

Can the Language-dominant Hemisphere Be Predicted by Brain Anatomy?

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Abstract

■ It has long been suspected that cortical interhemispheric asymmetries may underlie hemispheric language dominance (HLD). To test this hypothesis, we determined interhemispheric asymmetries using stereology and MRI of three cortical regions hypothesized to be related to HLD (Broca's area, planum temporale, and insula) in healthy adults in whom HLD was determined using functional transcranial Doppler sonography and functional MRI (15 left HLD, 10 right HLD). We observed no relationship between volume asymmetry of the gyral correlates of Broca's area or planum temporale and HLD. However, we observed a robust relationship between volume asymmetry of the insula and HLD ($p = .008$), which predicted unilateral HLD in 88% individuals (86.7% left HLD and 90% right HLD). There was also a subtle but significant positive correlation between the extent of HLD and insula volume asymmetry ($p = .02$), indicating that a larger insula predicted functional lateralization to

the same hemispheric side for the majority of subjects. We found no visual evidence of basic anatomical markers of HLD other than that the termination of the right posterior sylvian fissure was more likely to be vertical than horizontal in right HLD subjects ($p = .02$). Predicting HLD by virtue of gross brain anatomy is complicated by interindividual variability in sulcal contours, and the possibility remains that morphological and cytoarchitectural organization of the classical language regions may underlie HLD when analyses are not constrained by the natural limits imposed by measurement of gyral volume. Although the anatomical correlates of HLD will most likely be found to include complex intra- and interhemispheric connections, there is the possibility that such connectivity may correlate with gray matter morphology. We suggest that the potential significance of insular morphology should be considered in future studies addressing the anatomical correlates of human language lateralization. ■

INTRODUCTION

There have been longstanding hypothesized associations between hemispheric language dominance (HLD) and cerebral asymmetries, dating back to Paul Broca's work on language disorders after acquired unilateral brain damage (Broca, 1861) and anatomic asymmetries described by Eberstaller (1890). Work on cerebral asymmetries was reignited in the 1960s and 1970s by virtue of the identification of leftward asymmetry of posterior brain regions that were known to be important for receptive processing of language. In particular, asymmetry of the planum temporale was suggested to be related to HLD, given that macroscopic surface area and length asymmetry (Geschwind & Levitsky, 1968) and cytoarchitectonic asymmetry (Galaburda, Sanides, & Geschwind, 1978) were leftward in approximately two thirds of postmortem human brains. More recent studies have capitalized on the *in vivo* capacity of neuroimaging techniques that can simultaneously determine anatomic cerebral asymmetries and HLD. Some of these studies have investi-

gated the relationship between structure of the planum temporale and HLD (Josse, Mazoyer, Crivello, & Tzourio-Mazoyer, 2003; Tzourio, Nkanga-Ngila, & Mazoyer, 1998) and report that the size of the left planum may be related to the extent of language lateralization. However, these studies and others (Dorsaint-Pierre et al., 2006; Eckert, Leonard, Possing, & Binder, 2006) suggest that interhemispheric asymmetry of the planum temporale may not be a reliable marker for the direction of HLD. Furthermore, investigations of the relationship between the anterior speech region of Broca (i.e., the pars opercularis and pars triangularis of the third frontal convolution) and HLD have been compromised by inclusion of patients with brain damage, despite the reported relationship between asymmetry of the frontal operculum and side of HLD in patients with epilepsy (Dorsaint-Pierre et al., 2006; Foundas, Leonard, Gilmore, Fennell, & Heilman, 1996). The primary goal of the present manuscript was to determine the relationships between HLD and anatomical asymmetries of cortical regions known to be important for language in healthy adults in whom HLD was determined by functional neuroimaging methods.

The neuroanatomy mediating language function consists of a widespread network of cortical and subcortical

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structures and is not limited to the areas of cortex classically described by Broca (1861) and Wernicke (1874/1977). Indeed, widespread regions of the (usually the left) frontal, temporal, and parietal lobes and subcortical structures are activated during neuroimaging studies of language processing (Binder et al., 1997). The articulation of speech, once thought to be intimately associated with lateral frontal lobe regions, has more recently been shown to be crucially dependent on the functioning of the anterior insula (Ogar et al., 2006; Price, 2000; Wise, Greene, Buchel, & Scott, 1999; Donnan, Darby, & Saling, 1997; Dronkers, 1996). Furthermore, the topographical extent of cerebral lesions underlying Broca's aphasia is not limited to the left third frontal convolution. Infarction of the upper branch of the left middle cerebral artery distribution frequently damages the left insula (Mohr, 1979; Mohr et al., 1978). Given the importance of the insula for motor and expressive language in particular, we also investigated the relationship between the anatomical asymmetry of the insula and HLD.

Up to approximately 90% of the right-handed population are left hemisphere dominant for language lateralization (Knecht, Deppe, et al., 2000; Knecht, Drager, et al., 2000). The remaining population possess bilateral or right language lateralization (Knecht, Deppe, et al., 2000; Knecht, Drager, et al., 2000), and therefore the identification of people with unilateral right HLD is problematic, ordinarily requiring selection from left-handed or brain-damaged populations where there is a greater number of people with right HLD. Even from these populations, it is difficult to obtain a sample large enough to analyze the anatomical correlates of right HLD, given that only 2% to 10% of the left-handed population may have right HLD (Pujol, Deus, Losilla, & Capdevila, 1999) and, for example, deviance from left HLD (i.e., bilateral representation and right HLD) is observed in only up to 23% of patients with circumscribed left temporal lobe epilepsy (Adcock, Wise, Oxbury, Oxbury, & Matthews, 2003; Brazdil, Zakopcan, Kuba, Fanfrdlova, & Rektor, 2003). However, it is likely that pathological mechanisms may have reallocated language functions to the right hemisphere in some patients, and it is therefore questionable whether patients with left hemisphere damage and right HLD represent a natural feature of functional brain organization. In the present study, we identified a relatively large sample of 10 healthy right-handed adults with right HLD using functional transcranial Doppler sonography (fTCD) and functional MRI in the context of the Münster functional imaging study on the variability of hemispheric specialization in health and disease (Deppe, Knecht, Lohmann, & Ringelstein, 2004; Deppe, Ringelstein, & Knecht, 2004; Knecht et al., 1996, 2001, 2003; Deppe et al., 2000; Knecht, Deppe, et al., 2000; Knecht, Drager, et al., 2000; Knecht, Deppe, Ebner, et al., 1998; Knecht, Deppe, Ringelstein, et al., 1998; Deppe, Knecht, Henningsen, & Ringelstein, 1997). We compared MRI-derived anatomical asymmetries of Broca's area, planum temporale, and insula in these subjects with

anatomical asymmetries in those with left HLD, determined using the same *in vivo* neuroimaging techniques. We furthermore explored the relationship between HLD and morphological asymmetries of the cortical areas quantified, including morphology of the inferior frontal sulcus (which traditionally forms the dorsal border of Broca's area), diagonal sulcus (the presence of which is related to the size of Broca's area; Keller, Roberts, & Hopkins, 2009; Keller et al., 2007; Knaus, Corey, Bollich, Lemen, & Foundas, 2007), and shape of the posterior sylvian fissure (which defines the macroscopic posterior border of the planum temporale).

METHODS

Overview

We analyzed the anatomical MRI data sets of 25 healthy right-handed adults, 15 of whom had unilateral left HLD and 10 had unilateral right HLD. Functional TCD was used to determine HLD in 14 participants (8 left and 6 right), and fMRI was used in 11 participants (6 left and 5 right). HLD is correlated in a highly linear fashion between fTCD and fMRI, not only in side but also in the degree of lateralization (Deppe et al., 2000) (Figure 1). In the present study, we used identical word generation paradigms during fMRI and fTCD assessment for HLD to minimize between-modality discrepancies in analysis of HLD. Therefore, all subjects underwent assessment for interhemispheric lateralization of language expression. Quantitative image analysis of structural MRI data sets was performed using the same approach for all participants after the determination of, and blind to, HLD status.

Participants

This study had local ethics committee approval. All participants were native German speakers and provided written informed consent before the scanning sessions. The participants were also informed that the examination

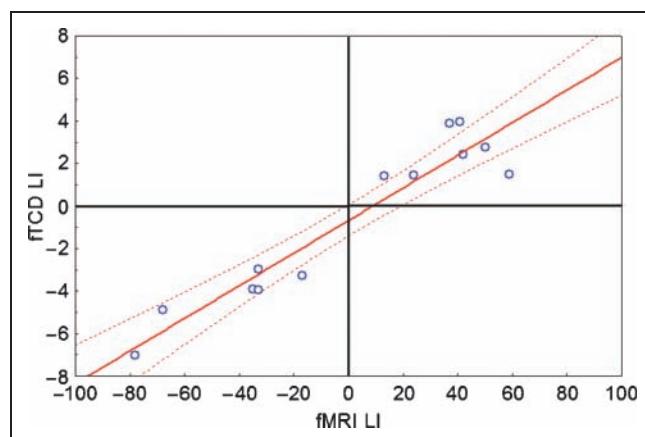


Figure 1. Reprise of the correlation between lateralization indices (LIs) obtained from fTCD and fMRI (Deppe et al., 2000).

could reveal potentially medically significant findings and were asked if they would like to be notified in this case. Twenty-five healthy participants (range = 22–43 years, mean age = 28 years, $SD = 5.80$ years) were selected from a large database of volunteers on the basis of (i) no history of neurological or psychiatric disorder, (ii) right-handedness, (iii) left and right HLD subjects being age and sex matched, (iv) no reported evidence of anomaly on MRI, (v) age (20–60 years), (vi) evidence of unequivocal unilateral left or right HLD, and (vii) availability of both functional imaging data and T1-weighted structural MRI for analysis. All participants were university students or graduates and were therefore believed to have higher than average intelligence and no cognitive deficits that may have been indicative of subtle brain damage related to, for example, atypical right HLD. Side of HLD was the only variable to significantly differ between groups. Mean (SD) age was 27 (4.66) and 29.7 (2.35) years for the left and right HLD groups, respectively ($t = 1.15, p = .26$). Twelve subjects with left HLD (80%) were men, and 6 subjects with right HLD (60%) were women (Fishers exact test, $p = .38$). It was assumed that left and right HLD subjects did not differ in language and cognitive and intellectual abilities on the basis of previous studies of HLD from our research group (Drager & Knecht, 2002; Knecht et al., 2001). The acquisition of the functional neuroimaging data was part of the Münster functional imaging study on the variability of hemispheric specialization in health and disease (Deppe, Knecht, et al., 2004; Deppe, Ringelstein, et al., 2004; Knecht et al., 1996, 2001, 2003; Deppe et al., 2000; Knecht, Deppe, et al., 2000; Knecht, Drager, et al., 2000; Knecht, Deppe, Ebner, et al., 1998; Knecht, Deppe, Ringelstein, et al., 1998; Deppe et al., 1997). To date, approximately 600 healthy volunteers of varied age, sex, handedness, neurological status (e.g., incidental findings on MRI), and investigation approach have been studied within the framework of the large-scale project. For information on the distribution of HLD and handedness in the general population from a proportion of these subjects, the reader is referred to previous studies from our research group (Knecht, Deppe, et al., 2000; Knecht, Drager, et al., 2000). The inclusion of 25 subjects investigated in the present study was based on the aforementioned seven inclusion criteria.

Functional Transcranial Doppler Sonography

Functional TCD measures cerebral perfusion changes related to neural activation in a way comparable with fMRI. The method contends itself with comparison of averaged, event-related blood flow velocity changes within the territories of the left versus the right middle cerebral artery during, and with respect to the present study, a standardized word generation paradigm (Knecht et al., 1996) for robust and reliable assessment of HLD. The combination of fTCD and word generation as used in the present study has been previously validated by direct comparison with the intracarotid amobarbital injection (Wada) procedure

(Knaake et al., 2003; Knecht, Deppe, Ebner, et al., 1998; Knecht, Deppe, Ringelstein, et al., 1998) and fMRI (Deppe et al., 2000; Schmidt et al., 1999), used to investigate the relationship between HLD, handedness (Knecht, Deppe, et al., 2000; Knecht, Drager, et al., 2000), and cognitive ability (Knecht et al., 2001) and used in conjunction with fMRI to study the neural correlates of atypical HLD (Knecht et al., 2003). This consistency is not restricted to HLD, as other studies have demonstrated strong agreement between fTCD and fMRI of hemispheric dominance of spatial attention (Jansen et al., 2004). A detailed description of fTCD to determine HLD using the standardized word generation paradigm can be found in Deppe, Ringelstein, et al. (2004). Briefly, subjects were presented a letter on a computer screen 2.5 sec after a cueing tone and had to generate as many words as possible, starting with the displayed letter. The performance was controlled by instructing subjects to report the words after a second auditory signal, which followed 15 sec after presentation of the letter. Functional TCD analysis (data conversion, artifact detection, heart cycle integration, data normalization, signal averaging, and calculation of laterality index [LI]; see Deppe, Ringelstein, et al., 2004) was performed using the software AVERAGE (Deppe et al., 1997). The LI_{fTCD} was calculated by AVERAGE according to the following formula:

$$LI_{fTCD} = \frac{1}{t_{int}} \int_{t_{max} - 0.5t_{int}}^{t_{max} + 0.5t_{int}} \Delta V(t) dt \quad (1)$$

where

$$\Delta V(t) = dV(t)_{left} - dV(t)_{right} \quad (2)$$

is the difference between the relative velocity change

$$dV = 100 \frac{V(t) - V_{pre.mean}}{V_{pre.mean}} \quad (3)$$

of the left and right middle cerebral arteries. $V_{pre.mean}$ denotes the mean velocity during a 15-sec interval in advance to the cueing tone. The time point t_{max} represents the latency of the absolute maximum of $\Delta V(t)$ within the word generation interval (5–22 sec). A period of $t_{int} = 2$ sec was chosen for the integration interval. To make LI_{fTCD} comparable with lateralization values from fMRI, we converted standard fTCD asymmetry indices into canonical LI values (LI_{fTCDc}) using the formula presented in the article of Deppe et al. (2000):

$$LI_{fTCDc} = \frac{LI_{fTCD} - 0.45}{0.083} \quad (4)$$

Equation 4 represents the empirically estimated regression function used to describe the relationship between fTCD and fMRI LIs. A positive sign of LI indicates left and a negative right dominant language processing.

The reader is referred to Deppe, Ringelstein, et al. (2004) for more detailed information.

fMRI

Functional MR images were acquired using a Magnetom Vision 1.5 T MR System (Siemens, Germany) equipped with a circularly polarized head coil. Ten axial slices of 3 mm thickness and 3.75 mm distance were acquired using a BOLD-sensitive multislice EPI sequence (echo time [TE] = 64 msec, repetition time [TR] = 3 sec, acquisition time = 1.44 sec, flip angle = 90°) for functional imaging and T1-weighted sequences (TE = 15 msec, TR = 350 msec, flip angle = 90°) for better anatomical assignment of the EPI planes. The slices were oriented parallel to the intercommissural AC–PC line. The slices were acquired with a matrix resolution of 64 × 128 voxels, corresponding to a voxel size of 1.64 × 3.28 × 3.0 mm and a field of view of 210 × 210 mm. Head motion was minimized by foam padding.

The fMRI word generation task was designed as similar as possible to the fTCD task in a classical categorical “box-car” paradigm. For language activation, subjects were asked to generate as many words as possible, beginning with an acoustically presented letter. Further details of the fMRI activation task and the fMRI data analysis are provided in Deppe et al. (2000). The functional MRI LI was defined by

$$LI_{\text{fMRI}} = 100 \frac{N_L - N_R}{N_L + N_R} \quad (5)$$

where N_L and N_R refer to the numbers of voxels activated in the left and right hemisphere, respectively.

Structural MRI

For structural MRI, a sagittal three-dimensional MPRAGE data set (matrix = 256 × 256, 160 slices, field of view = 256 × 256 mm, slice thickness = 1 mm, TE = 4.4, TR = 11.4 sec, flip angle = 15°) covering the whole head was acquired for each subject. All MR images were manually realigned perpendicular to the AC–PC plane using the Brainvoyager software (www.brainvoyager.com). All structural measurements were performed with no investigator knowledge of side of HLD.

The Cavalieri method of design-based stereology in conjunction with point counting (Roberts, Puddephat, & McNulty, 2000; Gundersen, Jensen, Kieu, & Nielsen, 1999; Mayhew, 1992; Gundersen & Jensen, 1987) was used as an unbiased estimator of the volume of the pars opercularis, pars triangularis, planum temporale, and insula of all subjects. By using the Cavalieri method, volume is directly estimated from equidistant and parallel MR images of the brain with a uniform random starting position. A second level of sampling is required to estimate the section area from each image by applying point counting within the ROI. The mathematical justification and implementation

of the methodology is simple, and it can be applied to structures of arbitrary shape (Garcia-Finana, Keller, & Roberts, 2009). This technique has been frequently applied to reliably estimate brain compartment volume on MR images (Keller, Baker, Downes, & Roberts, 2009; Keller & Roberts, 2009; Keller, Roberts, et al., 2009; Lux et al., 2008; Cowell et al., 2007; Keller et al., 2007; Salmenpera et al., 2005; Howard, Roberts, Garcia-Finana, & Cowell, 2003; Keller, Mackay, et al., 2002; Keller, Wiesmann, et al., 2002; Mackay et al., 2000; Mackay et al., 1998; Sheline et al., 1996) and more widely applied to study other aspects of anatomy with and without the use of MRI. Stereology has been shown to be at least as precise as tracing and thresholding volumetric techniques and substantially more time efficient, with validation relative to postmortem measurements (Garcia-Finana et al., 2009; Keller & Roberts, 2009; Garcia-Finana, Cruz-Orive, Mackay, Pakkenberg, & Roberts, 2003; Keshavan et al., 1995).

Pars Opercularis and Pars Triangularis

We have described in detail the anatomical boundaries, the difficulties encountered, the strategies for decision making, and the stereological methods for the pars opercularis and pars triangularis in previous anatomical articles (Keller, Crow, et al., 2009; Keller, Roberts, et al., 2009; Keller et al., 2007). Here we briefly described the sulcal contours and stereological parameters used for measurement of these structures.

The pars opercularis was demarcated caudally from the precentral gyrus by the inferior precentral sulcus, dorsally from the middle frontal gyrus by the inferior frontal sulcus, and rostrally from the pars triangularis by the anterior ascending ramus of the sylvian fissure. The diagonal sulcus, which is occasionally present within the pars opercularis, was not used as an anatomical boundary, but its presence and connections to surrounding sulci were recorded. The pars triangularis was demarcated caudally from the pars opercularis by the anterior ascending ramus, dorsally by the inferior frontal sulcus, and rostro-ventrally from the pars orbitalis by the anterior horizontal ramus of the sylvian fissure. These sulcal contours are shown on the lateral surface of a brain and through orthogonal MRI sections in Figure 2. All gray matter from the fundus of the inferior frontal sulcus to the circular insular sulcus/ anterior horizontal ramus was sampled. No white matter was included in any measurement. Volume estimation was achieved by counting the number of randomly oriented test probes overlaying the structure of interest on every second coronal MR image for the pars opercularis and every third coronal MR image for the pars triangularis using a grid size of 3 pixels (i.e., 0.3 cm²) using an in-house developed software (Keller et al., 2007). The pars opercularis and the pars opercularis were remeasured in 10 healthy subjects from our previous study (Keller et al., 2007) for new intra- and interrater analyses. These analyses revealed a high level of repeatability (intrarater, left pars

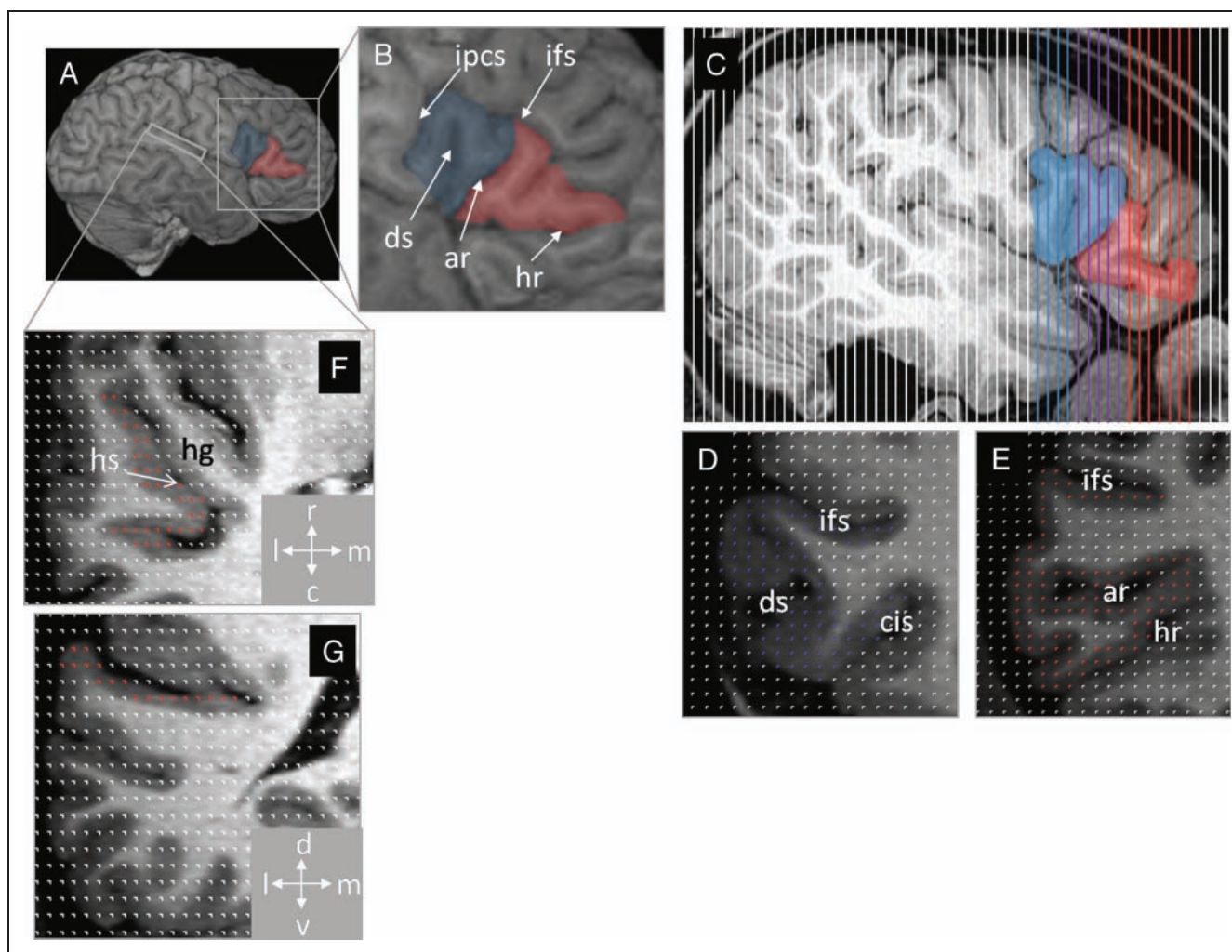


Figure 2. Anatomical definitions and stereological point counting for volume estimation of the pars opercularis, pars triangularis, and planum temporale (following Keller et al., 2007). All automated skull stripping and brain surface rendering was performed using MRICro (<http://www.sph.sc.edu/comd/rorden/micro.html>). (A) Whole brain for topological reference, indicating the pars opercularis (blue) and pars triangularis (red). (B) Magnification of the pars opercularis and pars triangularis, indicating the sulcal contours used for boundary definitions. (C) A parasagittal section from the same brain as panels A and B. The pars opercularis and the pars triangularis are again indicated in blue and red, respectively. The vertical lines schematically illustrate the sampling axis for point counting in the coronal plane. White vertical lines indicate coronal sections outside of the ROI; blue lines indicate coronal sections passing through the pars opercularis; purple lines indicate coronal sections passing through the pars opercularis and pars triangularis; red lines indicate coronal sections passing through the pars triangularis. (D) Coronal point counting for volume estimation of the pars opercularis. (E) Coronal point counting for volume estimation of the pars triangularis. (F) An axial section from the same brain showing the gray matter of the planum temporale (red points) at its greatest extent (this image was realigned orthogonal to the long axis of the sylvian fissure for optimal viewing of the dorsal surface of the planum temporale for illustrative reasons only). (G) Point counting (red) for volume estimation of the planum temporale on coronal sections. Abbreviations: ar = anterior ascending ramus of the sylvian fissure; c = caudal; cis = circular insular sulcus; d = dorsal; ds = diagonal sulcus; hg = Heschl's gyrus; hr = anterior horizontal ramus of the sylvian fissure; hs = Heschl's sulcus; ifs = inferior frontal sulcus; ipcs = inferior precentral sulcus; l = lateral; m = medial; r = rostral; v = ventral.

opercularis intraclass correlation [ICC] = .98, right pars opercularis ICC = .98, left pars triangularis ICC = .96, right pars triangularis ICC = .97) and reproducibility (interrater, left pars opercularis ICC = .94, right pars opercularis ICC = .92, left pars triangularis ICC = .95, right pars triangularis ICC = .95) of these measures.

Planum Temporale

The method of planum temporale volume estimation used in the present study was based on the methods reported in

our previous study (Keller et al., 2007). The posterior boundary of the planum temporale was defined as where the sylvian fissure turned to ascend in a more vertical plane or if it remained horizontal, at its termination. The medial boundary was the deepest extent of the sylvian fissure, and the anterior boundary was Heschl's sulcus (Figure 2). In those cases where there was more than one Heschl's gyrus or it bifurcated at any point along its length, the posterior gyrus was included in the planum temporale measurement. Volume estimation was achieved by sampling the planum temporale every second MR section using a grid

size of 4 pixels (i.e., 0.4 cm²). New intra- and interrater studies using the same subjects for the frontal reliability studies revealed a high level of repeatability (left planum ICC = .96, right planum ICC = .92) and reproducibility (left planum ICC = .92, right planum ICC = .91) of measures.

Cerebral Hemispheres

To compare the size of the brain between left and right HLD subjects, we used stereology to estimate the volume (gray and white matter together) of the left and right cerebral hemispheres using the same protocol as previously described (Keller & Roberts, 2009; Cowell et al., 2007; Mackay et al., 1998). Briefly, all supratentorial gray matter and white matter, excluding brainstem and cerebellum, were sampled on every 15th MR section using a grid size of 15 pixels (i.e., 1.5 cm²).

Insula

We measured the volume of insular cortices using the Cavalieri method on the basis of the anatomical guidelines provided by Naidich et al. (2004) and Kasai et al. (2003). Figure 3 illustrates the method used to quantify the volume of the insula in the present study.

Anatomy. The insula consists of two main gyri, the short insular gyrus located anteriorly and the long insular gyrus located posteriorly. The short insular gyrus typically consists of three distinct convolutions, referred to as the

anterior, the middle, and the posterior short insular gyri (although sometimes only two of these are present), whereas the long insular gyrus typically consists of two segments, the anterior and the posterior long insular gyri (Naidich et al., 2004). In the present study, the volume of the short and long insula gyri was estimated together using the following boundary definitions. At the posterior-most region of the long insular gyrus, tissue sampling begun on the section on which the circular insular sulcus (or peri-insular sulcus; Naidich et al., 2004) can be first visualized, which corresponds approximately to the coronal section on which the full profile of the pulvinar of the thalamus can be first demarcated from the adjoining thalamic nuclei and the coronal section on which Heschl's gyrus can be first visualized. The circular insular sulcus demarcates the superior and the inferior borders of the insula, and all cortices (i.e., gray matter) were sampled between these limits. The central insular sulcus, which separates the short and the long insular gyri, was not used for demarcation purposes. Tissue sampling of the insula terminated when the ROI could no longer be visualized and only the anterior horizontal ramus of the sylvian fissure could be seen.

Stereological parameters. To obtain a precise estimate of insular volume, like any other brain compartment, stereological parameters (i.e., size of test probes or "points," number of sections, etc.) are optimized to achieve a coefficient of error lower than 5% regardless of the structure measured. Strictly speaking, the coefficient of error is defined as the ratio of the square root of the variance

Figure 3. Insula anatomy and methods. (A) Postmortem specimen revealing the anterior (a), middle (m), and posterior (p) convolutions of the short insular gyrus (SIG, red) and the anterior and posterior convolutions of the long insular gyrus (LIG, yellow). White arrows indicate the circular insular sulcus. (B) A corresponding sagittal MR section indicating the gyri of the insula. (C) Tracing of the gyri in panel A schematically illustrating the distance of sampling for volume estimation of the insula (broke red lines). (D) Point counting on coronal sections for volume estimation of the insular cortices (yellow).

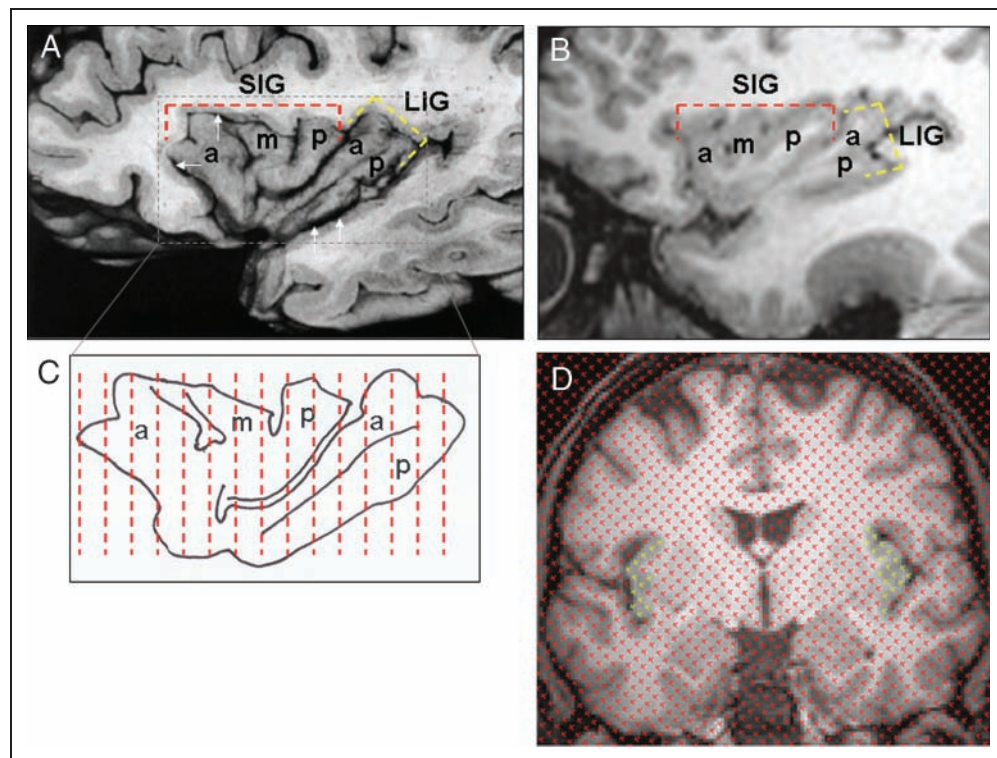
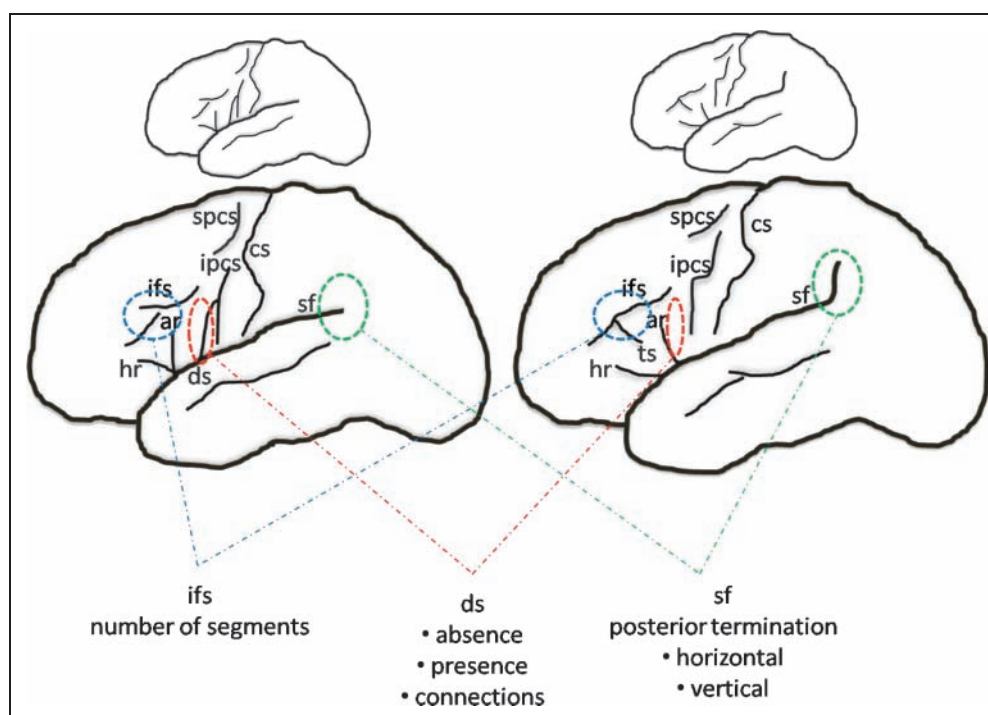


Figure 4. Schematic illustrations of the areas of sulcal variability recorded in the present study. There are several variations in sulcal configurations between the hemisphere on the left and the hemisphere on the right (the two smaller hemispheres at the top are the same as the larger hemispheres without labels enabling clearer visualization of the sulcal contours). The number of segments of the inferior frontal sulcus and the presence and connections of the diagonal sulcus were recorded, both of which are important features of Broca's area (Keller, Crow, et al., 2009; Keller, Roberts, et al., 2009; Keller et al., 2007). The general shape of the termination of the posterior sylvian fissure was classified as horizontal or vertical, which is related to the morphology of the planum temporale (Keller et al., 2007). Abbreviations: ar = anterior ascending ramus of the sylvian fissure; cs = central sulcus; ds = diagonal sulcus; hr = anterior horizontal ramus of the sylvian fissure; ifs = inferior frontal sulcus; ipcs = inferior precentral sulcus; ts = triangular sulcus; sf = sylvian fissure; spcs = superior precentral sulcus.



of the volume estimator to its mean. It provides information on the precision of each volume estimate and is dependent on the complexity and size of a structure. Detailed information on the estimation of the coefficient of error is provided elsewhere (Roberts, Garden, Cruz-Orive, Whitehouse, & Edwards, 1994; Roberts et al., 2000). Point counting was performed in the coronal orientation within the insular ROI. Separation between test points on the square grid used for point counting was 0.234 cm (i.e., 3 pixels), and slice interval was 4 mm (every fourth MR section). Insular transect area was obtained by multiplying the total number of points recorded by the area corresponding to each test point (i.e., $0.234 \times 0.4 = 0.094 \text{ cm}^2$). An estimate of insular volume was obtained as the sum of the estimated areas of the structure transects on consecutive systematic sections multiplied by the distance between sections. Approximately 250 points were recorded on approximately 18 systematic random sections, consistent with stereological volume estimation of other brain structures (Keller & Roberts, 2009). The contiguous sections were used for calculation of section area profiles to investigate the regional interhemispheric asymmetries of the insula, which enables visualization of slice-by-slice area profiles of structure volume (Keller, Mackay, et al., 2002). All asymmetry coefficients were calculated using a standard formula $([r - 1] / [r + 1])$. Interrater studies were undertaken for insula measurements in 10 subjects and revealed a high level of reproducibility (ICC = .96 for the left and right insula separately).

Morphological Analysis

The volume of the structures quantified in the present study is intrinsically related to the morphology of cortex. For example, the presence of the diagonal sulcus, which is located in the pars opercularis, will increase the volume of the pars opercularis (Keller, Roberts, et al., 2009; Keller et al., 2007; Knaus et al., 2007), and the shape of the posterior sylvian fissure will directly affect volume asymmetry of the planum temporale, inasmuch as a horizontal termination of the sylvian fissure generally gives a larger planum temporale volume relative to a vertical termination (Keller et al., 2007). Therefore, further to the analysis of cortical volume, we also explored the relationship between HLD and basic morphological features contributing to the definition of Broca's area and planum temporale. For each participant, the following was recorded via navigation through intrasulcal anatomy:

- (i) Broca's area—the presence and connections of the diagonal sulcus and the number of segments of the inferior frontal sulcus in the left and right hemisphere separately
- (ii) Planum temporale—general horizontal or vertical termination of the posterior sylvian fissure in the left and right hemisphere separately. It should be noted that this is a very crude classification system because there are some complex bifurcation patterns to this region of the brain (Ide, Rodriguez, Zaidel, & Aboitiz, 1996)

These morphological features are schematically illustrated in Figure 4.

Table 1. Demographic, Functional Neuroimaging, and Morphological Information for Each Participant

<i>Participant</i>	<i>Sex</i>	<i>Age</i>	<i>HLD Assessment</i>	<i>Standardized Lateralization</i>	<i>PTa</i>	<i>POPa</i>	<i>PTRa</i>	<i>Ia</i>	<i>DS</i>	<i>IFS</i>	<i>SF</i>
1	m	33	fMRI	31.83	27.34	-2.58	0.70	13.07	L = ipcs R = ipcs	L = 1 R = 2	L = V R = V
2	m	26	fMRI	20.95	9.34	2.64	-2.10	4.15	L = ar R = ar	L = 1 R = 2	L = H R = V
3	m	26	fMRI	-38.64	1.53	10.01	-18.36	-8.59	L = n/c R = ipcs	L = 1 R = 2	L = H R = V
4	m	41	fMRI	-39.30	-2.96	-14.84	16.08	-6.82	L = n/c R = n/c	L = 1 R = 1	L = H R = V
5	f	30	fMRI	-0.76	5.63	0.85	-1.43	-2.80	L = x R = x	L = 1 R = 1	L = H R = V
6	m	23	fMRI	46.38	-5.16	-15.83	13.91	15.91	L = ipcs R = ifs	L = 2 R = 2	L = H R = V
7	m	26	fMRI	-12.88	2.63	10.73	-3.85	-15.89	L = ar R = ar	L = 2 R = 2	L = H R = V
8	m	29	fMRI	33.57	6.92	10.61	-0.91	1.41	L = ipcs R = ifs	L = 1 R = 1	L = H R = H
9	m	27	fMRI	36.34	22.04	-7.71	4.34	6.58	L = ipcs R = ipcs	L = 2 R = 1	L = H R = H
10	m	25	fMRI	3.39	-13.24	8.25	-14.03	-24.60	L = ifs R = ipcs	L = 2 R = 2	L = V R = H
11	m	29	fMRI	34.50	11.57	-19.08	0.23	0.00	L = ifs R = x	L = 1 R = 2	L = H R = H
12	m	39	fTCD	11.45	4.99	-2.30	-4.45	13.41	L = n/c R = ipcs	L = 2 R = 2	L = V R = H
13	f	23	fTCD	42.29	16.86	20.20	-2.66	7.30	L = ar R = ipcs	L = 1 R = 1	L = H R = V
14	m	24	fTCD	27.95	11.54	25.17	-8.55	11.02	L = ipcs R = n/c	L = 2 R = 2	L = H R = H
15	f	22	fTCD	41.20	8.54	-23.00	-12.93	9.22	L = ipcs R = x	L = 1 R = 1	L = H R = V
16	m	27	fTCD	23.61	28.61	36.84	16.67	-11.28	L = ifs R = n/c	L = 1 R = 1	L = H R = V
17	m	25	fTCD	12.41	-7.68	-13.36	13.54	16.55	L = ipcs R = ifs	L = 2 R = 2	L = H R = H
18	f	22	fTCD	12.05	29.78	21.50	15.40	3.97	L = ipcs R = ifs & ipcs	L = 1 R = 1	L = H R = H
19	m	31	fTCD	11.45	-24.08	40.30	-16.29	31.40	L = n/c R = ipcs	L = 2 R = 2	L = H R = H

Table 1. (continued)

Participant	Sex	Age	HLD Assessment	Standardized Lateralization	PTa	POPa	PTRa	Ia	DS	IFS	SF
20	m	33	fTCD	-64.46	32.02	20.95	-0.72	-3.26	L = n/c R = n/c	L = 1 R = 2	L = H R = V
21	f	24	fTCD	-52.53	21.95	11.41	12.23	-7.23	L = x R = ipcs	L = 1 R = 1	L = H R = V
22	f	24	fTCD	-41.08	-4.35	5.93	-4.35	7.61	L = ipcs R = n/c	L = 1 R = 1	L = H R = V
23	m	23	fTCD	-53.01	37.11	-29.64	-2.08	-5.81	L = x R = n/c	L = 2 R = 2	L = H R = V
24	m	27	fTCD	-44.94	-7.23	18.90	21.34	-15.20	L = n/c R = ipcs	L = 2 R = 1	L = H R = H
25	f	43	fTCD	-90.12	28.73	14.99	18.82	-4.10	L = ar R = ar	L = 1 R = 2	L = H R = V

Note that negative values for HLD indicate rightward lateralization. Abbreviations: ar = diagonal sulcus connection with ascending ramus of the sylvian fissure; DS = diagonal sulcus; f = female; H = horizontal termination of the posterior sylvian fissure; IFS = inferior frontal sulcus; ifs = diagonal sulcus connection with inferior frontal sulcus; ipcs = diagonal sulcus connection with inferior precentral sulcus; L = left; LHD = left hemisphere language dominant; m = male; n/c = no connection of the diagonal sulcus with surrounding sulci; POPa = pars opercularis volume asymmetry; PTa = planum temporale volume asymmetry; PTRa = pars triangularis volume asymmetry; R = right; RHD = right hemisphere language dominant; SF = sylvian fissure; V = vertical termination of the posterior sylvian fissure; x = no DS.

Statistical Analysis

We used univariate ANOVAs to investigate the relationship between volume asymmetry of the planum temporale, pars opercularis, pars triangularis and insula, and side of HLD. The relationship between volume, volume asymmetries, and LIs were investigated using Pearson's correlation. Statistical analyses on the morphological data were performed using McNemar's tests.

RESULTS

Brain Volume and HLD

Demographic, functional, volumetric, and neuroanatomical information for each subject is provided in Table 1. A summary of volumetric asymmetries by HLD group is provided in Table 2. There was no difference between left and right HLD subjects in the volume of the whole brain ($t = 0.802$, $p = .443$). No relationship was found between HLD and volume asymmetry of the pars opercularis, $F(1, 24) = .46$, $p = .51$, pars triangularis, $F(1, 24) = .14$, $p = .71$, or planum temporale, $F(1, 24) = .69$, $p = .42$. Interestingly, group mean asymmetries of these regions were leftward, regardless of the side of HLD (Table 2). There was a significant relationship between HLD and asymmetry of the insula, inasmuch that leftward asymmetry was generally observed in left HLD subjects and rightward asymmetry in right HLD subjects, $F(1, 24) = 8.34$, $p = .008$ (Table 2). Twelve subjects (80%) with left HLD had leftward volume asymmetry of the insula, 2 subjects

(13.3%) had rightward volume asymmetry, and 1 subject (6.7%) had insular volume symmetry. Nine (90%) of the subjects with right HLD had rightward volume asymmetry of the insula, and one (10%) had leftward asymmetry. Individual plots of insular asymmetry against HLD LI values are shown in Figure 5. These values were significantly correlated ($r = .467$, $p = .02$), indicating that larger insula asymmetry values are generally found in subjects with larger LI values in the same direction. Inspection of Figure 5 also indicates that the degree of HLD was generally greater in subjects with right HLD (mean left LI = 25.95, mean right LI = -43.77, $t = 2.32$, $p = .03$). No other significant correlations were obtained for volume asymmetry or absolute volume ($p > .05$).

Figure 6 presents the section area profiles obtained from point counting of the whole insula along the anterior-posterior axis separately for (i) between-group comparisons of each hemisphere (i.e., left insula in left vs. right HLD/right insula in left vs. right HLD) and (ii) within-group

Table 2. Mean (SD) Volumetric Interhemispheric Asymmetries of the Planum Temporale (PT), Pars Opercularis (POP), Pars Triangularis (PTR), and Insula in Left and Right HLD Subjects

	PT	POP	PTR	Insula
Left HLD	8.48 (15.77)	5.44 (20.04)	0.19 (10.84)	6.54 (12.80)
Right HLD	11.51 (16.69)	4.93 (15.84)	3.77 (12.71)	-6.21 (6.65)

All values are leftward asymmetric (positive values), except of the insula in right HLD subjects.

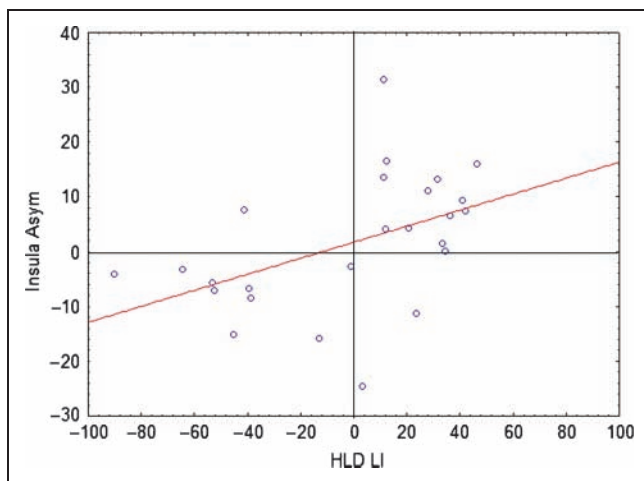


Figure 5. Scatterplot showing the significant correlation between volume asymmetry of the insula and HLD. HLD could be predicted in 88% of the sample by virtue of insular volume asymmetry. Of the remaining 12%, one case (4%, lying on the border of the reference line to the y-axis) was marginal, and two cases had inconsistent asymmetry and HLD.

comparison for interhemispheric asymmetry (i.e., left vs. right insula volumes in left and right HLD separately). The yellow shaded areas represent the insular regions exhibiting directional asymmetry consistent with the side of HLD. As can be seen, the structural–functional relationship was not localized to one particular region of the insula and is apparent in the anterior, middle, and posterior regions.

Brain Morphology and HLD

Although not quantified, visual inspection did not indicate any deviation from normal cerebral torque (right frontal–left occipital petalia) in all brains studied. Information on the morphological features recorded for each participant, including reference to demographic, structural, and functional lateralization data, can be found in Table 1.

With respect to Broca’s area, the diagonal sulcus was identified in 22/25 (88%) left hemispheres and 22/25 (88%) right hemispheres, consistent with our recent study (Keller,

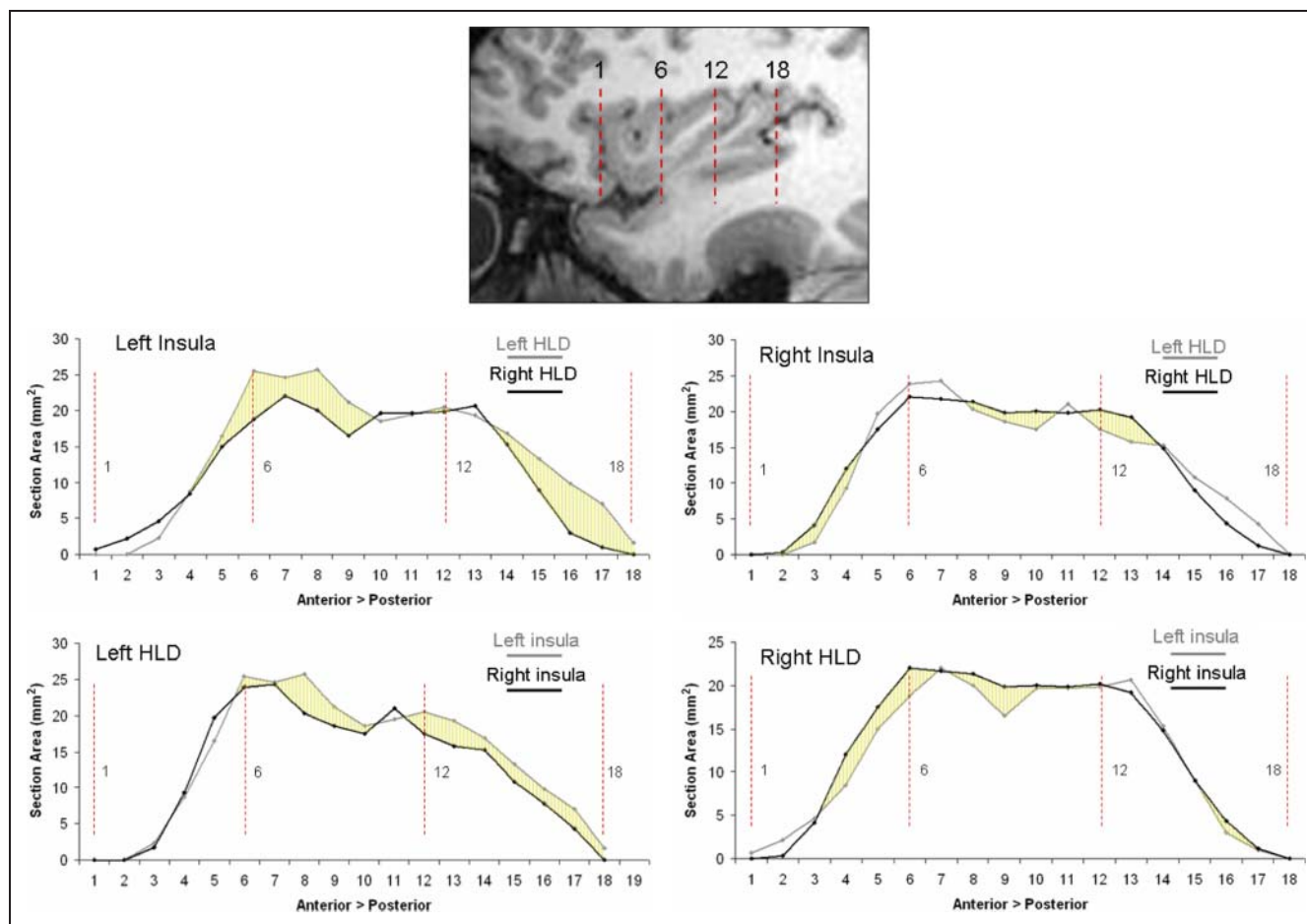


Figure 6. Relationship between the morphology of the insula along the anterior–posterior axis and HLD. The shaded yellow regions indicate mean regional asymmetry consistent with the side of HLD. Section area profiles were generated from the section-by-section point counts through the anterior–posterior extent of the insula. Results indicate that there is not one particular area of the insula related to HLD.

Roberts, et al., 2009). Of the 44 hemispheres with a diagonal sulcus, 7 (15.9%) had a connection with the anterior ascending ramus of the sylvian fissure, 7 (15.9%) with the inferior frontal sulcus, 19 (43.2%) with the inferior precentral sulcus, and 12 (27.3%) had no connection with surrounding sulci or rami (note that one diagonal sulcus had a connection with both the inferior frontal and the inferior precentral sulci, thus making the total exceed 100%). There was no case in our sample of an inferior frontal sulcus having more than two segments. We identified one segment in 52% (26/50) and two segments in 48% (24/50) of the hemispheres, which is identical to our previous study (Keller et al., 2007). There was no significant asymmetry of these structures, and no significant relationship between the number of segments of the inferior frontal sulcus, diagonal sulcus presence and type of connection, and side of HLD ($p > .05$, see Supplemental Tables).

The posterior sylvian fissure most frequently terminated horizontally in the left hemisphere (88% [22/25] of the left hemispheres) and most frequently terminated vertically in the right hemisphere (60% [15/25] of the right hemispheres). This interhemispheric difference in posterior sylvian fissure termination was statistically significant ($p = .006$, see Supplemental Tables). The unusual (Keller et al., 2007) combination of left vertical termination and right horizontal termination of the sylvian fissure occurred in two (8%) individuals, both of whom were left hemispheric dominant for language. Although the termination of the sylvian fissure for the left hemisphere was dominantly horizontal regardless of HLD, the termination of the sylvian fissure for the right hemisphere was significantly ($p = .02$) associated with HLD. In particular for the right hemisphere, the termination of the sylvian fissure was dominantly vertical for individuals with right HLD, whereas there was no clear trend for individuals with left HLD (for details, see Supplemental Tables).

DISCUSSION

The primary result from the present study is that interhemispheric asymmetry of insula volume was significantly related to the side of HLD. This morphological asymmetry predicted HLD in 88% (22/25) of our sample, which included a similar proportion of individuals with left and right HLD. The relationship was observed throughout the anterior–posterior extent of the insula. Conversely, we found no evidence of a relationship between side of HLD and interhemispheric macroscopic asymmetries of Broca's area or planum temporale in our relatively small but novel sample. We were unable to identify a gross morphological correlate of HLD in terms of the presence of the diagonal sulcus and the number of segments of the inferior frontal sulcus. However, the shape of the right posterior sylvian fissure was significantly related to HLD in right HLD subjects. We consider methodological issues pertaining to the present study before we discuss the biological interpretations of our data.

Methodological Issues

Participants

Our sample size may initially seem quite small. However, the recruitment of 10 neurologically healthy right-handed adults with right HLD requires investigation of a large population of subjects. For example, only up to 10% of left-handed subjects may be right hemisphere dominant for language (Pujol et al., 1999), and only 2% may show complete rightward lateralization (Pujol et al., 1999). Moreover, given that the incidence of right HLD is smaller in right-handed subjects (Knecht, Deppe, et al., 2000; Knecht, Drager, et al., 2000; Pujol et al., 1999), it is clear that the population of individuals to be screened for HLD required to obtain a sample of 10 right-handed subjects with right HLD needs to be large, probably in excess of 300 people. Given that we only studied right-handed subjects, we were able to confidently ascribe asymmetry–dominance relationships to HLD without the influence of handedness. It is also worth noting that right HLD subjects were more strongly lateralized for HLD relative to left HLD subjects ($p = .03$; Figure 5), which may in part explain the reduced variance in rightward asymmetry of the insula relative to the variance in asymmetries of other regions in left HLD subjects (Table 2). As our sample was comprised of 25 right-handed subjects and that the relationship between HLD and handedness occurs along a bimodal continuum (Knecht, Deppe, et al., 2000), it will be interesting to investigate the relationship between HLD and brain anatomy across a wider spectrum of neurologically healthy people, including enough men and women to incorporate analyses of sex-based differences in cerebral asymmetry and functional organization. All interpretations of our data pertain to the fact that 25 right-handed individuals were investigated, and this should be noted with respect to the null findings relating to Broca's area and planum temporale in particular.

Neuroimaging

The primary shortcoming of the present study is that both fTCD and fMRI values were not available for all 25 participants (we reported functional data from 14 individuals using fTCD and 11 individuals with fMRI). However, correlation between the direction and the extent of lateralization using fMRI and fTCD is very high (Jansen et al., 2004; Deppe et al., 2000; Schmidt et al., 1999), and we expected that very few differences in HLD would have been observed depending on the approach used. The Münster functional imaging study on the variability of hemispheric specialization in health and disease has repeatedly demonstrated the consistency between fTCD, fMRI, and the Wada test in the reproducible demonstration of global HLD, with the use of fTCD being preferentially advocated because of the ease of administration (Deppe, Knecht, et al., 2004; Deppe, Ringelstein, et al., 2004; Knecht et al., 1996, 2001, 2003; Deppe et al., 2000; Knecht, Deppe, et al., 2000; Knecht, Drager, et al., 2000; Knecht, Deppe, Ebner, et al.,

1998; Knecht, Deppe, Ringelstein, et al., 1998; Deppe et al., 1997). Importantly, we obtained functional measures of lateralization and structural measures of asymmetry independently without knowledge of results from the other modality, and therefore the robust insula–HLD relationship, for example, is not a result of experimenter bias in this study. We acknowledge that correlations were collapsed across neuroimaging approaches and that there were greater LIs in subjects with right HLD studied using fTCD relative to fMRI, which may have accounted for the increased extent of LIs in right HLD subjects relative to left HLD subjects. This does not affect the relationships between cerebral asymmetries and side of HLD but may have an influence on the relationship between *extent* of HLD and *degree* of cortical asymmetry. We therefore recommend that these analyses should be replicated using one functional neuroimaging approach.

One important point to consider was raised recently by Josse, Kherif, Flandin, Seghier, and Price (2009), who maintained that studies to date have correlated global HLD with brain asymmetry and not correlated, for example, regional activation during fMRI with corresponding gray matter morphology. Josse et al. (2009) reported correlations between fMRI activation during language tasks and gray matter concentration using voxel-based morphometry (VBM) in frontal and temporal language regions. This study provided new data on the relationship between the activation and concentration of presumably homologous gray matter voxels across the entire population, thus providing further insights into brain structure–function relationships. However, the goals of the current study were somewhat different as we aimed to predict the side of HLD using brain anatomy in individual people, which cannot be performed using VBM techniques (Keller & Roberts, 2008).

Biological Implications

Insula

The insula, particularly the anterior regions, plays a key role in the functional neuroanatomy of language. However, an association between interhemispheric cortical volume of this region and HLD has not been demonstrated until now, and although our results indicate a relationship between insular volume and HLD, this association was not limited to the anterior insula. The insular cortices, first described by Reil (1809) and later termed the island of Reil, consist of progressively granular to agranular cortex in the anterior–posterior direction (Flynn, Benson, & Ardila, 1999; Mesulam & Mufson, 1982a, 1982b). It has multiple reciprocal connections with local and distal cortical and subcortical regions (Flynn et al., 1999; Mesulam & Mufson, 1982a, 1982b, 1985; Mufson & Mesulam, 1984) and together with lateral orbital and temporal pole regions—which share a common cytoarchitectonic arrangement—form paralimbic cortex (Flynn et al., 1999; Mesulam & Mufson, 1982a, 1982b).

Furthermore, the insula functions in many visceral, autonomic, vestibular, and motor processes by virtue of multimodal sensory integration (Dupont, Boullieret, Hasboun, Semah, & Baulac, 2003; Flynn et al., 1999; Mesulam & Mufson, 1982a, 1982b). The contribution of the insula to speech production and articulation has been well documented (Ogar et al., 2006; Blank, Scott, Murphy, Warburton, & Wise, 2002; Price, 2000; Kuriki, Mori, & Hirata, 1999; Wise et al., 1999; Donnan et al., 1997; Dronkers, 1996; Mohr, 1979; Mohr et al., 1978). In particular, anterior regions have been preferentially associated with speech articulation (Dronkers, 1996). Broca’s aphasia ordinarily involves damage to the insula—and other regions—by virtue of infarction of the upper region of the middle cerebral artery (Mohr, 1979; Mohr et al., 1978).

Interhemispheric quantitative measures of insular morphology are quite rare in the literature, particularly relative to other regions known to play an important role in language processing. Given that, at least to our knowledge, no other study has investigated the relationship between insular morphology and HLD in healthy subjects, a search is required for leftward asymmetry of the insula because samples will be presumably mainly comprised of left HLD subjects, given the predominance of left HLD in the normal population. Cunningham (1892) noted a slight leftward asymmetry of the insular cortices in fetal, infant, and adult human brains: “.. it (is) probable that at all periods of life there is a relatively greater development of the island of Reil on the left side than on the right. The difference in extent of the insula on the two sides of the brain is very slight, but it is seen in every stage (of development)” (p. 109). This asymmetry may relate to frequent discontinued growth of the insula in the right hemisphere earlier than the left as suggested by Clark (1896) and Cunningham (1891), perhaps representing a programmed anatomic asymmetry for the acquisition of language, particularly as this asymmetry is attenuated or absent in lower primates (Carpenter, 1985). Such evidence led others to postulate an association between insular asymmetry and HLD (Flynn et al., 1999). Our data support the hypothesized relationship between HLD and insular morphology, but this finding must be replicated in larger cohorts of healthy subjects.

There is also more recent evidence of insula asymmetry from MRI studies. In particular, Hervé, Crivello, Percey, Mazoyer, and Tzourio-Mazoyer (2006) reported significant leftward gray matter volume asymmetry of the anterior and middle insula, with no focal rightward asymmetry of any insular region in 56 healthy right-handed (and presumably very few, if any, unilateral right HLD) adult men using VBM. Using the same technique, Watkins et al. (2001) also reported focal leftward asymmetry of the anterior and the middle insula. Interestingly, leftward asymmetry of these regions was more striking when the subject cohort was reduced in number to include only right-handed subjects (Watkins et al., 2001), which may suggest that an increased number of left-handed people with right (or “nonleft”) HLD may have attenuated leftward asymmetry. Leftward

asymmetry of the insula has also been demonstrated using other MRI techniques in samples that presumably comprised a vast majority subjects with left HLD (Jung et al., 2007).

Given the robust insula result obtained in the present study, future work will need to investigate how this structure–function cortical asymmetry relates to the organization of white matter architecture. In a neurologically healthy sample consisting of five subjects with right HLD and 19 right-handed subjects with presumably left HLD, our research group has recently reported asymmetrically higher fractional anisotropy of white matter directly adjacent to the insula in the hemisphere dominant for language relative to the homologous region in the contralateral hemisphere using diffusion tensor imaging techniques (Mohammadi, Jansen, Schwindt, Knecht, & Deppe, 2007). Although hypothetical, this relationship may suggest that increased myelin density or white matter tract alignment in regions adjacent to and connecting with the insula may relate to the increased volume of the insula so that both gray and white matter anatomy contribute to a neural network supporting hemispheric lateralization of language functions. It is also possible that insula asymmetry as an anatomical marker of HLD may be an indirect measure of underlying fiber architecture, which may be differentially organized in left and right HLD, given the differences in regional insular asymmetries between groups observed in Figure 6.

It would be interesting to investigate the morphology and the interhemispheric asymmetry of the insular cortices in chimpanzees and other great apes, given the absence of spoken language—but close evolutionary heritage—in these species. Recent MRI studies have investigated comparative neuroanatomical asymmetries in humans and chimpanzees, primarily focusing on Broca's area (Keller, Roberts, et al., 2009; Tagliabate, Cantalupo, & Hopkins, 2006; Cantalupo & Hopkins, 2001), planum temporale (Gannon, Holloway, Broadfield, & Braun, 1998; Hopkins, Marino, Rilling, & MacGregor, 1998) and fronto-occipital torque (Pilcher, Hammock, & Hopkins, 2001; Hopkins & Marino, 2000). Much of the evidence points toward concomitant comparative asymmetry or symmetry of these regions, inasmuch that both humans and great apes show similar interhemispheric structural organization. Work is now underway in our laboratory to measure the insular cortices on MR images in humans and chimpanzees using the methods developed in the present article to investigate whether both species have similar interhemispheric structural organization of the insula. This is particularly important given the insula's role in language articulation.

Broca's Area and Planum Temporale

Dorsaint-Pierre et al. (2006) reported a significant relationship between HLD and macroscopic gray matter concentration asymmetry of the pars opercularis in epilepsy patients, 20 of whom had left HLD and 11 had right HLD

as determined by the invasive Wada test. In particular, left HLD patients had more gray matter concentration (using VBM) of the left pars opercularis relative to right HLD patients and vice versa. However, the study population were neurological patients, and although the primary neurological insult in these epilepsy patients is relatively focal (i.e., the epileptogenic cortex), there are additional widespread cerebral abnormalities in these patients, including brain regions important for language (Keller & Roberts, 2008), thus making it difficult to draw parallels to the healthy human brain. In particular, it is possible that pathological mechanisms may have reallocated language functions to the right hemisphere in some of the patients, given the known increased incidence of “pathological” right HLD in patients with unilateral epilepsy (Adcock et al., 2003; Brazdil et al., 2003). It is therefore questionable whether epilepsy patients with right HLD represent a natural feature of functional brain organization or rather a pathological one of brain reorganization and plasticity, and so it is crucial to study brain morphology and architecture in neurologically healthy subjects with right HLD.

We have previously shown great variability in the intrasulcal anatomy of the pars opercularis and pars triangularis in the healthy brain (Keller et al., 2007), with the former exhibiting a subtle but significant leftward volume asymmetry and no volume asymmetry of the latter. However, we have been recently unable to replicate volume asymmetry of the pars opercularis in an independent study of neurologically healthy humans and chimpanzees (Keller, Roberts, et al., 2009). Indeed, morphological variability of this region is so great that it is difficult to imagine a direct relationship between interhemispheric asymmetry of the frontal operculum and HLD (Keller, Crow, et al., 2009). This is supported by the results obtained in the present study that showed no association between the frontal operculum and the HLD, given that both left and right HLD mean group asymmetries were leftward. However, it is possible that a gyral marker for HLD is not apparent in the human brain. The relationship between frontal regions and HLD recently reported by Josse et al. (2009) was based on the local concentration of gray matter and not gyral morphology. This is especially pertinent given that the frontal region crucial for language production is not restricted to individual gyri (Keller, Crow, et al., 2009). As we have recently stated, it is now important to investigate the architecture of Broca's area on a microscopic basis to determine whether a neural correlate of HLD exists within the anterior speech region, given that there appears to be no macroscopic relationship (Keller, Crow, et al., 2009; Keller, Roberts, et al., 2009). This is especially important as cytoarchitectonic boundaries are more closely related to the regional functional properties of cortex relative to sulcal landmarks (Fischl et al., 2008; Amunts, Schleicher, & Zilles, 2007).

The function of the planum temporale for language has been suggested to be confined to early auditory processing (Binder, Frost, Hammeke, Rao, & Cox, 1996). In a recent

review of fMRI studies of language processing, it was reported that the posterior planum temporale has importance for the semantic and syntactic ambiguity of sentences and the covert articulation of words (Price, 2010), therefore suggesting that the planum temporale has an important cognitive component for language function. There has been a long hypothesized relationship between asymmetry of the planum temporale and language lateralization on the basis of anatomical studies demonstrating leftward interhemispheric asymmetry of this structure in approximately two thirds of the population (Galaburda et al., 1978; Geschwind & Levitsky, 1968). However, lateralization is more obvious and consistent than asymmetry, and recent research has shown that the prediction of HLD by virtue of asymmetry of the planum temporale alone is unreliable (Dorsaint-Pierre et al., 2006). Indeed, planum temporale asymmetry is leftward regardless of the side of HLD, as shown in the present study and by Dorsaint-Pierre et al. (2006). Using relatively large sample of healthy adults, Eckert et al. (2006) showed that asymmetry of the planum temporale and HLD for single-word comprehension, although both significantly leftward, are unrelated, suggesting that language lateralization is a multidimensional construct and is far more complex than previously assumed. Furthermore, the significant association between the vertical termination of the posterior sylvian fissure and HLD in right HLD subjects was unexpected and is counterintuitive. Across the entire sample, we observed the well-established pattern of a horizontal sylvian fissure termination in the left hemisphere and a vertical termination in the right hemisphere, which gives rise to the greater volume of the planum temporale in the left hemisphere over the general population (Keller et al., 2007). However, we would have expected that atypical HLD would be accompanied by a concomitant reversed shape asymmetry of the posterior sylvian fissure so that a horizontal termination would be observed in the right hemisphere, giving rise to a rightward asymmetry of the planum temporale. We are therefore cautious in interpreting this particular result and suggest that future work prospectively examine the shape of the sylvian fissure in healthy people with atypical HLD.

Conclusions

It is probable that no one individual regional cortical asymmetry governs HLD exclusively. It is more likely that HLD is dependent on multiple intra- and interhemispheric neural networks and connections (Stephan, Fink, & Marshall, 2007), as has generally been proposed for fluid human cognition (Knight, 2007). This modern “systems neuroscience” approach to understanding human behavior differs from many traditional phrenological approaches that assume circumscribed structure–function relationships. Given that the insula is the only cortical brain region to integrate information from all sensory modalities (Mesulam & Mufson, 1982a, 1982b) by virtue of substantial connectivity to local and distal cortical and subcortical regions and

that this region is crucial for language production and articulation (Dronkers, 1996; Mohr, 1979; Mohr et al., 1978), it seems plausible to hypothesize that insular morphology plays a particular role in HLD. Our results show a robust relationship between interhemispheric asymmetry of insular volume and HLD, which requires further investigation in larger samples. We suggest that the potential significance of insular morphology should be considered in future studies addressing the anatomical correlates of human language lateralization.

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REFERENCES

- Adcock, J. E., Wise, R. G., Oxbury, J. M., Oxbury, S. M., & Matthews, P. M. (2003). Quantitative fMRI assessment of the differences in lateralization of language-related brain activation in patients with temporal lobe epilepsy. *Neuroimage*, *18*, 423–438.
- Amunts, K., Schleicher, A., & Zilles, K. (2007). Cytoarchitecture of the cerebral cortex—More than localization. *Neuroimage*, *37*, 1061–1065; discussion 1066–1068.
- Binder, J. R., Frost, J. A., Hammeke, T. A., Cox, R. W., Rao, S. M., & Prieto, T. (1997). Human brain language areas identified by functional magnetic resonance imaging. *Journal of Neuroscience*, *17*, 353–362.
- Binder, J. R., Frost, J. A., Hammeke, T. A., Rao, S. M., & Cox, R. W. (1996). Function of the left planum temporale in auditory and linguistic processing. *Brain*, *119*, 1239–1247.
- Blank, S. C., Scott, S. K., Murphy, K., Warburton, E., & Wise, R. J. (2002). Speech production: Wernicke, Broca and beyond. *Brain*, *125*, 1829–1838.
- Brazdil, M., Zakopcan, J., Kuba, R., Fanfrdlova, Z., & Rektor, I. (2003). Atypical hemispheric language dominance in left temporal lobe epilepsy as a result of the reorganization of language functions. *Epilepsy & Behavior*, *4*, 414–419.
- Broca, P. (1861). Remarques sur le Siège de la Faculté du Langage Articulé, Suivies d’une Observatoir d’aphémie (Perte de la Parole). *Bulletin de la Société Anatomique de Paris*, *6*, 330–357.
- Cantalupo, C., & Hopkins, W. D. (2001). Asymmetric Broca’s area in great apes. *Nature*, *414*, 505.
- Carpenter, M. (1985). *Core text of neuroanatomy* (3rd ed.). Baltimore, MD: Williams and Wilkins.
- Clark, T. E. (1896). The comparative anatomy of the insula. *Journal of Comparative Neurology*, *6*, 59–100.
- Cowell, P. E., Sluming, V. A., Wilkinson, I. D., Cezayirli, E., Romanowski, C. A., Webb, J. A., et al. (2007). Effects of sex and age on regional prefrontal brain volume in two

- human cohorts. *European Journal of Neuroscience*, *25*, 307–318.
- Cunningham, D. (1891). The development of the gyri and sulci on the surface of the island of Reil of the human brain. *Journal of Anatomy and Physiology*, *25*, 338–348.
- Cunningham, D. (1892). *Contribution to the surface anatomy of the cerebral hemispheres*. Dublin: Royal Irish Academy.
- Deppe, M., Knecht, S., Henningsen, H., & Ringelstein, E. B. (1997). AVERAGE: A Windows program for automated analysis of event related cerebral blood flow. *Journal of Neuroscience Methods*, *75*, 147–154.
- Deppe, M., Knecht, S., Lohmann, H., & Ringelstein, E. B. (2004). A method for the automated assessment of temporal characteristics of functional hemispheric lateralization by transcranial Doppler sonography. *Journal of Neuroimaging*, *14*, 226–230.
- Deppe, M., Knecht, S., Papke, K., Lohmann, H., Fleischer, H., Heindel, W., et al. (2000). Assessment of hemispheric language lateralization: A comparison between fMRI and fTCD. *Journal of Cerebral Blood Flow and Metabolism*, *20*, 263–268.
- Deppe, M., Ringelstein, E. B., & Knecht, S. (2004). The investigation of functional brain lateralization by transcranial Doppler sonography. *Neuroimage*, *21*, 1124–1146.
- Donnan, G. A., Darby, D. G., & Saling, M. M. (1997). Identification of brain region for coordinating speech articulation. *Lancet*, *349*, 221–222.
- Dorsaint-Pierre, R., Penhune, V. B., Watkins, K. E., Neelin, P., Lerch, J. P., Bouffard, M., et al. (2006). Asymmetries of the planum temporale and Heschl's gyrus: Relationship to language lateralization. *Brain*, *129*, 1164–1176.
- Drager, B., & Knecht, S. (2002). When finding words becomes difficult: Is there activation of the subdominant hemisphere? *Neuroimage*, *16*, 794–800.
- Dronkers, N. F. (1996). A new brain region for coordinating speech articulation. *Nature*, *384*, 159–161.
- Dupont, S., Boullieret, V., Hasboun, D., Semah, F., & Baulac, M. (2003). Functional anatomy of the insula: New insights from imaging. *Surgical and Radiologic Anatomy*, *25*, 113–119.
- Eberstaller, O. (1890). *Das Stirnbiirn*. Wien: Urban and Schwarzenberg.
- Eckert, M. A., Leonard, C. M., Possing, E. T., & Binder, J. R. (2006). Uncoupled leftward asymmetries for planum morphology and functional language processing. *Brain and Language*, *98*, 102–111.
- Fischl, B., Rajendran, N., Busa, E., Augustinack, J., Hinds, O., Yeo, B. T., et al. (2008). Cortical folding patterns and predicting cytoarchitecture. *Cerebral Cortex*, *18*, 1973–1980.
- Flynn, F. G., Benson, D. F., & Ardila, A. (1999). Anatomy of the insula—Functional and clinical correlates. *Aphasiology*, *13*, 55–78.
- Foundas, A. L., Leonard, C. M., Gilmore, R. L., Fennell, E. B., & Heilman, K. M. (1996). Pars triangularis asymmetry and language dominance. *Proceedings of the National Academy of Sciences, U.S.A.*, *93*, 719–722.
- Galaburda, A. M., Sanides, F., & Geschwind, N. (1978). Human brain. Cytoarchitectonic left-right asymmetries in the temporal speech region. *Archives of Neurology*, *35*, 812–817.
- Gannon, P. J., Holloway, R. L., Broadfield, D. C., & Braun, A. R. (1998). Asymmetry of chimpanzee planum temporale: Humanlike pattern of Wernicke's brain language area homolog. *Science*, *279*, 220–222.
- Garcia-Finana, M., Cruz-Orive, L. M., Mackay, C. E., Pakkenberg, B., & Roberts, N. (2003). Comparison of MR imaging against physical sectioning to estimate the volume of human cerebral compartments. *Neuroimage*, *18*, 505–516.
- Garcia-Finana, M., Keller, S. S., & Roberts, N. (2009). Confidence intervals for the volume of brain structures in Cavalieri sampling with local errors. *Journal of Neuroscience Methods*, *179*, 71–77.
- Geschwind, N., & Levitsky, W. (1968). Human brain: Left-right asymmetries in temporal speech region. *Science*, *161*, 186–187.
- Gundersen, H. J., & Jensen, E. B. (1987). The efficiency of systematic sampling in stereology and its prediction. *Journal of Microscopy*, *147*, 229–263.
- Gundersen, H. J., Jensen, E. B., Kieu, K., & Nielsen, J. (1999). The efficiency of systematic sampling in stereology—reconsidered. *Journal of Microscopy*, *193*, 199–211.
- Hervé, P. Y., Crivello, F., Perchey, G., Mazoyer, B., & Tzourio-Mazoyer, N. (2006). Handedness and cerebral anatomical asymmetries in young adult males. *Neuroimage*, *29*, 1066–1079.
- Hopkins, W. D., & Marino, L. (2000). Asymmetries in cerebral width in nonhuman primate brains as revealed by magnetic resonance imaging (MRI). *Neuropsychologia*, *38*, 493–499.
- Hopkins, W. D., Marino, L., Rilling, J. K., & MacGregor, L. A. (1998). Planum temporale asymmetries in great apes as revealed by magnetic resonance imaging (MRI). *NeuroReport*, *9*, 2913–2918.
- Howard, M. A., Roberts, N., Garcia-Finana, M., & Cowell, P. E. (2003). Volume estimation of prefrontal cortical subfields using MRI and stereology. *Brain Research, Brain Research Protocols*, *10*, 125–138.
- Ide, A., Rodriguez, E., Zaidel, E., & Aboitiz, F. (1996). Bifurcation patterns in the human sylvian fissure: Hemispheric and sex differences. *Cerebral Cortex*, *6*, 717–725.
- Jansen, A., Floel, A., Deppe, M., van Randenborgh, J., Drager, B., Kanowski, M., et al. (2004). Determining the hemispheric dominance of spatial attention: A comparison between fTCD and fMRI. *Human Brain Mapping*, *23*, 168–180.
- Josse, G., Kherif, F., Flandin, G., Seghier, M. L., & Price, C. J. (2009). Predicting language lateralization from gray matter. *Journal of Neuroscience*, *29*, 13516–13523.
- Josse, G., Mazoyer, B., Crivello, F., & Tzourio-Mazoyer, N. (2003). Left planum temporale: An anatomical marker of left hemispheric specialization for language comprehension. *Brain Research, Cognitive Brain Research*, *18*, 1–14.
- Jung, Y. C., Jang, D. P., Namkoong, K., Ku, J., Kim, J. J., Park, S., et al. (2007). Shape deformation of the insula in alcoholics: Reduction of left-right asymmetry. *NeuroReport*, *18*, 1787–1791.
- Kasai, K., Shenton, M. E., Salisbury, D. F., Onitsuka, T., Toner, S. K., Yurgelun-Todd, D., et al. (2003). Differences and similarities in insular and temporal pole MRI gray matter volume abnormalities in first-episode schizophrenia and affective psychosis. *Archives of General Psychiatry*, *60*, 1069–1077.
- Keller, S. S., Baker, G., Downes, J. J., & Roberts, N. (2009). Quantitative MRI of the prefrontal cortex and executive function in patients with temporal lobe epilepsy. *Epilepsy & Behavior*, *15*, 186–195.
- Keller, S. S., Crow, T., Foundas, A., Amunts, K., & Roberts, N. (2009). Broca's area: Nomenclature, anatomy, typology and asymmetry. *Brain and Language*, *109*, 29–48.
- Keller, S. S., Highley, J. R., Garcia-Finana, M., Sluming, V., Rezaie, R., & Roberts, N. (2007). Sulcal variability, stereological measurement and asymmetry of Broca's area on MR images. *Journal of Anatomy*, *211*, 534–555.

- Keller, S. S., Mackay, C. E., Barrick, T. R., Wieshmann, U. C., Howard, M. A., & Roberts, N. (2002). Voxel-based morphometric comparison of hippocampal and extrahippocampal abnormalities in patients with left and right hippocampal atrophy. *Neuroimage*, *16*, 23–31.
- Keller, S. S., & Roberts, N. (2008). Voxel-based morphometry of temporal lobe epilepsy: An introduction and review of the literature. *Epilepsia*, *49*, 741–757.
- Keller, S. S., & Roberts, N. (2009). Measurement of brain volume using MRI: Software, techniques, choices and prerequisites. *Journal of Anthropological Sciences*, *87*, 127–151.
- Keller, S. S., Roberts, N., & Hopkins, W. (2009). A comparative magnetic resonance imaging study of the anatomy, variability, and asymmetry of Broca's area in the human and chimpanzee brain. *Journal of Neuroscience*, *29*, 14607–14616.
- Keller, S. S., Wieshmann, U. C., Mackay, C. E., Denby, C. E., Webb, J., & Roberts, N. (2002). Voxel based morphometry of gray matter abnormalities in patients with medically intractable temporal lobe epilepsy: Effects of side of seizure onset and epilepsy duration. *Journal of Neurology, Neurosurgery and Psychiatry*, *73*, 648–655.
- Keshavan, M. S., Anderson, S., Beckwith, C., Nash, K., Pettegrew, J. W., & Krishnan, K. R. (1995). A comparison of stereology and segmentation techniques for volumetric measurements of lateral ventricles in magnetic resonance imaging. *Psychiatry Research*, *61*, 53–60.
- Knake, S., Haag, A., Hamer, H. M., Dittmer, C., Bien, S., Oertel, W. H., et al. (2003). Language lateralization in patients with temporal lobe epilepsy: A comparison of functional transcranial Doppler sonography and the Wada test. *Neuroimage*, *19*, 1228–1232.
- Knaus, T. A., Corey, D. M., Bollich, A. M., Lemen, L. C., & Foundas, A. L. (2007). Anatomical asymmetries of anterior perisylvian speech–language regions. *Cortex*, *43*, 499–510.
- Knecht, S., Deppe, M., Drager, B., Bobe, L., Lohmann, H., Ringelstein, E., et al. (2000). Language lateralization in healthy right-handers. *Brain*, *123*, 74–81.
- Knecht, S., Deppe, M., Ebner, A., Henningsen, H., Huber, T., Jokeit, H., et al. (1998). Noninvasive determination of language lateralization by functional transcranial Doppler sonography: A comparison with the Wada test. *Stroke*, *29*, 82–86.
- Knecht, S., Deppe, M., Ringelstein, E. B., Wirtz, M., Lohmann, H., Drager, B., et al. (1998). Reproducibility of functional transcranial Doppler sonography in determining hemispheric language lateralization. *Stroke*, *29*, 1155–1159.
- Knecht, S., Drager, B., Deppe, M., Bobe, L., Lohmann, H., Floel, A., et al. (2000). Handedness and hemispheric language dominance in healthy humans. *Brain*, *123*, 2512–2518.
- Knecht, S., Drager, B., Floel, A., Lohmann, H., Breitenstein, C., Deppe, M., et al. (2001). Behavioural relevance of atypical language lateralization in healthy subjects. *Brain*, *124*, 1657–1665.
- Knecht, S., Henningsen, H., Deppe, M., Huber, T., Ebner, A., & Ringelstein, E. B. (1996). Successive activation of both cerebral hemispheres during cued word generation. *NeuroReport*, *7*, 820–824.
- Knecht, S., Jansen, A., Frank, A., van Randenborgh, J., Sommer, J., Kanowski, M., et al. (2003). How atypical is atypical language dominance? *Neuroimage*, *18*, 917–927.
- Knight, R. T. (2007). Neuroscience. Neural networks debunk phrenology. *Science*, *316*, 1578–1579.
- Kuriki, S., Mori, T., & Hirata, Y. (1999). Motor planning center for speech articulation in the normal human brain. *NeuroReport*, *10*, 765–769.
- Lux, S., Keller, S. S., Mackay, C. E., Ebers, G., Marshall, J. C., Cherkas, L., et al. (2008). Crossed cerebral lateralization for verbal and visuo-spatial function in a pair of handedness discordant monozygotic twins: MRI and fMRI brain imaging. *Journal of Anatomy*, *212*, 235–248.
- Mackay, C. E., Roberts, N., Mayes, A. R., Downes, J. J., Foster, J. K., & Mann, D. (1998). An exploratory study of the relationship between face recognition memory and the volume of medial temporal lobe structures in healthy young males. *Behavioural Neurology*, *11*, 3–20.
- Mackay, C. E., Webb, J. A., Eldridge, P. R., Chadwick, D. W., Whitehouse, G. H., & Roberts, N. (2000). Quantitative magnetic resonance imaging in consecutive patients evaluated for surgical treatment of temporal lobe epilepsy. *Magnetic Resonance Imaging*, *18*, 1187–1199.
- Mayhew, T. M. (1992). A review of recent advances in stereology for quantifying neural structure. *Journal of Neurocytology*, *21*, 313–328.
- Mesulam, M. M., & Mufson, E. J. (1982a). Insula of the old world monkey: I. Architectonics in the insulo-orbito-temporal component of the paralimbic brain. *Journal of Comparative Neurology*, *212*, 1–22.
- Mesulam, M. M., & Mufson, E. J. (1982b). Insula of the old world monkey: III. Efferent cortical output and comments on function. *Journal of Comparative Neurology*, *212*, 38–52.
- Mesulam, M. M., & Mufson, E. J. (1985). The insula of Reil in man and monkey. Architectonics, connectivity and function. In A. Peters & E. G. Jones (Eds.), *Cerebral cortex* (Vol. 4, pp. 179–226). New York: Plenum.
- Mohammadi, S., Jansen, A., Schwindt, W., Knecht, S., & Deppe, M. (2007). Identifying anatomical correlates of right-hemispheric language processing: A diffusion tensor imaging study. *Neuroimage*, *36*, S37.
- Mohr, J. P. (1979). Broca's area and Broca's aphasia. In H. Whitaker & H. A. Whitaker (Eds.), *Studies in neurolinguistics*. New York: Elsevier.
- Mohr, J. P., Pessin, M. S., Finkelstein, S., Funkenstein, H. H., Duncan, G. W., & Davis, K. R. (1978). Broca aphasia: Pathologic and clinical. *Neurology*, *28*, 311–324.
- Mufson, E. J., & Mesulam, M. M. (1984). Thalamic connections of the insula in the rhesus monkey and comments on the paralimbic connectivity of the medial pulvinar nucleus. *Journal of Comparative Neurology*, *227*, 109–120.
- Naidich, T. P., Kang, E., Fatterpekar, G. M., Delman, B. N., Gultekin, S. H., Wolfe, D., et al. (2004). The insula: Anatomic study and MR imaging display at 1.5 T. *AJNR, American Journal of Neuroradiology*, *25*, 222–232.
- Ogar, J., Willock, S., Baldo, J., Wilkins, D., Ludy, C., & Dronkers, N. (2006). Clinical and anatomical correlates of apraxia of speech. *Brain and Language*, *97*, 343–350.
- Pilcher, D. L., Hammock, E. A., & Hopkins, W. D. (2001). Cerebral volumetric asymmetries in non-human primates: A magnetic resonance imaging study. *Laterality*, *6*, 165–179.
- Price, C. J. (2000). The anatomy of language: Contributions from functional neuroimaging. *Journal of Anatomy*, *197*, 335–359.
- Price, C. J. (2010). The anatomy of language: A review of 100 fMRI studies published in 2009. *Annals of the New York Academy of Sciences*, *1191*, 62–88.
- Pujol, J., Deus, J., Losilla, J. M., & Capdevila, A. (1999). Cerebral lateralization of language in normal left-handed people studied by functional MRI. *Neurology*, *52*, 1038–1043.
- Reil, J. C. (1809). Untersuchungen über den Bau des grossen Gehirns im menschen—Vierte Forsetzung Viii. *Archives of Physiology*, *9*, 136–146.

- Roberts, N., Garden, A. S., Cruz-Orive, L. M., Whitehouse, G. H., & Edwards, R. H. (1994). Estimation of fetal volume by magnetic resonance imaging and stereology. *British Journal of Radiology*, *67*, 1067–1077.
- Roberts, N., Puddephat, M. J., & McNulty, V. (2000). The benefit of stereology for quantitative radiology. *British Journal of Radiology*, *73*, 679–697.
- Salmenpera, T., Kononen, M., Roberts, N., Vanninen, R., Pitkanen, A., & Kalviainen, R. (2005). Hippocampal damage in newly diagnosed focal epilepsy: A prospective MRI study. *Neurology*, *64*, 62–68.
- Schmidt, P., Krings, T., Willmes, K., Roessler, F., Reul, J., & Thron, A. (1999). Determination of cognitive hemispheric lateralization by “functional” transcranial Doppler cross-validated by functional MRI. *Stroke*, *30*, 939–945.
- Sheline, Y. I., Black, K. J., Lin, D. Y., Christensen, G. E., Gado, M. H., Brunsten, B. S., et al. (1996). Stereological MRI volumetry of the frontal lobe. *Psychiatry Research*, *67*, 203–214.
- Stephan, K. E., Fink, G. R., & Marshall, J. C. (2007). Mechanisms of hemispheric specialization: Insights from analyses of connectivity. *Neuropsychologia*, *45*, 209–228.
- Tagliatela, J. P., Cantalupo, C., & Hopkins, W. D. (2006). Gesture handedness predicts asymmetry in the chimpanzee inferior frontal gyrus. *NeuroReport*, *17*, 923–927.
- Tzourio, N., Nkanga-Ngila, B., & Mazoyer, B. (1998). Left planum temporale surface correlates with functional dominance during story listening. *NeuroReport*, *9*, 829–833.
- Watkins, K. E., Paus, T., Lerch, J. P., Zijdenbos, A., Collins, D. L., Neelin, P., et al. (2001). Structural asymmetries in the human brain: A voxel-based statistical analysis of 142 MRI scans. *Cerebral Cortex*, *11*, 868–877.
- Wernicke, C. (1977). Der aphasische Symptomenkomplex: Eine psychologische Studie auf anatomischer Basis. In G. H. Eggert (Trans.), *Wernicke's works on aphasia: A sourcebook and review*. Mouton: The Hague. (Original work published 1874).
- Wise, R. J., Greene, J., Buchel, C., & Scott, S. K. (1999). Brain regions involved in articulation. *Lancet*, *353*, 1057–1061.