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WHITE MATTER SEXUAL DIMORPHISM OF THE ADULT HUMAN BRAIN

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Abstract

Sex-biased psychophysiology, behavior, brain function, and conditions are extensive, yet underlying structural brain mechanisms remain unclear. There is contradicting evidence regarding sexual dimorphism when it comes to brain structure, and there is still no consensus on whether or not there exists such a dimorphism for brain white matter. Therefore, we conducted a voxel-based morphometry (VBM) analysis along with global volume analysis for white matter across sex. We analyzed 384 T1-weighted MRI brain images (192 male, 192 female) to investigate any differences in white matter (WM) between males and females. In the VBM analysis, we found males to have larger WM, compared to females, in occipital, temporal, insular, parietal, and frontal brain regions. In contrast, females showed only one WM region to be significantly larger than males: the right postcentral gyrus in the parietal lobe region. Although, on average, males showed larger global WM volume, we did not find any significant difference in global WM volume between males and females.

Keywords

• VBM • morphometry • brain • neuroscience • gender • sex • white matter

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Introduction

There is a plethora of studies showing sex-biased neurological and neuropsychiatric conditions. In this regard, there is an evident prevalence of sex-biased conditions that also show symptomatological differences between males and females [1]. Examples of female-biased conditions include anxiety, anorexia nervosa, and depression, while male-biased conditions include dyslexia, autism, attention deficit/hyperactivity disorder, language impairment, and Tourette syndrome [1–4].

Therefore, investigating structural brain similarities and differences between males and females will identify where and how female and male brains differ which will aid in determining risk and resilience factors of such conditions, as well as distinguish associated mechanisms.

Moreover, it is clear that males and females have a capacity to have different behavioral and psychophysiological attributes. Given that, structural differences can be associated with differences in physiology and behavior [5]. Moreover, it is clear that there is a functional significance of brain structural findings and correlations between brain volume and cognitive performance [6]. Therefore, findings of sex-biased differences in brain structure will ultimately help in identifying mechanisms underlying behavioral, physiological, psychophysiological endpoints in males and females.

Although there is convincing evidence of differences in male and female brains from brain morphometry [6–10], there does remain some studies that found no such sex differences [11–13]. Also, contradicting results were found in previous region-of-interest and whole-brain studies of sex differences in developing human brains [4].

Furthermore, in regards to brain white matter, sex effects on global white matter (WM) still remain unclear [14]. One study found the there is significant difference in white matter between males and females [15], while another, more recent, study found no significant gender effects on white matter [16].

Given the above, it appears, that there is still no consensus on whether or not there are sex differences in whole-brain and regional white matter between the two human sexes. Also, if such a difference does exist, it still remains unclear which white matter regions show such a difference between males and females, thus, setting the basis for the rationale of this study. In this study we conducted a voxel-based morphometry (VBM) analysis to investigate white matter differences between males and females, and we have also investigated whether sex affects global white matter volume across different age groups.

Methods

Subjects

All subjects' brain images were acquired from an online cohort provided by Imperial College London (www.brain-development.org). The male group included 192 T1-weighted MRI brain images of normal and healthy male participants (*mean age: 46.92, median age: 46, std. dev.: 15.5*). The female group included 192 T1-weighted MRI brain images of normal and healthy female participants (*mean age: 46.92, median age: 46, std. dev.: 15.5*).

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MRI protocol

The brain images acquired from brain-development.org were all T1-weighted. The MRI acquisitions were from three different MRI scanners from three different hospitals in London. At Guy's Hospital a 1.5 T Philips Medical Systems Gyroscan Intera MRI system was used (TR = 9.8, TE = 4.6, reconstruction diameter = 240, flip angle = 8). The Institute of Psychiatry a 1.5 T GE MRI system was used, and at Hammersmith Hospital a 3T Philips Medical Systems Intera MRI system was used (TR = 9.6, TE = 4.6, reconstruction diameter = 240, flip angle = 8).

Voxel-based morphometry and image preprocessing

Voxel-based morphometry (VBM) was performed using SPM12 (The Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, London, UK). All 384 (192 male, 192 female) brain images were analyzed using SPM12. To optimize normalization, reorientation was done so that each brain image was centered at the anterior commissure (AC-PC orientation). Then each brain image was segmented into cerebrospinal fluid (CSF), gray matter (GM), and white matter (WM). To minimize between-subject structural variations, WM segmented images were respectively normalized to WM population templates generated from the complete set of images using the registration method: Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) [17]. The spatially normalized WM images were then smoothed using an 8 mm FWHM isotropic kernel.

The spatially normalized and smoothed WM images were subjected to a two-sample t-test in SPM12. The first sample included the 192 male WM images, and the second sample included the 192 female WM images. The threshold for statistical significance was set at $p<0.05$ with family wise error (FWE) correction for the following comparisons: male>female and female>male.

Statistical Analysis

Demographic differences between the two groups were assessed using independent sample t-tests. All statistical analyses were performed using SPSS software (IBM SPSS Statistics for Windows Version 22.0). The 2 groups of participants differed significantly only for education ($p=.01$). There was no difference in age. Thus, education level was entered as a covariate in the VBM statistical analyses to control for the effect of these variables in the main results.

We tested the WM volume changes between males and females using a t-test model for independent samples in SPM12. In the t test model, all scans of the two groups were included within one design matrix. The model also included the education for each subject as a covariate of no interest. Contrasts between the two groups (males vs. females) were performed to investigate the main WM regional volume differences. For all contrasts, the statistical threshold was set to Family Wise Error (FWE) $p < 0.05$, corrected for multiple comparisons.

Additionally, the global WM volume for each respective WM image was calculated in ml using Get_totals (www0.cs.ucl.ac.uk/staff/g.ridgway/vbm/get_totals.m). Then a two sample t-test (threshold: $p<0.05$) was performed, using SPSS software (IBM SPSS Statistics for Windows Version 22.0), for male vs. female global WM volumes, and between the following age groups for the same comparison: 20-39, 40-59, 60-79 years old.

Results

For the male to female comparison, there were 15 brain regions that showed significant difference in WM. These regions were larger in males compared to females. The brain regions that showed a significant difference between sexes included: frontal, temporal, parietal, occipital, and insular regions (Table 1, Figure 1). On the other hand, the female>male comparison only showed one WM brain region that was significantly larger for female compared to male. This region (Figure 2) was the WM of the postcentral gyrus in the right parietal lobe (*MNI coordinates: 34,-32,51; t value: 4.94; z score: 4.86; p(FWE)=0.028*).

As for global WM volume comparisons between the male and female groups, there was no statistical significance ($p>0.05$). Also, all three age group (20-39, 40-59, 60-79) comparisons between males and females, respectively, showed no significant WM volume differences between males and females ($p>0.05$).

Discussion

The current study used VBM to quantify any sex differences in human brain white matter morphology from a set of 384 MRI brain scans. The aim of this study was to examine where differences in WM volume exist between males and females, and whether or not there exists a significant sex effect on global WM volume. We did find regional differences in WM across sex. In our VBM analysis, we found that males have significantly larger WM in certain regions in all cerebral lobes respectively (Table 1, Figure 1), and that females only showed larger WM in the region of the postcentral gyrus in the right parietal lobe (Figure 2). These results cannot be explained by a general assumption that a male's brain is bigger than a female's brain. Indeed we did not find any additional significant differences in global WM between males and females.

Although, previous work found that males exhibit larger increase in WM volume during adolescence [18], there is contradicting evidence of effects of sex on global WM volume [16; 19] . Also localized sexual dimorphism of the adult human brain remains unresolved [13; 14; 20; 21].

In this study we found that males did not show significantly larger global WM volume than females. We also found that even across age groups (20-39, 40-59, 60-79 years old) males did not show significantly larger global WM volume compared to females. We take these results in light of previous work [16; 19] in which Lemaitre et al. (2005) found significant difference between male and female global WM volumes while Smith et al. (2007) found no such significant difference. In this case our results are consistent with that of Smith et al. (2007). Therefore, providing further research evidence that in the comparison of global WM brain volume between males and females there was no significant difference.

Table 1: Brain lobes, brain hemispheres, MNI coordinates, t-values, and z scores for male>female white matter comparison

Region	Hemisphere	MNI coordinates (mm)			t-value	z score	p(FWE)
		x	y	z			
Medial occipital	Right	10	-76	8	5	4.92	0.0220
Medial occipital	Right	2	-78	6	5	4.91	0.0220
Inferior temporal	Right	44	-22	-28	5.18	5.09	0.0100
Inferior parietal	Right	34	-45	42	5.11	5.02	0.0140
Superior temporal	Right	51	-4	3	5.1	5.01	0.0150
Superior parietal	Right	2	-72	24	5.06	4.98	0.0170
Inferior frontal	Right	34	28	0	5.06	4.97	0.0170
Medial occipital	Left	2	-74	-6	6.31	6.15	0.0001
Sub-lobar (extra-nuclear)	Left	-3	15	0	5.54	5.43	0.0020
Superior Temporal	Left	-46	-32	15	5.28	5.18	0.0060
Insula	Left	-44	-24	14	5.15	5.06	0.0120
Posterior frontal	Left	-48	-15	12	4.98	4.89	0.0240
Medial occipital	Left	-8	-98	2	5.13	5.04	0.0130
Inferior temporal	Left	-44	-22	-27	5.1	5.01	0.0150
Posterior frontal	Left	-50	-6	6	5.03	4.95	0.0190

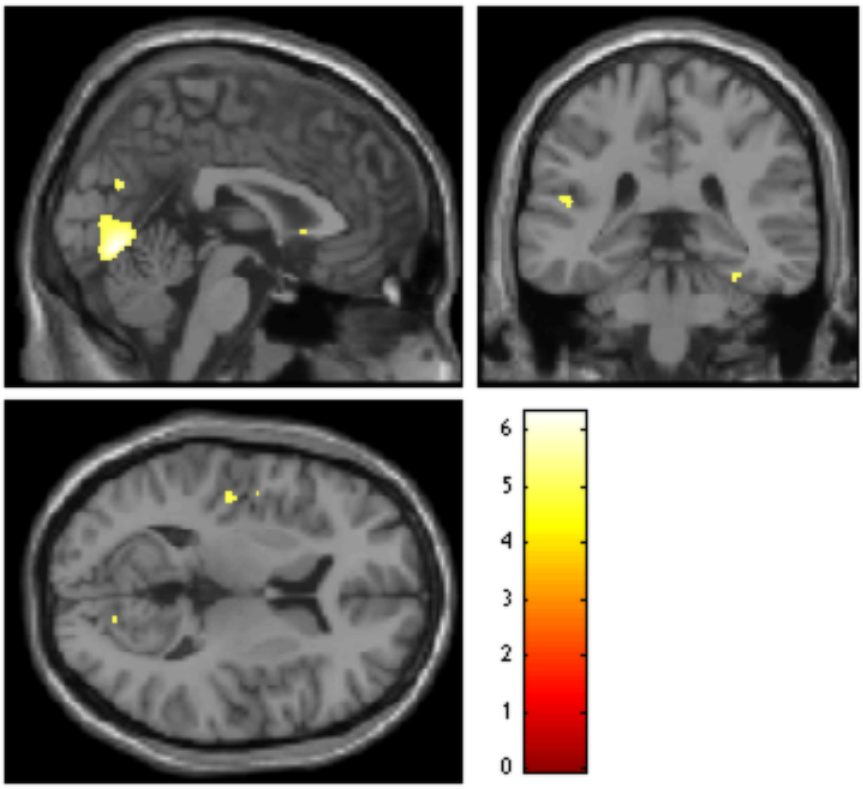

Figure 1: Transverse, sagittal, and coronal planes of the brain are provided where significant difference (blobs) are present for male>female comparison. The statistical parametric maps are rendered onto a single subject T1-weighted MRI scan of the brain.

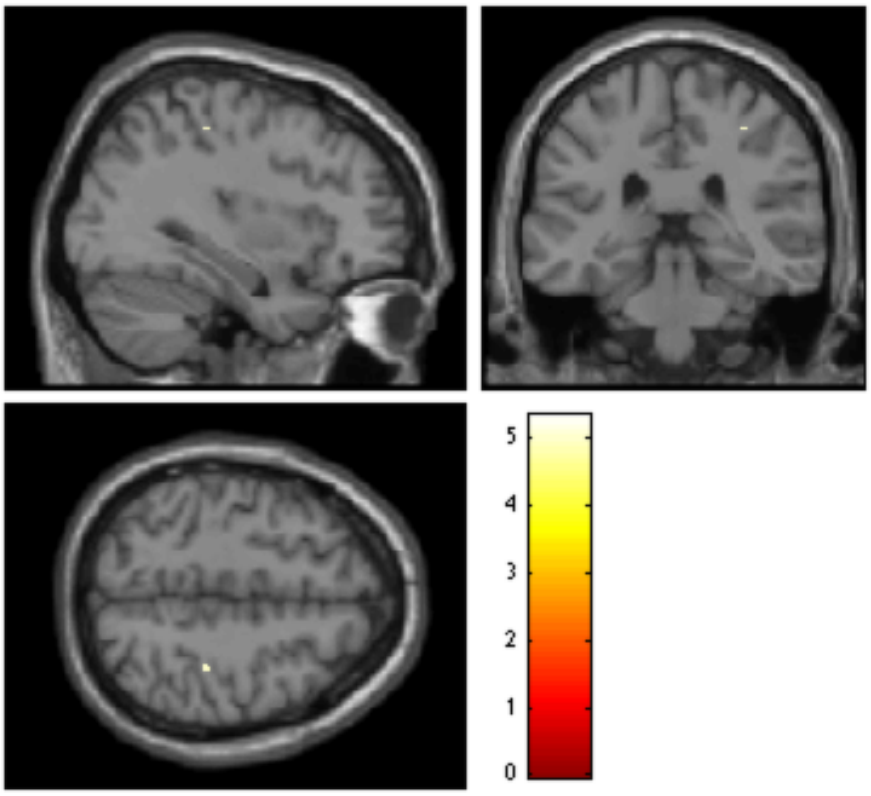

Figure 2: Transverse, sagittal, and coronal planes of the brain are provided where significant difference (blobs) are present for female>male comparison. The statistical parametric maps are rendered onto a single subject T1-weighted MRI scan of the brain.

Conclusion

Results of gender differences with respect to regional and global brain volumes remain contradictory. Our results of sexual dimorphism of the human brain are consistent with previous studies [21–23]. We found regional brain white matter sexual dimorphism, but we did not find any evidence of such dimorphism for global brain white matter. Although sex differences in brain structure may explain differences in behavior, conditions, and psychophysiology, studies that showed regional brain volume differences have been less consistent [13]. This is one of the main reasons this study was conducted, and in order to provide another insight on any global and regional brain WM differences between males and females. Also, reaching a consensus on regional brain differences between the two sexes will greatly help in explaining sex-biased behavior, cognitive function, psychophysiology, neurological conditions and underpinnings of various pathologies.

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