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ORIGINAL ARTICLE

Cerebellar vermis volume in major depressive disorder

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Abstract The vermis is located in the midline of the cerebellum and is involved in the regulation of affect and cognitive processes. Although changes in vermis size have been reported in several psychiatric disorders such as schizophrenia and bipolar disorder, no volumetric studies have been conducted on samples of patients with major depressive disorder (MDD). One-hundred and five adult subjects were recruited: 35 patients who were presenting for first treatment (FT; 22 females), 35 patients with known previous treatment (PT; 22 females), and 35 healthy controls (NC; 22 females), matched for age and gender. We compared the volumes of the total vermis, the anterior lobe (V1), the superior–posterior lobe (V2), and the inferior–posterior lobe (V3), among these study groups. Anterior vermis (V1) was larger in patients with MDD with a long history of antidepressant treatment compared to healthy controls. This finding was evident only in men [$F(2, 36) = 9.23$, $p = .001$]. Patients in the FT group did not differ from healthy controls in any vermian region. We found no correlations between vermian subregional volumes and clinical variables such as illness duration or age at onset of illness. We speculate that the larger anterior vermis volumes might arise from abnormalities in connectivity or as compensatory responses to the prefrontal dysfunction noted in patients with MDD but confirmation of this hypothesis awaits further studies.

Keywords Cerebellum · Vermis · Depression · Major depressive disorder · Volume

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Introduction

The cerebellum constitutes the largest part of the rhombencephalon that occupies the posterior fossa of the cranial cavity (Gray 2000). It is primarily involved in the integration of sensory perception and motor control (Fine et al. 2002). Recent studies of patients with cerebellar lesions have demonstrated that the cerebellum is involved not only in motor control, but may also be implicated in the regulation of emotion, affect, and cognitive processes as well (Schmahmann 2004; see Glickstein 2007 for summary of contrary evidence). Case studies of children with unilateral cerebellar hypoplasia have linked cerebellar abnormalities with motor problems, learning disabilities, speech and language disorders and behavioral problems (Poretti 2011). Cerebellar cognitive affective syndrome (CCAS) is associated with impairments in executive, visual-spatial, and

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linguistic abilities, and with affective disturbances ranging from emotional blunting and depression to disinhibition and psychotic features (Schmahmann 2004).

The vermis (Lat. *worm*) is located in the midline of the cerebellum and has been termed the *limbic cerebellum*, along with the fastigial nucleus, for its role in the regulation of affect and emotion, and cognitive processes (Schmahmann 2004; Schmahmann et al. 2007). Although the use of the term *limbic* has the potential for confusion, especially due to the ambiguity in the definition of the limbic system (see Kötter and Stephan 1997), it nevertheless highlights the largely overlooked interactions with the hippocampus, amygdala, and thalamus. Indeed, converging evidence both from animal and human studies has demonstrated extensive connectivity between the cerebellum and the hippocampus, parahippocampal gyrus, amygdala, anterior thalamic nuclei, cingulate cortex, and areas within the dorsolateral and ventral prefrontal cortices (Alalade et al. 2011; Heath and Harper 1974; Krienen and Buckner 2009; Middleton and Strick 2001; Salamon et al. 2007; Vilensky and van Hoesen 1981). The connectivity literature parallels the cognitive and affective components of behavioral manifestations that are frequently reported in individuals with altered cerebellar function. Particularly, dysregulation of affect observed in CCAS has been associated with lesions in the vermis (Schmahmann 2004; Schmahmann et al. 2007). In a functional magnetic resonance imaging (fMRI) study, Turner et al. (2007) has reported that individuals with cerebellar lesions due to stroke showed impaired subjective experiences of pleasant emotions in response to positive stimuli compared to healthy controls. Interestingly, these individuals were able to have normal emotional response to frightening stimuli, however, with a disrupted activation pattern within the prefrontal and limbic areas. Transient sadness (George et al. 1995) and anticipatory anxiety (Reiman et al. 1989) have been associated with vermian activation in functional imaging studies of healthy volunteers.

The cerebellum has been proposed as a region that may be relevant to understanding the pathophysiology of major depressive disorder (MDD) due to its widespread connectivity with neural regions that subserve emotion regulation and which are in-turn disrupted in MDD (see Ressler and Mayberg 2007; Schmahmann et al. 2007). However, there is a paucity of relevant neuroimaging studies to support the involvement of the cerebellar vermis in MDD. Changes in vermian size have been reported in structural magnetic resonance imaging (MRI) studies in other psychiatric disorders, particularly schizophrenia (Ichimiya et al. 2001; Joyal et al. 2004; Lee et al. 2007; Okugawa et al. 2007) and also attention deficit hyperactivity disorder (ADHD; Mackie et al. 2007), autism (Gothelf et al. 2008), and bipolar disorder (Baldaçara et al. 2011; Monkul et al. 2008; Womer et al. 2009). Levitt et al. (1999) found that reductions in vermis volume in patients with schizophrenia correlated with symptom severity. Similarly, Monkul et al. (2008) identified a trend toward smaller vermes in bipolar patients, which was associated with increased number of previous episodes. A more recent study by Baldaçara et al. (2011) reported smaller vermis volumes in patients with BD but did not find associations with illness burden variables. Shah et al. (1992) compared vermian area in 27 chronically depressed patients and age- and gender-matched controls and identified a significant decrease in the anterior, posterior, and total vermis areas in depression. Increased blood flow in the cerebellar vermis has been reported in two positron emission tomography (PET) studies of patients with depression and cognitive dysfunction (Bench et al. 1992; Dolan et al. 1992). An oculomotor study by Sweeney et al. (1998) reported that depressed patients had abnormal saccadic eye movements, implicating the prefrontal cortex and vermis during episodes of depression. Finally, the vermis modulates monoaminergic systems through connections with the brainstem, and disruptions in monoaminergic systems have been implicated in MDD for many years (Albert et al. 1985; Kerr et al. 1991; Morilak and Frazer 2004).

To our knowledge, there are no structural MRI studies in which volume of the vermis has been compared between treated and untreated patients with major depression. We therefore assessed the volumes of the vermis and its subregions in patients with MDD and age- and gender-matched healthy controls. To explore further the potential contribution of antidepressant therapy and recurrent illness burden to vermian volume, we compared the volumes of vermian subregions among patients with MDD with no lifetime exposure to psychotropic medication to patients with a long history of antidepressant treatment, with the groups matched for duration of illness and past number of episodes.

Method

Subjects

One-hundred and five adult subjects were recruited: 35 patients who were presenting for first treatment [FT; 22 females, mean age 34.3 (SD = 8.9) years], 35 patients with known previous treatment [PT; 22 females, mean age 38.0 (SD = 12.8) years], and 35 healthy controls [NC; 22 females, mean age 37.4 (SD = 11.7) years], matched for age and gender with the patients. Patients were recruited by the Mood Disorders Program at St. Joseph's Healthcare Hamilton, Ontario through inpatient and outpatient programs. The NC subjects were recruited through word of

mouth and local advertisements. NC participants had no current or lifetime history of psychiatric illness.

All patients were diagnosed by the Structured Clinical Interview for DSM-IV (SCID; First et al. 2001). No FT subjects had ever received pharmacological or psychotherapeutic treatment for a psychiatric illness prior to the entry to the study. The MRI scan was completed prior to or shortly after medication was initiated. Twenty of our FT patients received no medication prior to scanning. Ten FT patients received citalopram at an average dose of 19.8 (SD = 1.3) mg for an average of 48.7 (SD = 37.2) days prior to scanning. Two patients received venlafaxine at a mean dosage of 71.7 (SD = 22.2) mg for an average of 79.5 (SD = 67.2) days; one of these patients received adjunctive therapy with quetiapine with an average dose of 129.4 (SD = 29.7) mg for 96 days. Respectively, three patients received fluvoxamine with an average dose of 69.6 (SD = 6.1) mg for 127 days, 10 mg of paroxetine for 54 days, and 30 mg of mirtazapine for 70 days.

PT patients were confirmed to have multiple past episodes of depression and had an extensive history of illness episodes. All patients in our previously treated group received at least one prior trial of antidepressant medication with an average of three trials of medication per patient. Several PT patients had multiple antidepressant trials that included serotonergic, tricyclic, and monoamine oxidase inhibitor agents.

Symptom severity was assessed using the 17-item Hamilton Depression Rating Scale (Ham-D), the Young Mania Rating Scale (YMRS) to provide a secondary check that no patients were in a mixed state at the time of scan, and the Global Assessment of Functioning Scale (GAF). Healthy controls also received these measures to rule out the presence of sub-threshold psychiatric illness.

Exclusion criteria for all groups were: (1) substance-use related disorder within the past 6 months as determined by the SCID; (2) lifetime history of substance dependence as measured by the SCID; (3) PTSD as determined by the SCID; (4) use of alcohol or illicit psychoactive substance within 48 h of testing; (5) untreated medical illness such as uncontrolled diabetes or other endocrine disorders; (6) history of head injury with loss of consciousness; (7) history of neurological disease; and (8) past treatment with electroconvulsive therapy (ECT), transcranial magnetic stimulation, or psychotherapy.

MRI image acquisition and analysis

Seventy (66.6 % of the total) scans were obtained on a 1.5-T. Sigma GE Genesis-based Echo-Speed scanner (General Electric Medical Systems, Milwaukee, WI, USA) running version 5.7 software and using a standard 30-cm circularly polarized head coil. Sagittal anatomic images were acquired using a 3D/FSPGR/20 sequence [flip angle = 20; echo delay time in-phase (TE), minimum repetition time (TR) = 300 ms; inversion recovery = 300 ms; matrix = 512 × 256; field of view (FOV) = 24 cm; scan thickness = 1.2 mm]. The remaining 35 (33.4 % of the total) subjects were scanned on a 3-T MRI Sigma GE Genesis (General Electric Medical Systems, Milwaukee, WI, USA). Here, sagittal T-1 weighted images were acquired using a 3D FSPGR-IR sequence, (TR/TE = 10.3/2.1 ms; flip angle = 20; inversion time = 300; matrix = 512 × 256; FOV = 24; and slice thickness = 1.2 mm). The proportion of participants based on diagnosis was equal across the two scanners. The AFNI software package (National Institute of Mental Health, Bethesda, Maryland, MD, USA; http://afni.nimh.nih.gov/afni/) was used to analyze the data.

Vermian measurements

Vermian volumes were measured using the three planes in the following order: sagittal, coronal, and axial planes. The vermis is divided into the anterior (V1), superior–posterior (V2), and inferior–posterior (V3) lobes (Mackie et al. 2007; see Fig. 1). The anterior lobe is composed of lobules I–V (Mackie et al. 2007) and is located between the anterior (superior) medullary velum and the primary fissure. The primary fissure lies between the V1 and V2 regions. The V2 region consists of lobules VI and VIIA-folium (Mackie et al. 2007). It is separated from the V3 region by the prepyramidal fissure (Mackie et al. 2007). V3 includes the lobules VIIA–X (Mackie et al. 2007). Measurements began with delineation of the two fissures that demarcated the vermian subregions. The primary and the prepyramidal fissures are easily delineated on the mid-sagittal slice but become relatively less prominent laterally. The mid-sagittal slice was defined where the aqueduct of Sylvius was open, the cerebral fissures and corpus callosum were visible, and the occipital gyri were ambiguous. All three planes were used to follow the mid-sagittal fissure tracings. It is difficult to set the lateral borders of the vermis on both sides for V1 particularly, as the paravermian sulcus (which runs between vermis and cerebellar hemispheres) is not prominent or constant across slices throughout its course, especially in the mid-slices (Toga et al. 2000). The vermis abuts with an angle by the anterior medullary velum and continues with the vermian white matter. We chose the slice preceding the last slice where anterior medullary velum was still seen on the sagittal plane as the lateral borders of the vermis on both sides.

After tracing the V1 and V2 in the sagittal plane, we trimmed our tracings on the coronal plane until the slice where both cerebellar hemispheres connected in the midline, which is also the slice where the paravermian sulcus is still prominent. Although we included small amounts of

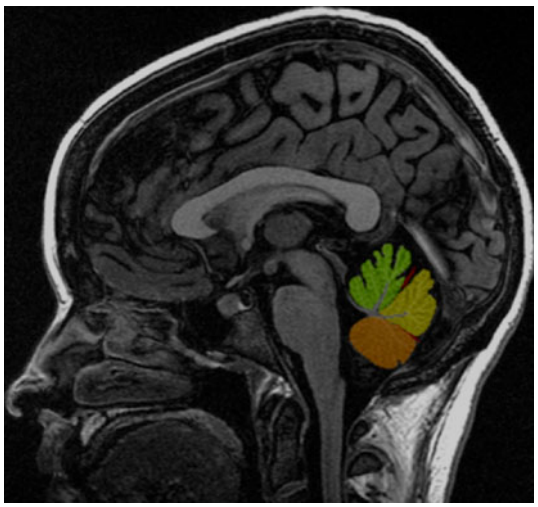

Fig. 1 A mid-sagittal slice displaying vermian subregions (V1 = *green*, V2 = *yellow*, V3 = *orange*), primary fissure superiorly (*red*), and prepyramidal fissure inferiorly

cerebellar hemisphere in the mid-slices and excluded some vermian tissue in the most posterior coronal slices in some subjects, our protocol was simple and reliable. We traced V3 on the sagittal plane until it disappeared on both sides, aided by the other planes simultaneously. The total vermis volume was the sum of these three subregions. Due to interscan variability in contrast parameters, the vermis was not parcellated into gray and white matter. Cerebellar tonsils and velum medullare (cerebellar white matter) were excluded.

We compared the volumes of the total vermis, the anterior lobe (V1), the superior posterior lobe (V2), and the inferior–posterior lobe (V3). Inter-rater reliabilities [intraclass correlation coefficient (ICC)] for V1, V2, and V3 were: .95, .97, and .88, respectively. All intra-rater reliabilities (ICC) for V1, V2, and V3 were .99. Measurements from one rater, A.N., were used for all vermian volumes.

Total cerebral volume (TCV) measurements

Total cerebral volume was defined as the gray and white matter of both hemispheres spanning the midbrain superior to the pons, a border chosen for its easy identification. The inter-rater reliability (ICC) between two raters was .99.

Statistical analysis

Raw vermis volumes were analyzed using a between-subject one-way analysis of variance (ANOVA), with the NC, FT, and PT groups. Analyses of co-variance (ANCOVA) were also used to examine vermian volumes with TCV as a co-variate. Following significant group main effects, post hoc analyses were conducted using Tukey's Honestly Significant Difference and Bonferroni correction for ANOVAs and ANCOVAs, respectively. Differences between demographic and clinical variables were calculated using ANOVA and *t* tests. An alpha level of .05 was used for all statistical tests. Analyses were performed using *SPSS 15.0 for Windows*.

Results

The groups did not differ significantly by any of the demographic variables including education, age, and gender. FT and PT patients did not differ significantly from each other on the GAF, YMRS and HAM-D scores, number of past episodes or illness duration (see Table 1).

There were no significant differences in TCV between groups $F(2, 102) = .86$, $p = .42$. There was a significant effect of group on V1 volumes $F(2, 102) = 3.96$, $p = .022$. Post hoc analyses revealed that PT patients had significantly larger V1 volumes when compared to controls ($p = .016$). FT patients did not differ from either NC ($p = .28$) or PT patients ($p = .41$). The pattern of results remained the same after co-varying the V1 volumes for TCV.

A significant gender–diagnosis interaction in V1 volumes $F(2, 99) = 5.14$, $p = .008$ was found. There was a significant difference between groups in V1 volume in men $F(2, 36) = 9.23$, $p = .001$, but not in women $F(2, 63) = .243$, $p = .78$ (see Table 2). Primarily, an increase in V1 volume was apparent in PT males when compared to NC males ($p = .002$). Adjusting for TCV volumes yielded similar results. There were no significant between-group differences in the volumes of other vermian regions.

There were no correlations between volume of any vermian region and clinical variables, including the age at scanning, age at disease onset, illness duration, or scores on the Ham-D, YMRS, and GAF. Running separate gender-specific correlation analysis also yielded no significant correlations with clinical variables.

Discussion

To our knowledge, this is the first volumetric study of the vermis in patients with MDD. We found larger volumes of the anterior vermis in patients with MDD with a long history of antidepressant treatment compared to healthy controls. This finding was prominent only in men. Patients who were equivalent in symptomatic and demographic domains but had never received treatment did not differ from healthy controls in any vermian region. Although we do not have direct evidence that this difference reflects the effect of medication, there were no differences between the

Table 1 Demographic and clinical characteristics of study sample

Variable	PT patients ($n = 35$) *M* (SD)	FT patients ($n = 35$) *M* (SD)	Normal controls ($n = 35$) *M* (SD)	Group effect *p*
Age (years)	38.0 (12.8)	34.3 (8.9)	37.4 (11.7)	.34
Education (years)	14.4 (3.5)	14.7 (2.8)	16.3 (3.2)	.06
Sex	22 F/13 M	22 F/13 M	22 F/13 M	–
GAF	65.1 (11.0)	60.7 (9.4)	82.6 (3.7)	.08
HAM-D	10.7 (6.8)	13.5 (7.0)		.12
YMRS	.2 (.6)	.2 (.7)		.86
Illness duration (years)	12.7 (12.4)	8.9 (8.6)		.16
Past episodes	4.8 (4.9)	4.8 (7.6)		.98

FT first presentation for treatment, *PT* pas1t treatment over multiple episodes, *NC* normal controls, *HAM-D* Hamilton Depression Rating Scale, *YMRS* Young Mania Rating Scale, *GAF* Global Assessment of Functioning Scale

Table 2 Absolute volumes and multiple comparisons of vermis subregions of study sample

ROI	FT Patients ($n = 35$) *M (SD)*	PT Patients ($n = 35$) *M (SD)*	NC ($n = 35$) *M (SD)*	FT versus PT	FT versus NC	PT versus NC
Anterior vermis (V1)						
Males	4690 (633)	5294 (941)	4233 (529)	.10 (.12)	.25 (.96)	.002* (.01*)
Females	4140 (542)	4181 (683)	4055 (583)	.97 (.99)	.89 (.99)	.77 (.99)
Superior–posterior vermis (V2)						
Males	3257 (650)	3697 (758)	3195 (631)	.24 (.39)	.97 (.99)	.16 (.82)
Females	3130 (610)	3150 (684)	3229 (463)	.99 (.99)	.85 (.99)	.90 (.99)
Inferior–posterior vermis (V3)						
Males	2687 (344)	3028 (655)	2670 (485)	.22 (.33)	.99 (.99)	.19 (.42)
Females	2548 (439)	2532 (514)	2552 (306)	.99 (.99)	.99 (.99)	.99 (.99)
Total vermis						
Males	10634 (1276)	12020 (1971)	10098 (1375)	.08 (.10)	.66 (.99)	.01* (.07)
Females	9818 (1333)	9863 (1516)	9837 (1019)	.99 (.99)	.99 (.99)	.99 (.99)
TCV						
Males	1202 (162)	1228 (131)	1130 (92)	.87	.35	.15
Females	1082 (87)	1087 (126)	1083 (96)	.98	.99	.99

Vermis volumes are presented as raw means in mm^3; TCV volumes are presented as means in cm^3

ROI region of interest, *TCV* total cerebral volume

Values outside of parantheses are *p* values (analysis of variance; Tukey's post hoc). Values in parentheses are total cerebral volume normalized *p* values (analysis of covariance; Bonferroni correction) $*p < .05$

patient groups on any current symptom measures or burden of illness variables. Furthermore, we found no correlations between vermian subregional volumes and clinical variables such as illness duration or age at onset of illness. The null association is in-line with a recent study on vermis volumes in BD (Baldaçara et al. 2011). In the absence of another explanation, it seems reasonable to hypothesize that we are observing an effect of long-term treatment with antidepressant medication in the PT group.

The anterior vermis is traditionally associated with sensorimotor functions, whereas the posterior vermis, in concert with the cerebellar hemispheres, is associated with the regulation of emotion and cognitive processes (Schmahmann 2004; Schmahmann and Sherman 1998). There are several studies, however, that demonstrate that the anterior vermis is not a region solely related to motor function (Anderson et al. 2006; Calarge et al. 2003; Crespo-Facorro et al. 1999; Kibby et al. 2008; Nopoulos et al. 1999; O'Hare et al. 2005; Supple and Kapp 1993, 1994). Anterior vermis volume was associated with phonological awareness, inattention, hyperactivity, and impulsivity in a study with children with dyslexia (Kibby et al. 2008). In addition, a relation between intelligence and anterior vermis volume was reported in patients with schizophrenia (Nopoulos et al. 1999). The anterior vermis has also been associated with non-motor functions such as

verbal learning and memory (Crespo-Facorro et al. 1999; Lee et al. 2007; O'Hare et al. 2005; Supple and Kapp 1993;1994), social cognition (Calarge et al. 2003), and reward systems and addiction (Anderson et al. 2006). Notably, each of these processes is dysregulated in patients with MDD (Airaksinen et al. 2004; Chau et al. 2004; Inoue et al. 2006).

Research into the functional connectivity impairments of the cerebellum in psychiatric conditions has proliferated, augmenting the findings from structural and task-related functional studies. A recent resting-state fMRI study of MDD identified altered connectivity between several cerebellum and cerebrum areas, including decreased connectivity of left vermis with ventramedial prefrontal cortex and posterior cingulate cortex (PCC) in MDD patients compared to controls (Alalade et al. 2011). Interestingly, the vermis–PCC connectivity was positively associated with symptom severity. Similar fronto-limbic-cerebellar network connectivity deficits have been reported in schizophrenia, where patients exhibited impaired functional connectivity between the left cerebrum and right cerebellum, particularly between the right anterior vermis and left inferior frontal gyrus, hippocampus, cingulate, and thalamus in comparison to healthy controls (Collin et al. 2011). These findings suggest that the increase in anterior vermis volume the present study reflects altered cerebellar-cerebrum connectivity patterns in MDD. The anterior vermis has connections with the thalamus, hippocampus, amygdala, septal region, orbitofrontal gyrus, gyrus rectus (Anand et al. 1959; Harper and Heath 1973), and reticular formation (Kerr and Bishop 1991)—regions that are consistently implicated in the pathophysiology of MDD (Konarski et al. 2008). The prefrontal cortex may be a key region for understanding the pathophysiology of patients with MDD (Drevets 2000) and it has been proposed that an increase in prefrontal activity is associated with a decrease in cerebellar activity (Lee et al. 2007). Bench et al. (1992) in their single photon emission tomography (SPECT) study found increases in cerebellar activity and decreases in prefrontal activity in patients with MDD. It is therefore interesting to speculate that the larger vermian volume observed in our depressed sample might have a relation to abnormal prefrontal function.

The anterior vermis is connected with brain stem regions and receives significant input from the serotonergic system (Kerr et al. 1991). Stimulation of the anterior vermis in rat decreases serotonin release, as well as increases dopamine turnover in nucleus accumbens (Albert et al. 1985). The anterior vermis receives particularly dense nicotinic projections which have a modulatory influence on the release of other neurotransmitters (De Filippi et al. 2005). The larger anterior vermis in patients with MDD with a long history of treatment with antidepressants might therefore stem from long-term exposure to medications that modify relevant monoaminergic systems (Morilak and Frazer 2004). However, recent work on social anxiety disorder by Cassimjee et al. (2010) has identified that a number of brain regions, including the vermis, show reductions following 12 weeks of treatment with escitalopram. In addition, increases in vermis volume may be linked to stressful situations during childhood, as a recent study has linked increased gray matter volume in the posterior vermis in children with PTSD (Carrion et al. 2009).

Larger anterior vermis volume changes might have a relation with psychomotor deficits observed in patients with MDD. Reduced saccade accuracy is associated with vermian abnormalities in patients with MDD, however, the authors implicated the posterior rather than the anterior vermis (Sweeney et al. 1998). Furthermore, psychomotor retardation may be the result of primary basal ganglia dysfunction (Sweeney et al. 1998), although studies are required to understand both the origins of psychomotor changes that are common in mood disorders and the contribution, if any, of vermian changes to this aspect of MDD.

Finally, it seems reasonable to suggest that the increased anterior vermis volumes in PT patients reflect, in part, glial cell proliferation in response to antidepressant medication, given that astrocytes account for over 25 % of the gray matter volume (Kimelberg and Norenberg 1989) and contain serotonergic receptors (Whitaker-Azmitia et al. 1993). However, recent literature on glial fibrillary acidic protein (GFAP), a specific marker for astrocytes, has demonstrated that not only are cerebellar GFAP levels lower than normal in depressed patients, but the use of antidepressants yields further decreases in GFAP levels (Fatemi et al. 2004). This research suggests that antidepressant therapies exert a negative effect on glial cell numbers, and therefore may not be a contributing factor in increased cerebellar volumes.

The cross-sectional design and modest sample size are limitations of this study. Furthermore, as our extensively treated patients had received treatment from several clinics throughout their illnesses, we did not have complete details of their medication exposure. Such information might have allowed for a more specific understanding of the role of antidepressant therapy in leading to differences in the size of the vermis for patients compared to healthy subjects. We also found that increased anterior vermis volumes were restricted to men with MDD. Our gender-specific finding is interesting but highly preliminary due to the small sample sizes when the groups were separated by sex. It is worth noting that Rossi et al. (1993) reported anterior vermis reductions only in men with schizophrenia and more recently, total vermis volumes were reported to be larger in men, but not women, with bipolar disorder compared to healthy controls (Womer et al. 2009). In the light of these findings, follow-up studies should include equal proportion

of sexes to increase the reliability of statistical inferences, given the problems associated with biological variability. Additionally, since our FT and PT patient groups did not differ on illness burden variables aside from medication history, a possible developmental precondition may be a confounding variable in our study. We cannot entirely rule out the possibility of the PT group having a developmentally larger than normal anterior vermis, possibly leading to different patterns of symptom presentation. In addition, future research will need to address whether altered vermian volumes are simply epiphenomena of structural changes elsewhere in the brain, or whether functional and structural changes in this area are closely associated with depressive symptomatology.

Of final note, the results of this study are limited by the report of vermian volumes without additional gray/white matter parcellation. The inclusion of these parameters and measures of total cerebellar volume in future work will support a fuller comparison with other studies in the reported literature.

In summary, we found larger anterior lobes of the vermis in men with MDD who had an extensive history of pharmacological treatment compared to those of healthy controls. Such differences were not apparent in patients with equivalent past illness burden but no previous treatment. We speculate that the larger anterior vermis volumes might arise from abnormalities in connectivity or as compensatory responses to the prefrontal dysfunction noted in patients with MDD but confirmation of this hypothesis awaits further studies.

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