

Gender difference analysis of cortical thickness in healthy young adults with surface-based methods

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We have examined gender differences of cortical thickness using a 3-D surface-based method that enables more accurate measurement in deep sulci and localized regional mapping compared to volumetric analyses. Cortical thickness was measured using a direct method for calculating the distance between corresponding vertices from inner and outer cortical surfaces. We normalized cortical surfaces using 2-D surface registration and performed diffusion smoothing to reduce the variability of folding patterns and to increase the power of the statistical analysis. In stereotaxic space, significant localized cortical thickening in women was found extensively in frontal, parietal and occipital lobes, including the superior frontal gyrus (SFG), superior parietal gyrus (SPG), inferior frontal gyrus (IFG) and postcentral gyrus (PoCG) in the left hemisphere and mostly in the parietal lobe, including the SPG in the right hemisphere. In the temporal lobe, small regions of the left and right caudal superior temporal gyrus (STG) and the left temporal pole showed significantly greater cortical thickness in women. The temporal lobe shows relatively less significant thickening than other lobes in both hemispheres. In native space, significantly greater cortical thickness in women was detected in left parietal region, including SPG and PoCG. No significant local increases of cortical thickness were observed in men in both spaces. These findings suggest statistically significant cortical thickening in women in localized anatomical regions, which is consistent with several previous studies and may support a hypothesis of sexual dimorphism.

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Introduction

Sexual dimorphism in brain morphology comparing brain tissue volume and brain tissue composition of the cerebrum has

been reported. Many previous quantitative magnetic resonance imaging (MRI) studies of brain volume have shown that, while gray matter (GM), white matter (WM) and brain size are smaller in women than in men—even after statistical control for sexual dimorphism in body size (Passe et al., 1997; Peters, 1991; Raz et al., 2004)—the relative proportions of GM tissue volume were higher in women (Allen et al., 2003; Gur et al., 1999). Regional sexual dimorphism and higher GM/WM ratio in women in anatomical subregions have also been reported using region of interest (ROI)-based methods (Allen et al., 2003; Goldstein et al., 2001; Nopoulos et al., 2000). Regions of significant sexual dimorphism in ROI studies have not been consistent because of intra- and interrater reliability issues and different ROI definitions. Voxel-based morphometry (VBM) (Ashburner and Friston, 2000), which is a fully automated and more observer-independent method than the ROI method, has revealed a significantly higher GM concentration in women in several cortical areas (Good et al., 2001; Verchinski et al., 2000). Recently, greater local volume of cortical GM in women was reported using a voxel-based measure of 3-D cortical surface (Luders et al., 2005). Previous reports have assumed that sexual dimorphism could be due to several factors, including geometric laws governing the relationship between size and shape (Gur et al., 1999), functional differences (Schlaepfer et al., 1995; Yurgelun-Todd et al., 2002) or differences in hormonal exposure (Nopoulos et al., 2000). However, these volumetric methods have difficulty suggesting accurate measurement of GM morphology and localization in the sulcal regions where the fine details of anatomy are often obscured by a partial volume effect. Cortical thickness measurement using cortical surface has been suggested in studies of GM morphometry as a strategy for overcoming the limitation of volumetric analyses (Fischl and Dale, 2000; Kabani et al., 2001). Cortical thickness analysis performed at the nodes of a 3-D polygonal mesh has the advantage of providing a direct quantitative index of cortical morphology. In contrast to volumetric analyses, cortical thickness measured from the cortical surfaces differentiates between cortices of opposing sulcal walls within the same sulcal bed, enabling

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more precise measurement in deep sulci and analysis of the morphology as a cortical sheet.

The purpose of this study was to investigate the gender difference of cortical thickness in young adults using an advanced surface-based method for more precise thickness measurement of the complex cerebral cortex structure and localized regional mapping. Cortical thickness was measured in stereotaxic space and native space to consider the influences of brain size normalizations on gender differences in morphological features. Since extracting a model of the cortical surface is difficult and a robust procedure for measuring cortical thickness using the 3-D surface model has only been established recently (Kabani et al., 2001; Lerch and Evans, 2005), as far as we know, this is the first study of gender effects in cortical thickness using a cortical surface model. To compare measures of cortical GM thickness from homologous cortical regions across subjects and to increase the power of the statistical analysis, we reduced the large anatomical variability using nonrigid surface-based registration normalization of only the cortical surface treated as a 2-D manifold (Fischl et al., 1999; Vaillant and Davatzikos, 1999; Van Essen et al., 1998).

Materials and methods

Subjects

Fifty-two normal right-handed young Korean subjects (31 men, 21 women) were recruited at Seoul National University Hospital. The age between two groups was well matched: men (mean (SD): 26.9 (6.0) years, range: 18–42 years), women (24.8 (4.3) years, 19–36 years). Annett's hand-preference questionnaire was used to evaluate the handedness of volunteers (Annett, 1970).

Image acquisition and preprocessing

Three-dimensional T1-weighted spoiled-gradient echo MR images for all subjects were acquired using a 1.5 T SIGNA Scanner (GE Medical Systems, Milwaukee, WI). Imaging parameters were as follows: 1.5 mm sagittal slices, echo time 5.5 ms, repetition time 14.4 ms, number of excitations 1, rotation angle 20°, field of view 21 × 21 cm and matrix size 256 × 256.

In order to measure the cortical thickness, several preprocessing algorithms were required (Fig. 1). First, intensity nonuniformity in the raw MR images resulting from magnetic field inhomogeneity was corrected using the N3 algorithm (Sled et al., 1998), so that the corrected volumes could be properly classified into GM, WM and cerebrospinal fluid (CSF). After comparing local histograms of image intensity in different spatial locations, the shift in the intensity histogram due to RF inhomogeneity was identified and corrected. Spatial normalization to a stereotaxic space was performed using a nine-parameter linear registration (Collins et al., 1994). Each subject's brain was classified into WM, GM, CSF and background using a 3-D stereotaxic brain mask and the INSECT (Intensity-Normalized Stereotaxic Environment for Classification of Tissues) algorithm (Zijdenbos et al., 1996, 1998). To reveal CSF in sulci, we utilized a probabilistic classification, which provided combined information on GM and CSF. The probabilistic CSF voxels outlined the sulcal walls.

Cortical surface extraction and measurement of cortical thickness

Cortical surfaces were automatically extracted from each MR volume using the Constrained Laplacian-based Automated Segmentation with Proximities (CLASP) algorithm (Kim et al., 2005), which is an improvement of the conventional Automated

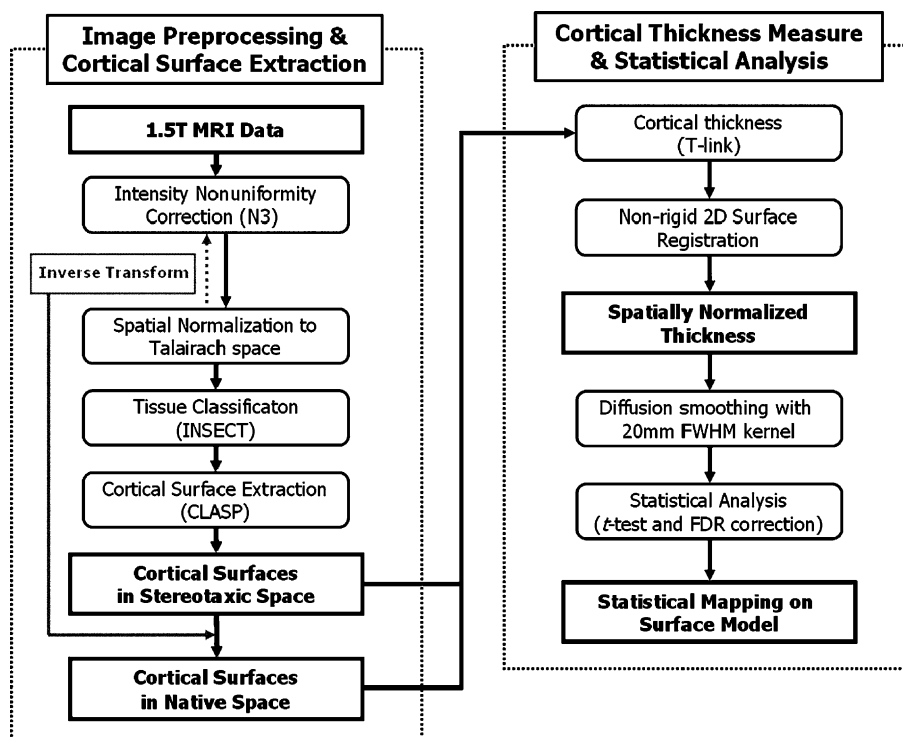


Fig. 1. Procedure for image preprocessing and cortical thickness measurement.

Segmentation with Proximities (ASP) algorithm (MacDonald et al., 2000). CLASP reconstructs the inner cortical surface by deforming a spherical mesh onto the GM/WM boundary. Deformation begins with a low-resolution polyhedral surface, which is then deformed to fit the image data and resampled to contain more triangles. Then, the outer cortical surface is expanded from the inner surface to the boundary between GM and CSF along a Laplacian map, which smoothly increases potential surfaces between WM and CSF. A CSF fraction image is skeletonized to determine the boundary of the outer cortex in buried sulci (Ma and Wan, 2001). We constructed hemispheric cortical surface models, each of which consisted of 81,920 polygons forming high-resolution meshes of discrete triangular elements. Since the cortical surface models were extracted from MR volumes transformed into stereotaxic space, to measure cortical thickness in native space, we applied inverse transformation matrix to cortical surfaces and reconstructed them in native space. Inner and outer surfaces had the same vertex number, and the correspondence of each vertex between surfaces was defined (Fig. 2). Thus, the cortical thickness was easily measured using the t_{link} method of calculating the Euclidean distance between linked vertices on the white matter surface and the GM/CSF intersection surface (Kabani et al., 2001; Lerch and Evans, 2005; MacDonald et al., 2000).

Nonrigid registration of 2-D cortical surfaces

To compare the thickness of corresponding regions of the surface model between the groups, the thickness value was spatially normalized using surface-based 2-D registration. In the

CLASP algorithm, since the cortical surfaces start from a spherical polygon model, the vertices are easily transformed to the spherical model. Two-dimensional surface registration used the sphere to sphere warping algorithm which was described in a framework of optimization. In order to match the pattern of sulcal folding, we used the crown distance transform feature. Vertices of each subject are nonlinearly registered to an average template on the sphere by matching crowns of gyri between subjects using the crown distance transform feature (Robbins, 2003). This algorithm was tuned for chosen parameter values, improving the resulting registrations. Sulcal variability was reduced in all areas of the cortex using optimal parameter values, which was proved by the method of entropy measure (Robbins et al., 2004). Using the transformation, thickness information on the vertices was transformed to a template.

Statistical analysis

Diffusion smoothing, which generalizes Gaussian kernel smoothing, with 20 mm FWHM (full-width half-maximum) was used to increase the signal-to-noise ratio and improve the ability to detect population changes (Chung et al., 2003). Twenty millimeters was chosen as the kernel size to maximize statistical power while still minimizing false positives (Chung et al., 2002; Lerch et al., 2005). Global difference of cortical thickness between men and women was examined with an independent sample t test using the mean value of the thickness of the whole vertex. Localized regional differences of cortical thickness were also analyzed using a t test. As stated above, data from all subjects were normalized to an

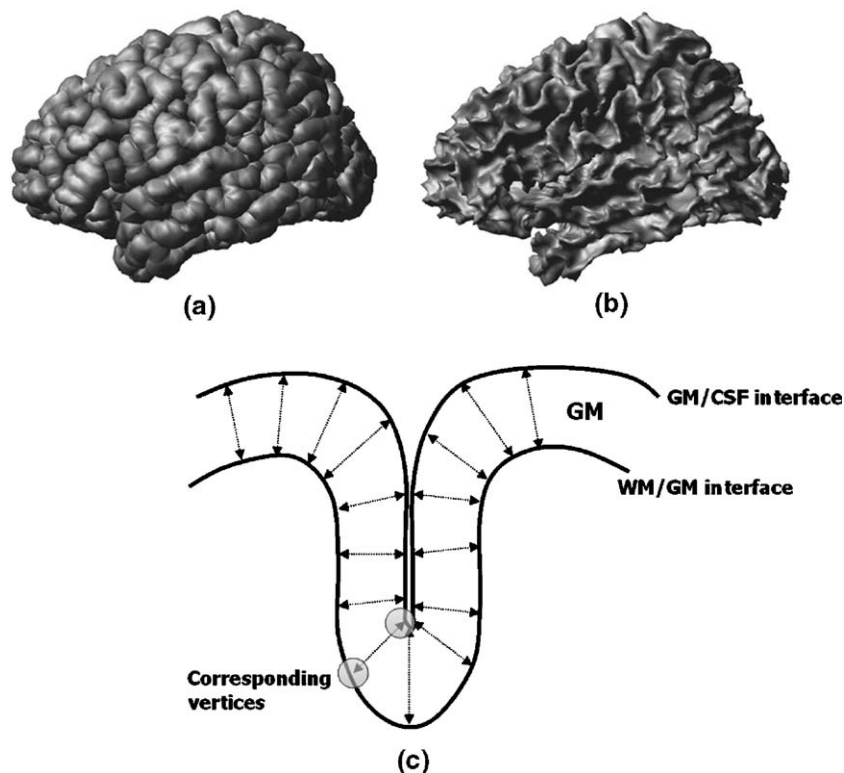


Fig. 2. GM/CSF boundary (a) and GM/WM boundary (b) surfaces automatically extracted using Constrained Laplacian-based Automated Segmentation with Proximities (CLASP) algorithm. Inner and outer surfaces of the cerebral cortex have the same vertex number, and the correspondence of each vertex between surfaces is defined (c). The cortical thickness was measured using the t_{link} method, calculating the Euclidean distance between corresponding vertices on the inner and outer surfaces.

Table 1
Effects of gender-related differences in mean cortical thickness

		Men	Women	<i>t</i>	Sig. (2-tailed)
Cortical thickness in stereotaxic space (mm)	Left	3.481 ± 0.179	3.651 ± 0.189	−3.292	0.002
	Right	3.520 ± 0.155	3.627 ± 0.167	−2.357	0.022
Cortical thickness in native space (mm)	Left	3.247 ± 0.174	3.282 ± 0.159	−0.821	0.416
	Right	3.282 ± 0.159	3.263 ± 0.134	0.471	0.640
Asymmetry index		−0.0115 ± 0.0375	0.0065 ± 0.0274	−1.884	0.065

Statistical significance levels are based on independent sample *t* tests. Women showed greater global cortical thickness of both hemispheres compared with men in stereotaxic space. Significant differences between genders in both hemispheres were not revealed in native space. Hemispheric asymmetry of cortical thickness tended to differ between genders, but this difference was not statistically significant.

average template, and each vertex between surfaces was related. The statistical analysis of regional cortical thickness was performed based on a vertex-by-vertex procedure, and a statistical map of differences in cortical thickness between men and women was constructed on a surface model. There are 40,962 vertices in cortical surface model, and correction of the thresholds for multiple comparisons was needed to control the false-positive rate. The false discovery rate (FDR)-controlling procedure for multiple comparisons was reported to be effective for the analysis of neuroimaging data (Genovese et al., 2002). We performed FDR correction for multiple comparisons at $P < 0.05$.

Results

The mean cortical thickness across the entire cortex was significantly different between men and women in stereotaxic space, after individual differences in brain size had been removed. The results presented larger global cortical thickness of both hemispheres in women compared with men. Significant differences of mean cortical thickness in both hemispheres were not revealed in native space (Table 1). In stereotaxic space, the left hemisphere showed a greater effective difference of mean cortical thickness

and a lower *P* value than the right hemisphere, which may be attributed to asymmetry of mean cortical thickness in men. The asymmetry index ($2 \times (L - R) / (L + R)$) was measured for investigating the difference of asymmetry in cortical thickness. The asymmetry index is independent of scaling effect of brain size. Men showed a little higher and rightward asymmetry, while women showed leftward asymmetry; however, statistically this asymmetry between men and women was not significant on a *t* test ($P = 0.065$).

In stereotaxic space, mapping the differences of cortical thickness between genders in millimeters revealed most regions of greater thickness in women (Fig. 3). Statistically, regional cortical thickening in women was shown in a map of *t* statistics on an average-surface model (Fig. 4). The critical *t* value was calculated in the specific threshold using the FDR procedure at a *q* value of 0.05. Significant localized cortical thickening in the left hemisphere in women was found extensively in frontal, parietal and occipital lobes, including the superior frontal gyrus (SFG), superior parietal gyrus (SPG), inferior frontal gyrus (IFG) and postcentral gyrus (PoCG). The most significant differences were found in the regions of the SFG (corrected $P < 0.01$) and SPG (corrected $P < 0.001$). In the right hemisphere, significant cortical thickening was found mostly in the parietal lobe, including the

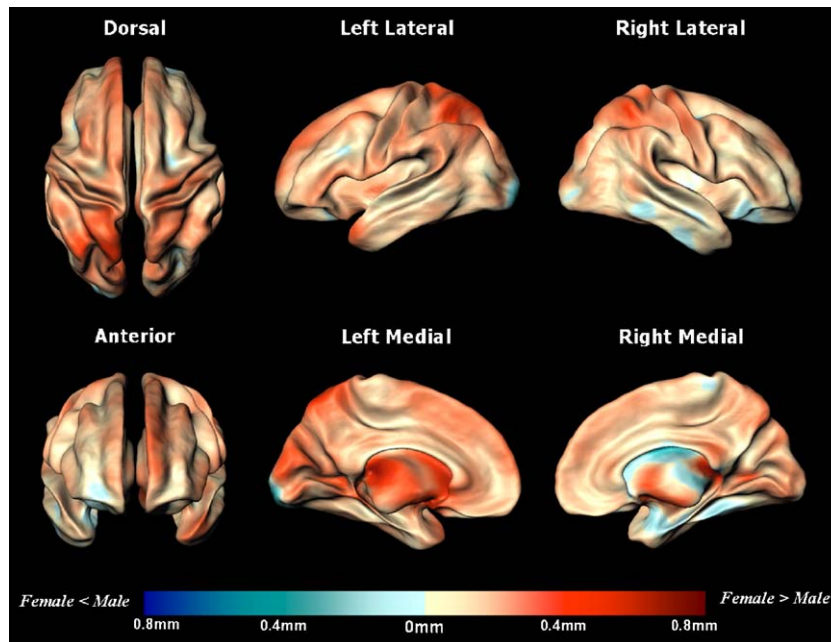


Fig. 3. Gender difference maps of cortical thickness in millimeters in stereotaxic space. The color scale at the bottom represents the difference of the mean cortical thickness in each voxel, with red and yellow indicating regions of greater cortical thickness in women.

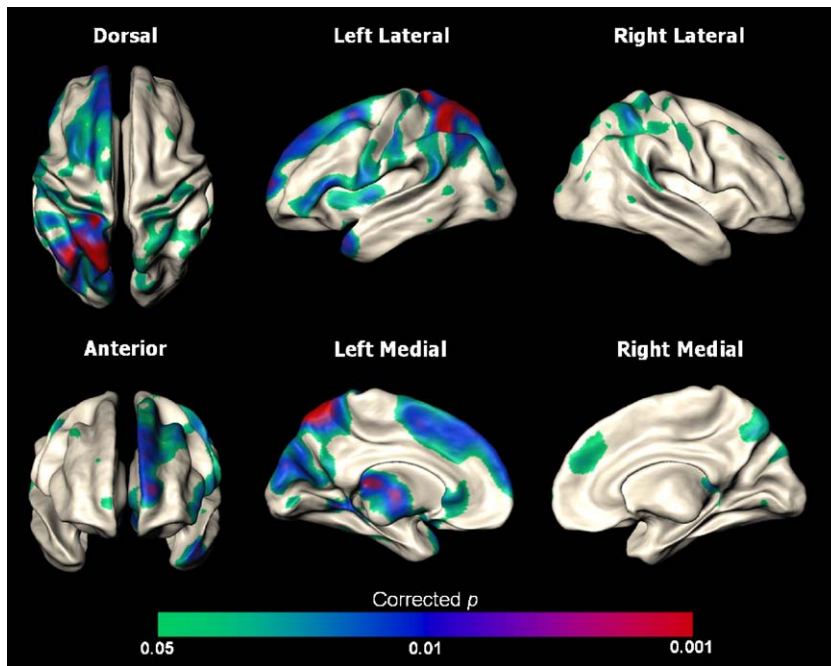


Fig. 4. Corrected t statistical maps showing greater cortical thickness in women in stereotaxic space. Significantly greater cortical thickness in women was found extensively in the left hemisphere frontal, parietal and occipital lobes, including the superior frontal gyrus (SFG), superior parietal gyrus (SPG), inferior frontal gyrus (IFG) and postcentral gyrus (PoCG). In the right hemisphere, significantly greater cortical thickness was found mostly in the parietal lobe, including the SPG, with higher significant difference than in other regions. In the temporal lobe, only small areas of the left and right caudal superior temporal gyrus (STG) and left temporal pole (TP) showed significantly greater cortical thickness in women.

SPG with a higher significant difference (corrected $P < 0.01$) than in other regions. The temporal lobe showed relatively less significant results than other lobes in both hemispheres, except for small regions of the left and right caudal superior temporal gyrus (STG) and left temporal pole (TP). Localized mapping of cortical thickness also showed that gender differences were detected more significantly and extensively in the left hemisphere.

When the brain sizes of men and women were preserved, the differences of cortical thickness between genders were observed in native space. Some regions showed greater cortical thickness in men; however, the differences of thickness values in millimeters were slight (Fig. 5). In native space, statistical analysis demonstrated no significant local increases of cortical thickness observed in men. Significantly greater thickness in women was shown in

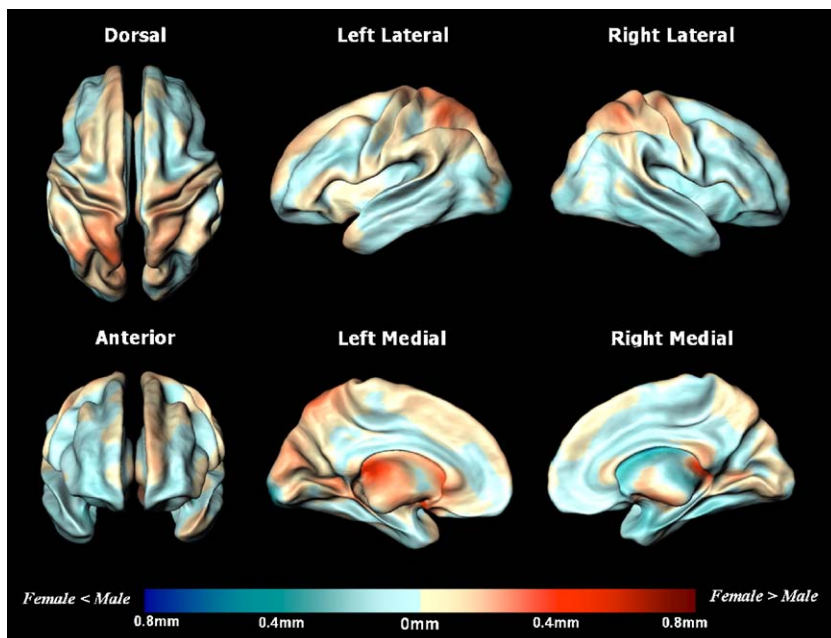


Fig. 5. Gender difference maps of cortical thickness in mm in native space. The color scale at the bottom represents the absolute difference of the mean cortical thickness in each voxel with red and yellow indicating regions of greater cortical thickness in women.

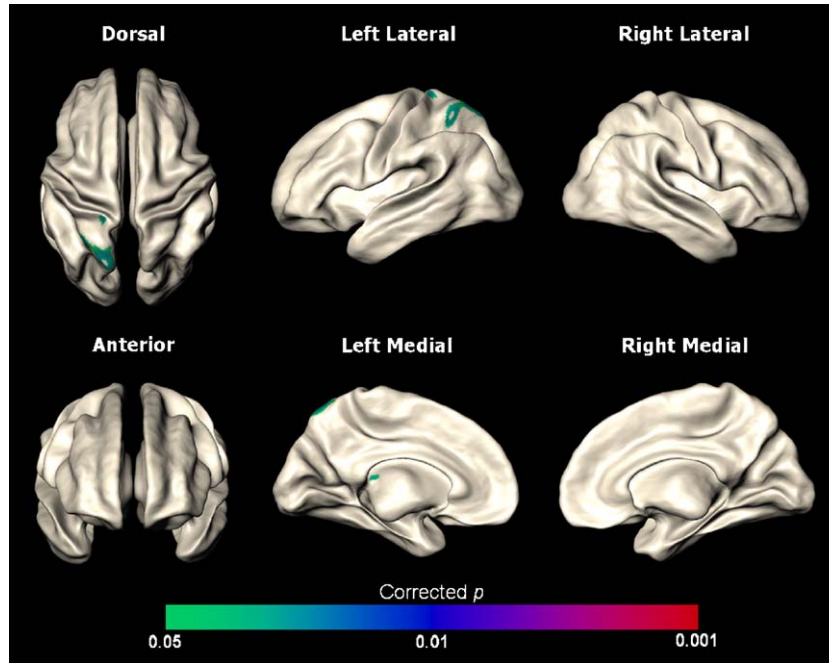


Fig. 6. Corrected t statistical maps showing greater cortical thickness in women in native space. Significantly greater cortical thickness in women was found in the left parietal region, including SPG and PoCG, although brain size is smaller in women than in men.

SPG and PoCG in left hemisphere (corrected $P < 0.05$), although brain sizes of men and women were not normalized (Fig. 6).

Discussion

This study analyzed gender differences of cortical thickness in stereotaxic and native space. Surface mapping analyses of cortical thickness in both spaces, considering the influences of brain size normalization, have not been proposed in previous gender difference analyses. The analyses detected significant global and regional greater cortical thickness in women, while no significant thickening was observed in men. When the images were transformed into stereotaxic space using a nine-parameter (translation, rotation and scaling) linear registration, inter-individual differences in brain size were removed owing to scaling factor. Gender effects influence brain size accounting for larger male and smaller female brains on average. While earlier studies have reported larger brain size and volumes of GM and WM in males (Good et al., 2001; Luders et al., 2005; Passe et al., 1997; Peters, 1991; Raz et al., 2004), GM/WM ratio and GM percentages relative to total brain volume irrelevant to brain size were higher in females (Allen et al., 2003; Goldstein et al., 2001; Gur et al., 1999; Luders et al., 2005; Nopoulos et al., 2000). In stereotaxic space, gender difference analysis aimed to detect regional differences in cortical thickness relative to cerebrum size and study sex effects in cortex structure excluding the effect of brain size. It was coherent with several previous analyses about GM/WM ratio. Previous VBM studies and others of gender difference were performed in a scaled standard space (Good et al., 2001; Luders et al., 2005; Verchinski et al., 2000). Native space approach without controlling for brain size differences revealed the real differences between men and women in cortical thickness. Statistical analyses in both spaces yielded significant gender differences in cortical thickness. On account of smaller brain size and larger scaling effect in women in image

normalization, statistically significant region in stereotaxic space showing greater cortical thickness in women was larger than the region in native space. However, as can be seen in difference maps of cortical thickness and statistical maps, the pattern of gender differences was consistent in both spaces. Statistically significant regions in stereotaxic space were nearly the same to reddish regions reflecting greater mean cortical thickness in female in native space (Figs. 4 and 5).

The results in stereotaxic space showed that the ratio of cortical thickness in specific regions relative to cerebrum size was higher in women than in men and were consistent with previous reports of a higher percentage of GM volume (Allen et al., 2003; Goldstein et al., 2001; Gur et al., 1999; Nopoulos et al., 2000) and greater GM concentration in women (Good et al., 2001; Luders et al., 2005; Verchinski et al., 2000). Using statistical analysis on a vertex-by-vertex basis, we also found localized regional differences of cortical thickness. The temporal lobe showed less significant difference compared with other lobes in both hemispheres, except for a small region of the left and right caudal STG and the left TP. The data were in agreement with previous volumetric studies that showed relatively less GM volume in the temporal lobe in women (Allen et al., 2003; Goldstein et al., 2001). Another previous study using volumetric ROI analyses reported higher relative GM volumes in the right parietal region, suggesting that the X chromosome may be involved in determining some aspects of relative tissue composition (Nopoulos et al., 2000). We found that cortical thickening in women was detected mostly in the right-hemisphere parietal lobe. Previous VBM studies also found extensively greater GM concentration in women (Good et al., 2001; Verchinski et al., 2000).

When brain size was not scaled, the results showed the actual differences of cortical thickness between genders. Significant differences of global mean cortical thickness in both hemispheres were not revealed in native space. These results were consistent with previous study which reported no gender differences of mean

cortical thickness in young adults (Salat et al., 2004). In regional statistical analysis, no regions showed significantly greater cortical thickness in men. Interestingly, significantly greater cortical thickness in women was detected in the left parietal region, including SPG and PoCG, although brain size is smaller in women than in men. The left parietal region also showed highly significant cortical thickening in women in stereotaxic space. The analyses in native space intensified the pattern of gender differences in cortical thickness which were revealed in stereotaxic space in this study and another previous study (Luders et al., 2005). No significant differences of mean cortical thickness and significant small region of greater cortical thickness in women in native space could corroborate previous studies suggesting that differences in brain size and GM/WM ratio between males and females were primarily attributable to WM volume (Allen et al., 2003; Passe et al., 1997).

Several factors could influence the localized gender differences of cortical thickness. Cortical thickening could compensate for a smaller intracranial space in women (Gur et al., 1999; Luders et al., 2004). Findings of regionally greater neuronal densities in women could support this hypothesis (Witelson et al., 1995). Differential exposure to steroid sex hormones during brain development could also produce regional differences in GM composition (Goldstein et al., 2001). Our study showed greater GM thickness in the frontal region in women, including the SFG, and less significant differences in temporal regions that are homologous with those identified in animal studies showing high or low levels of sex steroid receptors, and these data agreed with previous reports (Goldstein et al., 2001). Gender effects of cortical thickness could have a relationship with behavioral and cognitive functional differences (Schlaepfer et al., 1995; Yurgelun-Todd et al., 2002). A previous study found that women have improved language skills and greater GM volumes in regions that govern language, such as the STG, dorsolateral prefrontal cortex and IFG (Schlaepfer et al., 1995). We also detected greater regional cortical thickness in women in the left IFG and STG of both hemispheres. The data in this study indirectly suggest a relationship between cortical thickness in specific regions and functional organization. In future studies, analyzing gender differences by relating functional processes and cortical thickness could clarify this issue.

In this study, the left hemisphere showed greater differences between genders than the right hemisphere. We investigated the gender difference in the asymmetry of mean cortical thickness between hemispheres. In general, structural and functional hemispheric asymmetry has been assumed to be more pronounced in men than in women through many previous studies (Amunts et al., 2000; Kovalev et al., 2003; Wisniewski, 1998). Although the value of the asymmetry index in each group was small and statistical difference in asymmetry between genders was not significant in this study, men showed a little higher asymmetry of global cortical thickness (rightward asymmetry) than women. A greater number of subjects would increase the statistical power of a further study, and statistical analysis based on a vertex-by-vertex procedure between hemispheres might detect localized regional gender differences in asymmetry.

The technique of 3-D parametric surface modeling overcomes the limitations of volumetric segmentation and represents complex sulcal structures. We reconstructed cortical surfaces using the CLASP algorithm, which improves the performance of representing folded gyri using partial volume information and measured cortical thickness in deep sulcal regions more reliably (Kim et al.,

2005). However, errors in the cortical surface model still exist in folded regions because of the limit of the resolution in volume images. The t_{link} method, which calculates the distance between corresponding vertices from inner and outer surfaces, was used to measure cortical thickness (MacDonald et al., 2000). Previous studies evaluated the precision of several algorithms (Fischl and Dale, 2000; Jones et al., 2000; MacDonald et al., 2000) and suggested that t_{link} is the simplest and most precise method (Lerch and Evans, 2005). Nonrigid registration of 2-D cortical surfaces (Robbins, 2003; Robbins et al., 2004) and diffusion smoothing (Chung et al., 2003) with 20 mm FWHM was performed to improve statistical power (Chung et al., 2002; Lerch et al., 2005). Surface-based registration can achieve a higher performance than volumetric registration to reduce the large variability of cortical structure since the inherent geometry of the cortex is that of a 2-D sheet. In a functional study, surface-based alignment also provided more precise localization of functional foci than 3-D volumetric registration (Desai et al., 2005). Based on this robust procedure, this study has the advantage of automatically providing a more reliable localized map over the whole surface. In case of gender difference analysis of cortical thickness in native space, the regional mapping and analysis detected the localized cortical thickening in women, although the mean cortical thickness across the entire cortex was not significantly different between genders. GM thickness measurement and localization of gender differences of cortical thickness were performed more precisely in deep folded regions, compared with previous volumetric analyses. We can confirm that statistical mapping near the central sulcus differentiated between opposing sulcal walls, the PoCG and the precentral gyrus (PreCG) (more significant in the PoCG than the PreCG), while a previous study showed obscure local mapping in the same regions (Luders et al., 2005).

Conclusion

We investigated gender differences of cortical thickness using a cortical surface representing folded sulcal structure. Cortical thickness was measured as the distance between linked vertices from inner and outer cerebral surfaces. Global gender difference of cortical thickness was observed, and regionally greater cortical thickness was detected in women, mostly in the left frontal, parietal and right parietal regions and other small regions in stereotaxic space. In native space, significantly greater cortical thickness in women was detected in left parietal region. Our data support several previous studies and the hypothesis of sexual dimorphism.

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