

Large-scale analysis of structural brain asymmetries during neurodevelopment: associations with age and sex in 4265 children and adolescents

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Large-scale analysis of structural brain asymmetries during neurodevelopment: Associations with age and sex in 4265 children and adolescents

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Abstract

Only a small number of studies have assessed structural differences between the two hemispheres during childhood and adolescence. However, the existing findings lack consistency or are restricted to a particular brain region, a specific brain feature, or a relatively narrow age range. Here, we investigated associations between brain

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asymmetry and age as well as sex in one of the largest pediatric samples to date ($n = 4265$), aged 1–18 years, scanned at 69 sites participating in the ENIGMA (Enhancing Neuroimaging Genetics through Meta-Analysis) consortium. Our study revealed that significant brain asymmetries already exist in childhood, but their magnitude and direction depend on the brain region examined and the morphometric measurement used (cortical volume or thickness, regional surface area, or subcortical volume). With respect to effects of age, some asymmetries became weaker over time while others became stronger; sometimes they even reversed direction. With respect to sex differences, the total number of regions exhibiting significant asymmetries was larger in females than in males, while the total number of measurements indicating significant asymmetries was larger in males (as we obtained more than one measurement per cortical region). The magnitude of the significant asymmetries was also greater in males. However, effect sizes for both age effects and sex differences were small. Taken together, these findings suggest that cerebral asymmetries are an inherent organizational pattern of the brain that manifests early in life. Overall, brain asymmetry appears to be relatively stable throughout childhood and adolescence, with some differential effects in males and females.

KEYWORDS

adolescence, age, asymmetry, brain, childhood, cortical thickness, development, ENIGMA, gender, gray matter, sex

1 | INTRODUCTION

Despite its striking overall symmetric appearance at first glance, a closer look at the human brain reveals a multitude of asymmetries (Ocklenburg & Gunturkun, 2018). These asymmetries not only exist functionally—that is, the preference of one hand over the other (Papadatou-Pastou et al., 2020) or the lateralization of language to one hemisphere (Malik-Moraleda et al., 2022)—but also structurally. The brain's most prominent structural asymmetry is the Yakovlevian torque—a forward warp of the right hemisphere and a backward warp of the left hemisphere (Kong et al., 2021; LeMay, 1976). However, several other left–right differences exist, as summarized elsewhere (Jancke, 2003; Toga et al., 2009). For example, the left Sylvian fissure is often longer and runs more horizontally than the right, whereas the left hemisphere often contains only one Heschl's gyrus, but the right hemisphere contains two. While some structural asymmetries are consistent across brains and stable over time, others have been reported to differ across individuals and to change with increasing age (Guadalupe et al., 2017; Kong et al., 2018; Kong et al., 2022).

The majority of asymmetry studies have been conducted in adult populations (Chiarello et al., 2016; Good et al., 2001; Guadalupe et al., 2017; Jancke et al., 1994; Koelkebeck et al., 2014; Kong et al., 2018; Kong et al., 2022; Luders et al., 2006; Maingault et al., 2016; Plessen et al., 2014; Sha, Pepe, et al., 2021; Toga et al., 2009; Toga & Thompson, 2003; Zhou et al., 2013), and some of those studies cover the entire lifespan, including childhood and adolescence, but do not explicitly focus on these earlier periods in life

(Kong et al., 2018; Plessen et al., 2014; Zhou et al., 2013). So, it remains unclear when cerebral asymmetries arise and how they develop during childhood and adolescence. There is some evidence that cerebral asymmetries already exist in newborns (de Vareilles et al., 2022; Ge et al., 2022; Gilmore et al., 2007; Lehtola et al., 2019; Li et al., 2014; Li et al., 2015; Namburete et al., 2023; Steger et al., 2023) and even in the fetal brain (Abu-Rustum et al., 2013; Corballis, 2013; de Kovel et al., 2017; Namburete et al., 2023; Steger et al., 2023; Vasung et al., 2020). However, to date there is limited research investigating brain asymmetries and their age-related associations during childhood and adolescence. The few existing studies with an explicit focus on childhood and adolescence have resulted in inconsistent findings or in findings restricted to a particular brain region, a specific brain feature, or a relatively narrow age range (Levman et al., 2017; Raja et al., 2021; Shaw et al., 2009; Wang et al., 2015).

Our current study was designed to pool international data to provide crucial and high-powered insights into brain asymmetry with a focus on the age range of 1–18 years, capturing a multitude of brain features (cortical thickness, cortical surface area, as well as cortical and subcortical volumes), reflecting both regional and global measures. Moreover, we set out to analyze whether there are significant differences in brain asymmetry between males and females, given the often conflicting outcomes in prior (mostly adult) studies (Fan et al., 2010; Good et al., 2001; Guadalupe et al., 2015; Guadalupe et al., 2017; Jancke et al., 1994; Kong et al., 2018; Kong et al., 2022; Kurth et al., 2017; Kurth et al., 2018; Levman et al., 2017; Luders

et al., 2004; Luders et al., 2006; Plessen et al., 2014; Savic, 2014; Shaw et al., 2009; Takao et al., 2011; Toga et al., 2009; Toga & Thompson, 2003; Watkins et al., 2001; Zhou et al., 2013). If sex differences in brain asymmetry exist, such differences may already be present at their full extent early on in life or manifest only later (e.g., during puberty). Moreover, any existing sex differences may become stronger (or weaker) over time. Any significant change in sex differences in brain asymmetry over time would manifest as a sex-by-age interaction.

Altogether, this study was designed to answer the following four main questions: (1) are there any structural brain asymmetries in childhood and adolescence; (2) do brain asymmetries change with age during this period; (3) are there any sex differences in brain asymmetries in childhood and adolescence; and (4) do sex differences in brain asymmetries change during this period (sex-by-age interaction)?

2 | METHODS

2.1 | Dataset and sample

Our study sample consisted of typically developing children and adolescents aged 1–18 years (i.e., <19 years), scanned at 69 sites participating in the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) consortium (Boedhoe et al., 2018; Hoogman et al., 2019; Postema et al., 2019; Satterthwaite et al., 2014). At each site, data collection was performed after obtaining institutional ethics approval as well as informed consent/assent. The present study was conducted with additional approval from the University of Auckland Human Participants Ethics Committee (UAHPEC23851).

All brain scans were processed at the respective sites using FreeSurfer (Fischl, 2012), which resulted in a standard set of cortical thickness and surface area measures for 34 cortical regions-of-interest (ROIs) (Desikan et al., 2006) and of volume measures for 7 subcortical ROIs¹ (Fischl et al., 2002) in each hemisphere. In addition, the mean thickness and total surface area for each hemisphere as well as the total intracranial volume (TIV) were calculated. These individual measures, together with other relevant information (sex, age, scanner/site, and handedness), were shared with a central analysis team in the form of spreadsheets. In total, the central analysis team received information on 4331 participants. Of those, 66 participants lacked measures of cortical thickness, cortical surface area, and/or subcortical volume, and thus were excluded. The final sample of 4265 participants had a mean (SD) age of 12.2 (3.2) years (range: 1–18 years) and consisted of 41.2% females and 58.8% males. Information on handedness was available for 2391 participants, with 2126 (88.9%) right-handers reflecting the expected distribution of handedness in the population (Annett, 1973). Demographics of the final sample for each site are given in Supplementary Table 1.

¹Some sites included the lateral ventricles as an 8th ROI, while others did not. Thus, in our analyses, the lateral ventricles were omitted, resulting in a total of 7 subcortical ROIs.

2.2 | Existing measures and new calculations

As mentioned above, the different sites provided the left and right regional measures (regional cortical thickness, regional surface area, and regional subcortical volume) as well as the left and right global measures (total cortical thickness and total surface area).² The central analysis team calculated the following additional measures: (I) the left and right regional cortical volumes of the 34 ROIs in each hemisphere (thickness × surface area), (II) the left and right total cortical volume, and (III) the left and right total subcortical volume. Altogether, this resulted in 109 regional measures (34 × 3 cortical + 7 × 1 subcortical) as well as in four global measures in each hemisphere. Subsequently, for each of these hemispheric measures, the asymmetry index was calculated as $AI = (Left - Right) / (0.5 \times [Left + Right])$, with resulting positive values indicating leftward asymmetry and negative values indicating rightward asymmetry (Guadalupe et al., 2017; Kong et al., 2018; Kurth et al., 2015; Kurth et al., 2018).

2.3 | Statistical analysis

All analyses were run in Matlab 2018a (<http://www.mathworks.com/products/matlab>) using mixed models, where site was treated as a random effect³ and TIV as a variable of no interest. Overall, four analyses were run to assess (1) hemispheric asymmetry; (2) age-related changes in asymmetry; (3) sex differences in asymmetry; and (4) sex-by-age interactions in asymmetry. For all four analyses, the *dependent* variables were the asymmetry indices for each measurement, while the *independent* variables varied according to the analysis performed (see next sections). For all four analyses, the results were corrected for multiple comparisons by controlling the false discovery rate (FDR) at $p_{fdr} \leq 0.05$ (Benjamini & Yekutieli, 2001; Hochberg & Benjamini, 1990) within each set of measurements (i.e., [sub]cortical volumes, cortical thickness, and cortical surface areas).

In a supplementary stream, the aforementioned analyses were repeated (a) in a subsample of 2126 right-handers (45.9% female); (b) in a subsample of 2116 participants younger than 12 years of age (41.1% female); and (c) in a subsample of 2149 participants aged 12 years or older (41.2% female). The outcomes of these analyses are presented in Supplementary Tables 7–21 and Supplementary Figures 1–9.

2.3.1 | Analysis 1: Hemispheric asymmetry

The first analysis used the intercept of the mixed model as the independent variable to determine the presence of asymmetries. The effect size was calculated as $d = t/\sqrt{df}$ (Rosnow & Rosenthal, 2003). To capture the direction of the asymmetry

²Any empty cells—a result of classifying individual measures as outliers at the original sites and excluding them—were coded as missing values.

³If a site provided data from multiple scanners, the dataset from each scanner was treated as coming from a different site.

TABLE 1 Significant asymmetries at the population level.

ROI	Cortical volume			Cortical thickness			Cortical surface area			Subcortical volume		
	Direction	d	<i>P</i> _{dir}	Direction	d	<i>P</i> _{dir}	Direction	d	<i>P</i> _{dir}	Direction	d	<i>P</i> _{dir}
Banks superior temporal sulcus	Leftward	0.32	<.001	Rightward	-0.50	<.001	Leftward	0.58	<.001	-	-	n/a
Caudal anterior cingulate	Rightward	-0.41	<.001	Leftward	0.40	<.001	Rightward	-0.62	<.001	-	-	n/a
Caudal middle frontal	Leftward	0.52	<.001	-	-	n.s.	Leftward	0.48	<.001	-	-	n/a
Cuneus	Rightward	-0.42	<.001	Rightward	-0.12	<.001	Rightward	-0.41	<.001	-	-	n/a
Entorhinal	Leftward	0.40	<.001	Rightward	-0.27	<.001	Leftward	0.56	<.001	-	-	n/a
Fusiform	Leftward	0.24	<.001	Rightward	-0.06	<.001	Leftward	0.31	<.001	-	-	n/a
Inferior parietal	Rightward	-1.58	<.001	-	-	n.s.	Rightward	-1.56	<.001	-	-	n/a
Inferior temporal	Leftward	0.29	<.001	Rightward	-0.05	.001	Leftward	0.36	<.001	-	-	n/a
Isthmus cingulate	Leftward	0.62	<.001	Leftward	0.11	<.001	Leftward	0.61	<.001	-	-	n/a
Lateral occipital	Rightward	-0.09	<.001	Rightward	-0.16	<.001	Leftward	0.17	<.001	-	-	n/a
Lateral orbitofrontal	Leftward	0.12	<.001	Leftward	0.12	<.001	Leftward	0.09	<.001	-	-	n/a
Lingual	Rightward	-0.37	<.001	Rightward	-0.34	<.001	Rightward	-0.06	<.001	-	-	n/a
Medial orbitofrontal	Rightward	-0.05	.002	-	-	n.s.	Rightward	-0.08	<.001	-	-	n/a
Middle temporal	Rightward	-0.45	<.001	-	-	n.s.	Rightward	-0.56	<.001	-	-	n/a
Parahippocampal	Leftward	0.35	<.001	Leftward	0.16	<.001	Leftward	0.29	<.001	-	-	n/a
Paracentral	Rightward	-0.88	<.001	Rightward	-0.07	<.001	Rightward	-0.93	<.001	-	-	n/a
Pars opercularis	Leftward	1.09	<.001	-	-	n.s.	Leftward	1.11	<.001	-	-	n/a
Pars orbitalis	Rightward	-0.47	<.001	Leftward	0.05	.001	Rightward	-1.67	<.001	-	-	n/a
Pars triangularis	Rightward	-0.89	<.001	-	-	n.s.	Rightward	-0.95	<.001	-	-	n/a
Pericalcarine	Rightward	-0.70	<.001	Leftward	0.12	<.001	Rightward	-0.85	<.001	-	-	n/a
Postcentral	Leftward	0.47	<.001	Leftward	0.17	<.001	Leftward	0.43	<.001	-	-	n/a
Posterior cingulate	-	-	n.s.	Leftward	0.12	<.001	Rightward	-0.12	<.001	-	-	n/a
Precentral	Leftward	0.05	.004	Leftward	0.13	<.001	-	-	n.s.	-	-	n/a
Precuneus	Rightward	-0.51	<.001	-	-	n.s.	Rightward	-0.51	<.001	-	-	n/a
Rostral anterior cingulate	Leftward	1.26	<.001	Leftward	0.11	<.001	Leftward	0.45	<.001	-	-	n/a
Rostral middle frontal	-	-	n.s.	Leftward	0.08	<.001	Rightward	-0.31	<.001	-	-	n/a
Superior frontal	Leftward	0.15	<.001	Leftward	0.07	<.001	Leftward	0.43	<.001	-	-	n/a
Superior parietal	Leftward	0.15	<.001	Leftward	0.06	<.001	Leftward	0.12	<.001	-	-	n/a
Superior temporal	Leftward	0.22	<.001	Rightward	-0.06	<.001	Leftward	0.74	<.001	-	-	n/a
Supramarginal	Leftward	0.22	<.001	Leftward	0.06	<.001	Leftward	0.22	<.001	-	-	n/a
Frontal pole	Rightward	-0.45	<.001	Leftward	0.20	<.001	Rightward	-0.60	<.001	-	-	n/a
Temporal pole	Leftward	0.20	<.001	Rightward	-0.23	<.001	Leftward	0.27	<.001	-	-	n/a

TABLE 1 (Continued)

ROI	Cortical volume			Cortical thickness			Cortical surface area			Subcortical volume		
	Direction	<i>d</i>	<i>p</i> _{dir}	Direction	<i>d</i>	<i>p</i> _{dir}	Direction	<i>d</i>	<i>p</i> _{dir}	Direction	<i>d</i>	<i>p</i> _{dir}
Transverse temporal	Leftward	1.79	<.001	Rightward	-0.04	.029	Leftward	1.96	<.001	-	-	n/a
Insula	Leftward	0.04	.009	-	-	n.s.	-	-	n.s.	-	-	n/a
Thalamus	-	-	n/a	-	-	n/a	-	-	n/a	Leftward	0.11	<.001
Caudate	-	-	n/a	-	-	n/a	-	-	n/a	Rightward	-0.17	<.001
Putamen	-	-	n/a	-	-	n/a	-	-	n/a	Leftward	0.05	.002
Pallidum	-	-	n/a	-	-	n/a	-	-	n/a	Leftward	0.11	<.001
Hippocampus	-	-	n/a	-	-	n/a	-	-	n/a	Rightward	-0.08	<.001
Amygdala	-	-	n/a	-	-	n/a	-	-	n/a	Rightward	-0.15	<.001
Nucleus Accumbens	-	-	n/a	-	-	n/a	-	-	n/a	Rightward	-0.04	.012
Total cortical	-	-	n.s.	Leftward	0.09	<.001	Rightward	-0.13	<.001	-	-	n/a
Total subcortical	-	-	n/a	-	-	n/a	-	-	n/a	Leftward	0.05	.003

Note: Table restricted to ROIs, where at least one measure survived corrections for multiple comparisons. Abbreviations: *d*, Cohen's *d*; n.s., not significant; n/a, not applicable; *p*_{dir}, *p*-value; ROI, region of interest.

(leftward/rightward) we used the sign of the estimated intercept in the statistical model: a positive estimate signifies a leftward asymmetry, while a negative sign signifies a rightward asymmetry.

2.3.2 | Analysis 2: Change of asymmetries with age

The second analysis used age and age-squared as the independent variables to establish the link between asymmetry and age (age-squared, respectively), where age-squared was orthogonalized to age to avoid collinearity between the two regressors. The effect size was calculated as the partial correlation coefficient $r = t / (\sqrt{t^2 + df})$ (Rosnow & Rosenthal, 2003). To capture the direction of the asymmetry (leftward/rightward) as well as the trajectory of the asymmetry (increasing/decreasing), we used the fixed-effects estimate from the statistical model at the minimum and the maximum age (as calculated from the betas): the sign of the estimate indicates the direction, with positive values for leftward asymmetries and negative values for rightward asymmetries. A higher absolute estimate at the maximum age compared to the minimum age signifies a more pronounced asymmetry with increasing age, while a lower absolute estimate signifies a less pronounced asymmetry with increasing age. A switch in the sign indicates a change in the direction of asymmetry with age.

2.3.3 | Analysis 3: Sex differences in asymmetry

The third analysis used sex as the independent variable to determine if asymmetry was different between males and females. The effect size was calculated as $d = t(n_1 + n_2) / (\sqrt{t^2 + df})$ (Nakagawa & Cuthill, 2007). To capture the direction of the asymmetry (leftward/rightward) as well as the direction of the sex difference (more asymmetric in males/more asymmetric in females), we used the fixed-effects estimates from the statistical model for males and females (as calculated from the betas): a higher absolute value of the estimates in one sex signifies the direction of the sex effect (i.e., a more pronounced asymmetry than in the other sex). The sign of the estimate indicates the direction of the asymmetry, with positive values for leftward asymmetries and negative values for rightward asymmetries. Significant sex differences were followed up by assessing asymmetries within males and females, separately.

2.3.4 | Analysis 4: Sex-by-age interactions in asymmetry

The fourth analysis used sex, age as well as the sex-by-age interaction as independent variables to determine whether any age-related changes in asymmetry differ between males and females. Significant interactions were followed up by post hoc analyses assessing the Pearson correlation between asymmetry and age within males and females, separately.

3 | RESULTS

3.1 | Hemispheric asymmetry

When comparing both hemispheres, a multitude of significant left- and rightward asymmetries emerged both on a global and regional scale. More specifically, with respect to global measures, total cortical thickness and total subcortical volume showed a significant leftward asymmetry, total cortical surface area a significant rightward asymmetry, and total cortical volume no significant asymmetry. With respect to regional measures, as detailed in Table 1, all subcortical ROIs as well as the vast majority of cortical ROIs displayed significant asymmetries (for visualization of cortical effects, see Figure 1). Supplemental Table 2 provides statistics for all ROIs and sets of measurements, regardless of significance.

3.2 | Change of asymmetries with age

There was no significant association between asymmetry and age for any global cortical measurement, but a significant change in asymmetry

direction was observed for total subcortical volume. In contrast, several significant age-related changes in asymmetry were detected for regional cortical and subcortical measures. As detailed in Table 2, 15 regions overall displayed a significant association between asymmetry and age. More specifically, of those 15 regions, five showed an increase and six a decrease in asymmetry (two of those had additional associations with age-squared). One region showed a decrease in one measurement but a change in direction in another measurement. One region had a change in direction, and two others had an association with age-squared. For visualization of cortical effects, see Figure 2. For statistics for all areas and sets of measurement regardless of significance, see Supplemental Table 3.

3.3 | Sex differences in asymmetry

There was no significant association between asymmetry and sex for any global measurements. In contrast, significant sex differences in asymmetry were evident for regional cortical and subcortical measures. More specifically, as detailed in Table 3, males had significantly stronger asymmetries than females in two cortical ROIs (superior temporal gyrus and

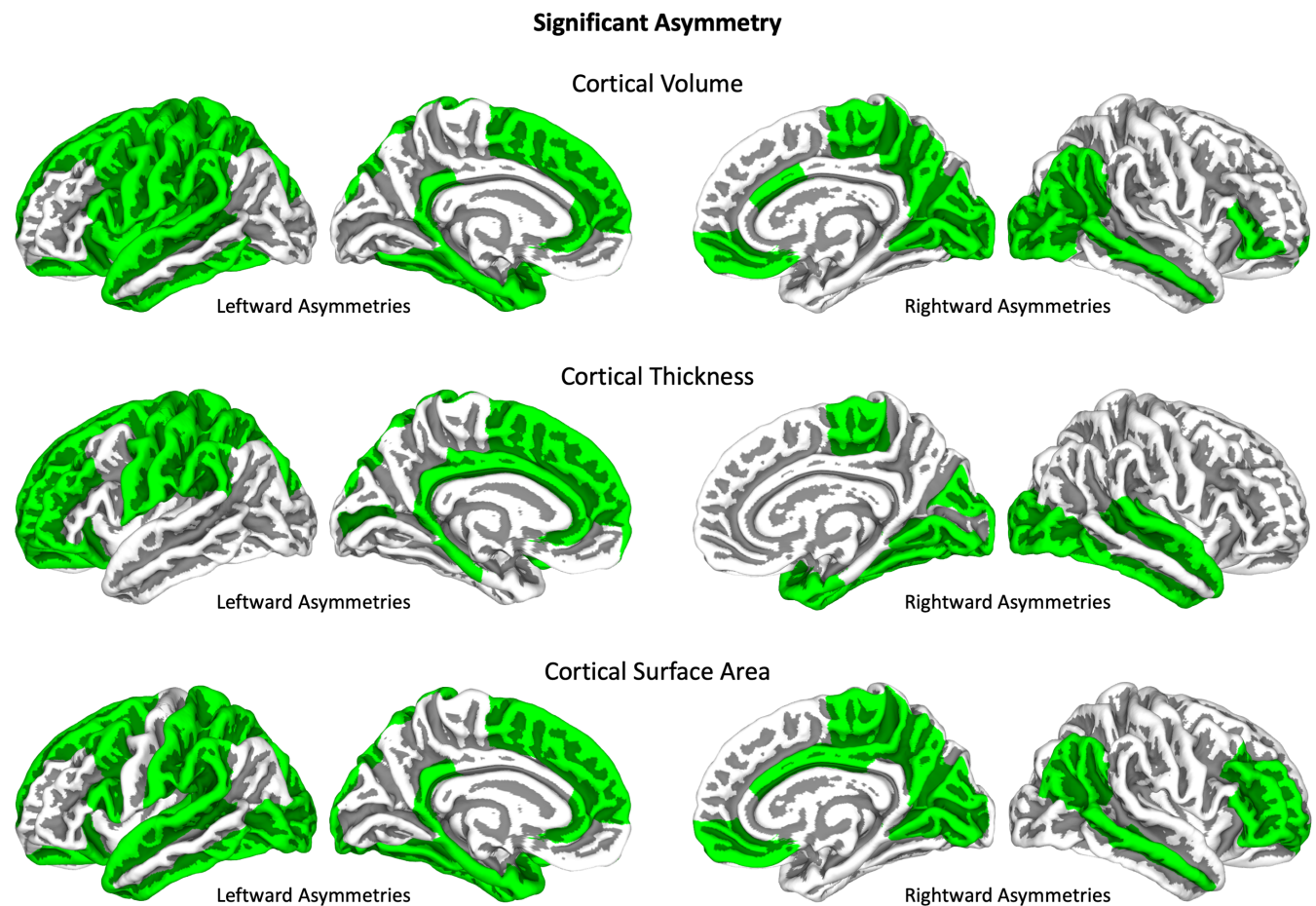


FIGURE 1 Hemispheric asymmetry. Cortical regions with significant asymmetries are indicated in green. The regions defined by the Desikan–Killiany atlas (Desikan et al., 2006) were projected onto the central surface of the FSAverage template using the CAT12 toolbox (Gaser et al., 2022). Rightward asymmetries are indicated on the right hemispheres, leftward asymmetries on the left hemispheres. All significant asymmetries are FDR-corrected using a threshold of 0.05 (Benjamini & Yekutieli, 2001; Hochberg & Benjamini, 1990).

TABLE 2 Significant effects of increasing age on asymmetry.

Cortical volume ROI	Direction	Age		Age ²	
		<i>r</i>	<i>p</i> _{fd}	<i>r</i>	<i>p</i> _{fd}
Fusiform	-	0.01	n.s.	-0.06	.003
Precuneus	Decrease rightward	0.06	.004	-0.05	.046
Supramarginal	Decrease leftward	-0.05	.009	0.02	n.s.
Cortical thickness ROI	Direction	Age		Age ²	
		<i>r</i>	<i>p</i> _{fd}	<i>r</i>	<i>p</i> _{fd}
Banks superior temporal sulcus	Decrease rightward	-0.04	.043	-0.05	n.s.
Inferior parietal	Left to right	-0.05	.013	0.01	n.s.
Inferior temporal	Left to right	-0.04	.043	0.03	n.s.
Lateral orbitofrontal	Decrease leftward	-0.06	.004	0.00	n.s.
Parahippocampal	Increase leftward	0.05	.012	0.02	n.s.
Paracentral	Increase rightward	-0.05	.004	-0.02	n.s.
Rostral anterior cingulate	Decrease leftward	-0.05	.004	0.00	n.s.
Rostral middle frontal	Increase leftward	0.05	.004	0.02	n.s.
Transverse temporal	Decrease rightward	0.06	.003	-0.05	.034
Cortical surface area ROI	Direction	Age		Age ²	
		<i>r</i>	<i>p</i> _{fd}	<i>r</i>	<i>p</i> _{fd}
Fusiform	-	0.01	n.s.	-0.05	.021
Inferior parietal	Decrease rightward	0.05	.042	-0.03	n.s.
Precuneus	Decrease rightward	0.06	.001	-0.03	n.s.
Subcortical volume ROI	Direction	Age		Age ²	
		<i>r</i>	<i>p</i> _{fd}	<i>r</i>	<i>p</i> _{fd}
Thalamus	-	0.03	n.s.	-0.05	.008
Putamen	Increase leftward	0.06	.002	0.01	n.s.
Nucleus accumbens	Increase rightward	-0.05	.003	-0.03	n.s.
Total subcortical	Right to left	0.05	.003	-0.03	n.s.

Note: Table restricted to ROIs, where at least one measure survived corrections for multiple comparisons. Abbreviations: *d*, Cohen's *d*; n.s., not significant; *p*_{fd}, *f*_{dr} corrected *p*-value (main analyses); ROI, region of interest.

inferior parietal cortex), while females had significantly stronger asymmetries in two cortical (rostral anterior cingulate and insula) as well as two subcortical (thalamus and nucleus accumbens) ROIs. For the transverse temporal gyrus males and females showed asymmetries in opposite directions (for visualization of cortical effects, see Figure 3). Follow-up analyses revealed that, except for the insula, asymmetries were significant when males and females were investigated separately. In other words, even if one sex displayed a more pronounced asymmetry than the other, the asymmetry was significant in both sexes. Supplemental Table 4 provides statistics for all areas and sets of measurements regardless of significance. Supplemental Table 5 provides additional statistics for the follow-up analyses.

3.4 | Sex-by-age interactions in asymmetry

There were no significant sex-by-age interactions for any global or regional measurement. Supplemental Table 6 provides statistics for all areas and sets of measurement regardless of significance.

4 | DISCUSSION

In the present study we characterized cerebral gray matter asymmetries during childhood and adolescence. For this purpose, we analyzed a large sample of >4000 children and adolescents between 1 and 18 years of age, scanned at 69 sites around the world. Hemispheric differences were determined with respect to various morphological features—cortical thickness, cortical surface area, as well as cortical and subcortical volumes—capturing both regional and global measures.

4.1 | Asymmetries

Asymmetries varied markedly between brain regions, ranging from minute differences between the hemispheres to extremely large differences, the latter observed, for example, for the cortical surface areas of the transverse temporal gyrus (34% larger on the left than on the right) and the inferior parietal cortex (20% larger on the right than

Significant Age-related Changes in Asymmetry

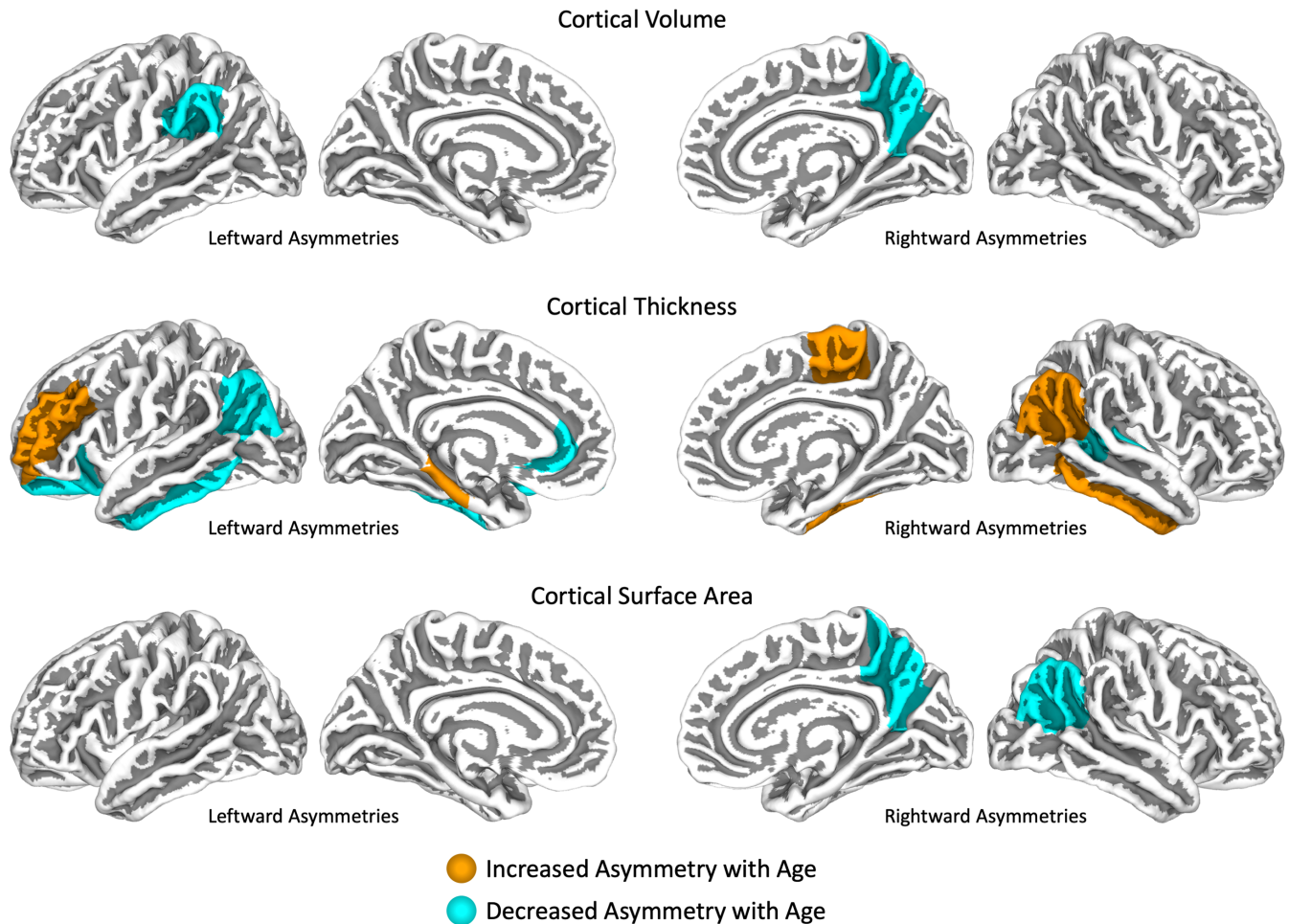


FIGURE 2 Age-related changes in asymmetry. Cortical regions with significant age-related changes in asymmetry are indicated in orange (increases) or cyan (decreases). Rightward asymmetries are indicated on the right hemispheres, leftward asymmetries on the left hemispheres. If asymmetry for a specific region changes in its direction with increasing age, the region is indicated in both left and right panels.

on the left). Overall, effects were most pronounced for cortical surface area (some large and very large effects) and least pronounced for cortical thickness and subcortical volumes (only small and medium effects).

While, historically, asymmetry studies relied on smaller sample sizes, some recent studies were able to draw from larger pools of participants comprising thousands or even tens of thousands of brains. The overall pattern of asymmetries in cortical thickness and cortical surface area as presently observed is very similar to that reported in the large-scale studies that were primarily based on adults (Guadalupe et al., 2017; Kong et al., 2018). More specifically with respect to cortical thickness, in accordance with Kong et al. (2018), there is a leftward asymmetry around the central sulcus which extends into frontal and prefrontal regions dorsolaterally and medially; and there is a rightward asymmetry in lateral and medial occipital cortical regions. With respect to cortical surface area, and also in accordance with Kong et al. (2018), there is a leftward asymmetry in superior frontal and inferior frontal (*pars opercularis*) regions, in perisylvian regions

including postcentral and supramarginal gyrus, in superior temporal regions including Heschl's gyrus, as well as in inferior temporal, lateral occipital, retrosplenial, dorsomedial frontal, and pregenual regions; there is a rightward asymmetry in prefrontal, middle temporal and inferior parietal as well as in medial occipital and parietal regions. In addition, both Kong et al.'s study (2018) and the present study detected a leftward asymmetry for total cortical thickness and a rightward asymmetry for total cortical surface area. Similarly, when comparing the present results to the other lifespan study focusing on subcortical volumes (Guadalupe et al., 2017), the direction of asymmetry is identical in both studies for all six subcortical regions examined.

Relating our findings to the outcomes of other smaller-scale asymmetry studies, there is a moderate degree of consistency. For example, the pattern of asymmetries in total cortical volume, thickness, and surface area matches the effects reported in children by Raja et al. (2021). Similarly, our finding of a leftward asymmetry in the cortical volume and surface area of the transverse temporal gyrus, the *pars opercularis* of the inferior frontal gyrus, and the region around the

TABLE 3 Significant sex differences in asymmetry.

ROI	Main analyses			Follow-up analyses (within each sex separately)			
	Sex effect			Asymmetry by sex			
	Direction	<i>d</i>	<i>p</i> _{fd}	Direction	Estimate	<i>d</i>	<i>p</i>
Cortical volume							
Inferior parietal	M > F: both rightward	0.09	.036	M: rightward	-0.19	-1.21	<.001
				F: rightward	-0.18	-0.94	<.001
Rostral anterior cingulate	F > M: both leftward	0.10	.035	M: leftward	0.25	0.91	<.001
				F: leftward	0.28	0.81	<.001
Superior temporal	M > F: both leftward	-0.13	.002	M: leftward	0.05	0.23	<.001
				F: leftward	0.04	0.15	<.001
Cortical thickness							
Superior temporal	M > F: both rightward	0.10	.018	M: rightward	-0.01	-0.07	<.001
				F: rightward	-0.01	-0.04	.023
Transverse temporal	M/F: opposite direction	0.15	<.001	M: rightward	-0.01	-0.08	<.001
				F: leftward	0.01	0.04	.019
Insula	F > M: both leftward	0.11	.009	M: leftward	0.00	0.00	n.s.
				F: leftward	0.01	0.04	.006
Cortical surface area							
Inferior parietal	M > F: both rightward	0.12	.002	M: rightward	-0.18	-1.20	<.001
				F: rightward	-0.17	-0.91	<.001
Superior temporal	M > F: both leftward	-0.17	<.001	M: leftward	0.07	0.61	<.001
				F: leftward	0.05	0.39	<.001
Subcortical volume							
Thalamus	F > M: both leftward	0.08	.049	M: leftward	0.04	0.11	<.001
				F: leftward	0.04	0.12	<.001
Nucleus accumbens	F > M: both rightward	-0.08	.049	M: rightward	-0.02	-0.03	.045
				F: rightward	-0.03	-0.05	.001

Note: Table restricted to ROIs, where at least one measure survived corrections for multiple comparisons in the main analysis.

Abbreviations: *d*, Cohen's *d*; F > M, females more asymmetric than males; F, females; M > F, males more asymmetric than females; M, males; n.s., not significant; *p*, uncorrected *p*-value (follow-up analyses); *p*_{fd}, *p*-value corrected for multiple comparisons (main analyses); ROI, region of interest.

central sulcus matches the effects reported in children and adolescents by Levman et al. (2017). Finally, our finding of a rightward asymmetry in the volume of the caudal anterior cingulate and a leftward asymmetry of the superior frontal gyrus matches effects detected in a study in children that focused specifically on the dorsal anterior cingulate cortex (Wang et al., 2015). Nevertheless, there are also some differences between the current findings and other previously reported effects, such as a leftward asymmetry in inferior parietal and a rightward asymmetry in inferior frontal regions with respect to cortical thickness (Zhou et al., 2013), a leftward asymmetry in inferior frontal regions with respect to cortical thickness (Plessen et al., 2014), and a leftward asymmetry in the lateral occipital cortex with respect to cortical volume (Levman et al., 2017). Such discrepancies, however, might be attributable to differences in sample characteristics, applied methods and/or scanning equipment and parameters, as discussed elsewhere (Kong et al., 2022). Importantly, asymmetry effects for regions where the current study detected very large effect sizes

(transverse temporal gyrus, etc.) have been largely consistent across studies (Kong et al., 2018; Levman et al., 2017; Plessen et al., 2014; Raja et al., 2021; Zhou et al., 2013).

4.2 | Effects of age

Recent large-scale studies addressing age-related changes in brain asymmetry across the entire life span reported an increasing leftward asymmetry of the putamen (Guadalupe et al., 2017), superior temporal gyrus, and entorhinal cortex (Kong et al., 2018). However, some of these effects only reached significance when covering an age range of more than 20 years. Thus, these life-time studies are not immediately comparable with the current study covering merely 18 years toward the beginning of the age spectrum (1–18 years), albeit there is some resemblance with respect to the effects, such as an increasing leftward asymmetry of the putamen

Significant Sex Differences in Asymmetry

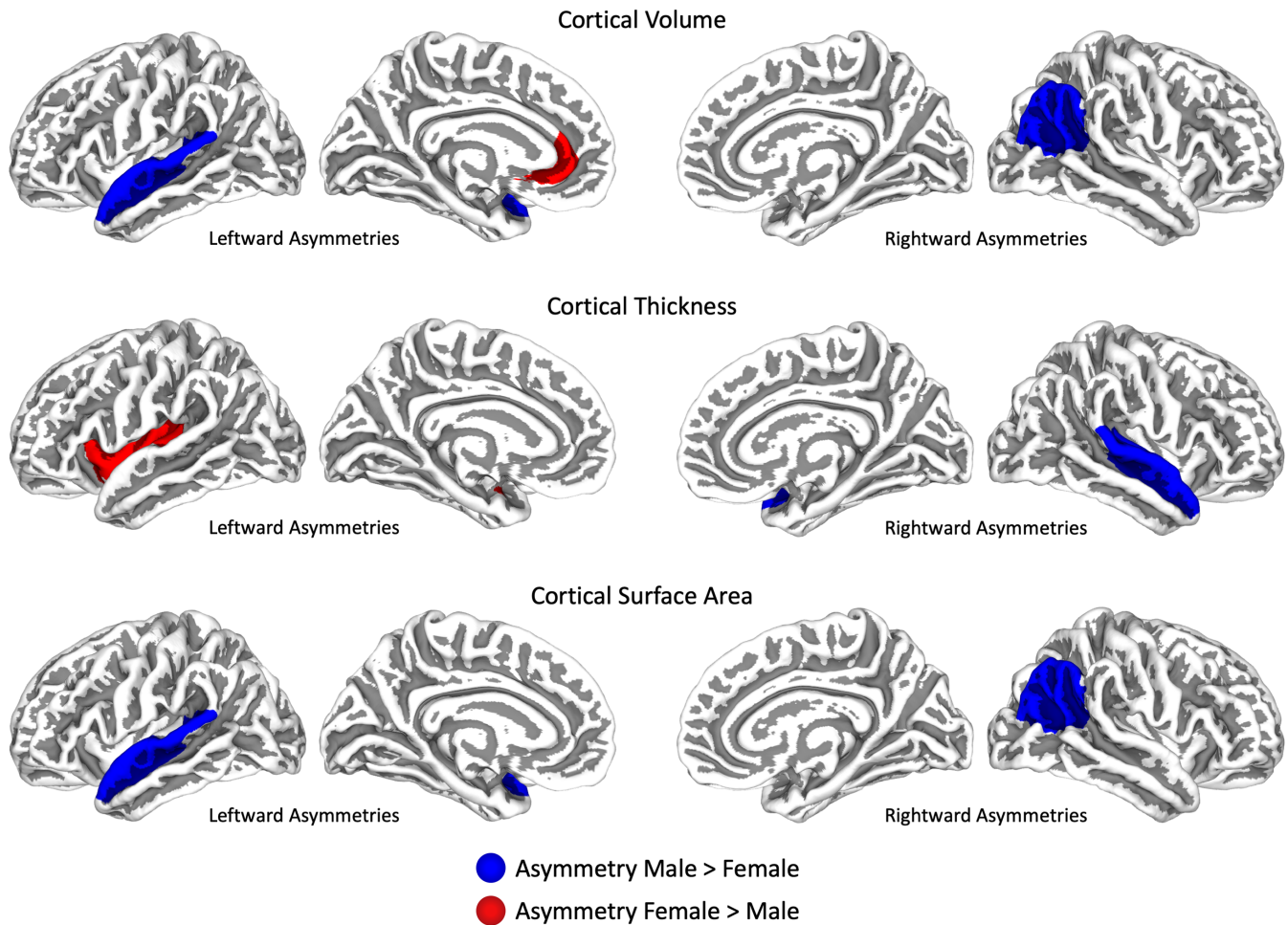


FIGURE 3 Sex differences in asymmetry. Cortical regions with significantly larger asymmetries in males are depicted in blue, and with significantly larger asymmetries in females in red. Rightward asymmetries are indicated on the right hemispheres, leftward asymmetries on the left hemispheres.

with age (Guadalupe et al., 2017). In contrast to those adult studies (Guadalupe et al., 2017; Kong et al., 2018)—which reported only 3 out of 41 regions to be significantly associated with age—the current study revealed more widespread associations between age and asymmetries during childhood and adolescence, with significant effects in 15 out of 41 regions. However, the effects of age were small in general. The localization of the present results somewhat agrees with the study by Shaw et al. (2009) in children and adolescents, even though there is also some disagreement on the direction of the age-related change. More specifically, with respect to cortical thickness, both the current study and Shaw's study (2009) detected a decreasing leftward asymmetry in the lateral orbitofrontal cortex. However, while Shaw et al. (2009) reported a decrease in rightward asymmetry in the middle occipital and angular gyri, our study revealed a change from leftward to rightward asymmetry in the inferior parietal cortex (i.e., a region that best matches the angular cluster described by Shaw et al., 2009).

4.3 | Effects of sex

Previous studies on sex differences in asymmetry revealed conflicting results (Good et al., 2001; Guadalupe et al., 2015; Guadalupe et al., 2017; Kong et al., 2018; Levman et al., 2017; Plessen et al., 2014; Shaw et al., 2009; Zhou et al., 2013), with findings indicating stronger asymmetries in men, stronger asymmetries in women, or no differences. Moreover, effects seem to depend on the brain region examined and the specific measures used. Recent large-scale studies reported significant sex differences, particularly around the Sylvian fissure, but also inferior parietal, lateral occipital and medial frontal as well as in subcortical structures, such as the putamen and globus pallidus (Guadalupe et al., 2015; Guadalupe et al., 2017; Kong et al., 2018). Our current study is consistent with these findings in part, revealing an increased leftward asymmetry in males compared to females in the superior temporal gyrus (cortical volume and surface area) and an increased rightward asymmetry in males compared to females in the inferior parietal cortex (cortical surface area). However,

we also observed more pronounced asymmetries in the rostral anterior cingulate, the insula, as well as the thalamus and nucleus accumbens in females compared to males. Interestingly, while the total number of regions exhibiting significant asymmetries was larger in females than in males, the magnitude of the significant asymmetries was larger in males. Moreover, the total number of measures indicating significant asymmetries was also larger in males (as we obtained more than one measurement per cortical region; that is, cortical thickness, cortical volume, and cortical surface area). Given that there were no significant sex-by-age interactions, these sex differences do not appear to change with age and remain stable throughout development.

5 | CONCLUSION

The multitude of asymmetries detected in our large sample of children and adolescents suggests that cerebral asymmetries manifest early in life. In terms of age effects, asymmetries became both smaller and larger with increasing age and sometimes even reversed in direction, depending on region or measure. However, in general, age effects were small. In other words, the pattern of asymmetry seems relatively stable throughout childhood and adolescence, which may seem surprising given that cerebral development is rather dynamic during that time. Cerebral asymmetries may therefore reflect a fundamental organizational pattern of the brain rather than a result of brain development and regional specialization. This view might be supported by reports of cerebral asymmetries as early as the first and second trimester of pregnancy (Abu-Rustum et al., 2013; Corballis, 2013; de Kovel et al., 2017; Namburete et al., 2023; Steger et al., 2023; Vasung et al., 2020) and by findings of asymmetries in gene activation (de Kovel et al., 2017; Francks, 2015; Karlebach & Francks, 2015; Ocklenburg et al., 2017). In addition, genes associated with variation in adult brain asymmetry, as identified in large-scale genome-wide association analyses, tend to be most active in the embryonic and fetal brain (Sha, Schijven, et al., 2021). In terms of sex differences, there were greater asymmetries in males than in females when investigating cortical volume and cortical surface area, while sex differences in the asymmetry of cortical thickness were more variable. However, these sex differences were small overall. Thus, brain asymmetry and its change over time appear to be relatively similar in males and females.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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