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Sexually Dimorphic Features of Vermis Morphology in Bipolar Disorder

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Abstract

Objectives—The cerebellar vermis is increasingly implicated in bipolar disorder (BD). In this study, we investigated vermis morphology in BD using a quantitative volumetric analysis.

Methods—Volumes for total vermis and vermis subregions, V1 (lobules I–V), V2 (lobules VI–VII), and V3 (lobules VIII–X), were calculated using high resolution structural magnetic resonance imaging obtained from 44 individuals with BD (25 females and 19 males) and 43 healthy comparison (HC) subjects (26 females and 17 males). Total vermis volumes were compared between the BD and HC groups. Potential effects of vermis subregions and clinical features were explored.

Results—Total vermis volumes were significantly larger in the BD group than in the HC group (P=0.02). There was a significant group by sex interaction (P=0.02). Total vermis volumes were significantly larger in males with BD than HC males (P=0.004); vermis volumes did not differ significantly between females with and without BD (P=0.95). Subregion analyses showed a trend-level interaction between diagnosis and subregion (P=0.07), in which subregion V1 volumes were significantly larger in BD participants (P=0.001), with differences primarily driven by males (P=0.001).

Conclusions—Our findings demonstrate increases in cerebellar vermis volumes in males with BD. These findings support the presence of structural alterations in the cerebellar vermis in BD and furthermore the influence of sex on such changes.

Keywords

Bipolar disorder; structural MRI; cerebellum; cerebellar vermis; sex difference

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INTRODUCTION

A role for the cerebellar vermis in bipolar disorder (BD) was first suggested by observations of affective changes in humans with vermis lesions, specifically manic-like symptoms (1–4). Its role in BD is further supported by preclinical literature as animal studies have shown modulation of emotional behavior through electrical stimulation and lesions in the vermis (5–7). Moreover, the vermis is interconnected with brain regions strongly implicated in BD, including the hypothalamus, amygdala, hippocampus, anterior cingulate and ventral prefrontal cortices (8–12).

Prior magnetic resonance imaging (MRI) studies have demonstrated variable findings of vermis structural abnormalities in BD (13–16). These studies have examined total vermis as well as vermis subregions, V1 (lobules I–V), V2 (lobules VI–VII), and V3 (lobules VIII–X) (14). Brambilla et al. suggested that abnormalities in total vermis volumes may be associated with familial cases of BD (13). An initial study by DelBello et al. reported smaller V3 in BD and was followed by a study of a larger sample by Mills et al. reporting smaller V2 and V3 in BD (14,15). Both these studies found that vermis abnormalities may be related to the number of prior affective episodes. Monkul et al. reported a similar trend in the effect of episode number on vermis subregion (V2) in adolescents and young adults with BD (16). In addition, they suggested that this trend may be more prominent in young males with BD. With the exception of Mills et al (15) who utilized volumetric measurements, the above studies investigated vermis subregions by measuring mid-sagittal cross-sectional areas.

In this study, our primary aim was to compare total vermis size between individuals with BD and healthy individuals using a quantitative volumetric approach. The potential effects of vermis subregions and clinical features on vermis abnormalities were explored.

METHODS

Participants

Participants with BD were recruited from the Yale School of Medicine Medical Center (New Haven, CT), the Veterans Affair Connecticut Healthcare System (West Haven, CT) and the greater New Haven community through clinical referrals and advertisements. Healthy comparison participants were recruited from the surrounding community through word-of-mouth and advertisements. Individuals were excluded if they 1) had a significant medical condition (with the exception of 4 BD females with treated hypothyroidism), 2) had a significant neurological condition, or 3) experienced loss of consciousness for 5 minutes or more.

The presence or absence of Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV) (17) diagnoses were determined by the Structured Clinical Interview for DSM-IV Disorders Version 2.0 (SCID) (18) for 44 individuals with BD (25 females and 19 males, ages 18 to 55 years) and 43 healthy comparison (HC) individuals (26 females and 17 males, ages 18 to 53 years). HC participants had neither personal history of DSM-IV Axis I disorders nor a history of a mood, psychotic, anxiety, or substance use disorder in their first-degree relatives. Written informed consent was obtained from all participants in accordance with the human investigation committees of the Yale School of Medicine and the Department of Veterans Affairs following a complete description of the research protocol.

Of the BD participants, 28 (64%) met criteria for rapid cycling, 21 (48%) had at least one first-degree relative with a primary mood disorder, and 13 (30%) had a history of psychotic features during mood episodes. At the time of scanning, 10 (23%) met DSM-IV criteria for a depressive episode, 13 (30%) met DSM-IV criteria for a manic, hypomanic or mixed episode, and 21

(48%) were euthymic at time of scanning. Co-morbidities included post-traumatic stress disorder (4, 9%), panic disorder (3, 7%), and specific phobia (1, 2%). Ten BD participants (23%) were unmedicated. The remaining participants were prescribed psychotropic medications that included lithium (14, 32%), anticonvulsants (22, 50%), atypical antipsychotics (17, 39%), antidepressants (13, 30%), benzodiazepines (7, 16%), and levothyroxine (4, 9%).

MRI Acquisition and Processing

MRI scans were obtained on a 3T Trio MR Scanner (Siemens, Erlangen, Germany) using a three-dimensional Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) T1-weighted sequence (TR=1500ms, TE=2.83ms, FOV=256 × 256 mm^2, matrix=256 × 256, slice thickness=1.0mm without gap, 160 slices, NEX=2). Images were adjusted for head tilt and rotation that occurred during scanning using both cerebral and cerebellar landmarks (19). The vermis was delineated in the sagittal plane on each slice that contained it using BioImage Suite software (www.bioimagesuite.org) by operators blinded to participant characteristics. The presence of the vermis was defined by 1) the presence of the prepyramidal fissure, 2) the retention of vermis shape, and 3) the presence of thin, branching white matter (characteristic of the vermis) (19,20). The vermis was divided into 3 subregions, V1 (lobules I–V), V2 (lobules VI–VII), and V3 (lobules VIII–X). The boundaries of V1 were determined superiorly by the superior medullary velum and inferiorly by the primary fissure. V2 was demarcated superiorly by the primary fissure and inferiorly by the prepyramidal fissure, and V3 was defined superiorly by the prepyramidal fissure and inferiorly by the vallecula with careful delineation from the cerebellar tonsils (14,15,19) (Figure 1). The cerebellar tonsils were identified by 1) ovoid shape, 2) an axis oriented parallel to the posterior surface of the medulla, and 3) gray and white matter appearing in a regular hatch-mark pattern at a 45–90 degree angle to the posterior surface of the medulla (19). Automated skull stripping and gray matter, white matter, and cerebrospinal fluid (CSF) segmentation were performed using the Statistical Parametric Mapping 99 (SPM99) (www.fil.ion.ucl.ac.uk) tissue classification algorithm (21). Total vermis, V1, V2, V3, and total brain volumes were calculated using all gray and white matter voxels within the volumes. Inter-rater reliabilities for total vermis, V1, V2, and V3 volumes, presented as intra-class coefficients, were 0.92, 0.99, 0.99 and 0.99 respectively.

Statistical Analysis

All statistical analyses were performed using the Statistical Analysis Software (SAS) version 9.1 (SAS Institute, Cary, NC). Vermis volumes were tested for normality using Kolmogorov-Smirnov test statistics. All p-values presented are two-tailed.

Total vermis volumes were analyzed using Analysis of Covariance (ANCOVA) with diagnostic group (BD, HC) and sex as between-subject factors and with age and total brain volume (TBV) as covariates. All multi-way interactions were tested. Least squares (LS) means were calculated from the model and plotted to interpret significant effects.

Exploratory analyses were performed to examine the effects of vermis subregion volumes using a linear mixed model with diagnostic group and sex as between-subject factors, vermis subregions as within-subject factors, and age and TBV as covariates. All multi-way interactions were tested. Exploratory analyses were also performed to determine the effects of each clinical variable within the BD group on total vermis volumes. These analyses were carried out separately for each clinical variable with the clinical variable and sex as between-subject factors and with age and TBV as covariates. The clinical effects analyzed included presence of rapid cycling, presence of a first-degree relative with a primary mood disorder, mood state at the time of scan, presence of lifetime psychosis, and medication status at scanning.

RESULTS

The HC and BD groups did not differ statistically in sex distribution ($X^2_{(1)}$=0.12, P = 0.73), but did differ in age (t_{85}=2.9, P=0.005), such that participants with BD (mean age 33.9 ± SD 10.8 years) were older than HC participants (mean age 27.7 ± SD 9.1 years). Mean ages for female and male participants were 31.4 ± SD 10.5 years and mean age 30.1 ± SD 10.4 years respectively. Female and male BD participants did not differ significantly in age, presence of rapid cycling, family history of a primary mood disorder, mood state, presence of lifetime psychosis, or medication status at scanning (P's >0.15).

Vermis volumes were approximately normal in distribution. There was a significant main effect of diagnostic group [F(1,81)=5.49, P=0.02] where BD participants had significantly larger total vermis volumes compared to HC participants. The diagnosis by sex interaction was also significant [F(1,81)=5.49, P=0.02]. BD males had significantly larger total vermis volumes than HC males [F(1,81)=8.81, P=0.004], while vermis volumes did not differ significantly between the female groups (P=0.94) (Figure 2). Exploratory analyses did not demonstrate any significant main effects of clinical variables or of their interactions with sex in influencing total vermis volume (P's>0.15).

Exploratory analysis of the vermis subregions revealed significant main effects of diagnosis [F(1,81)=5.46, P=0.02] and subregion [F(2,166)=422.52, P<0.0001]. There was a trend toward a diagnostic group by subregion interaction [F(2,166)=2.64, P=0.07]. This trend appeared to be driven by larger V1 volumes in the BD group when compared to the HC group [F(1,166) =10.58, P=0.001], particularly among males [F(1,166)=10.79, P=0.001], while groups did not differ significantly in volumes in V2 or V3 (P's > 0.20).

DISCUSSION

In this study, total vermis volumes were significantly larger in the BD group when compared to the HC group. Moreover, it appeared that these increases were specific to males; total vermis volumes were significantly larger in males with BD than in HC males, whereas vermis volumes did not differ significantly between females with and without BD. In addition, vermis subregion analyses suggested that the volume increases are most prominent in V1 with males primarily driving the differences in this subregion. Although the significant age difference between the BD and HC group poses a potential limitation, we are not aware of any evidence suggesting increased cerebellar volumes with age. Rather, evidence from post-mortem and imaging studies suggest that cerebellar volumes, including vermis volumes, decrease with age (22–25). Thus, the older age of BD participants likely limited our abilities to detect further differences between the BD and HC groups.

Increases in the vermis volume have been observed in other neuropsychiatric disorders, specifically autism and schizophrenia (20,26,27). This is of interest as there is evidence of shared genetic vulnerabilities among BD, autism and schizophrenia (28–31). These findings suggest commonalities in the pathophysiology of these disorders. For example, as evidence of white matter abnormalities in BD and schizophrenia are emerging, such commonalities could involve alterations in vermis white matter connectivity (27,32,33). However, studies of vermis morphology in autism and schizophrenia have had disparate findings (34–40). Thus, such implications of commonalities in the vermis are speculative until further investigation.

Previous neuroimaging studies have suggested decreases in the vermis in BD when compared to healthy individuals (14,15,41). However other studies in BD have reported findings of no differences in the vermis (13,16). In this study, vermis increases were found. The disparate findings among studies could reflect methodological differences, such as in measuring vermis area versus volume (13,14,42), determining the lateral boundaries of the vermis (43), or

correcting for head tilt during scanning (19). They could also reflect differences in the demographic and clinical features of the study samples. The increases reported herein appeared specific to males suggesting that the distribution of males and females in the study samples, and sufficient power to detect sexually dimorphic features, might influence findings. Other factors that might also influence findings include age, as well as aspects of clinical course such as episode history and medication exposure.

Prior MRI studies have not reported direct effects of sex on vermis volumes in BD, as was found in this study (13–16). However sexually dimorphic influences of genetic factors and early exposures on cerebellar development have been shown in rodent studies (44–50). These include more severe effects of mutations studied as models for neuropsychiatric disorders (e.g. mice heterozygous for the *reeler* mutation and mutation of the RORα gene of the *staggerer* mouse) and of prenatal and early environmental exposures to substances of abuse (e.g. cocaine) and neurotoxic agents (e.g. polychlorinated biphenyls) on the cerebellum of males (45–47, 49). The findings reported herein raise interesting questions regarding how sex-related factors, such as hormonal levels, may interact with the development of the vermis in BD and whether vermis abnormalities may contribute to clinical features of BD that tend to be more characteristic of males with the disorder. These features include a greater tendency in males with BD to experience manic than depressive episodes, as compared to females with BD (51). A role for the vermis in mania is suggested by the reports of manic-like behaviors subsequent to vermis lesions (2,4). In our sample, the large proportion of BD participants with rapid-cycling limited our ability to quantify manic episodes as these participants often had difficulty approximating the number of manic or depressive episodes in retrospective recall. The association between vermis abnormalities and number of manic episodes would be of interest to pursue in future studies. It is also possible that males are more likely to have other clinical characteristics that might produce the vermis differences. For example, males may differ in the likelihood of experiencing psychotic symptoms or being exposed to certain medications. In this study, males with BD did not differ from females with BD in any of the clinical features examined, nor were there any significant interactions between vermis volumes, sex and clinical features; however, our power to detect these associations was limited.

Previous studies of the vermis in BD have reported abnormalities in V2 and V3 in association with episode number rather than alterations in V1 (14,15). The reason for the differences between our study and previous studies is unclear. It may relate to methodological differences such as in delineation of the vermis subregions. Alternatively, it could relate to differences in the features of the participant samples. Our diagnosis by subregion interaction was at trend-level, so conclusions regarding the effects specific to subregion are tentative. However, the findings in V1 in BD are of interest as V1 has known connections with regions in which abnormalities have been previously demonstrated in BD, including the hypothalamus, hippocampus and orbitofrontal cortex (8). Further investigations are needed to determine how the vermis subregions are affected in BD.

In summary, the findings of this study support the presence of structural alterations in the cerebellar vermis in BD, and furthermore they demonstrate the influence of sex on these changes. The findings also underscore the need for future investigations to elucidate the role of the vermis in BD pathophysiology and the potential influences of sex on this role.

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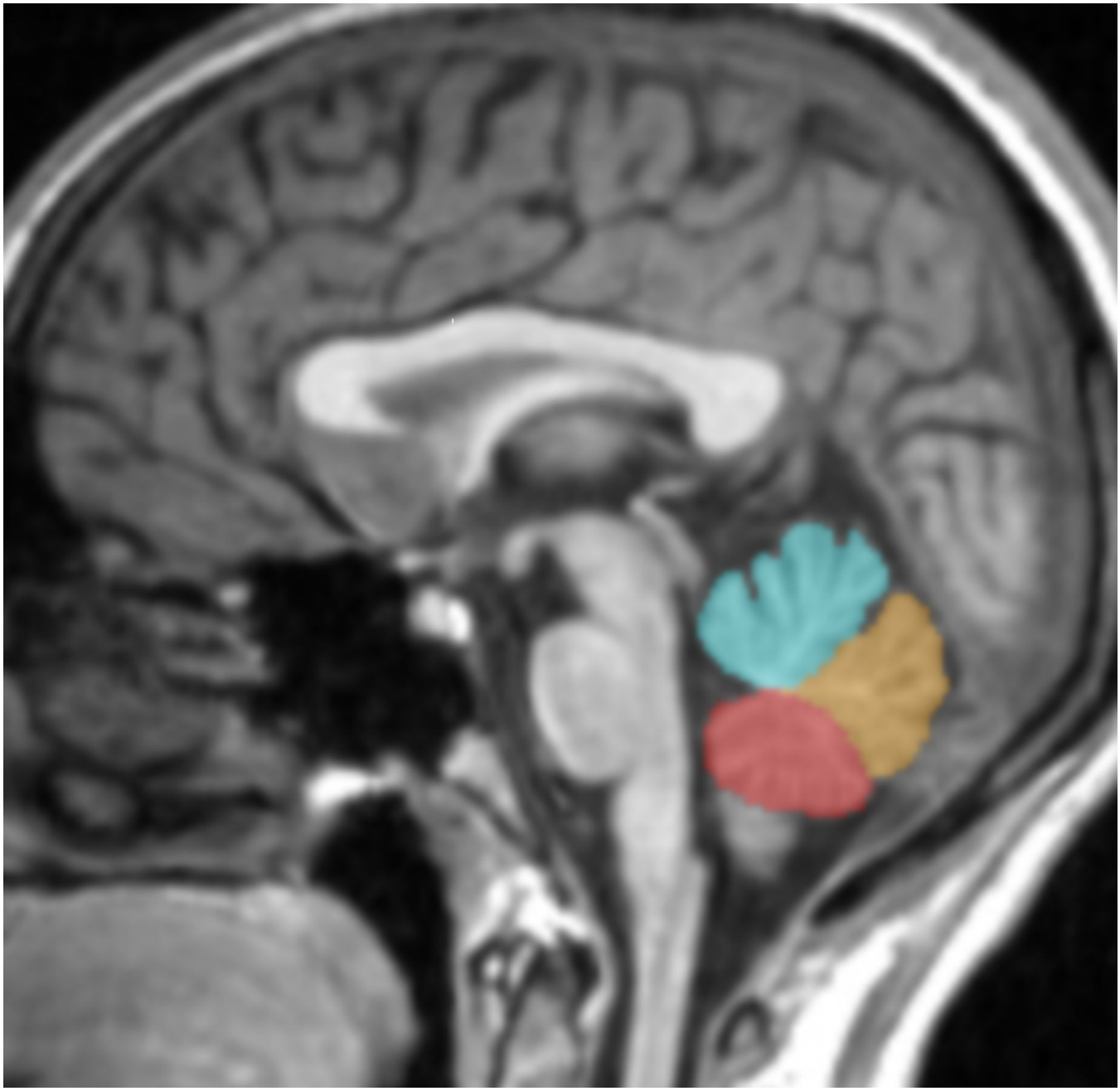

Figure 1.
Delineation of the Vermis Subregions
The T1-weighted image displays the delineation of vermis subregions (V1 in blue, V2 in yellow and V3 in red) in the sagittal plane.

Figure 2.
Vermis Volumes in Females and Males with and without Bipolar Disorder Least square means and standard errors of total vermis volumes for the BD and HC groups. Means are adjusted for age and TBV. The HC group consisted of 26 females and 17 males, and the BD group consisted of 25 females and 19 males.