (N=92), 1 fixed effect of diagnosis (BD and healthy), and random subject effects. Repeated measures were performed over the spatial domain for region (amygdala and hippocampus) and hemisphere (right and left). Age group, sex, and TBV served as covariates, and potential 2-, 3-, and 4-way interactions were examined. Terms that were not significant (*P* > .05) were eliminated via backward stepwise regression, with the constraint that the model at each step had to be hierarchically well formulated.³⁹ Data adhered to a normal distribution as assessed by means of the Kolmogorov-Smirnov test. Least squares means, SEs, and 95% confidence intervals were calculated in the mixed model for regional volumes and plotted to interpret diagnosis effects.

Exploration of Associations With Illness Features

Exploratory analyses were performed for potential main effects of clinical variables within the BD group on amygdala or hippocampal volumes by adding the clinical feature covariates to a linear mixed model and then eliminating nonsignificant terms via backward stepwise regression. Main effects examined were presence or absence of rapid cycling, medication status at the time of scanning (present or absent overall, and separately for the presence of lithium, anticonvulsants, or antidepressants at the time of scanning), history of alcohol dependence, and marijuana abuse/dependence. Additional



Amygdala and hippocampal least squares mean volume values and 95% confidence intervals for the bipolar disorder (BD) ($n=36$) and healthy control groups ($n=56$). Means are adjusted for age, sex, and total brain volume. The effect of diagnosis was significant at $P<.0001$.

Table 3. Summary of Least Squares Mean Volumes*

Factors	Least Squares Mean Volume (SE)	P Value†
Diagnosis		
Healthy controls	2672 (34)] <.0001
BD	2420 (43)	
Sex		
F	2457 (40)] .004
M	2637 (42)	
Hemisphere		
Left	2562 (28)] .04
Right	2532 (28)	
Region		
Amygdala	1970 (32)] <.0001
Hippocampus	3124 (44)	
Region, diagnosis		
Amygdala, control	2137 (40)] .001
Amygdala, BD	1803 (49)	
Hippocampus, control	3209 (54)] .054
Hippocampus, BD	3039 (68)	
Region, age group, diagnosis		
Amygdala, adolescent control	2169 (81)] .001
Amygdala, adolescent BD	1834 (93)	
Amygdala, adult control	2117 (60)] <.0001
Amygdala, adult BD	1780 (75)	
Hippocampus, adolescent control	3235 (100)] .049
Hippocampus, adolescent BD	2955 (120)	
Hippocampus, adult control	3191 (78)] .40
Hippocampus, adult BD	3090 (96)	

Abbreviation: BD, bipolar disorder.

*Mean volumes were adjusted for age, sex, hemisphere, region, and total brain volume. For purposes of this study, adults are aged 23 to 57 years; adolescents, 10 to 22 years.

†Calculated for the comparisons between the bracketed groups.

covariates were duration of illness, age at first episode, and number of hospitalizations. Interaction terms were not included because of the number of covariates explored compared with the number of subjects. Mood state was explored for the 22 adults with BD only using a similar mixed model. Analyses of mood state were not performed for the juvenile sample as, for the most part, they presented with varying degrees of mixed symptoms.

RESULTS

The BD and control groups did not differ significantly in age overall (Table 1), or between the adult (mean \pm SD ages of healthy vs BD adults, 37.8 ± 9.4 vs 40.7 ± 8.0 years; $P=.23$) or adolescent (mean \pm SD ages of healthy vs BD adolescents, 14.4 ± 3.5 vs 15.7 ± 4.0 years; $P=.29$) subgroups.

PRIMARY ANALYSES

The main effect of overall diagnosis was significant ($F_{1,88}=21.02$; $P<.0001$). The diagnosis \times region interaction approached significance ($F_{1,89}=3.35$; $P=.07$). None of the other 2- and 3-way interactions of region, hemisphere, sex, and age with diagnosis was significant ($P>.10$). A significant effect of TBV ($F_{1,88}=8.52$; $P=.004$) indicated that general scaling within the brain accounted for some of the variance in regional volume. Amygdala and hippocampal volumes were smaller in female than in male subjects ($F_{1,87}=8.55$; $P=.004$) and larger in the left than in the right hemisphere ($F_{1,91}=4.41$; $P=.04$).

The difference of least squares means between the diagnostic groups (Figure and Table 3) indicated that the stronger contribution to group differences was mainly derived from smaller bilateral amygdala volumes in the BD group compared with the healthy control group. Amygdala and hippocampal volumes were also evaluated individually, with Bonferroni correction for multiple comparisons with an overall type I error of .05. Amygdala volumes were decreased significantly in the BD group compared with the healthy control group by 15.6% ($P<.0001$). Hippocampal volumes were decreased to a lesser extent, 5.3%, that approached but did not reach significance ($P=.054$). Group least squares means were calculated for age subgroups and support a consistent diagnosis trend across age groups. Use of intracranial volume as a covariate in the analyses yielded similar results to analyses that used TBV (intracranial volume and TBV correlation, $r=0.97$).

EXPLORATORY ANALYSES

No significant main effects of illness features on regional volumes in BD were detected; however, this part of analysis is very preliminary given the number of covariates explored in relation to the sample size.

COMMENT

We found bilateral decreases in volumes of the amygdala in individuals with BD compared with healthy controls. Reduced volumes were observed in adolescent and adult samples, and age did not affect group comparisons. A nonsignificant trend toward decreases in volumes of the hippocampus bilaterally in BD subjects was also observed, although the magnitude of these volume reductions was much less prominent than in the amygdala.

The reduced volumes detected in this study could be a consequence of a number of different cellular pro-

cesses, including loss or atrophy of neurons or glia, an altered ratio of small to large cell types, or a decreased density of neuronal processes.⁴⁰ The limited available data on the cytoarchitectonic features of the amygdala and hippocampus in BD subjects provide suggestive, but not conclusive, evidence of the presence of cellular abnormalities. One study, for example, reported decreased glial cell density in the amygdala of BD subjects,⁴¹ whereas neuronal abnormalities have not yet been reported, to our knowledge. Studies of the cytoarchitecture of the hippocampus in BD are more numerous and suggest the presence of aberrant neurodevelopment and synaptic remodeling in the illness.⁴²⁻⁴⁹

Cellular and synaptic disturbances in the amygdala and hippocampus in BD could represent primary abnormalities in these structures, interactions between the structures (such as influences on the hippocampus from a more central abnormality of the amygdala), or consequences of primary abnormalities in other regions with which the amygdala and hippocampus are connected. A more central abnormality in the amygdala is suggested by the larger reductions in volume of the amygdala than of the hippocampus that were detected herein, as well as by previous imaging findings of excessive amygdala activity in BD subjects.^{20,21} In addition, preclinical studies have shown that excessive activity of the amygdala produces synaptic changes in the hippocampus that are similar to those observed in BD subjects in postmortem studies.^{45,47,50-52} The possibility of excessive glutamatergic input to the amygdala from the frontal cortices is suggested by findings in subjects with BD of hyperactivity in paralimbic cortices, which are densely interconnected with the amygdala and hippocampus, as well as by abnormalities in glutamate receptors within the medial temporal lobe.^{49,52-56}

Greater differences in hippocampal volume between the BD and healthy control groups were observed in the adolescent subgroup than in the adult subgroup. Thus, our findings do not support the presence of excessive degeneration of the hippocampus with age in subjects with BD, and presumably with increasing accumulation of stressful life experiences, a pathological process postulated in major depressive disorder.⁵⁷⁻⁵⁹ Our findings do not, however, contradict a potentially significant role for glucocorticoids in earlier developmental periods than those studied herein, and do not conflict with a role for glucocorticoids in the modulation of medial temporal function in already abnormal structures.

Potential behavioral consequences of amygdala and hippocampal abnormalities include deficits in adaptive responses to emotionally relevant stimuli in subjects with BD.⁶⁰⁻⁶⁶ Similar to individuals with amygdala lesions,⁶⁵ individuals with BD are impaired in their ability to recognize fearful faces,⁷⁻⁹ and preliminary evidence suggests that this deficit is associated with abnormal amygdala activity in response to the viewing of the fearful faces.⁷ Volumetric abnormalities in the hippocampus have been suggested to contribute to cognitive impairments, such as deficits in verbal learning, that have been reported in BD subjects.^{28,67,68} The dense connections of structures in the medial temporal lobe with the frontal cortices and the brainstem tegmentum, hypothalamus, and autonomic nuclei suggest that cognitive and neurovegeta-

tive functions may also be affected by amygdala and hippocampal abnormalities.^{56,61,69}

Volume abnormalities of the amygdala and hippocampus support consideration of these regions as potential pharmacological targets in the treatment of BD. Excessive activity in the amygdala and in cortical regions connected with the amygdala normalize during recovery from depression in individuals with BD who are taking mood-stabilizing medications.^{20,70} Abnormalities reported in the γ -aminobutyric acid, glutamate, serotonin, and opiate systems within the amygdala and hippocampus of BD subjects^{43,49,71-73} suggest potential pharmacological targets in developing new treatments for this illness.

Our findings are consistent with several previous reports of decreased amygdala and hippocampal volume in adult BD, although those findings tended to be unilateral.^{22,25,27} Previous observations of abnormalities in the volumes of the amygdala and hippocampus in patients with first-episode BD or affective psychoses^{23,27} support the presence of abnormalities in these structures early in the course of illness. Previous findings in BD, however, also include increased volumes or absences of significant group differences, compared with normal controls.²²⁻²⁶ Salient methodological differences in our study compared with previous studies may include increased signal to noise accomplished with 2 excitations used during image acquisition and the methods used to delineate amygdala and hippocampal volumes. The choice of the anterior commissure–posterior commissure plane as the reference plane for positional normalization,^{25,38,74-78} compared with the plane perpendicular to the long axis of the hippocampus,^{11,24,78-82} is thought to increase the reliability of amygdala volume measurements and thus may be optimal for studies focused on the amygdala.³⁸ Delineations included the full extent of the amygdala and hippocampus, and boundaries were confirmed in multiple viewing planes, which is thought to increase the reliability of volume measurements.^{38,76,83,84} Other groups vary in the relative inclusion of transitional structures and surrounding cortex, or in the viewing planes used for delineations.^{11,24,25,78-89} Use of TBV to covary for scaling effects, as performed in this study, may represent a salient difference from other studies. For example, temporal lobe volumes have also been used to correct for scaling effects within the brain,²⁴ but have been reported to be abnormal in BD,^{25,90} and could confound interpretation of group differences in amygdala volumes.

We did not detect significant effects of age, rapid cycling, the presence of medications, illness duration, or mood state; however, our ability to detect effects of these factors could have been limited by inadequate power. Furthermore, different characteristics in the BD subject samples of other studies may have contributed to the different results across centers. For example, samples studied by other groups included higher proportions of male subjects or older subjects,^{23,24} subjects with a history of psychosis, or subjects in primarily euthymic²⁴ or manic/mixed mood states.²³ Differences in medications in other studies may include higher proportions of subjects receiving lithium at the time of scanning and with a lifetime history of exposure to antipsychotic medication.^{23,24} Effects of individual medications may be revealed

by systematic study of specific agents. We also did not detect effects of the history of alcohol or marijuana dependence. However, features such as the duration of use of specific medications or features of alcohol history (eg, the number of withdrawals or the duration of alcohol abuse)⁹¹ may in future work be found to contribute significantly to volume abnormalities in BD, as has been found in other disorders. Individuals with other comorbid diagnoses were not present in sufficient numbers to permit systematic analyses; however, reports of structural abnormalities in association with diagnoses such as attention-deficit/hyperactivity disorder suggest that comorbidities have the potential to effect the data.^{88,92}

The ability to generalize from this patient sample is limited. This was a cross-sectional study. The patients in the 2 age groups might have had different pathophysiological subtypes of the disorder or different illness course features that could have affected the findings. Longitudinal study of the adolescents sampled herein might reveal changes with age in the morphologic characteristics of the amygdala or hippocampus not detected in the adults sampled. The selection of subjects was biased toward individuals who could tolerate the scanning procedure. The patient sample was further constrained to minimize the confounding effects of active comorbid substance abuse on regional volumes, although comorbid substance abuse is frequently seen in clinical BD populations.^{39,93,94} Furthermore, rates of other comorbid diagnoses such as attention-deficit/hyperactivity disorder were relatively low, as patients were excluded from the study if there was a question of whether their symptoms could be accounted for by another diagnosis.

CONCLUSIONS

This study provides preliminary evidence of structural abnormalities in the amygdala and hippocampus common to adolescent and adult BD. These common abnormalities may represent the expression of a common genetic vulnerability to BD, or they might represent biological consequences of earlier features of the illness. Studies of prepubescent samples, longitudinal investigations, and studies of family members may in the future help to identify phenotypes associated with a genetic risk for BD and help to elucidate the neurodevelopmental correlates of BD.

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