Stained images of Brodmann's area 45 in the left and right hemispheres of a human brain. Sections were stained using a modified Gallyas stain for Nissl substance. The image was taken using a Nikon E400 microscope and digitized with a resolution of 1.47 µm/pixel (Photograph by Natalie Schenker.)
MICROSTRUCTURAL ASYMMETRIES OF THE CEREBRAL CORTEX IN HUMANS AND OTHER MAMMALS

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ABSTRACT

The human brain shows marked gross anatomical and microstructural asymmetries that are presumably related to lateralized motor and cognitive functions. This chapter generally summarizes the extant data on gross morphological asymmetries in human and nonhuman mammal brains. In addition, the evidence of microstructural asymmetries, such as gray-level index, minicolumn width, and cellular organization, are presented. Although there are few studies of microstructural asymmetries in nonhuman primates, it is argued that such studies are important for validating morphological asymmetries as well as for understanding the cellular basis for hemispheric specialization in primates, including humans.

Keywords: microstructural asymmetry, histological asymmetry, cytoarchitectonics, primates, minicolumn asymmetry, primate brain evolution

INTRODUCTION

The cerebral cortex can be parcellated into areas that differ in their cytoarchitecture [Brodmann, 1909], chemoarchitecture [Krubitzer & Huffman, 2000; Krubitzer & Kahn, 2003], connectivity [Barbas & Rempel-Clower, 1997], and distribution of receptors for neurotransmitter molecules [Zilles et al., 2002]. It is well known that such regional variation in cortical microstructure contributes to the many distinct functional specializations of the cortex. For example, differential activation of cortical areas known to vary in microstructure has been demonstrated in numerous studies in humans, using functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and electroencephalography (EEG) [e.g., Azari et al., 2001; Beauregard et al., 2001;
The cerebral hemispheres are also often differentially recruited in divergent functional activities. Thus, a region that is recognized as homotopic between hemispheres on the basis of topology and basic cytoarchitectural organization may participate in different information processing in each hemisphere. The best documented example of such cerebral lateralization is language, where 95% of humans are left hemisphere dominant for the production and comprehension of language [Branche et al., 1964; Ojemann, 1991; Petersen et al., 1988]. As there are structural differences between cortical areas that exhibit functional variation, interhemispheric functional asymmetry in the cerebral cortex arises, in part, from differences in the connectivity and microstructure of homotopic cortical areas [Hutsler & Galuske, 2003]. Therefore, important insights into the anatomical substrates of the lateralized functions of the cerebral cortex can be gained through the incorporation of microstructural data.

At present, however, the majority of studies concerning human brain asymmetries are at the level of macrostructure. For example, the human brain exhibits large-scale asymmetries in the protrusion of the frontal and occipital lobes, called petalias [Holloway & de Lacoste-Lareymondie, 1982]. Furthermore, it is known that regions associated with language function are also asymmetric in their gross anatomy. Still, it is not entirely clear how such large-scale asymmetries are reflected in the microstructure of the cerebral hemispheres. It has been suggested that volumetric differences are primarily caused by changes in the number of cells, rather than by changes in cell density [Galaburda et al., 1986; Rosen, 1996]. However, other types of microstructural asymmetries also exist. Asymmetries in cell size, columnar organization, the complexity of dendritic arbors, and chemoarchitectural organization have been reported [Buxhoeveden et al., 2001; Garcia et al., 2004; Hayes & Lewis, 1995; Scheibel et al., 1985]. Here, we review known structural asymmetries in the human cerebral cortex, with special attention to the relatively small literature on microstructural asymmetries in the brains of other mammals. We discuss the implications of current data to our understanding of the evolution of functional cortical asymmetries in humans.

Gross Anatomical Asymmetries

Pioneering research on the human brain by Paul Broca drew attention to the functional asymmetries of the human inferior frontal cortex through evidence that lesions to the left cerebral hemisphere tend to result in language impairments [Broca, 1861]. These initial observations inspired an explosion of studies concerning the distribution of gross anatomical asymmetries of the human brain as they relate to functional asymmetries. While early efforts were constrained to rely on small samples of postmortem brains, in recent years, the advent of magnetic resonance imaging (MRI) and voxel-based morphometry
methods have allowed measurement of cerebral asymmetries in larger samples. With this proliferation of data, much has been learned regarding how gross anatomical asymmetries in the human cortex vary with age, sex, psychiatric, and neurological conditions. As a rule, these gross morphological data are interpreted to reflect corresponding changes in some aspect of underlying neural circuitry. Many asymmetries are measured using sulcal landmarks, which may [Brodmann, 1909] or may not [Amunts et al., 1999; Sherwood et al., 2003] reflect the boundaries of cortical areas as defined by microstructural details. Nonetheless, if we assume that gross morphological asymmetries emerge from some underlying factor that causes the displacement of tissue volumes, sulci, and gyri, then consideration of cortical asymmetry at the macroanatomical level yields suggestive evidence regarding regions where microstructural architecture may express asymmetry as well. Studies of this variety have primarily addressed the length of particular sulci as well as the volume of areas defined by sulcal boundaries [Tomaiuolo et al., 1999; White et al., 1997a].

Asymmetries in sulcal lengths and trajectories in humans have been described for the central sulcus and the Sylvian fissure. In one study, the length of the central sulcus at the cortical surface was found not to evince a consistent pattern of lateral asymmetry [White et al., 1997a]. The depth of the central sulcus, however, as measured on horizontal MR images, displays an interaction with sex and handedness [Amunts et al., 2000]. Asymmetry of the contralateral central sulcus was most pronounced in right-handed men, with a decreased degree of asymmetry in mixed- and left-handed men. In contrast, asymmetries in central sulcus depth did not differ across handedness in women. Likewise, the “hand knob” of primary cortex in chimpanzees does not display a significant population-level asymmetry [Hopkins & Cantalupo, 2004]. However, a correlation between the volumetric asymmetry of the hand knob in motor cortex and hand preference in a specific tool task was reported, with a tendency for leftward volumetric asymmetry to be associated with preference for using the right hand. Similarly, in male capuchin monkeys, asymmetries in the depth of the central sulcus are also correlated with hand dominance on a coordinated bimanual task [Phillips & Sherwood, 2005], suggesting that this neuroanatomical relationship to handedness may be more widespread among primates.

The length of the Sylvian fissure was found to be longer in the left hemisphere in humans [Blanton et al., 2001; Foundas et al., 1999], partly because of the difference in the shape of the sulcus between the hemispheres. The right sulcus typically contains an upward bend at the posterior end, whereas the left sulcus remains relatively horizontal [Foundas et al., 1999].

A few regions have been found to express volumetric asymmetry on the basis of gross morphological criteria. In humans, the cytoarchitectural subdivisions composing Broca’s area, a region involved with language production, frequently lie within the morphological boundaries of the inferior frontal gyrus (IFG). Within the IFG, the ascending (vertical) ramus of the Sylvian fissure separates pars opercularis (Brodmann’s area 44) from pars triangularis
(area 45), and the anterior (horizontal) ramus separates pars triangularis from pars orbitalis (area 47). Numerous studies have investigated macrostructural asymmetry in Broca’s area using these sulcal landmarks to subdivide the region. However, the results from these studies differ markedly, depending on methodology and anatomical definitions. While measures of the convexity of the cortical surface area of the frontal operculum (including the pars opercularis and the posterior portion of the pars triangularis) have not revealed significant population-level leftward dominance [Wada et al., 1975], asymmetries are significant when intrasulcal cortex is included [Falzi et al., 1982; Tomaiuolo et al., 1999]. Furthermore, some volumetric MRI-based studies have found that both pars triangularis and pars opercularis [Foundas et al., 1998, 2001] are leftward dominant, but others have not found volumetric asymmetry in pars opercularis [Knaus et al., 2006; Tomaiuolo et al., 1999]. Thus, a consensus has yet to be reached regarding macrostructural asymmetries in the human IFG. Nonetheless, population-level leftward asymmetry of fronto-orbital sulcal length, an external morphologic feature in this region of great apes, has been reported in chimpanzees [Cantalupo & Hopkins, 2001].

A multi-species MRI analysis of living ape brains found volumetric asymmetries in two structurally defined subdivisions of the frontal lobe: the dorsal sector (composed of most of the cortex on the lateral surface of the lobe) showed a rightward asymmetry, while the medial cortex (composed of the entire cortex on the medial surface of the lobe) showed a leftward asymmetry. The orbital sector shows no asymmetry [Schenker et al., 2005].

Gross morphological studies have also identified volumetric asymmetries of the planum temporale (PT, including the posterior part of Brodmann’s area 22; also known as Tpt), a temporal lobe region involved in language processing, in both humans and chimpanzees using MRI [Emmorey et al., 2003; Hopkins & Cantalupo, 2004; Hopkins et al., 1998; Penhune et al., 1996] and postmortem specimens [Anderson et al., 1999; Gannon et al., 2001]. A third region, the angular gyrus in the inferior parietal lobe, recently confirmed as a region in a language circuit [Catani et al., 2005], also exhibits the same left greater than right volumetric asymmetry [Watkins et al., 2001]. Furthermore, the region shows reversed (right greater than left) volumetric asymmetry in schizophrenic patients [Buchanan et al., 2004; Niznikiewicz et al., 2000]. A nearby region, occupying the posterior bank of the posterior ascending branch of the Sylvian fissure, shows a significant interaction between handedness and sex in the analysis of volumetric asymmetry. Right-handed men and left-handed women show a strong rightward asymmetry. Right-handed women also have a rightward asymmetry (but not as strong), while left-handed men show a weak leftward asymmetry [Jancke et al., 1994]. A study of the temporal lobes in MR images of living ape brains reported limited evidence of hemispheric asymmetry in gyrification and surface area [Rilling & Seligman, 2002]. Another study found no evidence of asymmetry in images of postmortem chimpanzee brains [Zilles et al., 1996].
Figure 1. Representative micrographs of cortex from the left and the right hemispheres of a human brain in areas 4, 45, and Tpt. Notice the overall similarity between cortical areas in each hemisphere. The asymmetries that have been detected have relied on quantitative methods that are capable of measuring subtle variations in histological features such as cell sizes, cell densities, and the space between minicolumns.
Gross anatomical studies of asymmetry have focused predominantly on areas that demonstrate functional asymmetry. Such studies have revealed asymmetries in motor cortex related to hand preference in both humans and chimpanzees. Studies of language related areas (IFG, PT, angular gyrus) report a tendency for these regions to exhibit leftward asymmetry, matching the prevalence of left hemisphere dominance for language, particularly among right-handed individuals. However, repeated studies of the IFG, with varying conclusions, reveal the continuing lack of consensus on the presence and magnitude of such macrostructural asymmetries.

Microstructural Asymmetries

While gross anatomical analyses can provide an overview of where structural asymmetries may exist, microstructural studies are necessary to elucidate particular hemispheric specializations of neural wiring that underlie functional lateralization. In addition, although comparative microarray analyses of gene expression in the brain can reveal interesting differences between the transcriptomes of humans and other primates [Caceres et al., 2003; Enard et al., 2002; Uddin et al., 2004], this approach is relatively insensitive to subtle variation in gene expression levels among small populations of cells [Geschwind, 2000]. This is especially problematic in analyses of regional differences in the cerebral cortex because of the cellular heterogeneity of its composition and large degree of interindividual variation. In this regard, it is noteworthy that a recent study, looking for differentially expressed genes, was unable to distinguish among three regions known to differ in function: human Broca’s area in the left hemisphere, its homotopic counterpart in the right, and left dorsolateral prefrontal cortex [Khaitovich et al., 2004]. This same study also could not detect greater differences in transcript levels between human and chimpanzee Broca’s area as compared to several other cortical areas. Therefore, to reveal the correlates of functional cortical lateralization, it is necessary to examine interhemispheric differences in microstructural organization. Several microstructural studies of histological specimens, including investigations of regional volume, cell density, dendritic structure, and cell size, have been performed to investigate asymmetries in human brain areas that have well-established patterns of population-wide gross morphological asymmetry. Figure 1 shows interhemispheric comparisons of human cortex in three of these regions demonstrating that variation between the hemispheres is expressed in quite subtle details of histological architecture. Before reviewing the current evidence concerning histological asymmetries in the cerebral cortex, it is important to note that very limited sample size is a problem that plaques all such studies. Indeed, it is not uncommon for samples to be smaller than \( n = 10 \). Thus, interpretation of negative findings should be considered with caution and should not necessarily be taken as definitive evidence of lack of asymmetry in the larger population.
**Volume.** Volumetric studies of histological samples based on cytoarchitectural criteria have been conducted in several regions of cortex, including primary motor (Brodman’s area 4), primary visual (area 17), and language related cortices (areas 44, 45, and part of 22).

In a study of six postmortem human brains of unknown handedness, five had a leftward asymmetry in the total volume of primary motor cortex, while the sixth had a larger motor area in the right hemisphere [Zilles et al., 1996]. However, another study of the same region, using 20 postmortem brains, did not find a significant population-level asymmetry in the total volume of primary motor cortex, with a similar number of brains having a leftward asymmetry as had a rightward one [White et al., 1997b]. When only the hand representation area of primary motor cortex was measured, there was a population-level leftward asymmetry that approached significance, but 6 of 20 specimens exhibited a rightward asymmetry [White et al., 1997b].

The primary visual cortex of humans shows a rightward asymmetry at the population level, although some individual brains show a leftward asymmetry. In a study of 31 brains, the volume of this region of cortex exhibited a significant rightward asymmetry across the sample [Murphy, 1985]. The average asymmetry, regardless of direction, was 8%; 24 of the 31 postmortem brains exhibited a rightward asymmetry, while the remaining 7 had a leftward asymmetry. In another cytoarchitectural study, a similar right-hemispheric bias in the volume of primary visual cortex was found in 11 of 14 brains, with a mean asymmetry of 13.7% [Andrews et al., 1997].

Volumetric asymmetries have also been reported in both anterior and posterior language areas, involved in production and comprehension, respectively. The anterior language area consists of Brodmann’s areas 44 and 45. Using computer-assisted observer-independent quantification of laminar cytoarchitectural variation, recent studies have been able to parcellate and measure the volume of areas 44 and 45 on the basis of the multivariate distances between their quantitative cytoarchitectural profiles [Amunts et al., 1999; Schleicher et al., 1999; Uylings et al., 2006]. When this method of volumetric measurement was applied to 10 adult human brains of both sexes, a robust leftward volumetric asymmetry was found in area 44 (all 10 brains had a larger area 44 in the left than in the right hemisphere). In area 45, the degree of asymmetry (without regard to direction) was similar to that found in area 44. All five female brains displayed leftward asymmetry, but there was no significant asymmetry detected among the five male brains [Amunts et al., 1999; Uylings et al., 2006]. In these studies, the location of cytoarchitectural boundaries among area 44, 45, and adjacent areas did not correspond to external sulcal landmarks. Of note, another study concerning the correspondence between the boundaries of area 44 in common chimpanzees as defined by cytoarchitecture, myeloarchitecture, and the distribution of nonphosphorylated neurofilament protein-immunoreactive neurons, also failed to reveal a correlation between the borders of this cortical area and external morphologic features [Sherwood et al., 2003].
The posterior language area includes part of Brodmann’s area 22. A study of area Tpt (which comprises the posterior part of area 22) in four human brains found left hemisphere volumetric dominance in all four specimens based on qualitative assessment of cytoarchitectural boundaries [Galaburda & Sanides, 1980]. A correlation between the volume of Tpt and the surface area of the grossly defined planum temporale has also been reported [Galaburda et al., 1978]. One of the four brains in this study had a slight rightward asymmetry in the planum temporale, but this was the brain with the least asymmetric area Tpt.

**Gray-Level Index (GLI).** Asymmetries of cell density have been analyzed indirectly by measurement of GLI, which estimates the fraction of tissue volume that is occupied by Nissl-stained cell bodies versus neuropil space. In the region of hand representation in primary motor cortex (area 4), the right hemisphere was found to have, on average, greater GLI than the left hemisphere in 12 postmortem human brains [Amunts et al., 1996]. This means that in the right hemisphere a greater percentage of the total tissue volume was occupied by cell soma than the corresponding region in the left hemisphere. In contrast, the left hemisphere contained relatively more neuropil space, which is occupied primarily by dendrites, axons, and synapses. This asymmetry was not confined to a single layer, but was observed across the entire cortical depth. In young children, asymmetry of GLI is present in this region as a whole, although development of adult-like asymmetry in supragranular cortical layers (layers II and III), which are involved in corticocortical association projections, is delayed as compared to infragranular layers (layers V and VI), which are involved in projections to subcortical structures [Amunts et al., 1997b].

Similar analyses of asymmetries in GLI have been conducted in the IFG. Amunts et al. [1999] found GLI to be greater in left area 44 than in the corresponding area in the right hemisphere in all of the male (n = 5) and three of the female brains (n = 5) studied. Thus, there may be a sex difference in the presence of asymmetry in this region. No asymmetry or sex difference in GLI was observed in area 45 [Amunts et al., 1999]. However, in a subsequent study, using a larger sample that included the brains from the earlier study, Amunts et al. [2003] reported a significantly greater GLI in areas 44 and 45 in the right hemisphere when the two areas were analyzed together. Furthermore, they found that asymmetry increases with age, with infants showing little or no asymmetry. GLI decreased in both areas with age, primarily during early childhood. However, the decrease differed between hemispheres, meaning that the adult pattern of asymmetry did not appear until relatively late in development (age 5 for area 45 and age 11 for area 44).

**Pyramidal Cell Somatodendritic Geometry.** The size of pyramidal cell dendritic arbors, the number and complexity of their branches, and their spine density are known to vary among cytoarchitectonic areas in humans [Jacobs et al., 2001] and macaques [Elston, 2000; Elston & Rockland, 2002] as well as among species [Elston et al., 2001]. These parameters may provide a picture of the complexity of the integrative capacity of individual pyramidal cells.
Several studies of human cortex have focused specifically on measuring asymmetry in the dendritic arbors of pyramidal cells based on Golgi impregnations. Scheibel et al. [1985] analyzed the dendritic profiles of pyramidal cells in the orofacial region of primary motor cortex and found that, overall, the number of dendritic segments was greater in the left hemisphere in a sample of six right-handed adult human males. However, total dendritic length was slightly greater in the right hemisphere. They also found an interaction between hemisphere and order of the segment (which is the distance of the segment from the cell body in terms of the number of branching points). The number and total length of segments more proximal to the soma were greater in the right hemisphere, while higher-order segments were greater in the left hemisphere.

Scheibel et al. [1985] also analyzed the IFG and found longer total dendritic length in the left frontal opercular region. However, as in the motor cortex, this difference was mainly due to the length of higher-order segments (those further from the cell body) in the left hemisphere, as lower-order segments were longer in the right [Scheibel et al., 1985]. In contrast, another study examined asymmetries in only the largest pyramidal cells in layer III of area 45 in humans [Hayes & Lewis, 1996]. This population of pyramidal neurons, known as magnopyramidal cells, mainly furnishes long corticocortical association projections. Total dendritic length, dendritic complexity (numbers of branches and maximal branch order), and spine densities were found to be greater in the right hemisphere. Contrary to the authors’ expectations, dendritic length was positively correlated with soma volumes of magnopyramidal cells only in the left hemisphere and not in the right [Hayes & Lewis, 1996]. This finding suggests that there are additional factors that significantly contribute to the size of cells and the size of their dendritic arbors. Furthermore, these two studies of pyramidal cell geometry in anterior language-related cortical areas indicate that there are differences in the somatodendritic geometry of different cell populations within a single region.

Studies of dendritic parameters in the planum temporale are somewhat more difficult to interpret. One study found a slight leftward asymmetry in total dendritic length averaged across 20 human individuals [Jacobs et al., 1993]. Individually, only 12 of the 20 brains showed a leftward asymmetry. A similar asymmetry in the number of dendritic spines was observed, however, no asymmetry in mean dendritic segment length was found. Furthermore, there was a significant negative correlation between age and total dendritic length, and accompanying the decrease in length was a decrease in asymmetry. That is, in younger individuals (<50 years), total dendritic length was significantly greater in the left than in the right hemisphere, but a clear asymmetry was not present in the older sample [Jacobs & Scheibel, 1993]. In contrast, another study found a right greater than left asymmetry in three dendritic parameters: total basal dendritic length, number of dendrite branches, and number of dendritic spines, in seven of nine individuals [Anderson & Rutledge, 1996]. But, like Jacobs and
Scheibel [1993], these authors also found a negative correlation between these three variables and age, with no corresponding difference in cell soma size.

**Cell Columns and Connectivity.** The isocortex (neocortex) is populated by vertically oriented aggregates of cells with strong vertical interconnections among layers, forming fundamental structural and functional units known as minicolumns [Douglas & Martin, 1992; Mountcastle, 1997]. The emergence of columnar organization is related to the migration of neuroblasts from the ventricular and subventricular zones into radial columns during development [Rakic, 1995]. Cellular minicolumns differ from pyramidal cell modules, which have also been identified as minicolumns [Rockland & Ichinohe, 2004]. Such modules are formed by a core of apical dendrites surrounded by neurons that do not necessarily align in vertical rows [Peters & Kara, 1987; Peters & Sethares, 1991; Rockland & Ichinohe, 2004]. In contrast, cellular minicolumns comprise single rows of neurons [Buxhoeveden & Casanova, 2002; Mountcastle, 1997]. The width of a cellular minicolumn is a measure of the size of the core region of the minicolumn, which contains the majority of the neurons and apical dendrites, and both myelinated and unmyelinated fibers [Buxhoeveden & Casanova, 2002; Mountcastle, 1997]. A cell-poor region, containing dendritic arbors, unmyelinated axons, and synapses, surrounds each minicolumn. The size of the cell-poor area is quantified as the distance between minicolumns. The width of these columns has been investigated in multiple auditory areas in the temporal lobe, including von Economo and Koskina’s areas TA, TB, and TC [Seldon, 1981]. Both the width and the distance between minicolumns were found to be greater in the left hemisphere than in the right throughout auditory cortex. In most auditory cortical areas, the length of basal dendrites was found to compensate for asymmetric differences in distance between columns, but not in the planum temporale. In the planum temporale, the tangential extent of dendrites was increased in the left hemisphere, but not to a degree that completely compensated for the differences in minicolumn spacing between hemispheres. Some of these findings have been replicated by recent studies of area Tpt, which found a greater width of minicolumns and a relatively larger volume of neuropil space in the left hemisphere of humans, but no such asymmetry in chimpanzees and rhesus macaques [Buxhoeveden & Casanova, 2000].

Interconnectivity among cell columns in posterior area 22 has also been studied using carbocyanine dye to anterogradely label axons and retrogradely label cells in postmortem human specimens [Galuske et al., 2000]. Labeled terminal axon arbors and labeled cells were found to be superimposed, forming regularly spaced clusters surrounding the injection site. The average size of the clusters was the same in the two hemispheres, but the distance among clusters was significantly larger in the left hemisphere. Such an asymmetry did not exist in primary auditory cortex. Galuske et al. [2000] suggest that the labeled clusters represent different subsystems of interconnected columns and that the greater distance between clusters in the left hemisphere implies the presence of
more subsystems within area 22 in the left hemisphere than in the right. However, it is also possible that larger cell columns may account for the distance between clusters in the left hemisphere. This would mean that axons in the right and left hemispheres reach across the same number of columns and that subsystems in the left hemisphere are simply more spread out, but not more numerous.

Using postmortem specimens and gross morphological boundaries, Anderson et al. [1999] found a volumetric asymmetry in white matter within the posterior superior temporal gyrus corresponding to a part of area Tpt in humans and then examined the contribution of various microstructural factors to this asymmetry. Although no interhemispheric differences were found in the number of nonphosphorylated neurofilament protein-immunoreactive neurons, the relative volume of glial cells, or the diameters of axons, the axons in the left hemisphere had significantly thicker myelin sheaths than their counterparts in the right hemisphere. It would be interesting to know whether comparable asymmetries in myelination might explain interhemispheric asymmetries in neuropil space reported in various other cortical areas.

**Cell Size and Number.** Another parameter in which asymmetries have been investigated is the size of individual cells. Neuronal soma volume is determined by the biosynthetic and metabolic requirements of the entire cell, including its dendritic arbors and axon [Kaas, 2000], suggesting that differences in cell volume may represent changes in the thickness and ramifications of cells’ neurites or differences in metabolic activity. Asymmetries in cell sizes have been found in several regions throughout human cortex. In primary visual cortex, the left hemisphere tends to have larger neurons than the right, an asymmetry that is markedly absent in dyslexic patients [Jenner et al., 1999]. However, this region has greater numbers of neurons in the right hemisphere in rhesus macaques [Suner & Rakic, 1996].

In frontal cortex, the presence and direction of asymmetry differs by the region analyzed. In dorsal area 4, no interhemispheric differences were found in the mean size of layer III magnopyramidal cells. In area 45, layer III magnopyramidal cells were larger in the left hemisphere, while in area 46 these cell types were larger in the right hemisphere. Within the right hemisphere, no difference in cell size was observed among the three areas. However, cells in left area 45 were significantly larger than those in either left area 46 or left area 4 [Hayes & Lewis, 1995].

Furthermore, asymmetry within area 45 is observable only in the largest pyramidal cells in layer IIIb [Hayes & Lewis, 1995]. If all pyramidal cells are sampled equally, there is no difference in mean cell size between area 45 in the right and left hemispheres. This suggests that the distribution of cell sizes differs between the two hemispheres. If the mean size of all pyramidal cells is equal in the two hemispheres, then left area 45 must also have more small cells than right area 45 in order to counterbalance the larger magnopyramidal cells. Total neuron count in the IFG of humans may also be asymmetrical [Uylings et al., 2006].
In a study of 10 human brains, Uylings et al. [2006] found neuron numbers in area 44 to be greater in the left than right hemisphere in all the 10 brains, but the difference only reached significance within 5 male brains. In area 45, neuron numbers were leftwardly asymmetric in all 5 female brains, but only in 2 of 5 male brains. However, no asymmetry was found in neuron density in this study.

A study of pyramidal cells in the superior temporal lobe found greater numbers of magnopyramidal cells throughout auditory cortex in the left hemisphere than in the right, including primary and secondary auditory cortex, as well as regions within Wernicke’s area, such as the planum temporale and the supramarginal gyrus. The largest interhemispheric differences were seen in the anterior regions (Heschl’s gyrus and anterior planum temporale) and the magnitude decreased posteriorly [Hutsler & Galuske, 2003].

Cell size asymmetries have also been found in particular subpopulations of pyramidal cells. Hutsler and Gazzaniga [1996] found size asymmetries in acetylcholinesterase-enriched cells in lower layer III of several regions in the posterior superior temporal lobe, not restricted to putative language areas. Another study also reports greater size of acetylcholinesterase-rich layer III magnopyramidal cells that is restricted to left area 45 of humans [Garcia et al., 2004]. Acetylcholinesterase is an enzyme responsible for the deactivation of acetylcholine. Density of the labeled cells was symmetrical, but differed among cortical areas. Interestingly, however, a previous study of choline acetyltransferase, an enzyme that facilitates the formation of acetylcholine, found that the concentration of this enzyme was significantly greater in the left hemispheres than in the right hemispheres of four individuals [Amaducci et al., 1981]. Peak concentration seemed to be located within layers II and IV in both hemispheres.

DISCUSSION

Functional Anatomy

Microstructural asymmetries have been primarily reported in four regions of the human brain, including primary motor cortex, primary visual cortex, and both anterior (Broca’s) and posterior (Wernicke’s) language areas.

Motor control is one of the most conspicuously lateralized functions. Most humans exhibit a preference for using one hand rather than the other for most tasks, with the majority showing right-hand dominance. Functional studies of primary motor cortex show that the strongest activation is generally within the primary motor cortex contralateral to the movement [Rao et al., 1995]. Greater usage is known to be related to the size of cortical areas within motor cortex in both humans [Amunts et al., 1997a; Karni et al., 1995; Pascual-Leone et al., 1995] and squirrel monkeys [Nudo et al., 1996]. Thus, if volumetric asymmetry of motor cortex reflects population-level right-hand dominance, we might find a leftward asymmetry in the total size of the motor cortex. The presence of such an asymmetry may [Zilles et al., 1996] or may not [White et al., 1997b] exist.
However, it is likely that such an asymmetry exists within the hand representation region of motor cortex [White et al., 1997b]. Other parameters also display asymmetry in portions of primary motor cortex. Relative neuropil volume seems to be greater in the left hemisphere in the hand region of area 4 [Amunts et al., 1996], which is particularly interesting if the same region expresses a volumetric asymmetry. Thus, in humans greater macrostructural asymmetry of the hand representation in the left hemisphere may be due in part to elaboration of interconnections in the dominant hemisphere. The complexity of connectivity also differs between hemispheres in the orofacial region as represented by dendritic geometry [Scheibel et al., 1985], but no interhemispheric difference has been found in cell size [Hayes & Lewis, 1995].

Vision is also functionally lateralized, with one eye being dominant. As with motor cortex, visual cortex is more strongly activated contralaterally [Miki et al., 2000, 2001]. However, despite the higher prevalence of right-eye dominant individuals [Annett, 2000], visual cortex more frequently exhibits a rightward volumetric asymmetry [Murphy, 1985] suggesting that the anatomical asymmetry is unrelated to eye dominance. Murphy [1985] has suggested the rightward bias in volume might underlie right hemisphere/left visual field superiority for a number of visual tasks [see Kimura & Durnford, 1974]. An asymmetry in the reverse direction is observed in cell size; the left hemisphere tends to have larger neurons than the right, an asymmetry that is markedly absent in dyslexic patients [Jenner et al., 1999].

The finding of an asymmetry in visual cortex that relates to language is interesting because language is an aspect of cognition that has garnered significant attention regarding both functional and anatomical lateralization. Broca [1861] and Wernicke [1874] first identified regions in the left hemisphere of the brain that are crucial to proper language function. Since those classical studies, the functional lateralization of these regions (IFG and posterior superior temporal) has been confirmed via countless studies using the lesion method and/or functional imaging. Furthermore, asymmetries have been reported in at least one language area for each microstructural parameter reviewed here.

Volumetric asymmetries have been reported in both anterior and posterior language areas. Population-level asymmetries were found in areas 44 and Tpt [Amunts et al., 1999; Galaburda & Sanides, 1980]. Asymmetry was also reported at the individual level in area 45, but not at the population level [Amunts et al., 1999]. Volumetric asymmetry in the white matter of the posterior superior temporal lobe has been found to be related to the thickness of the myelin sheaths encompassing axons [Anderson et al., 1999]. There is a greater percentage of neuropil space per unit volume in the dominant hemisphere in the IFG [Amunts et al., 2003].

Reports regarding dendritic parameters differ among cell populations and among regions. In the IFG, total dendritic length is greater in the left hemisphere [Scheibel et al., 1985], but if only magnopyramidal cells are examined,
then dendritic parameters are greater in the right hemisphere [Hayes & Lewis, 1996]. In the temporal language area, there seems to be substantial individual variation in dendritic parameters. Asymmetries with left- [Jacobs et al., 1993] or right-hemisphere [Anderson & Rutledge, 1996] dominance have both been reported.

Cell columns have been found to be larger in the left planum temporale than in the right [Buxhoeveden & Casanova, 2000]. This may correspond to reports that patterns of interconnectivity differ between the two hemispheres in this region [Galuske et al., 2000]. To our knowledge, cell columns and related interconnectivity have yet to be analyzed in the IFG.

The size of magnopyramidal cell soma in layer III displays asymmetry in area 45, such that this subpopulation of the largest pyramidal cells is larger in the left hemisphere. This is in contrast to a neighboring region with no known language involvement, area 46, in which the corresponding cells are larger in the right hemisphere [Hayes & Lewis, 1995]. Similar asymmetries have been observed in temporal auditory and language areas, with greater numbers of layer III magnopyramidal cells present in the left hemisphere [Hutsler & Galuske, 2003]. Also, acetylcholinesterase-enriched cells are larger in left auditory areas and area 45 than in the corresponding regions in the right hemisphere [Garcia et al., 2004; Hutsler & Gazzaniga, 1996].

**Individual Variability and Population-Level Asymmetry**

In all of the above studies that report individual values, there is strong evidence that individual variability is present. Thus, even where substantial asymmetry exists in individuals, it does not necessarily follow that population-level asymmetry is present. For example, in a sample of 10 human brains, 9 exhibited strong asymmetry in the volume of area 45 (>6%), but 4 favored the right hemisphere and 5 favored the left, meaning that no significant asymmetry was seen at the population level [Amunts et al., 1999].

Similarly, the presence of a population-level asymmetry does not rule out the presence of individual variability. In fact, the presence of substantial interindividual variability means that the population-level findings of a study can change with the addition of more individuals. This is evident by a comparison of Amunts and colleagues’ [1999, 2003] studies on asymmetries in Broca’s area. In the earlier study, the sample size was 10, which in histological studies is quite large. Nonetheless, the subsequent study included additional adult individuals (sample size of 16) and resulted in different conclusions. Furthermore, the differences between hemispheres in these two studies are quite small when compared with interindividual variability.

**Asymmetry in Nonhumans**

Very limited evidence is currently available to examine whether humanlike asymmetries are present in nonhuman species [Buxhoeveden et al., 2001;
Gannon et al., 2000; Kheck et al., 1999; Rosen et al., 1993; Sherwood et al., 2005]. In a direct comparison of the microstructure of area Tpt in humans, chimpanzees, and rhesus macaques, Buxhoeveden and colleagues [2001] reported that only humans have left dominant asymmetry of neuropil volume and minicolumn widths, suggesting that the microstructure of the dominant hemisphere has been reorganized in humans for its involvement in language function. Small samples of nonhuman species in this study, however, give reason to be cautious in concluding that such histological asymmetries are entirely absent. If population-level asymmetries are present, but to a lesser magnitude than found in humans, they would be more difficult to detect statistically in a small sample. In this regard, it is notable that another study that examined volumetric asymmetries of cytoarchitecturally defined area Tpt in long-tailed macaques, revealed significantly greater volume of this cortical area in the left hemisphere [Gannon et al., 2000]. Interestingly, asymmetries have also been described in the distribution of calcium-binding protein-immunoreactive inhibitory interneuron subtypes within area Tpt of macaques [Kheck et al., 1999]. Unfortunately, comparable data on interneuron distributions within area Tpt of humans does not exist. Taken together, these findings suggest that asymmetry of the size and some aspects of microcircuitry in area Tpt of humans may be an ancestral homology that is shared with other Old World primates. This interpretation is consistent with observations based on behavior, functional imaging, and lesion studies indicating that macaques are left hemisphere dominant for the processing of acoustic features in conspecific vocal calls [Hauser & Andersson, 1994; Heffner & Heffner, 1984; Petersen et al., 1978, 1984; Poremba et al., 2004].

It has been suggested that, given the conduction delays associated with interhemispheric transfer, functional and structural asymmetries evolve as an adaptation to preserve temporal fidelity in the processing of complex streams of serial information, such as the vocal calls of conspecifics and the performance of fine motor sequences [Ringo et al., 1994]. Thus, it might be expected that due to these network constraints, lateral asymmetries will emerge among any species that relies heavily on acoustic communication in its social interactions or that displays high dexterity of movements. Indeed, house mouse mothers exhibit a right ear preference in their orientation response to the ultrasonic distress calls of their pups [Ehret, 1987] and electrophysiological mapping reveals a greater extent of auditory cortex surface area in the left hemisphere compared to the right [Stiebler et al., 1997]. Furthermore, data from multiunit recordings in starlings show lateralization in the strength of neuronal activation in response to the presentation of species-specific songs, but not other artificial sounds, with interindividual variation in the dominant hemisphere [George et al., 2002]. Although the results of these studies would seem to suggest that humanlike asymmetry of auditory cortex is prevalent among vertebrates, a cytoarchitectural study of auditory cortical area Doppler-shifted constant frequency area (DSCF) in mustached bats did not find population-level asymmetries in neuronal densities, glial-neuron ratios, or the distribution of magnopyramidal cells.
This is in spite of the fact that mustached bats use a complex repertoire of vocalizations, with heteroharmonic calls that can last a second or more [Kanwal et al., 1994], and some auditory cortical neurons display specialized response properties for social vocalizations [Esser et al., 1997; Ohlemiller et al., 1996].

While functional asymmetry may be a common feature in processing social vocal communication among vertebrates, the microstructural correlates of this phenomenon have yet to be fully elucidated. Evidence from mice and macaques suggest that the volumetric extent of auditory cortical areas may express left hemisphere dominance. However, most studies of the intrinsic microstructure of the cortex in nonhumans have failed to reveal patterns of asymmetries that are homologous with humans. Some suggest that the particular pattern of asymmetries present in the human cortex is the defining characteristic of the human species [Crow, 1998a, 1998b]. The argument is that there are species-level asymmetries in humans, showing a consistency in the direction of asymmetry across individuals that may be absent in other species. Furthermore, certain psychological disorders, such as schizophrenia, may be associated with abnormal or absent asymmetries [Buchanan et al., 2004; Crow, 2004; Irle et al., 2005; Niznikiewicz et al., 2000] of the cortex, suggesting that typical asymmetries are important for normal human brain function. However, one must consider that the absence of evidence for asymmetries in nonhuman primates is not evidence of absence. Given the paucity of comparative data concerning microstructural cortical asymmetries, it is premature to assume that such asymmetries are absent among nonhumans.

### Future Directions

There is ample evidence for microstructural asymmetries in human isocortex. However, the evidence is neither consistent nor uniformly distributed. No parameter has been analyzed equivalently across many cortical areas, and repeated analyses of a single measure in one cortical area sometimes produce differing results. Furthermore, our knowledge of the presence or absence of asymmetries in nonhumans is even more limited than our knowledge of asymmetries in humans.

There are tremendous opportunities for additional research in this area. Much is not yet known regarding how asymmetry in a particular region reflects the function of that region, how much individual variability there is in asymmetry and how that variability is reflected in population-level asymmetry, nor how cortical asymmetries have evolved over time. Future studies are needed to fill this gap. Ongoing investigations include the analysis of cell columns in humans and their closest relatives (great apes and gibbons) in multiple regions and the mapping of individual cortical areas across species. Additional future studies should include increased investigations of both humans and nonhumans and examination of microstructural parameters that can be compared with
existing studies. Further studies of humans that can replicate and expand upon existing findings will help to elucidate the functional anatomy of asymmetry, while additional comparative analyses will serve to illuminate the evolution of asymmetry and further shed light on possible correlations with known functional asymmetry.

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REFERENCES


Esser, K.; Condon, C.; Suga, N.; Kanwal, J. Syntax processing by auditory cortical neurons in the FM-FM area of the mustached bat Pteronotus


Ringo, J; Doty, R; Demeter, S; Simard, P. Time is of the essence: A conjecture that hemispheric specialization arises from interhemispheric conduction delay. Cerebral Cortex 4: 331–343, 1994.


Wernicke, C. Das Aphasiche Symptomenkomplex. Breslau, Poland, Cohn and Weigart, 1874.


