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Posterior cerebellar vermal deficits in bipolar disorder

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Abstract

Background—Based on growing evidence of the crucial role of the cerebellum in emotional regulation, we sought to identify cerebellar structural deficits in a large sample of patients with bipolar disorder (BD).

Methods—Cerebellar gray matter density was examined in 49 BD patients (24 medication-naïve and 25 medication-treated) and 50 carefully matched healthy individuals, using voxel-based morphometry with a high-resolution spatially unbiased atlas template of the human cerebellum. This recently developed methodology is specifically optimized for the assessment of cerebellar structures. We further explored whether antimanic treatment could attenuate cerebellar structural deficits.

Results—BD patients showed a greater reduction in gray matter density of the posterior cerebellar regions, including the bilateral vermi and the right crus relative to healthy individuals (corrected $p < .05$). A stepwise linear reduction in gray matter density was observed in bilateral vermal regions between healthy individuals, medication-treated, and medication-naïve BD patients. Furthermore, positive correlations of longer duration of illness with bilateral vermal gray matter deficits were observed only in medication-naïve BD patients, but not in patients with medication history.

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Conflict of interest

Dr. Lyoo has received research support from Lundbeck, Eli Lilly, AstraZeneca, GSK, and Boryung Pharmaceutical. Dr. Renshaw has been a consultant for Ridge Diagnostics and Kyowa Hakko. Other authors report no financial relationships with commercial interests.

Limitations—This study adopted a cross-sectional design. The automatic intensity-normalization method for the measurement of cerebellar gray matter density may have a limitation in providing detailed anatomical information at a cerebellar folia level.

Conclusions—The current findings suggest that BD-related deficits in the posterior cerebellar regions, which appear to progress over the course of illness, could potentially be ameliorated by proper treatment with mood stabilizers.

Keywords

Bipolar disorder; Mood stabilizers; Magnetic resonance imaging; Cerebellum

1. Introduction

Neuroimaging studies using magnetic resonance imaging (MRI) have provided an important insight into the pathophysiology of bipolar disorder (BD). Existing knowledge from neuroimaging studies indicates that the prefronto-limbic regional abnormalities have been implicated in the development and progression of BD (Kempton et al., 2008; Arnone et al., 2009; Bora et al., 2010; Hallahan et al., 2011). These regional deficits appear to increase in relation to longer duration of illness (Lopez-Larson et al., 2002; Kempton et al., 2008; Frey et al., 2008; Hallahan et al., 2011). In contrast to this neurodegenerative disease progression, neuroplastic changes, consistent with normalization of BD-related cerebral volume reductions, have also been noted in lithium-treated patients (Yucel et al., 2007, 2008; Moore et al., 2000, 2009; Lyoo et al., 2010; Hallahan et al., 2011). A recent large-scale meta-analysis has also identified both treatment history and illness duration as factors influencing brain structural changes related to BD (Hallahan et al., 2011).

In addition to the well-replicated findings on the prefronto-limbic regional changes in BD (Kempton et al., 2008; Arnone et al., 2009; Bora et al., 2010; Hallahan et al., 2011), evolving evidence has raised the possibility that the cerebellum may also play an important role in the pathophysiology of BD (DelBello et al., 1999; Brambilla et al., 2001; Mills et al., 2005; Monkul et al., 2008; Womer et al., 2009). Since the first clinical observation more than a decade ago of secondary mania in patients with cerebellar lesions (Lauterbach, 1996; Schmahmann and Sherman, 1998), the involvement of the cerebellum in emotional processing, beyond its pivotal role in posture, balance and movement coordination, has received considerable attention for a potential role in the pathophysiology of several neuropsychiatric disorders (Konarski et al., 2005; Schmahmann et al., 2007; Hoppenbrouwers et al., 2008). Likewise, several neuroimaging studies, using region-of-interest based measurements, have specifically evaluated cerebellar volumes in BD patients although the issues on the regional specificity of cerebellar volume abnormalities have not yet been resolved (DelBello et al., 1999; Brambilla et al., 2001; Mills et al., 2005; Monkul et al., 2008; Womer et al., 2009; Baldacara et al., 2011). Furthermore, neurochemical aberrations as evidenced by decreased myo-inositol and choline concentrations have been reported in the cerebellar vermis of the high-risk youth for BD (Singh et al., 2011). A recent voxel-based morphometry (VBM) finding that temporal lobe volume reduction in BD patients is correlated with decreased cerebellar gray matter volume (Moorhead et al., 2007) may also corroborate a potential interconnective involvement of these brain areas in the

pathophysiology of BD. Taken together, the BD-related cerebellar structural changes and their implications may provide valuable understandings to develop a more comprehensive neurobiological model of BD that includes multiple, distributed neural circuits beyond the prefronto-limbic brain areas.

In the current study, we aimed to evaluate the regional pattern of cerebellar structural deficits in a large sample of BD patients in comparison with healthy individuals. Because the all previous findings were based on volumetric measurements, we implemented a recently developed VBM method using a high-resolution, spatially unbiased atlas template of the human cerebellum (Diedrichsen, 2006; Diedrichsen et al., 2009), in order to identify more localized BD-related cerebellar deficits. Among clinical variables that are tested for potential relationships with cerebellar deficits, we focused on clarifying the trait-state issue of these deficits. In particular, we expected to find potential relationships of cerebellar deficits with disease duration. In addition, we explored the possibility whether antimanic treatment might slow down or attenuate the progress of these deficits.

2. Methods

2.1. Subjects

Study participants were recruited through direct referrals to the Bipolar Research Programs at McLean Hospital and Massachusetts General Hospital and the University of Washington Center for Anxiety and Depression or advertisement. Having bipolar I or bipolar II disorders, as determined by a DSM-IV based structured clinical interview by experienced psychiatrists, was an inclusion criterion. Diagnostic agreement between study sites were established before subject recruitment. Exclusion criteria were any other comorbid Axis I disorder, substance abuse within the last 6 months or Axis II antisocial personality disorder, concurrent or history of any significant medical or neurological illnesses, history of head trauma, seizure, learning disorder, or attention deficit hyperactivity disorder, and any contraindications to MR scanning.

Forty-nine BD patients and 50 age- and sex-matched healthy individuals who were confirmed as having neither current nor previous Axis I psychiatric diagnosis were finally enrolled. All subjects provided written informed consents approved by the Human Subjects Review Boards of either center before their participation in the study.

Among BD patients, 24 had never been treated with mood stabilizers or antipsychotic medications (hereafter defined as the '*medication-naïve BD group*') and 25 were taking antimanic agents at the time of scanning (hereafter defined as the '*medication-treated BD group*'). Thirteen (52%) out of 25 medication-treated BD patients took lithium as a primary psychotropic medication. Seven BD patients (28%) were treated with valproate and 4 with atypical antipsychotic medications (16%) for their symptom control. One patient was under treatment with both lithium and valproate at the time of scanning. We further assessed for diagnostic subtypes of BD using a semi-structured psychiatric interview (Dager et al., 2004). Among 49 BD subjects, 29 patients met diagnostic criteria for bipolar I disorder while 19 did bipolar II disorder. Information on the specific BD subtype was not available for one BD patient. With respect to the proportion of BD subtypes, more cases of the medication-treated

BD subgroup, compared with the medication-naïve BD subgroup, were diagnosed as having bipolar I disorder ($n=19$, 76.0% and $n=10$, 43.5%, respectively; $\chi^2=5.30$, $p=.02$).

2.2. Magnetic resonance image acquisition and voxel-based morphometry

High-resolution, T1-weighted three-dimensional spoiled gradient echo pulse sequence (SPGR) images were obtained using the same 1.5-Tesla GE whole-body imaging system (Horizon Echo-Speed, General Electric Medical Systems, Milwaukee, WI) at both study sites, equipped with a custom-made linear birdcage coil to improve signal-to-noise ratio and homogeneity over values obtained using a standard quadrature head coil (Dager et al., 2004; Lyoo et al., 2004). Images were acquired using the following parameters: echo time (TE)=5 ms, repetition time (TR)=35 ms, 256×192 matrix, flip angle=45°, field of view (FOV)=24 cm, number of excitation (NEX)=1, 1.5-mm-thick slices, no skip. To screen for gross brain abnormalities, axial proton density and T2-weighted images (TE=30/80 ms, TR=3000 ms, 256×192 matrix, flip angle=45°, FOV=24 cm, NEX=.5, 3-mm-thick slices, no skip) were also obtained. To ensure the image quality for processing and the absence of any structural abnormalities, all MR images were examined by a board-certified neuroradiologist who was blind to the clinical information of subjects.

All image processing for the cerebellar VBM analysis was conducted using the statistical parametric mapping technique (SPM5, Wellcome Department of Cognitive Neurology, University College London, UK), executed in MATLAB 7.0.1 (Mathworks, Natick, MA, USA). The current study used a spatially unbiased infra-tentorial (SUIT) template toolbox version 2.4 (available at <http://www.icn.ucl.ac.uk/motorcontrol/imaging/suit.htm>) that provides an atlas template specific for the cerebellum and the brainstem aligned to the Montreal Neurological Institute (MNI) space. A SUIT template was developed through a non-linear atlas generation algorithm based on the high-resolution cerebellar images for the optimization and normalization of individual infra-tentorial structures (Diedrichsen, 2006). Because the SUIT template can provide fine anatomical details of the cerebellum including the primary or horizontal fissures, the level of overlap across individual cerebellar structures would be more accurate compared to values obtained by using a MNI whole-brain template (Diedrichsen, 2006; Diedrichsen et al., 2009).

To isolate infra-tentorial structures from the whole-brain T1 image, individual images were first aligned to a whole-brain MNI template and then segmented into gray/white matter and cerebrospinal fluid, using probability maps with a modified mixture model cluster analysis (Ashburner and Friston, 1997). The cerebellum was then cropped from the surrounding tissues according to Bayesian priors in MNI space. Subsequently, the isolation process was repeated using the new cerebellar template, instead of the MNI whole-brain template, to improve accuracy. The posterior probability of each voxel that belongs to the cerebellum was also calculated so that it could then be used as a mask at the subsequent normalization and reslicing steps.

Individual isolated cerebellar images were warped non-linearly into SUIT space using a cosine basis function (Ashburner and Friston, 1999), after masking the cropped images of the cerebellum with the individual binary image to classify the cerebellum from the background.

Each segmented gray matter map produced in the isolation step was masked by the smoothed binary image of the cerebellum and then resampled into SUI space, using the normalization parameters derived from the previous normalization step.

Resliced images were smoothed by convolving with a 6-mm full width at half-maximum isotropic kernel (Friston et al., 1996) to satisfy the Gaussian distribution for parametric statistical analysis. This process also increased the signal-to-noise ratio (Hagler et al., 2006) and attenuated the inaccuracy of spatial normalization, thus resulting in enhanced statistical power. Supplementary Fig. 1 summarizes the preprocessing steps for cerebellar VBM using the SUI template.

2.3. Statistical analyses

Demographic and clinical characteristics were compared between groups using unpaired t -tests and χ^2 tests for continuous and categorical variables, respectively.

Smoothed cerebellar images from both the BD and control groups were analyzed on a voxel-by-voxel basis for cerebellar gray matter density, by employing the framework of the general linear model. Diagnostic group effects on cerebellar gray matter density were determined within a model that included age, sex, and intracranial volume (ICV) as covariates. An alpha significance level of $p < .05$, false discovery rate (FDR)-corrected for multiple comparisons, was considered significant.

To further examine the effects of antimanic treatment on modifying BD-related cerebellar deficits, values of gray matter density were extracted from the significant clusters of diagnosis group effects for each participant. The mean values of clusters were then compared between medication-naïve BD patients, medication-treated BD patients, and healthy individuals, using analysis of covariance with a test for linear trend (Kirk, 1995). Multiple regression analysis was performed to examine the relationship between mean gray matter density values in clusters of diagnostic effects and illness duration in both the medication-naïve and medication-treated BD groups.

Statistical significance was determined at an alpha level of $<.05$ with 2-tailed test. Stata 11.0 (StataCorp, College Station, Texas) was used for statistical analyses.

3. Results

3.1. Clinical characteristics

Demographic characteristics, including age and sex composition, across diagnostic groups were not significantly different. There were no differences in age of onset or duration of illness between the medication-naïve and medication-treated BD groups ($t = -.69$, $p = .50$ and $t = -1.45$, $p = .15$, respectively). Mood state was assessed using the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) and the Young Mania Rating Scale (YMRS) (Young et al., 1978) at the time of scanning. The scale scores of the YMRS were not different between the BD subgroups ($t = .58$, $p = .56$), while the HDRS scores in the medication-naïve BD group were higher than those in the medication-treated BD group ($t =$

2.47, $p=.02$). Group comparisons of demographic and clinical characteristics are presented in Table 1.

3.2. Voxel-based morphometric analysis of the cerebellum

Voxel-wise analyses using the general linear model demonstrated that BD patients had significant gray matter density reductions in bilateral posterior-inferior vermal regions (lobules VIII and IX) relative to healthy individuals at FDR-corrected $p<.05$ (right vermal region, 17.8% reduction; left vermal region, 17.3% reduction)(Table 2 and Fig. 1.). A gray matter density reduction was also observed in the right posterior cerebellar hemispheric region (Crus I) of BD patients relative to healthy individuals at FDR-corrected $p<.05$ (19.1% reduction)(Table 2 and Fig. 1). Although image acquisition parameters were identical across the two study sites and regular quality control processes ensured an adequate reliability, we repeated the between-group analysis including study site as an additional covariate, in order to confirm stability of the results. Although the statistical levels decreased upon the inclusion of an additional covariate, the results from the repeated analysis including the study site covariate showed the similar regional pattern of cerebellar gray matter deficits to those from the initial analysis (Supplementary Fig. 2).

3.3. Clinical correlations of BD-related cerebellar gray matter deficits

Mean values of gray matter density from the bilateral vermal clusters (Fig. 2a) were compared among the medication-naïve BD, medication-treated BD, and the control groups. A stepwise linear reduction in mean gray matter density of the bilateral vermal clusters was observed, with the greatest density values in healthy individuals, then medication-treated BD patients, and finally medication-naïve BD patients ($t=-6.83$, p for trend $<.001$)(Fig. 2b). Results from individual vermal clusters of right and left cerebellum were similar and presented in Supplementary Fig. 3a and b.

This linear trend in density reduction of the cerebellar vermis remained unchanged when BD subtype was included as an additional covariate ($t=-2.89$, p for trend $=.005$). Furthermore, repeated analyses excluding 4 patients treated with atypical antipsychotics showed a similar linear trend in bilateral vermal gray matter density reductions among groups ($t=-6.97$, p for trend $<.001$). In contrast, BD-related right posterior hemispheric regional deficit (Crus 1) was not observed to be affected by a prior treatment history (Supplementary Fig. 3c).

The relationships between illness durations and vermal gray matter density reductions were different between the BD groups (p for interaction $=.026$). For instance, progressive vermal deficits over disease duration were observed only in the medication-naïve BD group ($\beta=-.45$, $p=.035$), but not in the medication-treated BD group ($\beta=.21$, $p=.34$)(Fig. 1c). These interaction effects were similarly observed when analyses were repeated in individual vermal clusters of bilateral cerebellar hemispheres (Supplementary Fig. 4a and b). However, there was no significant interaction effects observed in right posterior hemispheric region (Crus I) (Supplementary Fig. 4c).

Additional covariation of BD subtype (p for interaction $=.028$) or the total scores of HDRS (p for interaction $=.016$) produced similar results. We also repeated analyses excluding 4

patients who were treated with atypical antipsychotics and observed similar interaction effects (p for interaction = .027).

Finally, we examined whether the class of mood stabilizers may affect BD-related vermal gray matter density reductions. Gray matter density in the bilateral cerebellar vermi of lithium-treated BD patients ($n=13$) did not differ from those treated with either valproate or atypical antipsychotics ($n=11$) ($t=.51$, $p=.61$), despite numerically increased vermal gray matter density in lithium-treated patients (mean gray matter density of vermal cluster, .465) relative to other medication-treated patients (mean gray matter density of vermal cluster, .452). Also, there was no vermal gray matter density difference between lithium- ($n=13$) versus valproate- ($n=7$) treated BD patients ($t=1.57$, $p=.13$).

4. Discussion

In the current study, we have shown that BD patients had cerebellar gray matter density reductions bilaterally localized in the posterior vermi. This cerebellar region is increasingly recognized to play an important role in controlling emotional processing (Hoppenbrouwers et al., 2008; Konarski et al., 2005; Schmahmann et al., 2007). Notably, a stepwise reduction in gray matter density within the bilateral vermal regions was observed among healthy individuals, medication-treated BD patients, and medication-naïve BD patients. Furthermore, differential correlations of vermal deficits with disease durations according to the presence of antimanic treatment history suggest that treatment with either mood stabilizers or atypical antipsychotics may exert potential neuroprotective effects against BD-induced neurodegenerative progression of cerebellar vermal atrophy.

Among several neuroanatomical subregions of the cerebellum, the vermis, which is located on the midline of the cerebellum, is more likely to be involved in the pathophysiology of mood disorders (Konarski et al., 2005; Schmahmann et al., 2007; Hoppenbrouwers et al., 2008), because of its close reciprocal anatomical connections with other anterior limbic systems including the prefrontal regions, amygdala, hippocampus, and hypothalamus (Konarski et al., 2005; Allen et al., 2005; Adler et al., 2006; Hoppenbrouwers et al., 2008). Recent research using repetitive transcranial magnetic stimulation also suggests that cerebellar stimulation targeted to the vermis may increase emotional responses in healthy individuals (Schutter and van Honk, 2006, 2009; Schutter et al., 2009).

Furthermore, several case studies of patients with infarctions or tumors in the cerebellum have suggested associations between cerebellar vermal pathology and affective symptoms (Pollack et al., 1995; Levisohn et al., 2000). Inspired, in part, by these lesion studies, a few neuroanatomical imaging studies have thus far attempted to evaluate cerebellar vermal structural changes in relatively small samples of BD patients, using a region-of-interest-based volumetric approach (DelBello et al., 1999; Brambilla et al., 2001; Mills et al., 2005; Monkul et al., 2008; Womer et al., 2009). Results from these studies mostly support our findings that BD patients have decreased posterior cerebellar vermal volumes (DelBello et al., 1999; Mills et al., 2005). One study instead found increased anterior vermal volumes in BD that we could not replicate (Womer et al., 2009). Consistent with our current results, DelBello et al. (1999) and Mills et al. (2005) reported that the atrophic changes in the

posterior vermis of BD patients were progressive during the course of illness. In these previous studies, however, associations between antimanic treatment and structural changes in the posterior vermis were not reported (DelBello et al., 1999; Mills et al., 2005).

A recent VBM study using a whole-brain template in first-episode patients with BD (Adler et al., 2007) has reported increased gray matter density in several brain areas, including the bilateral cerebellar regions. This discrepancy in findings with our study may stem from several factors. It may in part be attributed to different analytic approaches using a whole-brain versus cerebellar-specific template. Although the ICBM 152 template has been widely used as a normalizing target in whole-brain VBM analysis and provides adequate anatomical details of the cerebrum, an increased anatomical variability of the infra-tentorial structures could hinder an accurate alignment of these structures when a whole-brain template was used (Diedrichsen, 2006). As suggested by the evidence for progressive cerebellar vermal atrophy in BD, differences in sample characteristics with respect to illness duration (first-episode versus approximately 16 years of disease duration in the current study) could also potentially account for the discrepancy in results. A VBM study that assessed longitudinal changes in cerebral gray matter density over the course of BD (Moorhead et al., 2007) supports our premise that progressive cerebellar gray matter losses may account for the absence of baseline group-differences in first-episode BD patients relative to healthy subjects.

Another finding of the current study is that BD patients showed differential relationships between illness duration and gray matter density of the cerebellar vermis as a function of treatment history. Preclinical evidence has suggested that lithium treatment may exert neuroprotective effects on cerebellar neurons against an experimental apoptotic condition (D'Mello et al., 1994; Inouye et al., 1995; Nonaka and Chuang, 1998; Nonaka et al., 1998; Manji et al., 2000; Machado-Vieira et al., 2009). Previous cross-sectional and longitudinal neuroimaging studies (Sassi et al., 2002; Yucel et al., 2007, 2008; Bearden et al., 2007, 2008; Foland et al., 2008; Moore et al., 2009; Lyoo et al., 2010) have also found that lithium treatment increases gray matter volumes in several prefronto-limbic regions including the anterior cingulate cortex, the amygdala, and the hippocampus, which are known to be anatomically and functionally connected with the cerebellar vermis. Valproate has similar action mechanisms targeting cellular plasticity, for example, modulating cell survival pathway, to those of lithium (Bachmann et al., 2005) despite a paucity of data specific for the cerebellum. Atypical antipsychotics, such as olanzapine, quetiapine, and risperidone, have also been reported to exert neuroprotective properties in animal models of psychostimulant-induced neurotoxicity (Qing et al., 2003; Richtand et al., 2006; He et al., 2009). Recent longitudinal observations on olanzapine-treated patients with schizophrenia have further supported atypical antipsychotics' action in preventing neurodegenerative changes of the cerebral cortex (Lieberman et al., 2005; Thompson et al., 2009).

We also, unexpectedly, found gray matter density deficits in the right cerebellar Crus I in BD patients relative to control subjects. A recent topographic meta-analytic approach to functional neuroimaging studies has demonstrated that this posterior cerebellar hemispheric region might be involved in higher-level tasks including language and executive functions. Along with activation of the posterior vermis, Crus I regions have also been implicated in

emotional processing as a part of the cerebellar-limbic circuitry (Stoodley and Schmahmann, 2010). Taken together, the posterior cerebellum, which is reciprocally linked to other prefronto-limbic brain areas, may work en bloc to modulate cognitive and emotional processing (Konarski et al., 2005; Schmahmann et al., 2007). Our findings of BD-related structural deficits in the posterior cerebellum encompassing the posterior vermis and parts of hemisphere may therefore have clinical relevance in that both regions play an important role in modulating emotional processing.

In summary, we have demonstrated a region-specific pattern of cerebellar gray matter density reductions in BD, predominantly in the posterior vermal regions, which are known to play a pivotal role in emotional processing and also closely connected with the anterior limbic systems, and that mood stabilizers are likely to have potential neuroprotective effects on cerebellar deficits in BD.

5. Limitations

The absence of information on cumulative duration of current drug treatment and detailed history of prior psychotropic medication use including drugs other than mood stabilizers and antipsychotics is a study limitation which should be considered in interpreting the results. In the current medication-treated sample with BD, 13 patients (52%) were regarded as being treated primarily with lithium, while 11 patients (44%) were taking valproate ($n=7$) or atypical antipsychotics ($n=4$) as a primary medication at the time of scanning. Although recent longitudinal neuroimaging studies have suggested that lithium-induced gray matter volume increases could be observed following even brief, as short as 4 weeks, exposures to medication (Yucel et al., 2008; Moore et al., 2000, 2009; Lyoo et al., 2010), longitudinal studies with a sufficient sample size of BD patients would be necessary to assess shared or differential effects of each class of psychotropic medications on cerebellar deficits.

We found the significant relationship between illness duration and vermal deficits in medication-naïve BD patients suggesting the neurodegenerative nature of BD-related vermal gray matter deficits. In addition to illness duration, the number of previous episodes would also be an important indicator of neurodegenerative illness load. Since this information was not accurately available for a substantial number of patients, relevant analysis was not conducted. This should be regarded as a study limitation. Future studies including more comprehensive information on clinical characteristics of BD will be required to replicate current findings.

Although additional covariation of BD subtype and total scores of HDRS did not change the current results, it should be noted that the symptom severity of BD patients may affect patients' decisions about whether or not to take medications. Therefore, the potential of the relationship between psychiatric symptoms severity and deficits in vermal gray matter should also be considered in interpreting results.

Most of the current medication-treated BD patients took lithium, valproate, or atypical antipsychotics as single primary psychotropic medication at the time of scanning. Only one patient was prescribed with both lithium and valproate. Furthermore, the symptom severity

of current sample, as determined by the HDRS and the YMRS, were likely to be in the mild range. Therefore, the fact that the current sample may not be representative of the general BD population with various types of episodes and different levels of symptom severity should be taken into consideration in interpreting the results.

The current method using the automatic intensity-based normalization may have a limitation in providing detailed anatomical information at a cerebellar folia level. For example, gray-white matter within folia level could not be readily discriminated by even using this improved voxel-by-voxel cerebellar normalization despite enhanced referencing for the cerebellar lobular labels (Diedrichsen et al., 2009). Future studies employing hand-parcellation methods for analyzing images, which are obtained from high field strength MR and therefore ensure much improved resolution (Marques et al., 2010), would be necessary to confirm the current results.

We have made an effort to carefully exclude subjects with alcohol or other substance abuses, and our BD patients had no history of drug abuse within the 6 months prior to study entry. However, the frequent comorbidity of substance use disorders in BD patients, and the potential for prior substance abuse in the current sample, may be a confounding factor for positive cerebellar findings given the previous evidence for alcohol-induced cerebellar degeneration (Thomas et al., 1998; Andersen, 2004; Fitzpatrick et al., 2008).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.jad.2013.04.050>.

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Fig. 1.
Cerebellar parcellation maps and results of cerebellar voxel-based morphometry. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 2.

Differences in gray matter density of the cerebellar vermal cluster between study groups and relationships between disease duration and gray matter density of the cerebellar vermal cluster. (a) Cerebellar vermal cluster showing a significant group effect and corresponding anatomical locations are presented in the coronal image of the cerebellum. (b) Individual and mean values of relative gray matter density of the bilateral cerebellar vermal clusters for each subgroup are presented. (c) Scatter plots and regression lines between disease duration and gray matter density of the cerebellar vermal cluster in medication-naïve and medication-treated BD groups.

Table 1

Demographic and clinical characteristics of study subjects^a.

	Healthy subjects (<i>n</i> =50)	All patients with BD (<i>n</i> =49)	<i>p</i> Value ^b for control vs. BD groups	BD patients		<i>p</i> Value ^b for medication-naïve and treated groups
				Medication-naïve group (<i>n</i> =24)	Medication-treated group (<i>n</i> =25)	
Demographics						
Age, yr	33.5 (10.5)	33.8 (11.3)	.88	31.2 (9.6)	36.3 (12.4)	.12
Sex, male, No. (%)	21 (42.0)	19 (38.8)	.74	11 (45.8)	8 (32.0)	.32
Clinical characteristics						
<i>BD subtype, no. (%) ♂</i>						
Bipolar I disorder	NA	29 (60.4)	NA	10 (43.5)	19 (76.0)	.02
Bipolar II disorder	NA	19 (39.6)	NA	13 (56.5)	6 (24.0)	
Age at onset, yr ^d	NA	17.7 (7.6)	NA	16.9 (8.6)	18.5 (6.6)	.50
Duration of illness, yr ^d	NA	16.6 (11.2)	NA	14.1 (7.8)	18.9 (13.4)	.15
HDRS at scan time	NA	16.2 (8.2)	NA	19.0 (8.8)	13.5 (6.8)	.02
YMRS at scan time	NA	6.7 (6.2)	NA	7.2 (7.2)	6.2 (5.2)	.56
<i>Main medication used at the time of scanning^e</i>						
Lithium	NA	14 (28.6)	NA	NA	14 (56.0)	NA
Valproate	NA	8 (16.3)	NA	NA	8 (32.0)	NA
Atypical antipsychotics	NA	4 (8.2)	NA	NA	4 (16.0)	NA

Abbreviations: BD, bipolar disorder; No, number; HDRS, 17-item Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; NA, not available or not applicable

^aData are given as mean (standard deviation) except where indicated otherwise.^bGroup differences were tested by independent *t*-tests for age, onset age, duration of illness, HDRS, and YMRS scores and by chi-square tests for sex and BD subtype.^cData were available in 23 drug-naïve and 25 drug-treated BD patients.^dData were available in 22 drug-naïve and 23 drug-treated BD patients.^eNumbers are not mutually exclusive. One patient of the medication-treated BD group was under treatment with both lithium and valproate at the time of scanning.

Table 2
Cerebellar regions of significant gray matter density reduction in BD patients compared with healthy individuals.

Region	MINI coordinate, mm			Number of voxels	pFDR-corrected	z Score
	x	y	z			
Posterior vermis, lobules VIII–IX, Right	8	–58	–34	341	.014	4.85
Posterior vermis, lobules VIII–IX, Left	–10	–58	–35	59	.021	4.12
Posterior hemisphere, Crus I, Right	51	–52	–39	41	.020	4.15

Abbreviations: BD, bipolar disorder; MINI, Montreal Neurological Institute; FDR, false discovery rate