Investigating sexual dimorphism in human brain structure by combining multiple indexes of brain morphology and source-based morphometry

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Abstract

Computational morphometry of magnetic resonance images represents a powerful tool for studying macroscopic differences in human brains. In the present study (*N* participants = 829), we combined different techniques and measures of brain morphology to investigate one of the most compelling topics in neuroscience: sexual dimorphism in human brain structure. When accounting for overall larger male brains, results showed limited sex differences in gray matter volume (GMV) and surface area. On the other hand, we found larger differences in cortical thickness, favoring both males and females, arguably as a result of region-specific differences. We also observed higher values of fractal dimension, a measure of cortical complexity, for males versus females across the four lobes. In addition, we applied source-based morphometry, an alternative method for measuring GMV based on the independent component analysis. Analyses on independent components revealed higher GMV in fronto-parietal regions, thalamus and caudate nucleus for females, and in cerebellar-temporal cortices and putamen for males, a pattern that is largely consistent with previous findings.

Keywords: sex differences; source-based morphometry; gray matter volume; surface area; cortical thickness; fractal dimension

Introduction

Human brains are characterized by remarkable inter-individual anatomical variability, which is of interest in both translational research and clinical practice. Recent advances in computational morphometry of magnetic resonance images (MRIs) enable the automated analysis of macroscopic changes across multiple facets of brain structure and morphology. In the present study, we used different techniques and measures of brain morphology to investigate one of the most compelling topics in neuroscience, that is, sexual dimorphism in brain structure.

Several brain regions have been shown to be anatomically different in males and females (e.g., Lotze et al., 2019; Ritchie et al., 2018; Wierenga et al., 2020), possibly as a consequence of the interaction of complex biological factors, such as hormonal and genetic influences (Lombardo et al., 2012; McCarthy et al., 2011; McEwen et al., 2017). However, despite the large number of studies accumulated in recent years, the evidence on the location, magnitude, and direction of sex-related anatomical differences remains partially inconsistent. One reason for this lack of consistency in the current neurostructural findings may be attributed to the use of morphological indexes that provide an incomplete description of brain morphology. Most prior studies have focused on examining gray matter (GM) properties, including gray matter volume (GMV), surface area (SA), and cortical thickness (CT). With regard to GMV, usually males are reported to have larger brain size and larger absolute volume in each brain tissue category (i.e., gray matter, white matter, and cerebrospinal fluid, Ruigrok et al., 2014). However, when adjusting for brain size, males exhibit, on average, larger GMV only in some regions, that are temporo-occipital regions, basal ganglia (e.g., putamen) and cerebellum, while females exhibit larger GMV in fronto-parietal regions (see also, Chen et al., 2007; Lotze et al., 2019; Ruigrok et al., 2014). Larger differences were found in SA, with males showing, on average, higher values across the whole brain (Ritchie et al., 2018; Wierenga et al., 2014). Findings from CT studies are more mixed. Indeed, some studies reported thicker cortex in females across the entire cortex (e.g., Ritchie et al., 2018), while only small

regions of the temporal lobes were found to be thicker in males (Im et al., 2006; Luders et al., 2006; Sowell et al., 2007). Other studies observed thicker cortex in males in brain regions across the four major lobes (Duerden et al., 2020; Escorial et al., 2015), whereas Wierenga et al. (2014) found very few sex differences, suggesting that males and females may be more similar in CT than in other indices of cortex structure.

In order to characterize different and complementary aspects of brain morphology, in this study we used a region-of-interest (ROI) approach to investigate sexual dimorphism in GM structure by combining GMV, SA, and CT. In addition, we also provide supplemental information on cortex morphology measuring the cortical complexity, which was quantified using fractal dimension (FD). Fractal geometry has been employed to describe the geometry of complex natural systems (Mandelbrot, 1967). Evidence showing that the brain has fractal properties (e.g., self-similarity) from the microscopic to the macroscopic level (Di Ieva, 2014, 2015) has prompted the use of FD as a measure of cortical folding complexity. FD can be defined as an estimate of shape complexity, which summarizes in a single numeric value the roughness and the irregularity of a natural object. The more irregular an object, the higher its FD value. Prior work reported that FD relates to cognitive abilities (Im et al., 2006; Mustafa et al., 2012), and is significantly different in clinical and non-clinical populations (e.g., schizophrenia: Yotter et al., 2011; Alzheimer's disease: King et al., 2009, 2010), as well as in healthy individuals across the lifespan (Kalmanti & Maris, 2007; Madan & Kensinger, 2016).

As a main novelty of the present study, we also addressed females-males differences in GMV using the source-based morphometry (SoBM) (Xu et al., 2009), which is a multivariate extension of the voxel-based morphometry (VBM) based on independent component analysis (ICA) (Xu et al., 2009). This technique identifies voxels with similar patterns of variance, and groups them into independent components (ICs). Statistical analyses are performed on the loading coefficients – i.e., scalar values representing how individual components are expressed in each participant – in order to test for differences between groups in each individual component (Gupta et

al., 2019). To the best of our knowledge, no study has used the SoBM to specifically address sex differences in GMV. SoBM, in particular, offers an innovative approach by providing information from a network perspective. Indeed, gray matter covariance is supposed to reflect shared morphological features within the same IC (Kašpárek et al., 2010), and these structural components are thought to correspond, at least in part, to resting-state ICs (Segall et al., 2012). Moreover, SoBM is supposed to provide several advantages with respect to VBM, taking into account covariation between voxels and acting as a spatial filter which identifies and removes artifacts from real brain signals (Xu et al., 2009).

Based on previous findings (see Chen et al., 2007; Rijpkema et al., 2012; Ruigrok et al., 2014), we expect to detect regional differences in GMV favoring both males and females. Moreover, we expect the SoBM to provide a better detailed description of differences in GMV. Specifically, we hypothesize that the SoBM will confirm previous findings, showing larger female volume in fronto-parietal regions, and larger male volume in occipito-temporal regions, cerebellum and subcortical regions. With regard to SA and CT, we hypothesize that males will show increased SA across the whole brain, whereas we expect to observe little differences in CT. While findings from CT and SA studies are numerous, to our knowledge only one study (Luders et al., 2004) used FD to specifically investigate sex differences in cortical complexity, observing higher FD in females in the superior frontal and parietal lobes bilaterally and in the right inferior frontal lobe. Our results might corroborate and further expand these previous findings.

Finally, we expect that the use of different techniques and multiple measures, which can capture different and complementary aspects of brain morphology, would provide the best multidimensional and realistic picture of sex differences in GM structure.

Materials and Methods

Participants

The sample of this study was provided by the Wu-Minn Human Connectome Project (HCP) dataset (Van Essen et al., 2013), which originally included 1206 participants with no history of psychiatric

or neurological disorders. We excluded participants who: (1) did not have MRI data; (2) had missing information; (3) had an Edinburgh Handedness Questionnaire score < 0. In addition, as the use of hormonal contraceptive might have a considerable impact on female's brain structure (Lisofsky et al., 2016; Pletzer et al., 2010), we also excluded female participants that declared to use birth control methods or did not report this information.

The final sample included 829 participants (380 F). Independent sample t-tests were performed to test differences between females and males in sociodemographic variables. Females were significantly older than males ($t = 7.43$, $p < 0.001$), while no difference emerged between the two groups for educational level and income ($p > 0.05$). Details about sociodemographic information are reported in Table 1.

Table 1 Mean, standard deviation (SD) and range of sociodemographic variables are reported for the entire sample, and for males and females separately.

	Sample (N = 829)	Females (N = 380)	Males (N = 449)
	Mean ± SD (range)	Mean ± SD (range)	Mean ± SD (range)
Age	28.77 ± 3.75 (22-36)	29.79 ± 3.65 (22-36)	27.91 ± 3.61 (22-36)
Education (Years)	14.85 ± 1.81 (11-17)	14.91 ± 1.84 (11-17)	14.8 ± 1.78 (11-17)
Income	4.98 ± 2.19 (1-8)	4.99 ± 2.21 (1-8)	4.98 ± 2.16 (1-8)

Image acquisition

High-resolution T1-weighted structural images were acquired for each participant on a 3T Siemens Skyra scanner with a 32-channel head coil. The following acquisition parameters were used: repetition time (TR) = 2400 ms; echo time (TE) = 2.14 ms; FOV = 224 mm; flip angle (FA) = 8°; matrix = 320, 256 sagittal slices; voxel size = 0.7 x 0.7 x 0.7 mm^3 (for details about the acquisition protocol, see Glasser et al., 2013).

Preprocessing

Detailed information on structural preprocessing is reported in Glasser et al. (2013). Each participant was preprocessed using the FMRIB Software Library (FSL version 5.0.9; Jenkinson et al., 2012). Briefly, during the PreFreeSurfer pipeline, distortion and bias correction was performed on T1w images, which were finally registered to MNI space. Structural images were then preprocessed using FreeSurfer version 5.2 (Fischl et al., 2012), which performs the segmentation of the volume into predefined structures, and the reconstruction of white and pial cortical surfaces, which were registered to the fsaverage atlas using the FreeSurfer's standard folding-based surface registration (Glasser et al., 2013).

Estimation of cortical measures. For each measure of interest, i.e., GMV (mm^3), SA (mm^2), CT (mm) and FD, we extracted an overall measure for the whole brain and local values for the 148 regions of the Destrieux cortical parcellation (Destrieux et al., 2010) (Fig. S1). Overall measures include total brain volume (TBV), average CT, total SA, and FD of the cortical ribbon.

For each ROI, the SA was calculated as the sum of the areas of all vertices within that ROI, while the cortical thickness was measured as the average distance between the gray-white boundary and the pial surface (Vuoksimaa et al., 2014). The fractal dimension was calculated using the calcFD toolbox, a publicly available MATLAB toolbox designed to measure the fractal dimensionality of a 3D structure using the intermediate files from the FreeSurfer pipeline (Madan & Kensinger, 2016; https://github.com/cMadan/calcFD).

Source-based morphometry. The SoBM was conducted to identify networks of GM covariance using the Group ICA of an fMRI Toolbox (GIFT; https://trendscenter.org/software/gift/). Prior to performing SoBM, segmented GM images were produced using the Computational Anatomy Toolbox v12.6 (CAT12; http://www.neuro.uni-jena.de/cat/index.html) (Gaser & Dahnke, 2016) running on SPM12 v7771 (https://www.fil.ion.ucl.ac.uk/spm/). GM images were resampled to 2x2x2 mm voxels (Segall et al., 2012) and smoothed with an 8x8x8 mm Full Width at Half Maximum (FWHM) Gaussian kernel. The number of independent components to extract was

automatically computed by GIFT using the 'minimum description length' (MDL) criterion (Li et al., 2007). The ICA was performed using the Infomax algorithm (Bell & Sejnowski, 1995). Briefly, the ICA algorithm creates two matrices: a subject by component matrix (i.e., mixing matrix) and a component by voxel matrix (i.e., source matrix). The mixing matrix represents the participants' contribution to each individual component (i.e., loading coefficients), while the source matrix represents the contribution of every voxel to each component (see Xu et al., 2009). In addition, the ICASSO algorithm (http://research.ics.aalto.fi/ica/icasso/) was used to increase the components stability, and the ICA was performed 100 times using bootstrapping and permutations. ICASSO returned a quality index (*Iq*) ranging from 0 to 1 and reflecting the compactness and repeatability of each component. This index was later used to identify and exclude components with low stability and repeatability. Subsequent statistical analyses were performed on the mixing matrix through the extraction of the loading coefficients for each participant and independent component.

Data Analysis

ROI analysis. All statistical analyses were performed on R v4.0.2. For each measure of interest, we tested sex differences in both overall measure and regional values using a general linear model (GLM), with sex as group factor and age as nuisance variable.

To check whether regional differences were a by-product of a brain-general difference between males and females, ROI analysis was also performed including into the model the corresponding overall measure as nuisance variable (Ritchie et al., 2018): TBV for GMV, total SA for SA, average CT for CT, and FD of the cortical ribbon for FD.

P-values were independently adjusted for each brain measure using the false-discovery rate (FDR) correction. Moreover, Cohen's d was calculated as the t-value multiplied by 2 and divided by the square root of the degrees of freedom (Ritchie et al., 2018). Note that negative t-values and effect sizes denote higher brain measures in males. For each cortical measure and ROI, effect sizes

were projected onto the fsaverage template using the *fsbrain* library running on R (Schaefer & Ecker, 2020).

Source-based morphometry. We extracted 95 ICs according to the MDL criterion (Li et al., 2007). Before performing statistical analyses, the *Iq* was used to assess the repeatability of each component with a threshold of $Iq \geq 0.9$. Thirty-five ICs were excluded due to this criterion. Three components that had large overlap with white matter were also excluded, leading to a final number of 57 ICs. A GLM was estimated to investigate sex differences for each individual IC separately. Loading coefficients were entered into the model as dependent variable, with sex as group factor and TBV and age as nuisance variables. Negative t-values and effect sizes indicate higher GMV in males. All p-values were adjusted for multiple comparisons using FDR correction.

Results

ROI analysis. Statistical analyses showed that males have significantly larger TBV (d = -1.48) and total SA (d = -1.42) than female. No difference emerged for average CT and FD of the cortical ribbon ($p > 0.05$) (Table 2). Males displayed higher raw values (i.e., not adjusted for the overall measure) of GMV, SA and FD across the brain, while analyses on raw values of CT showed differences favoring both males and females (Fig. S2, Table S1-S4).

When raw values of GMV and SA were corrected for the corresponding overall measure, differences between females and males were substantially reduced. With regards to cortical GMV, 13 ROIs showed higher volume in males than in females, with the largest differences being in the left (d = -0.44) and right insula (d = -0.4). Other regions with larger male volume include occipital poles, orbital sulci, and the left rectus (Fig. 1A-2A, Table S5). In contrast, 8 regions showed larger female volume, with the largest differences being in the left superior parietal gyrus (d = 0.31) and left occipital sulcus (d = 0.29). We detected larger volume in females in other regions, such as right superior parietal gyrus, postcentral gyrus, and bilateral superior frontal sulcus (Fig. 1B-2B, Table S5).

Analyses on the SA showed few group differences. We detected higher values in males in 6 ROIs and in females in 4 ROIs, corresponding to the same regions where we detected significantly different volumes. The largest difference was detected, respectively, in the right occipital pole (d = -0.28) and in the left superior occipital sulcus (d = 0.3) (Fig. 1C-2C, Table S6).

Differently, CT displayed large differences distribute across the entire brain and favoring both males and females. Indeed, 30 ROIs showed higher values in males than in females, with the largest effect size in the right insula, d = -0.67, and 30 ROIs showed larger thickness in females than in males, with the largest effect size in the left angular gyrus, d = 0.46 (Fig. 1, Table S7).

Large differences were observed also on FD: we found higher FD in males in all but 11 ROIs (largest difference in the left insula, d = -1.04) (Fig. 1D-2D, Table S8).

Table 2 Mean and standard deviation (SD) of total brain volume, total surface area, average cortical thickness, and fractal dimension of the cortical ribbon are reported for the entire sample, and for males and females separately.

	Sample (N = 829)	Females (N = 380)	Males (N = 449)
	Mean ± SD	Mean ± SD	Mean ± SD
Total brain volume (mm^3)	1253379 ± 127226.3	1168788 ± 93021.81	1324969 ± 106722.6
Total surface area (mm^2)	175562.8 ± 17881.64	164007.6 ± 13591.39	185342.2 ± 15019.73
Average cortical thickness (mm)	2.63 ± 0.08	2.63 ± 0.08	2.64 ± 0.09
Fractal dimension of the cortical ribbon	2.58 ± 0.01	2.58 ± 0.01	2.58 ± 0.01

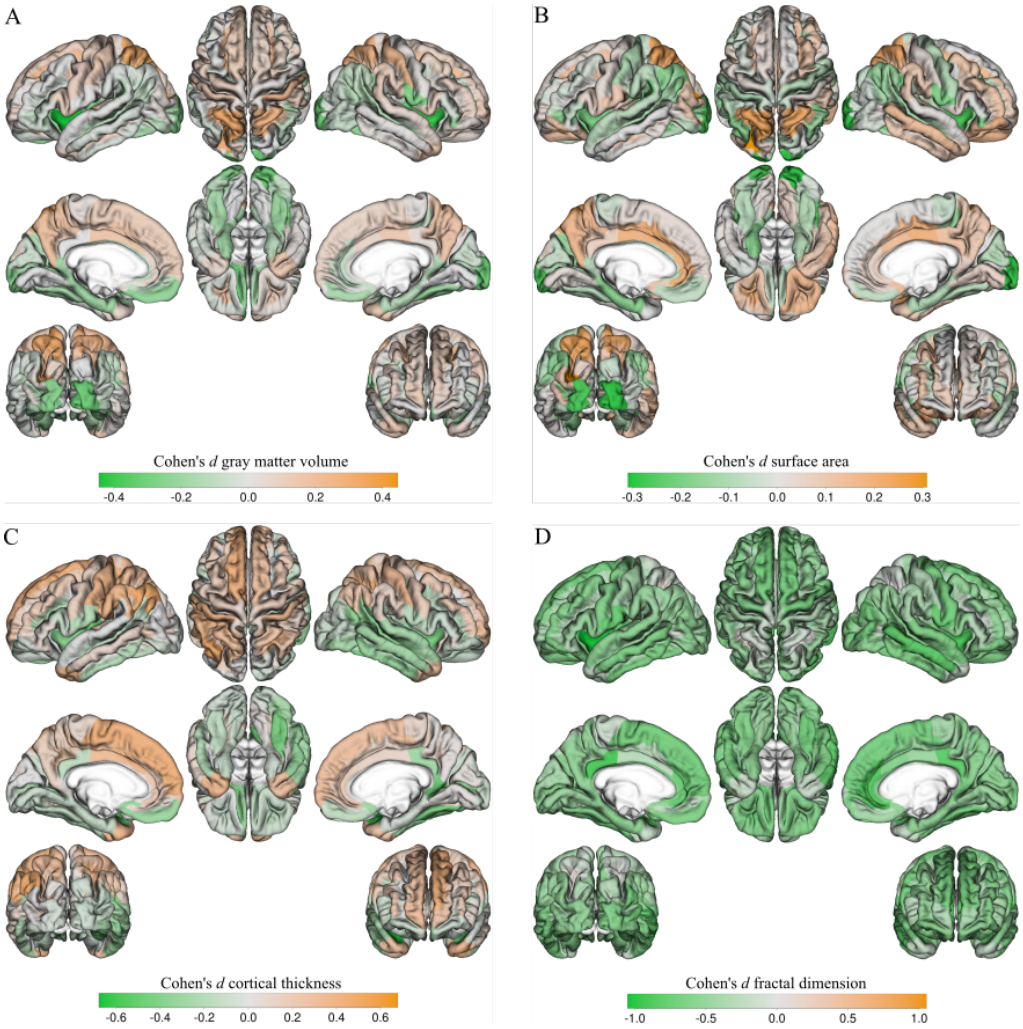

Fig. 1 Sex differences across regions of interest in gray matter volume (A), surface area (B), cortical thickness (C), and fractal dimension (D). The colormap is based on the direction and intensity of effects size. Color green indicates higher values for males (i.e., negative effects size), while color orange indicates higher values for females (i.e., positive effects size).

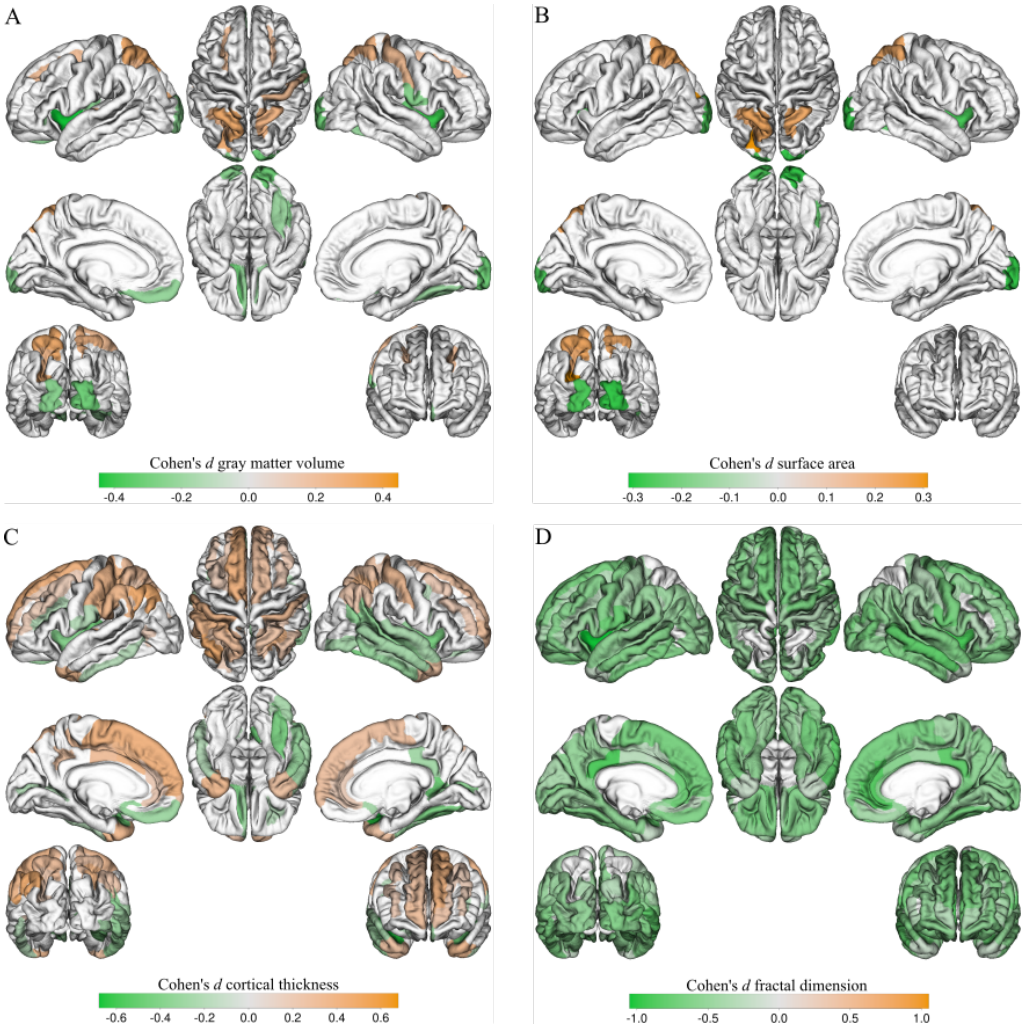

Fig. 2 Significant sex differences in gray matter volume (A), surface area (B), cortical thickness (C), and fractal dimension (D). Only effects size of regions significantly different between males and females are reported. The colormap is based on the direction and intensity of effects size. Color green indicates higher values for males (i.e., negative effects size), while color orange indicates higher values for females (i.e., positive effects size).

Source-based morphometry. Out of the 57 ICs meeting the inclusion criteria, we observed significant group difference in 26 components. In order to display only clusters that were strictly linked with their respective component, each component was converted to Z scores and thresholded at $|Z \geq 3.5|$. ICs are presented here divided into groups with similar spatial topography of the most relevent clusters. A detailed description of statistical analyses and clusters within each significant component is reported in the Supplementary materials (Table S9; Tables S10-S36).

Subcortical components. This group includes IC1, IC14, and IC17 comprising, respectively, bilateral thalamus, caudate nucleus, and putamen. The first two components showed higher GMV in females (d = 0.22 and 0.34, respectively), while the last one showed higher volume in males (d = -0.33) (Fig. S3).

Frontal components. All frontal components (IC13, IC27, IC29, IC36, IC49, and IC75), including anterior cingulate cortex, dorso- ventrolateral and medial orbitofrontal cortex, showed increased GMV in females (mean d = 0.27) (Fig. S4).

Temporal and parahippocampal components. This group includes lateral and medial temporal regions, specifically inferior temporal and parahippocampal cortices and fusiform gyri (IC3, IC19, and IC21). For all these components, we observed higher volume in males (mean d = -0.4). Females also showed higher volume in the right superior temporal cortex, extending through the inferior parietal lobule (IC43) (d = 0.27) (Fig. S5).

Parietal and pre-postcentral components. Females exhibited increased volume in ICs including regions of pre-postcentral gyri and inferior parietal lobules (IC18, IC31, IC51, and IC73) (mean d = 0.32) (Fig. S6).

Posterior components. Components of this group include precuneus and posterior/middle cingulate cortices (IC5, IC44), showing higher GMV in females (mean d = 0.22), and occipital regions (e.g., calcarine scissure, lingual gyrus, and cuneus) (IC16, IC50). Males showed higher volume in the most inferior part of the occipital lobes, including calcarine scissure and lingual gyri (IC16) (d = -0.93), while females revealed higher volume in the IC50, including more superior and medial regions of the occipital lobes (e.g., calcarine scissure and cuneus) (d = 0.21) (Fig. S7).

Cerebellar components. Cerebellar components (IC4, IC42, IC45, IC48, and IC64) showed higher GMV in males than in females (mean d = -0.32) (Fig. S8).

Discussion

In the present study, we investigated sex differences in GM structure by combining different techniques and multiple measures of brain morphology in a sample of 829 participants from the Human Connectome Project (HCP). We adopted a ROIs approach to investigate sex differences in four measures of cortical morphology: GMV, SA, CT, and FD. The use of distinct metrics provided us with a comprehensive picture of sex differences across the cerebral cortex. Indeed, different measures are supposed to carry unique biological information and describe distinct facets of cortical morphology (Madan & Kensinger, 2016; Panizzon et al., 2009; Raznahan et al., 2011). In addition, we performed a voxelwise analysis of sex differences in GMV using the SoBM. This technique, which has never been used to specifically address sex differences, provided us with a more detailed analysis of regional differences (Lotze et al., 2019).

ROI analysis. Consistently with previous findings (Escorial et al., 2015; Ritchie et al., 2018), we observed higher TBV and total SA in males. Moreover, we reported higher raw regional values of GMV and SA in males throughout the brain. When adjusting regional values for the appropriate overall measure, we observed only limited differences in GMV and SA. This finding indicates that the majority of regions do not differ between sexes, and that differences in raw values are attributable to the overall larger male brain. However, some regions were still significantly different between sexes after correcting for brain size. In males, the largest differences in volume were found in the bilateral insula and occipital poles, but we also reported significant differences in other regions, such as the bilateral orbitofrontal cortex (e.g., rectus, orbital sulcus), the right lateral occipito-temporal sulcus and the fusiform gyrus. For females, significant differences in volume were reported mainly in parietal and frontal regions bilaterally, such as the superior parietal gyrus, the superior frontal sulcus and the right postcentral gyrus. With regard to SA, we observed significant differences in the same regions that showed a different cortical volume, although with a smaller effects size.

For CT, we did not find significant differences in the average thickness as a function of sex. However, after adjusting for the average thickness, ROI analysis showed larger differences in CT

than for volume or SA. These findings suggest that sex differences in CT may be more extended than differences in other aspects of cortex morphology, and that they may be region-specific, and not only dependent on a general whole-brain difference. Our findings agree with Ritchie et al. (2018), who reported differences in thickness favoring both females and males and observed the largest effects size in the right insula for males, and in the inferior parietal cortex for females (Ritchie et al., 2018). However, we did not find evidence for significantly higher raw CT in females across the brain, as reported by Ritchie et al. (2018) and a number of previous studies (Luders et al., 2006; Lv et al., 2010; Sowell et al., 2007).

With respect to FD, we did not report a significant difference in the FD measured over the cortical ribbon, while we found that males have higher FD measured at the regional level across the whole brain. This finding has never been reported in the literature and was confirmed both when considering raw values of FD and after adjusting them for the overall measure. The only study that, to our knowledge, investigated differences in FD between males and females reported higher FD in females in the superior frontal and parietal lobes bilaterally and in the right inferior frontal lobe (Luders et al., 2004). Notably, although the FD has been found to be strongly correlated with other metrics of cortical morphology, especially the CT (King et al., 2010), it may be sensitive to other aspects of GM structure (Madan & Kensinger, 2016). Therefore, the combination of FD with other metrics of cortical morphology may lead to a more comprehensive picture of sex differences in GM structure, rather than providing redundant information. On these grounds, our results may be interpreted as indicating that higher male FD reflects facets of GM structure others than GMV, SA and CT. However, caution should be taken in interpreting this result. Indeed, while it does not appear that FD and brain size are meaningfully related (Madan & Kensinger, 2016), there is still relative paucity of studies using this measure, in particular for what concerns sex differences, and the relationship between FD and other facets of cortical morphology should be further explored in future research.

Source-based morphometry. Analyses on ICs revealed a consistent pattern of differences between females and males in GMV. On average, females showed higher cortical GMV in frontal and parietal components, precuneus and cingulate cortices. In contrast, males showed increased volume in lateral and medial temporal components (i.e., inferior temporal gyrus, fusiform gyrus, and parahippocampal cortex) and cerebellum. These findings support the evidence for higher cortical volume in fronto-parietal regions for females, and cerebellar- temporal cortices for males (Chen et al., 2007; Lotze et al., 2019; Ruigrok et al., 2014). Interestingly, regions where females showed higher GMV are also considered as core components of the default mode network (DMN), i.e., medial prefrontal cortex, posterior cingulate cortex/precuneus, and inferior parietal lobules (Raichle et al., 2001; Raichle, 2015). Our result confirms and expands prior findings that reported higher functional connectivity in females within the DMN (Biswal et al., 2010; Ritchie et al., 2018). Crucially, previous studies suggested that the DMN is an important part of the "social brain" (Amft et al., 2015; Mars et al., 2012). Our results, together with findings on other functional connectivity (Biswal et al., 2010; Ritchie et al., 2018), may help to explain the putative female advantage in social cognition (Gur & Gur, 2017).

As for subcortical regions, we detected higher volume for females versus males in the caudate nucleus and thalamus. These results received mixed support by prior studies. While Luders et al. (2009) observed higher female volume in the caudate, other studies did not observe a sexual dimorphism in this region (Rijpkema et al., 2011; Ritchie et al., 2018). For what concerns the thalamus, the finding of higher volume in females is consistent with Ruigrok et al. (2014), but not with Lotze et al. (2019) (increased thalamic GMV in males) and Ritchie et al. (2017) (no differences between males and females).

In contrast to previous studies (Lotze et al., 2019; Ruigrok et al., 2014), we did not observe higher male volume in motor cortices. However, we observed higher GMV for males in other structures subserving motor functions, specifically cerebellar and putaminal structures (Caligiore et al., 2017; Koziol et al., 2014; Marchand et al., 2008). A larger GMV in these regions for males,

consistently reported in previous studies (Rijpkema et al., 2012; Ruigrok et al., 2014), may be related to the putative male processing advantage in motor tasks (Gur & Gur, 2017).

Furthermore, the present study partially supports the evidence for higher male volume in occipital lobes. Indeed, males showed higher GMV in inferior and lateral occipital regions, including the calcarine scissure and the lingual gyri, as reported previously (Chen et al., 2007; Lotze et al., 2019). Crucially, this component showed the largest effect size (d = -0.93), suggesting broad sex differences in these regions (see Results). In contrast, females showed higher volume in more superior and medial regions, encompassing the calcarine scissure and the cuneus. Whether such structural differences between males and females are related to differences in the visual system (Vanston & Strother, 2016) or in visuospatial abilities (Gur & Gur, 2017; Moreno-Briseño et al., 2010), remains to be seen.

Limitations

In the present study, we did not assess sexual orientation, which has been suggested to affect brain structure characteristics (Votinov et al., 2021). Moreover, we did not account for the impact of sexual hormones on GM development (Neufang et al., 2009). On the other hand, a large sample size provided us with the statistical power to detect small effects.

Conclusions

Investigating where and to what extent males and females differ in brain structure and morphology is an important step to understand sexual dimorphism in cognitive abilities (e.g., Gur et al., 2012) and neurological/psychiatric disorders (e.g., Bao & Swaab, 2010), and the results provided herein may open up new opportunities for future research. The sex differences detected in the present study are arguably the result of the complex combination of biological factors such as sex-biased gene expression and steroid hormones (Lombardo et al., 2012; McCarthy et al., 2011; McEwen et al., 2017), whose influence on brain structure has been associated to synaptic pruning (Peper et al., 2009). In addition to combining four metrics of cortical morphology (i.e., GMV, CT, SA, and FD), we also adopted an alternative approach to VBM for measuring GMV, that is, the SoBM, which is

supposed to provide a more fine-grained analysis of differences in brain regions compared to a ROIs analysis (Lotze et al., 2019). On the whole, the current study suggests that major differences in cortical morphology between males and females can be found in CT and FD. Moreover, analyses on structural ICs revealed a pattern of sex differences in GMV which is largely consistent with that described by prior studies (e.g., see Chen et al., 2007; Lotze et al., 2019).

Declarations

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Conflicts of interest/Competing interests

The authors declare no conflict of interest.

Availability of data and material

The data are available through the Human Connectome Project (https://www.humanconnectome.org/).

Code availability

Not applicable.

Ethics approval

The Washington University Institutional Review Board (IRB # 201204036) approved all procedures for the Human Connectome Project (HCP).

Consent to participate

Written informed consent was obtained from all participants.

Consent for publication

Written informed consent for publication was obtained from all participants.

Rerefences

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