Gray-matter structural variability in the human cerebellum: Lobule-specific differences across sex and hemisphere

Christopher J. Steele[a,b,*], M. Mallar Chakravarty[a,c,*]

[a] Cerebral Imaging Center, Douglas Mental Health University Institute, Montreal, QC, Canada
[b] Department of Neurology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
[c] Departments of Psychiatry and Biological and Biomedical Engineering, McGill University, Montreal, QC, Canada

ABSTRACT

Though commonly thought of as a "motor structure", we now know that the cerebellum's reciprocal connections to the cerebral cortex underlie contributions to both motor and non-motor behavior. Further, recent research has shown that cerebellar dysfunction may contribute to a wide range of neuropsychiatric disorders. However, there has been little characterization of normative variability at the level of cerebellar structure that can facilitate and further our understanding of disease biomarkers. In this manuscript we examine normative variation of the cerebellum using data from the Human Connectome Project (HCP). The Multiple Automatically Generated Templates (MAGeT) segmentation tool was used to identify the cerebella and 33 anatomically-defined lobules from 327 individuals from the HCP. To characterize normative variation, we estimated population mean volume and variability, assessed differences in hemisphere and sex, and related lobular volume to motor and non-motor behavior. We found that the effects of hemisphere and sex were not homogeneous across all lobules of the cerebellum. Greater volume in the right hemisphere was primarily driven by lobules Crus I, II, and H VIIB, with H VIIIA exhibiting the greatest left > right asymmetry. Relative to total cerebellar gray-matter volume, females had larger Crus II (known to be connected with non-motor regions of the cerebral cortex) while males had larger motor-connected lobules including H V, and VIIIA/B. When relating lobular volume to memory, motor performance, and emotional behavior, we found some evidence for relationships that have previously been identified in the literature. Our observations of normative cerebellar structure and variability in young adults provide evidence for lobule-specific differences in volume and the relationship with sex and behavior – indicating that the cerebellum cannot be considered a single structure with uniform function, but as a set of regions with functions that are likely as diverse as their connectivity with the cerebral cortex.

Introduction

The cerebellum contains over half of the neurons in the human brain, is reciprocally connected to the cerebral cortex, and contributes to a huge variety of motor, cognitive, and emotional behavior in humans (Kansal et al., 2017; Ramnani, 2006; Schmahmann, 2010). Due to its dense reciprocal connectivity with the cerebral cortex, there has been recent interest in understanding how the cerebellum may contribute to a wide range of disorders including affective and language disorders (Adamaszek et al., 2015, 2014; Küper and Timmann, 2013; Schmahmann, 2010), Parkinson's disease (Mirdamadi, 2016; Wu and Hallett, 2013), autism spectrum disorder (D'Mello et al., 2015), multiple sclerosis (Kutzelnigg et al., 2007), and Alzheimer's disease (Sjöbeck and Englund, 2001), amongst others. Recent work in healthy

individuals has primarily focused on mapping motor and cognitive functions to lobules of the cerebellar cortex (Baer et al., 2015; Buckner et al., 2011; O'Reilly et al., 2010; Stoodley and Schmahmann, 2010, 2009), yet there is little known about the normative anatomical variability of the cerebellum and its subregions. Improving our understanding of how adaptive and maladaptive cerebellar neuroanatomy is phenotypically expressed in development, aging, or in neuropsychiatric disorders requires a detailed characterization of the normative structural variability of the cerebellum and its lobules.

Larsell and Jansen provided the most comprehensive nomenclature for the description of human cerebellar structure (1972). Their anatomical descriptions have been transformed into a three-dimensional stereotaxic atlas that is the basis for the localization of cerebellar functional and structural findings in virtually all human anatomical, clinical, and neuroi-

maging studies (Schmahmann et al., 1999). Though lobules were initially described relative to anatomical landmarks, there is considerable evidence that they exhibit a high degree of anatomical connectional (Strick et al., 2009) and functional specificity (Stoodley and Schmahmann, 2009). This well-characterized functional specificity strongly suggests that volumes of individual lobules are useful for further quantitative analyses. As such, the stereotaxic parcellation of Larsell's lobules introduced by Schmahmann et al. (1999, 2000) has been used as the basis for recent automatic segmentation algorithms (Bogovic et al., 2013; Diedrichsen, 2006; Park et al., 2014; Weier et al., 2014; Yang et al., 2016). These methodologies have improved our understanding of the structure-function relationship between cerebellar cortical lobules and motor performance, cognition, emotion, and disease.

To the best of our knowledge, relatively few anatomical MRI studies have explicitly assessed the variability of cerebellar lobular volumes. Makris et al. (2003, 2005) assessed the lobular volumes of a post-mortem brain from a single forty-one year old and applied the segmentation to ten individuals; Diedrichsen et al. (2009) reported lobular volumes from the cerebella of twenty young adult subjects, Balsters et al. (2010) compared lobular volumes in twenty adults to those of non-human primates, and a more recent paper by Weier et al. (2014) characterized lobular volumes in 150 adults. While these, and other research on the relationship between lobular volumes and behavior (e.g., Bernard et al., 2015; Bernard and Seidler, 2013), have set the stage for the characterization of normative cerebellar lobular structure, no single publication provides a comprehensive account of how structure may differ between hemispheres, sexes, and how structure is related to both behavior and the interaction between behavior and sex.

Previous research has identified differences in regional volumes between hemispheres and sexes in whole-brain analyses. Good and colleagues (Good et al., 2001) presented the first MRI-based confirmation of hemispherical asymmetries and sex differences in the entire brain, including a first indication of right > left asymmetry in the lateral cerebellum. Relatively consistent cortical asymmetry results have also been identified by others (e.g., Esteves et al., 2017; Goldberg et al., 2013), though sex differences may be more subtle and less reproducible (Esteves et al., 2017; Kang et al., 2015). In the cerebellum, total cerebellar volume has been reliably reported to be larger in males than females – with an estimated effect size of 1.68 (Cohen's d) (for review, Ruigrok et al., 2014). Regionally-specific sex differences (male > female) have also been identified, though not systematically investigated, within cerebellar cortical gray-matter (Diedrichsen et al., 2009; Dimitrova et al., 2006; Raz et al., 2001, 1998; Rhyu et al., 1999; Tiemeier et al., 2010; Weier et al., 2014). In addition, there is evidence that females have larger cerebella relative to total intracranial volume (Dimitrova et al., 2006; Weier et al., 2014).

In the present study, we set out to characterize cerebellar gray-matter lobular structure and its relationship to sex and behavior in a large normative sample. We used cerebellar lobular segmentations (Park et al., 2014) of high resolution T1-weighted structural magnetic resonance imaging (MRI) data from the Human Connectome Project (Van Essen et al., 2013) to estimate individual lobular volumes. We followed a three-pronged approach to characterizing cerebellar structure: 1) extraction of normative lobular volume and the assessment of hemispheric differences, along with the calculation of cerebellar gray-matter specific relative lobular volume and the assessment of sex differences, 2) assessment of the relationship between relative lobular volume and performance on tasks involving specific regions of the cerebellum, and 3) assessment of the relationship between sexually dimorphic structural regions and behavioral performance. Our work is based upon the premise that the cerebellum cannot be considered as a single structural or functional unit; thus, we hypothesized that the distribution of hemispherical and sex differences would differ across lobules and that the relationship between literature-defined regions and behavior would follow previously suggested patterns.

Materials and methods

Participants

All participants in this study were obtained from the preprocessed datasets made available through the Human Connectome Project S900 release (www.humanconnectome.org) (Van Essen et al., 2013). Only those right-handed individuals with handedness greater than or equal to 50 (Oldfield, 1971) who had undergone with both T1-weighted (T1w: 0.7 mm iso, TI/TE/TR=1000/2.14/2400 ms, FOV=224×224 mm) and diffusion-weighted imaging (DWI: 1.25 mm iso, TE/TR=89.5/5520 ms, FOV=210×180 mm, multiband 3, b-values=1000/2000/3000 s/mm^2, 90 diffusion directions across each b-value) were used in the present study. Sex, age, handedness, participant ID, and mother's ID were extracted as control variables and for identifying unrelated individuals. Fluid intelligence (PMAT24_A_CR), as measured with the shortened form A of Raven's Progressive Matrices, was also extracted to further describe the sample (Bilker et al., 2012). As described in section 2.3.2, an additional six behavioral variables were extracted to test for brain-behavior correlations in the cerebellum: NIH Toolbox List Sorting Test, age adjusted (ListSort_AgeAdj); Penn Word Memory Test, total correct (IWRD_TOT); NIH Toolbox 9-hole Pegboard Dexterity Test, age adjusted (Dexterity_AgeAdj); NIH Toolbox Grip Strength Test, age adjusted (Strength_AgeAdj); Penn Emotion Recognition Tests for anger and fear (ER40ANG, ER40FEAR); Variable Short Penn Line Orientation Test, total correct and total positions off (VSPLOT_TC, VSPLOT_OFF).

Image processing

Cerebellar lobular segmentation of the T1w images preprocessed by the HCP (Glasser et al., 2013; Glasser and Essen, 2011) was performed with the Multiple Automatically Generated Templates segmentation tool (MAGeT Brain: https://github.com/CobraLab/MAGeTbrain) (Chakravarty et al., 2013; Park et al., 2014). In brief, MAGeT Brain works by performing initial pair-wise non-linear registrations between five expert labeled cerebellar lobular atlases and twenty-one representative T1w images from the dataset, and are propagated into each template image to create five possible cerebellar labels for each template. Each template brain is then non-linearly registered to each subject, yielding 105 possible labels that are then fused by majority voting to produce the final lobular segmentations. The cerebellar segmentation contains 33 labeled structures (11 per hemisphere: H III, IV, V, VI, Crus I, Crus II, VIIB, VIIIA, VIIIB, IX, X; 11 vermal: I/II, III, IV, V, VI, VIIA, VIIB, VIIIA, VIIIB, IX, X).

To further refine the segmentation and correct for white-matter partial volume effects that are present in the original labels of the atlas segmentations (Park et al., 2014), DWI were used to create putative white matter (WM) masks to remove any residual white matter included in some of the original folia of the initial manual segmentations due to resolution and contrast constraints (Park et al., 2014). We first calculated fractional anisotropy (FA) from the b=3000 shell of the co-aligned DWI with MRtrix 3 (Tournier et al., 2012), created individual binary WM masks (FA > 0.35), and inverted and multiplied the masks and MAGeT segmentations to produce the final cerebellar lobule segmentations. Fig. 1 illustrates the original MAGeT segmentation and corresponding WM-corrected segmentation in a single subject. All image analyses where performed by converting data into the MINC file format (http://www.bic.mni.mcgill.ca/ServicesSoftware/MINC) and all nonlinear registrations were performed with the ANTs suite of tools (Avants et al., 2008).

Analyses

To examine population variability of cerebellar structure, we randomly selected a set of unrelated individuals from the HCP S900 dataset. Since the HCP includes a large number of twins and non-twin
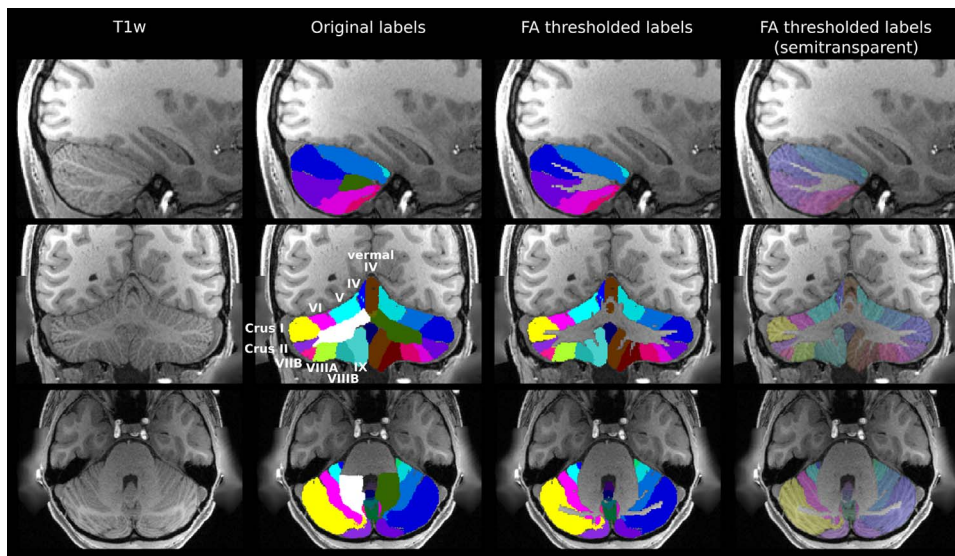
Fig. 1. Cerebellar MAGeT segmentation and white-matter refinement in a representative participant. Columns from left to right: 0.7mm isotropic T1w image, original labels, labels after thresholding at FA > 0.35 to reduce white-matter partial voluming, semitransparent FA thresholded labels. The right hemisphere is on the right of the image.

siblings, we chose only unrelated individuals to ensure that family structure did not become a confound in our analyses. All statistical analyses were conducted with the R statistical package (v3.3.0).

Cerebellar lobular structure

Normative cerebellar structure was first quantified by calculating the volume mean and standard deviation for each lobule of the cerebellum. This analysis presents the raw lobular volumes to provide an estimate of the population mean and variability. We then compared the lobular volumes of the right and left hemisphere to assess hemispheric differences using the lme4 linear mixed effects regression library in R (Bates et al., 2015) with the factor *hemisphere* (L, R) predicting lobular *volume* and participant identification number (*ID*) as a random intercept to account for between-subject variance (this analysis is similar to a paired *t*-test, but allows the inclusion of regressors of no interest). The variables *sex*, *age*, *handedness*, and *fluid IQ* were included as regressors of no interest to ensure that the results were not biased by any demographic differences in the sample. Significance was assessed by comparing models with and without the factor *hemisphere* using an analysis of variance (ANOVA) (full model: *volume ~sex+age+handedness+fluid IQ+hemisphere+(1|ID)*; reduced model: *volume~sex+age+handedness+fluid IQ+(1|ID)*), with α=0.05, Bonferroni corrected for the 11 hemispheric lobules and total hemispheric volume, without vermal regions (correction for 12 comparisons, equivalent to p < 0.0042). Volume estimates were split according to sex and plotted for illustration.

Relative lobular volumes were computed by dividing the volume of each lobule by total cerebellar gray-matter volume and multiplying by 100 to express as a percentage. This normalization step was used to control for the general effect of differences in total cerebellar volume between individuals and/or sexes that may obscure potential lobular differences (Mankiw et al., 2017). All subsequent analyses were performed on relative lobular volumes. As with the raw lobular volumes, relative volume estimates were split according to sex and plotted to illustrate trends. For completeness, relative volume of lobules with respect to the relevant hemisphere or vermis were also calculated.

Sex differences that may exist over and above the effect of sex on total cerebellar volume were quantified by assessing the significance of the factor *sex* in a linear regression model predicting regional lobular volume and controlling for demographic variables *age*, *handedness*, and *fluid IQ* (model: *relative volume~age+handedness+fluid IQ+sex*).

Significance was assessed at α=0.05, Bonferroni corrected for the 33 hemispheric and vermal lobules (equivalent to p < 0.0015), and effect sizes were expressed with Cohen's d and plotted for display. A separate identical set of analyses was performed on raw lobular volumes to illustrate baseline lobule-specific volume differences between males and females (α=0.05, Bonferroni corrected for the 33 hemispheric and vermal lobules, equivalent to p < 0.0015).

Brain-behavior regression

A subset of six behavioral tests assessing cognitive, motor, and emotional behavior were selected from the HCP S900 to investigate their potential relationship with cerebellar gray-matter volume. All tests were selected in order to provide metrics that could be interpreted in the context of recent studies linking behavior to cerebellar lobular function (e.g., Stoodley and Schmahmann, 2009) and/or structure (e.g., Bernard et al., 2015). Our selection included two memory tests (working memory – NIH Toolbox List Sorting, age adjusted; episodic memory – Penn Word Memory Test, total correct), two tests of motor function (dexterity – NIH Toolbox 9-hole Pegboard Dexterity test, age adjusted; strength – NIH Toolbox Grip Strength Test, age adjusted), and two tests of emotion recognition (fear – Penn Emotion Recognition Test, fear; anger – Penn Emotion Recognition Test, anger) (Barch et al., 2013). With the exception of the 9-hole pegboard test of motor dexterity, higher values reflect better performance. Linear regression models relating relative regional volume (independent variable) to behavioral performance (dependent variable) were constructed to test a set of a-priori hypotheses based upon previous work identifying the structural and functional correlates of cognitive, motor, and emotional behavior in the cerebellum. Relative lobular volumes were summed for analysis where there was evidence that the relationship with behavior spanned multiple adjacent lobules, and considered separately when the identified lobules were not adjacent and/or identified in different publications. Specifically, we hypothesized that working and episodic memory would be related to the sum of H VI and Crus I, and separately with H VIIIA (Bernard et al., 2015; Stoodley et al., 2012; Stoodley and Schmahmann, 2009); dexterity/strength would be related to the sum of the anterior lobe (H III, IV, V, VI), the sum of H VIIIA and VIIIB (R > L) (Stoodley and Schmahmann, 2009), and that dexterity would also be predicted separately by Crus I (Bernard and Seidler, 2013); anger and fear would be related to Crus I (L > R) (Adamaszek et al., 2015, 2014; Stoodley and Schmahmann, 2009), and H VI (R > L) (Stoodley and Schmahmann, 2009). In each case *sex*, *age*, *handedness*, and *fluid IQ*

were included as regressors of no interest as above, resulting in a linear model of the form: *behavior ~age+handedness+fluid IQ+sex+relative volume*. For these planned comparisons, linear regressions for each hemisphere were performed separately and the effect of *relative volume* considered significant at α=0.05 (uncorrected for multiple comparisons).

Lobule-specific sex differences and the relationship with behavior

To determine whether or not sex differences in relative lobular volume were behaviorally relevant, the existing literature on the relationship between cerebellar lobules and behavior was used to identify tasks within the HCP behavioral battery that are most closely linked to literature-defined lobular function. We compared a set of linear models with and without the effect of sex to assess its significance as a predictor of behavior. We tested for the main effect of sex (*behavior~relative volume+sex*) and then followed this up with a model to test for the interaction effect of sex and volume (*behavior~relative volume+sex+sex*relative volume*) with separate linear regression models. A significant difference in the model comparison indicates that sex is linked to a baseline shift in the relationship between relative volume and behavior (i.e., an offset difference), and a significant interaction effect provides evidence that the relationship between relative volume and behavior changes as a function of sex (i.e., a slope difference). As these analyses were intended to be exploratory in nature and help inform future studies, they were assessed for significance at an uncorrected two-tailed threshold of $p < 0.05$.

Results

A total of 327 unrelated right-handed participants were randomly selected from the HCP S900 release for use in our analyses (females/males: 193/134; mean age/range: 28.78/22−36 years; handedness mean (SD): 82.08 (14.56); fluid intelligence mean (SD): 16.80 (4.70)). There were originally 805 individuals after screening for the presence of complete T1w and diffusion images, 668 after selecting only those individuals who were predominantly right handed (handedness > 49), and 23 additional participants removed after failing inspection for quality control (rated 0 or 0.5 on a three-point scale, rejected either for registration failure [0] or due to the inclusion or exclusion of non-cerebellar/cerebellar material within the segmentation [0.5]). The remaining 645 individuals belonged to 327 families as identified by the variable Mother_ID, and a single individual from each family was randomly selected to make up the final sample of participants. There were no sex differences in fluid intelligence (t=1.00, p=0.32), but there were differences in age (t=3.23, p=0.001) and handedness (t=4.24, p < 0.001) between sexes in our randomly selected sample. Table 1 provides the mean, standard deviations, and statistics of the demographic variables for females and males.

Cerebellar lobular structure

The mean and standard deviation of each lobule of the cerebellum were computed to provide a baseline population estimate of normative cerebellar lobular structure. The mean and standard deviation of total cerebellar gray-matter volume was found to be 108433.43+/−10738.55 mm³, with volume in the right hemisphere (50172.12+/−5048.17 mm³) larger than that of the left (49550.82+/−5017.81 mm³). For each hemisphere, lobular volume showed an approximately logarithmic increase from anterior to posterior for both the superior and inferior aspects of cerebellar cortex. Volume increased from lobule H III to Crus I, and generally decreased from Crus I to lobule H X. Vermal volumes increased approximately linearly from anterior to posterior along the superior aspect of the cerebellum, and did not exhibit a clear pattern inferiorly (Fig. 2A). When comparing volumes between hemispheres, there was an overall difference in hemisphere size such that the right was significantly larger than the left (mean difference: 621.31 mm³). All lobules except H VIIIB had significantly different

Table 1
Summary of participant demographic variables. Mean and standard deviation for females and males on each of the demographic variables (age, handedness, and fluid intelligence) are listed with the t-value and p-values for two-tailed t-tests comparing sexes (uncorrected). Significant p-values are indicated in bold.

Demographic measure	Sex	Mean	Standard deviation	Sex differences t-value	p-value
Age	F	29.31	3.71	3.23	**1.37E-03**
	M	28.02	3.43		
Handedness	F	84.90	13.63	4.24	**3.08E-05**
	M	78.02	14.94		
Fluid intelligence (PMAT24_A_CR)	F	16.58	4.56	−1.00	0.32
	M	17.11	4.88		

volumes between the two hemispheres, with lobules IV, V, and VI of the anterior lobe, H VIIIA, and H IX exhibiting significantly greater volume on the left while H III, Crus I, II, H VIIB, and H X had greater volume on the right (Fig. 2B). Mean, standard deviations, and comparison statistics for each lobule in raw and relative volumes are provided in Table S1. For ease of comparison with other studies, we also calculated a laterality index for each hemispherical lobule (Left−Right)/(Left+Right) and have included it in Supplementary figure S1. Lobular volume relative to total cerebellar gray-matter volume (Fig. 3A) and relative to hemispheric/vermal volume (Fig. 3B) follow a similar overall pattern as that found in the raw volumes (Table S1, Fig. 2A).

Cohen's d for the difference between males and females revealed a spatial pattern of effect sizes that was similar between the two hemispheres, with spatially segregated regions where both males and females exhibited significantly larger relative volume. Interestingly, females had significantly larger relative volumes in bilateral Crus II and vermal VI while males had significantly larger relative volumes in right H V and lobules VIIIA, VIIIB (both hemispheres and vermis) (Fig. 4A). In contrast, raw lobular volumes were significantly greater in males in all lobules except vermal VIIA (Fig. 4B). The statistics for the comparison of lobule-specific differences between males and females in both relative and raw lobular volumes can be found in Table S2. Lobule-wise density plots illustrating the volume distributions of each lobule individually, right and left hemispheres, and comparing males and females for both raw (S2, S3) and lobular volumes relative to total cerebellar gray-matter volume (S4, S5) are presented in Supplementary figures S2-S5.

Brain-behavior regression

We performed a set of planned regressions between six behavioral scores and cerebellar regions that have been implicated in overlapping functional domains within the literature. We found no evidence that working memory was related to the sum of the relative volume of H VI and Crus I in the left (L) or right (R) hemispheres, nor was it related to relative volume of H VIIIA in the left. However, working memory was significantly correlated with volume in right H VIIIA (R − working memory: t=2.22, p=0.027). Episodic memory was not significantly related to either of the literature-defined regions in the right or left (H VI and Crus I; H VIIIA). For motor performance, dexterity was significantly related to the anterior lobe in the left (L − dexterity: t=−2.31, p=0.022) but not the right, nor to volume in H VIIIA/B or Crus I. Grip strength was not related to relative volume of the anterior lobe in either hemisphere, nor with relative volume in H VIIIA/B bilaterally. The only significant relationship between emotion and relative lobular volume was identified between fear and lobule H VI in the right hemisphere (R − fear: t=2.46, p=0.015). Table 2 includes
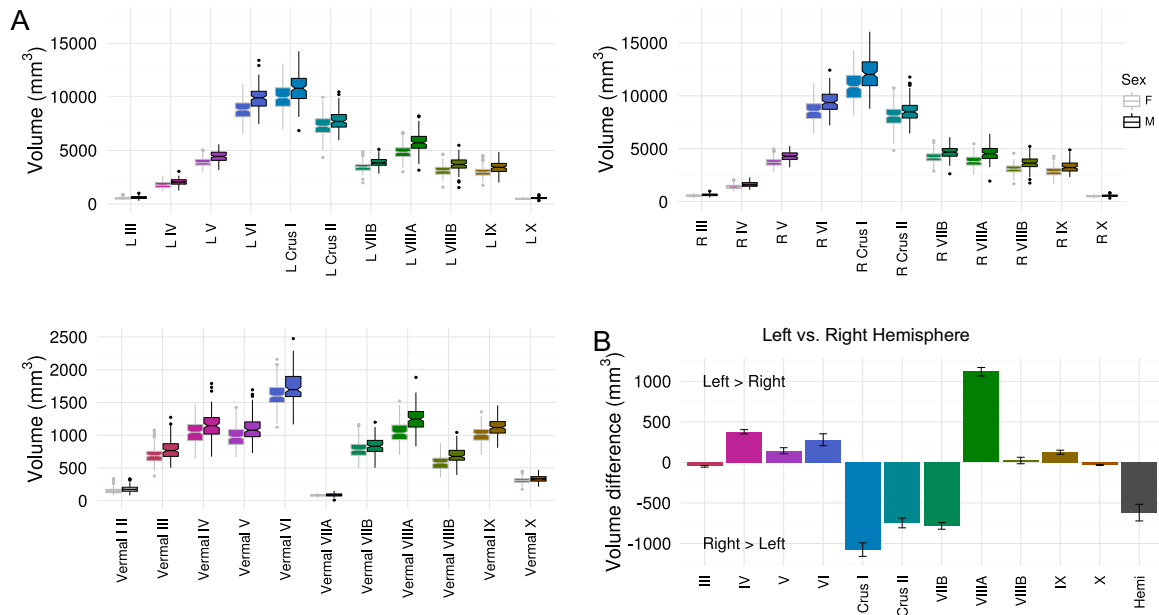
Fig. 2. Human cerebellar lobular volumes. A: Box and whisker plots of lobular volumes for both hemispheres and the vermis. B: Volume difference between lobules of the right and left hemispheres and total hemispheric difference. All lobules except VIIIB have statistically significant differences between hemispheres after Bonferroni correction for 12 comparisons, error bars represent 95% confidence intervals. Lobule colour-coding is consistent across plots. F=Female; M=Male.

the full list of statistics and a complete pair-wise correlation matrix with r and p-values has also been included in Supplementary figure S6 to provide an overview of the zero-order correlations between behavioral metrics and cerebellar lobules.

Lobule-specific sex differences and the relationship with behavior

We used linear regression analyses to determine how sex may modulate the relationship between relative volume and behavior after correcting for demographic variables. We identified behavioral tasks
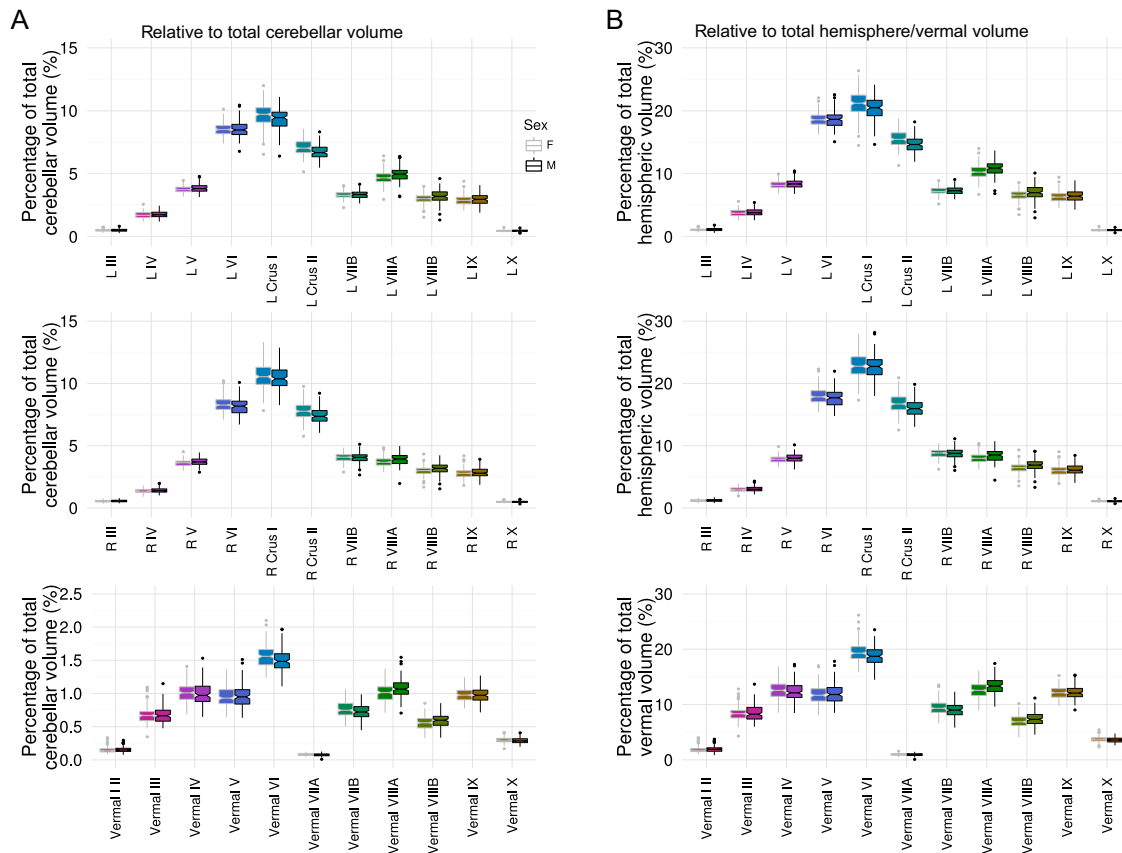

Fig. 3. Relative lobular volumes. A: Lobular volumes relative to total cerebellar gray-matter volume. B: Lobular volumes relative to respective hemispheric or vermal gray-matter volume. F=Female; M=Male.
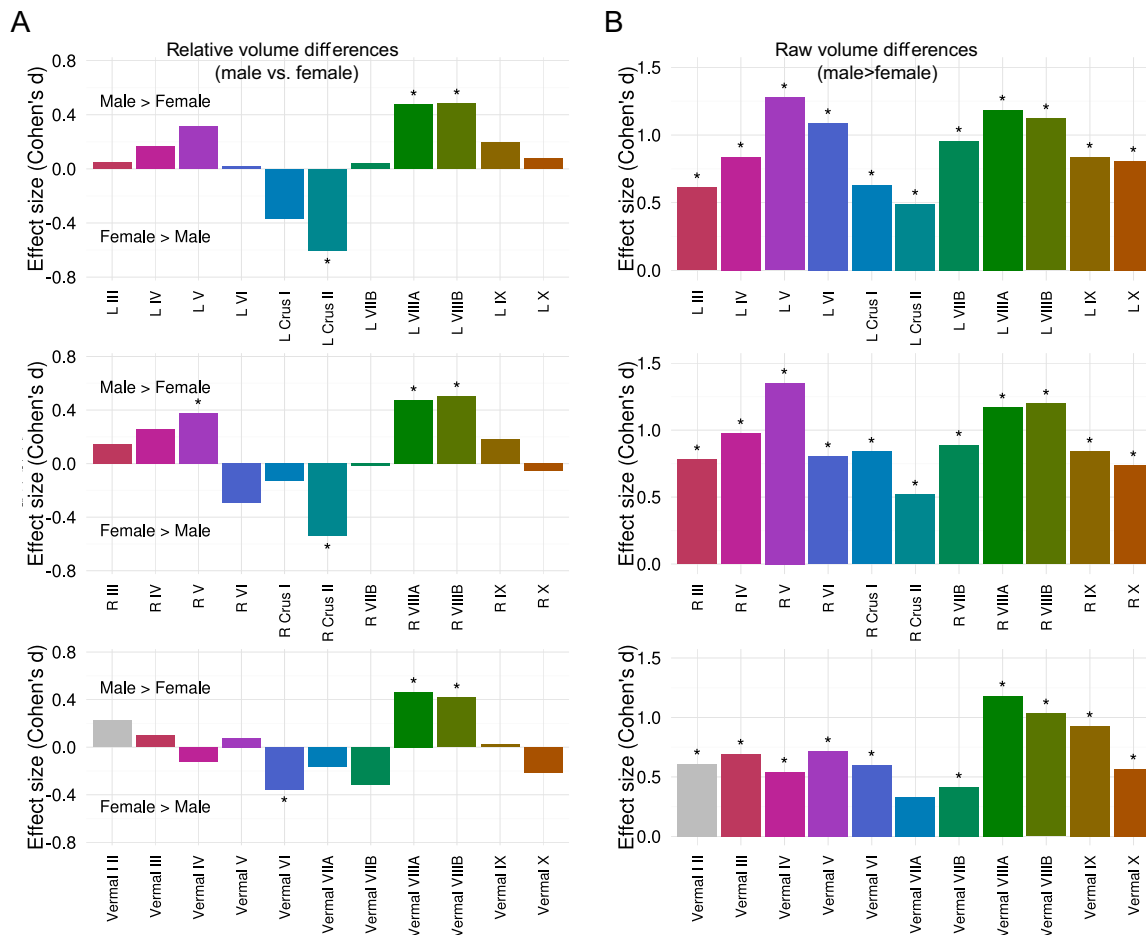
Fig. 4. Lobule-specific sex differences in the human cerebellum. A: Effect sizes of sex differences for relative lobular volume (percent of total cerebellar GM volume). Values above zero indicate that males have greater relative volume than females, and vice-versa for values below zero. B: Effect sizes of raw volume differences between males and females. All values are above zero, indicating that males have greater raw lobular volume than females. In both panels, * indicates lobules that are significantly different after Bonferroni multiple comparisons correction across all lobules.

from the HCP testing battery that were most closely linked to the cerebellar regions that showed significant sex differences in relative volume (Fig. 4A): Crus II – primarily implicated in spatial processing (Stoodley and Schmahmann, 2009) and mental rotation (Stoodley et al., 2012), functions that were most closely assessed with the total correct and error scores from the Variable Short Penn Line Orientation Test (Barch et al., 2013; Benton et al., 1978; Gur et al., 2010); bilateral H V, VIIIA, VIIIB, and vermal VIIIA, VIIIB – primarily implicated in hand sensorimotor function (Grodd et al., 2001; Stoodley et al., 2012), functions that were most closely assessed with the Dexterity (9-hole Pegboard) and Strength (Grip Strength Dynamometry) assessments (Barch et al., 2013).

We found that the main effect of sex on the relationship between Crus II and spatial processing was statistically significant for spatial processing error scores ($t=-2.62$, $p=.01$) but not total correct ($t=1.70$, $p=.09$). However, relative volume of Crus II was not a significant predictor of performance in the regression model in either case (total correct: $t=-1.67$, $p = 0.10$; error: $t=1.48$, $p=0.14$), and both effects were characterized by greater performance in males even though this region had greater relative volume in females. The effects of sex on the relationship between motor lobules and measures of motor behavior were both highly significant (dexterity: $t=-4.11$, $p=5.07\times10^{-5}$; strength: $t=20.06$, $p < 2\times10^{-16}$), and characterized by greater performance in males. As with spatial processing, however, relative volume was not significantly related to performance in the regression model (dexterity: $t=-0.40$, $p=0.69$; strength: $t=-0.61$, $p=0.54$). Linear models including the interaction between sex and relative volume did not

provide evidence for an effect on spatial processing total correct ($F=0.01$, $p=0.93$), spatial processing error ($F=0.58$, $p=0.45$), dexterity ($F=2.86$, $p=0.09$), or strength ($F=0.08$, $p=0.77$). In all cases, we found that males performed better than females with the same relative amount of regional cerebellar volume – though there was no evidence for a relationship between volume and performance.

Discussion

The present study characterized normative cerebellar lobular structure and its relationship with sex and behavior. We performed lobular segmentations from T1w images and refined them with thresholded FA maps to reduce white-matter partial voluming. Raw cerebellar volumes showed an increase across the hemispheres of the anterior lobe to Crus I, and then decreased towards lobule X. We found that the right hemisphere was significantly larger than the left, and that this effect was not consistent across all lobules. Relative lobular volumes showed a similar pattern of differences that can be used to compare results between sexes, patient groups, and species. Planned correlations between subsets of relative lobular volumes and task performance that were informed by recent cerebellar literature provided some evidence for previously identified relationships. Sex differences in raw lobular volume were statistically significant across virtually all lobules; however, a more specific analysis of differences in relative volume revealed significant effects that were restricted to lobules H V and VIIIA/B (males > females) and H Crus II (females > males). Regressions between these regions and performance on tasks

Table 2

Summary statistics and p-values for planned behavioral regressions. Uncorrected statistics (t, p) for planned regressions between behavioral measures and cerebellar gray-matter regions. All regression models included age, sex, handedness, and fluid intelligence as covariates of no interest. Significant p-values are indicated in bold. Figure S6 provides the complete uncorrected pair-wise zero-order correlations of all regions and behavioural measures listed here.

Behavioural measure	Cerebellar region	Hemisphere	t-value	p-value
Working memory	H VI & Crus I	L	−1.12	0.27
		R	−0.33	0.75
	VIIIA	L	0.93	0.35
		R	2.22	**0.03**
Episodic memory	H VI & Crus I	L	0.70	0.49
		R	0.14	0.89
	H VIIIA	L	−0.62	0.53
		R	0.00	1.00
Dexterity	Anterior lobe	L	−2.31	**0.02**
		R	−1.35	0.18
	H VIIIA and VIIIB	L	−0.41	0.68
		R	0.28	0.78
	Crus I	L	1.12	0.27
		R	0.77	0.44
Grip strength	Anterior lobe	L	−0.08	0.94
		R	−1.12	0.26
	H VIIIA and VIIIB	L	−0.43	0.67
		R	−0.58	0.56
Anger	H VI	L	0.91	0.36
		R	0.95	0.34
	Crus I	L	−0.66	0.51
		R	−1.09	0.28
Fear	H VI	L	1.42	0.16
		R	2.46	**0.01**
	Crus I	L	0.60	0.55
		R	0.59	0.56

testing for functions that have previously been linked to them did not provide evidence for a differential effect of sex on the relationship between relative volume and behavior. Our results provide the baseline quantification of population-wide normative structural variability of the human cerebellum and its relation to performance that can serve as the baseline from which to assess the impact of disease and develop cerebellum-based biomarkers.

Cerebellar hemispherical asymmetries

We found that the volume of the right hemisphere was larger than that of the left and that this overall difference was not consistently distributed across all lobules of the cerebellum. Though we identified significant hemispherical asymmetries between all lobules except VIIIB (see Fig. 2, Table S1, and Figure S1), the overall greater right hemisphere volume was primarily driven by Crus I, II, and H VIIB, while lobules H IV, V, VI, and VIIIA exhibited the most pronounced leftward asymmetry. Though the cerebellar gray-matter localization is not well described, an early voxel-based morphometry study identified asymmetries in gray-matter volume for left > right in the "medial cerebellum" and right > left in "lateral cerebellum" that is largely consistent with our results (Good et al., 2001). In addition, our lobular findings are partially consistent with the results of a recent analysis of lobular volumes in 150 (Weier et al., 2014) and twenty participants (Diedrichsen et al., 2009). Weier and colleagues

reported significant right > left asymmetries in Crus I and X (consistent with our findings), and right < left for Crus II (inconsistent) (2014); Diedrichsen and colleagues reported significant right > left asymmetries for lobules I-IV (consistent for lobule III, inconsistent for IV) and right < left asymmetries for lobule VI (consistent) (2009). Differences between the findings of these three atlas-based studies may be attributable to differences in the particular implementation of the "ground truth" rules (Schmahmann et al., 1999) on which the segmentations are based (Park et al., 2014).

The asymmetries that we have identified here are within the range reported for regional volumes in the cerebral cortex. Laterality scores for the cortex vary between approximately +/−0.13 (Esteves et al., 2017; Goldberg et al., 2013), denoting up to 13% greater regional volume. Our results indicate that the laterality index for raw cerebellar lobular volumes ranges between approximately +/−0.12 (Figure S1), significant after multiple comparisons correction in all lobules except H VIIIB (Fig. 2 & Figure S1). Though beyond the scope of the current work, future work could assess the degree of homology between hemispherical asymmetries of cerebellar lobules and cerebral cortical regions – with the hypothesis that anatomically connected regions exhibit similar laterality indices.

The relationship between relative cerebellar lobular volume and behavior

Our results provide additional evidence that the structure of specific regions of the cerebellum are related to specific cognitive functions. We found that working memory was related to right H VIIIA, dexterity to the left anterior lobe, and fear to right H VI (after correcting for age, sex, handedness, and fluid intelligence). In all cases, better performance was associated with greater relative lobular volume. Though we did confirm previously reported effects, the observed pair-wise correlations accounted for less than 5% of the variance (Figure S6). Recent work has shown that a combined cohort of cerebellar disease sufferers and healthy controls increases the variability of structural and behavioral scores that can be exploited to better identify brain-behavior correlations (Kansal et al., 2017). Though difficult to compare directly due to differences in behavioral measures and unreported correlation coefficients, the authors appear to have found stronger correlations between behavior and lobular volumes (visually estimated from Fig. 1 to be between r=0.20 and 0.60). It is unclear how the results would be affected if the authors explicitly controlled for total cerebellar gray-matter volume. Even though the effect that we identified is relatively small, it is important to note that the behavioral test battery used in the HCP was not designed to assess cerebellar function and that the division of cerebellar structure into lobular volumes implicitly implies that the entire lobule shares the same function. Lobular distinctions are based upon known anatomy (Larsell et al., 1972; Schmahmann et al., 1999) and are extremely useful – in particular for cases where the effects are known to be large such as in disease (e.g., Kutzelnigg et al., 2007; Mirdamadi, 2016) or development (Bernard et al., 2015; Bernard and Seidler, 2013), but they may miss subtle links between structure and function by averaging across different functional domains. Given that the cerebellum contains more neurons than the rest of the brain and is reciprocally connected to most regions of the cortex (Ramnani, 2006), it is reasonable to hypothesize that even cerebellar regions that are spatially close may be differentially connected (Steele et al., 2016; Strick et al., 2009) and exhibit distinct functional (Buckner et al., 2011; O'Reilly et al., 2010) and behavioral links (Stoodley et al., 2012). In addition, the effects that we identified may also have been reduced by the relative lack of variability in the homogenous population used in the current study (all healthy adults between 22 and 36 years of age, with high fluid intelligence). Even with these caveats that would likely reduce our ability to detect correlations within anatomically-defined regions, our findings provide further support for the link between motor and non-motor behavior and lobular structure in the

human cerebellum; a link that persists even after statistically controlling for the effects of age, sex, handedness, and fluid intelligence.

Sex differences in cerebellar volume

The majority of studies report greater total raw cerebellar volume in males (Diedrichsen et al., 2009; Dimitrova et al., 2006; e.g., Raz et al., 2001, 1998; Rhyu et al., 1999; Tiemeier et al., 2010; Weier et al., 2014), with a recent meta-analysis including 19 cerebellar studies estimating the size of this effect to be 1.68 (Cohen's d) (Ruigrok et al., 2014). We found a very similar effect (Cohen's d=1.37), and extend previous findings to show that the size of the effect varies across lobules (with Cohen's d for significant effects ranging from 0.4 in Vermal VIIB to 1.28/1.35 in L/R H V; Fig. 4B, Table S2) – indicating that sex has a differential impact on lobular volume. In contrast, while there is some indication of regional sex differences in the cerebral cortex (Good et al., 2001), the effect is likely to be relatively small (Esteves et al., 2017; Goldberg et al., 2013; Kang et al., 2015). In addition, after normalizing lobular volume to total cerebellar gray-matter volume we found that females had significantly larger relative volume in Crus II (which exhibits primarily non-motor structural connectivity) while males had larger relative volume in primarily motor lobules (H V, VIIIA/B; but also vermal VIIIA/B) (Coffman et al., 2011; Kelly and Strick, 2003). Though we hypothesized that the relationship between relative volume and performance on tasks known to recruit these regions would be influenced by sex, we found no evidence for this effect (i.e., no interaction). Our results did show that there was a main effect of sex such that, for a given relative volume, males performed better than females. However, since we there was no evidence for a correlation between relative volume and performance in these regions, we do not interpret our results as providing evidence that relative volume confers a specific performance advantage in one sex over the other on these tasks. This issue could potentially be addressed with a follow-up study that uses more specific and targeted behavioral testing of cerebellar function (e.g., Bernard et al., 2015; Bernard and Seidler, 2013; Kansal et al., 2017).

Cerebellar functional organisation

The spatial distribution of the effects that we identified is not entirely consistent with the idea that there are predominantly separate motor and non-motor lobules of the human cerebellum. While we did find that motor performance was linked with volume in "motor regions", so too was memory and emotion. This brings up the question of what the organising principle of the cerebellum is, and whether there are multiple overlapping organisations (Apps and Hawkes, 2009; Voogd, 2014). Given the homogenous nature of cerebellar cytoarchitecture, local cerebellar cortical function is predominantly driven by its white-matter connectivity – with mossy fibre input (arising primarily from pontine nuclei) interacting with climbing fibre input from the inferior olive (Apps and Garwicz, 2005) to drive cerebellar computations supporting motor and non-motor behaviour (Moberget and Ivry, 2016). Projections from climbing fibres usually form only one or two longitudinal sagittal strips (Apps and Hawkes, 2009) and this organisational principle can be used to divide the cerebellum into multiple sagittal zones (Voogd, 2014). Sagittal zones are aligned along the sagittal plane (i.e., differential connectivity when moving from medial to lateral cerebellar cortex, or vice versa) and roughly perpendicular to the gross anatomical organisation of the cerebellar lobules. On the systems level, work with human resting-state functional connectivity suggests that lobules have largely distinct profiles of connectivity between somatomotor and supramodal regions (O'Reilly et al., 2010), but that each lobule may participate in more than one functional network (Bernard et al., 2012; Buckner et al., 2011), though there has so far been no evidence that these networks can be segregated into sagittal zones. There is, however, task-based functional MRI evidence

that the somatotopic representation of the body spans multiple lobules in the anterior lobe (and H VIII) (Grodd et al., 2001; Rijntjes et al., 1999; Schlerf et al., 2010) that has been interpreted as aligning with sagittal zones (Grodd et al., 2001). There is also evidence for a corresponding gradient of somatotopic activity in the dentate nucleus (Bernard et al., 2014; Küper et al., 2012) that is influenced by the topography of projections from cerebellar cortex (Kelly and Strick, 2003; Steele et al., 2016). Based upon this detailed anatomical and connectional work, we posit that the lobular organisation of the cerebellum is a simplification that is generally correct, but can be further enhanced with more spatially specific information from non-human animal research and human connectional anatomy. As such, the seminal work of Schmahmann and Sherman identifying cerebellar cognitive affective syndrome (Schmahmann and Sherman, 1998, 1997) and subsequent work by Stoodley and colleagues (Stoodley et al., 2012; Stoodley and Schmahmann, 2010, 2009) and others (Bernard et al., 2015; Bernard and Seidler, 2013) provides good evidence that motor and non-motor cerebellar functions are largely segregated along lobular boundaries. These apparently competing views of cerebellar organisation illustrate the need for a more nuanced approach that integrates information from cerebellar gray-matter anatomy, white-matter connectional anatomy, and function. It is also important that we consider fundamental methodological issues such as segmentation (e.g., approaches and atlases), how to treat structural and behavioral data (e.g., raw vs. relative volume, grouping of measures) (Mankiw et al., 2017), and statistical methods (e.g., control variables, data reduction techniques) in order to more clearly specify the relationships between the cerebellum and behavior. Our study used lobular volumes relative to total cerebellar gray-matter volume and included age, sex, and fluid IQ as covariates of no interest. While sex and age are commonly used regressors, we also included fluid IQ to control for its potential relationship with cerebellar volume (e.g., Frangou et al., 2004). Removing this covariate had no effect on our findings (data not shown), but systematically including or not including additional control variables may allow the field to more accurately specify the structure-function relationship in the human cerebellum. While not within the scope of the current study, an interesting first step would be to use to data-driven approaches such as principal components (e.g., Bernard and Seidler, 2013) or partial least squares (McIntosh and Mišić, 2013) analyses to determine the relative importance of lobules to the relationships between cerebellar structure and a wide range of demographic variables and human motor and cognitive behavior.

Conclusion

In summary, our findings represent the largest and most specific population quantification of cerebellar lobular gray-matter volumes, hemisphere and sex differences, and relation to behavior in healthy young adults. We found that the effects of hemisphere and sex were not equal across all lobules of the cerebellum, providing further evidence that the cerebellum cannot be considered a single structure with uniform function.

Acknowledgements

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neuroimage.2017.04.066.

References

Adamaszek, M., D'Agata, F., Kirkby, K.C., Trenner, M.U., Sehm, B., Steele, C.J., Berneiser, J., Strecker, K., 2014. Impairment of emotional facial expression and prosody discrimination due to ischemic cerebellar lesions. Cerebellum 13, 338–345. http://dx.doi.org/10.1007/s12311-013-0537-0.

Adamaszek, M., Kirkby, K.C., D'Agata, F., Olbrich, S., Langner, S., Steele, C., Sehm, B., Busse, S., Kessler, C., Hamm, A., 2015. Neural correlates of impaired emotional face recognition in cerebellar lesions. Brain Res. 1613, 1–12. http://dx.doi.org/10.1016/j.brainres.2015.01.027.

Apps, R., Garwicz, M., 2005. Anatomical and physiological foundations of cerebellar information processing. Nat. Rev. Neurosci. 6, 297–311. http://dx.doi.org/10.1038/nrn1646.

Apps, R., Hawkes, R., 2009. Cerebellar cortical organization: a one-map hypothesis. Nat. Rev. Neurosci. 10, 670–681. http://dx.doi.org/10.1038/nrn2698.

Avants, B.B., Epstein, C.L., Grossman, M., Gee, J.C., 2008. Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. Med. Image Anal. 12, 26–41. http://dx.doi.org/10.1016/j.media.2007.06.004.

Baer, L.H., Park, M.T.M., Bailey, J.A., Chakravarty, M.M., Li, K.Z.H., Penhune, V.B., 2015. Regional cerebellar volumes are related to early musical training and finger tapping performance. Neuroimage 109, 130–139. http://dx.doi.org/10.1016/j.neuroimage.2014.12.076.

Balsters, J.H., Cussans, E., Diedrichsen, J., Phillips, K.A., Preuss, T.M., Rilling, J.K., Ramnani, N., 2010. Evolution of the cerebellar cortex: the selective expansion of prefrontal-projecting cerebellar lobules. Neuroimage 49, 2045–2052. http://dx.doi.org/10.1016/j.neuroimage.2009.10.045.

Barch, D.M., Burgess, G.C., Harms, M.P., Petersen, S.E., Schlaggar, B.L., Corbetta, M., Glasser, M.F., Curtiss, S., Dixit, S., Feldt, C., Nolan, D., Bryant, E., Hartley, T., Footer, O., Bjork, J.M., Poldrack, R., Smith, S., Johansen-Berg, H., Snyder, A.Z., Van Essen, D.C., 2013. Function in the human connectome: task-fmri and individual differences in behavior. Neuroimage 80, 169–189. http://dx.doi.org/10.1016/j.neuroimage.2013.05.033.

Bates, D.M., Mächler, M., Bolker, B., Walker, S., 2015. Fitting linear mixed-effects models using lme4 | Bates |. J. Stat. Softw. 67, 1–47. http://dx.doi.org/10.18637/jss.v067.i01.

Benton, A.L., Varney, N.R., Hamsher, K.D., 1978. Visuospatial judgment. A clinical test. Arch. Neurol. 35, 364–367.

Bernard, J.A., Leopold, D.R., Calhoun, V.D., Mittal, V.A., 2015. Regional cerebellar volume and cognitive function from adolescence to late middle age. Hum. Brain Mapp. 36, 1102–1120. http://dx.doi.org/10.1002/hbm.22690.

Bernard, J.A., Peltier, S.J., Benson, B.L., Wiggins, J.L., Jaeggi, S.M., Buschkuehl, M., Jonides, J., Monk, C.S., Seidler, R.D., 2014. Dissociable functional networks of the human dentate nucleus. Cereb. Cortex 24, 2151–2159. http://dx.doi.org/10.1093/cercor/bht065.

Bernard, J.A., Seidler, R.D., 2013. Relationships between regional cerebellar volume and sensorimotor and cognitive function in young and older adults. Cerebellum 12. http://dx.doi.org/10.1007/s12311-013-0481-z.

Bernard, J.A., Seidler, R.D., Hassevoort, K.M., Benson, B.L., Welsh, R.C., Wiggins, J.L., Jaeggi, S.M., Buschkuehl, M., Monk, C.S., Jonides, J., Peltier, S.J., 2012. Resting state cortico-cerebellar functional connectivity networks: a comparison of anatomical and self-organizing map approaches. Front. Neuroanat., 6. http://dx.doi.org/10.3389/fnana.2012.00031.

Bilker, W.B., Hansen, J.A., Brensinger, C.M., Richard, J., Gur, R.E., Gur, R.C., 2012. Development of abbreviated nine-item forms of the Raven's Standard Progressive Matrices Test. Assessment 19, 354–369. http://dx.doi.org/10.1177/1073191112446655.

Bogovic, J.A., Bazin, P.-L., Ying, S.H., Prince, J.L., 2013. Automated segmentation of the cerebellar lobules using boundary specific classification and evolution. Inf. Process. Med. Imaging 23, 62–73.

Buckner, R.L., Krienen, F.M., Castellanos, A., Diaz, J.C., Yeo, B.T.T., 2011. The organization of the human cerebellum estimated by intrinsic functional connectivity. J. Neurophysiol. 106, 2322–2345. http://dx.doi.org/10.1152/jn.00339.2011.

Chakravarty, M.M., Steadman, P., van Eede, M.C., Calcott, R.D., Gu, V., Shaw, P., Raznahan, A., Collins, D.L., Lerch, J.P., 2013. Performing label-fusion-based segmentation using multiple automatically generated templates. Hum. Brain Mapp. 34, 2635–2654. http://dx.doi.org/10.1002/hbm.22092.

Coffman, K.A., Dum, R.P., Strick, P.L., 2011. Cerebellar vermis is a target of projections from the motor areas in the cerebral cortex. PNAS 108, 16068–16073. http://dx.doi.org/10.1073/pnas.1107904108.

Diedrichsen, J., 2006. A spatially unbiased atlas template of the human cerebellum. Neuroimage 33, 127–138. http://dx.doi.org/10.1016/j.neuroimage.2006.05.056.

Diedrichsen, J., Balsters, J.H., Flavell, J., Cussans, E., Ramnani, N., 2009. A probabilistic MR atlas of the human cerebellum. NeuroImage 46, 39–46. http://dx.doi.org/10.1016/j.neuroimage.2009.01.045.

Dimitrova, A., Zeljko, D., Schwarze, F., Maschke, M., Gerwig, M., Frings, M., Beck, A., Aurich, V., Forsting, M., Timmann, D., 2006. Probabilistic 3D MRI atlas of the human cerebellar dentate/interposed nuclei. Neuroimage 30, 12–25. http://dx.doi.org/10.1016/j.neuroimage.2005.09.020.

D'Mello, A.M., Crocetti, D., Mostofsky, S.H., Stoodley, C.J., 2015. Cerebellar gray matter and lobular volumes correlate with core autism symptoms. NeuroImage Clin. 7, 631–639. http://dx.doi.org/10.1016/j.nicl.2015.02.007.

Esteves, M., Marques, P., Magalhães, R., Castanho, T.C., Soares, J.M., Almeida, A., Santos, N.C., Sousa, N., Leite-Almeida, H., 2017. Structural laterality is associated with cognitive and mood outcomes: an assessment of 105 healthy aged volunteers. Neuroimage 153, 86–96. http://dx.doi.org/10.1016/j.neuroimage.2017.03.040.

Frangou, S., Chitins, X., Williams, S.C.R., 2004. Mapping IQ and gray matter density in healthy young people. Neuroimage 23, 800–805. http://dx.doi.org/10.1016/j.neuroimage.2004.05.027.

Glasser, M.F., Essen, D.C.V., 2011. Mapping human cortical areas in vivo based on myelin content as revealed by T1- and T2-weighted MRI. J. Neurosci. 31, 11597–11616. http://dx.doi.org/10.1523/JNEUROSCI.2180-11.2011.

Glasser, M.F., Sotiropoulos, S.N., Wilson, J.A., Coalson, T.S., Fischl, B., Andersson, J.L., Xu, J., Jbabdi, S., Webster, M., Polimeni, J.R., Van Essen, D.C., Jenkinson, M., 2013. The minimal preprocessing pipelines for the Human Connectome Project. Neuroimage, Mapp. Connect. 80, 105–124. http://dx.doi.org/10.1016/j.neuroimage.2013.04.127.

Goldberg, E., Roediger, D., Kucukboyaci, N.E., Carlson, C., Devinsky, O., Kuzniecky, R., Halgren, E., Thesen, T., 2013. Hemispheric asymmetries of cortical volume in the human brain. Cortex 49, 200–210. http://dx.doi.org/10.1016/j.cortex.2011.11.002.

Good, C.D., Johnsrude, I., Ashburner, J., Henson, R.N.A., Friston, K.J., Frackowiak, R.S.J., 2001. 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. http://dx.doi.org/10.1006/nimg.2001.0857.

Grodd, W., Hülsmann, E., Lotze, M., Wildgruber, D., Erb, M., 2001. Sensorimotor mapping of the human cerebellum: fmri evidence of somatotopic organization. Hum. Brain Mapp. 13, 55–73. http://dx.doi.org/10.1002/hbm.1025.

Gur, R.C., Richard, J., Hughett, P., Calkins, M.E., Macy, L., Bilker, W.B., Brensinger, C., Gur, R.E., 2010. A cognitive neuroscience based computerized battery for efficient measurement of individual differences: standardization and initial construct validation. J Neurosci. Methods 187, 254–262. http://dx.doi.org/10.1016/j.jneumeth.2009.11.017.

Kang, X., Herron, T.J., Ettlinger, M., Woods, D.L., 2015. Hemispheric asymmetries in cortical and subcortical anatomy. Laterality 20, 658–684. http://dx.doi.org/10.1080/1357650X.2015.1032975.

Kansal, K., Yang, Z., Fishman, A.M., Sair, H.I., Ying, S.H., Jedynak, B.M., Prince, J.L., Onyike, C.U., 2017. Structural cerebellar correlates of cognitive and motor dysfunctions in cerebellar degeneration. Brain 140, 707–720. http://dx.doi.org/10.1093/brain/aww327.

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

Küper, M., Thürling, M., Stefanescu, R., Maderwald, S., Roths, J., Elles, H.G., Ladd, M.E., Diedrichsen, J., Timmann, D., 2012. Evidence for a motor somatotopy in the cerebellar dentate nucleus—An FMRI study in humans. Hum. Brain Mapp. 33, 2741–2749. http://dx.doi.org/10.1002/hbm.21400.

Küper, M., Timmann, D., 2013. Cerebellar mutism. Brain Lang. 127, 327–333. http://dx.doi.org/10.1016/j.bandl.2013.01.001.

Kutzelnigg, A., Faber-Rod, J.C., Bauer, J., Lucchinetti, C.F., Sorensen, P.S., Laursen, H., Stadelmann, C., Brück, W., Rauschka, H., Schmidbauer, M., Lassmann, H., 2007. Widespread demyelination in the cerebellar cortex in multiple sclerosis. Brain Pathol. 17, 38–44. http://dx.doi.org/10.1111/j.1750-3639.2006.00041.x.

Larsell, O., Jansen, J., Korneliussen, H.K., Mugnaini, E., 1972. The Comparative Anatomy and Histology of the Cerebellum: the Human Cerebellum, Cerebellar Connections, and Cerebellar Cortex. Univ of Minnesota Press.

Loken, C., Gruner, D., Groer, L., Peltier, R., Bunn, N., Craig, M., Henriques, Teresa, Dempsey, J., Yu, C.-H., Chen, J., Chong, Dursi, L.J., Scott Northrup, J., Pinto, J., Knecht, N., Zon, R.V., 2010. SciNet: lessons learned from building a power-efficient top-20 system and data centre. J. Phys.: Conf. Ser. 256, 12026. http://dx.doi.org/10.1088/1742-6596/256/1/012026.

Makris, N., Hodge, S.M., Haselgrove, C., Kennedy, D.N., Dale, A., Fischl, B., Rosen, B.R., Harris, G., Caviness, V.S., Schmahmann, J.D., 2003. Human cerebellum: surface-assisted cortical parcellation and volumetry with magnetic resonance imaging. J Cogn. Neurosci. 15, 584–599. http://dx.doi.org/10.1162/089892903321662967.

Makris, N., Schlerf, J.E., Hodge, S.M., Haselgrove, C., Albaugh, M.D., Seidman, L.J., Rauch, S.L., Harris, G., Biederman, J., Caviness, V.S., Jr., 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. http://dx.doi.org/10.1016/j.neuroimage.2004.12.056.

Mankiw, C., Park, M.T.M., Reardon, P.K., Fish, A.M., Clasen, L.S., Greenstein, D., Giedd, J.N., Blumenthal, J.D., Lerch, J.P., Chakravarty, M.M., Raznahan, A., 2017. Allometric analysis detects brain size-independent effects of sex and sex chromosome complement on human cerebellar organization. J. Neurosci.. http://dx.doi.org/10.1523/JNEUROSCI.2158-16.2017.

McIntosh, A.R., Mišić, B., 2013. Multivariate statistical analyses for neuroimaging data. Annu. Rev. Psychol. 64, 499–525. http://dx.doi.org/10.1146/annurev-psych-113011-143804.

Mirdamadi, J.L., 2016. Cerebellar role in Parkinson's disease. J. Neurophysiol. jn 01132, 2015. http://dx.doi.org/10.1152/jn.01132.2015.

Moberget, T., Ivry, R.B., 2016. Cerebellar contributions to motor control and language comprehension: searching for common computational principles. Ann. N.Y. Acad. Sci. 1369, 154–171. http://dx.doi.org/10.1111/nyas.13094.

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

O'Reilly, J.X., Beckmann, C.F., Tomassini, V., Ramnani, N., Johansen-Berg, H., 2010. Distinct and overlapping functional zones in the cerebellum defined by resting state functional connectivity. Cereb. Cortex 20, 953–965. http://dx.doi.org/10.1093/cercor/bhp157.

Park, M.T.M., Pipitone, J., Baer, L.H., Winterburn, J.L., Shah, Y., Chavez, S., Schira, M.M., Lobaugh, N.J., Lerch, J.P., Voineskos, A.N., Chakravarty, M.M., 2014. Derivation of high-resolution MRI atlases of the human cerebellum at 3 T and segmentation using multiple automatically generated templates. Neuroimage 95, 217–231. http://dx.doi.org/10.1016/j.neuroimage.2014.03.037.

Ramnani, N., 2006. The primate cortico-cerebellar system: anatomy and function. Nat. Rev. Neurosci. 7, 511–522. http://dx.doi.org/10.1038/nrn1953.

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.

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. http://dx.doi.org/10.1016/S0304-3940(99)00487-5.

Rijntjes, M., Buechel, C., Kiebel, S., Weiller, C., 1999. Multiple somatotopic representations in the human cerebellum. Neuroreport 10, 3653–3658.

Ruigrok, A.N.V., Salimi-Khorshidi, G., Lai, M.-C., Baron-Cohen, S., Lombardo, M.V., Tait, R.J., Suckling, J., 2014. A meta-analysis of sex differences in human brain structure. Neurosci. Biobehav. Rev. 39, 34–50. http://dx.doi.org/10.1016/j.neubiorev.2013.12.004.

Schlerf, J.E., Verstynen, T.D., Ivry, R.B., Spencer, R.M.C., 2010. Evidence of a novel somatopic map in the human neocerebellum during complex actions. J. Neurophysiol. 103, 3330–3336. http://dx.doi.org/10.1152/jn.01117.2009.

Schmahmann, J.D., 2010. The role of the cerebellum in cognition and emotion: personal reflections since 1982 on the dysmetria of thought hypothesis, and its historical evolution from theory to therapy. Neuropsychol. Rev. 20, 236–260. http://dx.doi.org/10.1007/s11065-010-9142-x.

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.

Schmahmann, J.D., Doyon, J., Petrides, M., Evans, A.C., Toga, A.W., 2000. MRI Atlas of the Human Cerebellum 1st ed. Academic Press.

Schmahmann, J.D., Sherman, J.C., 1998. The cerebellar cognitive affective syndrome. Brain 121, 561–579. http://dx.doi.org/10.1093/brain/121.4.561.

Schmahmann, J.D., Sherman, J.C., 1997. Cerebellar cognitive affective syndrome. Int. Rev. Neurobiol. 41, 433–440.

Sjöbeck, M., Englund, E., 2001. Alzheimer's disease and the cerebellum: a morphologic study on neuronal and glial changes. Dement Geriatr. Cogn. Disord. 12, 211–218, (doi:51260).

Steele, C.J., Anwander, A., Bazin, P.-L., Trampel, R., Schaefer, A., Turner, R., Ramnani, N., Villringer, A., 2016. Human cerebellar sub-millimeter diffusion imaging reveals the motor and non-motor topography of the dentate nucleus. Cereb. Cortex.. http://dx.doi.org/10.1093/cercor/bhw258.

Stoodley, C.J., Schmahmann, J.D., 2010. Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. Cortex 46, 831–844. http://dx.doi.org/10.1016/j.cortex.2009.11.008.

Stoodley, C.J., Schmahmann, J.D., 2009. Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. Neuroimage 44, 489–501. http://dx.doi.org/10.1016/j.neuroimage.2008.08.039.

Stoodley, C.J., Valera, E.M., Schmahmann, J.D., 2012. Functional topography of the cerebellum for motor and cognitive tasks: an fMRI study. Neuroimage 59, 1560–1570. http://dx.doi.org/10.1016/j.neuroimage.2011.08.065.

Strick, P.L., Dum, R.P., Fiez, J.A., 2009. Cerebellum and Nonmotor Function. Annu. Rev. Neurosci. 32, 413–434. http://dx.doi.org/10.1146/annurev.neuro.31.060407.125606.

Tiemeier, H., Lenroot, R.K., Greenstein, D.K., Tran, L., Pierson, R., Giedd, J.N., 2010. Cerebellum development during childhood and adolescence: a longitudinal morphometric MRI study. Neuroimage 49, 63–70. http://dx.doi.org/10.1016/j.neuroimage.2009.08.016.

Tournier, J.-D., Calamante, F., Connelly, A., 2012. MRtrix: diffusion tractography in crossing fiber regions. Int. J. Imaging Syst. Technol. 22, 53–66. http://dx.doi.org/10.1002/ima.22005.

Van Essen, D.C., Smith, S.M., Barch, D.M., Behrens, T.E.J., Yacoub, E., Ugurbil, K., 2013. The WU-Minn Human Connectome Project: an overview. Neuroimage, Mapp. Connect. 80, 62–79. http://dx.doi.org/10.1016/j.neuroimage.2013.05.041.

Voogd, J., 2014. What we do not know about cerebellar systems neuroscience. Front. Syst. Neurosci. 8, 227. http://dx.doi.org/10.3389/fnsys.2014.00227.

Weier, K., Fonov, V., Lavoie, K., Doyon, J., Collins, D.L., 2014. Rapid automatic segmentation of the human cerebellum and its lobules (RASCAL)–implementation and application of the patch-based label-fusion technique with a template library to segment the human cerebellum. Hum. Brain Mapp. 35, 5026–5039. http://dx.doi.org/10.1002/hbm.22529.

Wu, T., Hallett, M., 2013. The cerebellum in Parkinson's disease. Brain 136, 696–709. http://dx.doi.org/10.1093/brain/aws360.

Yang, Z., Ye, C., Bogovic, J.A., Carass, A., Jedynak, B.M., Ying, S.H., Prince, J.L., 2016. Automated cerebellar lobule segmentation with application to cerebellar structural analysis in cerebellar disease. Neuroimage 127, 435–444. http://dx.doi.org/10.1016/j.neuroimage.2015.09.032.