Sex differences in regional gray matter in healthy individuals aged 44–48 years: A voxel-based morphometric study

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Abstract

The study examined sex-related differences in regional gray matter (GM) in 44–48 year old healthy individuals. T1-weighted MRI scans were acquired in 411 subjects aged 44–48 from a random community sample and optimized voxel-based morphometry was applied to detect regional GM difference between men and women, correcting for effects of age, years of education, handedness, and total intracranial volume (TIV). Men had larger brain volumes and higher white matter (WM) to TIV ratios compared with women. Women had higher GM to TIV ratios than men. After controlling for age, years of education, handedness, and TIV, there were no significant differences between men and women in the total GM volumes. Regional sex dimorphism was present, with men having more GM volume in midbrain, left inferior temporal gyrus, right occipital lingual gyrus, right middle temporal gyrus, and both cerebellar hemispheres. Women showed more GM in dorsal anterior, posterior and ventral cingulate cortices, and right inferior parietal lobule. Our results suggest sex dimorphism in GM in middle aged healthy individuals, which is not likely to be explained by brain pathology. These differences may provide the structural brain basis for sex differences in certain cognitive functions.

Article Outline

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Introduction

Sex-related variations in human brain structure have been studied broadly in a number of investigations ([Breedlove, 1994], [Good et al., 2001a], [Kruggel, 2006] and [Swaab and Hofman, 1984]). The most consistent observation is that men have larger brain volumes than women ([Blatter et al., 1995], [Kruggel, 2006], [Luders et al., 2002], [Peters, 1991], [Skullerud, 1985] and [Swaab and Hofman, 1984]). There are a number of studies showing sex-related differences in brain compartments and particular brain structures, e.g., corpus callosum (Dubb et al., 2003), cingulate gyrus (Pujol et al., 2002), and parietal lobe (Nopoulos et al., 2000), which have not necessarily been shown by other researchers ([Came et al., 2006] and [Going and Dixon, 1990]). The discrepancy of sexual dimorphism in regional brain volumes may be due to various methodological issues, which include varying sample sizes, recruitment of convenience samples, confounding factors such as neurological diseases, and differences in neuroimaging protocols and processing techniques.

One important factor that contributes to this inconsistency is aging, with men and women having different age-related changes in the brain (Raz et al., 2004). It may be difficult to map sex-related morphological differences within a cohort with a broad age range, due to a possible nonlinear concurrent effect of aging. For example, age was found to be associated with smaller GM volumes in a cross-sectional study whereas this change was not replicated in one year longitudinal observation of the same group (Resnick et al., 2000). Although there is substantial evidence to show sex differences in ageing ([Coffey et al., 1996] and [Xu et al., 2000]), other studies failed to replicate this finding in subjects in the seventh and eighth decades ([Lemaître et al., 2005] and [Resnick et al., 2003]). Also, sex difference varied in different brain regions, e.g., larger frontomedial cortex in men

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were also compared, after controlling for effects of handedness, age, education years, and by using ANCOVA models. Although different scanners appeared to have no effect on brain volumes, it was included in the model as a covariate.

Regional gray matter volume differences were detected by applying a general linear model to form statistical parametric maps, in which statistical significances were tested on a voxel by voxel basis. Specifically, an ANCOVA analysis was performed for men and women, with age, handedness, years of education, scanner difference, and total intracranial volume (TIV) included as covariates. To locate significant regions, statistical threshold was set at $p < 0.001$ with family-wise correction for multiple comparisons. Significant coordinates were transferred to Talairach coordinates (<http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach>) and anatomical localizations were determined by the Talairach Daemon (Lancaster et al., 2000).

Result

Global volumetric measures

Demographic characteristics of the study sample are presented in Table 1. Global measures were compared between our sample and comparable studies in Table 2. Comparisons of global volumetric measures between men and women are shown in Table 3. Men had larger raw volumes of GM, WM, and CSF than women while women had higher ratio of GM and smaller ratios of WM and CSF to TIV. However, there were no significant difference when comparing volumes adjusted by age, handedness, and total years of education, scanner A or B, and TIV. In the multiple regression analysis, age, handedness, years of education, and scanner A or B were all non-significant contributors to the variance of GM across all subjects. There were no interaction effects between sex and age, and sex and years of education.

Table 1.

Descriptive characteristics of men and women in the study

Variables	Men (n = 184)	Women (n = 227)	Z/ χ^2	p value
Age (years)	46.66 (1.49)	46.73 (1.37)	- 0.594	0.553
Education (years)	15.15 (2.17)	14.63 (2.31)	- 1.829	0.067
Right-handed (%)	164 (89.1)	203 (89.4)	0.009	0.923
Scanner A (%)	84 (45.7)	71 (31.3)	8.939	0.003*

Note. p values are for Mann-Whitney U test of age and education, chi-square tests of handedness, and scanner used between men and women, * $p < 0.05$.

Table 2.

A summary of various studies that examined sex differences in brain volumetrics

Study	N	Age (years)	Total intracranial volume (TIV)		Gray matter (GM)		White matter (WM)		Cerebrospinal fluid (CSF)	
			Men	Women	Men	Women	Men	Women	Men	Women
The current study	411	44–48	1.65 (0.12)	1.44 (0.11)	0.74 (0.05)	0.67 (0.05)	0.50 (0.05)	0.43 (0.04)	0.41 (0.05)	0.35 (0.05)
Good et al. (2001a)	465	17–79	NA	NA	0.829 (0.069)	0.747 (0.064)	0.454 (0.044)	0.395 (0.041)	0.397 (0.04)	0.401 (0.048)
Luders et al. (2005)	60	24.32 $\pm$ 4.35 (women) 25.45 $\pm$ 4.72 (men)	1.40 (0.11)	1.22 (0.09)	0.72 (0.05)	0.64 (0.05)	0.55 (0.06)	0.47 (0.05)	0.13 (0.02)	0.11 (0.02)
Kruggel (2006)	290	18–32	1.62 (0.09)	1.49 (0.10)	0.71 (0.05)	0.67 (0.05)	0.70 (0.07)	0.64 (0.07)	0.18 (0.03)	0.18 (0.03)
Lemaitre et al. (2005)	662	63–75	1.45 (0.10)	1.29 (0.10)	0.58 (0.04)	0.53 (0.04)	0.49 (0.05)	0.43 (0.04)	0.39 (0.05)	0.33 (0.05)

Note. Volumes are presented in liters for the purpose of comparison. Age is presented in the forms as shown in papers.

Table 3.

Global volumetric measures in men and women

	Men (n = 184)	Women (n = 227)	df	t/F	p
Total intracranial volume (TIV)	1647.16 (124.61)	1441.80 (113.76)	409	17.436	< 0.001
Gray matter (GM)					
Raw volumes (ml)	741.35 (53.32)	666.54 (47.55)	409	15.018	< 0.001
Ratios to TIV	0.45 (0.02)	0.46 (0.02)	409	- 6.947	< 0.001
Adjusted volumes* (ml)	700.32 (2.23)	699.80 (1.95)	1	0.023	0.879
White matter (WM)					
Raw volumes (ml)	496.20 (49.96)	425.30 (40.35)	409	15.918	< 0.001
Ratios to TIV	0.30 (0.01)	0.29 (0.01)	409	4.365	< 0.001
Adjusted volumes* (ml)	457.96 (1.92)	456.30 (1.68)	1	0.332	0.565
GM/WM ratio	1.50 (0.10)	1.57 (0.10)	409	- 7.370	< 0.001
Cerebrospinal fluid (CSF)					
Raw volumes (ml)	409.61 (48.00)	349.96 (49.37)	409	12.332	< 0.001
Ratios to TIV	0.25 (0.02)	0.24 (0.02)	409	2.955	0.022
Adjusted volumes* (ml)	375.47 (2.91)	377.64 (2.54)	1	0.247	0.619

explain the discrepancies of the data. Another factor should be borne in mind for the variance of global measures is the age of study population. For example, Kruggel (2006) compared global volumes between young men and women aged 18–32, who had relatively less CSF than participants, all of whom aged 44–48 years, in our study. This is consistent with the evidence that absolute CSF volume is increasing with age not only in later life but also in early adulthood (Courchesne et al., 2000).

As was shown in Table 3, global measures in our study replicated previous findings of sex differences in brain compartments ([Allen et al., 2003], [Filipek et al., 1994], [Kruggel, 2006] and [Passe et al., 1997]), although conflicting reports exist ([Nopoulos et al., 2000] and [Schlaepfer et al., 1995]). It is well established that men have larger brains than women, as seen in MRI studies (Gur et al., 2002a) as well as a postmortem reports (Dekaban, 1978). GM/WM ratio is also higher in women than in men (Allen et al., 2003), which is consistent with the result of higher relative GM in women and WM in men in this study. Previous research of sex differences in fractional volumes has not been consistent, e.g., fractional GM was reported to be higher in men ([Good et al., 2001a] and [Sullivan et al., 2004]) or women ([Gur et al., 1999] and [Kruggel, 2006]) by different authors. Brain tissue volume ratios vary with age. It is known that GM and WM grow in an asynchronous manner in adolescence (Courchesne et al., 2000), and decrease by a different slope with aging in the two sexes (Jernigan et al., 2001). The hypothesis for sex dimorphism is that in women, a smaller skull size is compensated during development by a relative increase in the somatodentritic tissue necessary for processing of information, rather than connecting axons for transportation of information (Gur et al., 1999).

Regional GM volumes

Sex differences in certain brain regions have been reported in previous volumetric studies. Men were shown as having larger absolute regional GM volumes, e.g., bilateral frontal, temporal, or left parietal lobes (Came et al., 2006). Men have also been reported to have larger hippocampal formation (Raz et al., 1997), frontomedial cortex, amygdala, and angular gyrus (Goldstein et al., 2001) than women. While taking skull size into account, sex differences were not shown in several regions including dorsolateral prefrontal cortex, somatosensory cortex, and hippocampal formation. In a volumetric study of hippocampus in adults aged 60–64, hippocampus volume was found larger in men than women, but the opposite was true when total intracranial volume was controlled for (Maller et al., 2006). Regional higher GM volumes, e.g., amygdala, hippocampi, entorhinal perirhinal cortex, left anterior temporal gyrus, were found in men by another VBM study as well (Good et al., 2001a). Previous studies, either ROI-based or VBM-based, jointly presented evidence of sex dimorphism, while giving different details.

In our study, regional sex dimorphism was seen bilaterally in the temporal lobes, with men having more GM than women. Results of previous volumetric ROI studies of temporo-limbic structures have not been consistent. Men had larger inferior temporal cortex, hippocampus, and parahippocampal gyrus (Raz et al., 2004), but no difference in amygdala and hippocampus volumes in another study (Gur et al., 2002a). Inferior temporal cortex, however, was reported to be more vulnerable to shrinkage with aging in men than in women (Raz et al., 2004), suggesting effects of sex–age interaction in this region. Therefore, studies of sex difference in this region may give inconsistent results if aging effects are not appropriately controlled for. Our results, however, strengthened by the large study population younger than 50 years old and correcting for the small age range, largely overcomes the error introduced by aging. Although the exact biological explanation for these findings is unclear, genetics may be one important factor that affects human temporal lobe morphometry. Volumetric studies in patients with Turner syndrome (46, X) showed enlarged temporal lobe (Rae et al., 2004) and decreased GM in temporal gyri in Klinefelter syndrome (47, XXY) (Patwardhan et al., 2000), suggesting effects of X chromosome on temporal volume, which might allude to the mechanism of sex dimorphism in temporal cortex.

It has been widely documented that women have higher regional GM volumes than men in various structures. Our study replicated previous findings in cingulate (Paus et al., 1996) and inferior parietal lobe (Nopoulos et al., 2000), but not in the superior temporal cortex (Harasty et al., 1997), caudate and thalamic nuclei (Murphy et al., 1996), or dorsolateral prefrontal cortex (Schlaepfer et al., 1995), which are believed to be related to sex dimorphism in language and visuospatial function (Schlaepfer et al., 1995). However, a positron emission topography (PET) study showed higher glucose metabolism in temporo-limbic region and lower in cingulate regions in men than in women, suggesting functional correlates of sex dimorphism that are consistent with our results. In addition, more GM was demonstrated in women than men in the perisylvian right temporal cortices (Van Laere and Dierckx, 2001), orbital frontal cortices (Gur et al., 2002a) and even wider area in temporal, frontal and parietal lobes in another VBM study (Good et al., 2001a). Women showed widespread increased regional cortical thickness of GM and larger quantity of gyrification and fissuration of the brain surface than men in a young cohort ([Luders et al., 2004] and [Luders et al., 2006]).

Sex dimorphism, aging, and other factors

Brain volume changes over time, with about 50% of its variance being explained by age. Given that aging probably affects the brain in a nonlinear fashion ([Allen et al., 2005] and [Walhovd et al., 2005]), this will confound the sex differences in a cohort with a wide age range. If examined in the elderly, sexual difference in volumetric measures of the brain is prone to be affected by lesions that are prevalent in old age, e.g., lacunes and white matter hyperintensities. In the current study, we performed the investigations in a community-dwelling cohort within a narrow age band. Besides, in our study global as well as voxel wise comparisons of brain volumes did not show any differences in association with age or any age–sex interactions, unlike what has been reported by some researches ([Cowell et al., 1994], [Gur et al., 1999] and [Murphy et al., 1996]). Furthermore, the cohort is in the forties, which is widely believed to be earlier than the age of considerable decline in brain volume. Previous studies suggested that total brain volumes change slightly before age 50 but substantially afterwards ([DeCarli et al., 2005] and [Pfeifferbaum et al., 1994]). We therefore consider this to be a suitable sample to examine sex differences and as far as we know, this is the first study addressing sex differences in brain morphometry in a middle-aged population using the VBM method.

Sex dimorphism in GM is subject to the influence of various factors. There is substantial evidence showing that age-related brain decline is sex- and region-specific, although the results are inconsistent. Sex differences of brain volumes loss with ageing were not detected in a longitudinal study (Tang et al., 2001), as well as a cross-sectional study (Raz et al., 2003). When regional brain volumes were examined, men showed a steeper volume loss in frontal and temporal lobes (Murphy et al., 1996), and the globus pallidus (Gunning-Dixon et al., 1998), with relatively stable hippocampus and parietal lobes volumes (Murphy et al., 1996), but not all reports were consistent with these findings ([Raz et al., 2004] and [Xu et al., 2000]). Also, men had a stronger correlation between age and decrease in GM of dorsolateral prefrontal cortices than women (Gur et al., 2002b).

Contrastingly, women showed steeper age-related decline in the caudate and the effect was stronger in the right

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Appendix A. Supplementary data

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Microsoft Word file 1.

Table S1. Comparisons of global volumetric measures between two scanners

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