The Contribution of Cortical Thickness and Surface Area to Gray Matter Asymmetries in the Healthy Human Brain

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Abstract: Human cortical gray matter (GM) is structurally asymmetrical and this asymmetry has been discussed to be partly responsible for functional lateralization of human cognition and behavior. Past studies on brain asymmetry have shown mixed results so far, with some studies focusing on the global shapes of the brain's surface, such as gyrification patterns, while others focused on regional brain volumes. In this study, we investigated cortical GM asymmetries in a large sample of right-handed healthy volunteers ($n = 101$), using a surface-based method which allows to analyze brain cortical thickness and surface area separately. As a result, substantially different patterns of symmetry emerged between cortical thickness and surface area measures. In general, asymmetry is more prominent in the measure of surface compared to that of thickness. Such a detailed investigation of structural asymmetries in the normal brain contributes largely to our knowledge of normal brain development and also offers insights into the neurodevelopmental basis of psychiatric disorders, such as schizophrenia. *Hum Brain Mapp 35:6011–6022, 2014.* © 2014 Wiley Periodicals, Inc.

Key words: asymmetry; cortical thickness; cortical volume; lateralization; surface area

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INTRODUCTION

In healthy adults, cortical gray matter (GM) is structurally asymmetrical or lateralized [Toga and Thompson, 2003]. Anatomically visible significant leftward brain asymmetry in the planum temporale (PT), which subserves language- and sound production, was determined and reproduced repeatedly [Geschwind and Lewitsky, 1968, ch. 2.3]. This lateralization effect has been found to be enhanced by factors such as handedness and gender [Good et al., 2001] as well as frequent use of brain areas, which Luders et al. [2004] demonstrated in their investigation of a population of healthy musicians with and without absolute pitch. Other than the mentioned PT, frequently reported to be anatomically lateralized are the right frontal and left occipital petalia [LeMay, 1976]. Recently, Goldberg et al. [2013] summarized in their study on GM volume asymmetries that areas implicated in visual processing show rightward asymmetries, while, in contrast, somatosensory, auditory and parts of the premotor cortex show leftward asymmetries. Cykowski et al. [2008] reported a leftward asymmetry of the central sulcus. However, for some areas of the brain, controversial results have been reported regarding the direction of asymmetries. For example, for the Heschl's gyrus (HG) Campain and Minkler [1976] found a rightward asymmetry, while Penhune et al. [1996] reported a lateralization to the left. Also, for the anterior cingulate cortex (ACC) Fornito et al. [2004] found a lateralization to the left, while Pujol et al. [2002b] found a rightward asymmetry of the ACC. Controversial findings of brain asymmetry have previously been attributed, for instance, to small sample sizes [Cykowski et al., 2008] and to biased results due to differences of segmentation methods [Kovalev et al., 2003].

Structural asymmetry has been hypothesized to form the basis of functional lateralization, seen, for example, in language function [Blackmon et al., 2010; Deutsch, 1985; Geschwind and Lewitsky, 1968]. Then again, negative results regarding correlations between structural asymmetry of PT and language lateralization have been reported [Eckert et al., 2006], and the hypothesis of a simple correlation has been abandoned in favor of more multifaceted causal relationships. For example, Dos Santos Sequeira et al. [2006] found that gender, handedness and functional lateralization of dichotic listening contributed to a complex pattern of PT asymmetry, indicating a strong interindividual variability.

Differences in the microstructure of the cortical GM are considered to underlie structural brain asymmetry [Hutsler and Galuske, 2003; Uylings et al., 2006]. The volume of GM is a composite of thickness and surface area [Panizzon et al., 2009]. As the cerebral cortex is organized into columns [Mountcastle, 1997], GM thickness reflects microstructural factors as the number of cells within each column [Rakic, 1988], density of neurons, glia, and their processes, for example, regional myelination [Paus et al., 1996; Sowell et al., 2004], while GM surface area mirrors neuron density [Sisodiya et al., 1996; Sisodiya and Free, 1997] and/or number of columns in each region [Glantz et al., 2006]. These two structural measurements have been argued to be highly heritable and apparently driven by distinct evolutionary, cellular and genetic mechanisms [Im et al., 2008; Panizzon et al., 2009]. Considering the microstructural and modular organization of the cortex, thickness and surface area are likely to be two variables that would separately and independent of each other contribute to the neural network formation and realization of its functions [Ecker et al., 2013].

Knowledge of the complex patterns of hemispheric lateralization and the distinct contribution of brain surface area and thickness to cortical GM structure in the healthy brain is crucial, informing on distinct neurobiological structural bases involved in the pathophysiology of neuropsychiatric conditions, such as schizophrenia. Abnormalities of GM asymmetries have been identified in schizophrenia [Bilder et al., 1994] which may be genetically determined [Crow, 1998]. Altered asymmetry in the PT has been shown to be related to reduced functional connectivity and to clinical symptoms such as auditory hallucinations [Oertel-Knochel et al., 2013]. However, only few studies separately assessed the contribution of GM thickness and surface area to structural asymmetries in the healthy brain, and the functional relevance of the findings is not yet known. A recent study on the human auditory-related cortex assessed cortical volume and thickness as well as surface area [Meyer et al., in press]. It was demonstrated that the surface area of the cortex showed a leftward asymmetry, while a rightward asymmetry was found for GM thickness in the primary and the secondary auditory cortex. Regarding cortical thickness asymmetries, Crespo-Facorro et al. [2011] investigated 76 healthy volunteers, correlating cortical thickness asymmetries to cognitive functioning and gender. They showed a greater leftward asymmetry of cortical thickness in men. Luders et al. [2006] showed diffuse and widespread cortical thickness asymmetries in a lager sample of healthy volunteers, with generally thicker cortex in the left hemisphere. Taken together, cortical thickness has mainly been found to be leftward lateralized, including the temporal and occipital sulci, ACC and superior temporal sulcus (STS) in the healthy brain. Surface area asymmetries have been assessed by Pujol et al. [2002b] and data revealed that the right ACC was larger, although more pronounced in women than in men. Lyttelton et al. [2009] investigated the cortical surface area of a large sample of young adults. Their study could confirm leftward hemispheric asymmetries in the supramarginal gyrus, the left HG and PT region, as well as a rightward asymmetry of the surface area in a band around the medial junction between the occipital lobe and parietal and temporal lobes. Hutsler et al. [1998] measured cortical asymmetry in a whole-brain approach, and specifically the postcentral and the cingulate gyrus of 10 male subjects. While a general tendency of asymmetries has been confirmed in these regions, the mean asymmetry scores did not reach significance. In summary, the few available studies on surface area asymmetries concentrated on specific structures, were performed in very small samples of participants or did not relate results on surface area to cortical thickness.

In this study, we will therefore assess the components of cortical GM volumes, thickness and surface area separately in a large sample of healthy volunteers, using a surface-based morphometric approach [FreeSurfer; Dale et al., 1999; Fischl et al., 1999]. Our aim is to identify brain regions with structural asymmetry in either thickness or surface area measures, as well as their relative contribution to observed differences in regional GM volume asymmetries in a whole-brain approach.

MATERIALS AND METHODS

Participants

The study group consisted of 101 right-handed healthy individuals [53 female; mean age (years): 33.0 (standard deviation: 10.6), range: 19–56; mean years of education: 14.4; SD: 2.7]. Verbal (V) and performance (P) IQ were assessed with a short version of the WAIS-R (vocabulary and block design) [Wechsler, 1981] [$n = 99$: verbal IQ: 113.7; SD: 16.4; performance IQ: 115.9; SD: 15.0]. Healthy volunteers were recruited via word of mouth and local advertisement. All were Japanese natives. None of them had a personal or family history of psychiatric illness. The Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-patient Edition (SCID-I/NP) [First et al., 2002] was used to exclude the presence of psychiatric disorders. Exclusion criteria for all individuals were a history of head trauma, serious neurological, medical or surgical illness, and substance abuse. No participant was on psychotropic medication. Handedness was assessed using the Edinburgh Handedness Inventory (EHI) [Oldfield, 1971]. As we included only right-handed persons, the mean laterality quotient of EHI was 89.7 (SD: 13.9; range: 20–100). This valid and reliable measure assesses the subject's dominant hand based on 10 items (plus two additional items) in their daily lives, history of correction of handedness, left-handedness in the family, and history of brain disease in their childhood. Four participants had to be excluded for gross anatomical abnormalities discovered in the structural magnetic resonance imaging (MRI) images. Those were checked by visual inspection and additional exploratory box plot analyses in the statistical software SPSS version 21.0 (SPSS, Chicago, IL) were used to identify extreme outliers. After a complete description of the study, participants gave written informed consent. The study design was approved by the Committee on Medical Ethics of Kyoto University and conforms to the Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/index.html; last access to all referred HP: 06/18/2014).

MRI Acquisition and Processing

Image acquisition

All participants received MRI scans using a 3.0 T whole-body scanner equipped with a 40 mT/m gradient and a receiver-only 8-channel phased-array head-coil (Trio, Siemens, Erlangen, Germany). The scanning parameters for the three-dimensional magnetization-prepared, rapid-gradient echo (3D-MPRAGE) sequences were as follows: echo time = 4.38 ms; repetition time = 2,000 ms; inversion time = 990 ms; field of view = 225×240 mm^2; matrix = 240×256; resolution = $0.9375 \times 0.9375 \times 1.0$ mm^3; 208 axial sections without intersection gaps.

Image processing

Cortical reconstruction and volumetric segmentation was performed with the FreeSurfer image analysis suite, which is documented and freely available for download online (version 4.5.0; http://surfer.nmr.mgh.harvard.edu/). The 3D-MPRAGE images were used to calculate thickness and surface area of the cerebral cortex throughout the cortical mantle. In brief, the processing stream includes a Talairach transform of each participant's native brain, removal of non-brain tissue and segmentation of GM/white matter (WM) tissue. The GM/WM boundary was tessellated to generate multiple vertices across the whole brain. The cortical surface of each hemisphere was inflated to a sphere to locate the pial surface and the GM/WM boundary. The entire cortex of each participant was visually inspected and any topological defects were corrected manually, blind to participant identity. After the creation of cortical representations, all vertices were assigned neuroanatomical labels on a cortical surface model based on the automated labeling system, and the entire cortex of each hemisphere was parcellated into 33 brain regions [see Desikan et al., 2006]. Cortical thickness was computed as the shortest distance between the pial surface and the GM/WM boundary at each vertex across the cortical mantle. The cortical volume was defined by surface-based volumetric calculation (area $\times$ thickness). The (inner) surface area of a region was computed by adding up the area of the vertices in that region [Greve et al., 2013].

The cortical volume (in mm^3), mean thickness (in mm) and surface area (in mm^2) were calculated for each brain region for both hemispheres separately. We calculated the Laterality Index (LI) for cortical volume, thickness, and surface area of each brain region according to the formula of $2 \times$ (left-right)/(left+right). To test the leftward or rightward asymmetry, we conducted one sample t-tests for LIs for each brain region. A significance level of $P < 0.0015$ (0.05/33 brain regions) was assumed due to Bonferroni corrections to prevent inflated error rates.

Additionally, we investigated the possible influence of age and gender, as they are known to have a significant impact on asymmetries of GM volumes [Good et al., 2001a,b]. General Linear Models were applied separately for LIs of volume, thickness and surface area data, with brain regions (33) as a within-subject factor, gender as a

TABLE I. Cortical volumes and laterality index (LI) for each brain region

Region labels in freesurfer	Volume Mean R (mm^3)	Std. dev. R	Volume Mean L (mm^3)	Std. dev. L	Laterality index L > R	P LI
Rostral anterior cingulate cortex	1,935	412	2,509	534	0.255	0.000
Transverse temporal gyrus	968	201	1,241	258	0.244	0.000
Inferior frontal gyrus - pars opercularis	4,617	967	5,432	1,126	0.160	0.000
Postcentral gyrus	9,647	1,395	10,387	1,734	0.071	0.000
Caudal middle frontal gyrus	6,593	1,321	7,084	1,512	0.068	0.001
Temporal pole	2,002	389	2,129	436	0.060	0.017
Isthmus of cingulate gyrus	2,280	412	2,397	490	0.046	0.027
Superior frontal gyrus	22,305	3,094	23,281	3,261	0.042	0.000
Paracentral lobule	3,872	682	3,550	655	0.037	0.019
Lateral occipital cortex	11,613	1,875	12,040	1,974	0.035	0.014
Supramarginal gyrus	11,033	1,837	11,412	1,859	0.034	0.019
Lateral orbitofrontal cortex	7,502	907	7,683	975	0.023	0.009
Inferior temporal gyrus	10,826	2,100	10,998	1,803	0.020	0.212
Entorhinal cortex	1,832	463	1,856	447	0.013	0.582
Fusiform gyrus	9,423	1,687	9,511	1,592	0.010	0.510
Precentral gyrus	13,997	1,951	14,019	1,804	0.003	0.736
Lingual gyrus	6,453	930	6,495	1,168	0.000	0.994
Superior parietal lobule	13,499	1,821	13,418	1,626	−0.004	0.665
Insula	6,496	726	6,456	655	−0.005	0.257
Precuneus	9,511	1,329	9,421	1,268	−0.009	0.325
Superior temporal sulcus	12,238	1,666	12,101	1,772	−0.013	0.209
Posterior cingulate cortex	3,503	508	3,363	504	−0.042	0.008
Cuneus	2,851	528	2,735	533	−0.043	0.012
Rostral middle frontal gyrus	16,461	2,999	15,721	2,715	−0.044	0.001
Medial orbitofrontal cortex	5,043	785	4,638	665	−0.082	0.000
Parahippocampal gyrus	2,156	365	2,235	355	−0.088	0.000
Middle temporal gyrus	13,503	1,983	11,957	2,001	−0.124	0.000
Inferior frontal gyrus - pars triangularis	4,617	996	4,004	778	−0.136	0.000
Caudal anterior cingulate cortex	2,186	451	1,897	434	−0.145	0.000
Inferior parietal lobule	16,664	2,334	14,005	1,844	−0.172	0.000
Pericalcarine cortex	2,347	476	1,908	375	−0.204	0.000
Inferior frontal gyrus - pars orbitalis	2,746	512	2,213	460	−0.216	0.000
Frontal pole	893	192	677	176	−0.279	0.000

between-subject factor and age as a covariate. Interaction terms included in the models are region and age as well as region and gender. We also included IQ (VIQ and PIQ) in the initial models. However, as this had no effect on the results, we will not report on these data. A significance level of $P < 0.05$ was set, and if we found significant interaction between region and age or gender, effects of age and gender were further examined in post hoc region-specific analyses.

Last, we correlated LIs of GM thickness and GM surface using Pearson product-moment correlation coefficients. The aim was to explore differential contribution patterns of GM thickness and surface area to overall GM volume, and the statistical significance threshold was set at $P < 0.05$.

For all statistical analyses, SPSS version 21.0 was used.

RESULTS

Cortical Volume

Significant leftward asymmetries were located in the rostral ACC, the transverse temporal gyrus, the inferior frontal gyrus (IFG) (pars opercularis), the postcentral gyrus, the caudal middle frontal gyrus, and the superior frontal gyrus.

Significant rightward asymmetries were found in the medial orbitofrontal cortex (OFC), rostral middle frontal gyrus, the parahippocampal gyrus, the middle temporal gyrus, the IFG (pars orbitalis, pars triangularis), the caudal ACC, the inferior parietal lobule, the pericalcarine cortex, and the frontal pole.

RESULTS OF THE CORTICAL VOLUMES AND ITS LI ARE PRESENTED IN TABLE I AND FIGURE 1

Cortical Thickness

The regions with significant leftward asymmetries were the rostral ACC, the isthmus cinguli, and the caudal ACC.

Regions of significant rightward asymmetries were found in the transverse temporal gyrus, the IFG (pars opercularis, pars triangularis), the temporal pole, the lateral occipital cortex, the entorhinal cortex, the STS, and the middle temporal gyrus.

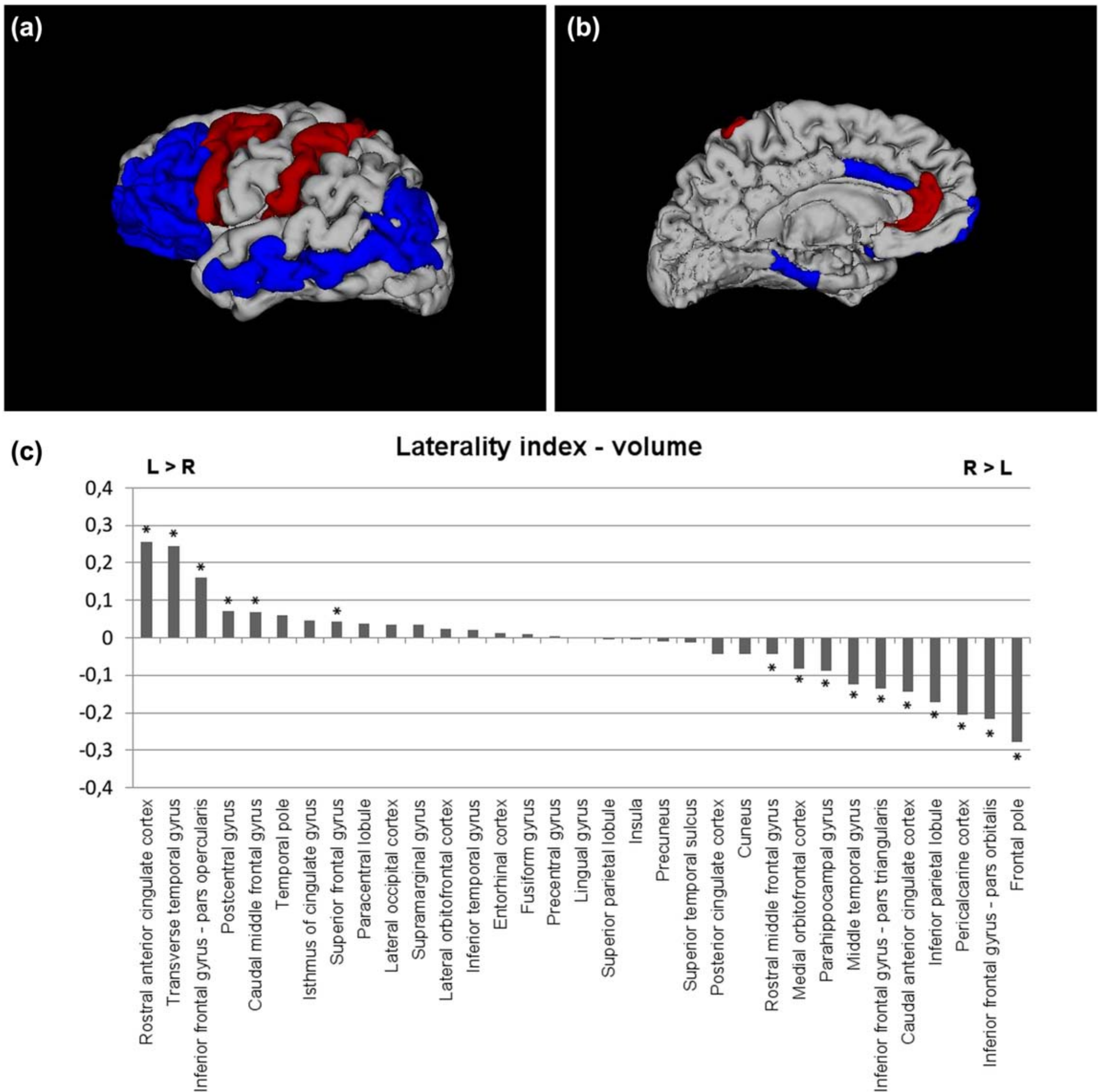

Figure 1.

Brain regions of significantly positive Laterality Index (LI) (leftward asymmetry) or negative LI (rightward asymmetry) in cortical volume (Bonferroni-corrected, $P < 0.0015$). 3D models generated with 3Dslicer (http://www.slicer.org/). Red color = brain regions showing significant leftward asymmetry; blue color = brain regions showing significant rightward asymmetry. The results are shown on the left hemisphere. (**a**) lateral, (**b**) medial view, and (**c**) LI for cortical volumes of each brain region is displayed by histogram. * indicates significant LI increase or decrease controlling for age and gender in region-specific analyses (Bonferroni-corrected, $P < 0.0015$).

RESULTS OF THE CORTICAL THICKNESS AND ITS LI ARE PRESENTED IN TABLE II AND FIGURE 2

Surface Area

Regions with significant leftward asymmetries were identified in the transverse temporal gyrus, the rostral ACC, the IFG (pars opercularis), the postcentral gyrus, the caudal middle frontal gyrus, the temporal pole, the superior frontal gyrus, the lateral occipital cortex, and the entorhinal cortex.

Regions with significant rightward asymmetries were identified in the IFG (pars orbitalis, triangularis), the paracentral lobule, the medial OFC, the middle temporal gyrus, the caudal ACC, the inferior parietal lobule, the pericalcarine cortex, and the frontal pole.

TABLE II. Cortical thickness and laterality index (LI) for each brain region

Region labels in freesurfer	Thickness Mean R (mm)	Std. dev. R	Thickness Mean L (mm)	Std. dev. L	Laterality index L > R	P LI
Caudal anterior cingulate cortex	2.67	0.24	2.82	0.25	0.056	0.000
Isthmus of cingulate gyrus	2.56	0.21	2.68	0.21	0.048	0.000
Rostral anterior cingulate cortex	3.03	0.25	3.11	0.21	0.027	0.000
Frontal pole	2.81	0.31	2.88	0.42	0.020	0.217
Fusiform gyrus	2.65	0.13	2.68	0.12	0.010	0.031
Precentral gyrus	2.62	0.13	2.64	0.12	0.007	0.071
Inferior parietal lobule	2.59	0.14	2.61	0.13	0.006	0.108
Postcentral gyrus	2.14	0.14	2.15	0.11	0.005	0.052
Superior frontal gyrus	2.93	0.13	2.94	0.13	0.005	0.368
Posterior cingulate cortex	2.63	0.16	2.64	0.16	0.004	0.479
Paracentral lobule	2.47	0.15	2.48	0.15	0.003	0.546
Parahippocampal gyrus	2.56	0.22	2.58	0.30	0.003	0.769
Precuneus	2.37	0.13	2.38	0.13	0.001	0.739
Lateral orbitofrontal cortex	2.68	0.14	2.68	0.13	0.000	0.985
Medial orbitofrontal cortex	2.71	0.16	2.71	0.16	−0.001	0.895
Pericalcarine cortex	1.50	0.11	1.50	0.10	−0.002	0.770
Supramarginal gyrus	2.64	0.15	2.64	0.13	−0.002	0.586
Lingual gyrus	1.94	0.10	1.93	0.12	−0.004	0.235
Rostral middle frontal gyrus	2.52	0.11	2.51	0.12	−0.004	0.392
Cuneus	1.84	0.13	1.83	0.12	−0.006	0.382
Inferior temporal gyrus	2.79	0.13	2.77	0.13	−0.007	0.114
Caudal middle frontal gyrus	2.68	0.13	2.66	0.14	−0.008	0.078
Superior parietal lobule	2.26	0.14	2.24	0.12	−0.009	0.019
Inferior frontal gyrus - pars orbitalis	2.79	0.19	2.76	0.21	−0.012	0.124
Inferior frontal gyrus - pars triangularis	2.67	0.16	2.62	0.17	−0.019	0.001
Insula	3.14	0.16	3.08	0.23	−0.022	0.022
Inferior frontal gyrus - pars opercularis	2.74	0.16	2.67	0.15	−0.023	0.000
Lateral occipital cortex	2.17	0.12	2.11	0.11	−0.026	0.000
Superior temporal sulcus	2.92	0.15	2.84	0.17	−0.027	0.000
Middle temporal gyrus	3.05	0.15	2.97	0.15	−0.029	0.000
Transverse temporal gyrus	2.38	0.21	2.31	0.23	−0.032	0.001
Temporal pole	3.75	0.39	3.53	0.40	−0.062	0.000
Entorhinal cortex	3.33	0.34	3.12	0.31	−0.064	0.000

RESULTS OF THE SURFACE AND ITS LI ARE PRESENTED IN TABLE III AND FIGURE 3

Effect of Gender and Age

For GM volume and GM thickness, there were no main effects of age, gender or interactions of region and age or region and gender.

For GM surface, a significant main effect of gender [$F(1,98) = 5.14$; $P < 0.05$] was found. Post hoc comparisons indicated a significantly stronger asymmetry [$F(1,98) = 5.142$; $P < 0.05$] of GM surface area to the right in males (mean = −0.01; SD: 0.02) than in females (mean = −0.005; SD: 0.02) over all regions.

There were no significant main effects of age or interaction effects of region × age or region × gender.

Correlational Analysis

In the correlational analysis between GM thickness and surface area, significant correlations have been confirmed in the following brain regions: the caudal ACC ($r = 0.4$), the isthmus cinguli ($r = 0.24$), and the lateral OFC ($r = 0.32$) showed positive correlations, while the fusiform gyrus ($r = -0.22$), the IFG (pars opercularis) ($r = -0.27$), the insula ($r = -0.21$), the medial OFC ($r = -0.27$), the parahippocampal gyrus ($r = -0.31$), the precentral gyrus ($r = -0.30$), the superior frontal gyrus ($r = -0.25$), the superior parietal lobule ($r = -0.28$), and the supramarginal gyrus ($r = -0.22$) showed negative correlations.

DISCUSSION AND CONCLUSION

The aim of our study was to determine cortical asymmetries in healthy volunteers with specific regard to subcomponents of GM volume, namely GM thickness and GM surface area. The study was conducted in a large sample of healthy volunteers, providing the necessary statistical power to detect the effects of interest, creating a detailed map of normal GM asymmetries. We also tested possible impact of age or gender on the LIs but overall

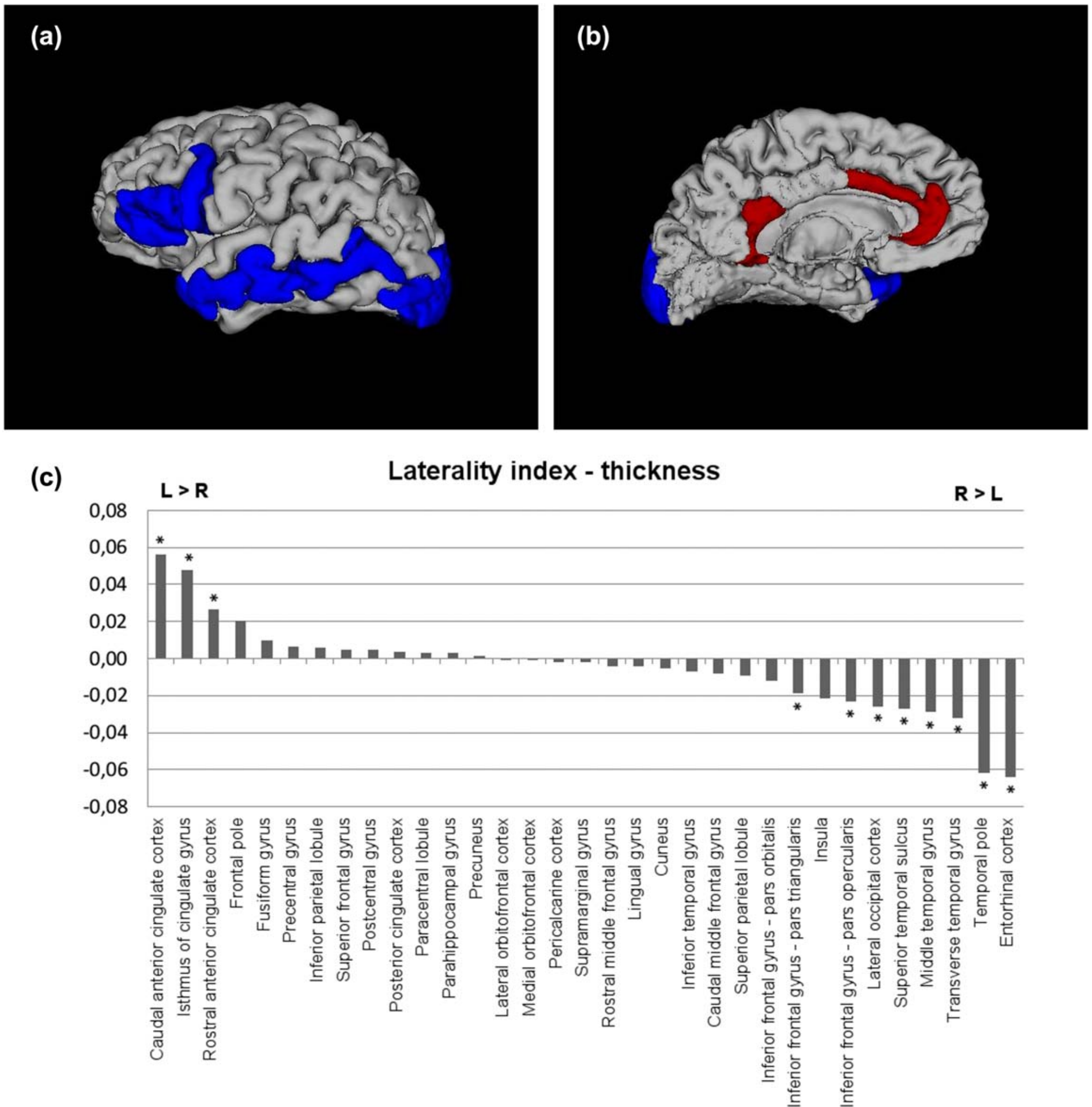

Figure 2.

Brain regions of significantly positive LI (leftward asymmetry) or negative LI (rightward asymmetry) in cortical thickness (Bonferroni-corrected, $P < 0.0015$). 3D models generated with 3Dslicer (http://www.slicer.org/). Red color = brain regions showing significant leftward asymmetry; blue color = brain regions showing significant rightward asymmetry. The results are shown on the left hemisphere. (**a**) lateral, (**b**) medial view, and (**c**) LI for cortical thickness of each brain region is displayed by histogram. * indicates significant LI increase or decrease controlling for age and gender in region-specific analyses (Bonferroni-corrected, $P < 0.0015$).

lateralization patterns were found to be affected neither by gender nor by age.

With regard to GM volumes, our data, for the most part, agree with previous studies [e.g. Luders et al., 2004]. However, we found some exceptions. Tanaka et al. [2012] identified a trend for a greater rightward asymmetry of cortical GM volume for all brain regions. While in our analysis we found a leftward asymmetry for the rostral ACC and a rightward asymmetry for the caudal ACC, Paus et al. [1996] demonstrated a right larger than left asymmetry of the ACC using a voxel-based approach. Contrary to our findings, Hammers et al. [2007], using manual region-of-interest analyses, noticed no lateralization of GM in the IFG, while we found parts of the IFG (pars orbitalis, pars

TABLE III. Cortical surface area and laterality index (LI) for each brain region

Region labels in freesurfer	Surface Mean R (mm^2)	Std. dev. R	Surface Mean L (mm^2)	Std. dev. L	Laterality index L > R	*P* LI
Transverse temporal gyrus	354	65	479	93	0.298	0.000
Rostral anterior cingulate cortex	551	115	698	129	0.238	0.000
Inferior frontal gyrus - pars opercularis	1,510	304	1,786	328	0,168	0.000
Temporal pole	359	61	399	62	0.108	0.000
Entorhinal cortex	379	87	419	97	0.097	0.000
Caudal middle frontal gyrus	2,193	410	2,414	480	0.093	0.000
Postcentral gyrus	3,986	508	4,240	595	0.060	0.000
Lateral occipital cortex	5,099	850	5,356	822	0.051	0.000
Inferior temporal gyrus	3,324	560	3,443	479	0.039	0.009
Superior frontal gyrus	6,736	875	7,006	932	0.039	0.000
Supramarginal gyrus	3,792	614	3,902	596	0.030	0.034
Isthmus of cingulate gyrus	797	141	818	149	0.025	0.148
Parahippocampal gyrus	735	105	754	110	0.025	0.123
Superior parietal lobule	5,268	725	5,340	584	0.017	0.092
Superior temporal sulcus	3,643	433	3,709	459	0.017	0.069
Lateral orbitofrontal cortex	2,617	290	2,629	296	0.004	0.606
Insula	2,096	470	2,080	180	0.003	0.769
Lingual gyrus	3,197	406	3,200	476	−0.002	0.850
Fusiform gyrus	3,216	532	3,194	448	−0.004	0.777
Precentral gyrus	4,867	643	4,808	606	−0.011	0.247
Precuneus	3,833	502	3,733	450	−0.025	0.003
Cuneus	1,454	251	1,417	244	−0.027	0.094
Rostral middle frontal gyrus	5,714	989	5,514	919	−0.034	0.007
Posterior cingulate cortex	1,218	169	1,165	160	−0.044	0.004
Medial orbitofrontal cortex	1,646	232	1,524	205	−0.076	0.000
Middle temporal gyrus	3,631	488	3,292	518	−0.101	0.000
Paracentral lobule	1,437	206	1,284	195	−0.113	0.000
Inferior frontal gyrus - pars triangularis	1,524	297	1,340	228	−0.122	0.000
Caudal anterior cingulate cortex	725	135	619	113	−0.156	0.000
Inferior parietal lobule	5,725	807	4,791	615	−0.175	0.000
Pericalcarine cortex	1,688	290	1,399	241	−0.187	0.000
Inferior frontal gyrus - pars orbitalis	795	132	628	129	−0.238	0.000
Frontal pole	229	48	170	37	−0.297	0.000

triangularis) lateralized to the right and parts to the left (pars opercularis). Different findings might be due to differences of methodology or populations (Asian vs. Westerners) [Chee et al., 2011].

While there is sufficient data on asymmetries of GM volumes, only little data has been published on lateralization of cortical thickness and surface area. Regarding cortical thickness, our study showed regions of highly significant leftward cortical thickness asymmetries in the caudal ACC, the isthmus cinguli and the rostral ACC. These findings are in line with results of Wang et al. [2007], who found left larger than right asymmetry in thickness of the ACC in healthy volunteers. Kang et al. [2012] found in a study on GM thickness that the thickness of the temporal pole was larger in the right hemisphere than in the left, which corresponds to our own results. Moreover, in a study by Eckert et al. [2008], similar to our findings, significant leftward asymmetry of cortical thickness was demonstrated, although the study was conducted with children. In a study by Zhou et al. [2013], the authors found a rightward lateralization of the IFG and the occipital lobe that we could replicate. We could not replicate findings by Luders et al. [2006], however, who showed a greater leftward asymmetry in GM thickness in women, most prominently in the temporal and the frontal regions, using a cortical pattern matching system.

Regarding the GM surface area, widespread regions in the frontotemporal areas were found either with leftward or rightward asymmetry. While in general our data is in line with previous studies, it, unlike the data of Pujol et al. [2002a], does not suggest gender-specific asymmetry toward the right ACC. Rather, our data suggests a subregion-specific asymmetry pattern within the ACC, that is, the left rostral ACC exhibited a leftward and the caudal ACC a rightward asymmetry. ACC is the region where sulcogyral variations are the most prominent [Fornito et al., 2006], thus, the discrepancy among the asymmetry studies should be further investigated, applying multiple methodologies of surface area calculation and subregion definitions. Lyttelton et al. [2009] found leftward

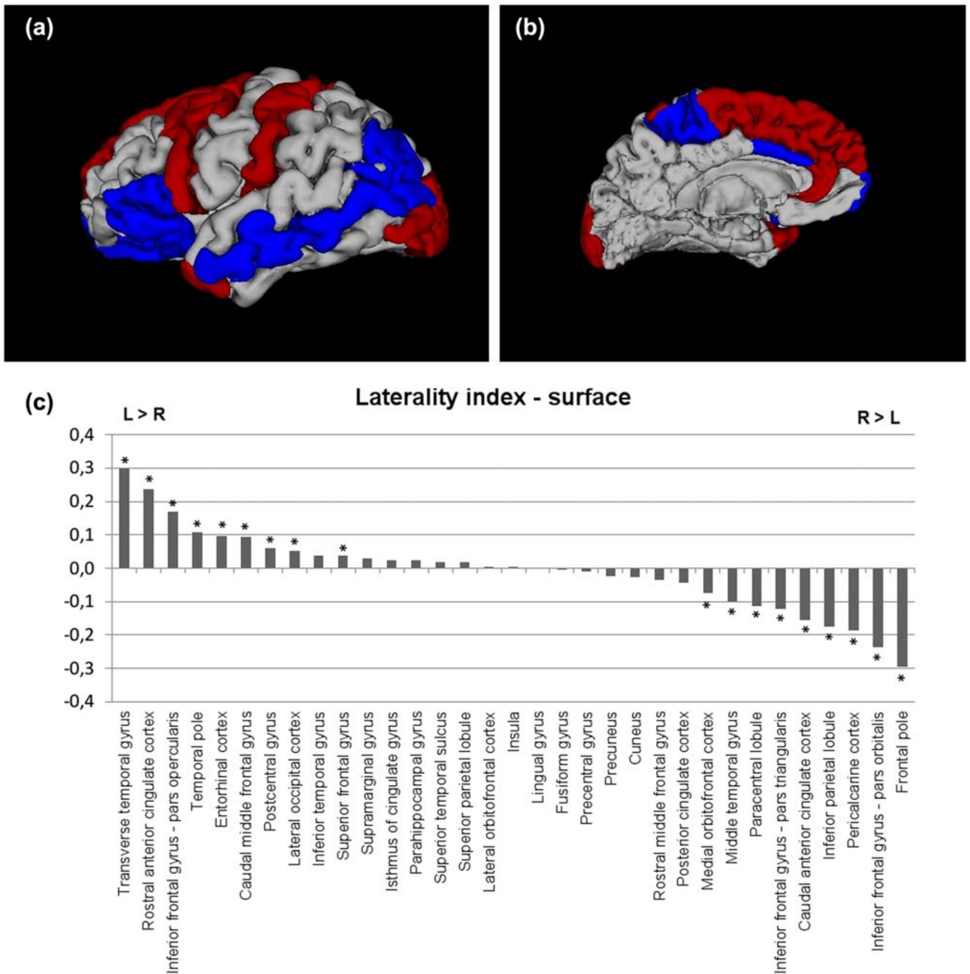

Figure 3.

Brain regions of significantly positive LI (leftward asymmetry) or negative LI (rightward asymmetry) in cortical surface area (Bonferroni-corrected, $P < 0.0015$). 3D models generated with 3Dslicer (http://www.slicer.org/). Red color = brain regions showing significant leftward asymmetry; blue color = brain regions showing significant rightward asymmetry. The results are shown on the left hemisphere. (**a**) lateral, (**b**) medial view, and (**c**) LI for surface area of each cortical region is displayed by histogram. * indicates significant LI increase or decrease controlling for age and gender in region-specific analyses (Bonferroni-corrected, $P < 0.0015$).

asymmetry in the supramarginal gyrus, which we observed as, although not significantly, lateralized to the left, a rightward asymmetry in the OFC, which we could replicate for the medial part, as well as an asymmetry in the temporal parts of the brain, excluding the inferior temporal gyrus. Finally, authors showed a rightward asymmetry for the parietal parts of the brain, which we could demonstrate for the inferior parietal lobules. A rightward asymmetry in the occipital lobes we could not replicate. While we found a significant leftward asymmetry of the postcentral gyrus, Hutsler et al. [1998] could not detect a lateralization of GM surface area in this region.

Most noticeable in our study are the differences in the overall asymmetry patterns between thickness and surface area (Figs. 2 and 3), which suggest that separate consideration of both aspects of cortical asymmetry is important [see e.g. Winkler et al., 2010]. A similar pattern of the contribution of GM thickness and surface area has previously been shown for the auditory-related cortex, including the HG, the PT, and the superior temporal gyrus [Meyer et al., in press]. The lateralization pattern of the HG (transverse temporal gyrus) we found was basically consistent with Meyer et al.'s results. In addition, we were able to identify an even more complex nature of the relationship between GM thickness and surface area by expanding the analyses to the whole-brain level.

As mentioned in the introduction, GM thickness mirrors the number of cells [Rakic, 1988], the density of neurons, the glia, as well as regional myelination [Paus et al., 1996; Sowell et al., 2004], while neuron density [Sisodiya et al., 1996; Sisodiya and Free, 1997] and/or number of columns [Glantz et al., 2006] most probably impacts on GM surface area. Our current results indicate differential contribution of these microscopic processes on different cortical areas, resulting in macroscopic levels of cortical asymmetry. Thus, for example, the thickness of the caudal ACC (as part of the cognitive division of the ACC) [Bush et al., 2000] is lateralized to the right side, while the surface area rostral ACC (as the affective division) is lateralized to the left side. While WM microstructure has been linked to cognitive functioning [Metzler-Baddeley et al., 2012], it might also be assumed that not only the asymmetry of GM structures in itself but also their architectonical structure might play a role in development and functional specialization.

Our analyses revealed significant correlations between LI of GM thickness and that of surface area, and, intriguingly, the majority correlated negatively. As the lateralization pattern of GM thickness and surface area seems complex and region-specific, it is, thus, difficult to identify a general principle. However, possible options to explain this differential asymmetrical pattern of GM thickness and surface area are the "tension-based theory" [Van Essen, 1997] and the "balloon model" [Seldon, 2005]. According to these hypotheses, WM growth expands the cortex and causes the surface to fold, resulting in a larger surface area and reduced thickness. Regionally different patterns of thickness/surface ratios might thus arise from a variable growth of underlying WM.

Several limitations of the study need to be addressed. As IQ has been found to have an impact on GM asymmetries [Frangou et al., 2004; Narr et al., 2007], the comparably high mean IQ of the study group could have biased our results. However, IQ has been included as a covariate of no interest in our analyses, which showed no significant effect, a finding which has previously been reported by Yeo et al. [1987]. Also, we included only right-handed subjects. Thus, the results are not applicable to left-handed individuals.

In summary, we could show that widespread areas of the healthy brain are asymmetrical in their structure. We found different patterns of asymmetry between cortical thickness and surface area. This study not only contributes to the understanding of human brain asymmetry but also offers reference data in understanding the pathophysiology of some neuropsychiatric disorders, such as schizophrenia, in which abnormal brain asymmetry is considered to be a part of the pathogenesis.

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