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MRI Study of the Cerebellum in Young Bipolar Patients

E. Serap Monkul^{a,b}, John P. Hatch^{a,c}, Roberto B. Sassi^d, David Axelson^e, Paolo Brambilla^{f,g}, Mark A. Nicoletti^{a,h}, Matcheri S. Keshavanⁱ, Neal D. Ryan^e, Boris Birmaher^e, and Jair C. Soares^{a,h,*}

^a Department of Psychiatry, The University of Texas Health Science Center at San Antonio, San Antonio, Texas, U.S.A.

^b Department of Psychiatry, Dokuz Eylül University School of Medicine, Izmir, Turkey

^c Department of Orthodontics, The University of Texas Health Science Center at San Antonio, San Antonio, Texas, U.S.A.

^d Department of Psychiatry, University of Sao Paulo School of Medicine, Sao Paulo, Brazil

^e Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, PA, U.S.A.

^f Department of Pathology and Experimental and Clinical Medicine, Section of Psychiatry, University of Udine, Udine, Italy.

^g Scientific Institute IRCCS E. Medea, Italy.

^h Center of Excellence for Research and Treatment of Bipolar Disorder (CERT-BD), Department of Psychiatry, UNC School of Medicine, Chapel Hill, NC, USA

ⁱ Department of Psychiatry and Behavioral Sciences, Wayne State School of Medicine, Detroit, MI, U.S.A.

Abstract

Prior studies demonstrate structural abnormalities of cerebellar vermis in adult bipolar patients. Cerebella of 16 young bipolar patients (mean age $\pm$ S.D. = 15.5 ± 3.4) and 21 healthy controls (mean age $\pm$ S.D. = 16.9 ± 3.8) were examined using magnetic resonance imaging. The volumes of right, left and total cerebellum, vermis, and areas of vermal regions V1 (lobules I–V), V2 (lobules VI–VII), and V3 (lobules VIII–X) were measured. Analysis of covariance, with age, gender, and intra-cranial brain volume as covariates, revealed no significant differences in cerebellum or vermis measures between patients and controls; however, there was a trend to smaller vermis V2 areas in patients ($p=0.06$). The number of previous affective episodes and vermis area V2 were inversely correlated (partial correlation coefficient = -0.97 , $P = 0.001$) in the male bipolar patient group. Our results are preliminary, but consistent with the findings from studies in adult bipolar patients suggesting the involvement of structural changes in cerebellar vermis in the pathophysiology of bipolar disorder.

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Correspondence should be addressed to Jair C. Soares, M.D., Center of Excellence for Research and Treatment of Bipolar Disorder (CERT-BD), Department of Psychiatry, Campus Box 7160, University of North Carolina, Chapel Hill, NC 27599-7160. Phone: (919) 966-8832 FAX: (919) 966-7659, Email: jsoares@med.unc.edu .

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Keywords

Bipolar disorder; Brain imaging; Cerebellum; Magnetic resonance imaging; Mood disorders; Vermis

1. Introduction

Bipolar disorder is a common, life-long progressive illness that typically begins in adolescence, with a lifetime prevalence of 1.0% in adolescents (Lewinsohn et al., 1995). Emerging literature suggests that early-onset bipolar disorder is associated with a chronic course, substantial morbidity with repeated hospitalizations, and a mixed symptom presentation with comorbid disruptive disorders (Biederman et al., 2000; Weckerly, 2002). The cerebellum is implicated in the pathophysiology of bipolar disorder (Soares and Mann, 1997; Strakowski et al., 2002). It has connections, largely via thalamus, to many brain areas relevant to cognition and behavior, including the dorsolateral prefrontal cortex, medial frontal cortex, anterior cingulate and the posterior hypothalamus (Rapoport et al., 2000). There are noradrenergic, serotonergic and dopaminergic inputs to the cerebellum from brainstem nuclei (Schmahmann, 1996). Through its connections with limbic areas and cortical associative areas, the cerebellum could be involved in the regulation of sensorial, procedural, linguistic and emotional activities, as well as motor function (Rapoport et al., 2000; Middleton and Strick, 2001). A cerebellar cognitive affective syndrome, characterized by deficits in executive function, spatial cognition, linguistic processing and affect regulation, has been described (Schmahmann and Sherman, 1998). The cerebellar cognitive affective syndrome also occurs in children, where lesions of the vermis, in particular, are associated with dysregulation of affect (Lewinsohn et al., 2000).

Prior computerized tomography studies revealed smaller total cerebellar size in adult bipolar patients compared to schizophrenia patients and healthy controls (reviewed in Soares and Mann, 1997), but the three published MRI studies, using manual region of interest tracing approaches (DelBello et al., 1999; Brambilla et al., 2001; Mills et al., 2005), did not find significantly smaller cerebellar hemispheres in adult bipolar patients compared with healthy subjects. Brambilla and colleagues (2001) studied primarily middle-aged adults (mean age: 36 ± 10 y), whereas DelBello et al. (1999) had a younger sample, mean ages for first-episode patients being 24 ± 4 y and for the multiple-episode patients 29 ± 5 y. The age range in the Mills et al. study (2005) was 16–35 y, with patients hospitalized for their first manic episode having a mean age of 22 ± 6 y, and patients with at least two prior manic episodes having a mean age of 25 ± 6 y. In contrast, a recent study by Adler and colleagues (2007), using voxel-based morphometry (VBM), reported larger bilateral cerebellar gray matter volume in a mixed sample of adolescents and adults (age range 13–41 y) with bipolar I disorder compared to healthy subjects.

Although three out of four published MRI studies report no cerebellar volume abnormalities in bipolar disorder subjects, vermal abnormalities related to repeated illness episodes have been reported. DelBello and colleagues found that vermis area V3 (the inferior posterior and flocculonodular lobes, lobules VIII–X) is significantly smaller in multiple-episode than in first-episode bipolar patients and healthy volunteers, suggesting that the cerebellar vermis may undergo atrophy during the course of bipolar illness. This finding was supported by Mills and colleagues (2005) who showed that patients with multiple manic episodes have smaller V3 volumes than healthy subjects, and by Brambilla and colleagues (2001) who showed a trend ($p = 0.075$) for an inverse correlation between number of episodes and vermis area V3. In addition, Mills et al. (2005) reported that bipolar patients with multiple episodes have smaller V2 (superior posterior vermis, neocerebellar vermal lobules VI–VII) volumes compared with first-episode patients and healthy subjects. They also noted that patients with multiple manic episodes have significantly smaller V2 volumes than first-episode patients. Taken together,

these findings suggest superior posterior (i.e. limbic cerebellum) and possibly flocculonodular vermal abnormalities in bipolar disorder.

In this MRI study, we examined anatomical abnormalities in cerebellum and vermis in young bipolar patients and healthy subjects. We hypothesized that young bipolar disorder patients would not show cerebellar volume abnormalities, but consistent with prior studies in adult bipolar patients, would show vermal abnormalities reflecting possible neurodegeneration with repeated illness episodes. Such a finding in young bipolar patients would suggest that neuropathological processes affecting the vermis are present early in the illness course.

2. Methods

2.1. Participants

We recruited 16 young people with bipolar disorder (12 with bipolar I disorder, 8 females, mean age $\pm$ S.D. = 15.5 ± 3.4 y, range 10 to 21 y), as determined by the Structured Clinical Interview for DSM IV (SCID) (First et al., 1997) for patients aged 18–21, and the Schedule for Affective Disorders and Schizophrenia for School Age Children, Present and Lifetime Version (K-SADS-PL) interview (Kaufman et al., 1997) for patients younger than 18. There were 5 individuals in the patient group who were 18–21 years of age. All subjects under the age of 18 underwent a diagnostic interview consisting of a KSADS-PL plus the mood disorders section of the KSADS-P performed by an experienced psychiatric nurse or masters level clinician who was trained to administer the KSADS. All of these subjects also had a confirmatory clinical diagnostic interview with a board-certified child psychiatrist. Patients were recruited through advertisements in the community or from the outpatient clinics at the Western Psychiatric Clinic and Institute, University of Pittsburgh School of Medicine. Patients did not have axis I comorbid psychiatric disorders, with the exception of ADHD ($n = 5$), conduct disorder ($n = 1$) and oppositional defiant disorder ($n = 1$). Subjects with a history of neurologic disorders, head trauma and learning disabilities were excluded. Furthermore, they did not have any serious current medical problems or alcohol/substance abuse in the 6 months preceding the study.

Twenty-one healthy control subjects (9 females, mean age $\pm$ S.D. = 16.9 ± 3.8 y, range 11 to 21 y) also participated in the study, after evaluation with SCID-IV (First et al., 1997) and K-SADS-PL (Kaufman et al., 1997) to rule out psychiatric disorders. Healthy subjects were recruited through advertisements in the local community. There were 12 individuals in the control group who were 18–21 years of age. The healthy control subjects had no current serious medical illnesses, no past or current psychiatric disorder, and no history of alcohol/substance abuse, neurologic disorders, head trauma and learning disabilities and no first-degree relative with a diagnosed psychiatric disorder.

The study protocol was approved by the University of Pittsburgh Biomedical IRB and carried out in accordance with the latest version of the Declaration of Helsinki. All subjects, as well as their parents if subject younger than 18, gave their informed consent, after the nature of the procedures had been fully explained.

2.2. MRI Procedures

A 1.5T GE Signa Imaging System running version Signa 5.4.3 software (General Electric Medical Systems, Milwaukee, WI) was used to acquire the MRI images. 3D gradient echo imaging (Spoiled Gradient Recalled Acquisition, SPGR) was performed in the coronal plane (TR = 25ms, TE = 5ms, nutation angle = 40° , FOV = 24cm, slice thickness = 1.5 mm, NEX = 1, matrix size = 256×192) in order to obtain 124 images covering the entire brain. All images were analyzed using Scion Image for Windows Beta-3b version (Scion Corporation Inc.,

Frederick, Md., USA) on a PC workstation. A trained rater (E.S.M.), who achieved intra-class correlation coefficients for each of the cerebellum regions of > 0.90 versus a second independent rater (M.A.N.) by tracing 10 training scans, did all anatomical measurements with the subjects' identity and group assignment masked.

2.3. Anatomical Landmarks of Cerebellum and Vermis

The first slice in cerebellum tracing was the one where the cerebellum appeared laterally to the pons. When the brain stem disappeared completely, we traced around the cerebellum with the tentorium cerebelli as the superior limit and the base of the cerebellum as the inferior border, excluding the transverse sinus and the cisterna magna. We divided right and left cerebellar hemispheres by a straight line. The last slice was the one in which the cerebellum disappeared or was no longer distinguishable from the transverse sinus. Additional details on the utilized imaging and tracing methodologies and neuroanatomical landmarks can be found elsewhere (Brambilla et al., 2001). Cerebellum volumes (cm^3) were obtained by multiplying the measured areas (cm^2) by the slice thickness (0.15 cm) (Figure 1).

The vermis volume tracing started at the slice where the superior and/or inferior vermis appeared. The superior and inferior vermis were traced separately until the 4th ventricle disappeared. On average about 20 slices were traced. The areas of the vermis sub-regions were measured in the mid-sagittal slice where the three vermis areas were the most distinguishable and reported as cm^2 . We initially measured the total vermal area. The primary fissure and 4th ventricle demarcated vermis area V1 (the anterior lobe). The pyramidal fissure and the pre-pyramidal fissure were the boundaries for the vermis area V2 (the superior posterior lobe), and we used the pre-pyramidal fissure and the 4th ventricle to demarcate vermis area V3 (the inferior posterior and flocculonodular lobes). We excluded the cerebellar tonsils (Figure 1).

2.4. Statistical Analysis

All statistical analyses were conducted using the SYSTAT (SPSS Science, Chicago, IL) software, version 8, and a 2-tailed statistical significance level was set at $p < 0.05$. Analysis of covariance (ANCOVA) was conducted with ICV, age and sex as covariates. Partial correlation analysis with ICV, age and sex as covariates was used to assess the association between number of affective episodes and length of illness with cerebellar and vermal structures. Logarithmic transformation of number of affective episodes was applied to normalize this variable for the partial correlation analysis. An independent samples t-test was used to compare the bipolar and control subjects with respect to mean age, Fisher's exact test was used to compare the sex, handedness and ethnic group distributions, and Mann-Whitney U test was used to compare the educational levels. Because of the preliminary nature of this research no adjustments were made for multiplicity in the number of subregions assessed and multiple secondary analyses performed.

3. Results

Table 1 shows the clinical characteristics of the bipolar patients. Fifteen patients (94%) had a positive family history of mood disorders in a first-degree relative, and one patient had a negative family history. The mean age of disease onset was 11.7 ± 4.08 y (range 4–19 y), with a mean length of disease of 3.78 ± 2.37 (range 1–10 y). The number of previous affective episodes was the sum of all previous manic, hypomanic, depressive or mixed episodes. Only 2 patients were drug-free, and 14 patients were on medication treatment during the study (6 were on lithium, 4 were on valproate, 4 were on both lithium and valproate). Three patients had a history of previous antipsychotic use, while 13 patients had no such history. The bipolar patients did not differ significantly from the healthy controls in terms of age, sex, race,

handedness and educational achievement, although bipolar patients had numerically less years of education than healthy subjects (Table 2).

We found no statistically significant differences between patients and controls for cerebellum and vermis measures, except for a trend level smaller V2 area in bipolar patients (Table 3). In addition, the effect size measure partial eta-squared for the main effects ranged from 0.005 (for V1 area) to 0.103 (for V2 area), which means that the effect sizes were only small to modest. One of our subjects was a rapid cyler, with 27 previous affective episodes in 3 years. We repeated the ANCOVA with this subject excluded, and our results did not change. We also compared subgroups of subjects with ADHD comorbidity ($n=5$), without ADHD comorbidity ($n=11$) and healthy controls ($n=21$), and no statistically significant differences were found (ANCOVA, age, gender and ICV as covariates) (Table 4).

No significant differences were detected between patients currently on lithium treatment ($n = 6$), valproate treatment ($n = 4$) or on both medications ($n = 4$) (ANCOVA, age, gender and ICV as covariates).

Partial correlation analyses controlling for age, gender, and ICV showed a trend for an inverse correlation between vermis area V2 and number of previous affective episodes in the patients (partial correlation coefficient = -0.53 , $P = 0.06$) (Figure 2). This correlation was driven by the male patients (partial correlation coefficient = -0.97 , $P = 0.001$ for all male patients ($n = 8$); partial correlation coefficient = -0.95 , $P = 0.013$ with the patient with 27 episodes omitted; partial correlation coefficient = 0.52 , $P = 0.29$ for female patients).

We found no significant correlation between length of illness and cerebellar or vermal structures.

Age was inversely correlated with vermis area V3 in the bipolar patient group (controlling for gender and ICV, partial correlation coefficient = -0.55 , $P = 0.04$), but not in the healthy control group (partial correlation coefficient = 0.04 , $P = 0.88$) (Figure 3). When the patient with 27 episodes was omitted from this analysis, the correlation was still in the same direction, although non-significant (partial correlation coefficient = -0.37 , $P = 0.213$).

4. Discussion

We did not find statistically significant differences between bipolar patients early in their illness course and age matched healthy controls in any of the cerebellum and vermis regions measured; however, there was a nonsignificant tendency for smaller vermis V2 area (i.e. limbic cerebellum) in patients. There was also a significant inverse correlation between the number of prior affective episodes and V2 area in male bipolar subjects. Our results are preliminary, due to our small sample size and multiple analyses without correction, and so should be interpreted cautiously; yet, they point to neuropathological processes affecting the vermis present in young bipolar patients, as we hypothesized.

Two prior MRI studies conducted in adult bipolar patients (DelBello et al., 1999; Brambilla et al., 2001) did not find structural abnormalities in the total cerebellum or vermis volume. In contrast, one VBM study (Adler et al., 2007) reported larger bilateral cerebellar gray matter volume in a mixed sample of adolescents and adults with bipolar I disorder. However, when comparing the results of this study with region of interest (ROI) studies of cerebellar/vermal volume and/or area, it must be kept in mind that the output of VBM analysis is a relative measure of gray matter, as opposed to the absolute volumes obtained in the ROI analyses, and that discrepant results may be caused by the methodological differences between manually delineated ROI analyses and whole brain VBM measurements (Giuliani et al., 2005). Another recent study in young adult bipolar patients (Mills et al., 2005) did not find significant

differences in right, left or total cerebellar volumes compared to healthy controls, but vermis V2 volume was smaller in bipolar patients with multiple episodes compared with first-episode patients and healthy volunteers, an association mainly driven by prior manic episodes. Our findings of a trend for smaller vermis V2 area in patients, and an inverse correlation between the number of prior affective episodes and V2 area in male patients point in the same direction as the finding of Mills and colleagues (2005) and raise the possibility of V2 neurodegeneration with repeated episodes. Our results in a very young bipolar sample further suggest that this may already be present early on in the illness course. One study (Jernigan and Tallal, 1990) examined age-related changes in cerebellum and vermis in 9 healthy children (age range: 8–10 y) and 15 healthy adults (age range 25–39 y), and reported significant increase in cerebellar volume and vermal areas VI–VII (vermis V2 area) in the age range of 8–10 years, and that vermis areas I–V (area V1) reach their full size by age 8. Interestingly, the ratio of vermis area V2 to vermis area V1 was larger in females than in males in this study. Although statistically not significant, our male bipolar patients had more previous episodes (8.1 vs. 5.1), younger age of illness onset (10.7 y vs. 12.6 y) and a higher percentage of comorbid conditions (62% vs. 25%) compared to female bipolar patients, and possibly a more severe form of the disorder, which might explain this gender discrepant finding. As we did not distinguish among previous manic, depressive and mixed episodes, we cannot comment on the potential effects of various episode types.

Mills and colleagues (2005) also reported that V3 volume was smaller in patients with multiple manic episodes compared to healthy controls, and that first-episode patients did not differ from healthy controls. In the DelBello et al. study (1999), the number of previous depressive episodes inversely correlated with vermis V3 area, but the number of previous manic episodes did not. We found an inverse correlation between age and vermis area V3 in bipolar patients (when the patient with 27 episodes was omitted from this analysis, the correlation was still in the same direction, but nonsignificant), suggesting a more pronounced age-related decrease in vermis area V3 in young bipolar patients compared with healthy individuals. Although Mills et al., interpreted the V3 volume reduction associated with depressive episodes as a possible result of antidepressant exposure, when combined with our finding of age-related decrease in V3 area in bipolar patients only, it could also represent an illness-related neurodegenerative gray matter loss over time. Giedd et al (1996) examined 104 healthy children (age range: 4–18 y) and reported that cerebellum volume did not change significantly across this age range. Another study (Jernigan and Tallal, 1990) examining age-related changes in healthy children and adults noted cerebellar volume and V2 area increase with age, but this study lacked subjects between 10–25 years of age. To our knowledge, no study has compared the cerebellar or vermal area/volume trajectories with age among bipolar and healthy subjects. One prospective study by Keller et al. (2003) compared the total cerebellar volume, midsagittal vermal area and posterior inferior vermal lobe volume in 50 children and adolescents with schizophrenia (mean age: 14.8 ± 2.5 y) and 50 healthy volunteers at baseline and every 2 years thereafter. Although there were no significant differences between the two groups at the baseline, there was a progressive cerebellar volume loss with age only in the schizophrenic group.

Smaller cerebellar vermal size in multiple-episode bipolar patients may be a neurodegenerative event as suggested by DelBello and colleagues (1999), but we cannot rule out the beneficial or toxic effects of chronic treatment. A more recent study (Adler et al., 2007) by the same group, using voxel-based morphometry, reported larger bilateral cerebellar volumes, in patients with bipolar I disorder who were receiving lithium, divalproex, antiepileptic medications, antipsychotics, and antidepressants, alone or in combination, a finding possibly related to medication effects. Bipolar patients on conventional antipsychotics have lower absolute blood volume in all cerebellar regions than those on atypical antipsychotics, suggesting that antipsychotic treatment influences cerebellar blood volume (Loeber et al, 2002). Furthermore, cerebellum is one of the brain regions where chronic lithium treatment is associated with a

doubling of myo-inositol monophosphatase 1, one of the targets for the mood-stabilizing action of lithium (Parthasarathy et al., 2003). In the present study (and previous studies), the vast majority of the patients were on medications at the time they were studied. In the present study patients on lithium, valproate or both did not differ from each other, but the numbers in each subgroup were very small and we cannot exclude the possibility that the changes found reflect medication effects. Future studies involving larger samples of untreated bipolar patients will be needed to distinguish illness-related neurodegeneration from effects induced by chronic treatment.

Cerebellar abnormalities have been reported in childhood-onset schizophrenia (Jacobsen et al., 1998) and ADHD (Berquin et al., 1998). Boys with ADHD have smaller cerebellum and vermis posterior inferior lobes (lobules VIII–X) compared to healthy controls (Berquin et al., 1998). Posterior inferior cerebellar vermis also is smaller in girls with ADHD compared to healthy controls (Castellanos et al., 2001). As 5 out of 16 subjects in the bipolar group had a comorbid diagnosis of ADHD, this could be a significant confounding variable for this study. We compared subgroups of subjects with ADHD comorbidity (n=5), without ADHD comorbidity (n=11) and healthy controls (n=21), and no statistically significant volume differences were found. Therefore, it is unlikely that the results were materially influenced by the presence of these 5 subjects with comorbid ADHD.

5. Conclusion

Abnormalities of the cerebellar vermis may be present early in the course of bipolar illness and are possibly involved in the neuropathology of bipolar disorder, as a neurodegenerative consequence of repeated illness episodes. Unfortunately, there is a paucity of postmortem and functional connectivity studies examining this brain structure in bipolar disorder. Longitudinal studies with larger samples of patients or subjects at risk for bipolar disorder are needed to determine whether the reported cerebellar and vermal changes result from abnormal development, the disease process itself, or medication exposure.

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Figure 1.

(a) The boundaries for the cerebellar hemispheres are illustrated on a coronal MRI slice. (b) The anatomical boundaries of the cerebellar vermis are illustrated on a coronal MRI slice. (c) The anatomical boundaries for the vermis sub-regions are illustrated on a midsagittal MRI slice.

Figure 2. Vermis area V2 as a function of log₁₀ number of affective episodes for the male bipolar subjects (partial correlation coefficient = -0.97 , $P = 0.001$).

Figure 3.

Vermis area V3 as a function of age for all bipolar subjects (partial correlation coefficient = -0.55 , $P = 0.04$) and vermis area V3 as a function of age for healthy subjects (partial correlation coefficient = 0.04 , $P = 0.88$).

Table 1

Clinical characteristics of bipolar patients

Subject	Age (y) at the time of study	Age (y) at onset	Gender	Diagnosis	Mood status	No. of previous affective episodes
1	21	19	M	BD I	D	27
2	19	17	F	BD I	E	2
3	10	7	M	BD NOS	D	3
4	15	14	F	BD I	E	3
5	21	15	M	BD I	E	3
6	14	12	M	BD I	E	11
7	18	15	F	BD I	E	4
8	14	11	F	BD II	E	9
9	17	13	F	BD II	E	6
10	13	10	F	BD I	E	6
11	18	8	F	BD I	E	7
12	14	10	M	BD I	E	3
13	10	4	M	BD I	E	5
14	12	6	M	BD II	E	4
15	17	12	M	BD I	E	9
16	15	14	F	BD I	E	4

BD: Bipolar disorder, D: Depressed, E: Euthymic, M: Male, F: female. Previous affective episodes include all identifiable manic, hypomanic or depressive episodes.

Table 2

Demographic characteristics of subjects with bipolar disorder and healthy comparison subjects

Demographic variables	Bipolar subjects (n = 16)	Healthy comparison subjects (n = 21)	<i>P</i>
Age (years)	15.5 (3.4)	16.9 (3.8)	0.26
Sex (male)	8 (50)	12 (57.1)	0.46
Race			
White	15 (93.8)	18 (85.7)	0.41
Black	1 (6.3)	3 (14.3)	
Education ^a	2.3 (0.9)	3.0 (1.1)	0.06
Handedness (right)	13 (81.3)	20 (95.2)	0.20

No significant differences exist between groups in age, gender, race, education and handedness. Results are reported as means (SD) or as numbers (%).

^aEducational codes: 1 = completed through grade 6; 2 = completed through grade 7–12; 3 = graduated high school; 4 = some college; 5 = graduated 2-year college; 6 = graduated 4-year college; 7 = some graduate/professional school; 8 = completed graduate/professional school.

Table 3

MRI morphometric measurements

Variable	Bipolar patients (n=16)	Healthy controls (n=21)	<i>P</i>	<i>Effect size</i> (<i>partial eta-squared</i>)
Total cerebellum	132.2 (8.8)	135.4 (15.5)	0.15	0.063
Right cerebellum (total)	65.5 (4.2)	67.3 (7.4)	0.09	0.090
Right cerebellum (gray)	54.0 (5.5)	54.3 (8.0)	0.66	0.019
Left cerebellum (total)	67.2 (5.8)	69.0 (8.1)	0.18	0.079
Left cerebellum (gray)	48.6 (6.6)	50.7 (9.6)	0.35	0.028
Vermis volume (gray)	10.1 (0.8)	10.1 (1.0)	0.95	0.000
Vermis total area	12.7 (1.3)	13.1 (1.2)	0.12	0.073
Vermis area 1	5.3 (0.5)	5.1 (0.8)	0.69	0.005
Vermis area 2	3.1 (0.5)	3.4 (0.5)	0.06	0.103
Vermis area 3	3.4 (0.7)	3.7 (0.4)	0.10	0.082

Cerebellar volumes (cm³) and areas (cm²) are reported as mean (S.D.), and ANCOVA is used with age, gender, and ICV as covariates.

Table 4

MRI morphometric measurements in bipolar patients with and without attention deficit and hyperactivity disorder (ADHD) comorbidity and healthy subjects.

Variable	Bipolar – ADHD (n=11)	Bipolar + ADHD (n=5)	Healthy controls (n=21)	<i>P</i>
Total cerebellum	131.9 (9.7)	132.9 (7.4)	135.4 (15.5)	0.37
Right cerebellum (total)	65.5 (4.6)	65.4 (4.2)	67.3 (7.4)	0.23
Right cerebellum (gray)	54.4 (5.2)	53.2 (6.9)	54.3 (8.0)	0.52
Left cerebellum (total)	67.1 (6.6)	67.5 (4.1)	69.0 (8.1)	0.27
Left cerebellum (gray)	49.2 (5.6)	47.3 (9.1)	50.7 (9.6)	0.47
Vermis volume (gray)	10.2 (0.9)	10.0 (0.7)	10.1 (1.0)	0.80
Vermis total area	12.7 (1.4)	12.7 (1.1)	13.1 (1.2)	0.30
Vermis area 1	5.3 (0.6)	5.1 (0.4)	5.1 (0.8)	0.47
Vermis area 2	3.1 (0.5)	3.2 (0.6)	3.4 (0.5)	0.17
Vermis area 3	3.4 (0.8)	3.6 (0.4)	3.7 (0.4)	0.25

Cerebellar volumes (cm³) and areas (cm²) are reported as mean (S.D.), and ANCOVA is used with age, gender, and ICV as covariates.