available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

BRAIN RESEARCH

Research Report

Sexual dimorphism and asymmetry in human cerebellum: An MRI-based morphometric study

Lingzhong Fan[a], *Yuchun Tang*[a], *Bo Sun*[a], *Gaolang Gong*[b], *Zhang J. Chen*[b], *Xiangtao Lin*[c], *Taifei Yu*[c], *Zhenping Li*[a], *Alan C. Evans*[b], *Shuwei Liu*[a,*]

[a]*Research Center for Sectional and Imaging Anatomy, School of Medicine, Shandong University, Jinan 250012, China*
[b]*McConnell Brain Imaging Center, Montreal Neurological Institute, McGill University, Montreal H3A 2B4, QC, Canada*
[c]*Shandong Medical Imaging Research Institute, Jinan 250021, China*

ARTICLE INFO

Article history:
Accepted 13 July 2010

Keywords:
Sexual dimorphism
Asymmetry
Cerebellum
Voxel-based morphometry
Volumetric analysis
Magnetic resonance image

ABSTRACT

Structural sexual dimorphism and asymmetry in human cerebellum have been described in previous research, but results remain inconclusive or even conflicting. In this study, gender differences and hemispheric asymmetries in global and regional human cerebellum gray matter (GM) were estimated in an age-matched sample ($n=112$) of young Chinese adults. An optimized voxel-based morphometry (VBM) in spatial unbiased infratentorial template (SUIT) space together with an automated atlas-based volumetric approach were performed for mapping regional gray matter (GM) gender-related differences across the entire cerebellum. The two methods provided consistent findings on gender differences. The cerebellar GM volume was significantly larger in the anterior and middle posterior lobes of male group. In addition, a trend of greater GM volume in lateral posterior lobe of female group was observed. With the created symmetric cerebellar template, the asymmetric properties of cerebellar hemisphere were also assessed by VBM analysis, showing rightward asymmetry distributed in most cerebellar lobules and leftwards asymmetry distributed in the lobules around the medial posterior lobe. Gender differences in males showed higher leftward asymmetry sparsely within a few lobules and lower rightward asymmetry mainly within lobule Crus II, as compared with females. The acquired detailed morphologic knowledge of normal human cerebellum could establish a baseline for comparison with pathologic changes in the cerebellum. Moreover, our results might help to address controversies in thestudy of sexual dimorphisms and asymmetric patterns in human cerebellum.

1. Introduction

Biological and behavioral differences between genders are widely recognized, and a large number of postmortem histological and in vivo morphological studies on sexual dimorphisms have been dedicated to the human brain (Allen et al., 1989; Cosgrove et al., 2007; Good et al., 2001a; Nopoulos et al., 2000; Rabinowicz et al., 1999). It is also well known that the human brain is asymmetric in both its structures and functions. Anatomical brain asymmetries have also been

---

* *Corresponding author*. Fax: +86 531 88563495.
E-mail address: liusw@sdu.edu.cn (S. Liu).
Abbreviations: FDR, false discovery rate; FWHM, full-width half maximum; GLM, general linear model; GM, gray matter; MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; ROI, region of interests; Spm, statistical parametric mapping; SUIT, spatial unbiased infratentorial template; TR, repetition time; TE, echo time; TIV, total intracranial volume; VBM, voxel-based morphometry

0006-8993/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2010.07.031

Please cite this article as: Fan, L., et al., Sexual dimorphism and asymmetry in human cerebellum: An MRI-based morphometric study, Brain Res. (2010), doi:10.1016/j.brainres.2010.07.031

studied extensively with various neuroimaging techniques (Amunts et al., 1996; Good et al., 2001a; Luders et al., 2006; Toga and Thompson, 2003). However, previous studies mainly investigated the patterns of gender differences and asymmetric properties in cerebral cortex, and few studies have specifically probed into the cerebellum. A precise characterization of gender-related differences and hemispheric asymmetries in the regional morphology of cerebellar cortex is necessary for future fundamental research and disorder-related issues.

Thus far, the reported findings about gender-related cerebellar differences in postmortem histological or magnetic resonance imaging (MRI) studies are anatomically unspecific and inconsistent. In an earlier postmortem morphologic study, the researchers reported that the total number of Purkinje cells in the male was 6–8% higher than in the female (Hall et al., 1975). However, another study reported no significant sex, lateral or interaction effects involving the cerebellum (Henery and Mayhew, 1989). By using neuroimaging techniques, many studies have shown that men had larger gross cerebellar hemispheres, cerebellar vermis, as compared with women (Chung et al., 2005; Escalona et al., 1991; Filipek et al., 1994; Luft et al., 1998; Raz et al., 1998, 2001). Nevertheless, other studies reported no gender difference in cerebellar volume when the volume was corrected by brain size (Luft et al., 1998; Nopoulos et al., 2000; Szabo et al., 2003). Conversely, in another MRI study, women evidenced a higher proportion of cerebellar GM after adjustment for brain size (Hutchinson et al., 2003).

Previous region-of-interest (ROI)-based volumetric studies also demonstrated asymmetrical patterns in normal human cerebellum. For instance, in a semi-automated volumetric study, right-to-left asymmetries were significant for the cerebellum after being adjusted for total cerebral volumes (Szabo et al., 2003). In another sample, Szeszko et al. (2003) found right-greater than left anterior volume asymmetry and left-larger than right posterior asymmetry in normal cerebellum. However, other researchers did not find significant hemispheric asymmetry in regional human cerebellum (Luft et al., 1998). The regions of interest were outlined manually regardless of the inter-individual anatomic differences; however, the processes are labor-intensive and time-consuming and the ROI selection was based on a prior hypothesis.

So far, some whole brain approaches such as voxel-based morphometry (VBM) have been used in neuroimaging studies, which would complement and extend the ROI findings. Without Jacobian modulation, the VBM approaches only test for regional differences in concentration of GM, which are less sensitive to shape differences (Ashburner and Friston, 2000). Unlike the previous results, the latest VBM results can be modulated to account for the variable shape changes in nonlinear normalization, and thus preserve the volume of the particular tissue within a voxel (Good et al., 2001b). A few prior VBM studies have reported the cerebellar morphometries, but always with anatomically vague, or even contradictory results (Chen et al., 2007; Good et al., 2001a; Herve et al., 2006; Luders et al., 2004). Sometimes, the cerebellum was excluded during the data preprocessing to improve the accuracy in analyzing the human cerebrum (Allen et al., 2003; Watkins et al., 2001). Even with the cerebellum included, gender-related differences and asymmetric results regarding the cerebellum were always reported roughly as additional results. Therefore, the effects of gender and asymmetric patterns are still in a state of dispute for not only the cerebellum taken in its entirety but also taken regionally; those issues need to be further explored.

In addition, several developmental neuropsychiatry disorders such as autism, attention deficit hyperactivity disorder (ADHD), dyslexia and schizophrenia involve the cerebellar structures and afflict a significantly larger proportion of males. For instances, boys are more at risk for autism and ADHD than girls, and schizophrenia manifests at an earlier age in men (Andreasen and B., 2001; Keller et al., 2003; Moretti et al., 2002). Furthermore, various pathological disorders, such as schizophrenia (Loeber et al., 2001; Szeszko et al., 2003), epilepsy (Lawson et al., 2000), dyslexia (Kibby et al., 2008), autism (Bloss and Courchesne, 2007), tumors (Safavi-Abbasi et al., 2007), drug abuse (Sim et al., 2007), could cause asymmetrical changes in the human cerebellum. Therefore, establishing norms for cerebellar volume and detailed evaluation of sex effects and asymmetric patterns would be necessary for reliable diagnoses and neurosurgical approaches to these disorders.

Recently, a common coordinate proportional scaling system with labels for identifying cerebellar landmarks and features was proposed as the human cerebellum template and probabilistic atlases (Diedrichsen, 2006; Diedrichsen et al., 2009; Schmahmann et al., 1999). In addition, both VBM and ROI-based analyses provide us different types of information, and should thus be used in tandem (Giuliani et al., 2005). Here, an optimized VBM in SUIT space, together with an atlas-based volumetric approach were performed for the cerebellar morphologic analysis in an adequate sample ($n=112$) of in vivo MRI data. The purpose of the present study is not only to assess the gender-related morphological differences and asymmetrical properties in the cerebellar GM, but to provide a more objective and exhaustive re-evaluation of the anatomical organization in the human cerebellum (Table 1).

2. Results

2.1. Gross and regional cerebellar GM volumes

In this study, we first acquired quantitative neuroimaging data of gross and regional cerebellar GM volumes with an atlas-based volumetric approach. The total cerebellar GM volumes in male and female groups were: 111.73 ± 14.11 cm^3 and 102.89 ± 11.45 cm^3. The average GM volumes of the left and right cerebellar hemispheres and vermis for both groups were as follows: in male group, Left = 52.72 ± 6.68 cm^3; Right = 53.64 ±

Table 1 – Characteristics of the sample. Note. Mean ± SD = mean ± standard deviation.

Group	Age (years, Mean ± SD)	Age range	Number
Male	24.7 ± 2.0	18–32	66
Female	24.8 ± 3.6	18–33	46

Please cite this article as: Fan, L., et al., Sexual dimorphism and asymmetry in human cerebellum: An MRI-based morphometric study, Brain Res. (2010), doi:10.1016/j.brainres.2010.07.031

6.69 cm^3; Vermis=5.36±0.74 cm^3; in female group, Left=48.49±5.33 cm^3; Right=49.45±5.43 cm^3; Vermis=4.91±0.69 cm^3. More detailed volumetric data of each cerebellar lobule is shown in Table 2.

Results from several previous volumetric neuroimaging studies of human cerebellum are listed in Table 3(Diedrichsen et al., 2009; Keuthen et al., 2007; Makris et al., 2003, 2006; Raz et al., 2001). We noticed that there were some discrepancies in the gross or regional cerebellar GM volume, which might be caused by racial differences (Tang et al., 2010) or different scanning protocols and measuring methods applied in the studies (Diedrichsen et al., 2009; Schmahmann et al., 1999). Nonetheless, the gross and regional cerebellar volumes obtained in the current study were reasonable in scope according to the previous studies.

2.2. *Gender differences*

In terms of the global effects of sex, the male group had significantly larger absolute cerebellar GM volumes than the female group ($T=4.75$, $p<0.001$, age-adjusted, see Table 2). However, after adjusting the total intracranial volume (TIV) and age as nuisance variables, no statistically significant between-group differences were observed of the total cerebellar GM volumes in our samples.

The average cerebellar GM volumes and sex differences of the two groups are shown in Table 2. Significant gender-related differences were shown in the bilateral lobules V and VIIIb (male>female, Cohen's d>1.0). Although our results showed non-significant-associated increase in female cerebellum, there was a trend of greater GM volume in several lobules (e.g. bilateral Crus II and right VIIb).

Next, to visualize the VBM-based regional differences, we superimposed the SPM coordinates and significant voxels onto the customized cerebellar GM template. Cerebellar lobules were estimated based on the probabilistic cerebellar atlas and the MNI coordinates of the peak voxels are reported in Table 4. In Fig. 2, the significant increases of regional GM volumes in male group were shown in warm color (i.e. positive voxel values) in SPM-T maps. The significantly greater cerebellar GM volumes in male group were observed in the anterior (e.g. vermis V) and middle posterior lobules (e.g. left Crus II, left VII and bilateral VIIIb). In addition, with an uncorrected voxelwise threshold of $p<0.05$, we observed greater GM volumes in several lateral posterior lobules (e.g. bilateral CrusII, right CrusI and left IX) of female group, which were illustrated in winter color (i.e. negative voxel values).

2.3. *Asymmetry*

The statistical analysis of the cerebellum asymmetry patterns demonstrated similar location distributions in both groups. The asymmetry patterns in male and female groups were shown on sectioned planes of averaged cerebellar GM template, respectively (see Fig. 3).

For the whole group, significant rightward asymmetries were observed in most cerebellar lobules and leftward asymmetries were observed in the medial parts of cerebellar posterior lobe (see Fig. 4 and Table 5).

Table 2 – Gender effects on the regional cerebellum GM volumes by volumetric study. The mean cerebellar lobules volumes (cm^3) were acquired by using automated atlas-based volumetric approach. The cerebellar lobules (i.e. bilateral V and VIII b) were larger in male with adjustment TIV ($p=0.0024$, FDR corrected for multiple comparisons). Mean±SD=mean±standard deviation. Except for the *p* and *t* values, Cohen's *d* was also calculated as effect size.

Lobule	Male			Female			Gender-related differences					
	Left	Right	Vermis	Left	Right	Vermis	Left		Right		Vermis	
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	P/T	Cohen's *d*	P/T	Cohen's *d*	P/T	Cohen's *d*
I_IV	3.147±0.434	3.502±0.481	/	2.904±0.378	3.249±0.411	/	0.177/1.358	0.597	0.289/1.636	0.566	/	/
V	4.019±0.468	4.149±0.450	/	3.621±0.334	3.731±0.316	/	**0.0023/3.107**	0.979	**0.001/3.510**	1.075	/	/
VI	8.396±0.832	8.081±0.795	1.963±0.248	7.731±0.669	7.466±0.646	1.840±0.257	0.040/2.083	0.881	0.063/1.880	0.849	0.510/0.661	0.487
CrusI	12.879±1.497	13.694±1.544	0.011±0.004	12.012±1.259	12.859±1.266	0.010±0.003	0.758/0.309	0.619	0.869/−0.165	0.783	0.968/−0.040	0.283
CrusII	8.464±1.148	7.957±1.118	0.431±0.074	8.014±0.936	7.537±0.849	0.395±0.068	0.411/−0.825	0.430	0.329/−0.981	0.423	0.347/0.944	0.507
VIIb	4.188±0.483	4.508±0.554	0.233±0.031	3.926±0.430	4.301±0.474	0.214±0.027	0.784/0.275	0.573	0.495/−0.684	0.402	0.183/1.341	0.654
VIIIa	4.286±0.602	4.319±0.566	0.992±0.124	3.982±0.398	4.027±0.467	0.895±0.106	0.564/0.579	0.596	0.731/0.345	0.563	0.083/1.752	0.841
VIIIb	3.586±0.538	3.669±0.457	0.525±0.082	2.992±0.394	3.053±0.445	0.472±0.081	**0.000/4.523**	1.260	**0.000/4.827**	1.366	0.069/1.835	0.650
IX	3.061±0.499	3.077±0.533	0.958±0.118	2.685±0.392	2.639±0.419	0.855±0.100	0.052/1.965	0.994	0.022/2.329	0.914	0.016/2.455	0.942
X	0.697±0.177	0.685±0.193	0.251±0.060	0.621±0.138	0.585±0.139	0.227±0.048	0.828/0.217	0.479	0.184/1.334	0.595	0.662/0.438	0.442
Total	52.723±6.680	53.641±6.689	5.363±0.740	48.488±5.328	49.448±5.432	4.909±0.691						

Please cite this article as: Fan, L., et al., Sexual dimorphism and asymmetry in human cerebellum: An MRI-based morphometric study, Brain Res. (2010), doi:10.1016/j.brainres.2010.07.031

Table 3 – Cerebellar volume in normal humans based on MRI volumetric studies. It needs to be emphasized that there was an obvious discrepancy in the cerebellar vermis volumes among the reviewed studies. Note that in both Diedrichsen's study and ours, the vermis for lobules I_IV was not defined in the probabilistic cerebellar atlas. As in the anterior lobe, the vermis does not have a clear anatomical boundary that separates it from the hemispheres. In addition, with normal aging, a significant atrophy was observed in cerebellum, so a smaller average vermis volume was reported in Raz's study.

Literatures references	Sample size and age range (years)	Main results: cerebellar GM volume (cm^3)	
		Global (Male, M ; Female, F)	Hemispheres (Left, L; Right, R ; Vermis, V)
Raz et al. (2001)	N = 190;18–81	Total = 129.79 ± 14.17	Total = 127.09 ± 13.82; V = 2.97 ± 0.35
Makris et al. (2003)	N = 1; 40	M = 124.4	L = 55.5; R = 57.7; V = 11.2
Makris et al. (2005)	N = 10;	Total = 124.95 ± 7.82	L = 56.45 ± 2.90; R = 56.52 ± 3.43; V = 11.98 ± 1.49
Keuthen et al. (2007)	N = 12;18–45	F = 108.30 ± 9.5	L = 54.0 ± 4.6; R = 54.3 ± 5.0; V = 11.9 ± 1.0
Diedrichsen et al. (2009)	N = 20; 19–27	M = 118.86; F = 109.32	L = 48.05 ± 0.61; R = 47.31 ± 0.53; V = 4.64 ± 0.45
The current study	N = 112;18–33	M = 111.73 ± 14.11; F = 102.89 ± 11.45	Male: L = 52.72 ± 6.68; R = 53.64 ± 6.69; V = 5.36 ± 0.74 Female: L = 48.49 ± 5.33; R = 49.45 ± 5.43; V = 4.91 ± 0.69

2.4. *Interaction of sex with asymmetry*

Gender differences were also noted in the structural asymmetry analysis. The male group demonstrated increased rightward asymmetry within lobules (e.g. I_IV, IX, Crus I) and decreased leftward asymmetry within lobules (e.g. Crus II, VIIb) compared to female group (Fig. 5, Table 6).

3. Discussion

We first acquired a quantitative neuroimaging data of human cerebellum with newer high-resolution MRI acquisition techniques and an advanced image processing protocol. The detailed regional and gross cerebellar GM volumes were acquired with an automated atlas-based volumetric approach, which were comparable to previous reported volumes. Therefore, the results could serve as a reliable baseline for comparison with pathologic changes in the cerebellum of young adults. Secondly, addressing the issues of gender differences and asymmetries in human cerebellum, various morphometry studies have yielded heterogeneous results, and that most of the previous cerebellar studies have used global measures only. Here, the human cerebellum template and probabilistic atlas (Diedrichsen, 2006; Diedrichsen et al., 2009) used in our study provided a common coordinate proportional scaling system and labels for quantitative and uniform measurement, which avoided vague results in previous human cerebellum studies. Sex differences and hemispheric asymmetries in human cerebellum were explored using both VBM and atlas-based approaches. Put briefly, our results revealed greater GM volume in anterior and middle posterior lobules for males, while showed trends for greater GM volume in the lateral posterior lobules for females. Rightward cerebellar asymmetry was observed in most regions, with males demonstrating increased rightward asymmetry in some regions (e.g. I_IV, IX, Crus I), and decreased leftward asymmetries in other regions (e.g. Crus II, VIIb) relative to females.

Compared with previous ROI-based and whole brain VBM studies on cerebellum morphology, the current study not only partially confirmed previous findings but also provided new

Table 4 – Gender effects on the regional cerebellum GM volumes by VBM study. Comparison of the regions detected in the male > female and female > male contrasts in our sample, with the maximum *t*-values and their MNI coordinates. Note. *x*, *y*, *z* are the coordinates of significant voxels in stereotactic space (MNI spaces). For the male > female comparison, *T*-values were significant values set at $p < 0.05$ (voxel level), corrected for multiple comparison. And for the female > male comparison, the results were reported at uncorrected *p* value ($p < 0.05$) thresholds.

Comparisons	Anatomic location	Stereotaxic coordinates, mm			T values	$p < 0.05$
		x	y	z		
Male > Female (FDR-corrected)	Left_VIIIb	–17	–54	–62	6.03	0.001
	–	–8	–68	–52	5.20	0.001
	Right_VIIIb	11	–56	–62	5.59	0.001
		6	–66	–50	5.40	0.001
	Vermis_V	–4	–67	–8	4.27	0.003
	Left_ CrusI	–7	–79	–25	4.18	0.004
	Left_ CrusII	–7	–88	–28	4.07	0.005
	Left_VIIb	–24	–64	–45	4.10	0.004
Female > Male (uncorrected)	Right_CrusII	48	–69	–47	3.39	0.000
	Right_CrusI	54	–55	–33	2.56	0.006
	Left_IX	–12	–46	–41	3.26	0.001
	Left_CrusII	–30	–86	–43	3.02	0.002
	Right_CrusII	42	–76	–46	2.68	0.004
	–	36	–81	–42	2.33	0.011

Please cite this article as: Fan, L., et al., Sexual dimorphism and asymmetry in human cerebellum: An MRI-based morphometric study, Brain Res. (2010), doi:10.1016/j.brainres.2010.07.031

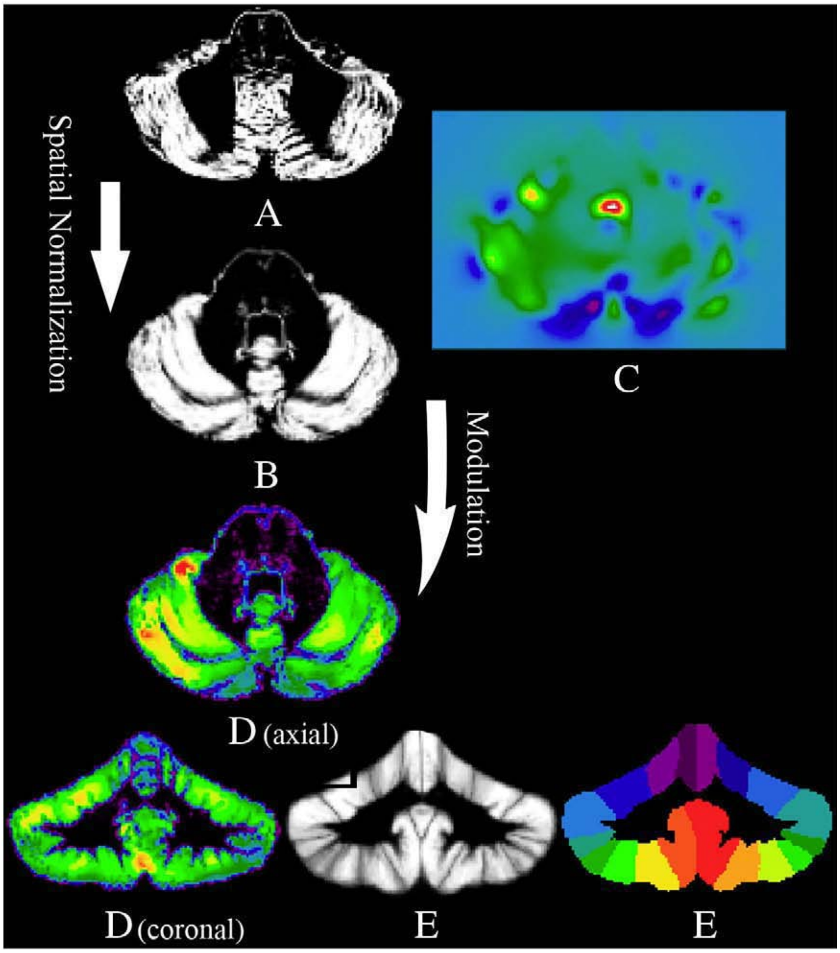

Fig. 1 – The flowchart of the atlas-based volumetric analysis in SUIT space. Spatial normalization was performed by a linear transformation followed by a non-linear deformation for the native cerebellar GM (A) registration to the study-specific GM template. The voxel values in the normalized segmented image (B) were multiplied by the Jacobian determinants (C) derived from the spatial normalization to compensate for any volumetric differences introduced during normalization (modulation). Subsequently, the structure probability maps (E) and the maximum likelihood probabilistic cerebellar atlas (F) were multiplied with modulated GM images (D) to yield lobule-specific GM images of the 28 cerebellar lobules for each subject.

and detailed findings of sex differences in normal human cerebellum. For the gross cerebellar GM volume, after TIV adjustment, no significant difference was estimated in our sample, which was in agreement with several previous studies (Luft et al., 1998; Nopoulos et al., 2000). Moreover, we found greater absolute and regional cerebellar GM volumes and an increased rightward asymmetry in men. In accordance with our findings, one prospective MR-based ROI study of sex differences in cerebellum was performed in 190 healthy volunteers (aged 18–81 years, 113 women and 77 men), demonstrated significantly larger GM volume in both cerebellar hemispheres of males (especially the right). Meanwhile, a greater anterior vermis volume in men was revealed in their data, which also agrees with our VBM results. However, the comparison should be examined with caution, because only the body height was served as a covariate in their statistical model, suggesting that the study design might be inappropriate for estimating regional differences (Raz et al., 2001). In addition, with a large sample of 465 subjects, one whole brain VBM study revealed men had greater GM volume in the anterior cerebellum (Good et al., 2001a), which was consistent with our results (i.e. larger vermis V revealed by VBM and larger bilateral lobules V revealed by volumetric analysis in male group). However, the differences do not always favor men. In another sample, women showed greater volume of medial cerebellar hemispheres and the lobules VI and VII after adjustment for the total cerebellar size (Rhyu et al., 1999). Here, after adjustment for TIV, the results did not show significantly greater cerebellar GM volume in female group. Nonetheless, some trends of greater GM volume were observed in the posterior lobules of cerebellar hemispheres (e.g. bilateral Crus II and right VIIb in volumetric analysis and bilateral Crus II, right Crus I and left IX in VBM findings with uncorrected threshold). Nevertheless, one study performed by Hutchinson demonstrated that the absolute cerebellar volumes are equivalent in male and female groups, whereas a larger normalized cerebellar GM volume after adjusting for the brain size (i.e. relative cerebellar volume) were shown in female group. It should be noted, however, that the sample studied in this research was a group of musicians and the

Please cite this article as: Fan, L., et al., Sexual dimorphism and asymmetry in human cerebellum: An MRI-based morphometric study, Brain Res. (2010), doi:10.1016/j.brainres.2010.07.031

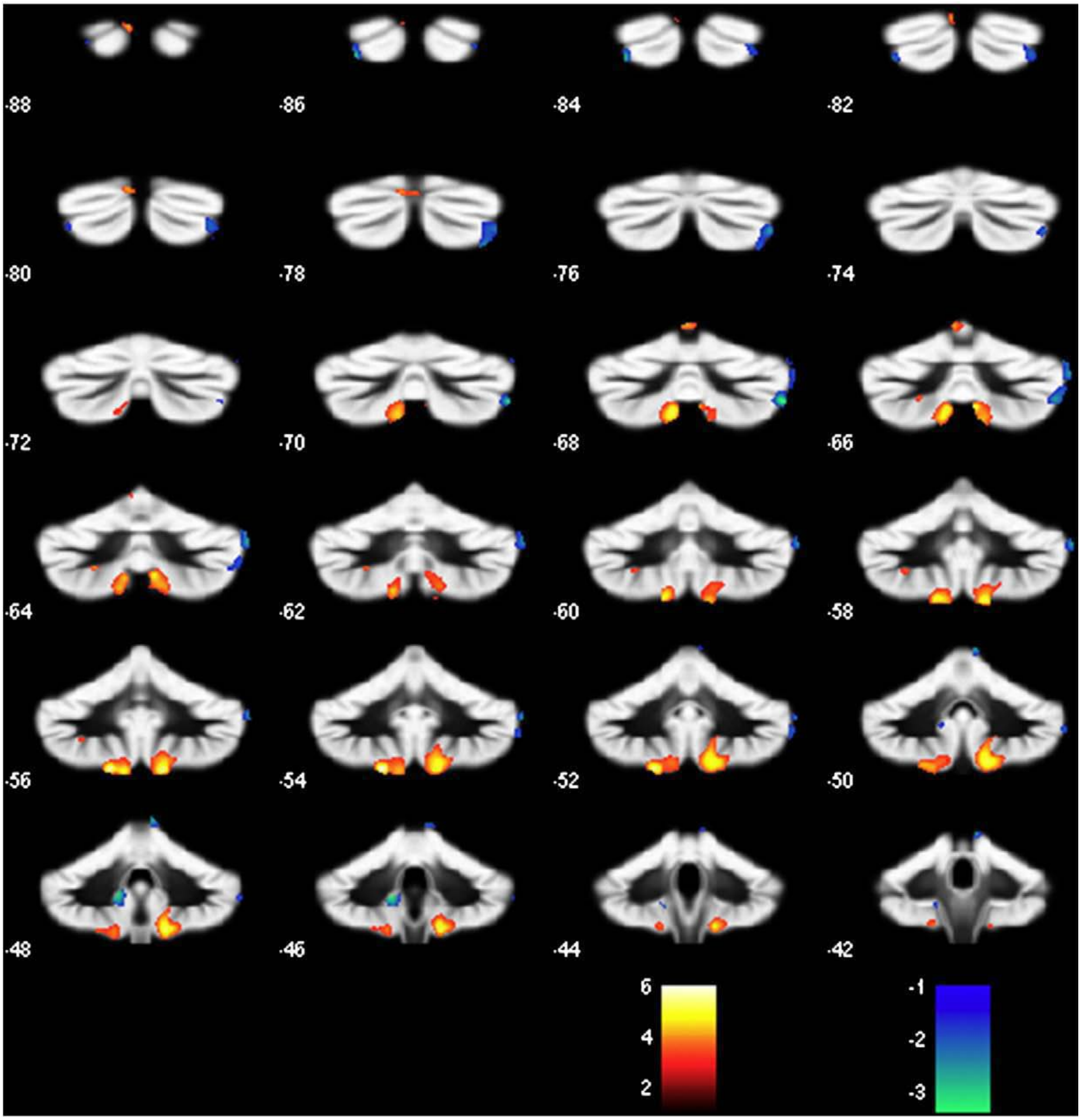

Fig. 2 – Statistical parameters (t-statistics) maps showing regions of gender-related differences. Significant increases and decreases regional GM volume in male group compared with female group are shown with warm color (i.e. positive voxel values) and winter color (i.e. negative voxel values). The results were superimposed on coronal slices from $y=-88$ mm to $y=-42$ mm, with 2 mm interval, in the averaged GM template. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

mean age for the male and female groups was not properly matched (i.e., more younger for the female group)(Hutchinson et al., 2003).

Our study showed a dominant rightward GM asymmetry in most of the cerebellum with some small foci of leftward GM asymmetry, which was consistent with several previous MRI studies (Lawson et al., 2000; Loeber et al., 2001; Szeszko et al., 2003). Still, the cerebellar hemispheres did not show any asymmetry in another ROI analysis (Luft et al., 1998). In a recent study, the left posterior cerebellar hemispheres were found to be larger. But, the asymmetry patterns were examined only in a group of 30 participants including both left-handed and right-handed individuals (Szabo et al., 2003).

In summary, the discrepancies among the above MRI-based studies could probably reflect multiple factors, including varying subjects' characteristics (Szabo et al., 2003) and sample sizes, differences in neuroimaging protocols and analysis strategies, such as manual tracing on comparably few sections (Luft et al., 1998), various landmarks for compartmentalization of the cerebellum (Escalona et al., 1991; Filipek et al., 1994; Good et al., 2001a; Hutchinson et al., 2003; Luft et al., 1998; Raz et al., 2001; Szabo et al., 2003),

Please cite this article as: Fan, L., et al., Sexual dimorphism and asymmetry in human cerebellum: An MRI-based morphometric study, Brain Res. (2010), doi:10.1016/j.brainres.2010.07.031

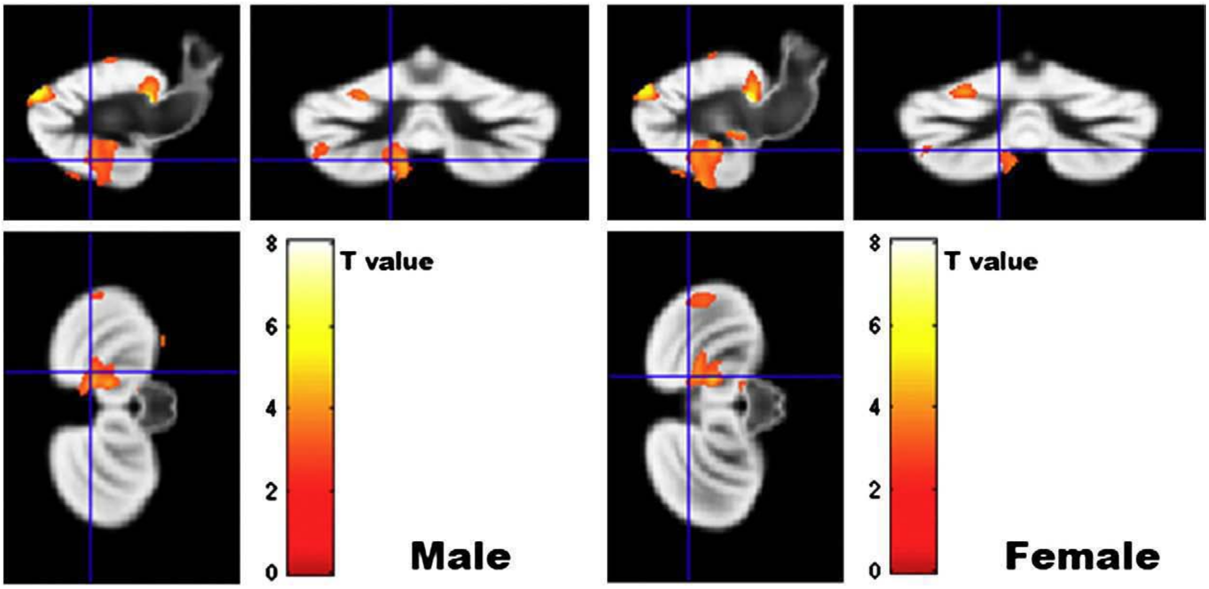

Fig. 3 – Asymmetry patterns in cerebellar GM of the male and female groups.The cerebellar GM volume asymmetry patterns demonstrated almost similar regional distributions in the male and female groups.

analysis of volumes normalized for height (Raz et al., 2001), total brain size (Luft et al., 1998; Nopoulos et al., 2000). Another important factor that might contribute to the inconsistency is aging, with men and women having different age-related structural changes in the brain, including cerebellum (Jernigan et al., 2001; Oguro et al., 1998; Raz et al., 2004). Also, two functional studies tried to evaluate the gender differences in baseline measures of cerebellar metabolism and acquired reverse results, which might be mainly related to different age groups being analyzed (Gur et al., 1995; Volkow et al., 1997). Thus, given the possibility of nonlinear concurrent effect of aging, analyzing sex-related morphological differences within a group of broad age range would inevitably produce inaccurate results. We removed the aging factor during analysis (ages ranged from 18 to 33 years) which provided a more stable and accurate population base for examining the gender effects on cerebellum.

A descriptive study, such as ours cannot elucidate the mechanisms of differences in nature. The neurobiological underpinnings of the gender effects on cerebellum remain unclear. It has been suggested that the hormonal effects, such as neurosteroids via estrogen and progesterone receptors could be responsible for the sex differences of cerebellar function and development formation (Dean and McCarthy, 2008; Perez et al., 2003; Tsutsui, 2006). Further research is still needed to determine the exact underlying mechanisms.

Nevertheless, we can safely conclude that the gender differences in human behavior and function are probably accompanied by a biologically unusual targeted enlargement of related regions. Such alterations in the neural tissue volumes between the genders may contribute to the gender-related differences in facilitating an efficient processing of information transformation during motor or cognitive abilities (Gur et al., 1999; Kimura, 1999). For instance, Gur et al. (1995) reported that men had relatively higher metabolism than women in the cerebellum when at rest. In another fMRI study, men exhibited more cerebellar activation than women when both were trying to perform a task involving remembering specific pitches (Gaab et al., 2003). However, the correspondence between anatomical landmarks and functional areas within the cerebellum is poorly understood, and gender effects on specific cerebellar functions have not been examined (Hantz et al., 1996; Kansaku et al., 2000; Sanders and Wenmoth, 1998). From previous behavioral and clinical studies, the primary sensorimotor functions were ascribed to lobules I/II, III, IV, and V (Allen et al., 1997; Nitschke et al., 1996), and the secondary sensorimotor functions ascribed to the medial portion of lobule VIII (Woolsey, 1952). Here, we found greater cerebellar GM volume in the anterior (e.g. left V) and middle posterior lobules (e.g. left VIIIb, right VIIIb) of the male, which could be related to sex effects on motor functions. There is also some evidence suggesting the role of the right posterolateral cerebellum in language functions, which could be lateralized as much as it is for cerebral cortex areas (Gebhart et al., 2002; Jansen et al., 2005; Mathiak et al., 2002). Interestingly, the trends of gender-related size differences observed in the cerebellar lobule right Crus II (i.e. female>-male) may be associated with the functional differences in language based on the connectivity with the cerebral cortex (Habas et al., 2009; Kelly and Strick, 2003; Schmahmann and Pandya, 1997).

Moreover, the bilateral cerebellar hemispheres are not only anatomically, but also functionally asymmetric (Hu et al., 2008). The cerebellar functional asymmetry may be associated with the pattern of connectivity between brain areas and specific cerebellar functional regions. For instance, in normal adults, one study found greater regional metabolic rates of glucose in the right mesio-anterior cerebellum analyzed with positron emission tomography (Willis et al., 2002). Other studies, an fMRI study was carried out during letter-cued word generation and revealed that the cerebellar activation was confined to the lateral posterior cerebellar hemisphere

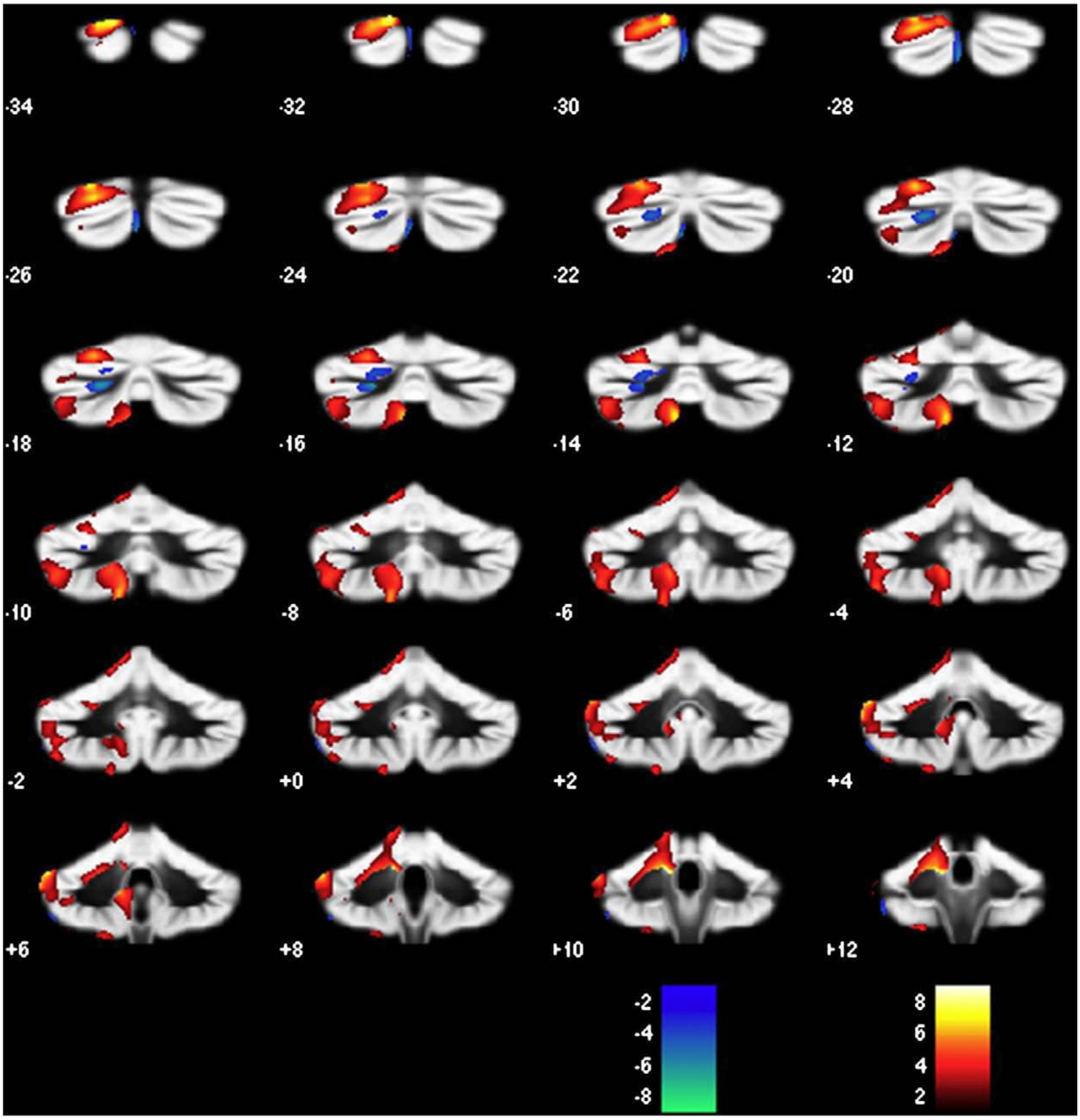

Fig. 4 – Asymmetry patterns in cerebellar GM of the whole group. Significant increases and decreases regional GM volume in rightwards compared with leftwards are shown with warm and winter colors, respectively. The cerebellar GM structural asymmetries were superimposed on coronal slices from y = −34 mm to y = +12 mm, with 2 mm interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(e.g. right lobule VI, VIIb, Crus I, Crus II). Likewise, clinical studies on patients with cerebellar disease support a role for the right lateral cerebellum for language processing (Leggio et al., 2000). One recent meta-analysis of neuroimaging studies in neocerebellum proposed a functional asymmetric pattern with language right-lateralized and spatial manipulation left-lateralized in cerebellar hemispheres (Stoodley and Schmahmann, 2009). The rightward and leftward structural asymmetry patterns demonstrated here might reflect such functional asymmetry in human cerebellum.

Furthermore, gender-related asymmetric cerebellar activation patterns were observed during various emotions in previous studies. Men showed significantly increased blood flow compared to women in the left cerebellum and cerebellar vermis during positive mood and negative mood induction (Hofer et al., 2007). Interestingly, in the current study, the male group demonstrated increased rightward asymmetry within lobules (e.g. I_IV, IX, Crus I) and decreased leftward asymmetry within lobules (e.g. Crus II, VIIb) compared to female group. However, more precise structure–function relationships in human cerebellum still needed to be clarified in future research.

Methodological issues: The human cerebellum, as a complex and morphologically convoluted structure located

Please cite this article as: Fan, L., et al., Sexual dimorphism and asymmetry in human cerebellum: An MRI-based morphometric study, Brain Res. (2010), doi:10.1016/j.brainres.2010.07.031

Table 5 – Leftward and rightward cerebellar GM volume asymmetries. Rightward asymmetry located in most cerebellar lobules and leftwards asymmetry distributed in the medial parts of cerebellar posterior lobe. Note. *x*, *y*, *z* are the coordinates of significant voxels in stereotactic space (MNI spaces). *T*-values were significant values set at $p<0.05$ (voxel level), corrected for multiple comparison, testing for greater or smaller GM volume within a voxel.

Comparisons	Anatomic location	Stereotaxic coordinates, mm			*T* values	$p<0.05$ FDR-corrected
		x	y	z		
Right>Left	I_IV	−12	−43	−27	9.90	0.000
	CrusI	−13	−85	−23	8.21	0.000
	–	−26	−78	−22	7.26	0.000
	CrusI	−48	−47	−29	7.64	0.000
	VIIb	−44	−57	−55	5.01	0.000
	CrusII (lateral)	−42	−65	−48	4.95	0.000
	VIIIb	−26	−37	−55	7.62	0.000
	–	−8	−64	−55	7.00	0.000
	–	−12	−62	−60	6.04	0.000
	IX	−11	−47	−39	6.23	0.000
	–	−4	−49	−34	4.04	0.000
Left>Right	CrusII (medial)	−20	−71	−38	6.35	0.000
	–	−2	−82	−41	5.76	0.000
	VIIIa	−3	−71	−48	5.67	0.000
	CrusII (medial)	−2	−85	−30	3.95	0.007

in the posterior fossa, has been particularly challenging to visualize and measure in vivo. Here, images were acquired with a 3D Fast Spoiled Gradient Recalled acquisition protocol, which yielded a relatively high signal noise ratio and resolution in cerebellum (Schmitz et al., 2005), thereby minimizing partial volume effects and improving the precision of tissue segmentation in the preprocessing than previous studies.

In addition, doing VBM with SUIT has two main advantages: First, the overlap of cerebellar structures is improved compared with previous whole brain VBM approaches (Bookstein, 2001), and secondly, by masking the cerebellum before transforming it into the cerebellar atlas space, the results are not biased due to the supra-tentorial GM. Likewise, mapping group or individual differences by VBM should be used in conjunction with regional volumetric analysis, with the former accentuating the advantages and ameliorating the limitations of latter (Kennedy et al., 2009). Here, the volumetric results obtained with automated atlas-based method were almost identical with the VBM results, and both demonstrated a similar trend for the gender effects on the cerebellum. Volumetric data obtained in our study is comparable to the results of previous studies, which were based on the extremely labor-intensive manual tracing techniques in large datasets (Diedrichsen et al., 2009; Makris et al., 2003, 2005; Raz et al., 2001). The overlapping results of both analytic approaches could be as additional evidence for the anatomical plausibility of our findings.

Several potential limitations still exist in the current study. First, prior studies found men and women presenting different age-related changes in the cerebellar development and aging. Although our study's narrow age range (18–33 years) is typical and worthy of reference for normal adults research, the results are not representative of individuals outside that range. A more generalizable set of results of gender effects on cerebellum for different age groups will be necessary in future research. Second, even though the trends for greater GM volume in lateral posterior cerebellum of female group were observed, we are unable to conclude that the results we observed are reliable. Third, although the population-based cerebellar probabilistic atlas could provide population statistics, it was acquired from a small sample of just twenty individuals. Lastly, there are still some inherent limitations of VBM analysis due to differences in gyrification patterns, contrast, or problems with registration (Kennedy et al., 2009). For instance, the automatic intensity-based normalization method failed to achieve a good registration of some fissures (e.g. the lateral aspects of the primary fissures) between individuals (Diedrichsen et al., 2009). It may be necessary to employ hand-parcellation or semi-automatic algorithms that assigned voxels to lobules based on detailed information about the anatomy of the cerebellar fissures (Makris et al., 2003, 2005).

In conclusion, with a well age-matched sample of right-handed young Chinese adults and spatially unbiased SUIT template, our results could help to address the controversies over sexual dimorphisms and hemispheric asymmetric patterns in human cerebellum. More importantly, the validated approach and detailed morphological knowledge focusing on the normal cerebellum morphology will be valuable for the future volumetric studies of the cerebellum in basic functional and clinical neuroscience.

4. Experimental procedures

4.1. *Subjects*

The present study included 112 young Chinese adults (Mean age = 24.7 ± 2.8 years, the detailed information see Table 1) selected from the dataset of the ongoing "Chinese Brain Atlas" project (Tang et al., 2010). All subjects were right-handed as assessed by Edinburgh Handedness Inventory and were free of any psychiatric or neurological abnormalities (Oldfield, 1971).

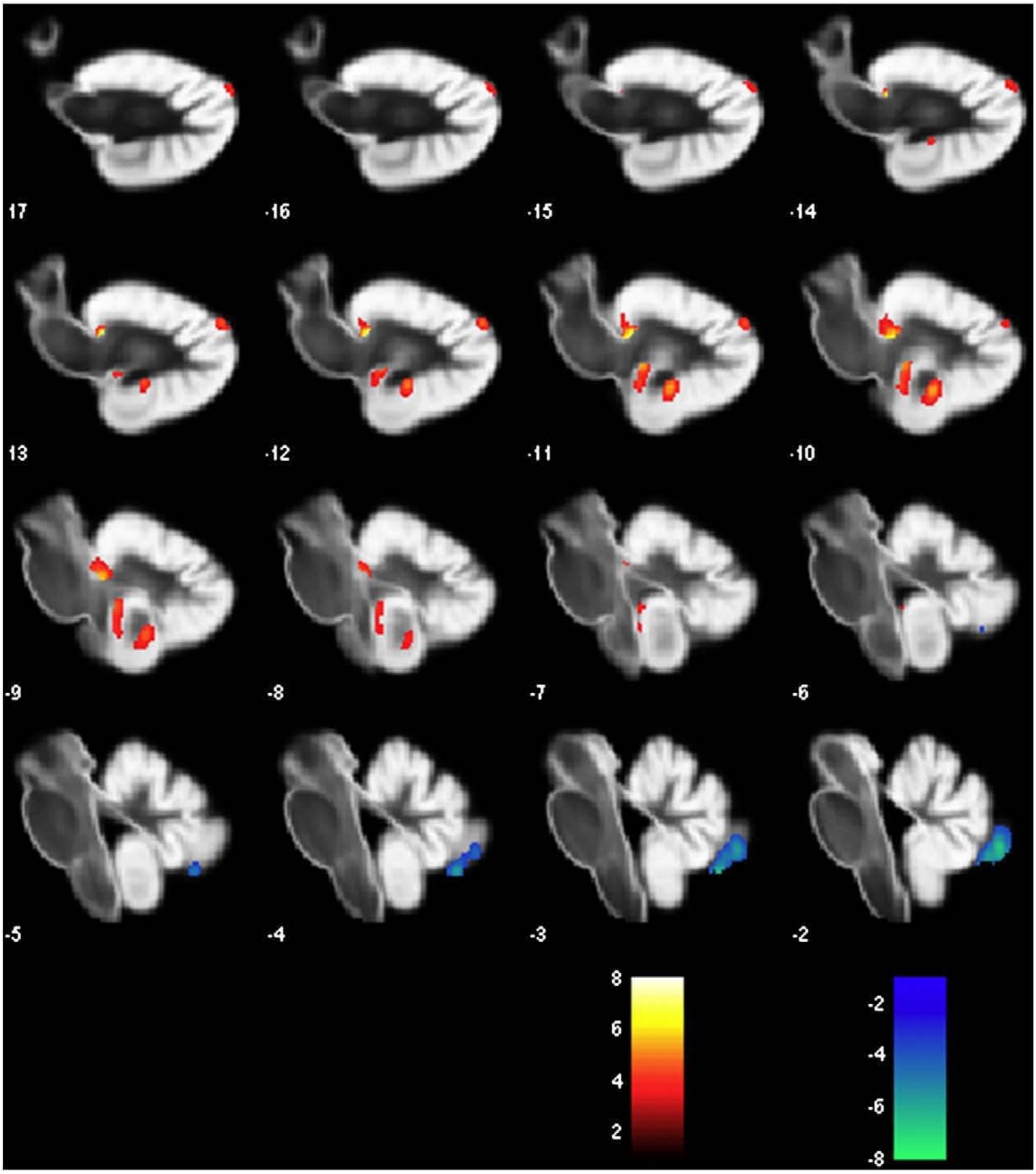

Fig. 5 – Gender effects on the cerebellar GM structural asymmetry. Significant increases regional GM volume rightwards and leftwards in male and female group are shown with warm and winter colors, respectively. The results were superimposed on sagittal slices from y=−17 mm to y=−2 mm, with 1 mm interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The study was approved by the Ethics Committee of Shandong University, and all subjects gave written informed consent to take part in the study.

4.2. *MRI acquisition and Image preprocessing*

All scans were performed on the same GE Signa (General Electric, Milwaukee, USA) 3.0 Tesla MRI scanner with an eight-channel phase array head coil at Shandong Medical Imaging Research Institute. A set of high-resolution axial T1-weighted images were acquired with a 3D fast three-dimensional spoiled gradient (FSPGR) sequence using the following scan parameters: TR/TE=6.68/2.88 ms; flip angle=10°; slices thickness=1.4 mm; number of excitations=2; field of view: 24×24 cm; matrix size: 512×512×248, and the voxel size: $0.47 \times 0.47 \times 0.7$ mm^3.

Please cite this article as: Fan, L., et al., Sexual dimorphism and asymmetry in human cerebellum: An MRI-based morphometric study, Brain Res. (2010), doi:10.1016/j.brainres.2010.07.031

Table 6 – Gender effects on cerebellar GM asymmetry. The male group demonstrated increased rightward asymmetry within lobules (i.e. I_IV, IX, Crus I) and decreased leftward asymmetry within lobules (i.e. Crus II, VII b) compared to female group. Note. *x, y, z* are the coordinates of significant voxels in stereotactic space (MNI spaces). *T*-values were significant values set at $p<0.05$ (voxel level), corrected for multiple comparison, testing for greater or smaller GM volume within a voxel.

Comparisons	Anatomic location	Stereotaxic coordinates, mm			T values	$p<0.05$ FDR-corrected
		x	y	z		
Male > Female	I_IV	−12	−43	−27	7.45	0.000
	IX	−11	−47	−39	5.39	0.000
	–	−10	−58	−47	5.35	0.000
	CrusI	−12	−84	−24	4.63	0.003
Female > Male	CrusII (medial)	−1	−79	−39	7.27	0.000
	VIIb	−3	−75	−48	6.27	0.000

After being converted into MINC format, all the structural MR images were processed using the CIVET pipeline (http://wiki.bic.mni.mcgill.ca/index.php/CIVET, version1.1.9) developed at the Montreal Neurological Institute (MNI) for fully automated structural image analysis. First, the images were corrected for non-uniformity artifacts due to the magnetic field inhomogeneities in the scanner using the N3 algorithms. The individual MR images were then transformed into the standardized MNI space by registering to a standard brain imaging template (International Consortium for Brain Mapping nonlinear average brain template ICBM 152) using linear and nonlinear transformations. The resulting images after linear registration were further segmented into GM, white matter, cerebrospinal fluid and background using an advanced neural net classifier. Then the partial volume estimation was performed, which is a step in tissue classification that tries to correctly estimate the proportions of tissue within each voxel. In these volumes, each voxel is represented as a partial volume estimate of a particular tissue type. Then the GM was warped back to the individual native space using the inverse of the linear transform.

To isolate the individual cerebellum, the cerebellar mask in the MNI space was nonlinearly warped back to the individual MRI volume and then carefully refined manually for each subject using Display (MNI, Canada), which allowed simultaneous visualization of the structures in three planes. Next, the cerebellar GM for each subject was isolated from the whole brain using the newly acquired cerebellar mask in the native space.

According to Bayesian prior of the cerebellum in MNI space, the isolation algorithm to acquire the cropped images of cerebellum with an LPI (left-posterior-inferior) orientation is from the SUIT toolbox (http://www.icn.ucl.ac.uk/motorcontrol/imaging/suit.htm), which is included in the statistical parametric mapping (Wellcome Department of Cognitive Neurology; SPM5), running in Matlab version 7.1 (MathWorks, Natick, MA, USA).The isolated cerebellum GM was then resliced into the space same as the cropped images (Fig. 1A). Next, the spatial normalization including both linear and nonlinear registrations was performed for transforming the cerebellar GM into the SUIT template, and then the transformed images were averaged to obtain a customized cerebellar GM template. All the native cerebellar GM images were linearly and nonlinearly aligned to this template (Fig. 1B). Subsequently, a modulation of the segmented GM probability map was undertaken to compensate for volume changes during the spatial normalization by multiplying intensity value in each voxel with the Jacobian determinants (Good et al., 2001b) (Fig. 1C). The volumes of 28 cerebellar regions were calculated by multiplying the number of voxels in modulated images with the structure probability maps and the maximum likelihood probabilistic cerebellar atlas using the in-house software for Matlab (see Fig. 1D, E, and F). The linear and nonlinear registrations were implemented using local MNI registration tools embedded in CIVET pipeline in the MR data preprocessing.

For the asymmetric analysis: we first flipped all the cerebellar volumes in the SUIT space. A symmetric cerebellar template was then constructed by averaging the original and flipped volumes. Next, the native cerebellar GM volumes were normalized into the symmetric template. In order to examine the asymmetries, a new set of mirror GM images for each subject was generated by flipping the normalized original GM images vertically in the midsagittal plane ($x=0$). We then obtained a new group of GM images by subtracting the original GM images from the mirror GM images.

Finally, all the resulting GM probability images were smoothed with a 4 mm full-width half maximum (FWHM) smooth kernel in SPM5 to satisfy the Gaussian distribution assumption for statistical analysis to test regional differences. All images were visually inspected to ensure that the preprocessing steps were successful and that quality of each image was acceptable for subsequent analysis. Anatomical localizations (i.e. cerebellar lobules) were determined by the probabilistic MRI atlas of the human cerebellum developed by Diedrichsen and his colleagues (Diedrichsen et al., 2009).

4.3. *Statistical analysis*

4.3.1. *Atlas-based volumetric analysis*

First, we performed statistical analysis in the general linear model (GLM) to test the gender effects on the relative and absolute gross cerebellar GM volumes both with and without adjustment for the total intracranial volume (TIV) acquired from the CIVET pipeline.

We assessed the gender differences in the 28 cerebellar lobules volumes between male and female individuals using two-sample *t*-tests in the GLM after adjusting age and TIV. Significance corrections for multiple comparisons were done using false discovery rate (FDR) correction ($p<0.05$) (Genovese et al., 2002). The above statistical analyses were conducted using SurfStat (http://www.math.mcgill.ca/keith/surfstat/) toolbox in Matlab7.1 (MathWorks, Natick, MA, USA).To describe the robustness of the findings, the effect size (Cohen's d) was calculated using the means and standard deviations of two groups (Cohen, 1988).

4.3.2. *VBM analysis*

In the following step, the already smoothed GM probability images from two groups were analyzed using the SPM5, which employs the framework of the GLM. The resulting set of voxels from each contrast represented a statistical parametric map of the *t*-statistic (SPM-*t*), which was all thresholded for the groups comparison at p value <0.05 and corrected for multiple comparisons by using FDR.

First group comparisons for cerebellar GM volume differences between sexes were performed using two-sample *t*-test with age and TIV as covariates of no interest in GLM in SPM5.

Second, a paired *t*-test was performed between the original and rotated images to provide maps of significant left–right differences in male and female groups respectively. After that, the asymmetry patterns were illustrated in the whole group with the GLM including age and gender as covariates of no interest.

Lastly, we examined the gender effects on the cerebellar GM asymmetries. The smoothed subtracted GM images of the two groups were analyzed using a two-sample *t*-test in the GLM to represent the gender effects on the GM asymmetric patterns.

Acknowledgements

This work was funded by the National Natural Science Foundation of China, Grant number 30871305. The MRI data processing was done in McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University.

REFERENCES

Allen, L.S., Hines, M., Shryne, J.E., Gorski, R.A., 1989. Two sexually dimorphic cell groups in the human brain. J. Neurosci. 9, 497–506.

Allen, G., Buxton, R.B., Wong, E.C., Courchesne, E., 1997. Attentional activation of the cerebellum independent of motor involvement. Science 275, 1940–1943.

Allen, J.S., Damasio, H., Grabowski, T.J., Bruss, J., Zhang, W., 2003. Sexual dimorphism and asymmetries in the gray-white composition of the human cerebrum. Neuroimage 18, 880–894.

Amunts, K., Schlaug, G., Schleicher, A., Steinmetz, H., Dabringhaus, A., Roland, P.E., Zilles, K., 1996. Asymmetry in the human motor cortex and handedness. Neuroimage 4, 216–222.

Andreasen NC, Black, DW., 2001. Introductory textbook of psychiatry, Vol., American Psychiatric Publishing, Inc, Washington, DC.

Ashburner, J., Friston, K.J., 2000. Voxel-based morphometry–the methods. Neuroimage 11, 805–821.

Bloss, C.S., Courchesne, E., 2007. MRI neuroanatomy in young girls with autism: a preliminary study. J. Am. Acad. Child Adolesc. Psychiatry 46, 515–523.

Bookstein, F.L., 2001. "Voxel-based morphometry" should not be used with imperfectly registered images. Neuroimage 14, 1454–1462.

Chen, X., Sachdev, P.S., Wen, W., Anstey, K.J., 2007. Sex differences in regional gray matter in healthy individuals aged 44–48 years: a voxel-based morphometric study. Neuroimage 36, 691–699.

Chung, S.C., Lee, B.Y., Tack, G.R., Lee, S.Y., Eom, J.S., Sohn, J.H., 2005. Effects of age, gender, and weight on the cerebellar volume of Korean people. Brain Res. 1042, 233–235.

Cohen, J., 1988. Statistical Analysis for the Behavioral Sciences, Vol., Lawrence Erlbaum Associates, Hillsdale, NJ.

Cosgrove, K.P., Mazure, C.M., Staley, J.K., 2007. Evolving knowledge of sex differences in brain structure, function, and chemistry. Biol. Psychiatry 62, 847–855.

Dean, S.L., McCarthy, M.M., 2008. Steroids, sex and the cerebellar cortex: implications for human disease. Cerebellum 7, 38–47.

Diedrichsen, J., 2006. A spatially unbiased atlas template of the human cerebellum. Neuroimage 33, 127–138.

Diedrichsen, J., Balsters, J.H., Flavell, J., Cussans, E., Ramnani, N., 2009. A probabilistic MR atlas of the human cerebellum. Neuroimage 46, 39–46.

Escalona, P.R., McDonald, W.M., Doraiswamy, P.M., Boyko, O.B., Husain, M.M., Figiel, G.S., Laskowitz, D., Ellinwood Jr., E.H., Krishnan, K.R., 1991. In vivo stereological assessment of human cerebellar volume: effects of gender and age. AJNR Am. J. Neuroradiol. 12, 927–929.

Filipek, P.A., Richelme, C., Kennedy, D.N., Caviness Jr., V.S., 1994. The young adult human brain: an MRI-based morphometric analysis. Cereb. Cortex 4, 344–360.

Gaab, N., Keenan, J.P., Schlaug, G., 2003. The effects of gender on the neural substrates of pitch memory. J. Cogn. Neurosci. 15, 810–820.

Gebhart, A.L., Petersen, S.E., Thach, W.T., 2002. Role of the posterolateral cerebellum in language. Ann. N. Y. Acad. Sci. 978, 318–333.

Genovese, C.R., Lazar, N.A., Nichols, T., 2002. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage 15, 870–878.

Giuliani, N.R., Calhoun, V.D., Pearlson, G.D., Francis, A., Buchanan, R. W., 2005. Voxel-based morphometry versus region of interest: a comparison of two methods for analyzing gray matter differences in schizophrenia. Schizophr. Res. 74, 135–147.

Good, C.D., Johnsrude, I., Ashburner, J., Henson, R.N., Friston, K.J., Frackowiak, R.S., 2001a. Cerebral asymmetry and the effects of sex and handedness on brain structure: a voxel-based morphometric analysis of 465 normal adult human brains. Neuroimage 14, 685–700.

Good, C.D., Johnsrude, I.S., Ashburner, J., Henson, R.N., Friston, K.J., Frackowiak, R.S., 2001b. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 14, 21–36.

Gur, R.C., Mozley, L.H., Mozley, P.D., Resnick, S.M., Karp, J.S., Alavi, A., Arnold, S.E., Gur, R.E., 1995. Sex differences in regional cerebral glucose metabolism during a resting state. Science 267, 528–531.

Gur, R.C., Turetsky, B.I., Matsui, M., Yan, M., Bilker, W., Hughett, P., Gur, R.E., 1999. Sex differences in brain gray and white matter in healthy young adults: correlations with cognitive performance. J. Neurosci. 19, 4065–4072.

Habas, C., Kamdar, N., Nguyen, D., Prater, K., Beckmann, C.F., Menon, V., Greicius, M.D., 2009. Distinct cerebellar contributions to intrinsic connectivity networks. J. Neurosci. 29, 8586–8594.

Hall, T.C., Miller, A.K.H., Corsellis, J.A.N., 1975. Variations in the human Purkinje cell population according to sex and age. Neuropathol. Appl. Neurobiol. 1, 267–292.

Hantz, E.C., Marvin, E.W., Kreilick, K.G., Chapman, R.M., 1996. Sex differences in memory for timbre: an event-related potential study. Int. J. Neurosci. 87, 17–40.

Henery, C.C., Mayhew, T.M., 1989. The cerebrum and cerebellum of the fixed human brain: efficient and unbiased estimates of volumes and cortical surface areas. J. Anat. 167, 167–180.

Herve, P.Y., Crivello, F., Perchey, G., Mazoyer, B., Tzourio-Mazoyer, N., 2006. Handedness and cerebral anatomical asymmetries in young adult males. Neuroimage 29, 1066–1079.

Hofer, A., Siedentopf, C.M., Ischebeck, A., Rettenbacher, M.A., Verius, M., Felber, S., Wolfgang Fleischhacker, W., 2007. Sex differences in brain activation patterns during processing of positively and negatively valenced emotional words. Psychol. Med. 37, 109–119.

Hu, D., Shen, H., Zhou, Z., 2008. Functional asymmetry in the cerebellum: a brief review. Cerebellum 7, 304–313.

Hutchinson, S., Lee, L.H., Gaab, N., Schlaug, G., 2003. Cerebellar volume of musicians. Cereb. Cortex 13, 943–949.

Jansen, A., Floel, A., Van Randenborgh, J., Konrad, C., Rotte, M., Forster, A.F., Deppe, M., Knecht, S., 2005. Crossed cerebro-cerebellar language dominance. Hum. Brain Mapp. 24, 165–172.

Jernigan, T.L., Archibald, S.L., Fennema-Notestine, C., Gamst, A.C., Stout, J.C., Bonner, J., Hesselink, J.R., 2001. Effects of age on tissues and regions of the cerebrum and cerebellum. Neurobiol. Aging 22, 581–594.

Kansaku, K., Yamaura, A., Kitazawa, S., 2000. Sex differences in lateralization revealed in the posterior language areas. Cereb. Cortex 10, 866–872.

Keller, A., Castellanos, F.X., Vaituzis, A.C., Jeffries, N.O., Giedd, J.N., Rapoport, J.L., 2003. Progressive loss of cerebellar volume in childhood-onset schizophrenia. Am. J. Psychiatry 160, 128–133.

Kelly, R.M., Strick, P.L., 2003. Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. J. Neurosci. 23, 8432–8444.

Kennedy, K.M., Erickson, K.I., Rodrigue, K.M., Voss, M.W., Colcombe, S.J., Kramer, A.F., Acker, J.D., Raz, N., 2009. Age-related differences in regional brain volumes: a comparison of optimized voxel-based morphometry to manual volumetry. Neurobiol. Aging 30, 1657–1676.

Keuthen, N.J., Makris, N., Schlerf, J.E., Martis, B., Savage, C.R., McMullin, K., Seidman, L.J., Schmahmann, J.D., Kennedy, D.N., Hodge, S.M., Rauch, S.L., 2007. Evidence for reduced cerebellar volumes in trichotillomania. Biol. Psychiatry 61, 374–381.

Kibby, M.Y., Fancher, J.B., Markanen, R., Hynd, G.W., 2008. A quantitative magnetic resonance imaging analysis of the cerebellar deficit hypothesis of dyslexia. J. Child Neurol. 23, 368–380.

Kimura, D., 1999. Sex and cognition, Vol., Cambridge: MIT.

Lawson, J.A., Vogrin, S., Bleasel, A.F., Cook, M.J., Bye, A.M., 2000. Cerebral and cerebellar volume reduction in children with intractable epilepsy. Epilepsia 41, 1456–1462.

Leggio, M.G., Silveri, M.C., Petrosini, L., Molinari, M., 2000. Phonological grouping is specifically affected in cerebellar patients: a verbal fluency study. J. Neurol. Neurosurg. Psychiatry 69, 102–106.

Loeber, R.T., Cintron, C.M., Yurgelun-Todd, D.A., 2001. Morphometry of individual cerebellar lobules in schizophrenia. Am. J. Psychiatry 158, 952–954.

Luders, E., Gaser, C., Jancke, L., Schlaug, G., 2004. A voxel-based approach to gray matter asymmetries. Neuroimage 22, 656–664.

Luders, E., Narr, K.L., Thompson, P.M., Rex, D.E., Jancke, L., Toga, A. W., 2006. Hemispheric asymmetries in cortical thickness. Cereb. Cortex 16, 1232–1238.

Luft, A.R., Skalej, M., Welte, D., Kolb, R., Burk, K., Schulz, J.B., Klockgether, T., Voigt, K., 1998. A new semiautomated, three-dimensional technique allowing precise quantification of total and regional cerebellar volume using MRI. Magn. Reson. Med. 40, 143–151.

Makris, N., Hodge, S.M., Haselgrove, C., Kennedy, D.N., Dale, A., Fischl, B., Rosen, B.R., Harris, G., Caviness Jr., V.S., Schmahmann, J.D., 2003. Human cerebellum: surface-assisted cortical parcellation and volumetry with magnetic resonance imaging. J. Cogn. Neurosci. 15, 584–599.

Makris, N., Schlerf, J.E., Hodge, S.M., Haselgrove, C., Albaugh, M.D., Seidman, L.J., Rauch, S.L., Harris, G., Biederman, J., Caviness Jr., V.S., Kennedy, D.N., Schmahmann, J.D., 2005. MRI-based surface-assisted parcellation of human cerebellar cortex: an anatomically specified method with estimate of reliability. Neuroimage 25, 1146–1160.

Makris, N., Kaiser, J., Haselgrove, C., Seidman, L.J., Biederman, J., Boriel, D., Valera, E.M., Papadimitriou, G.M., Fischl, B., Caviness Jr., V.S., Kennedy, D.N., 2006. Human cerebral cortex: a system for the integration of volume- and surface-based representations. Neuroimage 33, 139–153.

Mathiak, K., Hertrich, I., Grodd, W., Ackermann, H., 2002. Cerebellum and speech perception: a functional magnetic resonance imaging study. J. Cogn. Neurosci. 14, 902–912.

Moretti, R., Bava, A., Torre, P., Antonello, R.M., Cazzato, G., 2002. Reading errors in patients with cerebellar vermis lesions. J. Neurol. 249, 461–468.

Nitschke, M.F., Kleinschmidt, A., Wessel, K., Frahm, J., 1996. Somatotopic motor representation in the human anterior cerebellum. A high-resolution functional MRI study. Brain 119 (Pt 3), 1023–1029.

Nopoulos, P., Flaum, M., O'Leary, D., Andreasen, N.C., 2000. Sexual dimorphism in the human brain: evaluation of tissue volume, tissue composition and surface anatomy using magnetic resonance imaging. Psychiatry Res. 98, 1–13.

Oguro, H., Okada, K., Yamaguchi, S., Kobayashi, S., 1998. Sex differences in morphology of the brain stem and cerebellum with normal ageing. Neuroradiology 40, 788–792.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.

Perez, S.E., Chen, E.Y., Mufson, E.J., 2003. Distribution of estrogen receptor alpha and beta immunoreactive profiles in the postnatal rat brain. Brain Res. Dev. Brain Res. 145, 117–139.

Rabinowicz, T., Dean, D.E., Petetot, J.M., de Courten-Myers, G.M., 1999. Gender differences in the human cerebral cortex: more neurons in males; more processes in females. J. Child Neurol. 14, 98–107.

Raz, N., Dupuis, J.H., Briggs, S.D., McGavran, C., Acker, J.D., 1998. Differential effects of age and sex on the cerebellar hemispheres and the vermis: a prospective MR study. AJNR Am. J. Neuroradiol. 19, 65–71.

Raz, N., Gunning-Dixon, F., Head, D., Williamson, A., Acker, J.D., 2001. Age and sex differences in the cerebellum and the ventral pons: a prospective MR study of healthy adults. AJNR Am. J. Neuroradiol. 22, 1161–1167.

Raz, N., Gunning-Dixon, F., Head, D., Rodrigue, K.M., Williamson, A., Acker, J.D., 2004. Aging, sexual dimorphism, and hemispheric asymmetry of the cerebral cortex: replicability of regional differences in volume. Neurobiol. Aging 25, 377–396.

Rhyu, I.J., Cho, T.H., Lee, N.J., Uhm, C.S., Kim, H., Suh, Y.S., 1999. Magnetic resonance image-based cerebellar volumetry in healthy Korean adults. Neurosci. Lett. 270, 149–152.

Safavi-Abbasi, S., Di Rocco, F., Chantra, K., Feigl, G.C., El-Shawarby, A., Samii, A., Samii, M., 2007. Posterior cranial fossa gangliogliomas. Skull Base 17, 253–264.

Sanders, G., Wenmoth, D., 1998. Verbal and music dichotic listening tasks reveal variations in functional cerebral asymmetry across the menstrual cycle that are phase and task dependent. Neuropsychologia 36, 869–874.

Schmahmann, J.D., Pandya, D.N., 1997. The cerebrocerebellar system. Int. Rev. Neurobiol. 41, 31–60.

Schmahmann, J.D., Doyon, J., McDonald, D., Holmes, C., Lavoie, K., Hurwitz, A.S., Kabani, N., Toga, A., Evans, A., Petrides, M., 1999. Three-dimensional MRI atlas of the human cerebellum in proportional stereotaxic space. Neuroimage 10, 233–260.

Schmitz, B.L., Aschoff, A.J., Hoffmann, M.H., Gron, G., 2005. Advantages and pitfalls in 3T MR brain imaging: a pictorial review. AJNR Am. J. Neuroradiol. 26, 2229–2237.

Sim, M.E., Lyoo, I.K., Streeter, C.C., Covell, J., Sarid-Segal, O., Ciraulo, D.A., Kim, M.J., Kaufman, M.J., Yurgelun-Todd, D.A.,

Please cite this article as: Fan, L., et al., Sexual dimorphism and asymmetry in human cerebellum: An MRI-based morphometric study, Brain Res. (2010), doi:10.1016/j.brainres.2010.07.031

Renshaw, P.F., 2007. Cerebellar gray matter volume correlates with duration of cocaine use in cocaine-dependent subjects. Neuropsychopharmacology 32, 2229–2237.

Stoodley, C.J., Schmahmann, J.D., 2009. Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. Neuroimage 44, 489–501.

Szabo, C.A., Lancaster, J.L., Xiong, J., Cook, C., Fox, P., 2003. MR imaging volumetry of subcortical structures and cerebellar hemispheres in normal persons. AJNR Am. J. Neuroradiol. 24, 644–647.

Szeszko, P.R., Gunning-Dixon, F., Ashtari, M., Snyder, P.J., Lieberman, J.A., Bilder, R.M., 2003. Reversed cerebellar asymmetry in men with first-episode schizophrenia. Biol. Psychiatry 53, 450–459.

Tang, Y., Hojatkashani, C., Dinov, I.D., Sun, B., Fan, L., Lin, X., Qi, H., Hua, X., Liu, S., Toga, A.W., 2010. The construction of a Chinese MRI brain atlas: a morphometric comparison study between Chinese and Caucasian cohorts. Neuroimage 51, 33–41.

Toga, A.W., Thompson, P.M., 2003. Mapping brain asymmetry. Nat. Rev. Neurosci. 4, 37–48.

Tsutsui, K., 2006. Biosynthesis, mode of action and functional significance of neurosteroids in the developing Purkinje cell. J. Steroid Biochem. Mol. Biol. 102, 187–194.

Volkow, N.D., Wang, G.J., Fowler, J.S., Hitzemann, R., Pappas, N., Pascani, K., Wong, C., 1997. Gender differences in cerebellar metabolism: test–retest reproducibility. Am. J. Psychiatry 154, 119–121.

Watkins, K.E., Paus, T., Lerch, J.P., Zijdenbos, A., Collins, D.L., Neelin, P., Taylor, J., Worsley, K.J., Evans, A.C., 2001. Structural asymmetries in the human brain: a voxel-based statistical analysis of 142 MRI scans. Cereb. Cortex 11, 868–877.

Willis, M.W., Ketter, T.A., Kimbrell, T.A., George, M.S., Herscovitch, P., Danielson, A.L., Benson, B.E., Post, R.M., 2002. Age, sex and laterality effects on cerebral glucose metabolism in healthy adults. Psychiatry Res. 114, 23–37.

Woolsey, T.A., 1952. Summary of papers on the cerebellum. Res. Publ. Assoc. Res. Nerv. Ment. Dis. 30, 334–336.

Please cite this article as: Fan, L., et al., Sexual dimorphism and asymmetry in human cerebellum: An MRI-based morphometric study, Brain Res. (2010), doi:10.1016/j.brainres.2010.07.031