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MRI study of posterior fossa structures and brain ventricles in bipolar patients

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Abstract

Previous brain imaging studies have suggested anatomical abnormalities in posterior fossa structures and brain ventricles in bipolar patients. Such abnormalities could possibly be implicated in the pathophysiology of bipolar disorder. Twenty-two DSM-IV bipolar outpatients (mean age ± S.D. = 36 ± 10 years) and 22 healthy controls (mean age ± S.D. = 38 ± 10 years) underwent an 1.5T MRI (3D-gradient echo-imaging SPGR), performed in the coronal plane (TR = 25 ms, TE = 5 ms, slice thickness = 1.5 mm). The brain structures of interest were traced blindly with a semi-automated software. No significant differences were found between bipolar patients and healthy controls for any posterior fossa measures, or for measures of third or lateral ventricles (MANOVA, age covariate, $P > 0.05$). Age was directly correlated with 3rd ventricle volumes in bipolar patients (Pearson correlation coefficient = 0.458, $P = 0.032$), but not in healthy controls (Pearson correlation coefficient = 0.313, $P = 0.155$). There was a significant direct correlation between the number of prior illness episodes and right lateral ventricle volumes (Partial correlation coefficient = 0.658, $P = 0.011$). Familial patients had smaller left and right cerebellar hemispheres and total vermis volumes, and larger left lateral ventricle volumes compared with non-familial ones (MANOVA, age covariate, $P < 0.05$). In this preliminary study, we were not able to replicate previous findings of abnormalities in cerebellum or brain ventricles in bipolar individuals. However, there were suggestions that abnormalities in cerebellum, vermis, and lateral ventricle sizes may be present in familial cases of the disorder, which should be further examined in future studies with larger patient samples.

Keywords: Bipolar disorder; Neuroimaging; Cerebellum; Vermis; Brainstem; Ventricles

1. Introduction

Prior controlled computerized tomography (CT) and magnetic resonance imaging (MRI) studies reported smaller cerebellum and vermis sizes in bipolar disorder patients (Nasrallah et al., 1981; Nasrallah et al., 1982a; Lippmann et al., 1982; Weinberger et al., 1982; Rieder et al, 1983). The cerebellum, besides its involvement in motor and vestibulo-ocular regulation, is also thought to be involved in integrative functions and modulation of mood (Botez et al., 1989; Bracke-Tolmitt et al., 1989; Akshoomoff & Courchesne, 1992; Ivry and Baldo, 1992; Leiner et al., 1993; Ryding et al., 1993). It has projections to brain regions that modulate complex non-motor functions (Snider et al., 1976; Leiner et al., 1993), and cortical associative areas reach the cerebellum through the pons and the red nucleus (Schmahmann, 1991; Leiner et al., 1993). Therefore, abnormalities in the cerebellum could be possibly implicated in the pathophysiology of mood disorders.

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There are case reports suggesting a relationship between lesions in the brainstem and manic symptoms (Greenberg et al., 1985; Maurizi, 1985; Drake et al., 1990; Kalayam et al., 1994; Lauterbach, 1996; Ghaziuddin et al., 1999). In a post-mortem study, bipolar patients had abnormally increased neuronal density in the locus coeruleus (Baumann et al., 1999). Also, the connections between the association cortex and the cerebellar cortex are located in the brainstem region, and involve neural loops that connect the red nucleus, the inferior olive, and the dentate nucleus (Snider et al., 1976; Leiner et al., 1993). Thus, abnormalities in the brainstem could also possibly be implicated in the pathophysiology of bipolar disorder.

Increased size of the 3rd ventricle (3rdV) and lateral ventricles (LV) was found in controlled CT and MRI studies in bipolar individuals (Nasrallah et al., 1982b; Pearlson et al., 1984; Lippmann et al., 1985; Dewan et al., 1988; Andreasen et al., 1990; Figiel et al., 1991; Strakowski et al., 1993, 1999; Zipursky et al., 1997; Hauser et al., 2000), but not in all studies (Tanaka et al., 1982; Weinberger et al., 1982; Dupont et al., 1987; Dewan et al., 1988; Iacono et al., 1988; Lim et al., 1999; Swayze et al., 1990; Harvey et al., 1994). Therefore, the presence of significant 3rdV and LV abnormalities in bipolar patients remains unclear (Elkis et al., 1995; Soares & Mann, 1997).

Two prior controlled PET and MRI studies reported abnormally decreased glucose metabolism and gray matter content in sub-genual prefrontal cortex of familial mood disorder patients (Drevets et al., 1997; Hirayasu et al., 1999). Increased rates of leukoencephalopathy in members of a family with a strong history of bipolar disorder have been reported in an MRI study (Ahearn et al., 1998). So, these studies suggested that the presence of a familial history of mood disorders may be an important factor related to specific brain abnormalities in bipolar disorder subjects.

This study was conducted to attempt to replicate prior findings of smaller cerebellum and vermis sizes and enlarged brain ventricles in bipolar patients compared with healthy controls. Moreover, we wanted to examine the relationship between number of prior affective episodes and vermis measurements, as smaller size of vermis area-3 in multiple-episode compared with first-episode bipolar patients and healthy controls were recently reported (DelBello et al., 1999). We also examined the relationship between age and the size of posterior fossa structures and brain ventricles, as previous neuroimaging studies suggested possible age effects in these brain structures in bipolar disorder patients (Rieder et al., 1983; Schlegel and Kretzschmar, 1987; Loeber et al., 1999). On an exploratory fashion, we examined whether brainstem abnormalities were present in bipolar individuals. Last, we examined whether there would be any significant differences for any of the measured brain structures between familial (F-BP) and non-familial bipolar (NF-BP) subjects.

2. Methods

2.1. Subjects

Forty-four subjects (mean age $\pm$ S.D $= 37 \pm 10$ years) were recruited for the present study, of which 22 were DSM-IV bipolar disorder outpatients, as determined by the Structured Clinical Interview for DSM-IV (SCID; Spitzer et al., 1994), and 22 were healthy individuals (Table 1). They were all recruited through advertisements in the community, or through referrals from the outpatient clinics at the Western Psychiatric Clinic and Institute, University of Pittsburgh School of Medicine. All patients provided signed informed consent, after having understood all issues involved in participation in the study protocol. This research study was approved

Table 1
Demographic characteristics and clinical variables[a]

	Healthy controls ($n=22$)	Total patient sample ($n=22$)	Drug-free patients ($n=8$)	Lithium-treated patients ($n=14$)
Age (years; mean, S.D.)	38±10	36±10	40±9	33±10
Gender: males/females	14/8	13/9	3/5	10/4
Race: Caucasians, Afro-Americans, Asians	18/3/1	22/0/0	8/0/0	14/0/0
Bipolar type I/II		17/5	4/4	13/1
Depressed/euthymic/hypomanic		10/11/1	7/0/1	3/11/0
Age at onset (years; mean, S.D.)		20±7	23±7	18±6
Length illness (years; mean, S.D., median)		16±9, 15	17±8, 19	15±10, 14
No. of illness episodes (mean, S.D., median)		10±12, 6 (7 missing values)	16±19, 9	7±6, 5
Familial/non-familial patients		10/12	5/3	5/9
Lithium dose (mg; mean, S.D., median)				1114±298, 1050
Weeks of lithium treatment before the MRI (mean, S.D., median)				80±108, 31

[a] S.D. = standard deviation; mg = milligrams; MRI = magnetic resonance imaging scan.

by the local biomedical IRB. The Bech-Rafaelsen Mania Scale (Bech et al., 1979) and the Hamilton Depression Rating Scales (HRDS; Hamilton, 1960) were used to rate the clinical symptoms, and were administered within a week of the MRI study. At the time of participation in the study, eight patients were off all psychotropic drugs for at least 2 weeks, and off lithium for at least 1 month, and 14 patients were on lithium monotherapy (Table 1). Patients with any axis-I comorbid psychiatric disorder, current medical problems, or alcohol or substance abuse within the 6 months preceding the study were excluded. Healthy controls had no DSM-IV axis-I disorders, as determined by the SCID-IV non-patient version (SCID-NP), no current medical problems, and no history of psychiatric disorders among first-degree relatives. Patients and healthy controls did not differ significantly regarding their educational level (12 patients and 10 controls had completed high school, while 10 patients and 10 controls completed college and/or a professional school; $\chi^2 = 3.234$, d.f. = 2, $P = 0.198$). Patient clinical information was retrieved from patients' psychiatric interviews and medical charts (Table 1). The SCID interviews, from which we collected most of the clinical information, were completed at the Depression and Manic Depression Prevention Program (directed by Dr. Ellen Frank), by trained social workers, who have extensive experience in doing SCID interviews. As part of their training, they had to be fully reliable for at least two SCIDs, which were conducted with a senior clinician well-trained to do the SCID, after having watched several SCID interviews. Also, we regularly held post-SCID consensus meetings with the treating psychiatrist and a senior investigator to assure reliability of the SCID diagnoses. The reliability for the symptom ratings with the Bech Rafaelsen Mania Scale and HDRS were established and regularly monitored utilizing similar procedures. The number of prior affective episodes, defined according to DSM-IV criteria, included the total number of manic, depressive, and mixed episodes. The information on family psychiatric history was retrieved by directly questioning patients and/or accompanying relatives, and by reviewing patients' charts. First-degree relatives were considered positive for mood disorders if there was a past history of ever having received a diagnosis of unipolar or bipolar disorder by a physician, according to what was reported by the patients and/or relatives, and also based on information available in clinical charts. Patients with at least one first-degree relative with a history of mood disorders were considered familial mood disorder patients.

2.2. Imaging protocol

MRI scans were acquired with a 1.5T GE Signa Imaging System running version Signa 5.4.3 software (General Electric Medical Systems, Milwaukee, WI). Patients were provided with earplugs to reduce noise disturbances. A sagittal scout series was first obtained to verify patient position, image quality, and locate a midline sagittal image. A T-weighted sagittal scout image was obtained for graphic prescription of the coronal and axial images. 3D gradient echo imaging (Spoiled Gradient Recalled Acquisition, SPGR) was performed in the coronal plane (TR = 25 ms, TE = 5 ms, nutation angle = 40°, FOV = 24 cm, slice thickness = 1.5 mm, NEX = 1, matrix size = 256×192) to obtain 124 images covering the entire brain. Additionally, a double echo-spin echo sequence was used to obtain T2 and proton density images in the axial plane to screen for neuroradiological abnormalities.

2.3. Image morphometry

Anatomical measurements were conducted in a PC workstation (Dell Dimension, Pentium II 400, Windows NT 4.0), using the semi-automated software Scion Image Beta-3b for Windows (Scion Corporation, INC. Frederick, MD). All anatomical measurements were conducted blindly to group assignment and subjects' identity. The brain structures of interest were manually traced by P.B., except for the lateral ventricles, which were traced by another trained rater. All raters were trained by an experienced rater (K.H.), and achieved high reliability in comparison to this rater by tracing 10 training scans, as defined by intra-class correlation coefficients (ICCs) over 0.90 (Table 2).

Posterior fossa structures and LV were traced in the coronal plane and their volumes were calculated by multiplying the measured areas by the slice thickness (0.15 cm). Third ventricle volume was obtained in the

Table 2
Intra-class correlation coefficients (ICCs) for posterior fossa structures, brain ventricles, and intra-cranial volume tracings

	ICCs
Total right cerebellum	0.97
Right cerebellum gray matter	0.99
Total left cerebellum	0.96
Left cerebellum gray matter	0.97
Total vermis volume	0.93
Vermis gray matter volume	0.97
Vermis area-1	0.91
Vermis area-2	0.91
Vermis area-3	0.96
Total brainstem	0.92
Total midbrain	0.98
Total pons	0.99
Total medulla oblongata	0.92
3rd ventricle	0.95
Right lateral ventricle	0.98
Left lateral ventricle	0.99
Intracranial volume	0.98

axial plane by multiplying its area by 0.19 cm, because the slice thickness increased after re-slicing from the coronal to the axial plane. All volumes were reported in cm^3. The areas of the vermis sub-regions were measured in the sagittal plane, and reported in cm^2. The intracranial volumes (ICVs) were measured by tracing in the coronal plane; total cerebral gray and white matter volumes, CSF, dura mater and sinuses were included. For the ICV measurements, the volumes were calculated by multiplying the final area by 0.3 cm. All individual measures for the various brain structures were corrected for brain size by dividing the measurements by the respective ICVs, and multiplying the result by the mean ICV for the total sample. The values for gray matter, white matter and CSF were obtained by applying a histogram obtained with the software NIH Image, version 1.62, after the structures had been traced (Keshavan et al., 1994, 1995).

2.4. Statistical analyses

All analyses were performed using the SPSS for Windows software, version 8.0 (SPSS Inc., Chicago). Shapiro–Wilks tests showed that all volumetric measures were normally distributed. Two-tailed statistical significance levels were set at $P<0.05$. MANCOVA with age as a covariate was performed to compare the values of the anatomical structures between bipolar patients and healthy controls, and also between F-BP and NF-BP. Non-parametric Mann–Whitney U tests were used to compare drug-free patients with lithium-treated patients. In order to reduce the possibility of a type-I error due to multiple comparisons, three blocks of anatomically related structures were examined in separate analyses: (1) cerebellum and vermis; (2) brainstem and its sub-regions; (3) 3rdV and LV. The effect size, which is the difference in the observed means divided by the pooled standard deviation of the samples, was calculated for every anatomical measurement. Possible effects of age on the anatomical brain measurements were evaluated by the Pearson's correlation coefficients. The relationship between the brain measurements and clinical variables were examined with partial correlation analyses controlled for age, after transforming them in normally distributed variables by using square root transformation (SQRT). Gender effects were evaluated with ANCOVA, using Scheffe as post-hoc test.

2.5. Anatomical landmarks

2.5.1. Cerebellum and brainstem

The first slice included in the measurements was the one where the pons and the substantia nigra joined at both sides. We traced around the brainstem, keeping the superior colliculus as the superior limit. The inferior limit was at the beginning of the pons and the medulla oblongata. Moving backward, we included the cerebellar peduncles and the cerebral aqueduct. The pineal body was not included. As the cerebellum appears laterally to the pons, we included it in the tracing separately from the brainstem (Fig. 1a). Once the brainstem disappears completely, the tentorium cerebelli was the superior limit, and the base of the cerebellum itself acted as the inferior limit. A straight line divided the right from the left cerebellum hemisphere. By tracing along the cerebellum, the transverse sinus and the cisterna magna were excluded (Fig. 1b). The last slice included was the one at which the cerebellum was no longer distinguishable from the transverse sinus or disappeared. In average, about 45 slices were included.

2.5.2. Brainstem sub-regions: midbrain, pons and medulla oblongata

In order to outline the midbrain, a flat line was traced going backward under the interpeduncular cistern, and between the superior cerebellum-pontine cisterns. The pons was divided from the medulla oblongata by drawing a line between the inferior cerebello-pontine cisterns. The cerebellar peduncles were excluded (Fig. 1c). On average, about 20 slices were traced.

2.5.3. Vermis volume and areas

For the measures of vermis volume, we started at the slice where the superior vermis and/or the inferior vermis appeared, and traced them separately until the slice where the 4th ventricle was no longer visible. The cerebellum medullary body was excluded, and we traced backward around the vermis until it was no more visible (Fig. 1d). On average, around 20 slices were traced.

For the measures of vermis area, we chose the midsagital slice where the three vermis areas were the most distinguishable, and initially measured the total area. The primary fissure and the 4th ventricle were the boundaries for vermis area-1. Vermis area-2 was demarcated by tracing along the pyramidal fissure and the pre-pyramidal fissure. The pre-pyramidal fissure and the 4th ventricle were used as the landmarks for vermis area-3. The tonsils were excluded (Fig. 1e).

2.5.4. Ventricles

2.5.4.1. 3rd Ventricle. The slice in the coronal plane where the pons first appeared was repositioned horizontally in the axial plane with the NIH Image software. We started to measure the 3rdV at the slice where it began to appear inferior and medial to both of the lateral ventricles. The septum pellucidum was the anterior border. The splenium of the corpus callosum was the posterior border, and when it disappeared, a line connecting the stria medullaris became the posterior border; once the habenular commissure appeared, it acted as the posterior border (Fig. 1f). The last slice traced was the one before the cerebral aqueduct

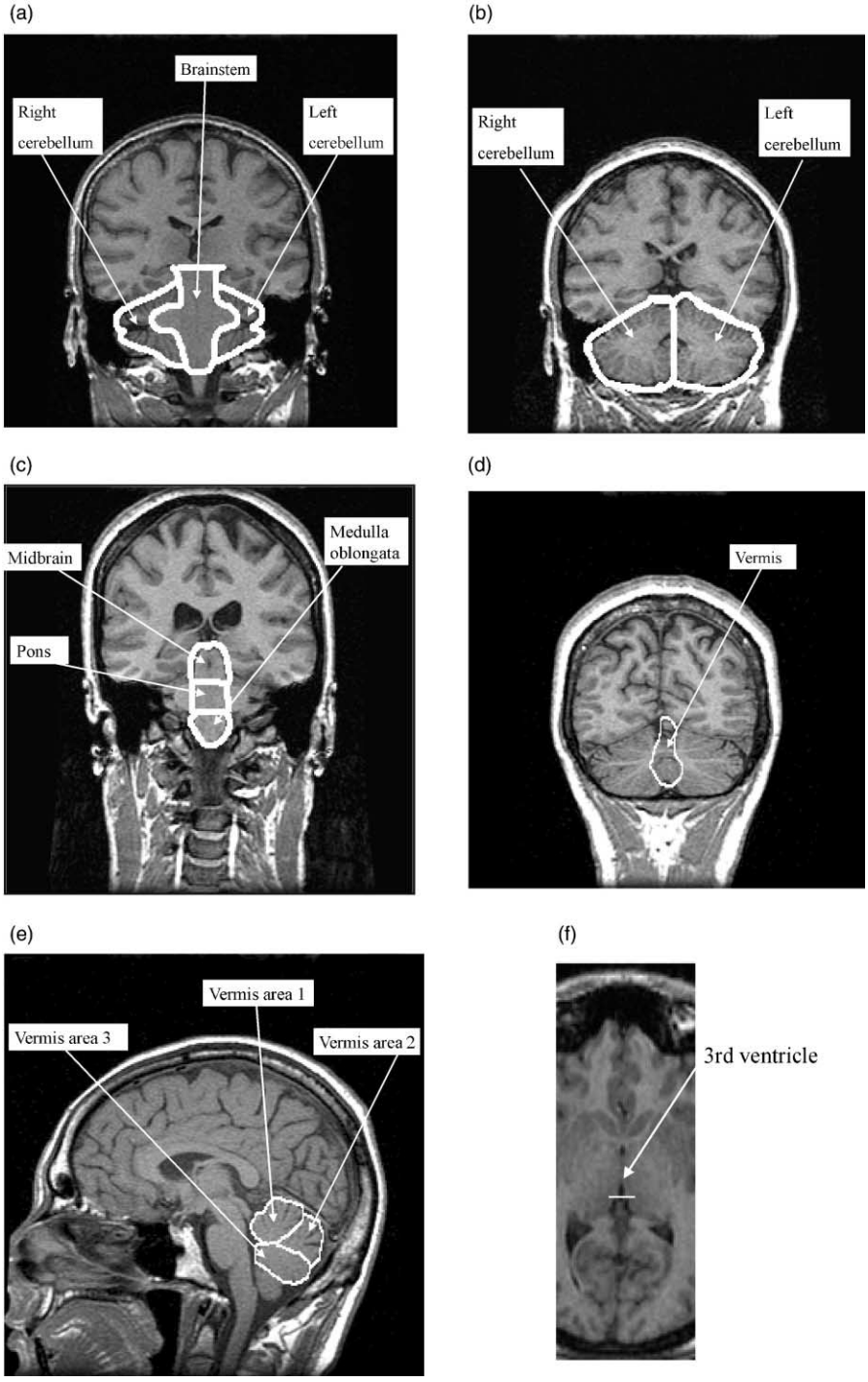

Fig. 1. (a) The boundaries for the brainstem and cerebellar hemispheres are illustrated on a coronal MRI slice. We traced around the brainstem, keeping the superior colliculus as the superior limit, and the medulla oblongata as the inferior limit, and around the cerebellum, separating it from the brainstem. (b) The boundaries for the cerebellar hemispheres are illustrated on a coronal MRI slice. Once the brainstem disappeared completely, the tentorium cerebelli was the superior limit, and the base of cerebellum was the inferior limit. A straight line divided the right from the left cerebellar hemisphere, and the transverse sinus and the cisterna magna were excluded. (c) The brainstem sub-regions are illustrated on a coronal MRI slice. A flat line traced between the superior cerebellum-pontine cisterns divided the midbrain from the pons, which was separated from the medulla oblongata by drawing a line between the inferior cerebello-pontine cisterns. The cerebellar peduncles were excluded. (d) The anatomical boundaries for the cerebellar vermis are illustrated on an MRI coronal slice. The cerebellum medullary body was excluded, and we traced around the vermis until it was no longer visible. (e) The anatomical boundaries for the vermis sub-regions are illustrated on an MRI midsagital slice. The primary fissure and the 4th ventricle were the boundaries for vermis area-1. Vermis area-2 was demarcated by tracing along the pyramidal fissure and the pre-pyramidal fissure. The pre-pyramidal fissure and the 4th ventricle were used as the landmarks for vermis area-3. The tonsils were excluded. (f) Boundaries for the 3rd ventricle are illustrated on an MRI axial slice. The splenium of the corpus callosum was the posterior border, and when it disappeared, a line connecting the stria medullaris became the posterior border.

appeared in the pons. On average, about 13 slices were utilized.

2.5.4.2. Lateral ventricles. The measurements started at the point where they were first seen. Moving backward, we continued to measure them until they were no longer seen. The inferior horn was included.

3. Results

3.1. Anatomical measurements

The mean ± S.D for all anatomical measures before ICV correction in drug-free and lithium-treated patients and healthy controls are reported in Table 3. For our analyses, the ICV-corrected measurements were utilized. No statistically significant differences were found between patients and controls (MANCOVA, age as covariate) for cerebellar and vermis measures (Hotelling-T: $F = 0.610$, d.f. = 9/33, $P = 0.780$), for brainstem and its sub-regions (Hotelling-T: $F = 1.100$, d.f. = 4/38, $P = 0.371$), or for 3rdV and LV volumes (Hotelling-T: $F = 1.233$, d.f. = 3/39, $P = 0.311$; Table 4). Effect sizes are generally considered small if 0.2, medium if 0.5, and large if 0.8 (Cohen, 1988). The calculated effect sizes in our present study were medium to large for the 3rdV, and moderate to small for the remaining structures (Table 4).

No differences have been found between drug-free patients and lithium-treated patients for any anatomical measures (Mann–Whitney U test, $P > 0.05$). When we considered only the Caucasian individuals, there were still no significant differences between bipolar patients ($n = 22$), and healthy controls ($n = 18$; MANCOVA, age as covariate, $P > 0.05$).

Our analyses were repeated after excluding eight bipolar patients who had a prior history of substance abuse, and the results remained unchanged, with no significant differences between bipolar patients and healthy controls (MANCOVA, age as covariate, $P > 0.05$).

3.2. Age effects

Age was not significantly different across drug-free and lithium-treated patients, and healthy controls (ANOVA: $F = 1.656$, d.f. = 2/41, $P = 0.203$). Age was directly correlated with 3rdV in the total subject sample (Pearson correlation coefficient = 0.406, $P = 0.006$). However, no significant correlation was found between age and any other measured anatomical structure. We further analyzed the relationship between age and 3rdV in healthy controls and in bipolar patients, and a significant direct correlation was present in patients (Pearson correlation coefficient = 0.458, $P = 0.032$), but not in healthy controls (Pearson correlation coefficient = 0.313, $P = 0.155$).

3.3. Clinical variables

For seven of 22 patients we were not able to determine with certainty the prior number of affective episodes, and these were considered missing values (Table 1). Partial correlation analyses controlled for age found a significant direct correlation with right LV volumes (Partial correlation coefficient = 0.658, d.f. = 12, $P = 0.011$), and a trend for a significant inverse correlation between number of episodes and vermis area-3 (Partial correlation coefficient = −0.490, d.f. = 12, $P = 0.075$). No other significant correlation with number

Table 3
Anatomical measurements (not ICV-corrected)[a]

	Healthy controls ($n = 22$; mean, S.D.)	Drug-free patients ($n = 8$; mean, S.D.)	Lithium-treated patients ($n = 14$; mean, S.D.)
Total right cerebellum (ml)	63.3±5.6	60.7±7.0	65.5±6.3
Right cerebellum gray matter (ml)	51.4±6.0	47.9±7.7	51.8±7.0
Total left cerebellum (ml)	61.5±6.0	59.1±7.3	63.2±5.9
Left cerebellum gray matter (ml)	48.1±6.2	44.2±8.4	47.7±7.0
Total vermis volume (ml)	9.2±1.2	9.4±1.2	9.4±0.9
Vermis gray matter volume (ml)	8.2±1.1	8.2±1.5	8.1±1.2
Vermis area-1 (cm^2)	4.5±1.0	4.6±0.6	4.7±0.8
Vermis area-2 (cm^2)	2.7±0.7	3.4±1.3	2.9±0.8
Vermis area-3 (cm^2)	3.2±0.9	3.3±0.9	3.5±0.4
Total brainstem (ml)	26.2±2.3	27.1±4.0	28.3±3.2
Total midbrain (ml)	6.5±0.8	6.8±1.1	7.1±0.7
Total pons (ml)	9.8±1.3	10.2±1.7	10.5±1.5
Total medulla oblongata (ml)	3.3±0.5	2.9±0.6	3.5±0.5
3rd ventricle (ml)	1.1±0.5	0.9±0.5	0.8±0.3
Right lateral ventricle (ml)	5.9±3.9	6.5±4.8	4.3±2.2
Left lateral ventricle (ml)	6.2±4.1	5.7±3.9	4.9±2.5

[a] S.D. = standard deviation; ml = milliliter.

of prior illness episodes was found for the remaining brain structures.

No significant correlation between age at onset of illness, HRDS scores, or number of weeks on lithium and any brain measures was found (Partial correlation analyses, controlled for age, $P > 0.05$).

3.4. Gender effects

Bipolar males, bipolar females, male controls and female controls did not differ significantly for any of the anatomical measures (ANCOVA, Scheffe as post-hoc test, $P > 0.05$).

3.5. Family psychiatric history

Familial patients ($n = 10$) compared with NF-BP ($n = 12$) had significantly smaller right (mean $\pm$ S.D. $= 61.0 \pm 3.7$ and 64.5 ± 4.2 ml, respectively) and left (mean $\pm$ S.D. $= 58.9 \pm 3.8$ and 62.5 ± 3.7 ml, respectively) total cerebellar hemisphere volumes ($F = 5.042$, d.f. $= 1/19$, $P = 0.037$; $F = 6.340$, d.f. $= 1/19$, $P = 0.021$, respectively), smaller total vermis volume (mean $\pm$ S.D. $= 8.9 \pm 0.8$ and 9.7 ± 1.1 ml, respectively; $F = 4.725$, d.f. $= 1/19$, $P = 0.043$), and significantly larger left LV (mean $\pm$ S.D. $= 6.5 \pm 2.7$ and 3.8 ± 2.1 ml, respectively; $F = 6.074$, d.f. $= 1/19$, $P = 0.023$), but not significantly different compared with healthy controls (MANCOVA, age as covariate, $P > 0.05$). A trend for larger right LV was also found in F-BP compared with NF-BP (mean $\pm$ S.D. $= 6.4 \pm 4.1$ and 3.8 ± 1.6 ml, respectively; $F = 3.738$, d.f. $= 1/19$, $P = 0.068$). No other significant differences were found between these two groups for the remaining anatomical structures.

No significant differences were present across F-BP and NF-BP, and healthy controls for age (ANCOVA: $F = 0.900$, d.f. $= 2/41$, $P = 0.414$), gender ($\chi^2 = 0.735$, d.f. $= 2$, $P = 0.692$), or educational level ($\chi^2 = 4.871$, d.f. $= 4$, $P = 0.301$), and between F-BP and NF-BP for medication status ($\chi^2 = 1.473$, d.f. $= 1$, $P = 0.225$), bipolar sub-type ($\chi^2 = 0.78$, d.f. $= 1$, $P = 0.781$), episode type ($\chi^2 = 2.053$, d.f. $= 2$, $P = 0.358$), length of illness (ANCOVA: $F = 0.295$, d.f. $= 1/20$, $P = 0.593$), number of prior affective episodes (ANCOVA: $F = 0.087$, d.f. $= 1/$

Table 4
Posterior fossa and ventricles measurements (ICV-corrected)[a]

	Healthy controls ($n = 22$; mean, S.D.)	Bipolar patients ($n = 22$; mean, S.D.)	F (d.f. $= 1/41$)	P	Effect size	Power
Total right cerebellum (ml)	63.9 ± 5.1	62.9 ± 4.3	0.468	0.498	0.208	0.10
Right cerebellum gray matter (ml)	51.9 ± 6.5	49.7 ± 6.6	1.645	0.207	0.333	0.16
Total left cerebellum (ml)	62.0 ± 5.0	60.9 ± 4.1	0.603	0.442	0.238	0.10
Left cerebellum gray matter (ml)	48.6 ± 6.1	45.8 ± 6.8	2.298	0.137	0.428	0.25
Total vermis volume (ml)	9.3 ± 1.0	9.3 ± 1.1	0.003	0.959	0.050	0.06
Vermis gray matter volume (ml)	8.3 ± 1.1	8.1 ± 1.3	0.568	0.455	0.169	0.10
Vermis area-1 (cm^2)	4.5 ± 0.9	4.6 ± 0.6	0.364	0.550	0.213	0.10
Vermis area-2 (cm^2)	2.7 ± 0.7	3.1 ± 1.1	1.287	0.263	0.351	0.25
Vermis area-3 (cm^2)	3.2 ± 0.9	3.4 ± 0.7	0.643	0.427	0.259	0.16
Total brainstem (ml)	26.5 ± 2.2	27.5 ± 2.4	2.191	0.146	0.431	0.25
Total midbrain (ml)	6.6 ± 0.7	6.9 ± 0.6	2.815	0.101	0.457	0.36
Total pons (ml)	9.9 ± 1.3	10.3 ± 1.3	1.317	0.258	0.271	0.16
Total medulla oblongata (ml)	3.3 ± 0.5	3.2 ± 0.5	0.744	0.394	0.229	0.10
3rd ventricle (ml)	1.1 ± 0.5	0.8 ± 0.4	2.897	0.096	0.574	0.49
Right lateral ventricle (ml)	5.9 ± 4.2	4.9 ± 3.2	0.523	0.474	0.278	0.16
Left lateral ventricle (ml)	6.3 ± 4.2	5.1 ± 2.7	0.958	0.333	0.355	0.25

[a] S.D. = standard deviation; ml = milliliter; d.f. = degree of freedom; MANCOVA, age as covariate.

Table 5
Demographic characteristics and clinical variables for familial and non-familial bipolar patients

	Familial patients ($n = 10$)	Non-familial patients ($n = 12$)
Age (years; mean, S.D.)[a]	38 ± 12	34 ± 12
Gender: males/females	5/5	8/4
Bipolar type I/II	8/2	9/3
Depressed/euthymic/hypomanic	6/4/0	4/7/1
Length illness (years; mean, S.D.)	15 ± 12	17 ± 7
Number of illness episodes (mean, S.D.)	11 ± 16	9 ± 6
Weeks of lithium treatment before the MRI (mean, S.D.)	120 ± 198	65 ± 75
History of substance abuse: yes/no	3/7	5/7

[a] S.D. = standard deviation.

13, $P=0.772$), number of weeks on lithium (ANCOVA: $F=0.724$, d.f. $=1/19$, $P=0.406$), or prior history of substance abuse ($\chi^2=0.321$, d.f. $=1$, $P=0.571$; Table 5).

4. Discussion

We were not able to replicate the findings of abnormalities in cerebellar and vermis size in bipolar patients reported in some of the prior studies (Nasrallah et al., 1981, 1982a; Lippmann et al., 1982; Weinberger et al., 1982). However, our negative findings are consistent with other controlled CT studies (Yates et al., 1987; Dewan et al., 1988; Wilcox, 1991). Furthermore, no evidence of anatomical abnormalities in midbrain, pons, medulla oblongata, or total brainstem volume was found in bipolar subjects. To our knowledge, this is the first MRI study that examined the volumes of brainstem structures in bipolar patients. Additionally, our study confirmed the negative findings for abnormalities in the size of the 3rdV and LV in bipolar patients reported in most of the prior CT (Tanaka et al., 1982; Weinberger et al., 1982; Schlegel and Kretzschmar, 1987; Dewan et al., 1988; Iacono et al., 1988) and MRI studies (Dupont et al., 1987; Johnstone et al., 1989; Swayze et al., 1990; McDonald et al., 1991; Harvey et al., 1994; Roy et al., 1998; Hauser et al., 2000).

Interestingly, our preliminary findings indicate that age-related increases in 3rdV size could possibly be more pronounced in bipolar patients compared with healthy individuals. If so, these differences could possibly reflect atrophy in nearby brain structures, and suggest that age may be an important factor in existing anatomical brain abnormalities in bipolar patients (Brambilla et al., 2001a, 2001b). Nonetheless, as our present sample is primarily composed by middle-aged adults, the potential relevance for the pathophysiology of bipolar disorder of any differential age effects on the size of particular brain structures will need to be further investigated in longitudinal studies involving older bipolar patients and healthy controls.

The significant direct correlation between the number of prior affective episodes and right LV volumes may be related to eventual cortical atrophy as a result of illness course. If replicated, these findings could contribute to explain the neurobiological mechanisms possibly underlying the more refractory cases of the disorder, with multiple illness episodes. Also, a trend for a significant inverse correlation between number of prior affective episodes and vermis area-3 was found. These findings, although not statistically significant, point in the same direction as the findings of DelBello et al. (1999), which may indicate that atrophy of this particular sub-region of the vermis may occur as a result of illness course.

Our preliminary results also suggest that F-BP may have reduced cerebellum and vermis volumes, and larger left lateral ventricles compared with NF-BP. If confirmed, these abnormalities would indicate that familial bipolar disorder constitutes a more severe, and possibly more biologically loaded sub-type of bipolar illness. However, some potential limitations to our present findings should be considered. First, the familial and non-familial groups were relatively small, and our familial bipolar sample was slightly older, and had a higher proportion of individuals who were depressed and unmedicated (Table 5). These factors could have confounded the analysis, even though differences between groups were not statistically significant for these variables, and age was included as a covariate in these analyses. Furthermore, because no anatomical differences for these brain structures were found between F-BP and healthy controls, our present findings should be viewed cautiously. Last, we have ascertained the psychiatric family history without utilizing direct structured interviews with all first-degree relatives, which is a significant limitation. Therefore, future studies attempting to clarify the role of family history of mood disorders in brain imaging abnormalities found in affective disorder patients should include direct diagnostic structured interviews with all first-degree relatives, as a way to accurately ascertain diagnosis among the family members.

In conclusion, our study failed to demonstrate significant differences between bipolar patients and healthy controls for the size of posterior fossa structures or brain ventricles. Nonetheless, we found very interesting suggestions that family history of mood disorders, in addition to age, may be important factors on any possibly existing abnormalities in these brain structures in bipolar disorder. However, our findings, overall, have an important limitation due to relatively modest sample size for the comparions between bipolar sub-groups, which could have limited the statistical power, and potentially account for the negative findings here reported. Longitudinal studies involving larger patient samples will be needed to conclusively examine the role of posterior fossa and brain ventricle abnormalities in the pathophysiology of bipolar disorder. Such studies are likely to be instrumental to clarify the potential involvement of abnormalities in these specific brain structures in the mechanisms underlying bipolar disorder, and their relationship with illness course, and specific clinical characteristics of the illness.

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References

Ahearn EP, Steffens DC, Cassidy F, Van Meter SA, Provenzale JM, Seldin MF, Weisler RH, Krishnan KR. Familial leukoencephalopathy in bipolar disorder. American Journal of Psychiatry 1998;155:1605–7.

Akshoomoff NA, Courchesne E. A new role for the cerebellum in cognitive operations. Behavioral Neuroscience 1992;106:731–8.

Andreasen NC, Swayze Vd, Flaum M, Alliger R, Cohen G. Ventricular abnormalities in affective disorder: clinical and demographic correlates. American Journal of Psychiatry 1990;147:893–900.

Baumann B, Danos P, Krell D, Diekmann S, Wurthmann C, Bielau H, Bernstein HG, Bogerts B. Unipolar-bipolar dichotomy of mood disorders is supported by noradrenergic brainstem system morphology. Journal of Affective Disorders 1999;54:217–24.

Bech P, Bolwig TG, Kramp P, Rafaelsen OJ. The Bech-Rafaelsen mania scale and the Hamilton depression scale. Acta Psychiatrica Scandinavica 1979;59:420–30.

Botez MI, Botez T, Elie R, Attig E. Role of the cerebellum in complex human behavior. Italian Journal of Neurological Science 1989;10:291–300.

Bracke-Tolkmitt R, Linden A, Canavan AGM, Rockstroh B, Scholz E, Wessel K, Diener H-C. The cerebellum contributes to mental skills. Behavioral Neuroscience 1989;103(2):442–6.

Brambilla P, Harenski K, Nicoletti M, Mallinger AG, Frank E, Kupfer DJ, Keshavan MS, Soares JC. Differential effects of age on brain gray matter in bipolar patients and healthy individuals. Neuropsychobiology 2001a;43:242–7.

Brambilla P, Harenski K, Nicoletti MA, Mallinger AG, Frank E, Kupfer DJ, Keshavan MS, Soares JC. Anatomical MRI study of basal ganglia in bipolar disorder patients. Psychiatry Research 2001b;106:65–80.

Cohen J. Statistical power analysis for the behavioral sciences. Hillsdale, NJ: Lawrence Erlbaum Associates, 1988.

DelBello MP, Strakowski SM, Zimmerman ME, Hawkins JM, Sax KW. MRI analysis of the cerebellum in bipolar disorder: a pilot study. Neuropsychopharmacology 1999;21:63–8.

Dewan MJ, Haldipur CV, Lane EE, Ispahani A, Boucher MF, Major LF. Bipolar affective disorder. I. Comprehensive quantitative computed tomography. Acta Psychiatrica Scandinavica 1988;77:670–6.

Drake Jr. ME, Pakalnis A, Phillips B. Secondary mania after ventral pontine infarction. Journal of Neuropsychiatry and Clinical Neuroscience 1990;2:322–5.

Drevets WC, Price JL, Simpson Jr. JR, Todd RD, Reich T, Vannier M, Raichle ME. Subgenual prefrontal cortex abnormalities in mood disorders. Nature 1997;386:824–7.

Dupont RM, Jernigan TL, Gillin JC, Butters N, Delis DC, Hesselink JR. Subcortical signal hyperintensities in bipolar patients detected by MRI. Psychiatry Research 1987;21:357–8.

Elkis H, Friedman L, Wise A, Meltzer HY. Meta-analyses of studies of ventricular enlargement and cortical sulcal prominence in mood disorders. Comparisons with controls or patients with schizophrenia. Archives of General Psychiatry 1995;52:735–46.

Figiel GS, Krishnan KR, Rao VP, Doraiswamy M, Ellinwood Jr. EH, Nemeroff CB, Evans D, Boyko O. Subcortical hyperintensities on brain magnetic resonance imaging: a comparison of normal and bipolar subjects. Journal of Neuropsychiatry and Clinical Neurosciences 1991;3:18–22.

Ghaziuddin N, DeQuardo JR, Ghaziuddin M, King CA. Electroconvulsive treatment of a bipolar adolescent postcraniotomy for brain stem astrocytoma. Journal of Child and Adolescence Psychopharmacology 1999;9:63–9.

Greenberg DB, Brown GL. Mania resulting from brain stem tumor. Journal of Nervous and Mental Dis 1985;173:434–6.

Hamilton M. A rating scale for depression. Journal of Neurology and Neurosurgery Psychiatry 1960;23:56–62.

Harvey I, Persaud R, Ron MA, Baker G, Murray RM. Volumetric MRI measurements in bipolars compared with schizophrenics and healthy controls. Psychological Medicine 1994;24:689–99.

Hauser P, Matochik J, Altshuler LL, Denicoff KD, Conrad A, Li X, Post RM. MRI-based measurements of temporal lobe and ventricular structures in patients with bipolar I and bipolar II disorders. Journal of Affective Disorders 2000;60:25–32.

Hirayasu Y, Shenton ME, Salisbury DF, Kwon JS, Wible CG, Fischer IA, Yurgelun-Todd D, Zarate C, Kikinis R, Jolesz FA, McCarley RW. Subgenual cingulate cortex volume in first-episode psychosis. American Journal of Psychiatry 1999;156:1091–3.

Iacono WG, Smith GN, Moreau M, Beiser M, Fleming JA, Lin TY, Flak B. Ventricular and sulcal size at the onset of psychosis. American Journal of Psychiatry 1988;145:820–4.

Ivry RB, Baldo JV. Is the cerebellum involved in learning and cognition? Curr Opin Neurobiol 1992;2:212–6.

Johnstone EC, Owens DG, Crow TJ, Frith CD, Alexandropolis K, Bydder G, Colter N. Temporal lobe structure as determined by nuclear magnetic resonance in schizophrenia and bipolar affective disorder. Journal of Neurology, Neurosurgery and Psychiatry 1989;52:736–41.

Kalayam B, Young RC, Tsuboyama GK. Mood disorders associated with acoustic neuromas. International Journal Psychiatry Medicine 1994;24:31–43.

Keshavan MS, Beckwith C, Bagwell W, Pettegrew W, Krishnan KR. An objective method for edge detection in MRI morphometry. European Psychiatry 1994;9:205–7.

Keshavan MS, Anderson S, Beckwith C, Nash K, Pettegrew JW, Krishnan KR. A comparison of stereology and segmentation techniques for volumetric measurements of lateral ventricles in magnetic resonance imaging. Psychiatry Research: Neuroimaging 1995;61:53–60.

Lauterbach EC. Bipolar disorders, dystonia, and compulsion after dysfunction of the cerebellum, dentatorubrothalamic tract, and substantia nigra. Biological Psychiatry 1996;40:726–30.

Leiner HC, Leiner AL, Dow RS. Cognitive and language functions of the human cerebellum. Trends in Neuroscience 1993;16:444–7.

Lim KO, Rosenbloom MJ, Faustman WO, Sullivan EV, Pfefferbaum A. Cortical gray matter deficit in patients with bipolar disorder. Schizophrenia Research 1999;40:219–27.

Lippmann S, Manshadi M, Baldwin H, Drasin G, Rice J, Alrajeh S. Cerebellar vermis dimensions on computerized tomographic scans of schizophrenic and bipolar patients. American Journal of Psychiatry 1982;139:667–8.

Lippmann S, Manshadi M, Baldwin H, Drasin G, Wagemaker H, Rice J, Alrajeh S. Cerebral CAT scan imaging in schizophrenic and bipolar patients. Journal of the Kyoto Medical Association 1985;83:13–15.

Loeber RT, Sherwood AR, Renshaw PF, Cohen BM, Yurgelun-Todd DA. Differences in cerebellar blood volume in schizophrenia and bipolar disorder. Schizophrenia Research 1999;37:81–9.

Maurizi CP. Influenza and mania: a possible connection with the locus coeruleus. Southern Medical Journal 1985;78:207–9.

McDonald WM, Krishnan KR, Doraiswamy PM, Blazer DG. Occurrence of subcortical hyperintensities in elderly subjects with mania. Psychiatry Research 1991;40:211–20.

Nasrallah HA, Jacoby CG, McCalley-Whitters M. Cerebellar atrophy in schizophrenia and mania. Lancet 1981;1:1102.

Nasrallah HA, McCalley-Whitters M, Jacoby CG. Cortical atrophy in schizophrenia and mania: a comparative CT study. Journal of Clinical Psychiatry 1982a;43:439–41.

Nasrallah HA, McCalley-Whitters M, Jacoby CG. Cerebral ventricular enlargement in young manic males—a controlled CT study. Journal of Affective Disorders 1982b;4:15–19.

Pearlson GD, Garbacz DJ, Breakey WR, Ahn HS, DePaulo JR. Lateral ventricular enlargement associated with persistent unemployment and negative symptoms in both schizophrenia and bipolar disorder. Psychiatry Research 1984;12:1–9.

Rieder RO, Mann LS, Weinberger DR, van Kammen DP, Post RM. Computed tomographic scans in patients with schizophrenia, schizoaffective, and bipolar affective disorder. Archives of General Psychiatry 1983;40:735–9.

Roy PD, Zipursky RB, Saint-Cyr JA, Bury A, Langevin R, Seeman MV. Temporal horn enlargement is present in schizophrenia and bipolar disorder. Biological Psychiatry 1998;44:418–22.

Ryding E, Decety J, Sjoholm H, Stenberg G, Ingvar DH. Motor imagery activates the cerebellum regionally. A SPECT rCBF study with 99mTc-HMPAO. Brain Research and Cognitive Brain Research 1993;1:94–9.

Schlegel S, Kretzschmar K. Computed tomography in affective disorders. Part I. Ventricular and sulcal measurements. Biological Psychiatry 1987;22:4–14.

Schmahmann JD. An emerging concept. The cerebellar contribution to higher function. Archives Neurology 1991;48:1178–87.

Snider RS, Maiti A, Snider SR. Cerebellar pathways to ventral midbrain and nigra. Exploratory Neurology 1976;53:714–28.

Soares JC, Mann JJ. The anatomy of mood disorders—review of structural neuroimaging studies. Biology and Psychiatry 1997;41: 86–106.

Spitzer RL, Williams JBW, Gibbon M, First MG. Structural clinical interview for DSM-III-R (SCID). Washington, DC: American Psychiatric Press, 1994.

Strakowski SM, Wilson DR, Tohen M, Woods BT, Douglass AW, Stoll AL. Structural brain abnormalities in first-episode mania. Biological Psychiatry 1993;33:602–9.

Strakowski SM, DelBello MP, Sax KW, Zimmerman ME, Shear PK, Hawkins JM, Larson ER. Brain magnetic resonance imaging of structural abnormalities in bipolar disorder. Archives of General Psychiatry 1999;56:254–60.

Swayze VWd, Andreasen NC, Alliger RJ, Ehrhardt JC, Yuh WT. Structural brain abnormalities in bipolar affective disorder. Ventricular enlargement and focal signal hyperintensities. Archives of General Psychiatry 1990;47:1054–9.

Tanaka Y, Hazama H, Fukuhara T, Tsutsui T. Computerized tomography of the brain in manic-depressive patients—a controlled study. Folia Psychiatry Neurology Japn 1982;36:137–43.

Weinberger DR, DeLisi LE, Perman GP, Targum S, Wyatt RJ. Computed tomography in schizophreniform disorder and other acute psychiatric disorders. Archives of General Psychiatry 1982: 778–83.

Wilcox JA. Cerebellar atrophy and catatonia. Biological Psychiatry 1991;29:733–4.

Yates WR, Jacoby CG, Andreasen NC. Cerebellar atrophy in schizophrenia and affective disorder. American Journal of Psychiatry 1987;144:465–7.

Zipursky RB, Seeman MV, Bury A, Langevin R, Wortzman G, Katz R. Deficits in gray matter volume are present in schizophrenia but not bipolar disorder. Schizophrenia Research 1997;26:85–92.