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Research report

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-naive 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-naive BD patients. Furthermore, positive correlations of longer duration of illness with bilateral vermal gray matter deficits were observed only in medication-naive BD patients, but not in patients with medication history.
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.

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

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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-insoitol 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-naive 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 1 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-naive 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