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Brain Size and Cortical Structure in the Adult Human Brain

Kiho Im[1], Jong-Min Lee[1], Oliver Lyttelton[2], Sun Hyung Kim[1], Alan C. Evans[2] and Sun I. Kim[1]

[1]Department of Biomedical Engineering, Hanyang University, Seoul, 133-605 South Korea and [2]McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, Quebec, H3A 2B4 Canada

We investigated the scale relationship between size and cortical structure of human brains in a large sample of magnetic resonance imaging data. Cortical structure was estimated with several measures (cortical volume, surface area, and thickness, sulcal depth, and absolute mean curvature in sulcal regions and sulcal walls) using three-dimensional surface-based methods in 148 normal subjects (*n* [men/women]: 83/65, age [mean ± standard deviation]: 25.0 ± 4.9 years). We found significantly larger scaling exponents than geometrically predicted for cortical surface area, absolute mean curvature in sulcal regions and in sulcal walls, and smaller ones for cortical volume and thickness. As brain size increases, the cortex thickens only slightly, but the degree of sulcal convolution increases dramatically, indicating that human cortices are not simply scaled versions of one another. Our results are consistent with previous hypotheses that greater local clustering of interneuronal connections would be required in a larger brain, and fiber tension between local cortical areas would induce cortical folds. We suggest that sex effects are explained by brain size effects in cortical structure at a macroscopic and lobar regional level, and that it is necessary to consider true relationships between cortical measures and brain size due to the limitations of linear stereotaxic normalization.

Keywords: cortical thickness, MRI, scaling exponent, sex effect, sulcal convolution, sulcal depth

Introduction

Brain size has a close relationship to brain structure. The number of neurons and glial cells is increased in large brains (Pakkenberg and Gundersen 1997; Samuelsen et al. 2003; Larsen et al. 2006), and as such introduces the problem of how the brain maintains the proportion of connections that each neuron has with others (Kaas 2000). To keep efficient cortical function, brain structure is optimized to follow the minimal axon length principle, which assumes that the brain tries to save energy and time in cortical networks (Cherniak 1995; Kaas 2000; Karbowski 2003; Klyachko and Stevens 2003; Laughlin and Sejnowski 2003). This optimization can cause macroscopic changes of cortical geometry according to brain size. The relative proportion of cortical gray matter (GM) volume, surface area, and cortical thickness are not constant in response to the change of brain size in mammalian brains, meaning that the cortical geometry of large brains is not simply a scaled-up version of small brains (Frahm et al. 1982; Hofman 1989, 1991; Prothero 1997a, 1997b; Zhang and Sejnowski 2000; Changizi 2001; Finlay et al. 2001; Laughlin and Sejnowski 2003). This relationship between brain size and cortical structure has been interpreted as holding important clues for understanding the principles underlying brain development (Zhang and Sejnowski 2000; Changizi 2001; Laughlin and Sejnowski 2003).

Previous studies have investigated the relationships between brain size and cortical structure in the human brain. In an imaging study, the correlation between brain size and GM proportion was negative in the healthy human brain, with larger brains exhibiting relatively smaller proportions of GM (Luders et al. 2002). However, that study was confined to gross volumetric analysis, and the measure of GM volume was insufficient for definitive representation of cortical structure. Recently, various cortical measures using sophisticated three-dimensional (3-D)–based methods, such as cortical thickness, curvature-based cortical gyrification, and sulcal depth have been suggested to analyze cortical structure (Kochunov et al. 2005; Lerch and Evans 2005; Luders, Thompson, et al. 2006; Rettmann et al. 2006; Van Essen et al. 2006). However, to the best of our knowledge, there has not been an imaging study that has investigated the relationship between brain size and these cortical measures.

A postmortem study investigated the change of cortical thickness with brain size, but no significant correlation was found. A large cortical volume was accompanied by a major increase of cortical surface area and a markedly smaller increase of cortical thickness (Pakkenberg and Gundersen 1997). In another postmortem study, increases in the gyrification index (GI) (the ratio between the length of the pial contour and the length of the external contour in a coronal section) were associated with brain size for the 1st stage of brain growth (Armstrong et al. 1995). However, after that time, a constant degree of cortical folding was shown, meaning that brain size effects on cortical folding were not detected in normal adult brains. Methodologically, the cortical measurements estimated on 2-dimensional (2-D) slices in postmortem data are dependent on brain orientation and the direction of slicing. They are less accurate than 3-D surface-based measurements that respect the topology of the cortical surface. Moreover, although the GI and cortical surface area measurements reflect the overall degree of cortical folding (Zilles et al. 1988; Wiegand et al. 2005; Luders, Thompson, et al. 2006), these single measurements do not allow us to distinguish increased folding caused by cortical shape with deeper sulci as distinct from that with more convolutions. It is important to provide more information about cortical folding shape with several measurements because then we can suggest more detailed biological and neurodevelopmental implications.

The aim of this study was to investigate the relationships between brain size and cortical structure using 3-D analytical techniques and cortical surfaces on normal adult human brains in a large sample of magnetic resonance imaging (MRI) data.

We measured cortical volume, thickness, and folding shape to reflect cortical structure. Cortical folding shape is so complex that several measures were employed to provide definite representations (cortical surface area, sulcal depth, and absolute mean curvature in sulcal regions and sulcal walls).

Materials and Methods

Data Acquisition

This study used the ICBM 152 data set, which has been described elsewhere (Watkins et al. 2001). The subjects scanned were 152 unselected normal volunteers. Each subject gave written informed consent; the Research Ethics Committee of the Montreal Neurological Institute (MNI) and Hospital approved the study. Each subject was scanned using MRI on a Phillips Gyroscan 1.5-T superconducting magnet system. The sequence that was used yielded T_1-weighted images (3-D fast field echo scan with 140–160 slices, 1-mm isotropic resolution, time repetition = 18 ms, time echo = 0 ms, flip angle = 30°). Out of the 152 subjects, we excluded 4 subjects due to errors of surface modeling. The final sample consisted of 83 men and 65 women. Their age ranged from 18 to 44 years (mean ± SD: 25.0 ± 4.9 years). On a short handedness questionnaire, 15 subjects were dominant for left-handed use on a number of tasks and 124 subjects preferred to use their right hand. The handedness of the scan of 9 subjects was not known.

Image Processing

Images were processed using the standard MNI anatomical pipeline. The native MR images were normalized into a standardized stereotaxic space using a linear transformation and corrected for intensity nonuniformity (Collins et al. 1994; Sled et al. 1998). The registered and corrected volumes were classified into white matter (WM), GM, cerebrospinal fluid, and background using an advanced neural-net classifier (Zijdenbos et al. 1996). The hemispheric surfaces of the inner and outer cortex, which consisted of 40,962 vertices, were automatically extracted using the Constrained Laplacian-Based Automated Segmentation with Proximities algorithm (Kim et al. 2005). The accuracy of this technique was recently demonstrated in a phantom-based quantitative cross-validation study, showing the best geometric and topologic accuracies and mesh characteristics of the cortical surface (Lee et al. 2006). Because MR volumes were transformed into stereotaxic space to extract cortical surface models, in order to estimate cortical structure in native space, we applied an inverse transformation matrix to the cortical surfaces (Im, Lee, Lee, et al. 2006).

Automatic Lobe Parcellation of Cortical Surface

For lobar regional analysis, we manually parcellated a surface group template into frontal, temporal, parietal, and occipital lobes using SUMA (http://afni.nimh.nih.gov). The surface group template is an unbiased, high-resolution iterative registration template from a group of 222 subjects' hemispheres (Lyttelton et al. 2007). Each individual cortical surface and iterative group template was aligned using 2-D surface registration that performs sphere-to-sphere warping. Then the lobar labels were taken at each vertex in individual surface data (Fig. 1). Automatic surface parcellation for lobar regions using a surface registration algorithm has been performed efficiently in a previous study that extracted the lobar regional cortical thickness (Yoon et al. 2007). In this study, we employed an improved surface registration algorithm and an unbiased iterative group template showing enhanced anatomic detail (Lyttelton et al. 2007).

The validation study for automatic lobe parcellation was performed with a randomly selected sample of 10 left cortical surfaces that had been previously used and manually parcellated (Im, Lee, Yoon et al. 2006). Manual lobe parcellation in our previous study was evaluated, and showed high interrater reliability. To validate the automatic parcellation technique, a similarity index (SI) in each lobar region was measured. The SI is an indicator of geometric and anatomic similarities or differences between 2 regions. The SI was defined as the ratio of twice the common area to the sum of the individual areas (Zijdenbos et al. 1994), and is sensitive to both differences in size and location. When 2 regions by automatic and manual parcellation are similar, the SI will be a high value, close to 1. The average SI values in the parcellated lobar regions of 10 left cortical surfaces were measured and are shown in Table 1. The SI values in all lobar regions were more than 0.9. This means that automatic lobe parcellation using surface registration in the current study is reliable. The SI in the occipital

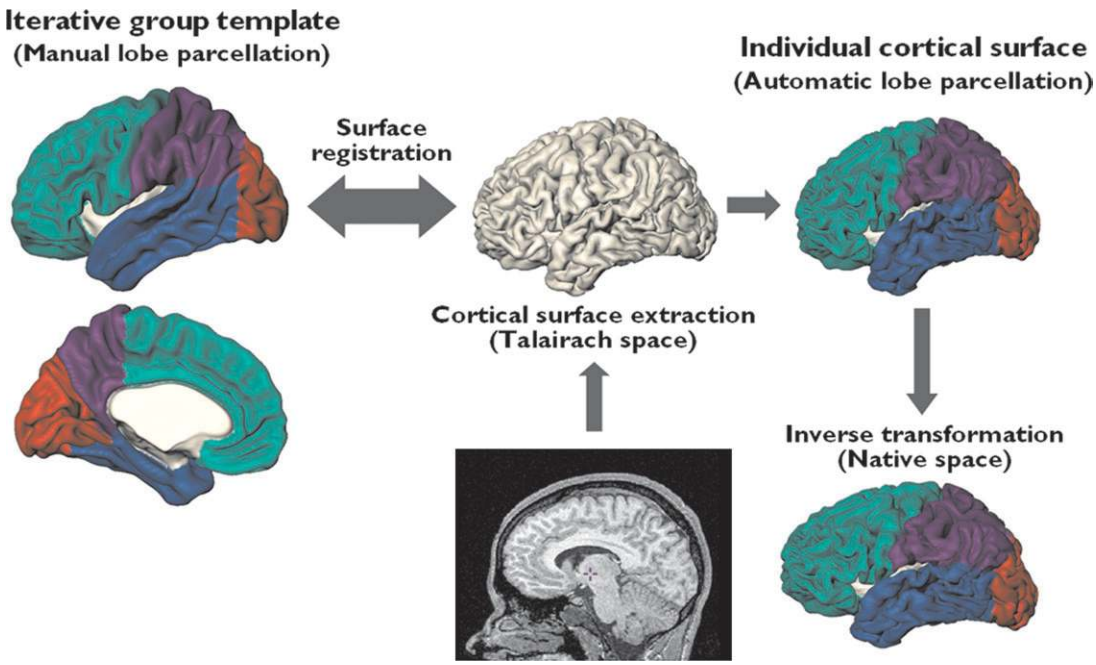

Figure 1. Automatic lobe parcellation for individual cortical surfaces using surface registration. An iterative group template is manually parcellated into frontal, temporal, parietal, and occipital lobes. Each individual cortical surface and the iterative group template are aligned using 2-D surface registration. Lobar labels are taken at each vertex in individual surface data. Then the cortical surface is transformed inversely to native space.

Table 1
Left lobar surface area (cm^2) for automatic and manual parcellation and SI between 2 parcellated regions with 10 cortical surfaces

Region	Automatic parcellation	Manual parcellation	SI
Frontal	387.86 ± 27.12	384.73 ± 29.96	0.98 ± 0.003
Temporal	245.06 ± 20.63	238.50 ± 21.06	0.95 ± 0.015
Parietal	235.18 ± 18.58	245.12 ± 21.58	0.93 ± 0.018
Occipital	139.12 ± 8.66	127.59 ± 12.06	0.91 ± 0.047

region was lower than in other regions because the border of that region is ambiguous and cannot be defined by a definite sulcal line.

Intracranial Volume
Skull growth is determined by brain expansion, which takes place during the normal growth of the brain (Falkner 1977; Sgouros et al. 1999). Thus, in normal adults, intracranial volume (ICV) is closely related to brain size (Hentschel and Kruggel 2004). ICV measurement has been used by many researchers to estimate brain size (Gur et al. 1999; Jenkins et al. 2000; Edland et al. 2002; Luders et al. 2002; Wolf et al. 2003). ICV is defined as the total volume of GM, WM, and cerebrospinal fluid. We calculated the ICV by measuring the volume of voxels within the brain mask. The brain mask was generated using the FMRIB Software Library bet algorithm (Smith 2002). The ICV for 148 subjects ranged from 1.15 to 1.92 ($\times 10^6$ mm^3) (mean ± SD: 1.50 ± 0.15).

Cortical Volume
Extracted inner and outer cortical surfaces in native space were masked to original images. We isolated the voxels of the cerebral cortex that were located between 2 surfaces. The cortical volume was calculated by measuring the volume of the voxels in the whole cortex and in each lobar region.

Cortical Surface Area
We measured cortical surface area, which has been used to suggest an overall degree of folding (Wiegand et al. 2005; Luders, Thompson, et al. 2006). The middle cortical surface lies at the geometric center between the inner and outer cortical surfaces. It provides a relatively unbiased representation of sulcal versus gyral regions. In contrast, the inner cortical surface model overrepresents sulcal regions, and the outer cortical surface model overrepresents gyral regions (Van Essen et al. 2006). We used the middle cortical surface and calculated the surface area in the whole cortex and each lobar region, which was the straightforward sum of the areas of the triangles making up the surface model.

Cortical Thickness
The inner and outer surfaces had the same number of vertices, and there was a close correspondence between the counterpart vertices of the inner and outer cortical surfaces. The cortical thickness was defined as the Euclidean distance between these linked vertices (Lerch and Evans 2005). We measured the averaged value of the thickness in the whole cortex and each lobar region.

Sulcal Depth
We measured sulcal depth, which is an important aspect of cortical shape. Previous studies have reported age- or disease-related changes in sulcal depth, which are thought to be related to WM development (Kippenhan et al. 2005; Kochunov et al. 2005; Rettmann et al. 2006; Van Essen et al. 2006). In order to measure sulcal depth, 1st we overlapped and masked the middle cortical surfaces to the images to isolate inner voxels of the cerebral surface. Then masked volume images were binarized. We performed a 3-D morphological closing operation on the binarized image using a structuring element of spherical shape. The radius of the structuring element was chosen as 10 mm, which is larger than the maximal radius of the sulci. The aim of this step is to close the sulci so that a smooth brain volume results in which the sulci are no longer visible but the overall shape of the brain is retained. We detected the edge of the image with the Laplacian of Gaussian mask and constructed a cerebral hull volume that wrapped around the hemisphere but did not encroach into sulci (Fig. 2*A*). Sulcal depth maps were generated for each individual hemisphere by measuring the 3-D Euclidean distance from each vertex in the middle cortical surface to the nearest voxel on the cerebral hull volume (Fig. 2B). The Euclidean distance as a measure of sulcal depth has been used in previous studies (Van Essen 2005; Van Essen et al. 2006).

Definition of Sulcal Region
To analyze cortical folding shape, we defined sulcal regions from the sulcal depth map of the middle cortical surface. A vertex is defined to be in a sulcal region if its depth is greater than a threshold. We chose 3 mm for the threshold to include true sulcal regions reliably (Van Essen 2005). All vertices on the cortical surface that are deeper than 3 mm were defined as sulcal regions, and other vertices as gyral regions. Figure 2*C* illustrates the reliable representation of sulcal regions for an individual cortical surface. Sulcal depth and absolute mean curvature were measured and averaged for the vertices in sulcal regions for the whole cortex and each lobar region.

Absolute Mean Curvature
Absolute mean curvature was computed at the vertices that lie within sulcal regions in the middle cortical surface (Taubin 1995). The measure of mean curvature on the cortical surface model has been widely used to quantify the complexity of cortical folding (Magnotta et al. 1999; Batchelor et al. 2002; Tosun et al. 2004; Gaser et al. 2006; Rettmann et al. 2006; Tosun et al. 2006). Because mean curvature is susceptible to noise features and small geometric changes of shape, we smoothed the cortical surface model geometrically. The smoothing algorithm changed the 3-D position of each vertex p_i toward the barycenter of its 1st neighbors as 1 step (Toro and Burnod 2003; Im, Lee, Yoon, et al. 2006). At smoothing step $t + 1$, the vertex p_i is defined as a function of its N_i neighbor vertices $V_j(p_i)$ as:

$$p_i^{t+1} = \frac{1}{N_i}\sum_{j}^{N_i} V_j\left(p_i^t\right).$$

Mean curvature was measured on the middle cortical surface after 10 iterations of smoothing, preserving the original folding pattern (Fig. 3) (Im, Lee, Yoon, et al. 2006).

Absolute Mean Curvature on Sulcal Walls
The averaged absolute mean curvature is affected both by the folding sharpness of the sulcal fundus and by convolutions of the sulcal shape (Fig. 4*A*). It could include the effect of sulcal width because the sharpness of the sulcal fundus can be associated with the degree of sulcal widening (Fig. 4*B*). We suggested an additional measurement that estimates the degree of sulcal convolution regardless of the effect of sulcal fundic sharpness in order to differentiate between these scenarios because each might have different biological implications. The basic concept is to extract the areas of the cortex that lie along the sulcal walls and measure the mean curvature for the vertices only in these areas. We define the areas of the sulcal wall as lying between 3 and 4 mm deep, as determined by the sulcal depth map (Fig. 5). Absolute mean curvatures for those areas were measured to reflect the only sulcal convolution.

The Isometric Scaling Relationships between ICV and Cortical Volume, Surface Area, Thickness, Sulcal Depth, and Mean Curvature
If the surface of an object remains geometrically identical as its size increases, we can describe isometric scaling relationships between measurements such as volume, surface, and thickness using mathematical principles. In brain structure, if cortex shape is invariant with respect to brain size, cortical volume should increase proportionally with increasing ICV. Cortical thickness and sulcal depth calculated by the Euclidean distance should scale as the 1/3 power of ICV, and cortical surface area as the 2/3 power. When brain size increases as the

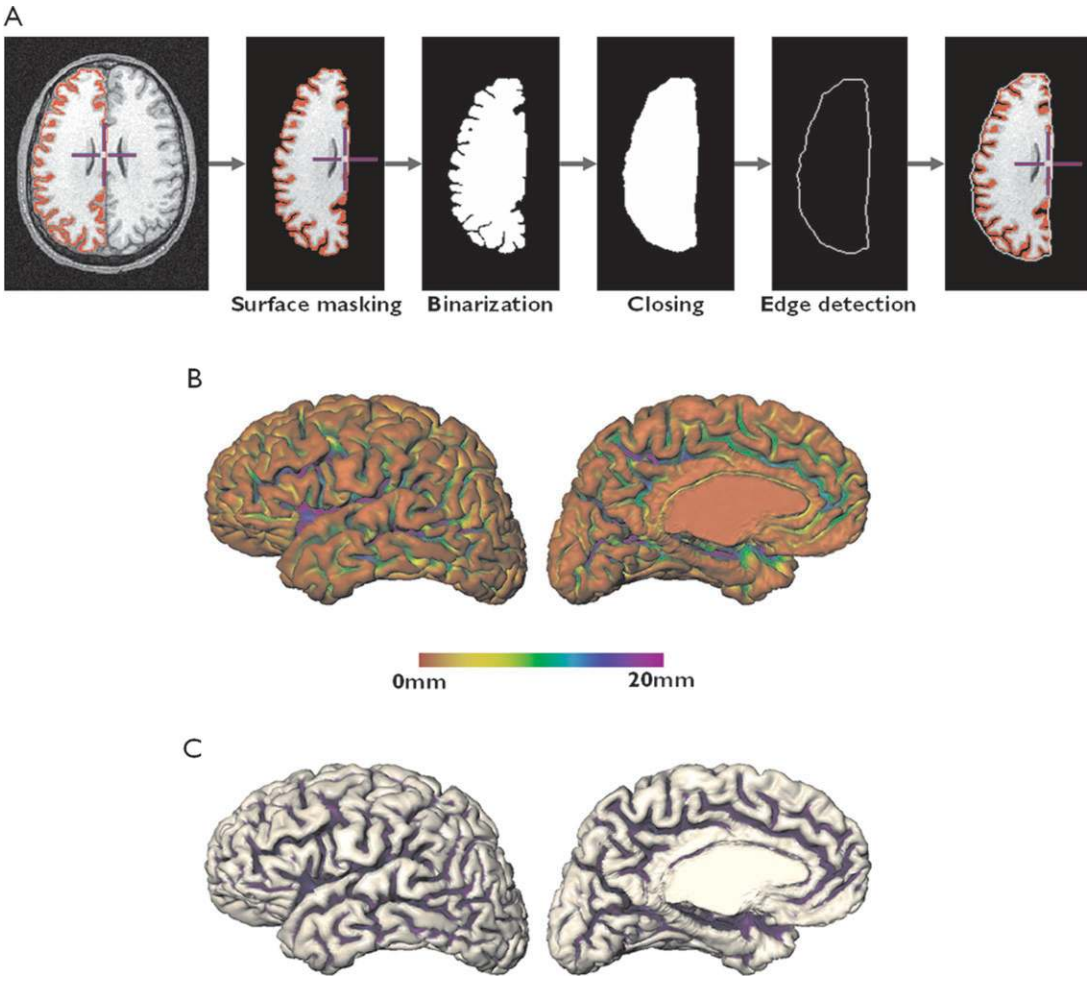

Figure 2. Summary of image processing steps for sulcal depth measure (*A*), and a sulcal depth map on cortical surface of an individual brain (*B*). The vertices on the cortical surface whose depth values are more than 3 mm are defined as sulcal regions (*C*).

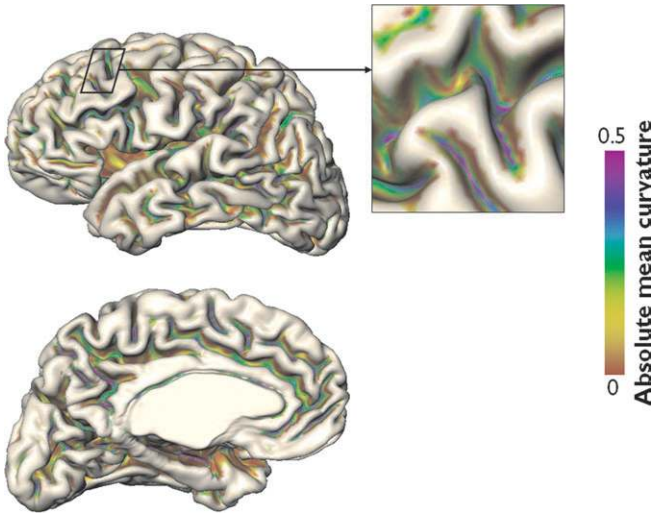

Figure 3. Absolute mean curvatures on the smoothed middle cortical surface of an individual brain preserving the native folding pattern. Darker (purple/blue) areas represent higher absolute mean curvature

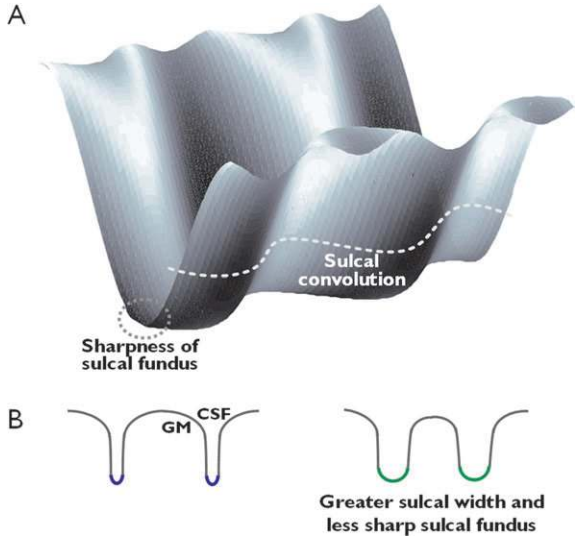

Figure 4. Schematic diagram of sulcal folding. Sulcal folding is affected by both sharpness of the sulcal fundus and sulcal convolution (*A*). The sharpness of sulcal fundus is associated with the degree of sulcal widening. Greater sulcal width can result in less sharp sulcal fundus (*B*).

scaling factor m, discrete mean curvature for a surface mesh (Taubin 1995) is inversely proportional to the size of the mesh, indicating that it scales as $1/m$ times (Tosun et al. 2006). Hence, it should scale with ICV to the power of –1/3. These scaling relationships are presented in Figure 6. However, if cortical structure is not invariant under scaling, empirical scaling relationships will differ significantly from predicted values.

Statistical Analysis

All measurements were computed for the whole cortex and lobar regions (left and right frontal, temporal, parietal, and occipital lobes). To assess the scaling exponents between ICV and the cortical measurements (cortical volume, surface area, thickness, sulcal depth, and absolute mean curvature in sulcal regions and sulcal walls), we transformed the measures logarithmically and performed multiple regression analyses that have been shown in previous allometric analyses (Zhang and Sejnowski 2000; Changizi 2001). The dependent variable was $\log_{10}$ measures, and independent variables were sex (coded as a dummy variable) and $\log_{10}$ ICV (Luders et al. 2002). Age-related changes in microscopic structures (neurons, glial cells, and WM fibers) and WM, GM, and whole brain volumes have been found in human brains (Pakkenberg and Gundersen 1997; Wanifuchi et al. 2002; Marner et al. 2003; Sowell et al. 2003; Pelvig et al. 2007). Therefore, we also used age as an independent variable to control for its effect. In these analyses, regression coefficients are the empirically estimated scaling exponents of ICV. Regression coefficients were compared using t tests with those predicted under the null hypothesis that cortical structure is invariant under scaling. Specifically, the predicted regression coefficients for cortical volume, surface area, thickness, sulcal depth, and mean curvature are 1, 2/3, 1/3, 1/3, and –1/3, respectively.

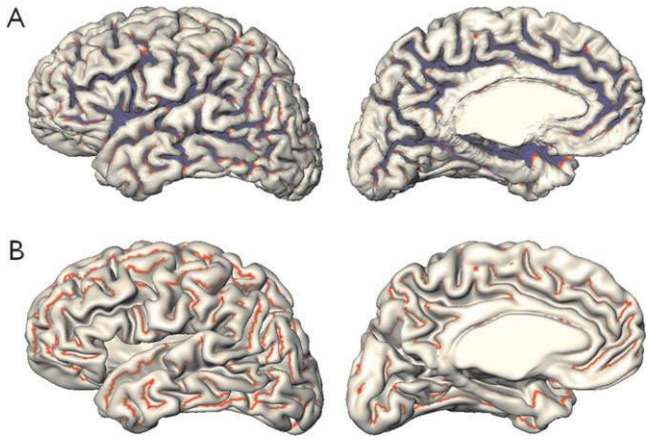

Figure 5. Sulcal wall regions on the cortical surface of an individual brain. The area of sulcal wall is defined as lying between 3 and 4 mm as determined by the sulcal depth map (*A*). Sulcal wall regions are represented on an inflated surface for better visualization (*B*).

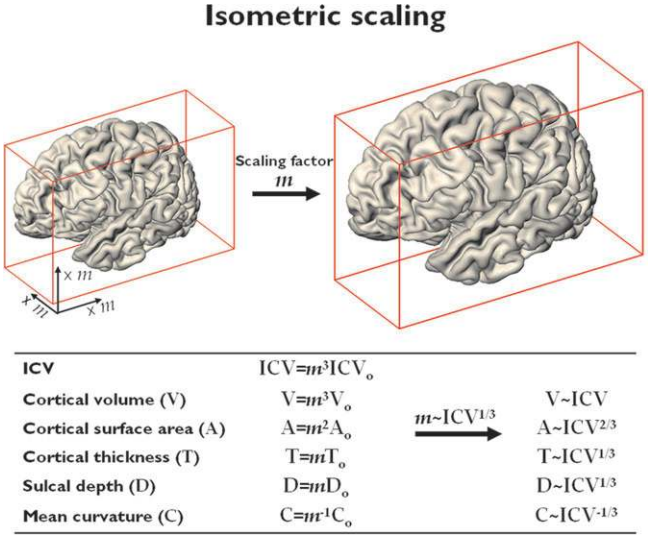

Figure 6. Isometric scaling of cortical volume, surface area, thickness, sulcal depth, and mean curvature with ICV. When brain size scales up with identical cortical shape as the scaling factor, m, predicted scaling exponents are 1, 2/3, 1/3, 1/3, and −1/3 for cortical volume, surface area, thickness, sulcal depth, and mean curvature, respectively.

Results

Regression statistics for the whole cortex are reported in Table 2 along with the statistical results of comparisons between the regression coefficients and predicted scaling exponents. All measures were significantly associated with ICV ($P < 0.0001$), but not with sex. As brain volume increases, cortical volume, surface area, thickness, and sulcal depth increase, and mean curvature decreases. Furthermore, regression coefficients (empirical scaling exponents) for the cortical measures are significantly different from predicted scaling exponents. The regression coefficient for cortical volume was significantly smaller than 1 ($P < 0.0001$). Cortical surface area showed a significantly larger regression coefficient than 2/3 ($P < 0.004$). On the other hand, the coefficient for cortical thickness was significantly smaller than 1/3 ($P < 0.005$). Significantly larger coefficients for absolute mean curvature in sulcal regions ($P < 0.0001$) and sulcal walls ($P < 0.0004$) were found when compared with –1/3. There was no significant difference between the coefficient for sulcal depth and the predicted exponent, 1/3. We provide scatter plots of the logarithm of the cortical measures versus the logarithm of ICV for the whole cortical region, which show data distributions and the differences of slopes between regression coefficients and mathematically predicted coefficients (Fig. 7).

Regression analyses were performed in each lobar region to reveal region specificity. Regression coefficients and statistics of the logarithm of ICV and sex are presented in Table 3.

Table 2
Regression coefficients and statistics for $\log_{10}$ ICV and sex in the whole cortex

Measure		*B*	*t*	*P*
$\log_{10}$ cortical volume	$\log_{10}$ ICV	0.874	32.888	<0.0001
			−4.667 (NH, $B = 1$)	<0.0001
	Sex	0.002	0.745	0.457
$\log_{10}$ surface area	$\log_{10}$ ICV	0.754	25.267	<0.0001
			2.900 (NH, $B = 2/3$)	0.004
	Sex	−0.002	−0.879	0.381
$\log_{10}$ cortical thickness	$\log_{10}$ ICV	0.236	6.994	<0.0001
			−2.853 (NH, $B = 1/3$)	0.005
	Sex	0.003	1.081	0.281
$\log_{10}$ sulcal depth	$\log_{10}$ ICV	0.302	12.060	<0.0001
			−1.240 (NH, $B = 1/3$)	0.217
	Sex	−0.002	−0.805	0.422
$\log_{10}$ absolute mean curvature	$\log_{10}$ ICV	−0.224	−11.820	<0.0001
			5.737 (NH, $B = -1/3$)	<0.0001
	Sex	0.000	−0.134	0.894
$\log_{10}$ absolute mean curvature on sulcal walls	$\log_{10}$ ICV	−0.225	−7.607	<0.0001
			3.600 (NH, $B = -1/3$)	0.0004
	Sex	0.002	0.800	0.425

Note: NH: null hypothesis; *B*: regression coefficient.

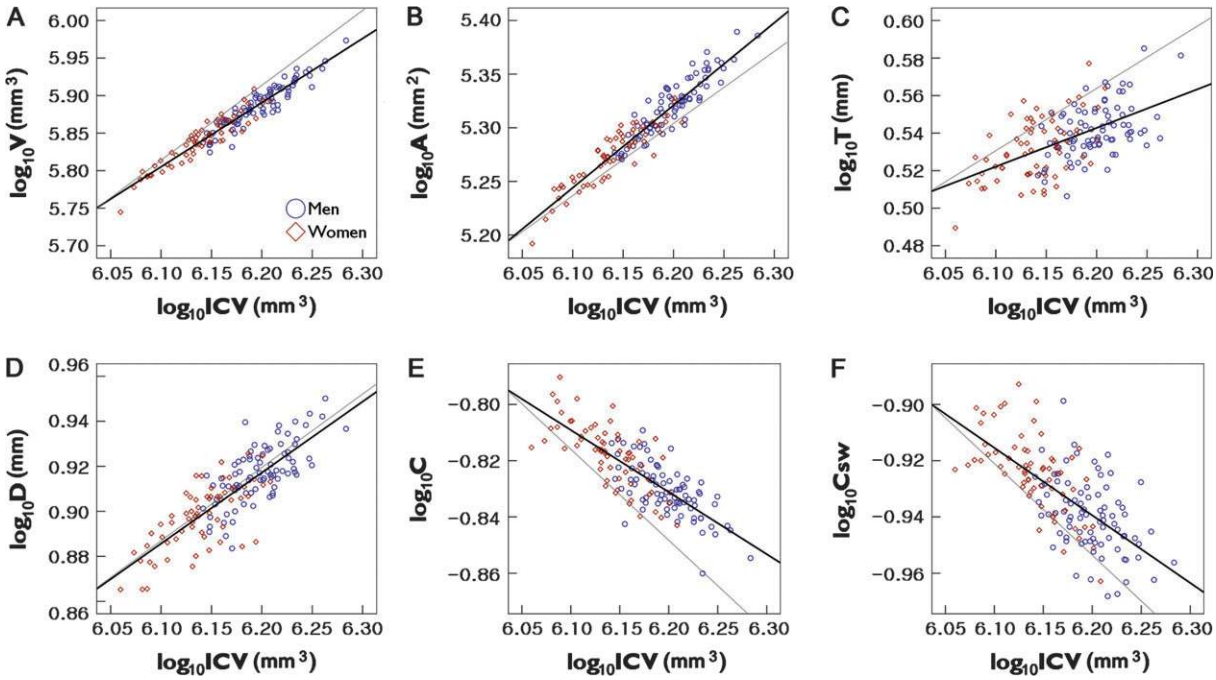

Figure 7. Scatter plots of the logarithm of the cortical volume (*A*), surface area (*B*), thickness (*C*), sulcal depth (*D*), absolute mean curvature (*E*), and absolute mean curvature on sulcal walls (*F*) versus the logarithm of ICV for the whole cortical region. The plots show data distributions and the differences of slopes between regression coefficients (thick black lines) and mathematically predicted coefficients (thin gray lines) (*V*: cortical volume; *A*: cortical surface area; *T*: cortical thickness; *D*: sulcal depth; *C*: absolute mean curvature; C_{sw}: absolute mean curvature on sulcal walls).

Table 3
Regression coefficients and statistics for $\log_{10}$ ICV and sex in lobar regions

Measure			Frontal	Temporal	Parietal	Occipital
$\log_{10}$ cortical volume	$\log_{10}$ ICV	L	0.836[a**,b**]	0.901[a**,b**]	0.880[a**,b**]	0.872[a**,b*]
		R	0.828[a**,b**]	0.902[a**,b*]	0.898[a**,b*]	0.798[a**,b**]
	Sex	L	0.001	0.004	0.001	0.001
		R	0.000	0.004	0.004	−0.002
$\log_{10}$ surface area	$\log_{10}$ ICV	L	0.723[a**]	0.763[a**,b*]	0.823[a**,b**]	0.733[a**]
		R	0.736[a**]	0.729[a**]	0.798[a**,b**]	0.690[a**]
	Sex	L	0.000	−0.001	−0.008	−0.003
		R	−0.002	−0.006	−0.002	0.000
$\log_{10}$ cortical thickness	$\log_{10}$ ICV	L	0.235[a**,b*]	0.204[a**,b**]	0.246[a**,b*]	0.320[a**]
		R	0.220[a**,b**]	0.250[a**,b*]	0.218[a**,b**]	0.248[a**]
	Sex	L	0.002	0.004	0.003	0.007
		R	0.002	0.003	0.005	0.005
$\log_{10}$ sulcal depth	$\log_{10}$ ICV	L	0.257[a**]	0.306[a**]	0.377[a**]	0.357[a**]
		R	0.276[a**]	0.352[a**]	0.266[a**]	0.252[a**]
	Sex	L	−0.004	−0.002	0.001	−0.010
		R	−0.003	−0.005	0.005	−0.003
$\log_{10}$ absolute mean curvature	$\log_{10}$ ICV	L	−0.224[a**,b**]	−0.274[a**]	−0.216[a**,b**]	−0.256[a**,b*]
		R	−0.195[a**,b**]	−0.242[a**,b*]	−0.193[a**,b**]	−0.219[a**,b**]
	Sex	L	0.002	−0.003	0.000	−0.001
		R	0.002	−0.002	−0.002	0.000
$\log_{10}$ absolute mean curvature on sulcal walls	$\log_{10}$ ICV	L	−0.221[a**,b*]	−0.333[a**]	−0.312[a**]	−0.134[b*]
		R	−0.184[a**,b**]	−0.321[a**]	−0.152[a*,b**]	−0.159[a*,b*]
	Sex	L	0.003	−0.005	0.003	0.008
		R	0.007	−0.008	0.003	0.002

Note: $*P < 0.05$, $**P < 0.00625$.
[a]A *t* test of the null hypothesis, *B* (regression coefficient) = 0.
[b]A *t* test of the null hypothesis, $B = 1, 2/3, 1/3, 1/3$, and $-1/3$ for cortical volume, surface area, thickness, sulcal depth, and mean curvature, respectively.

The regression statistics were set to a significance threshold of $P = 0.00625$ to control for multiple comparisons. We consider results with $0.00625 < P < 0.05$ to have a trend toward significance. Most lobar regions showed significant relationships between ICV and cortical measures at the 0.00625 level of *P*. Only absolute mean curvature on sulcal walls, and right parietal, and occipital lobes showed a trend toward significance with a $P < 0.05$, and the left occipital lobe showed no statistical significance, indicating that the absolute mean curvature on sulcal walls is invariant with respect to brain size. Like the whole cortical analysis, when ICV was included as a covariate in the statistical model, there was no significant sex influence on

cortical measures. Smaller coefficients for cortical volume compared with 1 were found in frontal, left temporal and parietal, right occipital ($P < 0.00625$), and right temporal and parietal lobes ($P < 0.05$). The exponents of ICV for surface area were larger than 2/3 in both parietal lobes ($P < 0.00625$) and left temporal lobe ($P < 0.05$). For cortical thickness, we found smaller coefficients than 1/3 in the left temporal, right frontal, and parietal ($P < 0.00625$), and left frontal, parietal, and right temporal lobes ($P < 0.05$). Regression coefficients for sulcal depth were not significantly different from 1/3 in all lobar regions. For absolute mean curvature, larger coefficients compared with −1/3 were observed in the frontal, parietal, and right occipital ($P < 0.00625$), left occipital, and right temporal lobes ($P < 0.05$). Among these lobar regions, the right frontal, parietal ($P < 0.00625$), left frontal, and both occipital lobes ($P < 0.05$) also showed larger coefficients for absolute mean curvature measured on sulcal walls.

Discussion

The Relationships between Brain Size and Cortical Structure in Human Brains

This study investigated the relationships between brain size and several cortical measurements using 148 MRI data sets of normal subjects and showed that human cortices are not simply scaled versions of one another. As expected, larger brains showed significantly larger cortical volume, surface area, thickness, and sulcal depth (exponents larger than 0) and smaller absolute mean curvature (exponents smaller than 0) than smaller brains. However, the cortical measurements did not vary as the predicted power of ICV. The results showed a significantly lower increase of cortical volume (exponent smaller than 1), indicating that the ratio of cortical GM volume to ICV decreases as brain size increases. This result corroborates previous studies investigating the organization of GM in human brains (Luders et al. 2002). Our findings are consistent with the hypothesis that the expansion of WM rather than GM would be favored in larger brains, which show the increased number of neurons and glial cells, to support cortical connectivity (Zhang and Sejnowski 2000; Luders et al. 2002; Samuelsen et al. 2003; Larsen et al. 2006; Pelvig et al. 2007).

Interestingly, the cortex thickened only slightly (exponent smaller than 1/3), but its area increased greatly (exponent larger than 2/3) as brains enlarged. This indicates that the increases in cortical GM volume in larger brains are driven more by increases in cortical surface area than by cortical thickening. These results based on a large sample of MRI data using 3-D cortical measurements are consistent with a postmortem study showing that a large cortex volume is mainly caused by areal expansion of cortical surface (Pakkenberg and Gundersen 1997). Recently, this cortical organization was reproduced using a simulated morphogenetic model (Toro and Burnod 2005). Our results support a previous theoretical study reporting that cortical cellular growth would occur preferentially along tangential axes, the path of least resistance, because the radial axis would be mechanically stiffer than the tangential axes (Van Essen 1997). It has also been suggested that, according to the radial unit hypothesis of cortical convolution, an increase in the number of neurons results in surface expansion, rather than in a thicker cortex (Rakic 1988, 2004).

In addition to the measure of the overall degree of cortical folding (cortical surface area), we used 3-D surface-based measurements estimating sulcal depth and convolution for more detailed cortical folding analysis. Our results show that the increase in cortical surface area in larger brains is accommodated by increased sulcal convolution, rather than by a systematic change in sulcal depth. This is consistent with our previous study, which showed that the number of folds and the convolution of sulcal shape were more associated with cortical complexity than sulcal depth (Im, Lee, Yoon, et al. 2006). Our empirical findings of cortical folding shape are consistent with previous theoretical hypotheses. Previous studies have reported that the characteristic shape of cortical convolutions and the arrangement of cortical areas can be explained by an evolutionary design strategy for the minimization of axonal length (Cherniak 1995; Van Essen 1997; Kennedy et al. 1998; Karbowski 2003; Klyachko and Stevens 2003; Laughlin and Sejnowski 2003). Because cortical areas participate in information-processing circuits through rich interareal connections, cortical networks are optimized to reduce wiring costs and save energy and time during signaling. In the case of larger brains, longer fibers are required to communicate between distant cortical areas. It has been reported that, theoretically, as brain size increases, there must be a fall in interhemispheric connectivity, due to the increasing time constraints of transcallosal conduction delay, and that consequently, a greater local clustering of interneuronal connections is required (Ringo 1991; Ringo et al. 1994; Anderson 1999). A tension-based theory has suggested that tension along axons in the WM between nearby cortical areas is the primary driving force for cortical folds at specific locations in relation to areal boundaries (Van Essen 1997). Recent study analyzed the quantitative connectional data including the densities and trajectories of cortical projections obtained from retrograde tract-tracing experiments for primate prefrontal cortices (Hilgetag and Barbas 2006). It has provided quantitative evidence for a significant role of mechanical factors in cortical morphology and supported the axonal tension hypothesis. Based on these studies, we suggest that the more convoluted sulcal shape in larger brains might result from the intensified mechanical tension of greater local corticocortical connections, as a reflection of the increased local processing. This might increase the performance of brain function and enhance cortical computation. Our results are derived from a large sample of data with enough range of ICV to support the hypotheses. The lack of observation for WM fibers could preclude us from associating the empirical results with fiber tension-based theory. However, the effect of fiber connectivity on the shape and size of cortical sulci has not been proved with any other direct observations. Our study, like others that have speculated on the relation between sulcal shape and fiber connectivity provides not direct evidence on WM characteristics (Davatzikos and Bryan 2002; White et al. 2003; Kippenhan et al. 2005; Kochunov et al. 2005; Im, Lee, Yoon, et al. 2006; Van Essen et al. 2006). Additional investigation, particularly diffusion tensor-based imaging, would be helpful for future work.

The results observed for lobar regions were consistent with the whole brain analysis and were largely bilateral. However, some regional differences were found in the relationships between brain size and cortical structure. For cortical thickness, significantly less thickening in large brains was detected in left temporal, right frontal, and parietal lobes, but not in both occipital lobes. Future work will investigate

whether these scaling relationships vary locally on the cortex using vertex-based cortical analysis techniques. Moreover, it may be biologically meaningful to analyze brain size effect in different cortices (paleocortex, archicortex, and neocortex) categorized by laminar organization.

Comparison with Previous Interspecies Studies

Many previous interspecies studies have shown there is allometric scaling of cortical structure in mammals. They have reported the slow thickening and fast areal expansion of cortex for larger brains in mammals. This mammalian cortical scaling was explained using a theoretical model with the relationship to neuron density and the number of neurons in a minicolumn (i.e., along a line through cortical thickness) (Changizi 2001). Although the current study is focused on human brains, our results agree well with previous interspecies studies. However, the theoretical model underlying the cortical scaling between species (mammalian brains) may not apply to intrahuman cortical scaling. In order to compare the cortical scaling, we examined the values of the scaling exponent. Measured scaling exponents for cortical thickness and surface area against cortical GM volume in whole brain have been measured to be around 0.1 and 0.9, respectively, in mammals (Hofman 1989, 1991; Prothero 1997a, 1997b; Zhang and Sejnowski 2000; Changizi 2001; Laughlin and Sejnowski 2003). From our results in Table 3 (cortical volume [V], thickness [T], and surface area [A], V~ICV$^{0.874}$, T~ICV$^{0.236}$, A~ICV$^{0.754}$), we can mathematically extract corresponding values in human brains. The scaling exponents against cortical volume are 0.270 and 0.863 for cortical thickness and surface area, respectively (T~$V^{0.270}$, A~$V^{0.863}$). The exponent values for human brains are comparatively different to those for mammalian brains. We suggest that the principles underlying cortical scaling between species and among humans are not the same.

The Limitation of Linear Stereotaxic Normalization

Previous voxel-based morphometry and surface-based cortical methods have been used to analyze linearly normalized (size-scaled) images to control for brain size (Good et al. 2001; Lerch et al. 2005). Linear normalization to stereotaxic space for removing effects of brain size is sufficient only under the hypothesis that cortical shape is invariant under scaling. Because our results show that cortical structure does not maintain geometric similarity when it scales, linear scaling of the data would lead to over- or under-scaling of the cortical measures and introduce confounding group differences that are not related to biology, but to the inappropriate scaling process. Because cortical measurements significantly increased or decreased with brain size, cortical analysis in native space could not control for brain size effect either. We suggest that native space cortical measure, followed by an analysis that includes brain size as a covariate is a preferable alternative.

Considerations as Regards a Sex Effect on Cortical Structure

A crucial confounding effect in many neuroanatomical studies on sex differences is brain size, because men show 8–10% larger brains than women (Peters et al. 1998). Previous studies have suggested that sex differences of the human brain structure reported in the scientific literature can be better explained by an underlying effect of brain size (Jancke et al. 1997; Luders et al. 2002; Luders, Narr, Zaidel, et al. 2006). In our results, when the effect of brain size was removed, there were no significant differences in cortical measurements between sexes. The results show that sex effects are mostly explained by brain size effects in the cortical structure of human brains. Previous studies investigated sex differences in cortical structure and found greater cortical thickness and gyrification in women than men (Luders et al. 2004, 2005; Im, Lee, Lee, et al. 2006; Luders, Narr, Thompson, et al. 2006; Luders, Thompson, et al. 2006). The data in these previous studies were normalized to stereotaxic space using linear scaling. As noted previously, this simple strategy cannot remove effects of brain size completely. For empirical support, we provide scatter plots of cortical thickness and absolute mean curvature in sulcal regions against ICV in actual values. Strong correlations between cortical measures and ICV are confirmed in native space regardless of sex (Fig. 8*A*,*B*). If the effect of brain size was controlled completely through linear stereotaxic normalization, any significant relationship between cortical measures and native ICV would not be found. However, it is interesting that the correlations between cortical measures and ICV remain and the correlation patterns are reversed in stereotaxic space (Fig. 8*C*,*D*). These results are due to the difference of cortical shape according to brain size and the inappropriate scaling process. Hence, the remaining effect of brain size in stereotaxic space may have been misunderstood as a sex effect in previous studies.

For sex differences in cortical thickness, in spite of processing in native space, greater cortical thickness in small female brains has been found in localized regions (Im, Lee, Lee, et al. 2006; Luders, Narr, Thompson, et al. 2006), which conflicts with the results in our current study. Discrepancies in findings may be attributable to different levels in the measurement of cortical thickness. We used mean cortical thickness in the whole cortex and each lobar region, whereas previous analyses were performed at a vertex level. In future work, vertex-based analysis could detect more localized regional specificity. In addition, previous studies have reported neuronal differences between sexes in the human brain cortex (Witelson et al. 1995; Pakkenberg and Gundersen 1997; Rabinowicz et al. 2002). Therefore, our findings set limits to a macroscopic structural and lobar regional level.

Surface-Based Cortical Folding Measures

Significant correlation between brain size and GI has not been observed in normal adult brains in previous studies because of limitations in the use of 2-D measurement and postmortem data (Armstrong et al. 1995). The various 3-D–based measurements used in our study provide a detailed characterization of the differences in cortical folding structure between small and large brains. Measurement of mean curvature on the cortical surface model has been used to quantify cortical complexity in previous studies (Tosun et al. 2004, 2006; Rettmann et al. 2006). However, the quantity of mean curvature could be a combination of the folding sharpness of sulcal fundus regions and the sulcal convolution. In this study, we proposed the novel measure of absolute mean curvature on sulcal walls, in order to isolate the effect of sulcal convolution.

Conclusion

In conclusion, we reveal significant changes of cortical shape according to brain size in the adult human brain. Our empirical

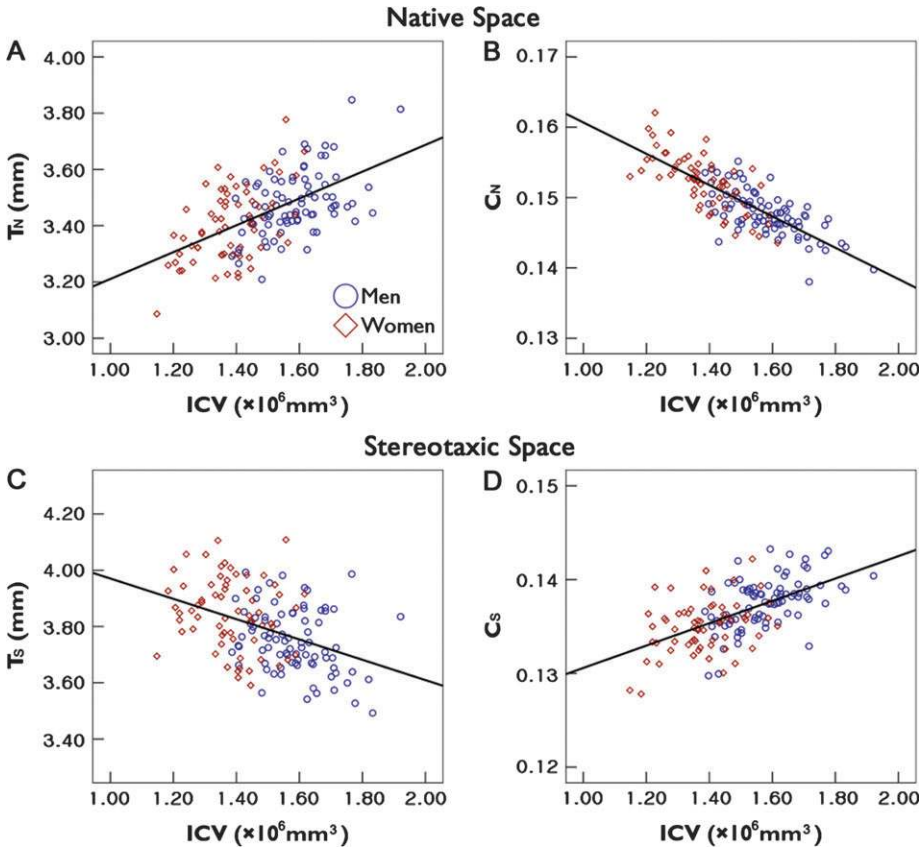

Figure 8. Scatter plots of cortical thickness and absolute mean curvature in sulcal regions against ICV in native and stereotaxic spaces. Positive correlation of cortical thickness (*A*) and negative correlation of absolute mean curvature (*B*) with ICV are shown in native space. After linear normalization to stereotaxic space, the correlations between cortical measures and ICV remain and the correlation patterns are reversed (*C*, *D*). The variance of cortical measurements is not explained by a sex effect in either space (T_N: cortical thickness in native space; C_N: absolute mean curvature in native space; T_S: cortical thickness in stereotaxic space; C_S: absolute mean curvature in stereotaxic space).

results are consistent with previous theoretical hypotheses, providing clues for the principles underlying cortical organization in the human brain. This paper also considers the limitation of linear stereotaxic normalization in brain image processing and suggests that sex effects on cortical structure are mostly explained by brain size effect at a macroscopic structural and lobar regional level.

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Address correspondence to Jong-Min Lee, Department of Biomedical Engineering, Hanyang University, PO Box 55, Sungdong, Seoul 133-605, South Korea. Email: ljm@hanyang.ac.kr.

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