Mapping cortical brain asymmetry in 17,141 healthy individuals worldwide via the ENIGMA Consortium

Xiang-Zhen Kong[a,1], Samuel R. Mathias[b], Tulio Guadalupe[a], ENIGMA Laterality Working Group[2], David C. Glahn[b,c], Barbara Franke[d,e], Fabrice Crivello[f], Nathalie Tzourio-Mazoyer[f], Simon E. Fisher[a,g], Paul M. Thompson[h], and Clyde Francks[a,g,1]

[a]Language and Genetics Department, Max Planck Institute for Psycholinguistics, 6525 XD Nijmegen, The Netherlands; [b]Department of Psychiatry, Yale University School of Medicine, New Haven, CT 06511; [c]Olin Neuropsychiatry Research Center, Institute of Living, Hartford Hospital, Hartford, CT 06106; [d]Department of Human Genetics, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, 6525 GA Nijmegen, The Netherlands; [e]Department of Psychiatry, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, 6525 GA Nijmegen, The Netherlands; [f]Institut des Maladies Neurodégénératives, UMR 5293, Groupe d'Imagerie Neurofonctionnelle, Commissariat à l'énergie atomique et aux énergies alternatives–CNRS–Université de Bordeaux, 33076 Bordeaux cedex, France; [g]Donders Institute for Brain, Cognition and Behavior, Radboud University, 6525 EN Nijmegen, The Netherlands; and [h]Imaging Genetics Center, Mark and Mary Stevens Neuroimaging and Informatics Institute, Keck School of Medicine, University of Southern California, Marina del Rey, CA 90292

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Hemispheric asymmetry is a cardinal feature of human brain organization. Altered brain asymmetry has also been linked to some cognitive and neuropsychiatric disorders. Here, the ENIGMA (Enhancing NeuroImaging Genetics through Meta-Analysis) Consortium presents the largest-ever analysis of cerebral cortical asymmetry and its variability across individuals. Cortical thickness and surface area were assessed in MRI scans of 17,141 healthy individuals from 99 datasets worldwide. Results revealed widespread asymmetries at both hemispheric and regional levels, with a generally thicker cortex but smaller surface area in the left hemisphere relative to the right. Regionally, asymmetries of cortical thickness and/or surface area were found in the inferior frontal gyrus, transverse temporal gyrus, parahippocampal gyrus, and entorhinal cortex. These regions are involved in lateralized functions, including language and visuospatial processing. In addition to population-level asymmetries, variability in brain asymmetry was related to sex, age, and intracranial volume. Interestingly, we did not find significant associations between asymmetries and handedness. Finally, with two independent pedigree datasets (n = 1,443 and 1,113, respectively), we found several asymmetries showing significant, replicable heritability. The structural asymmetries identified and their variabilities and heritability provide a reference resource for future studies on the genetic basis of brain asymmetry and altered laterality in cognitive, neurological, and psychiatric disorders.

brain asymmetry | lateralization | cortical thickness | surface area | meta-analysis

Understanding the functional specialization of the cerebral hemispheres is a long-standing and central issue in human neuroscience research. At the population level, hemispheric asymmetry, or lateralization, is involved in various perceptual and cognitive functions, including language (1), face processing (2, 3), visuospatial processing (4, 5), and reasoning (6), as well as handedness (7). For example, language lateralization involves leftward dominance for various processes involved in speech perception and production in most people (1). Moreover, altered hemispheric lateralization has been associated with numerous cognitive and neuropsychiatric disorders, including dyslexia (8), Alzheimer's disease (9), attention-deficit/hyperactivity disorder (ADHD) (10), psychotic disorders (11–13), autism (14), and mood disorders (15, 16). Various aspects of brain asymmetry, including anatomical asymmetries of perisylvian language-related cortical regions, appear in utero during the second trimester of gestation (17, 18). Thus, brain laterality is likely to be under the control of genetic-developmental programs which are inherently lateralized, such as those that have been described for the left–right visceral axis (affecting the placement of the heart, lungs, etc.) (19, 20). Together, these observations indicate that asymmetry is a core element of the brain's usual organization, which is required for optimal functioning and influenced by genetic factors.

Although structural and functional asymmetries are likely to be interrelated in the typically lateralized human brain, the nature of structure–function relations is far from clear. For example, it is still not understood whether anatomical asymmetries around the Sylvian fissure are an important aspect of left-hemisphere language dominance (21, 22). Furthermore, variations in structural and functional asymmetry have been reported to correlate poorly (23–26), which further complicates assessment of the structure–function relations and dependencies. The literature,

Significance

Left–right asymmetry is a key feature of the human brain's structure and function. It remains unclear which cortical regions are asymmetrical on average in the population and how biological factors such as age, sex, and genetic variation affect these asymmetries. Here, we describe by far the largest-ever study of cerebral cortical asymmetry, based on data from 17,141 participants. We found a global anterior–posterior "torque" pattern in cortical thickness, together with various regional asymmetries at the population level, which have not been previously described, as well as effects of age, sex, and heritability estimates. From these data, we have created an online resource that will serve future studies of human brain anatomy in health and disease.

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Data deposition: The complete statistics from the meta-analyses, and scripts have been deposited in GitHub (https://github.com/Conxz/neurohemi).

[1]To whom correspondence may be addressed. Email: xiangzhen.kong@outlook.com or clyde.francks@mpi.nl.

[2]A complete list of the ENIGMA Laterality Working Group can be found in the *SI Appendix*.

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however, has been based on generally small sample sizes and heterogeneous methods for assessing asymmetries and their variabilities, leading to confusion about which structures are actually anatomically asymmetrical at the population level, and to what degrees. This has also been the case for asymmetry-disorder studies. In this context, and as motivation for the present study, it is important to characterize anatomical asymmetries in a large sample of healthy individuals to provide a definitive and normative reference for future studies of hemispheric specialization in both healthy and clinical populations.

One aspect of structural asymmetry in the human brain is "Yakovlevian torque," an overall hemispheric twist giving rise to the frontal and occipital petalia, which describes protrusions of the right frontal and left occipital regions over the midline (27, 28). At a regional level, later studies that applied computational methods to MRI data mainly focused on volumetric measures of cortical structures and revealed both replicable and inconsistent findings of asymmetries. For example, Goldberg et al. (29) summarized in their study that regions implicated in visual processing show rightward volumetric asymmetries, while, in contrast, somatosensory, auditory, and parts of the premotor cortices show leftward volumetric asymmetries. One recent study replicated this distribution of regional asymmetries, especially in the lateral view (30), but several studies have shown quite different asymmetry results (27, 31, 32). For example, Goldberg et al. (29) and Esteves et al. (30) found a greater superior frontal volume in the left hemisphere, while Watkins et al. (27) found greater superior frontal volume in the right.

Cortical volume is, by definition, a product of two distinct aspects of the brain, i.e., cortical thickness and surface area (33, 34); researchers have also attempted to assess the asymmetries of cortical thickness and surface area separately, using surface-based approaches (35, 36). Regarding cortical thickness, a number of studies have found mixed results for asymmetry patterns. For example, Luders et al. (37) found greater left-sided thickness in parts of the cingulate, precentral gyrus, orbital frontal gyrus, and temporal and parietal lobes, and greater right-sided thickness in the inferior frontal gyrus. However, other studies (38–41) revealed somewhat inconsistent patterns of thickness asymmetry. For instance, Zhou et al. (41), studying individuals of an age range similar to that in Luders et al. (37), did not find leftward asymmetry in the precentral gyrus, but revealed a strong rightward asymmetry in the lateral parietal and occipital regions. For an overview of mixed results of asymmetry patterns observed in previous studies, refer to *SI Appendix*, Fig. S1. Regarding regional surface area asymmetries, some repeatable findings have been found for the supramarginal gyrus (leftward) (38, 39, 42), the middle temporal gyrus (rightward) (38, 39), and the anterior cingulate gyrus (rostral: leftward; caudal: rightward) (38, 39). However, there are also many inconsistent results across studies, such as for the lateral occipital cortex, which showed a strong rightward asymmetry in Chiarello et al. (43), but leftward asymmetry in Koelkebeck et al. (38) (see a summary in ref. 44). These mixed results of brain structural asymmetry may reflect differences in many factors, including statistical power and confidence intervals related to sample sizes, as well as differences in scanning, brain segmentation, and parcellation methods. Thus, a large-scale survey using harmonized approaches is needed to give a clearer picture of the lateralization in the human brain.

Another potential source for the mixed results in the literature is variability across individuals and in relation to factors like age and sex (45–47). For example, a recent study observed that males show, on average, more pronounced gray matter volume asymmetries in superior temporal language regions than females (48). Changes in structural asymmetries with age have also been reported (10, 49), but not consistently (41). Another potential factor linked to brain lateralization is handedness, although the associations are very weak as reported (26, 39, 50). For example, with >100 left-handed participants and ~2,000 right-handed participants, Guadalupe et al. (26) suggested an association of handedness with the surface area of the left precentral sulcus, but this was not significant after multiple testing adjustments. In addition, greater cortical asymmetry has been observed in participants with larger overall brain size (44). Thus, the existing literature on variability in brain structural asymmetries suggests influences of individual differences in age, sex, handedness, and brain size, but, again, a large-scale study is needed to clarify the nature of any such relations. The largest previous studies of brain asymmetries were conducted by Plessen et al. (40) and Zhou et al. (41) in relation to sex and age in sample sizes of 215 and 274 participants, and Maingault et al. (39) in a sample size of 250 (120 left-handers) in relation to handedness. Each of these studies used different methodological approaches. Thus, a large-scale study of thousands of participants would be a major step forward in achieving a more accurate description of the typical asymmetries of the human brain, as well as variation in these asymmetries and some key biological factors which affect them.

The ENIGMA (Enhancing NeuroImaging Genetics through Meta-Analysis) Consortium provides the opportunity for large-scale meta-analysis studies of brain anatomy based on tens of thousands of participants with structural MRI data (51). We used a "meta-analysis" model, for which it was not necessary to send individual data out of the laboratories where they were collected. This helped to maximize participation and therefore the overall sample size. In this study, we present the largest analysis of structural asymmetries in the human cerebral cortex, with MRI scans of 17,141 healthy individuals from 99 datasets worldwide, in a harmonized multisite study using meta-analytic methods. Our aim was to identify cortical regions that consistently show asymmetry with regard to either cortical thickness or surface area, to provide a clear picture of population-level asymmetries in the human brain. We also assessed potential influences of age, sex, handedness, and brain size (indexed by intracranial volume; ICV) on the variability in asymmetries, as well as of the methodological factor of MRI scanner field strength. Furthermore, as a first step toward elucidating the genetic basis of variability in brain asymmetry, we further analyzed two independent pedigree datasets, i.e., the Genetics of Brain Structure (GOBS; n = 1,443) and Human Connectome Project (HCP; n = 1,113) datasets, to estimate heritability of the asymmetry measures.

Results

Ninety-nine independent datasets were contributed by members of the Lateralization Working Group within the ENIGMA Consortium (51), including data from 17,141 individuals from population or healthy control cohorts. Fig. 1 summarizes the sample sizes and age ranges of each dataset (for more details, see Dataset S1).

Meta-Analysis of Population-Level Asymmetry. Meta-analysis of population-level asymmetry revealed widely distributed asymmetries in both cortical thickness and surface area. Specifically, we found global differences between the two hemispheres, with generally thicker cortex in the left hemisphere (b = 0.13, Z = 3.64, P = 0.00040; Fig. 2), but larger surface area in the right hemisphere (b = −0.33, Z = −11.30, P = 1.36e-29; Fig. 3).

Substantial, regionally specific differences between the two hemispheres were also observed for both cortical thickness and surface area. In terms of cortical thickness, 76.5% (26/34) of the regions showed significant asymmetry, after correcting for multiple comparisons ($P < 0.05$, Bonferroni corrected). Specifically, regions showing significant leftward asymmetry (i.e., left > right) of cortical thickness were identified in the anterior cortex, including the lateral, dorsal, and medial frontal cortex, the primary sensory, superior parietal, cingulate, and medial temporal cortices (Fig. 4 and Dataset S2). In contrast, rightward asymmetry

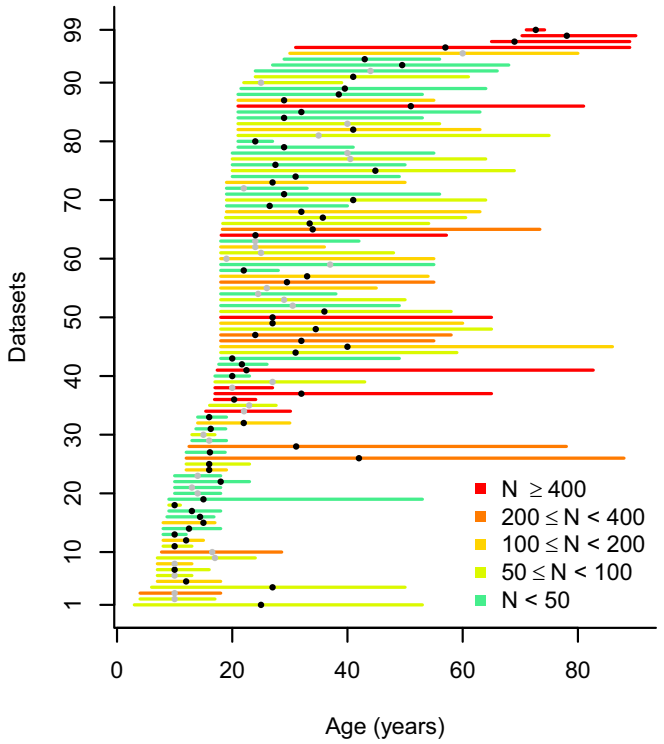

Fig. 1. The age ranges and sizes of each dataset. Each line covers the age range of an individual dataset, with different colors indicating the sample sizes (see color key). The position of the gray/black dot on each line indicates the median age of that dataset. Black dots indicate datasets with handedness information available. For more details, see Dataset S1.

(i.e., right > left) was prominent in the posterior regions, including lateral and medial parts of the temporal, parietal, and occipital cortices. This fronto-occipital asymmetry pattern in cortical thickness is striking (Fig. 4) and may also relate to the petalia and Yakovlevian torque effects described above (*Discussion*). In addition, three temporal regions (especially the inferior temporal and fusiform gyri) showed a trend of rightward asymmetry as defined by uncorrected $P < 0.05$ (inferior temporal: $b = -0.11$, $Z = -2.92$, uncorrected $P = 0.0035$; fusiform: $b = -0.09$, $Z = -2.64$, uncorrected $P = 0.0082$; middle temporal: $b = -0.10$, $Z = -2.19$, uncorrected $P = 0.029$).

Similarly, 91.1% (31/34) of the regions showed significant asymmetries of their surface areas after correcting for multiple comparisons ($P < 0.05$, Bonferroni corrected). However, unlike thicknesses, the surface area asymmetries showed no obvious leftward or rightward patterns involving neighboring areas or generally along the fronto-occipital axis (Fig. 5 and Dataset S2). Two language-related regions showed the largest leftward asymmetries of surface area, which were the opercular part of the inferior frontal gyrus (posterior part of the Broca's area) and the transverse temporal gyri (Heschl's gyri). In contrast, however, another two language-related regions, i.e., the triangular part of the inferior frontal gyrus (anterior part of the Broca's area) and the inferior parietal gyrus, showed strong rightward asymmetries of surface area. These findings suggest that opposite asymmetries in morphology of regions within a given network (i.e., language network), or within one functional area (the Broca's area), might be linked to different roles of each constituent part (*Discussion*).

Effect sizes of cortical thickness and surface area were found to be independent, as illustrated by the absence of a significant correlation between thickness and surface area asymmetries across all cortical regions ($r = -0.14$, $P = 0.416$).

Moderator Analyses Using Metaregression. As shown above, we observed moderate to substantial heterogeneity in the asymmetry distributions across datasets. To further address the heterogeneity

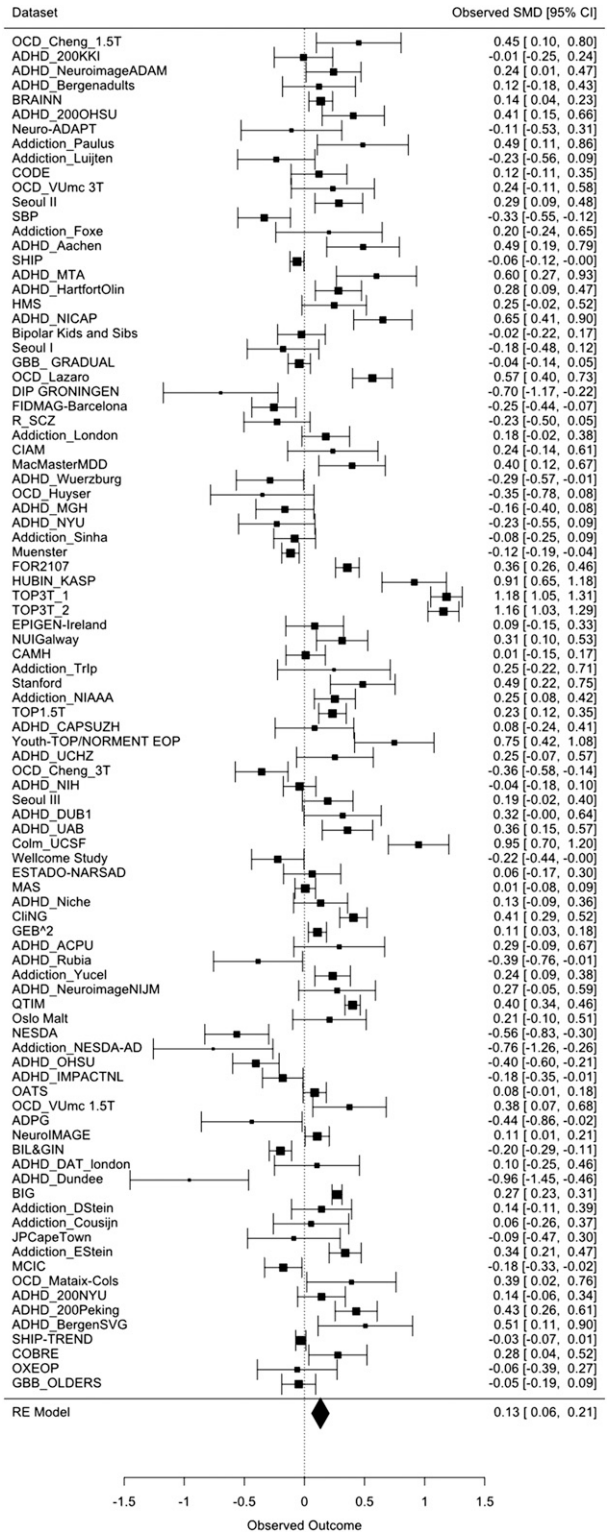

Fig. 2. Forest plot of asymmetry score per dataset, for the overall asymmetry in cortical thickness. Asymmetry score indicates the effect size of the interhemispheric difference. The size of a square is proportional to the weights assigned in meta-analysis. The confidence intervals are shown, as well as a dashed vertical line to indicate the point of an asymmetry score of zero.

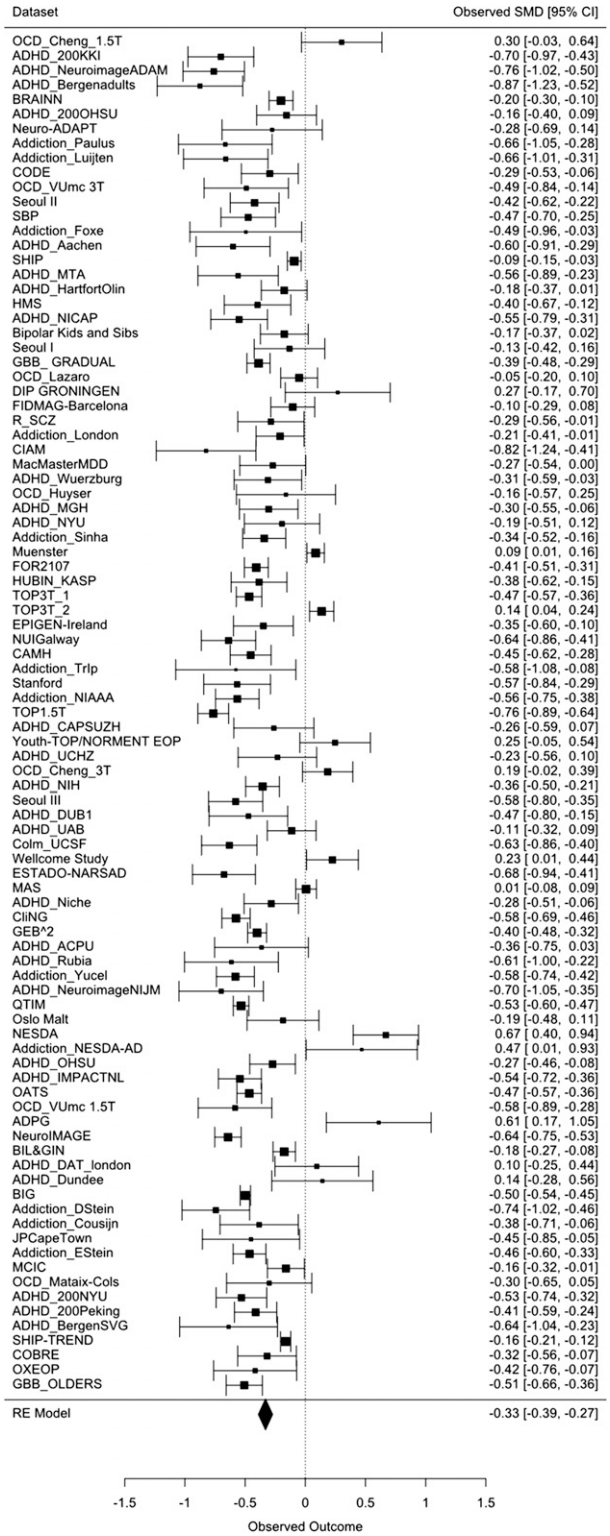

Fig. 3. Forest plot of asymmetry score per dataset, for the overall asymmetry in surface area. Asymmetry score indicates the effect size of the interhemispheric difference. The size of a square is proportional to the weights assigned in meta-analysis. The confidence intervals are shown, as well as a dashed vertical line to indicate the point of an asymmetry score of zero.

in the meta-analyses, we investigated several moderating variables, including sex ratio, median age, handedness ratio, and median ICV. Moderator analyses revealed an influence of the median age of samples on the global hemispheric difference in surface area ($Z = 2.09$, $P = 0.036$), suggesting a reduced rightward asymmetry with increasing age. In addition, we observed an influence of the median age on the surface area asymmetry of the paracentral gyrus ($Z = -4.35$, $P = 1.38e\text{-}5$) and an influence of median ICV on the surface area asymmetry in the insula ($Z = -3.18$, $P = 0.0014$). No other potential moderators showed significant effects (*SI Appendix, SI Results*).

Meta-Analysis of Sex Effects on Cortical Asymmetries. No significant sex effect on the asymmetry index, defined as $(L - R)/((L + R)/2)$, of total mean cortical thickness was found ($P > 0.10$), but notable regionally specific effects on thickness asymmetries were observed in the medial temporal regions (Fig. 6), including the parahippocampal gyrus ($Z = 3.57$, $P = 0.00036$) and the entorhinal cortex ($Z = 3.61$, $P = 0.00030$), after correcting for multiple comparisons. Together with the population-level asymmetry observed, these results indicate that males show more leftward and less rightward asymmetry in cortical thickness of the parahippocampal gyrus and the entorhinal cortex, respectively.

We found a significant sex difference in global asymmetry of surface area ($Z = -2.62$, $P = 0.0088$), indicating that males have more rightward overall asymmetry in surface area, compared with females. In addition, metaregression analysis showed that this effect changed with the median ages of samples: We found larger effects of sex (females > males) in the younger samples, compared with the older samples ($Z = 2.80$, $P = 0.0052$). Regionally specific effects of sex on surface area asymmetry were also revealed (Fig. 6), located in the frontal (superior frontal gyrus, the pars orbitalis region of the left inferior frontal gyrus), temporal (superior temporal gyrus, temporal pole, parahippocampal gyrus, and fusiform gyrus), parietal (inferior parietal gyrus and supramarginal gyrus), and anterior cingulate cortices. In addition, various other regions showed nominally significant sex effects (uncorrected $P < 0.05$) without surviving correction for multiple comparisons. More information can be seen in Dataset S3.

Meta-Analysis of Age Effects on Cortical Asymmetries. An initial analysis of samples with an age range of >5 y showed no significant effects of age on global asymmetries of either cortical thickness or surface area ($P > 0.10$). Several regionally specific, nominally significant effects were found: the superior temporal gyrus (cortical thickness: $Z = 2.38$, $P = 0.017$), the banks of superior temporal sulcus (surface area: $Z = -1.97$, $P = 0.049$), and the entorhinal cortex (surface area: $Z = 2.84$, $P = 0.0045$). However, when restricting the analysis to only those datasets with wider age ranges (at least 20-y range), we observed significant age effects. Specifically, increasing age was associated with more pronounced leftward overall asymmetry in cortical thickness ($Z = 2.65$, $P = 0.0081$), which partly reflects a similar age effect on the thickness asymmetry of the superior temporal gyrus ($Z = 3.17$, $P = 0.0015$; Fig. 6). In addition, a similar effect on regional surface area asymmetry was observed in the entorhinal cortex ($Z = 3.21$, $P = 0.0013$). An age effect on surface area asymmetry of the banks of the superior temporal sulcus was nominally significant ($Z = -1.96$, $P = 0.050$). More information can be found in Dataset S4.

Meta-Analysis of Group Differences by Handedness on Cortical Asymmetries. We did not find significant associations of handedness with cortical asymmetries, even with this unprecedented sample size (555–608 left-handers vs. 6,222–7,243 right-handers from 11–14 datasets, depending on the specific regional asymmetry measure). Given the considerable preponderance of right-handers in most datasets, which might complicate the estimation of handedness effects, we further confirmed these findings within one of the datasets (i.e., BIL&GIN) which was roughly balanced for handedness (right: $n = 248$; left: $n = 205$). In the meta-analysis, several temporal regional surface area asymmetries

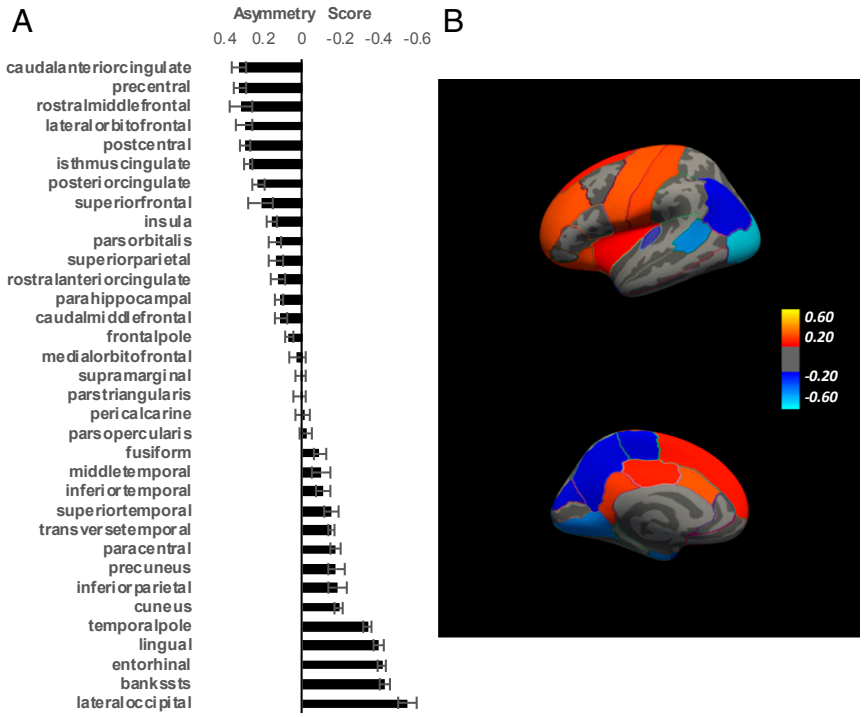

Fig. 4. Average regional asymmetries in cortical thickness reveal a fronto-occipital pattern. Positive asymmetry (*A*, left side; red in *B*) indicates leftward asymmetry, while negative asymmetry (*A*, right side; blue in *B*) indicates rightward asymmetry. Asymmetry score indicates the effect size of the interhemispheric difference. Error bars indicate SEM. L, left; R, right.

showed nominally significant associations with handedness, including the fusiform gyrus: $Z = 2.00$, $P = 0.046$; the parahippocampal gyrus: $Z = -2.33$, $P = 0.020$; and the superior temporal gyrus: $Z = -2.04$, $P = 0.042$. More information can be found in Dataset S5.

Meta-Analysis of ICV Effects on Cortical Asymmetry. ICV showed a significant positive effect (i.e., increased leftward asymmetry) on the overall asymmetry in cortical thickness ($Z = 2.14$, $P = 0.032$). Similar regionally specific effects on cortical thickness asymmetry were found for the inferior parietal gyrus ($Z = 4.51$, $P = 6.53\text{e-}6$) and insula ($Z = 3.71$, $P = 0.00021$). A negative effect of greater ICV (i.e., decreased leftward asymmetry) was seen in the rostral anterior cingulate gyrus ($Z = -5.23$, $P = 1.68\text{e-}7$) (Fig. 6). No significant effect of ICV was found for the overall asymmetry in surface area ($P > 0.10$), but a number of regionally specific effects were revealed (in different directions). Positive effects of greater ICV (i.e., increased leftward/decreased rightward asymmetry)

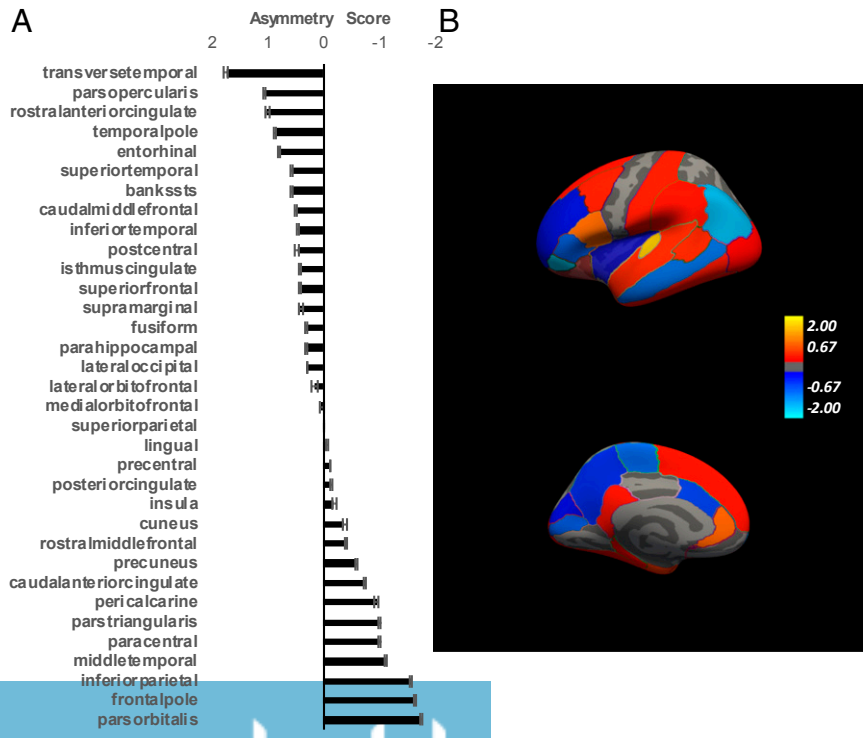

Fig. 5. Average asymmetry pattern in surface area. Positive asymmetry (*A*, left side; red in *B*) indicates leftward asymmetry, while negative asymmetry (*A*, right side; blue in *B*) indicates rightward asymmetry. Asymmetry score indicates the effect size of the interhemispheric difference. Error bars indicate SEM. L, left; R, right.

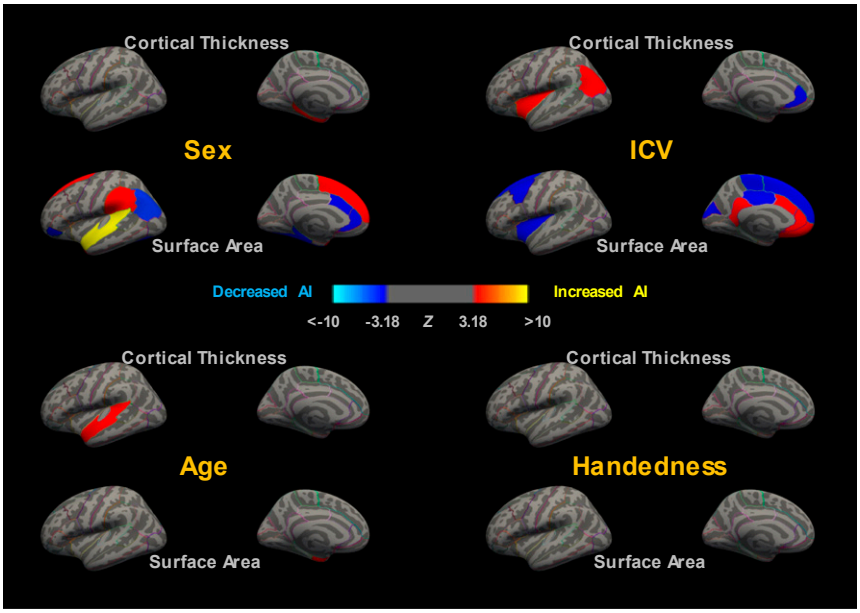

Fig. 6. Meta-analysis results for effects of sex, age, ICV, and handedness on regional asymmetry indexes in cortical thickness and surface area. Red–yellow indicates an increased asymmetry index (AI) in males/with age and ICV; blue–light blue indicates a decreased AI in males/with age and ICV. AI was defined as (L − R)/((L + R)/2). A Z threshold of 3.18 ($P = 0.05$, Bonferroni corrected) was used. For more details, see Datasets S3–S6.

were observed in the medial orbitofrontal gyrus ($Z = 4.17$, $P = 3.10e\text{-}5$), two anterior cingulate gyri (caudal: $Z = 5.71$, $P = 1.10e\text{-}8$; rostral: $Z = 5.67$, $P = 1.45e\text{-}8$), and the isthmus cingulate gyrus ($Z = 4.32$, $P = 1.59e\text{-}5$) (Fig. 6). In addition, negative effects of greater ICV (i.e., increased rightward/decreased leftward asymmetry) were seen for the superior frontal gyrus ($Z = -6.58$, $P = 4.82e\text{-}11$), the caudal middle frontal gyrus ($Z = -3.65$, $P = 0.00026$), the paracentral gyrus ($Z = -5.19$, $P = 2.11e\text{-}7$), the insula ($Z = -5.92$, $P = 3.13e\text{-}9$), the posterior cingulate gyrus ($Z = -3.24$, $P = 0.0012$), and the cuneus ($Z = -4.49$, $P = 7.12e\text{-}6$) (Fig. 6). More information can be seen in Dataset S6.

Heritability of Cerebral Cortical Anatomical Asymmetries. In the GOBS dataset, the overall hemispheric asymmetries of both cortical thickness and surface area showed low but statistically significant heritabilities (cortical thickness asymmetry: $h^2 = 0.10$, $P = 0.005$; surface area asymmetry: $h^2 = 0.17$, $P = 0.00024$). The most heritable asymmetries in regional cortical thickness were found in the isthmus ($h^2 = 0.17$) and caudal anterior cingulate gyrus ($h^2 = 0.13$), the superior ($h^2 = 0.13$) and rostral middle frontal gyrus ($h^2 = 0.18$), the parahippocampal gyrus ($h^2 = 0.15$), and the lateral occipital gyrus ($h^2 = 0.16$) ($P < 0.05$, Bonferroni corrected; Table 1). The most heritable asymmetries in regional surface area were found in the entorhinal cortex ($h^2 = 0.24$), the superior temporal gyrus ($h^2 = 0.19$), the inferior parietal gyrus ($h^2 = 0.19$), and the isthmus cingulate gyrus ($h^2 = 0.17$) ($P < 0.05$, Bonferroni corrected; Table 1). For each of these regions, we also estimated the genetic correlation between the measures of the left and right structures. While these correlations were high (indicating high pleiotropy), all were significantly different from 1 (Table 1). These results indicate that most genetic effects on structural variation are shared bilaterally, but some independent genetic effects exist on each hemisphere, which constitute the heritable contributions to structural asymmetry. Finally, we found that the heritability of most of these regions was validated in the HCP dataset. For more details, see Dataset S7.

Discussion

In the largest-ever analysis of asymmetry of cerebral cortical structure, we applied a meta-analytic approach to brain MRI data from 17,141 healthy individuals from datasets across the world. The findings revealed substantial interhemispheric differences in both regional cortical thickness and surface area and linked some of these asymmetries to sex, age, and ICV. Handedness was not significantly associated with cortical asymmetries. While previous findings are based on low hundreds of participants and different methodological approaches, this study of >17,000 participants is a major step forward in achieving a more accurate description of the typical asymmetries of the human brain, as well as variation in these asymmetries and some key individual differences factors which affect them. Moreover, with two independent pedigree datasets (i.e., GOBS and HCP), we revealed that several regions showed significant heritability of asymmetry measures.

Cortical Thickness. Regions with significant leftward asymmetry in thickness (i.e., left > right) were identified mainly in the frontal cortex, as well as the primary sensory, superior parietal, and medial temporal cortices, while rightward asymmetry was prominent in the posterior cortex, including lateral and medial parts of the temporal, parietal, and occipital cortices. This striking asymmetry pattern along the fronto-occipital axis is similar to that reported by Plessen et al. (40) and may be related to the Yakovlevian torque, i.e., the frontal/occipital bending in the human brain (28). Specifically, the torque refers to the phenomenon of crossing of the interhemispheric fissure by one hemisphere into the domain of the other. The frontal and occipital bending are the main twisting effects of the torque in opposite directions, with right frontal bending to the left and left occipital bending to the right (52). At the population level, we found that the frontal regions showed leftward asymmetry in cortical thickness, while the occipital regions showed rightward asymmetry.

There were some inconsistencies when comparing our results with previous studies. For example, in 215 healthy participants, Plessen et al. (40) observed a leftward asymmetry in the inferior frontal cortex, which includes Broca's area in the inferior frontal gyrus. The authors suggested that this might correspond anatomically with the functional asymmetry for expressive language in these regions, as has been reported on the basis of brain lesion studies and functional neuroimaging studies (53, 54). However, this interpretation should be considered with caution in light of a recent study on cortical thickness asymmetries with 250 adults showing an opposite direction of asymmetry (rightward) in this region (38). In the present study, with a much larger sample size, we failed to detect any cortical thickness asymmetry in this region (i.e., the pars opercularis and pars triangularis of the inferior frontal gyrus, uncorrected $P > 0.45$). Another difference with

Table 1. Significant heritabilities for asymmetry measures based on the GOBS family dataset

	AI heritability		Left–right genetic correlation			Left–right phenotypic and environmental correlation	
Structure	h2	*P*	Rho	*P* (rho = 0)	*P* (rho = 1)	Rho-phen	Rho-env
Thickness							
Hemisphere	0.10	0.0051	0.99	4.37E-22	0.024	0.95	0.90
Caudalanteriorcingulate	0.13	0.00037	0.72	0.0000016	0.0023	0.29	0.11
Isthmuscingulate	0.17	0.00026	0.82	4.64E-19	0.000045	0.55	0.27
Lateraloccipital	0.16	0.00062	0.91	7.68E-19	0.0012	0.74	0.58
Parahippocampal	0.15	0.00075	0.90	5.1E-28	0.0038	0.66	0.47
Rostralmiddlefrontal	0.18	0.000028	0.88	1.74E-15	0.000053	0.71	0.57
Superiorfrontal	0.13	0.0012	0.95	1.17E-14	0.0051	0.83	0.75
Surface area							
Hemisphere	0.17	0.00025	0.99	3.73E-24	0.0036	0.96	0.93
Entorhinal	0.24	0.0000047	0.74	6.15E-09	0.0039	0.44	0.29
Inferiorparietal	0.19	0.000085	0.76	2.43E-11	0.000055	0.50	0.33
Isthmuscingulate	0.17	0.00028	0.73	3.5E-10	0.00015	0.40	0.18
Superiortemporal	0.19	0.000014	0.84	2.64E-18	0.000069	0.59	0.36

In the left part of the table are the heritability and *P* values; in the center part are the genetic correlations between the left and right structural measures and *P* values for whether the genetic correlations differ significantly from 0 or 1. In the right part of the table are the environmental (rho-env) and phenotypic (rho-phen) correlation estimates between the left and right regions.

previous findings concerns the supramarginal gyrus, which showed a strong leftward asymmetry in Plessen et al. (40), but no asymmetry in two other studies (37, 38) and also not in the present study. This indicates an absence of population-level lateralization in cortical thickness in the supramarginal gyrus and again underlines the value of the present study in achieving a more accurate characterization of the average anatomical brain laterality.

There are several issues that may contribute to discrepancies of our present results with these previous studies, including the large sample size that we used, as well as the worldwide population. Varying demographic factors, such as sex and age, across the various previous studies might also have played an important role. In the present study, we identified several regions showing significant effects of these factors on the asymmetry of cortical thickness. For sex, notable effects were observed in the medial temporal regions, including the parahippocampal gyrus (more leftward in males) and the entorhinal cortex (more rightward in females), while mixed results have been obtained in previous studies (40, 44). Considering the critical roles of these two regions in visuospatial processing and spatial navigation (e.g., refs. 55 and 56), these sex differences may be related to the tendency for a slight male advantage on spatial tasks (57–59). In addition, these regions are important for Alzheimer's disease (e.g., ref. 60), which also shows sex differences in prevalence (61, 62). In contrast to Plessen et al. (40), we found no sex differences in cortical thickness asymmetry of core regions of the language network, including the pars opercularis and pars triangularis of the inferior frontal gyrus (the Broca's area), the transverse temporal gyrus (the Heschl's gyrus), and the supramarginal gyrus (uncorrected $P > 0.05$). These results are consistent with two other studies (37, 44) and indicate that subtle sex differences in the performance on language tasks and language lateralization (57) cannot be linked to sex differences in cortical thickness asymmetry of these regions.

In terms of age effects, when limiting our analysis to only the datasets with an age range >20 y, we found a significant correlation between age and the overall hemispheric asymmetry in cortical thickness (i.e., increasing age correlated with more pronounced leftward asymmetry), which was mainly contributed by the superior temporal gyrus. This finding is consistent with previous studies (40, 41), although we did not detect age effects in other regions reported by Plessen et al. (40). Brain size is another factor that can affect functional organization (63). In the present study, we found a significant effect of ICV on the overall asymmetry in cortical thickness, such that the leftward asymmetry in cortical thickness increases in larger brains. This effect was the most pronounced in the inferior parietal gyrus and the insula. Our findings on ICV are in accord with the hypothesis that asymmetries increase in larger brains, which might relate to the increased interhemispheric distance and transfer time in larger brains (64).

In addition, previous studies have suggested that magnet field strengths could affect cortical thickness measures, likely due to differences in the intensity and contrast of the images (e.g., ref. 65). However, in the present study, we focused on asymmetry measures as relative not absolute left–right differences, which likely reduced any potential effects from different scanners unless they would be unilateral. As expected, we did not find a significant effect of magnet field strength on cortical thickness asymmetry in the moderator analyses, and separate meta-analysis for 1.5- and 3-T scanners showed comparable results (*SI Appendix*, *SI Results*). These findings suggest that any effects of magnet field strength on the asymmetry measures were limited.

Surface Area. Regarding surface area, population-level asymmetry was generally more prominent compared with that of cortical thickness. A large majority of regions showed significant asymmetry in surface area, although with no obvious directional pattern affecting neighboring regions, or along the anterior–posterior axis, as we observed for thicknesses. The present study detected some similar asymmetry patterns of surface area to those of two previous studies (38, 43). Specifically, consistent results included leftward asymmetry of the superior frontal gyrus, the postcentral gyrus, supramarginal gyrus, and the entorhinal cortex, and rightward asymmetry in the caudal anterior cingulate cortex and the middle temporal gyrus (38, 39, 43, 44). The leftward asymmetry of surface area in the supramarginal gyrus is consistent with the widely observed volume asymmetry in the perisylvian regions, which is related to an asymmetrical shift caused by the brain torque (27, 31, 32, 39, 66). In addition, previous studies of postmortem anatomy found that in most people, the planum temporale on the left side is larger than the

right (55–67%) (67, 68). Consistent with this, we found leftward asymmetry of the superior temporal gyrus, although there is no region specifically defined in the Desikan–Killiany atlas (69) that is directly comparable with this earlier literature.

We identified several additional regions that are asymmetric in terms of surface area and were not previously described. Among these regions, two language-related regions, including the opercular part of the inferior frontal gyrus (the posterior part of Broca's area) and the transverse temporal gyrus (Heschl's gyrus), showed the largest leftward asymmetries. Based on these findings, the asymmetry of surface area [rather than cortical thickness as suggested in Plessen et al. (40)] may correspond anatomically with language lateralization in these regions, although further study is needed investigating both structure and function. Moreover, we found two other language-related regions showing strong asymmetry in the opposite direction (rightward), including the triangular part of the inferior frontal gyrus (the anterior part of Broca's area) and the inferior parietal gyrus. Taking these observations together, it appears that the structural basis of functional language lateralization is more complex than previously thought. For example, as mentioned above, for Broca's area, one of the most well-established areas for language function and language lateralization, while we did not detect asymmetry in terms of cortical thickness, we indeed observed strong asymmetry in surface area within this region. Moreover, the asymmetry was in different directions in two subregions of this area: leftward for the posterior part and rightward for the anterior part. These findings may be closely related to distinct roles of these two subareas in language functions: These two subregions are involved in, respectively, phonology and syntax, related to their distinct connections with areas in inferior parietal and temporal cortex (70, 71). Thus, these findings suggested that the opposite directions of structural asymmetry affecting regions within one network or within one functional area might reflect different functional involvements of each component region. Future studies with both structural and functional data in same participants may help link the structural asymmetries to functional asymmetries in the human brain.

The effects of biological factors on surface area asymmetries were more prominent than on thickness asymmetries. Very few previous studies have reported sex effects. Kang et al. (44) found no sex differences in asymmetries for surface areas in 138 young adults, while Koelkebeck et al. (38) only reported a male > female effect for the asymmetry of surface area at the overall hemispheric level in 101 healthy individuals. We also found that males, on average, showed more rightward asymmetry in overall surface area, compared with females, which is consistent with Koelkebeck et al. (38). We additionally observed a number of regionally specific effects, among which surface area asymmetry in the superior frontal gyrus showed the strongest relation to sex (i.e., males showed more leftward asymmetry in surface area in this region compared with females).

In terms of age, when including only those datasets with an age range of >20 y, we found a weak positive correlation between age and the asymmetry of surface area of the entorhinal cortex—that is, the leftward asymmetry of this region was slightly greater in older participants. As far as we are aware, no previous studies have reported possible age effects on the asymmetries of surface area, except one that showed no significant results in 101 participants (38). Note that, in our analyses for either sex or age effects, ICV was included as a covariate to obtain sex- or age-specific effects. In terms of ICV effects themselves (correcting for sex and age), no significant effect was found on the overall asymmetry of surface area, but a number of regionally specific effects were revealed. Specifically, positive effects (increased leftward/decreased rightward asymmetries with ICV) were observed mainly in medial regions such as the anterior cingulate gyri, while negative effects (decreased leftward or increased rightward asymmetries with ICV) were seen in spatially diverse locations, including the posterior cingulate gyrus, the insula, and the caudal middle frontal gyrus. It has been suggested that increased brain size might lead to the development of additional sulci (44), which could have an impact on regional asymmetries as assessed with the FreeSurfer atlas-based approach (69).

General Discussion. Our findings bear on the relationship between asymmetry of cortical thickness and surface area. Previous studies have suggested that thickness and surface area are evolutionarily, genetically, and developmentally distinct (34, 72) and that therefore separate consideration of these aspects of cortical anatomy is important (73). With a large MRI twin sample, Panizzon et al. (72) showed that, although average cortical thickness and total surface area are both highly heritable (>0.80), they are essentially unrelated genetically (genetic correlation = 0.08). This genetic independence of cortical thickness and surface area was also found in a large extended family study (73). These results suggest relative independence of the two surface-based measures and potentially therefore their asymmetry patterns. Data from two recent studies have indeed indicated that the asymmetry measures of cortical thickness and surface area are relatively independent at the overall hemispheric level (38, 39). With our larger sample size in the present study [including the BIL&GIN dataset used in Maingault et al. (39)], we confirmed a lack of correlation across regions between the asymmetries of thickness and surface areas, which further supports their independent natures. Moreover, by including data on participants' sex, age, handedness, and ICV, our findings further elaborated the largely independent nature of regional area vs. thickness variability (*SI Appendix*, *SI Results*). Note that, when zooming in on some individual regions, there may be identifiable relations between thickness and surface area asymmetries, such as reported for the fusiform gyrus and the cingulate cortex (38, 39, 43), although further investigation is needed. In future studies of cortical asymmetry, the simultaneous investigation of both cortical thickness and surface area will be important. For example, this may be necessary to approach the genetics of brain asymmetry (26) and its links with functional lateralization (e.g., language lateralization) (74).

With the pedigree datasets from the GOBS and HCP, we revealed that several regions showed significant heritability of their asymmetry measures. These data on heritability will be useful in targeting future studies of brain laterality with, for example, genome-wide association scanning aimed at identifying genes involved. Interestingly, cortical asymmetry of the human brain may also be associated with interhemispheric differences in gene expression (75, 76).

Our data revealed extensive variability in cortical asymmetry across participants and samples. Besides sex, age, ICV, handedness, and heritable effects, further studies on individual variability are needed, from the perspective of cognitive and neuropsychiatric disorders. Some disorders, such as dyslexia (8), Alzheimer's disease (9), ADHD (10), psychotic disorders (11–13), autism (14), and mood disorders (15, 16), may be associated with abnormal cortical asymmetries, although these complex links have not been fully explored. Asymmetry measures may even be more accurate than unilateral cortical measures to distinguish healthy controls from patients in some contexts (77), suggesting the potential for cortical asymmetry to be used as an important biomarker. In this respect, the findings in this work provide a reference for cortical asymmetry in healthy populations, which may help for further understanding the nature of these disorders in future studies.

Regarding handedness, we did not find significant associations between asymmetries and handedness, which is consistent with recent studies (26, 39). It remains possible that handedness is associated with asymmetry measures of other structural metrics and/or in more narrowly defined regions. However, it is clear from the present results that left-handedness does not involve any broad or substantial alterations of cortical asymmetry. Moreover, the present study treated handedness as a categorical trait, which is supported by the bimodal distribution of overall hand preference

when compiled across a number of tasks (e.g., refs. 78 and 79) and its robust test–retest repeatability (e.g., refs. 78 and 80). However, some aspects of handedness might be more accurately defined by degree and not category. Future studies using continuous handedness measures, when available in very large samples, may provide more information. In addition, it is interesting to note that paleoneurologists have attempted to use skull endocasts to assess cerebral asymmetries and to infer the evolution of handedness in hominins (81). Since we found no significant association between brain anatomical asymmetries and handedness, our analysis does not support the use of indirect measures of brain anatomy to infer the handedness of individuals.

Limitations and Future Directions. This study has several limitations that could be overcome in future studies. First, for age effects, as most datasets included a wide age range, our meta-analysis–based approach cannot rule out that age effects might differ across different age groups. Given the important roles of development and aging on cortical structures, this issue should be investigated in future research using datasets which are individually very large. In addition, the cross-sectional study design limits the interpretation of results. Longitudinal studies should ideally be performed to support the findings.

Second, when combining already collected data across worldwide samples, data-collection protocols are not prospectively harmonized. Imaging acquisition protocols and handedness assessments therefore differed across studies, which resulted in possible sources of heterogeneity. On the other hand, this heterogeneity can be taken as an advantage of our approach, in the sense that our findings are representative of the real-world diversity of MRI acquisition currently in use in the field and not limited to a single laboratory-specific protocol.

Third, we note that variability of asymmetry in surface area across samples was relatively lower than that of asymmetry in cortical thickness, at both the global hemispheric and regional levels. The relatively consistent asymmetry in regional surface area across datasets might be, to an extent, driven by the same parcellation scheme (i.e., Desikan–Killiany atlas) having been used across all samples. The potential impact of parcellation dependence will be an important topic for future studies. In addition, we applied a region-based approach, rather than a vertex-wise approach. The key idea of the region-based approach is that if we define the regions of interest in each hemisphere based on each hemisphere's own particular features such as its sulcal and gyral geometry, we can then obtain the corresponding relationships between hemispheres. To this end, we applied an automated labeling program from FreeSurfer for subdividing the human cerebral cortex from MRI scans. The labeling system incorporates hemisphere-specific information about sulcal and gyral geometry with spatial information regarding the locations of brain structures and shows a high accuracy when comparing with manual labeling results (69). Thus, reliable measures of each region can be extracted for each subject and regional asymmetries then accurately assessed. Moreover, compared with a vertex-wise approach, the region-based approach is a more feasible solution for large-scale, collaborative, meta-analysis–based projects. Nonetheless, the region-based approach is necessarily limited in terms of spatial resolution, related to the number of cortical regions defined. A vertex-wise approach combined with cross-hemispheric registration methods is likely to be useful for future cortical asymmetry studies (39, 44, 82).

Besides the directions of the asymmetries, the present study provided the exact effect size distributions for each region with a very large sample size. The results can act as a guide and provide a reference normative resource for future studies of cortical asymmetry. For example, with the population-level effect sizes, researchers can estimate sample sizes required to detect specific effects of interest. Researchers can query the meta-analysis summary statistics with the query tool (conxz.net/neurohemi/).

Finally, future research may also consider the degree of laterality (e.g., the unsigned magnitude of the asymmetry index) as being potentially both heritable and linked to other biological factors. Comparative analysis of human and chimpanzee data has indicated that the degree of laterality in either direction (left or right) may be a distinct and partly heritable aspect of human brain asymmetry (83).

Summary. In summary, we showed that diverse regions of the human cerebral cortex are asymmetrical in their structural features (i.e., cortical thickness and surface area) with different effect sizes and that the asymmetry patterns are different between cortical thickness and surface area. Moreover, we showed widespread effects of several biological factors (e.g., sex, age, and ICV) on the cortical asymmetries, but found no significant handedness effects. Finally, we revealed that the human brain is composed of regions with significant heritability of the asymmetry characteristics. This study not only contributes to the understanding of human brain asymmetry in the healthy population, but also provides informative data for future studies of the genetics of brain asymmetry and potentially abnormal brain asymmetry in cognitive and neuropsychiatric disorders.

Materials and Methods

The primary datasets used in this study for large-scale meta-analysis were from members of the Lateralization Working Group within the ENIGMA Consortium (51). There were 99 independent samples with MRI data, including 17,141 healthy participants from diverse ethnic backgrounds. Samples were drawn from the general population or were healthy controls from clinical studies. All local institutional review boards permitted the use of extracted measures of the completely anonymized data. The present study mainly focused on the asymmetry in cortical thickness and surface area and its variability related to sex, age, handedness, and ICV. The asymmetry index was defined as $(L - R)/((L + R)/2)$. Image processing and effect size estimations were conducted at each participating site, and then we combined the output statistics from each dataset using random-effect meta-analysis with the R package *metafor* (84). Two additional datasets with MRI data were used to estimate heritability of asymmetry measures, i.e., the GOBS and HCP datasets. GOBS is a family study comprising 1,443 individuals with MRI data (836 females), aged between 18 and 85 y at the time of scanning (85). The HCP is a large-scale project comprising 1,113 individuals (twins and nontwin siblings; 606 females, age range 22–37 y at the time of scanning) (https://www.humanconnectome.org/). The complete statistics from the meta-analyses are included in SI Datasets S1–S7 and the query tool (conxz.net/neurohemi/). Scripts are also available from the query tool (conxz.net/neurohemi/). Materials and methods are described in detail in *SI Appendix, SI Materials and Methods*.

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