Asymmetry Map of Human Brain in Young Adults

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Abstract

Although, asymmetry is a central organizational aspect of human brain, it has not been clearly described yet. Here, we have studied structural brain asymmetry in 1113 young adults using data obtained from Human Connectome Project. A significant rightward asymmetry in mean global cerebral cortical thickness, surface area and gray matter volume as well as volumes of cerebral white matter, cerebellar cortex and white matter, hippocampus, putamen, caudate nucleus, nucleus accumbens and amygdala was observed. Thalamus showed a leftward asymmetry. Regionally, most cerebral cortical regions show a significant rightward asymmetry in thickness. However, cortical surface area and gray matter volume are more evenly distributed between two hemispheres with almost half of the regions showing a leftward asymmetry. In addition, a strong correlation between cortical surface area and gray matter volume as well as their asymmetry indices was noted which results in concordant asymmetry patterns between cortical surface area and gray matter volume in most cortical regions.

Key words

Asymmetry, Human Brain, Young Adult, Gender, Human Connectome Project

INTRODUCTION

Human brain is a lateralized structure (1). Several lines of evidence suggest that this feature is centrally involved in numerous tasks including cognitive and affective processes in physiological as well as pathological states (2-7). However, despite over a century of research, this important hallmark has not been clearly understood yet. To date, different and frequently conflicting reports about how human brain is lateralized and affected by variables like gender and age have been published (8-14). Variability in methods and populations, subtle and varying nature of asymmetry with age as well as vast inherent individual variability are considered some of the reasons for previous inconsistent reports (11, 13, 15-18). Young Adult Human Connectome Project (HCP) has applied standardized parcellation and imaging methods to study 300 families of 22-35 years old twin and non-twin siblings which are diverse enough to reflect ethnic diversity of the United States (19). This provides an excellent opportunity to study brain asymmetry in young adults and how is affected by specific variables like gender. Furthermore, HCP data set allows us to study asymmetry in different cortical and subcortical structures in same group of participants since ever growing data indicate that they actively participate in cardinal brain functions (20-22). In this study, we have studied asymmetry patterns in three measures of the cerebral cortex: thickness, surface area, gray matter volume, as well as cerebral white matter, cerebellar cortex and white matter, hippocampus, pallidum, putamen, caudate nucleus, nucleus accumbens, amygdala and thalamus.

MATERIALS AND METHODS

All analyses were performed on datasets downloaded from the Young Adult HCP database (19). The process of acquisition and processing of the MRI images are

explained here (23). The structural data of 1113 participants, 606 female and 507 male, who were between 22-35 years old was analyzed. Statistical analyses were performed using SPSS software ver. 24.0 (IBM, Armonk, NY, USA). Asymmetry Index (AI) of thickness, surface area and gray matter volume of each cortical region as well as volumes of cerebral white matter, hippocampus, pallidum, putamen, caudate nucleus, nucleus accumbens, amygdala and thalamus was calculated for each subject according to the formula of $2 \times (\text{left-right})/(\text{left+right})$. Positive and negative AIs indicate leftward or rightward asymmetry respectively. A single group *t*-test was carried out for comparison of AI means. A significance level of $P < 0.0011$ ($0.05/44$ brain regions) was assumed due to Bonferroni corrections to prevent inflated error rates. Effect size was expressed as Cohen's-d (*d*). A Multivariate Analysis of Variance (MANOVA) test was conducted to evaluate effect of gender as between-subject factor and age as a covariate on AIs of studied structures. Results were analyzed with region specific *post hoc* tests. Coefficient of Variation (CV) was calculated according to the formula: $\text{CV} = \text{standard deviation}/\text{mean}$ to evaluate variability of metrics in the cerebral cortex. Pearson correlation coefficient (R) was calculated to study relationship between them. For correlation analysis statistical significance threshold was set at $P < 0.05$.

RESULTS

Cerebral Cortex

A significant rightward asymmetry is observed in mean global cortical thickness, surface area as well as mean global cortical gray matter and cerebral white matter volumes. (Table.1 and Fig.1). However, at regional level differential asymmetry patterns were observed as follows.

1. Thickness. 85% (29/34) of cerebral cortical regions show a significant degree of asymmetry in thickness with 76% (26/34) presenting a rightward asymmetry. Insula, caudal anterior and posterior cingulate cortices show a significant leftward asymmetry. Parahippocampal and precentral gyri as well as rostral anterior cingulate, pericalcarine and cuneus cortices display a non-significant difference. All other regions show a significant rightward asymmetry in thickness (Table.2 and Fig.2).

2. Area. 94% (32/34) of the cerebral cortical regions present a significant asymmetry in surface area. However, distribution of regions between two hemispheres is more even relative to cortical thickness. 41% (14/34) show a rightward and 53% (18/34) present a leftward asymmetry. Regions with rightward asymmetry are widely distributed on all cerebral surfaces including frontal pole, pars orbitalis, pars triangularis, insula, middle temporal gyrus and inferior parietal, pericalcarine, caudal anterior cingulate cortices. Regions with leftward asymmetry show a tendency to peri-Sylvian areas and include superior temporal and supramarginal gyri, temporal pole, pars opercularis as well as transverse temporal, entorhinal and rostral anterior cingulate cortices (Table.3 and Fig.3).

3. Gray matter volume. 88% (30/34) of cerebral cortical regions show a significant asymmetry in their gray matter volumes. 41% (14/34) display a rightward and 47% (16/34) a leftward asymmetry. Regions with leftward asymmetry indices include transverse temporal, rostral anterior cingulate, pars opercularis, caudal anterior cingulate and entorhinal cortices. On the other hand, middle temporal gyrus, pars triangularis, banks of superior temporal sulcus, inferior parietal cortex, pars orbitalis and frontal pole regions present a rightward asymmetry (Table.4 and Fig.4).

Cerebellum, Hippocampus and Subcortical Structures

Mean of volumes of the cerebellar cortex and white matter, hippocampus, pallidum, putamen, caudate nucleus, nucleus accumbens and amygdala show a significant rightward asymmetry. Thalamus present a significant leftward asymmetry (Table.5 and Fig.5).

Variation of the Cerebral Cortical Metrics

Cerebral cortical surface area (CV=14) and gray matter volume (CV=14) display more global variability than thickness (CV=6) (Fig.6A).

Correlation between the Cerebral Cortical Metrics

We observed a tendency towards a negative correlation between cortical thickness and surface area across cortical regions ($R^2=0.04$, $P = 0.24$) as well as the corresponding AIs ($R^2=0.1$, $P = 0.08$) which do not reach the statistical significance. Furthermore, thickness and the gray matter volume do not show a significant correlation ($R^2=0.032$, $P = 0.31$), neither their corresponding AIs ($R^2=0.003$, $P = 0.76406$). However, surface area and gray matter volume ($R^2=0.96$, $P < 0.0000001$) as well as their corresponding AIs ($R^2=0.6$, $P < 0.0000001$) present a strong and significant correlation together (Fig.6 and 7).

Gender

MANOVA revealed a significant effect of gender on AIs of the studied structures [F (113, 998) 1.9; $P < 0.0000005$, partial $\eta^2=0.18$]. However, even though, a number of nominally significant regions with exaggerated asymmetry patterns between genders was noted in *post-hoc* analysis, none survived Bonferroni correction (Table.6).

Age

Age does not show a significant effect on AIs of studied structures [F (113, 998) 1; $P = 0.35$, partial $\eta^2=0.11$].

DISCUSSION

To best of our knowledge, this is, by far, the largest study of asymmetry in healthy young adults which have been analyzed by standardized parcellation and imaging methods. Previous reports have either studied smaller groups which would not provide necessary statistical power or analyzed the data which have been obtained through heterogeneous methods. Moreover, this is the first study which has studied asymmetry in three metrics of the cerebral cortex as well as cerebral white matter, cerebellar cortex and white matter, hippocampus and six subcortical structures in the same group of individuals. A major finding of this study is the almost ubiquitous rightward asymmetry in mean of gray and white matter volumes in the studied structures. Volumes of the cerebral as well as cerebellar cortex and white matter, hippocampus and all subcortical structures except thalamus show a significant rightward asymmetry. In addition, mean global cerebral cortical thickness and surface area present a rightward asymmetry as well (Table.1 and 5), (Fig.1 and 5). The findings are in agreement with a previous study describing a rightward asymmetry in the cortical gray matter as well as cerebral white matter volumes (24). In addition, although, only a few studies has addressed hemispheric asymmetry in cortical surface area, thickness and gray matter volume in the same group of participants, a global rightward asymmetry in all these metrics has been reported before (25). Moreover, rightward asymmetry of the cerebral gray matter volume, and cortical surface area has been described in other studies (13, 26). Nevertheless, conflicting asymmetry patterns have been also reported (12, 13, 27, 28). Despite the global rightward asymmetry of cortical metrics, differential patterns at regional level were observed. Although, most cortical regions show a rightward asymmetry in thickness (Table.2 and Fig.2), surface

area presents a more even distribution between two hemispheres with 53% of regions showing a significant leftward asymmetry (Table.3 and Fig.3). It is notable that in the lateral surface of the cerebral cortex, asymmetry in surface area shows a relationship with the distance to Sylvian fissure leading to a leftward asymmetry in peri-Sylvian regions which has been frequently reported before (13, 25, 29-31). For example, both caudal middle and inferior frontal (pars opercularis) gyri display a leftward asymmetry in surface area. However, rostral middle and inferior frontal (pars orbitalis and pars triangularis) gyri show a rightward asymmetry. A similar pattern is observed in parietal cortex. Postcentral and supramarginal gyri show a leftward asymmetry in surface area. However, inferior and superior parietal cortices show a rightward asymmetry. In medial surface of cerebrum an anterior-left, posterior-right pattern of asymmetry in surface area is observed. Superior frontal as well as rostral anterior cingulate regions show a leftward asymmetry. However, precuneous, cuneous, caudal anterior and posterior cingulate cortices show a rightward asymmetry. Between structural variables of cortical gray matter volume (32), surface area shows more global variability (CV=14) compared with thickness (CV= 6) (Fig.6A), which is in agreement with previous reports (29, 33). This is probably why global variability (CV=14%) as well as the volume of cortical gray matter often follows cortical surface area ($R^2=0.96$, $P < 0.0000001$) (Fig.6). Concordantly, the asymmetry patterns of the cortical gray matter volume mostly pursue surface area (Fig.7A). This includes leftward asymmetry of cortical gray matter volume in peri-Sylvian regions including transvers temporal cortex, superior temporal gyrus, temporale pole, pars opercularis and supramarginal gyrus which is in agreement with previous reports (Table.4 and Fig.4) (9, 10, 26, 34). Regions with concordant rightward asymmetry between surface area and gray matter volume include

middle temporal gyrus, pars orbitalis, pars triangularis, insula, inferior parietal, cuneus, precuneus and posterior cingulate cortices which are mostly in line with a previous study (30). Regions with opposite asymmetry pattern between surface area and gray matter volume are not numerous and include banks of superior temporal sulcus, caudal rostral cingulate and medial orbitofrontal gyri where gray matter volume follow asymmetry pattern of the cortical thickness (Table.2 , 4 and Fig.2, 4). Consistently, unlike a previous report (25), we noticed a strong global relationship between AIs of the cortical surface area and gray matter ($R=0.6$, $P < 0.000001$) compared with a non-significant relationship between AIs of the cortical thickness and gray matter ($R^2=0.003$, $P = 0.76406$) which is in line with a previous report (33). Fig. 7B). This supports the notion of independent character of cortical thickness and surface area as neuroanatomical unites (30, 33, 35). A good example of how variation in surface area influences asymmetry of the gray matter volume is Broca's area. Although, both parts of Broca's area, pars triangularis and pars opercularis, present a rightward asymmetry in thickness, the gray matter volume follows asymmetry pattern of surface area, i.e. rightward in pars triangularis and leftward in pars opercularis. In fact, difference in surface area asymmetry places the gray matter volume asymmetry of pars triangularis ($d=-1.2$) and pars opercularis ($d=1.1$) among strongest opposite asymmetries in whole brain. Interestingly, a similar pattern is observed in another language related region, supramarginal gyrus i.e. a rightward asymmetry in thickness and leftward asymmetry in surface area and gray matter volume. Although, many of the asymmetry patterns in cortical metrics described here, has been reported in different studies (9, 13, 25, 26, 28-30), it is the first time, in our knowledge, that above mentioned relationship between cortical metrics in determining asymmetry patterns

across cerebral cortex has been described. The results of this study in regional cortical asymmetry are similar to a previous report (30). However, probably lower number of cases and lack of necessary statistical power in addition of strict correcting for multiple comparisons by Bonferroni procedure has led to many statistically insignificant results in above mentioned study. In addition, we could replicate many of the asymmetry patterns reported by other studies (12, 29, 31), even though, inconsistencies exist which detailed discussion about it is beyond the scope of this paper. However, we have to emphasize that a part of the inconsistencies could be due to the age of participants as reports suggest it affects asymmetry patterns (17, 18). On the other hand, although, our results show similarities with another large data analysis (13), especially on asymmetries in cortical surface area, we could not replicate reported leftward hemispheric asymmetry as well as many regional asymmetries in cortical thickness. Important heterogeneity in asymmetry results between analyzed data sets which has been acknowledged by the authors could be one of the reasons of this discrepancy (13).

Cerebellum, Hippocampus and Subcortical Structures

Although, fewer studies on the asymmetry of subcortical structures are available, discrepancies prevail here as well. Apart from putamen and pallidum, the observed rightward asymmetry in hippocampus, amygdala, caudate nucleus and nucleus accumbens as well as leftward asymmetry in thalamus are in agreement with the largest met-analysis published on asymmetry of subcortical structures (11) as well as other reports (27, 36). The reason of the reported leftward asymmetry in putamen and pallidum in above mentioned studies can be a more rapid decline in volume of right putamen and pallidum and a leftward shift in the asymmetry with age which has been reported before

(11, 37). The observed rightward asymmetry in the cerebellum is in agreement with previous studies as well (26, 27, 38). Although, a leftward asymmetry has been also reported (10). Regarding the effects of gender on brain asymmetries, while, no region survives Bonferroni correction in *post hoc* analysis, a few points about observed nominally significant asymmetries (Table.6) worth to be discussed. First, about 12% of cortical regions show a nominal gender effect on at least one of the metrics. Second, most of exaggerated tendencies to either side belong to male brain. This suggests male probably has a more lateralized brain which is in agreement with previously reported structural as well as functional studies (1, 10, 27, 39, 40). Third, the observed asymmetries are relatively subtle, with a Cohen's-*d* range of -0.19 to 0.19 (Table.6) which is also in line with previous reports (27, 41). Fourth, an important part of cortical language as well as visuospatial regions display following gender specific tendencies in male. Transverse temporal cortex, superior temporal and supramarginal gyri as well as inferior parietal cortex present an exaggerated rightward asymmetry in thickness. In addition, surface area displays an exaggerated leftward asymmetry in temporal pole, superior temporal and supramarginal gyri. Finally, an exaggerated leftward asymmetry in gray matter volume of temporal pole and supramarginal gyrus as well as a rightward asymmetry in superior parietal cortex was noted. The observed accentuated asymmetries in male are in agreement with reports indicating more left lateralized language (39) and right lateralized visuospatial functions in males (42). Furthermore, medial orbitofrontal cortex gray matter volume present an opposite tendency in asymmetry between genders i.e. rightward in female and leftward in male ($P < 002$, uncorrected). In addition, amygdala present an exaggerated rightward asymmetry in female. Although, several lines of

evidence suggest that medial prefrontal cortex and amygdala show a differential asymmetrical organization between genders which contribute to distinct cognitive and affective information processing, underlying mechanisms are far from being clear (43-46). The presence (10, 13, 14, 47) or absence of a significant effect of gender on asymmetry (18, 27, 28, 31, 34, 48) has been frequently reported. In addition of previous mentioned reasons of inconsistencies, this could reflect the fact that asymmetry as a principal developmental feature of human brain follows similar trajectories in both genders yielding only to subtle differences (18, 41). In addition, some reports suggest that gender effects on asymmetry might change with age (17). Furthermore, since the absolute values of intracranial volume as well as body size are larger in males, it is challenging to differentiate gender effects on asymmetry from those related to above mentioned factors (13, 31, 49). Finally, we did not observed a significant age effects on the asymmetry indices of structures studied. However, this obviously would not preclude a relationship between age and asymmetry as participants in this project has been chosen from young adults. This study, for the first time, has provided the asymmetry picture of whole brain structures in unprecedented number of carefully chosen young adults yielding to highly significant results. This provides a basis which would help to understand better this important hallmark of human brain.

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Table 1. Global asymmetry index for each metric of cerebral cortex and white matter.

			AI			<i>P</i>
			Mean	SD	<i>d</i>	
Cerebrum	Cortex	Thickness	-0.014	0.021	-0.65	0.000000
		Surface Area	-0.006	0.011	-0.54	0.000000
		Gray Volume	-0.018	0.019	-0.98	0.000000
	White Matter		-0.014	0.009	-1.51	0.000000

Fig. 1. Global asymmetry indices for metrics of cerebral cortex and white matter volume. Negative asymmetry ($R > L$) indicates rightward asymmetry. Error bars represent SEM

Table 2. Asymmetry Index for thickness of each cortical region

Region	AI			<i>P</i>
	Mean	SD	<i>d</i>	
Caudal anterior cingulate cortex	0.07	0.11	0.62	0.000000
Insula	0.01	0.05	0.28	0.000000
Posterior cingulate gyrus	0.01	0.07	0.21	0.000000
Parahippocampal gyrus	0.01	0.08	0.08	0.009564
Rostral anterior cingulate cortex	0.00	0.07	0.06	0.042102
Precentral gyrus	0.00	0.03	0.04	0.204130
Pericalcarine cortex	0.00	0.05	-0.03	0.303877
Cuneus cortex	0.00	0.05	-0.07	0.019816
Frontal pole	-0.01	0.07	-0.12	0.000041
Lingual gyrus	-0.01	0.05	-0.16	0.000000
Isthmus of cingulate gyrus	-0.03	0.17	-0.16	0.000000
Lateral orbitofrontal cortex	-0.01	0.04	-0.18	0.000000
Fusiform gyrus	-0.01	0.03	-0.19	0.000000
Caudal middle frontal gyrus	-0.01	0.03	-0.21	0.000000
Rostral middle frontal gyrus	-0.01	0.03	-0.22	0.000000
Paracentral sulcus	-0.01	0.04	-0.27	0.000000
Postcentral gyrus	-0.01	0.03	-0.32	0.000000
Pars orbitalis	-0.02	0.05	-0.34	0.000000
Inferior temporal gyrus	-0.01	0.04	-0.35	0.000000
Pars opercularis	-0.02	0.04	-0.40	0.000000
Precuneus cortex	-0.01	0.03	-0.42	0.000000
Superior frontal gyrus	-0.01	0.03	-0.44	0.000000
Entorhinal cortex	-0.04	0.08	-0.47	0.000000
Transverse temporal cortex	-0.03	0.06	-0.47	0.000000
Superior temporal gyrus	-0.02	0.03	-0.57	0.000000
Supramarginal gyrus	-0.02	0.03	-0.58	0.000000
Pars triangularis	-0.02	0.04	-0.60	0.000000
Lateral occipital cortex	-0.02	0.04	-0.63	0.000000
Superior parietal cortex	-0.02	0.03	-0.64	0.000000
Middle temporal gyrus	-0.02	0.03	-0.73	0.000000
Temporal pole	-0.06	0.08	-0.80	0.000000
Banks of superior temporal cortex	-0.04	0.05	-0.82	0.000000
Inferior parietal cortex	-0.03	0.03	-0.95	0.000000
Medial orbitofrontal cortex	-0.07	0.06	-1.15	0.000000

Fig. 2. Asymmetry indices of thickness in cortical regions. Positive asymmetry indicates leftward asymmetry (L > R), while negative asymmetry (R > L) indicates rightward asymmetry. Error bars represent SEM.

Table 3. Asymmetry Index for surface area of each cortical region

Region	AI			<i>P</i>
	Mean	SD	<i>d</i>	
Transverse temporal cortex	0.30	0.15	2.02	0.000000
Rostral anterior cingulate cortex	0.26	0.20	1.33	0.000000
Pars opercularis	0.17	0.16	1.10	0.000000
Temporal pole	0.13	0.14	0.97	0.000000
Entorhinal cortex	0.17	0.19	0.90	0.000000
Superior temporal gyrus	0.05	0.07	0.66	0.000000
Medial orbitofrontal cortex	0.07	0.12	0.55	0.000000
Caudal middle frontal gyrus	0.08	0.15	0.53	0.000000
Supramarginal gyrus	0.06	0.12	0.52	0.000000
Postcentral gyrus	0.04	0.09	0.51	0.000000
Banks of superior temporal cortex	0.07	0.15	0.47	0.000000
Isthmus of cingulate gyrus	0.10	0.23	0.43	0.000000
Lateral orbitofrontal cortex	0.03	0.06	0.41	0.000000
Inferior temporal gyrus	0.04	0.11	0.39	0.000000
Superior frontal gyrus	0.02	0.07	0.34	0.000000
Parahippocampal gyrus	0.04	0.13	0.33	0.000000
Fusiform gyrus	0.03	0.10	0.30	0.000000
Lateral occipital cortex	0.02	0.09	0.24	0.000000
Superior parietal cortex	0.00	0.08	-0.02	0.606280
Lingual gyrus	-0.01	0.09	-0.07	0.017981
Posterior cingulate gyrus	-0.03	0.16	-0.18	0.000000
Cuneus cortex	-0.02	0.14	-0.18	0.000000
Precentral gyrus	-0.02	0.07	-0.22	0.000000
Rostral middle frontal gyrus	-0.04	0.07	-0.51	0.000000
Precuneus cortex	-0.05	0.08	-0.67	0.000000
Caudal anterior cingulate cortex	-0.17	0.26	-0.67	0.000000
Insula	-0.06	0.08	-0.70	0.000000
Pericalcarine cortex	-0.09	0.12	-0.78	0.000000
Paracentral sulcus	-0.13	0.13	-1.04	0.000000
Pars triangularis	-0.15	0.14	-1.08	0.000000
Middle temporal gyrus	-0.10	0.08	-1.31	0.000000
Frontal pole	-0.32	0.18	-1.78	0.000000
Inferior parietal cortex	-0.18	0.10	-1.85	0.000000
Pars orbitalis	-0.22	0.12	-1.89	0.000000

Fig. 3. Asymmetry indices of surface area in cortical regions. Positive asymmetry indicates leftward asymmetry (L > R), while negative asymmetry (R > L) indicates rightward asymmetry. Error bars represent SEM.

Table 4. Asymmetry Index for gray matter volume of each cortical region.

Region	AI			<i>P</i>
	Mean	SD	<i>d</i>	
Transverse temporal cortex	0.25	0.17	1.45	0.000000
Rostral anterior cingulate cortex	0.25	0.22	1.15	0.000000
Pars opercularis	0.17	0.16	1.07	0.000000
Caudal anterior cingulate cortex	0.15	0.25	0.59	0.000000
Entorhinal cortex	0.11	0.19	0.59	0.000000
Parahippocampal gyrus	0.07	0.14	0.52	0.000000
Supramarginal gyrus	0.05	0.12	0.42	0.000000
Caudal middle frontal gyrus	0.06	0.16	0.37	0.000000
Postcentral gyrus	0.04	0.10	0.37	0.000000
Temporal pole	0.06	0.16	0.36	0.000000
Isthmus of cingulate gyrus	0.06	0.17	0.35	0.000000
Superior temporal gyrus	0.02	0.08	0.31	0.000000
Lateral orbitofrontal cortex	0.02	0.06	0.30	0.000000
Fusiform gyrus	0.03	0.11	0.30	0.000000
Inferior temporal gyrus	0.02	0.12	0.18	0.000000
Superior frontal gyrus	0.01	0.07	0.16	0.000000
Lateral occipital cortex	0.00	0.10	0.05	0.123153
Medial orbitofrontal cortex	-0.01	0.12	-0.06	0.040444
Posterior cingulate gyrus	-0.01	0.15	-0.09	0.002520
Lingual gyrus	-0.01	0.11	-0.10	0.001182
Precentral gyrus	-0.01	0.07	-0.14	0.000007
Cuneus cortex	-0.03	0.14	-0.23	0.000000
Superior parietal cortex	-0.02	0.09	-0.27	0.000000
Rostral middle frontal gyrus	-0.05	0.08	-0.63	0.000000
Insula	-0.04	0.07	-0.66	0.000000
Precuneus cortex	-0.06	0.08	-0.71	0.000000
Paracentral sulcus	-0.13	0.14	-0.89	0.000000
Pericalcarine cortex	-0.11	0.12	-0.90	0.000000
Banks of superior temporal cortex	-0.25	0.24	-1.04	0.000000
Pars triangularis	-0.19	0.16	-1.20	0.000000
Middle temporal gyrus	-0.12	0.09	-1.42	0.000000
Pars orbitalis	-0.23	0.13	-1.78	0.000000
Frontal pole	-0.31	0.18	-1.78	0.000000
Inferior parietal cortex	-0.21	0.10	-2.02	0.000000

Fig. 4. Asymmetry indices of gray matter volume in cortical regions. Positive asymmetry indicates leftward asymmetry (L > R), while negative asymmetry (R > L) indicates rightward asymmetry. Error bars represent SEM.

Table 5. Asymmetry Index for hippocampus, cerebellum and subcortical structures

Region	AI			<i>P</i>
	Mean	SD	<i>d</i>	
Pallidum	-0.10	0.13	-0.79	0.000000
Accumbens Area	-0.06	0.13	-0.45	0.000000
Amygdala	-0.05	0.08	-0.64	0.000000
Caudate Nucleus	-0.03	0.04	-0.75	0.000000
Cerebellum Cortex	-0.03	0.03	-0.99	0.000000
Cerebellum White Matter	-0.02	0.05	-0.29	0.000000
Hippocampus	-0.02	0.07	-0.22	0.000000
Putamen	-0.01	0.08	-0.18	0.000000
Thalamus	0.13	0.06	2.33	0.000000

Fig. 5. Asymmetry indices of hippocampus, cerebellum and subcortical regions. Positive asymmetry indicates leftward asymmetry ($L > R$), while negative asymmetry ($R > L$) indicates rightward asymmetry. Error bars represent SEM.

Fig.6. Cortical gray matter volume follows and strongly correlates with surface area across cortical regions ($R^2=0.96$, $p < 0.000001$) (A, B). However, cortical thickness does not show a significant correlation with surface area or gray matter volume (B). In addition, surface area (CV=14) and gray matter volume (CV=14) show more global variability compared with cortical thickness (CV=6) (A). Thickness and surface area values were multiplied by a constant to make comparison easier.

Fig 7. Asymmetry indices of cortical gray matter volume frequently follow and strongly correlate with asymmetry indices of surface area ($R^2=0.6$, $p < 0.000001$) (A, B). However, asymmetry indices of cortical thickness do not show a significant correlation with asymmetry indices of surface area or gray matter volume (B).

Table 6. Regions with nominally significant gender effect on asymmetry index

		Region	Gender	AI		<i>P</i>
				Mean	SD	
Thickness	Middletemporal gyrus	M	-0.028	0.034	-0.19	0.002
		F	-0.022	0.033		
	Superiorfrontal cortex	M	-0.013	0.027	-0.14	0.016
		F	-0.010	0.025		
	Transversetemporal cortex	M	-0.033	0.058	-0.14	0.017
		F	-0.024	0.061		
	Superiortemporal gyrus	M	-0.020	0.033	-0.14	0.017
		F	-0.016	0.029		
	Inferiorparietal cortex	M	-0.029	0.030	-0.13	0.025
		F	-0.025	0.027		
	Isthmuscingulate cortex	M	-0.039	0.184	-0.13	0.026
		F	-0.017	0.153		
Surface Area	Supramarginal gyrus	M	-0.019	0.030	-0.12	0.044
		F	-0.015	0.029		
	Isthmus of cingulate cortex	M	0.123	0.245	0.18	0.002
		F	0.080	0.223		
	Superiortemporal gyrus	M	0.055	0.074	0.18	0.002
		F	0.042	0.071		
	Supramarginal gyrus	M	0.071	0.119	0.17	0.006
		F	0.051	0.112		
	Temporal pole	M	0.145	0.137	0.17	0.006
		F	0.122	0.135		
	Medial orbitofrontal cortex	M	0.077	0.121	0.15	0.012
		F	0.059	0.122		
Gray Volume	Paracentral sulcus	M	-0.144	0.131	-0.13	0.030
		F	-0.127	0.129		
	Medial orbitofrontal cortex	M	0.004	0.116	0.18	0.002
		F	-0.017	0.114		
	Caudal anterior cingulate cortex	M	0.168	0.255	0.16	0.009
		F	0.129	0.240		
	Isthmus of cingulate cortex	M	0.075	0.162	0.15	0.011
		F	0.049	0.177		
	Paracentral sulcus	M	-0.140	0.144	-0.15	0.015
		F	-0.119	0.142		
	Insula	M	-0.049	0.066	-0.15	0.016
		F	-0.039	0.066		
Subcortical regions	Supramarginal gyrus	M	0.059	0.124	0.13	0.026
		F	0.043	0.117		
	Superior parietal cortex	M	-0.029	0.086	-0.13	0.027
		F	-0.018	0.087		
	Temporal pole	M	0.069	0.172	0.12	0.047
		F	0.050	0.152		
	Cerebellum white matter	M	-0.022	0.060	-0.19	0.001
		F	-0.011	0.049		
	Caudate nucleus	M	-0.035	0.041	-0.14	0.022
		F	-0.029	0.042		
	Amygdala	M	-0.045	0.077	0.13	0.029
		F	-0.055	0.079		

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