Right, Left, and Center: How Does Cerebral Asymmetry Mix with Callosal Connectivity?

Nicolas Cherbuin,[1]* Eileen Luders,[2] Yi-Yu Chou,[2] Paul M. Thompson,[2] Arthur W. Toga,[2] and Kaarin J. Anstey[1]

[1]*Centre for Research on Ageing, Health, and Wellbeing, Australian National University, Canberra, Australia*
[2]*Laboratory of Neuro Imaging, Department of Neurology, UCLA School of Medicine, Los Angeles, California*

Abstract: *Background:* Prior research has shown that cerebral asymmetry is associated with differences in corpus callosum connectivity. Such associations were detected in histological and anatomical studies investigating callosal fiber size and density, in neuroimaging investigations based on structural and diffusion tensor imaging, as well as in neuropsychological experiments. However, little is known about typical associations between these factors, and even less about the relative influences of magnitude and direction of cerebral asymmetries. Here, we investigated relationships between callosal connectivity and cerebral asymmetry using precise measures of callosal thickness and selected cerebral structures. We considered both the direction and magnitude of the asymmetries. *Methods:* Associations between cerebral asymmetry and callosal thickness were investigated in 348 cognitively healthy older individuals. *Results:* The magnitude and direction of cerebral lateralization were significant independent predictors of callosal thickness. However, associations were small. Leftward asymmetry and increased magnitude of asymmetry were generally associated with increased callosal thickness, mostly in the callosal midbody and isthmus. *Conclusions:* When a large sample of normal individuals is considered, cerebral asymmetries are only subtly associated with callosal thickness. *Hum Brain Mapp 00:000–000, 2012.*

Key words: laterality; MRI; white matter; planum temporale; supramarginal gyrus; pars opercularis; temporal gyrus

INTRODUCTION

Numerous studies have demonstrated that the cerebral hemispheres are anatomically [Luders et al., 2006a; Toga and Thompson, 2003] and functionally lateralized [Boles, 1998; Hugdahl and Davidson, 2003]. However, the origins and functional benefits of cerebral asymmetries are still poorly understood. Recent findings have demonstrated that functional lateralization is associated with cognitive performance [Boles et al., 2008; Chiarello et al., 2009]. Callosal development is likely to be associated with the development of cerebral lateralization [Caparelli-Daquer and

Contract grant sponsor: NHMRC of Australia; Contract grant numbers: 973302, 179805, 157125; Contract grant sponsor: NHMRC Research Fellowship; Contract grant numbers: 471501, 1002560; Contract grant sponsor: NIH; Contract grant number: U54 RR021813; Contract grant sponsor: National Center for Research Resources (NCRR), NIH; Contract grant numbers: P41 RR013642, M01 RR000865; Contract grant sponsor: NIBIB; Contract grant numbers: R01 EB007813, R01 EB008281, R01 EB008432; Contract grant sponsor: NICHHD; Contract grant number: R01 HD050735; Contract grant sponsor: NIA; Contract grant number: R01 AG020098.

N.C. and E.L. have contributed equally to this work.

*Correspondence to: Nicolas Cherbuin, Centre for Research on Ageing, Health, and Wellbeing, 63 Eggleston Road, Australian National University, Canberra, ACT 0200, Australia.
E-mail: nicolas.cherbuin@anu.edu.au

Received for publication 16 May 2011; Revised 13 November 2011; Accepted 28 November 2011

DOI: 10.1002/hbm.22022

Published online in Wiley Online Library (wileyonlinelibrary.com).

Schmidt, 1991; Gazzaniga, 2000], and callosal connectivity is also associated with cognitive performance of specific tasks [Hutchinson et al., 2009], as well as with global cognition in childhood [Luders et al., 2011], early adulthood [Luders et al., 2007] and late adulthood [Voineskos et al., 2010]. This suggests that there is a link between anatomical cerebral asymmetries and callosal characteristics.

Two main hypotheses have been proposed to explain possible associations between anatomical and functional cerebral asymmetry and callosal connectivity. Some have suggested that with brain expansion through evolution the costs of intra- and interhemispheric communication (time delay and signal reduction) became progressively too onerous. This may have led to increased modularity of function within and across hemispheres and thus to functional and anatomical lateralization [Ringo et al., 1994]. Lateralization of function in this context is associated with a reduced need for interhemispheric communication and consequently proportionally reduced callosal fiber size and/or density. Others have argued that while an increase in brain size led to increased modularity, anatomical and biological constraints to further brain expansion (as well as other factors) have contributed to hemispheric specialization, so cerebral functions would not be duplicated across the cerebral hemispheres [Gazzaniga, 2000]. The consequence of hemispheric specialization here is an increased need for interhemispheric communication to access functions (e.g., language) not available on one side more effectively. These hypotheses need not be mutually exclusive and evidence supporting each of them is available [Aboitiz et al., 1992a; Gazzaniga, 2000; Rosen et al., 1989]. For example, Jancke et al. [1997] demonstrated that while corpus callosum (CC) size does increase with larger brain volume, the increase in callosal volume is less than would be predicted by the concurrent increase in brain volume and thus is more consistent with Ringo's theory. These findings have been further confirmed by Leonard et al. [2008]. In contrast, Eckert et al. [2006] found that individuals with smaller brains, after controlling for gender, tended to be more strongly lateralized for language. This finding is inconsistent with Ringo's theory, thus suggesting other factors may also be at play as proposed by Gazzaniga et al. [2000].

While some studies have investigated relationships between anatomical cerebral asymmetries and callosal size, they have mostly examined language regions implicated in highly lateralized processes such as Broca's area or the *planum temporale* [Hines et al., 1992; Luders et al., 2003; Zaidel et al., 1995]. There is evidence showing asymmetrical projections in a number of callosal regions [Putnam et al., 2010] but most previous studies have not considered the independent contributions of the direction and magnitude of anatomical cerebral asymmetry when investigating possible associations with callosal properties. The aim of this study was therefore to investigate associations between callosal thickness and the asymmetry of a number of gray matter (GM) regions involved in lateralized functions, while considering both direction and magnitude of their asymmetry.

It was previously thought that anatomical and functional cerebral asymmetry was fixed, determined early in development, and that "normal" lateralization was associated with better performance. However, more recently, it was demonstrated that the cerebral hemispheres continue to differentiate themselves throughout childhood [Sowell et al., 2002]. Moreover, it was argued that normal lateralization is an elusive construct in that it varies substantially between individuals, across cerebral regions and cognitive processes and with no simple rule of association between asymmetry of structure and function [Boles et al., 2008].

Much of the individual variation in brain structure is apparent early in development, with fine tuning of the cerebral architecture (involving initial dendritic proliferation and subsequent pruning) unfolding into late childhood—and probably until the mid-20s for the CC [Lebel et al., 2008]. A number of studies support the case of important genetic influences in the determination of brain structure. In baboons, for example, cerebral gyrification, a measure of cortical folding, is highly heritable (~40% of morphological variability in sulcal area, depth, and length) [Kochunov et al., 2010]. While this influence appears to be weaker in humans, it still accounts for ~25% of the variance in cortical folding [White et al., 2010]. Other cerebral characteristics, such as GM volume, have also been shown to be largely determined by genetic influences with up to 90% of the variance in regional volume in frontal areas [Thompson et al., 2001] and 20–30% of white matter (WM) connectivity mostly in frontal and occipital regions [Jahanshad et al., 2010] being genetically determined.

This is not to say that environmental influences are not equally important and relevant. Environmental factors ranging from pre- and perinatal conditions [Gillam et al., 2008], parenting style [Frye et al., 2010], physical and psychological stress [McEwen, 2008], motor training [Taubert et al., 2011], education [Draganski et al., 2006], financial hardship [Butterworth et al., 2011], diet [Qiu et al., 2010], to name a few, have significant effects on brain structure. It has also been demonstrated in twin studies that the development of cerebral asymmetry, both anatomical and functional, is likely influenced by hormonal levels in the womb and by pre- and perinatal traumatic events [Eckert et al., 2002]. While in older individuals varying cerebral asymmetries have been shown to be associated with different degrees of cognitive impairment [Cherbuin et al., 2010].

Anatomical cerebral asymmetry, particularly in the language centers, has also been shown to be significantly genetically determined [Jahanshad et al., 2010; Thompson et al., 2001]. Moreover, animal and human *postmortem* and neuroimaging studies found associations between cerebral lateralization and callosal characteristics. Earlier studies reported negative associations between the magnitude of anatomical cerebral asymmetry and connectivity through the CC [Aboitiz et al., 1992a; Rosen et al., 1989], but recent findings suggest a more complex picture. Luders et al. [2003] found that while asymmetry of the Sylvian fissure

was negatively associated with anterior callosal surface area, asymmetry of the post central sulcus was positively associated with surface area in the splenium. Interestingly, while the superior temporal sulcus was also found to be significantly lateralized in this study, its asymmetry did not relate to callosal area. These findings suggest that the direction and magnitude of associations differ across brain regions but their determinants are unclear.

Intra-twin correlations in callosal connectivity were revealed in a recent diffusion tensor imaging study [Brouwer et al., 2010]. This suggests that significant genetic factors influence callosal structure (mostly in the callosal genu and splenium). Thus, it is possible (a) that genetically determined callosal features lead to specific patterns of cerebral lateralization, (b) that genetically determined patterns of cerebral asymmetry lead to patterns of callosal connectivity, (c) that cerebral asymmetry and/or callosal connectivity are shaped by environmental factors, or (d) a combination of these. We believe an interaction between genetic and environmental influences is most likely for the following reasons: cerebral WM connectivity has been shown to be determined both by genetic (20–30%) and by shared environmental factors (15%) [Jahanshad et al., 2010]; functional cerebral asymmetry continues to develop into adulthood [Sowell et al., 2002] and is thought to be linked to the development of the CC [Boles, 1998]; and environmental influences such as socioeconomic status are associated with cerebral asymmetry [Boles, 2011].

Although genetic and environmental factors are not the focus of this study, it is important to consider their possible contributions since, in light of the reviewed literature, it would be expected that their interaction would lead to different outcomes depending on whether they occur earlier or later in development. For example, later environmental influences might have less impact on cerebral regions that mature earlier, such as the callosal splenium and primary sensory areas, than on those with longer developmental timelines, such as the callosal genu and the frontal lobes [Lebel et al., 2008; Trivedi et al., 2009]. Support for such effects has been demonstrated in a diffusion tensor imaging study in monozygotic and dizygotic twins which showed that a greater proportion of WM variance was explained by genetic factors in the occipital lobe than in the frontal lobe, whereas the occipital lobe matures earlier than the frontal lobe [Lee et al., 2008].

Moreover, regions whose variance is less genetically determined, such as the right hemisphere [Thompson et al., 2001], the planum temporale [Steinmetz, 1996], and the callosal body [Brouwer et al., 2010] may be more susceptible to environmental influences. Consequently, while greater anatomical cerebral asymmetry may be related to greater callosal connectivity in some regions, the reverse (or no relationship) might be true for other regions, and substantial interindividual variability is to be expected.

Thus, the aim of this study was to clarify the nature of relationships between callosal connectivity and anatomical cerebral asymmetry in a large sample of subjects. We used precise measures of callosal thickness and cerebral lobes gray and WM and other selected cortical structures known to be asymmetrical and/or involved in lateralized processes. Moreover, we considered not only the direction but also the magnitude of asymmetries.

METHODS

Study Population

The overall sample of this study included 348 healthy subjects (147 men and 201 women), ranging between 44 and 49 years. This sample was drawn from the PATH Through Life Project designed to study the risk and protective factors for normal aging, dementia and other neuropsychiatric disorders [Anstey et al., 2005]. This study focuses on the middle-age sample of the PATH Project, composed of 2,530 individuals randomly selected from the population of Canberra, Australia. A subsample of 656 participants, randomly selected from those participants who had previously indicated they would be willing to undergo an MRI scan ($n = 2{,}076$), were offered a magnetic resonance imaging (MRI) scan, which 503 accepted, and 431 eventually completed [Wen et al., 2009]. The reasons for not undergoing MRI after having initially agreed included subsequent withdrawal of consent, medical conditions contraindicating MRI, and claustrophobia or other anxiety about the procedure. There were no differences in age, sex, and years of education between those who had an MRI scan and those who did not. Since participants were randomly selected from the electoral roll and since voting is compulsory in Australia this sampling method is the closest to randomly selecting from the population. Participants were not selected based on an increased risk for dementia or any other condition. One scan was lost due to a technical fault, giving a total number of 430 scans. For the current analysis, another 82 scans were excluded due to stroke (4), severe head injury (21), epilepsy (4), missing data (25), movement artifacts (5), or low-scan quality for cortical parcellation (23), leaving 348 scans. Participants' handedness was assessed with the Edinburgh Inventory [Oldfield, 1971] which produces an index ranging from −1 (extreme left handedness) to +1 (extreme right handedness). Participants with scores equal to or lower than 0 are classified as left-handed ($n = 34$) and those with scores greater than 0 are classified as right-handed ($n = 314$). Associations between handedness and callosal thickness are not considered here but have been reported elsewhere [Luders et al., 2010]. The study was approved by the ethics committees of the Australian National University, Canberra and the University of New South Wales, Sydney, Australia. All participants gave written informed consent to be included in this study.

MRI Scan Acquisition

T1-weighted 3D structural MRI images were acquired in coronal plane using fast field echo (FFE) sequence on a 1.5

T Gyroscan scanner (ACS-NT, Philips Medical Systems, Best, The Netherlands). About midway through this study, for reasons beyond the researchers' control, the original scanner (scanner A) was replaced with a similar Philips scanner (scanner B). The scanning parameters were kept essentially the same. The first 163 subjects were scanned on scanner A with TR = 8.84 ms, TE = 3.55 ms, a flip angle of 8°, matrix size = 256 × 256, slices 160, and the field of view (FOV) 256 × 256 mm^2. Slices were contiguous with slice thickness of 1.5 mm. For the remaining 268 subjects scanned on scanner B, the TR = 8.93 ms, TE = 3.57 ms values were slightly different in order to improve image quality, but all other parameters were exactly the same. To ensure the reliability and compatibility of the data, we compared the subjects scanned on the two scanners on sociodemographic and imaging parameters. There were no significant differences on age or years of education, but significantly more women were scanned on scanner B than A ($P = 0.003$). The GM, WM, and cerebrospinal fluid (CSF) volumes obtained from the two scanners did not differ significantly.

Image Preprocessing and Callosal Outlining

To correct for differences in head alignment, images were placed into the Talairach standard space using automated six-parameter rigid-body transformations [Collins et al., 1994]. In addition, automated radiofrequency bias field corrections were applied [Sled et al., 1998] to correct images for intensity drifts caused by magnetic field inhomogeneities. The CC was then outlined automatically based on the Chan–Vese model for active contours [Chan and Vese, 2001] using the LONI pipeline processing environment [Rex et al., 2003]. This resulted in two midsagittal callosal segments (i.e., the upper and lower callosal boundaries) for each subject, as detailed elsewhere [Luders et al., 2006b]. Subsequently, each callosal segment was overlaid onto the respective individual anatomical image and visually inspected to insure that automatically generated callosal outlines followed precisely the natural course and boundaries of the CC. Contours that did not match this criterion were corrected manually by one rater (N.C.).

Cortical Parcellation and Cerebral Asymmetry Measures

Images were analyzed with FreeSurfer [http://surfer.nmr.mgh.harvard.edu/; Fischl et al., 2002, 2004], which allows automatic reconstruction of the cortical surface from T1-weighted MRI images. Major steps during image analyses include motion correction, removal of non-brain tissue, automated Talairach transformation, subcortical and cortical matter segmentation, intensity correction and delineation of gray/white/pial boundaries. After the creation of cortical models, deformation procedures are applied including cortical inflation, registration to a spherical atlas and parcellation of the cerebral cortex into gyral and sulcal units.

TABLE I. Sample characteristics

Demographic variables	$n = 348$
Female (%)	201 (57.78)
Age, years (SD)	46.74 (1.43)
Education, years (SD)	14.83 (2.28)
Caucasian (%)	332 (95.40)
Left handedness (%)	34 (9.80)
Handedness magnitude (SD)	0.60 (0.47)
Diabetes (%)	8 (2.30)
Hypertension (%)	89 (25.60)

Handedness measures are based on the Edinburgh Inventory [Oldfield, 1971] which produces an index ranging from −1 (extreme left handedness) to +1 (extreme right handedness). Participants with scores equal to or lower and greater than 0 are classified as left- and right-handed, respectively. Handedness magnitude is the absolute value of the handedness index.

The focus of this study was limited to the frontal, temporal, parietal, and occipital cerebral lobes gray and WM [Zadina et al., 2006; Zilles et al., 1996] and to other structures known to be anatomically asymmetrical and/or functionally lateralized including the *planum temporale*, the motor and somatosensory cortices [Amunts et al., 2000], the hippocampus [Zaidel, 1995], the cingulate gyrus [Kovalev et al., 2003], the *pars opercularis* (including Broca's area) [Jung et al., 2009; Keller et al., 2009; Knaus et al., 2007], and the supramarginal gyrus [including Wernicke's area; Kovalev et al., 2003; Lyttelton et al., 2009]. Asymmetry indices were computed with the formula (left volume − right volume)/(left volume + right volume). The resulting positive and negative indices were then used to compute two variables representing the direction of asymmetry (0 = left larger and 1 = right larger) and the magnitude of asymmetry (absolute value of the asymmetry index ranging from 0 to 1).

Statistical Analysis

Descriptive analyses were conducted using chi-squared analysis for categorical data and *t*-tests to compare groups on continuous variables. Associations between the direction and magnitude of cerebral asymmetry and callosal thickness were investigated using multiple regression analyses while controlling for intracranial volume. Differences in putative associations between magnitude and direction of cerebral asymmetries and callosal thickness were assessed by testing interaction factors between these variables in the analyses. Alpha was set at 0.05 and false discovery rate (FDR) corrections were applied [Benjamini and Hochberg, 1995].

RESULTS

Participants' characteristics are presented in Table I. Table II shows the number of participants with a left or right asymmetry for each cerebral structure considered as

TABLE II. Asymmetry measures

	Left asymmetry		Right asymmetry	
	n	Average deviation % (SD)	*n*	Average deviation % (SD)
GM				
Frontal	130*	1.0% (0.7)**	218*	1.2% (0.9)**
Temporal	288*	2.8% (1.9)*	60*	1.4% (1.2)*
Parietal	80*	1.3% (1.0)*	268*	2.6% (1.7)*
Occipital	89*	2.6% (2.0)***	259*	3.4% (2.6)***
Motor	165	3.1% (2.6)	183	3.2% (2.4)
Somato-sensori	279*	6.1% (3.9)*	69*	3.3% (2.5)*
Cingulate	159	4.9% (4.1)	189	5.7% (4.1)
Pars opercularis (incl. Broca)	269*	9.6% (6.7)*	79*	5.2% (3.8)*
Supramarginal (incl. Wernicke)	261*	7.4% (5.0)*	87*	4.0% (3.1)*
Planum temporale	264*	14.1% (9.6)*	84*	5.85% (5.2)*
Hippocampus	29*	1.2% (1.2)*	319*	4.3% (2.6)*
WM				
Frontal	118*	0.9% (0.6)*	230*	1.5% (1.1)*
Temporal	304*	3.1% (2.0)*	44*	1.1% (0.9)*
Parietal	35*	1.4% (1.2)*	313*	3.1% (1.8)*
Occipital	130*	2.8% (2.3)***	218*	3.5% (2.5)***

*$P < 0.001$, **$P < 0.05$, ***$P < 0.01$.
Chi-square $n = 348$, df $= 1$; *t*-test $n = 348$, df $= 347$.

well as the average percent deviation from perfect symmetry. Of all 10 GM structures considered, 5 presented with a stronger left asymmetry, 3 with a stronger right asymmetry, and 2 showed no significant asymmetry. Of all four lobar WM structure considered, three had a stronger right asymmetry (frontal, parietal, and occipital) and only the temporal WM showed a left asymmetry.

Associations between regional asymmetry measures and callosal thickness are presented in Figure 1. For the direction of asymmetry, three regions (i.e., the hippocampus, motor cortex, and supramarginal cortex, including Wernicke's area) showed an association with callosal thickness. That is, for the hippocampus, right asymmetry was associated with lower callosal thickness, while the reverse association was found for motor and supramarginal cortices. For magnitude of asymmetry, three regions (i.e., the hippocampus, parietal cortex, and supramarginal cortex) showed an association with callosal thickness. That is, greater asymmetry of the hippocampus was associated with lower callosal thickness (negative association), whereas greater parietal and supramarginal cortex asymmetries were associated with greater callosal thickness (positive association).

Interactions between the direction and magnitude of asymmetry were also detected in three GM regions and three WM regions and are presented in Figure 2. More specifically, with respect to *rightward asymmetry*, increased callosal thickness was associated with greater asymmetry of the somato-sensori, cingulate, as well as parietal cortices. In contrast, greater asymmetry of the frontal, temporal, and parietal WM was associated with lower callosal thickness (negative association). With respect to *leftward asymmetry*, increased callosal thickness was associated with greater asymmetry for frontal and parietal WM as well as parietal and cingulate cortices (positive association). No negative association was detected between cortical thickness and degree of leftward asymmetry. No associations were detected between callosal thickness and *planum temporale*, *pars opercularis*, or temporal gray or WM.

DISCUSSION

Four key findings emerged from this study. First, most cerebral regions were significantly asymmetrical, but these asymmetries had relatively weak associations with callosal thickness. Second, where associations were detected, leftward asymmetry was more strongly associated with decreased callosal thickness. Third, increased magnitude of cortical asymmetry, irrespective of direction, was associated with increased callosal thickness, while increased magnitude of WM asymmetry was associated with decreased callosal thickness. Finally, where interactions between magnitude and direction of cerebral asymmetry

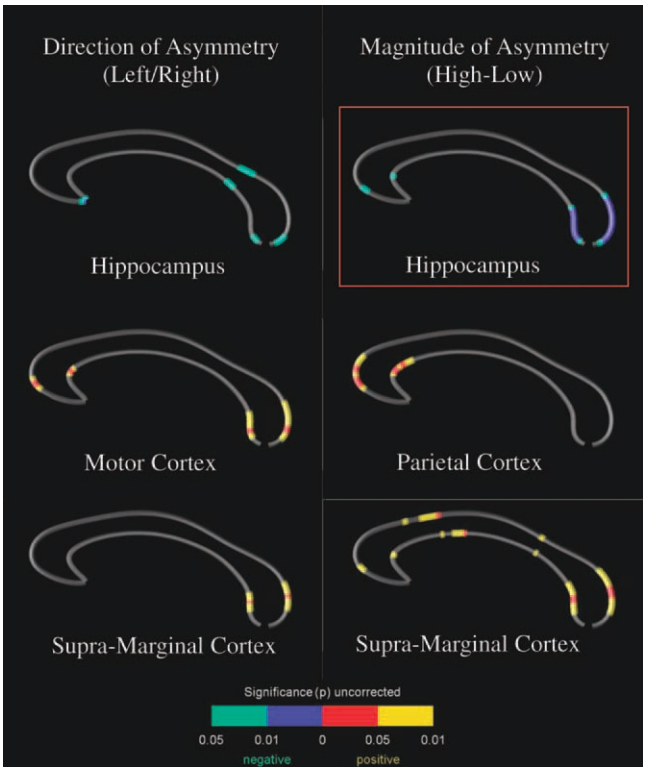

Figure 1.
Associations between direction or magnitude of cerebral asymmetry and callosal thickness. Significance at $\alpha = 0.05$, red frame highlights significant association after FDR correction.

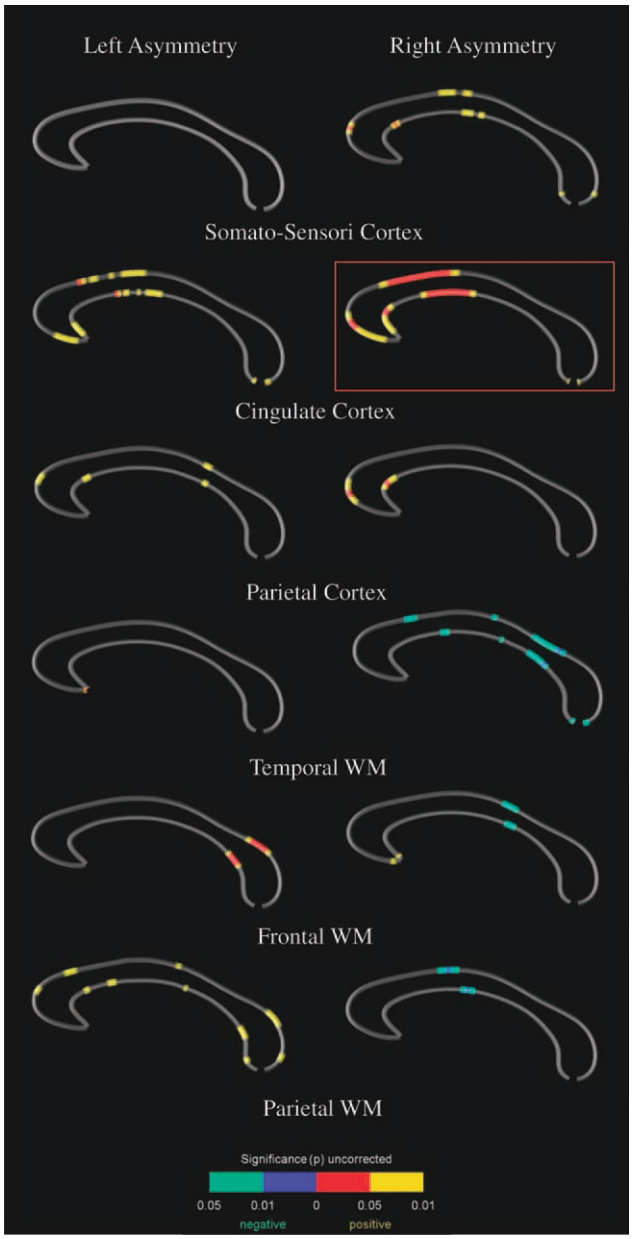

Figure 2.
Interactions between direction and magnitude of cerebral asymmetry. Significance at $\alpha = 0.05$, red frame highlights significant associations after FDR correction.

were detected, associations between degree of asymmetry and callosal thickness were stronger for right than left asymmetry.

It could be argued that the relative lack of association presented here may be due to the fact that callosal thickness is not a direct measure of callosal fiber connectivity or that fibers from one cortical region cross the CC through multiple segments while mixing with fibers originating in different areas, thus making their detection very difficult. While this may be the case, previous studies have shown that callosal surface area (and by extension thickness), is related to the number and size of callosal fibers [Aboitiz et al., 1992a; Hoptman and Davidson, 1994]. Moreover, fibers connecting frontal areas through the rostrum and occipital areas through the splenium tend to be more discretely organized into bundles [Hoptman and Davidson, 1994], yet many associations demonstrated in this study relate more to fibers crossing through the callosal midbody which are thought to be more diffusely organized and therefore more difficult to detect. Consequently, we do not believe that these factors were the main determinants of our results. Rather, when a large representative sample is used, spurious associations—which may be found in smaller samples due to their greater variability—are not detectable in large cohorts, unless consistently present at the population level.

Some of the strongest associations were found between callosal thickness and the asymmetry of the cingulate and motor cortices—two structures not significantly lateralized at the sample level. In contrast, the *planum temporale*, the *pars opercularis* which comprises Broca's area, and the somato-sensori and temporal cortices—areas that presented with the strongest average left asymmetry—showed no or very few associations with callosal thickness. This may suggest that where associations between cerebral asymmetry and callosal connectivity are found, they may reveal important functional benefits rather than conspicuous hemispheric specialization. Thus, whereas interhemispheric connectivity may not need to be strongly associated with language production, it is essential for rapid left/right motor control coordination and visuomotor synchronization [Wahl et al., 2007] as well as for higher-order cognitive processes such as attention control and executive functions. Consequently the development of callosal fibers may be more sensitive to asymmetries in motor and higher associative areas or, alternatively, the asymmetry of these areas may be more strongly affected by callosal connectivity.

Insights Into the Origins of Cerebral Morphological Asymmetries

As in a number of previous studies, greater cortical asymmetry was in general associated with greater callosal connectivity. But these associations should not be overstated as they were only present in few callosal regions, and only for a minority of cerebral areas.

Moreover, both greater parietal cortex asymmetry and smaller right parietal WM asymmetry were associated with decreased callosal thickness, albeit in different callosal regions, findings which again emphasize the notion that simple rules cannot account for variations in callosal connectivity.

Overall, while this study was not designed to provide conclusive answers on the origins of cerebral asymmetries, the finding that strong anatomical asymmetries were not

consistently associated with greater callosal connectivity appears to be more consistent with Ringo et al.'s [1994] theory. More specifically, although Ringo's theory could be compatible with positive, null, or even negative correlations between cerebral laterality and callosal thickness, a competing theory suggesting that lateralization occurred for reasons independent of brain size would imply that greater cerebral lateralization would be associated with greater callosal connectivity. Since this was not reflected in the present results, Ringo's theory appears more consistent, or at least less inconsistent, with our findings. However, the presence of some positive associations between callosal thickness (in spatially limited locations) and anatomical asymmetry in a number of structures with no or little lateralization at the cohort level (particularly the cingulate cortex) also suggests that other factors are at play. To shed more light on this question, the relationship between brain size, anatomical asymmetries, and other individual characteristics in this cohort will be investigated in a separate study.

Considerations on Genetic and Environmental Influences

As demonstrated by interactions between the direction and magnitude of asymmetry, variability in right hemisphere asymmetry was more strongly associated with callosal thickness. Consistent with this, environmental influences have been found to have a stronger influence on the right hemisphere, while variance in left hemisphere structure appears more strongly genetically determined [Thompson et al., 2001]. Similarly, many associations were detected in the callosal body, a region whose variance is less influenced by genetic control [Brouwer et al., 2010].

An exception to the general trend worth highlighting relates to the frontal WM. This structure was one of the least lateralized (1.3%) with a slight bias to the right. However, greater posterior callosal body thickness was associated with greater left, but not right, frontal asymmetry. The implication of these results cannot be resolved in this study but may be significant given the known functional asymmetries of this structure and the modulating role played by frontal processes in attention, mood, and other cognitive functions.

Regional Specificity

The strongest associations were found in the hippocampus, the cingulate, and the supramarginal cortex (including Wernicke's area). The hippocampus presented with a strong right asymmetry which was negatively related to callosal thickness while the supramarginal cortex had a strong left asymmetry, which was positively related to callosal thickness. These findings might reflect the fact that the supramarginal gyrus underlies language functions, which are themselves extremely lateralized and timing sensitive [Arimitsu et al., 2011; Halderman, 2011]. Language functions require fast interhemispheric transfer to be integrated with other language processes, such as prosody—for which the right hemisphere is known to be specialized and which have been shown to rely on callosal integrity [Sammler et al., 2010]. It is therefore possible that those with greater anatomical asymmetry in the supramarginal gyrus require greater callosal connectivity to integrate important speech processes. In contrast, while consistently reported as asymmetrical in this and other studies, the hippocampus is not known to be functionally highly lateralized. However, the contribution of the hippocampus to emotion regulation, selection of goal-oriented behavior, and memory (which are partially lateralized functions) could suggest that hippocampal asymmetry is more related to intra- rather than interhemispheric factors. These functions might require less callosal connectivity and particularly so in more asymmetrical brains (for the regional networks implicated).

Unlike the hippocampus and supramarginal cortex, the cingulate gyrus is not significantly lateralized at the cohort level. Despite this difference, greater asymmetry at the individual level in the left, but even more so in the right direction, is associated with greater connectivity in the anterior body. Given the anterior cingulate multiple functions (motor planning, goal selection, emotion regulation, and cognitively demanding information processing), it is difficult to interpret its association with callosal connectivity. However, cingulate functions require high degrees of synchronization across the hemispheres, a characteristic which may require increased callosal transfer when cingulate asymmetry is greater.

Surprisingly, the *planum temporale* whose anatomical asymmetry has been extensively studied and found to be negatively related to callosal characteristics in previous research [Aboitiz et al., 1992b; Dorion et al., 2000; Luders et al., 2003] did not produce any significant associations in this study. The reason for this difference is unclear but might be due to substantial methodological variability across studies (postmortem vs. in vivo; measurement: area estimates, sulcal length, volumetry; sample size; participants characteristics and selection; covariates). Since the present sample is the largest and the most representative, the observed differences between studies are likely attributable to the measures used or the more selected nature of other samples.

Limitations

This study had a number of limitations. The fact that it relies on a cross-sectional design means that causal associations cannot be tested. A longitudinal design spanning childhood and adulthood would be preferable but very costly and difficult to conduct. The narrow age range considered is both strength and limitation. While it cannot uncover age-dependent associations between CC and cerebral asymmetry, it is also much less prone to cohort effects. The regions of interest (ROIs) were selected to balance functional specificity, patterns of lateralization, and likelihood that the variability in their callosal connections could be detected with the proposed methodology. As a

consequence the ROIs were not functionally very specific which limits the significance of these findings in relation to discrete cognitive functions. Another possible limitation is that ROIs were measured using a semi-automated method which might not be as sensitive as some manual method. However, particular care was taken in processing and segmentation results were checked slice by slice for each participant. A major strength of this investigation, however, is that it was conducted in a large community-based sample of healthy volunteers. This provided good statistical power to detect the effects of interest, while being representative of the general adult population.

In conclusion, despite significant individual difference in cerebral anatomical asymmetries, few were associated with callosal thickness. This suggests that, in generally healthy adults, these associations are subtle and may become more conspicuous in clinical populations or in smaller nonrepresentative samples.

ACKNOWLEDGMENTS

The authors are grateful to Andrew Janke, Anthony Jorm, Patricia Jacomb, Karen Maxwell, and the path interviewers. Statistical analysis was done by Nicolas Cherbuin.

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