

MAPPING BRAIN ASYMMETRY

Arthur W. Toga and Paul M. Thompson

**Laboratory of Neuro Imaging
Department of Neurology, UCLA School of Medicine
Los Angeles, CA, USA**

A Review Article for:

Nature Reviews Neuroscience

Please address correspondence to:

Dr. Arthur W. Toga

Laboratory of Neuro Imaging, 4238 Reed Neurology

Dept. of Neurology, UCLA School of Medicine

710 Westwood Plaza, Los Angeles, CA 90095-1769, USA

Phone: (310) 206-2101 **Fax:** (310) 206-5518 **E-mail:** toga@loni.ucla.edu

References=148

Words=11831

Figures=5

MAPPING BRAIN ASYMMETRY

Arthur W. Toga and Paul M. Thompson
Laboratory of Neuro Imaging
Department of Neurology, UCLA School of Medicine

Abstract

Brain asymmetry has been observed in animals and humans structurally, functionally, and behaviorally. This lateralization is thought to originate from evolutionary, hereditary, developmental, experiential and pathological factors. This paper reviews the diverse literature describing brain asymmetry, focusing primarily on those observations characterizing anatomical differences between the hemispheres.

Introduction

Most biological systems demonstrate some degree of asymmetry¹. From humans to lower animals, normal variation and specialization produce asymmetries of function and structure. Even gross external features of the face and extremities evidence this asymmetry². In humans and many other mammals, the two brain hemispheres differ in their anatomy and function. While cursory examination of the gross features of the human brain fails to expose profound left/right differences, careful examination of its structure reveals a variety of asymmetric features. This lateralized specialization is thought to originate from evolutionary, developmental, hereditary, experiential and pathological factors. For example, the evolutionary expansion of the left-hemisphere language cortices, in particular, may have led to marked volume asymmetries in Broca's speech area, the *planum temporale* (an auditory processing structure in the posterior temporal lobe), and in other structures crucial for speech production, perception, and motor dominance. Asymmetries in the brain's functional layout, cytoarchitecture, and neurochemistry have also been correlated with asymmetrical behavioral traits, such as handedness, auditory perception, motor preferences, and sensory acuity. Here, we review a variety of methods and their resulting observations about the structural and functional asymmetries in the brain with a particular focus on anatomic differences. Brain mapping approaches, in particular, can detect and visualize patterns of asymmetries in whole populations, including subtle alterations in disease, with age, and during development. These and other tools show great promise for assessing factors that modulate cognitive specialization in the brain, including the ontogeny, phylogeny and genetic determinants of brain asymmetry.

Language and Handedness

Language. The specialization of the left hemisphere for language was one of the earliest observations of brain asymmetry. Reported in the 19th century by Broca³ and Wernicke⁴, language was found to be more severely impaired in response to tumors or strokes in the left hemisphere. Language production and some aspects of syntactic processing^{5,6} have subsequently been localized primarily to areas of the anterior left hemisphere, including the *pars triangularis* and *pars opercularis* of the inferior frontal gyrus (Broca's area; see Figure 1). Language comprehension, such as understanding spoken words⁷, on the other hand, is primarily confined to the posterior temporal-parietal region, including Wernicke's area (Brodmann areas 39, 40, posterior 21 and 22, and part of 37). Numerous behavioral tasks have further elucidated language circuits, including tests of grammatical processing, semantic knowledge and syntax^{8,5-6,9}.

Handedness. The relationship between brain asymmetry and handedness has sparked considerable interest and debate¹⁰⁻¹². A rightward hand preference might be expected to result from, or even induce, asymmetries in the motor cortex. Even so, motor cortex asymmetries are quite subtle¹³. Intriguingly, hand preference correlates more strongly with structural and functional asymmetries in language processing structures such as the *planum temporale* and other primary auditory and association cortices surrounding the Sylvian fissures. Language dominance and handedness are not perfectly correlated either. Right-handers (but not left-handers) typically display a strong leftward specialization for speech and language comprehension¹⁴. Approximately 97% of right-handers have their speech and language localized to the left hemisphere, while only 3% demonstrate a right-hemisphere lateralization or bilateral language representation. These relationships degrade to only 70/30 in left-handed individuals¹⁵. Thus, some right-handed patients have a right-hemisphere dominance for language, while left-handers may display a leftward dominance¹⁶.

Clearly, brain asymmetry, language laterality and handedness are interrelated but in a complex way¹⁷⁻¹⁹. Many factors affect these gradients, including genetics^{20, 21}, developmental events (Grimshaw et al., 1985), neurochemical asymmetries²³ (see *Inset Box 1*), experience and disease.

[Inset Box 1]

Neurochemical Asymmetries

Some investigators have linked chemical asymmetries with the specialized functional roles of the two hemispheres. Tucker and Williamson²⁴ argued that the left and right hemispheres are relatively rich in processes that depend on dopamine and norepinephrine, respectively. Autopsy studies show a leftward asymmetry in dopamine levels in the globus pallidus²³ and so do radioligand PET scans of the basal ganglia²⁵. Noradrenergic neurons are also strongly lateralized in the thalamus, being relatively abundant in the right ventral-lateral nuclei²⁶.

Glick et al. also noted behavioral asymmetries that mirrored these neurotransmitter differences: dopaminergic drugs induced motor changes in rats causing them to circle strongly in one direction. This behavioral asymmetry was proportional to the asymmetry in dopaminergic activity, as well as nigrostriatal dopamine sensitivity. Tucker and Williamson²⁴ proposed that the left hemisphere became organized around a dopamine activation system, which made it superior for complex motor programming (leading to a right manual preference), and speech. They further argued that the right hemisphere became organized around a noradrenergic arousal system. This maintains alertness, orients the individual to new stimuli, and integrates bilateral perceptual information. The idea that the hemispheres perform analytical (left) and holistic (right) processing is an old one, and is hotly debated¹⁹. Nonetheless, the idea that specific neurochemical asymmetries lead to cognitive specialization is readily testable. It also leads to tantalizing links between molecular and behavioral asymmetries. Other models of laterality^{27, 2} suggest that the left hemisphere is specialized for specific types of motor function, verbal and non-verbal, and that the lateralization of language emerged from the leftward dominance over motor function.

[End of Inset Box 1]

Macroscopic Anatomical Asymmetries

Petalia and Yakovlevian torque. Gross anatomical asymmetries in the brain have been observed for over a century²⁸. More recently, numerous structural MRI studies have documented anatomical differences between the hemispheres. These investigations of asymmetry focus most frequently on the *planum temporale* because of its relationship to handedness and language laterality (see also *Inset Box 2: Asymmetries in Microscopic Anatomy*).

[Inset Box 2]

Asymmetries in Microscopic Anatomy

Cytoarchitecture. Asymmetries in brain organization are also found at the cellular level. Cytoarchitectural studies by Galaburda et al.²⁹ found a perfect rank-order correlation between gross planum temporale asymmetry and the area of the cellular field Tpt, which is located on and around the planum. This cellular field is implicated in higher-order auditory functions. Similar asymmetries were found for parietal architectonic regions (e.g., language area PG³⁰). The magnitude of planum asymmetries also correlates negatively with the total size of the planum (left plus right). This means that rather than having extra tissue, people with planar asymmetries usually have volume reductions (and hypothetically, fewer neurons) on one side, relative to individuals with symmetrical plana. Using [³H]-thymidine techniques to label neurons undergoing their last mitosis, Rosen et al.³¹ found that there were no subsequent hemispheric differences in labeling ratios between left and right sides, regardless of degree of asymmetry. Cortical area asymmetries were therefore thought to result from earlier asymmetries, prior to cell labeling, in progenitor cell proliferation (and/or early cell death), rather than differences in post-migrational cell death (which would have led to subsequent differences in cell labeling). Such studies tracking cellular changes in cortical development implicate early developmental events in the formation of asymmetric cortical areas—specifically, events occurring during progenitor cell proliferation and/or death (i.e., before the birth of the first neuron), rather than during later neuroblast division³¹.

Dendritic Arborization. A further provocative finding came in 1985 when Scheibel et al.³² reported that the extent of high-order dendritic branching was greater in the left-hemisphere speech areas (including Broca's area) than in their homologs on the right. Lower order dendrites were, however, longer in the right hemisphere. The authors also noted the right hemisphere develops faster in the first year of postnatal life, but is eventually surpassed by the left hemisphere. In the first postnatal year, left-hemisphere language regions consistently lag behind their right-hemisphere homologs in their state of development, perhaps to await speech development³³. The hemispheres may follow separate developmental programmes³⁴, with a variety of physical asymmetries emerging in utero, in childhood and in the teenage years.

[Inset Box 2 ends here]

Among the most prominent observations of brain asymmetry are the right frontal and left occipital petalias, or protrusions of the surface of one hemisphere relative to the other³⁵. These impressions on the inner skull surface provide a negative of the brain's surface topology and a signature of regional hemispheric asymmetries. CT and MRI studies show that these petalias are more prominent in right-handers^{36, 37}. Similar, but lesser, asymmetries are seen in phylogenetically older primates (and other species), as evidenced by endocasts from fossilized cranial bones (K. Zilles, *personal comm.*). Asymmetries seen in comparative studies provide strong evidence for phylogenetic origins of brain lateralization. The massive evolutionary expansion of the prefrontal cortex may, in part, reflect its role in speech production.

Although the two brain hemispheres are similar in weight and volume, the distribution of tissue differs markedly between hemispheres. First, the right hemisphere protrudes anteriorly beyond the left, and the left hemisphere extends posteriorly beyond the right (Fig. 2). A second feature, sometimes regarded as separate from the frontal and occipital protrusions (petalias), is that the right frontal/central region is often wider than the left, and the left occipital region is often wider than the right. These features of overall brain shape reflect lateralized volume differences in frontal (R > L) and occipital regions (L > R). Another prominent geometric distortion of the

hemispheres is known as *Yakovlevian anticlockwise torque*. This encompasses the features described above, and includes the frequent extension of the left occipital lobe across the midline (over the right occipital lobe), bending the interhemispheric fissure towards the right. This general pattern is established prenatally, and is illustrated in Figure 2.

Perisylvian Asymmetry. The asymmetric trajectory of the Sylvian fissure was one of the first anatomical asymmetries to be described^{28, 38}. At its posterior limit, the right Sylvian fissure curves upward more anteriorly than the left, and the left has a gentler slope¹⁰ (Fig. 3). The height of the end-point of the Sylvian fissure is also negatively correlated with the volume of the *planum temporale*³⁵. This region, in the posterior superior temporal lobe, is important for phonological encoding and speech perception, and is the epicenter of a mosaic of left hemisphere language regions. It analyzes the amplitude and frequency of sounds, as well as other acoustic information involved in speech perception. The *planum* shows marked leftward volume asymmetry³⁹ related to the degree of right-handedness⁴⁰. Using an asymmetry index (AI) that corrects for total *planum* size ($AI = (\text{right-left})/0.5(\text{right+left})$), Steinmetz⁴¹ analyzed 154 MRI scans and found that right-handers exhibit greater *planum* asymmetry (mean AI = $-0.30 \pm 0.28SD$; N=121), while left-handers show a weaker, but still leftward, asymmetry (mean AI = $-0.16 \pm 0.31SD$; N=33). In this study, no gender effects or gender by handedness interactions were found, suggesting that these may be subtle if present^{42, 43}.

Although the left *planum* is an extension of Wernicke's posterior receptive language area, the *planum* asymmetry also appears in higher non-human primates (including chimpanzees⁴⁴). Its dramatic increase in humans suggests a link with the evolution of language. In humans, the left *planum* is up to 10 times larger than its right-hemisphere counterpart, and is perhaps the most prominent and functionally significant human brain asymmetry⁴¹. Broca's speech area (in the left frontal lobe) is also larger in volume than its homolog in the right hemisphere^{45, 46}.

The greatest asymmetries of structure are clearly localized to the perisylvian language area. Hochberg and LeMay⁴⁷ studied the location of the posterior tip of the Sylvian fissure, and found that it was higher on the right in 67 of the 100 right-handers they studied, but only in 6 of 28 non-right-handers (i.e., 21%). Heschl's gyrus is also larger on the left side⁴⁸, a feature attributed to greater amounts of underlying white matter⁴⁹. These asymmetries are also found in children^{50, 51}. Their magnitude increases throughout childhood and the teenage years, even after adjusting for developmental increases in brain volume⁵². This suggests that there may be hemispheric differences in white matter maturation, perhaps during the many regional growth spurts in myelination that occur in childhood⁵³. In addition, exposure to gonadal steroid hormones during critical developmental periods may differentially affect the growth of each side of the brain. The anatomical connectivity of the anterior temporal and inferior frontal lobes is also thought to be more highly developed in the right hemisphere. The uncinate fasciculus, which connects these two regions, has been found to be asymmetrical in both sexes, being 27% larger and containing 33% more fibres in the right than the left hemisphere⁵⁴.

Sulcal Pattern Asymmetry. In addition to the *planum temporale*, other gyral regions have received considerable attention in the quest to map the profile of cortical asymmetries (Fig. 3). The central sulcus, which houses the primary motor cortex, was found to be deeper and larger in the right hemisphere of both males and females⁵⁵. Positional asymmetries were gender specific, observed only in males. These measures remain controversial, as Amunts et al.⁵⁶ found the central sulcus to be deeper on the left, in males. Methodological differences and age effects may explain the inconsistencies. Nonetheless, clear motor asymmetries are found in regions that are more proximal to the motor effectors. The right cortico-spinal tract is larger than the left in 75% of subjects, and the left pyramid crosses more rostrally and is larger than the right in 82-87% of subjects⁵⁷. In physiological studies of squirrel monkeys⁵⁸, the sizes of cortical somatotopic areas representing the distal forelimb also depend on limb preference. The size of these areas is greater in the hemisphere opposite the dominant limb (see *Inset Box 3: 'Why is the Brain Asymmetrical?'*). It is not currently known how extensive these asymmetries are cytoarchitecturally.

[Inset Box 3]

Q. Why is the brain asymmetrical?

A. Functional asymmetries in the brain were initially thought to be uniquely human, reflecting unique processing demands required to produce and comprehend language. Nonetheless, functional and structural asymmetries have been identified in non-human primates and many other species⁵⁹. Passerine birds produce song primarily under left-hemisphere control⁶⁰ and Japanese Macaques exhibit a right-ear advantage for processing auditory stimuli⁶¹. Language is commonly lateralized to the left hemisphere, and some argue that this is advantageous: first, it avoids competition between hemispheres for control of the muscles involved in speech; second, it may be more efficient to transfer language information between a collection of focal areas in a single hemisphere. More asymmetrical brains, for example, have a corpus callosum with a reduced midsagittal area relative to more symmetrical ones⁶². This may reflect fewer and/or thinner fibers connecting the two hemispheres, perhaps due to differences in axonal pruning. The massive evolutionary expansion of the brain may have resulted in a level of complexity where duplication of structures was no longer efficient, relative to specialization of functions within a hemisphere. Time limits in callosal transfer of information between the brain hemispheres, in larger brains, may also favor development of unilateral networks.

The main pitfall in arguing that left-hemisphere dominance provides an evolutionary advantage is that bilateral language representation, or rightward dominance, are also common. In addition, leftward dominance does not, in general, provide a cognitive advantage⁶³.

Others suggest that the left hemisphere's dominance over language evolved from its control of the right hand (an idea first proposed by Condillac in 1746): its programming of skilled movement and gesture may have evolved to encompass control of the motor systems involved in speech². Broca's area, in particular, is a premotor module in the neocortex. It sequences complex articulations that are not limited to speech. Great apes, including chimpanzees, bonobos, and gorillas, also have an enlarged area 44 (part of Broca's area). This area controls muscles of the face and vocal tract, although this area is not as massively interconnected with the homolog of Wernicke's area as it is in humans⁶⁴. Cantalupo and Hopkins⁶⁵ suggest that non-human primates developed a homolog of Broca's area due to a link between primate vocalization and gesture: captive apes usually gesture with the right hand as they vocalize. Lieberman⁶⁶ suggests that language is a relatively recent evolutionary adaptation (not more than 200,000 years old) that the Neanderthal vocal tract was incapable of articulating the range of modern human speech sounds.

Research on indigenous gestural languages invented by children in Taiwan⁶⁷ and in Nicaragua⁶⁸ provides some evidence for the innate relation between gesture and language. Functional neuroimaging studies also suggest that deaf subjects using a gestural sign language activate many of the systems involved in verbal language production⁶⁹. These congruences in functional anatomy may support the hypothesis that verbal language evolved from gestural language as an outgrowth of the already asymmetric motor control system⁷⁰.

[End of Inset Box 3]

Composite Brain Maps. More recently, digital brain maps have visualized the profile of cortical asymmetries in 3 dimensions^{71, 13, 72}. Figure 3 shows an average representation of the primary sulcal pattern derived from MRI scans of 20 right-handers⁷³. Using computational methods, 3D models of cortical sulci can be reflected in the interhemispheric plane, and the 3D distance can be computed between the mean structure on the left and a reflected version of the mean structure on the right. The magnitude of this asymmetry can then be plotted as a color-coded map. The degree of asymmetry is different in different parts of the brain (greater asymmetries are shown here in red). By comparing the average magnitude of these asymmetries with their standard error (or in 3D, their covariance field), regions with statistically significant asymmetries are readily identified (*significance map*, Fig. 3).

As these maps indicate, the Sylvian fissure is, in general, longer in the left hemisphere than the right. Strikingly, some right-hemisphere structures are ‘torqued forward’ relative to the left. This is consistent with the direction of the petalia (Fig. 2), in which the right frontal lobe juts forward relative to the left. Nonetheless, the effect is comparatively localized, and perisylvian structures exhibit the strongest asymmetries. Other studies have evaluated the incidence of sulci in one hemisphere relative to the other, compiling stereotaxic maps for the *planum temporale* in standardized atlas coordinates⁷⁴. Paus et al.⁷⁵ generated a probabilistic map to describe the location of the cingulate and paracingulate sulci (when present) in each brain hemisphere. In MRI data from 247 healthy young volunteers, the paracingulate sulcus occurred more frequently in the left hemisphere⁷⁵, a feature thought to be linked with the participation of the left anterior cingulate cortex in language tasks. Subsequent functional MRI studies revealed that task related brain activation, during a word generation task, rarely extended into the cingulate sulcus when a prominent paracingulate sulcus was present, but if no paracingulate sulcus was present, these activations spread into the cingulate sulcus⁷⁶. Group studies of functional anatomy rarely stratify their samples into groups with different normal anatomic variations, but such studies are needed to elucidate how these normal variants impact functional organization and cerebral asymmetries.

Statistical Maps. Besides examining sulci or other features of the brain’s surface, voxel-based morphometric analyses have further characterized the extent of cerebral asymmetry^{77, 78}. In this type of approach, the entire brain volume is assessed on a voxel by voxel basis with MRI. Avoiding manual delineations of regions of interest but requiring smoothed data (12 mm), these approaches are automated and enable efficient large-*N* studies. Good et al.⁷⁷ found significant asymmetries in grey and white matter distribution in the occipital, frontal, and temporal lobes, including Heschl’s gyrus, the *planum temporale* and the hippocampus, and Watkins et al.⁷⁸ discovered previously undetected volume asymmetries, in both sexes, in the anterior insular cortex ($R > L$). In the largest MRI study to date, Good et al.⁷⁷ did not find a relationship between asymmetry and handedness, but did find several gender-related differences. Males exhibited a greater leftward asymmetry in the *planum* and Heschl’s gyrus compared with females, consistent with the notion that brain structure is more lateralized in males than in females⁷⁹.

Mapping Asymmetry with Brain Atlases. Building on these automated methods, digital brain atlases now compile brain data from hundreds, or even thousands of subjects^{80, 81}. These tools empower large-scale studies of brain asymmetry, as they reveal how factors such as age⁵², gender⁴³, and disease⁷² affect or modulate these asymmetries (see below).

Brain structure is so complex and variable that systematic asymmetries can be difficult to localize, and distinguish from random fluctuations. Population-based brain atlases surmount this problem by averaging 3D models of anatomy across subjects, while storing statistics on anatomic variation. Figure 4 shows average 3-dimensional shape models for the lateral ventricles, in two different groups of subjects: twenty-six subjects with Alzheimer’s disease, and twenty elderly controls. In the average brain maps, a marked ventricular asymmetry emerges in both groups, with the left ventricle visibly larger than the right. (As expected, the ventricles are also significantly enlarged in dementia). The anatomic asymmetry is clearly localized to the occipital horn, which extends (on average) 5.1 mm more posteriorly on the left than the right. This is consistent with the petalia and torque effects described earlier (and illustrated in Fig. 2).

Ventricular asymmetry is an example of a statistically significant effect that becomes clear in a group average brain map, but is not universally apparent in individual subjects. It is, however, consistent with volumetric measures (e.g. Shenton et al.⁸²). In normal subjects, occipital horns are on average around 17% larger on the left ($4070 \pm 480 \text{ mm}^3$ vs. $3475 \pm 334 \text{ mm}^3$; $p < 0.05$), but no significant asymmetry is observed in the superior or inferior horns ($p > 0.19, 0.37$). This ventricular asymmetry may reflect rapid, asymmetric growth in the overlying language systems; it can occasionally be seen in the embryonic brain, using ultrasound, as early as 29-31 weeks post conception⁸³.

Factors that Affect Anatomical Asymmetries

Fetal Orientation. Previc⁸⁴ suggests that asymmetric influences in the prenatal environment, even due to fetal posture, may lead to perceptual and motor asymmetry. Two-thirds of fetuses are confined to a leftward fetal position in the third trimester, with their right side facing outwards. Lateralization of language perception may result from asymmetries in their auditory experience. The right ear may even be better positioned to discriminate high-frequency speech sounds. In an elaborate model of motor dominance, Previc⁸⁴ also argues that asymmetrical vestibular stimulation *in utero* may produce behavioral asymmetries later in life. In an intriguing epidemiological study, Kieler et al.⁸⁵ surveyed 179,395 men born in Sweden between 1973 and 1978, and concluded that ultrasound exposure in fetal life increases the chances of being left-handed, by about 30%. The controversial suggestion that routine prenatal ultrasound affects the fetal brain has stimulated further research into its potential effects on embryogenesis, as ultrasound exposure has not previously been associated with any childhood malignancy or behavioral sequelae.

Heredity and Environment. Embryonic processes that lead to functional and structural asymmetry of the language cortex are the focus of intense study, as their failure may lead to decreased functional specialization in the cortex. Schlaug et al.⁸⁶ also studied musicians with perfect pitch (i.e., the ability to identify any musical note without comparing it to a reference note). In musicians, planar asymmetry was twice as great as in non-musicians, and greatest of all in those with perfect pitch. Exaggerated asymmetries may therefore indicate increased capabilities in processing certain auditory features⁴¹. A follow-up study⁸⁷ revealed that the exaggerated asymmetry in the perfect pitch group was attributable to a smaller right (rather than an enlarged left) *planum*, relative to non-musician controls and musicians without perfect pitch. The absolute size of the right *planum* (not the left) predicted group membership, perhaps implying neurodevelopmental “pruning” of the right *planum* in musicians with perfect pitch. The authors pointed to a possible genetic determination for the increased *planum* asymmetry.

Recent genetic brain-mapping techniques, applied to MRI scan data from identical and fraternal twins, suggest that heredity plays a strong role in structuring the perisylvian cortex. Gray matter volumes in perisylvian areas are under tight genetic control and are highly heritable^{88, 89}. Gyrus/sulcal patterns appear much less heritable^{90, 91} (Thompson et al., 2002). Studies of monozygotic twins (who are genetically identical) reveal low intraclass correlations for the *planum* asymmetry index⁴¹ ($r \leq 0.2$). Nonetheless, low statistical power may preclude detection of these genetic effects^{88, 92}.

Laterality cannot be influenced exclusively by an individual's genotype, as many identical twins are discordant for handedness and differ considerably in *planum* asymmetry⁹³. A recent study of twins discordant for handedness found that genetic factors influenced the left and right hemisphere volumes twice as strongly in right-handed twin pairs, relative to discordant pairs. The decrement in genetic control of cerebral volumes in the non-right-handed pairs supports the notion of a "right-shift" genotype¹¹ that is lost in non-right-handers, resulting in decreased cerebral asymmetry⁹⁴. Whatever the genetic determinants of laterality, many pre- and postnatal (but non-genetic) factors modulate anatomical and functional asymmetry. These include asymmetrical brain damage⁹⁵, embryonic position *in utero*⁸⁴, chemical and genetic gradients⁹⁶, and fetal testosterone effects⁹⁷. Laland et al.⁹⁸ proposed a population genetics model of handedness incorporating both genetic and environmental factors. They suggested that cultural factors brought to bear by parents on their children can strongly influence a child's handedness, perhaps to an even greater degree than genetic influences. This environmental factor complicates the arguments for strictly

Mendelian inheritance of handedness, or for a genetic “right-shift” factor as the overriding determinant of handedness.

Laterality and Gender. Several studies have pointed to differences in brain asymmetry between men and women, some suggesting that the male brain may be, on average, more lateralized or asymmetrical than the female brain⁹⁹. In tests designed to assess perceptual asymmetries (see ‘*Dichotic Listening*’, below), some studies report a greater lateralization of auditory or visual processing skills in men than women^{100, 101}. Kimura¹⁰² suggests that this may mean either (1) that the functions of the hemispheres may not be as sharply differentiated in women as in men, or alternatively (2) that larger commissural systems in women may act to reduce the difference in response scores between hemispheres. Whichever of these possibilities is true, sex differences in brain organization, both within and between hemispheres, are thought to underlie sex differences in motor and visuospatial skills, linguistic performance, and vulnerability to deficits following stroke and other focal lesions¹⁰². Sex differences have also been reported in the structural asymmetry of the *planum temporale*, with greater asymmetries in males¹⁰³, but these findings have been contested. A more robust sex difference appears in the anatomy of the *planum parietale*, another asymmetric structure in the parietal lobe, at the posterior end of the Sylvian fissure. This structure is typically larger on in the right hemisphere, and in right handers this asymmetry is greater in men, but in left handers the asymmetry is greater in women¹⁰³. How these asymmetries might relate to differences in visuospatial processing are not yet understood.

Hormonal Effects on Asymmetry. In animal studies, more pervasive sex differences have been found in the pattern of structural brain asymmetries, and their determinants are better understood. In male rats, the right neocortex is thicker than the left, and females display a non-significant trend towards the opposite pattern¹⁰⁴. The male asymmetry is mediated in part by early androgen exposure, as castration at birth, which prevents the flow of androgens from the testis to the brain, blocks the formation of the normal rightward brain asymmetry. The female pattern can be reversed to the male pattern by neonatal ovariectomy. Maternal environmental or nutritional stress also reverses the male-typical asymmetry to the female pattern in fetal male rats; it both shifts and depresses a testosterone surge that normally occurs on gestational day 18¹⁰⁵. These findings suggest that levels of androgenic and ovarian sex steroids, before and after birth, play a role in modulating brain asymmetry, at least in rodents. Their modulatory effects on rates of cell death and axon elimination are also likely to be sex specific¹⁰⁶. Finally, the masculinizing effect of androgens on male cortical asymmetry appears to be mediated by their conversion to estrogen, rather than testosterone acting directly, as the effect is blocked by aromatase blocker ATD (1,4,6-androstatriene-3,17-dione¹⁰⁷).

It is less clear, however, whether these sex specific asymmetries are found in humans. In human male fetuses a larger right hemisphere volume has been identified, but so far no equivalent pattern has been reported in adults¹⁰². In their widely-cited theory of cerebral lateralization, Geschwind and Galaburda⁵¹ suggested that elevated testosterone effects may be responsible for deviations from the normal dominance pattern (i.e. right-handed and leftward language dominance, as well as rightward visuospatial dominance). According to the theory, if testosterone levels are higher than normal *in utero*, consequences include masculinization, a smaller left hemisphere, and even anomalous dominance, due to a delay of left hemispheric growth. This model was posited to explain the different maturational rates of the sexes (with females generally maturing faster³⁴), and the relative male superiority in right-hemisphere visuospatial tasks and female superiority in left-hemisphere linguistic tasks¹⁰⁸. It may also explain the greater incidence of left-handedness in males¹⁰⁹. The role of androgens in modulating brain asymmetry is attractive, given their key role in inducing other neuroanatomical sex differences in humans and other species^{110, 111}.

Functional Adaptation. Experience-dependent plasticity and asymmetric behaviors may also induce different neuronal changes in the two hemispheres. In rats, the asymmetric use of only one forelimb in the post-weaning period induces an asymmetrically larger neuropil volume and lower cell packing density in the motor cortex¹¹². In mice with a hereditary asymmetry in their whisker pads, a dominant right whisker pad has been associated with left paw preference¹¹³. Limb preference may therefore be associated with asymmetries in sensory input, although it is not known whether this relationship is causal. These findings suggest that some brain asymmetries are not

necessarily genetically determined, and may result from lateralized sensory stimulation in pre- and post-natal development.

Aberrant Asymmetries and Disease. Reduced *planum* volume asymmetries have been reported in some subjects with reading disorders or developmental dyslexia¹¹⁴⁻¹¹⁶ Galaburda, 1995) and in some people with an unusual right-hemisphere dominance for speech. Hynd et al.¹¹⁴ reported a *reversed* planar asymmetry (i.e. right larger) in 9 of 10 right-handed dyslexic children studied with MRI. Dyslexics with phonological processing deficits also show reduced *planum* asymmetry¹¹⁵. Analogously, functional MRI studies reveal a pattern of brain activation in stutterers that is shifted towards the right in both motor and auditory language areas. This may suggest an inherent difference in the way in which normal subjects and stutterers process language¹¹⁷. Controversy surrounds reports of reduced or altered planar asymmetry in schizophrenia^{118, 119, 43}. At the same time, there is great interest in the perisylvian region in schizophrenia, as it houses the primary auditory cortex, which may be implicated in auditory hallucinations¹²⁰.

Disease processes may also interact with existing brain asymmetries or exacerbate them. An increased asymmetry of cerebral function in males is thought to underlie the greater male incidence of language impairment following stroke, and possibly also the increased incidence of learning disorders in males. The right hemisphere has a larger blood supply overall than the left¹²¹, and there is a higher mortality in cases of similar but right sided hemispheric lesions¹²².

Some diseases also progress asymmetrically. Patients with semantic dementia generally show asymmetric anterolateral temporal atrophy (typically worse on the left side) with relative sparing of the hippocampal formation. In Alzheimer's disease, a spreading wave of gray matter loss emerges initially in entorhinal and temporal-parietal cortices, sweeping into frontal and ultimately sensorimotor territory as the disease progresses^{123, 124}. This sequence occurs in both hemispheres, but left-hemisphere regions are affected earlier and more severely. The right hemisphere following a similar pattern roughly two years later (Fig. 5). Sylvian fissure CSF volumes also rise more sharply on the left than the right in dementia (left 32% higher, but on the right only 20% higher than controls¹²⁵). PET studies also show left-greater-than-right metabolic dysfunction in early dementia^{126, 127} Corder *et al.*, 1997). These disease process asymmetries suggest either (1) that the left hemisphere is more susceptible than the right to neurodegeneration in AD, or (2) that left hemisphere pathology results in greater structural change and lobar metabolic deficits¹²⁶.

Functional Asymmetries

The degree to which functional asymmetries parallel those observed anatomically has been studied using a variety of methods. These include measurements of neuronal and hemodynamic changes during lateralized behaviors. In addition, models to isolate or inhibit cortical activity and circuits in one hemisphere provide fundamental data on functional asymmetry.

Measuring Functional Asymmetries. Many tests of functional brain asymmetries derive from surgical mapping techniques (stimulation, local anesthesia and recording of the cortex) designed to identify and avoid resection of key language areas. These techniques determine which hemisphere is dominant for language. Pioneering work by Wilder Penfield and colleagues¹²⁷ revealed that speech was blocked by electrical stimulation of the left hemisphere, but rarely the right (cf. Ojemann et al.¹²⁸). By contrast, hallucinations and illusions were elicited more commonly by stimulating the right, rather than the left, temporal cortex.

A related technique is the Wada test¹²⁹. This procedure uses an intracarotid injection of sodium amytal to locate speech areas¹³⁰. Transient anesthesia occurs in the hemisphere ipsilateral to the injection. In the dominant hemisphere, this anesthesia transiently blocks speech. Aphasic errors occur until speech function fully returns. In left-dominant subjects, injection to the right hemisphere affects speech only minimally, but it can affect singing,

causing it to become monotone¹³¹. Language dominance, ascertained with the Wada test, is also correlated with *planum temporale* asymmetry¹³². Nonetheless, even in highly lateralized subjects, some aspects of linguistic function, such as processing the prosaic, emotional, and melodic aspects of language, are thought to be performed by the non-dominant hemisphere. Rather than processing the literal meanings of words, the right hemisphere is thought to interpret the figurative meanings in language, conveyed by humor, metaphor, as well as hesitations and tone of voice.

Split-Brain Patients. Cognitive tests in split-brain patients have also yielded key information on hemispheric specialization. In these patients, the *corpus callosum* was surgically resected to control intractable seizures (Sperry, 1984). This also disrupts the communication of perceptual, cognitive, mnemonic, learned and volitional information between the two brain hemispheres¹³³. As a result, unique tests can be performed, presenting auditory or visual stimuli selectively to a single, isolated hemisphere^{134, 135}. While fixating on a central spot on a screen, patients could verbally report words flashed on the right side of the screen (i.e. processed by the left hemisphere). Patients could not verbally repeat words flashed on the left side of the screen (processed by the right hemisphere) but they could identify them by picking up with the *left hand* a physical item matching a word. Thus, language was isolated in the left hemisphere but the information processing necessary to recognize and identify the object was not lateralized.

Dichotic Listening. Less invasive tests can assess functional asymmetries in normal subjects who had not undergone surgery. Typically, these use auditory or visual stimuli that are presented asymmetrically. Dichotic listening studies^{136, 137, 102} reveal that verbal material is more readily analyzed if presented to the right ear (which has preferential access to the left hemisphere). Musical material, by contrast, is more effectively analyzed if presented to the left ear (right hemisphere). Using dichotic listening to study laterality in auditory processing, Kimura²⁷ presented digit pairs (1-2, 5-3, etc.) over stereo headsets, sending one digit to one ear and the other to the other ear. Most subjects recalled the right-ear digits with greater accuracy than the left, reflecting a left-hemisphere auditory-processing advantage.

Functional Brain Imaging. Since the 1980s, cortical blood flow and metabolism have been measurable in living humans. Functional brain imaging techniques such as positron emission tomography (PET) and, more recently, functional magnetic resonance imaging (fMRI) have been widely applied to study functional asymmetries. With different tracer compounds, PET scans can map rates of regional blood flow, as well as oxygen and glucose utilisation. Functional MRI can map blood flow in real time during cognitive tasks, based on the paramagnetic effect of deoxygenated hemoglobin. Statistical mapping techniques¹³⁸ can then process these functional images and map task-related fluctuations (in both PET and fMRI), showing cortical regions activated in tasks such as reading, hearing, or speaking. The success of brain mapping has been promoted by the international adoption of a coordinate-based 3D reference system for brain data. After images and maps are aligned with a standard brain template, or atlas, cortical maps and locations can then be referenced in standard 3D coordinates. This helps pool brain data from multiple studies, and also assists in computing group differences and hemispheric asymmetries in cortical activation.

In PET studies of language comprehension (listening to a story), Tzourio et al.^{139, 140} found that left-handed subjects, unlike right-handers, activated the right middle temporal gyrus, and showed less leftward lateralization of activation in the superior temporal gyri (STG) and temporal poles. The percentage increase in regional cerebral blood flow in the left STG also correlated with the size of the left *planum temporale* (although not with the degree of asymmetry). In a single-word repetition task, Karbe et al.¹⁴¹ also noted that regional cerebral glucose metabolism in the right hemisphere decreased, and in some left-hemisphere language regions increased, in proportion to the leftward *planum* asymmetry. These and other brain mapping studies suggest that widely reported anatomical asymmetries in this region may have a functional correlate as well.

Other cognitive dominance and brain-mapping studies have examined the right-hemisphere dominance for certain visuospatial processing tasks. In the classic Shephard-Metzler 'mental rotation' task¹⁴², subjects are shown pairs of perspective drawings of various 3-dimensional shapes. They are asked to mentally rotate one onto the other, to

decide whether the two shapes are replicas or mirror-images of one another. Some studies found a right-hemisphere laterality effect, with faster reaction times to shapes presented in the left visual field^{143, 144} indicating a right-hemisphere dominance. More recent neuroimaging studies^{145, 146} mainly implicate the right parietal lobule in this task, suggesting a right-hemisphere dominance, although this is not entirely consistent across subjects (see Hugdahl¹⁴⁷ for a review).

Conclusion

We have surveyed a variety of studies that examine asymmetries in brain structure and function. The gross anatomy and functional layout of the brain are organized asymmetrically, with hemispheric specializations for key aspects of language and motor function. These asymmetries are first observed around 29-31 weeks gestational age. Differing developmental programmes structure the two hemispheres well into childhood and beyond, leading to lateralized differences in maturational rates, dendritic arborization, metabolism, and functional activation. The loss or modulation of these asymmetries in disorders such as dyslexia or dementia is of particular interest, as is their exaggeration in individuals with special abilities. The pattern of asymmetries varies with handedness, gender, age, and with a variety of genetic factors and hormonal influences.

Asymmetries defined in animal studies may not be easy to extrapolate to humans (see *Inset Box 2*), as the precursors of language-related asymmetries in humans may not be present in other species. The mechanisms that underlie some cerebral asymmetries in humans might differ substantially from those that underpin brain asymmetry in other mammals, suggesting the need to compare data, where possible, from human neuroimaging, cognitive, and animal studies.

Studies of the molecular mechanisms involved in the formation of cerebral asymmetries are in their infancy¹⁴⁸. Future studies of this type will be led by a detailed knowledge of how the brain deviates from symmetry both in healthy individuals and in disease. Among other approaches, brain mapping techniques can help measure and visualize asymmetric patterns of structure and function, revealing how they vary in entire populations. Large-scale neuroimaging analyses can also optimize the detection of asymmetric features. They can identify or confirm factors that might modulate patterns of brain asymmetries, such as specific genetic polymorphisms, hormonal changes, demographic factors, and developmental differences. The merger of neuroimaging and genetic databases may ultimately be used to discover and explore genetic, demographic, and maturational events that play a role in the determination of brain asymmetry.

Future Research

While predicting specific future research advances is impossible, it seems likely that integration of data from the widely different approaches will provide a more unified understanding of the mechanisms of brain lateralization. The increased sensitivities afforded by improved brain mapping approaches will undoubtedly provide a clearer description of structural and functional brain asymmetries. Integrating these observations with genetic databases will provide an opportunity to establish the genotype/phenotype relationships that influence hemispheric specialization. Certainly the rapidly emerging databases of brain image data will enable retrospective structural studies of large N populations.

Acknowledgments

Grant support was provided by a P41 Resource Grant from the National Center for Research Resources (RR13642). Additional support for algorithm development was provided by the National Library of Medicine (LM05639), the National Institute of Mental Health (MH65166), and by a *Human Brain Project* grant to the International Consortium for Brain Mapping, funded jointly by NIMH and NIDA (MH52176).

Author Biographies

Arthur Toga is Professor of Neurology at the University of California at Los Angeles (UCLA). His research is focused on neuroimaging, mapping brain structure and function, and brain atlas. He also studies cerebral metabolism and neurovascular coupling. He was trained in neuroscience and computer science and has written more than 450 papers, chapters and abstracts, including eight books. Recruited to UCLA in 1987, he formed and directs the Laboratory of Neuro Imaging. This 65-member laboratory includes graduate students from computer science, biostatistics and neuroscience. It houses one of the largest computing facilities of any University of California research laboratory, and is funded by National Institutes of Health and National Science Foundation grants and industry partners. He is Director of the Training Program in Neuroimaging, Co-Director of the Division of Brain Mapping, and Editor-in-Chief of the journal *NeuroImage*.

Paul Thompson is Assistant Professor of Neurology at the UCLA School of Medicine, and is a member of the UCLA Laboratory of Neuro Imaging. He received his M.A. in Mathematics and Classical Languages from Oxford University, England, and his Ph.D. in Neuroscience from UCLA. After research as a Fulbright Scholar and Howard Hughes Investigator at UCLA, Dr. Thompson has published over 200 collaborative articles, chapters, and abstracts describing novel mathematical and computational strategies for mapping brain structure and function in health and disease. His work focuses on developing new methods to map dynamic (4D) processes in brain development and in Alzheimer's Disease, for mapping genetic influences on brain structure, and for mapping medication response and disease progression in dementia and schizophrenia. Dr. Thompson serves on the Editorial Board of the journal *Medical Image Analysis*, and is an Associate Editor of the journal *Human Brain Mapping*.

Figure Legends

Figure 1. *Language Areas Displaying Anatomical and Functional Asymmetries.* Broca's speech area (*shown in green*) and Wernicke's language comprehension area (*shown in blue*) are identified on a transparent surface model of the human cerebral cortex. All cortical regions are heavily interconnected with corresponding systems in the opposite brain hemisphere, via the *corpus callosum* (*rendered here in white*). The language areas show profound asymmetries, both structurally and functionally: the left hemisphere is also dominant for language in most right-handed individuals.

Figure 2. *Petalia and Yakovlevian torque.* This 3D rendering of the inferior surface of a human brain is derived from an *in vivo* MRI scan exaggerated to illustrate prominent asymmetries found in the gross anatomy of the two brain hemispheres. Noticeable protrusions of the hemispheres, anteriorly and posteriorly, are observed, as well as differences in the widths of the frontal (*F*) and occipital (*O*) lobes. These protrusions also induce imprints on the inner skull surface, known as *petalias*. A twisting effect is also observed, known as *Yakovlevian torque*, in which structures surrounding the right Sylvian fissure are torqued forward relative to their counterparts on the left. The left occipital lobe is also splayed across midline and skews the interhemispheric fissure in a rightward direction. A related shape asymmetry is also commonly observed in the occipital horns of the lateral ventricles. These tend to project more deeply into the occipital lobes on the left than on the right (see Fig. 4).

Figure 3. *Multi-Subject Maps of Brain Asymmetry.* Image analysis techniques make it possible to distinguish systematic asymmetries in a population, or a specific group of subjects, from random fluctuations in anatomy. After aligning and scaling individual MRI scans into a standard 3D space, 3D curves representing the primary sulcal pattern are digitized (a). [Sulci include central (CENT), precentral (preCENT), postcentral (poCENT), intraparietal (IP), superior frontal (SFS), inferior frontal (IFS), superior temporal and Sylvian fissures (SF)]. Averaging these curves across 20 normal subjects (b), the magnitude of asymmetry in the average anatomy is shown in color (red colors denote greater asymmetry). Extension of these methods to surfaces (c,d) reveals prominent asymmetries in Broca's anterior speech area and in language regions surrounding the Sylvian fissure. By comparing the average magnitude of these asymmetries to their standard error, regions of significant asymmetry are identified (f).

Asymmetries are greatest in brain regions with greatest gyral pattern variability across subjects (g,h). The tensor map (h) shows that the preferred directions of inter-subject anatomical variability are also approximately aligned with the direction of inter-hemispheric asymmetry.

Figure 4. Ventricular Asymmetry. The 3-dimensional anatomy of the lateral ventricles is shown across subjects to create an average anatomical model. Separate averages are shown, in this case, for a group of normal elderly control subjects (*NC*; $N=20$) and a group of age-matched patients with Alzheimer’s disease (*AD*; $N=26$). In addition to the disease effect (larger ventricles in patients), note the prominent left larger than right ventricle in both groups. This surface asymmetry is induced by volumetric asymmetries in the overlying language cortices. It may go unnoticed in individual subjects due to the high inter-subject variability of anatomy: local anatomical variability is shown as a 3D r.m.s. measure of deviation from the group average model (red colors denote regions with greatest anatomical variability).

Figure 5. Asymmetrical Progression of Alzheimer’s Disease. These maps show the average profile of gray matter loss in a group of 17 patients with mild to moderate Alzheimer’s disease¹²⁴. Average percent reductions in the local amount of gray matter are plotted, relative to the average values in a group of 14 healthy age and gender matched elderly controls. Initially, the left hemisphere is much more severely affected (b) than the right (a), but the deficits progress to encompass more of the left hemisphere (c). Maps of regional gray matter (*green colors*, (d)) are here computed from MRI brain scans acquired longitudinally over a 1.5 year period from both patients and controls.

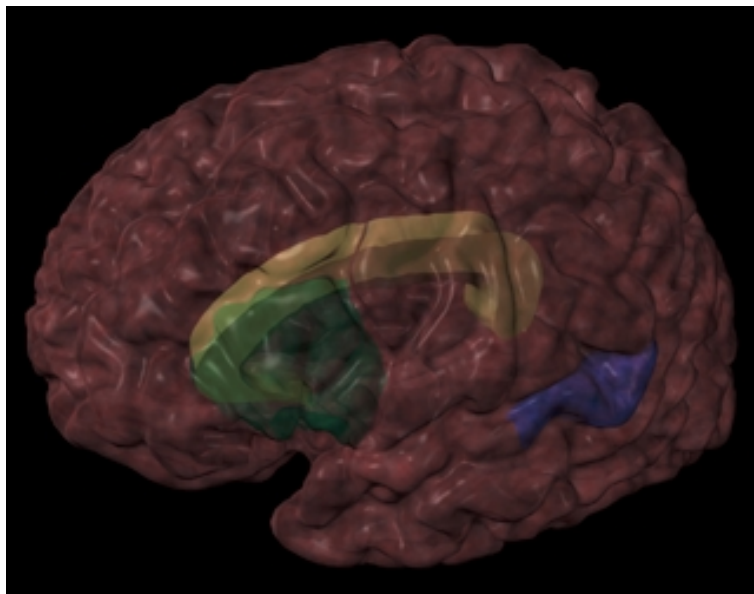


Figure 1



Figure 2

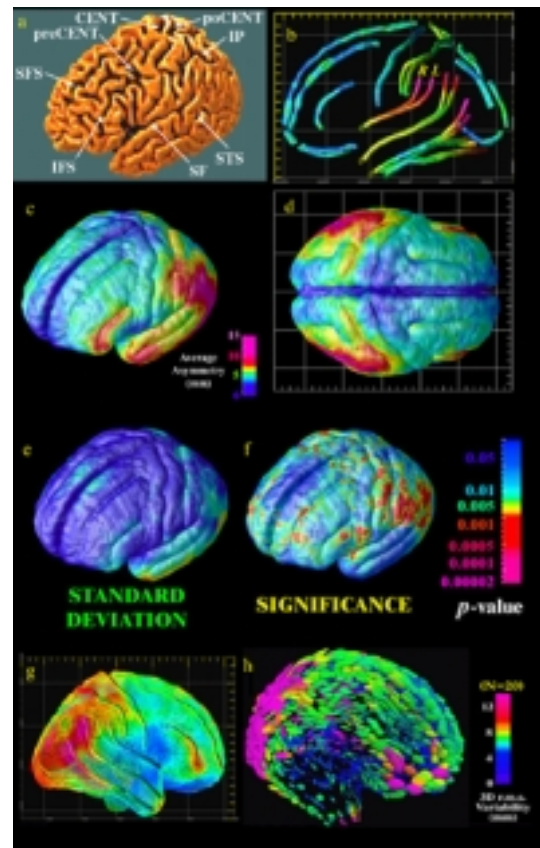


Figure 3

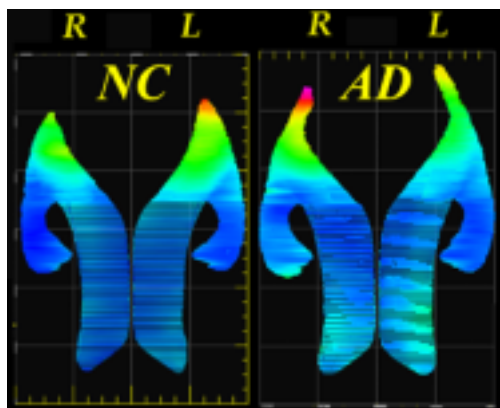


Figure 4

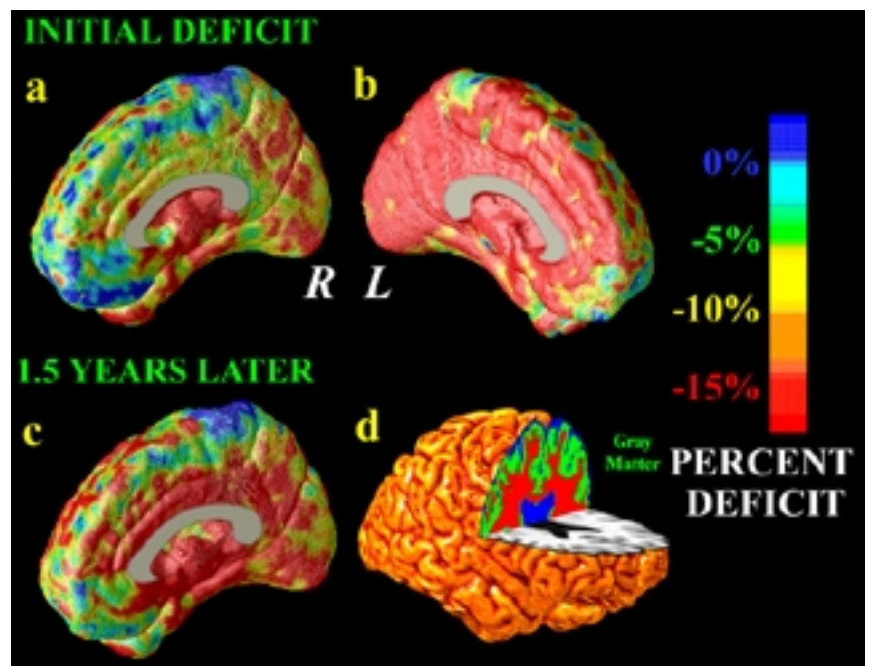


Figure 5

References

1. Geschwind, N. & Galaburda, A. M. Cerebral lateralization. Biological mechanisms, associations and pathology. *Arch Neurology*. 428-459 (1985).
2. Kimura, D. The asymmetry of the human brain. *Sci Am*. **228(3)**, 70-8 (1973).
3. Broca, P. Remarques sur le siege de la faculte du langage articule, suivies d'une observation d'aphemie. *Bulletin de la Societe d'anthropologie*. **6**, 330-357 (1861).
4. Wernicke, C. Der Aphasische Symptomenkomplex: Eine Psychologische Studie auf Anatomischer Basis. Breslau: Cohn und Welgert (1874).
5. Dapretto, M. & Bookheimer, S. Y. Form and content: dissociating syntax and semantics in sentence comprehension. *Neuron*. **24(2)**, 427-32 (1999).
6. Binder, J. The new neuroanatomy of speech perception. *Brain*. **123(12)**, 2371-2 (2000).
7. Price, C. J. The anatomy of language: contributions from functional neuroimaging. *J Anat*. **197(3)**, 335-59. Review (2000).
8. Zatorre, R. J. On the representation of multiple languages in the brain: old problems and new directions. *Brain Lang*. **36(1)**, 127-47 (1989a).
9. Pouratian, N., Bookheimer, S. Y., Rex, D. E., Martin, N. A. & Toga, A. W. Utility of preoperative functional magnetic resonance imaging for identifying language cortices in patients with vascular malformations. *J Neurosurg*. **97(1)**, 21-32 (2002).
10. Geschwind, N. & Levitsky, W. Human Brain: Left-Right Asymmetries in Temporal Speech Region. *Science*. **161**, 186 (1968).
11. Annett, M. *Left, Right, Hand and Brain: The Right Shift Theory*. Lawrence Erlbaum: (London, 1985).
12. Beaton, A. A. The relation of planum temporale asymmetry and morphology of the corpus callosum to handedness, gender and dyslexia: a review of the evidence. *Brain and Language*. **60**, 255-322 (1997).
13. Zilles, K., Dabringhaus, A., Geyer, S., Amunts, K., Qu, M., Schleicher, A., Gilissen, E., Schlaug, G. & Steinmetz, H. Structural asymmetries in the human forebrain and the forebrain of non-human primates and rats. *Neurosci Biobehav Rev*. **20(4)**, 593-605 (1996).
14. Witelson, S. F. & Kigar, D. L. Sylvian fissure morphology and asymmetry in men and women: bilateral differences in relation to handedness in men. *J Comp Neurol*. **323**, 326-340 (1992).
15. Coren, S. in *The Left-Hander syndrome- The Causes and Consequences of Left-Handedness* (Free Press, New York, 1992).
16. Desmond, J. E., Sum, J. M., Wagner, A. D., Demb, J. B., Shear, P. K., Glover, G. H., Gabrieli, J. D. & Morrell, M. J. Functional MRI measurement of language lateralization in Wada-tested patients. *Brain*. **118(6)**, 1411-9 (1995).
17. Koff, E., Naeser, M. A., Pieniadz, J. M., Foundas, A. L. & Levine, H. L. Computed tomographic scan hemispheric asymmetries in right- and left-handed male and female subjects. *Arch Neurol*. **43(5)**, 487-91 (1986).
18. Davidson, R. J. & Hugdahl, K. in *Brain asymmetry* (MIT Press, Cambridge, Massachusetts, 1995).
19. Hellige, J. B. in *Hemispheric asymmetry: What's right and what's left* (Harvard Press, 2001)
20. Annett, M. Genetic and nongenetic influences on handedness. *Behaviour Genetics*. **8**, 227-249 (1978).
21. McManus, I. C. & Bryden, M. P. The genetics of handedness, cerebral dominance and lateralization (eds Rapin, I. & Segalowitz, S. J.) *Handbook of Neuropsychology*. **6**, *Developmental Neuropsychology*. **6**, 115-144. (Elsevier Science, Amsterdam, 1992).
22. Grimshaw, G. M., Bryden, M. P. & Finegan, J. K. Relations between prenatal testosterone and cerebral lateralization in children. *Neuropsychology*. **9**, 68-70 (1995).
23. Glick, S. D., Ross, D. A. & Hough, L. B. Lateral asymmetry of neurotransmitters in human brain. *Brain Res*. **234(1)**, 53-63 (1982).
24. Tucker, D. M. & Williamson, P. A. Asymmetric neural control systems in human self-regulation. *Psychological Review*. **91**, 185-215 (1984).
25. Wagner, H. N. Jr, Burns, H. D., Dannals, R. F. & Wong, D. F, et al. Imaging dopamine receptors in the human brain by positron emission tomography. *Science*. **221**, 1264-1266 (1983).
26. Oke, A., Keller, R., Mefford, I. & Adams, R. N. Lateralization of norepinephrine in human thalamus. *Science*. **200(4348)**, 1411-3 (1978).
27. Kimura, D. Cerebral dominance and the perception of verbal stimuli. *Canadian Journal of Psychology*., **15**, 156-165 (1961).
28. Eberstaller, O. Zür Oberflachen Anatomie der Grosshirn Hemisphaeren. *Wien Med*. **7**, 479,642,644 (1884).
29. Galaburda, A., LeMay, M. & Kemper, T. et al. Left-right asymmetries in the brain. *Science*. **199**, 852-856 (1978).

30. Eidelberg, D. & Galaburda, A.M. Symmetry and Asymmetry in the Human Posterior Thalamus: I. Cytoarchitectonic Analysis in Normal Persons. *Arch. Neurol.* **39(6)**, 325-332 (1982).
31. Rosen, G. D. Cellular, morphometric, ontogenetic and connectional substrates of anatomical asymmetry. *Neurosci Biobehav Rev.* **20(4)**, 607-15 Review (1996).
32. Scheibel, A. B., Paul, L.A., Fried, I., Forsythe, A. B., Tomiyasu, U., Wechsler, A., Kao, A. & Slotnick, J. Dendritic organization of the anterior speech area. *Exp Neurol.* **87(1)**, 109-17 (1985).
33. Stromswold, K. The cognitive and neural bases of language acquisition (ed Gazzaniga, M.) *The cognitive neurosciences*. 855-870 (MIT Press, Cambridge, Massachusetts, 1995).
34. Taylor, D. C. Different rates of cerebral maturation between sexes and between hemispheres. *Lancet.* **2**, 140-142 (1969).
35. LeMay, M. Morphological cerebral asymmetries of modern man, fossil man, and nonhuman primate. *Ann N Y Acad Sci.* **280**, 349-66 (1976).
36. LeMay, M. & Kido, D. K. Asymmetries of the cerebral hemispheres on computed tomograms. *Journal of Computer Assisted Tomography.* **2**, 471-6 (1978).
37. Kertesz, A., Black, S. E., Polk, M. & Howell, J. Cerebral asymmetries on magnetic resonance imaging. *Cortex.* **22(1)**, 117-27(1986).
38. Cunningham, D. J. Contribution to the Surface Anatomy of the Cerebral Hemispheres. *Cunningham Memoirs (R. Irish Acad.)*. **7**, 372 (1892).
39. Fleschig, P. Bemerkungen Über die Hörsphäre des Menschlichen Gehirns. *Neurologie Zentral Blatt.* **27**, 2-7 (1908).
40. Habib, M., Robichon, F., Levrier, O., Khalil, R. & Salamon, G. Diverging asymmetries of temporo-parietal cortical areas: a reappraisal of Geschwind/Galaburda theory. *Brain Lang.* **48(2)**, 238-58 (1995).
41. Steinmetz, H. Structure, functional and cerebral asymmetry: in vivo morphometry of the planum temporale. *Neurosci Biobehav Rev.* **20(4)**, 587-91. Review (1996).
42. Kulynych, J., Vldar, K., Jones, D. & Weinberger, D. A 3D surface rendering in MRI morphometry: a study of the planum temporale. *J Comput Assisted Tomogra.* **17**, 529-535 (1993).
43. Narr, K. L., Thompson, P. M., Sharma, T., Moussai, J., Zoumalan, C. I., Rayman, J. & Toga A. W. 3D Mapping of Gyral Shape and Cortical Surface Asymmetries in Schizophrenia: Gender Effects. *Am J Psychiatry.* **158(2)**, 244-255 (2001).
44. Yeni-Komshian, G. H., & Benson, D. A. Anatomical study of cerebral asymmetry in humans, chimpanzees and rhesus monkeys. *Science.* **192**, 387-389 (1976).
45. Falzi, G., Perrone, P. & Vignolo, L. Right-left asymmetry in anterior speech region. *Arch.Neurol.* **39**, 239-240 (1982).
46. Amunts, K., Schleicher, A., Burgel, U., Mohlberg, H., Uylings, H. B. & Zilles, K. Broca's region revisited: cytoarchitecture and intersubject variability. *J Comp Neurol.* **412(2)**, 319-41 (1999).
47. Hochberg, F. & LeMay, M. Arteriographic correlates of handedness. *Neurology.* **25**, 218-222 (1975).
48. Rademacher, J., Caviness, V. S. Jr, Steinmetz, H. & Galaburda, A. M. Topographical Variation of the Human Primary Cortices: Implications for Neuroimaging, Brain Mapping and Neurobiology. *Cerebral Cortex.* **3(4)**, 313-329 (1993).
49. Penhune, V. B., Zatorre, R. J., MacDonald, J. D. & Evans, A. C. Interhemispheric anatomical differences in human primary auditory cortex: probabilistic mapping and volume measurement from magnetic resonance scans. *Cereb Cortex.* **6(5)**, 661-72 (1996).
50. Galaburda, A. M. & Geschwind, N. *Anatomical Asymmetries in the Adult and Developing Brain and their Implications for Function*, *Adv. Pediatr.* **28**, 271-292 (1981).
51. Geschwind, N., & Galaburda, A. M. in *Cerebral Lateralization* (The MIT Press, London, 1987).
52. Sowell, E. R., Thompson, P. M., Rex, D., Kornsand, D., Tessner, K. D., Jernigan, T.L. & Toga, A. W. Mapping sulcal pattern asymmetry and local cortical surface gray matter distribution *in vivo*: Maturation in perisylvian cortices, *Cerebral Cortex.* **12**,17-26 (2002).
53. Thompson, P. M., Giedd, J. N., Woods, R. P., MacDonald, D., Evans, A. C. & Toga, A. W. Growth Patterns in the Developing Brain Detected By Using Continuum-Mechanical Tensor Maps, *Nature.* **404(6774)**, 190-193 (2000a).
54. Highley, J. R., Walker, M. A., Esiri, M. M., Crow, T. J. & Harrison, P. J. Asymmetry of the uncinate fasciculus: a post-mortem study of normal subjects and patients with schizophrenia. *Cereb Cortex.* **12(11)**, 1218-24 (2002).
55. Davatzikos, C. & Bryan, R. N. Morphometric analysis of cortical sulci using parametric ribbons: a study of the central sulcus. *J Comput Assist Tomogr.* **26(2)**, 298-307 (2002).
56. Amunts, K., Schlaug, G., Schleicher, A., Steinmetz, H., Dabringhaus, A., Roland, P. E. & Zilles, K. Asymmetry in the human motor cortex and handedness. *Neuroimage.* **4(3 Pt 1)**, 216-22 (1996).
57. Yakovlev, P. I. & Rakic, P. Patterns of decussation of bulbar pyramids and distribution of pyramidal tracts on two sides of the spinal cord. *Trans. Am. Neurol. Assoc.* **91**, 366-367 (1966).

58. Nudo, R. J., Jenkins, W. M., Merzenich, M. M., Prejean, T. & Grenda, R. Neurophysiological correlates of hand preference in primary motor cortex of adult squirrel monkeys. *J Neurosci.* **12(8)**, 2918-47 (1992).
59. Glick, S. D. & Hinds, P. A. Differences in amphetamine and morphine sensitivity in lateralized and non-lateralized rats: locomotor activity and drug self-administration. *Eur J Pharmacol.* **118(3)**, 239-44 (1985).
60. Nottebohm, F. Neural lateralization of vocal control in a passerine bird. I. Song. *J Exp Zool.* **177(2)**, 229-61 (1971).
61. Petersen, M. R., Beecher, M. D., Zoloth, S. R., Moody, D. B., Stebbins, W. C. Neural lateralization of species-specific vocalizations by Japanese macaques (*Macaca fuscata*). *Science.* **202(4365)**, 324-7 (1978).
62. Witelson, S. F. The brain connection: the corpus callosum is larger in left-handers. *Science.* **229(4714)**, 665-8 (1985).
63. Hardyck, C., Petrinovich, L. F., & Goldman, R. D. Left-handedness and cognitive deficit. *Cortex.* **12(3)**, 266-79 (1976).
64. Aboitiz, F. & Garcia, R. The anatomy of language revisited. *Biol Res.* **30(4)**, 171-83 (1997).
65. Cantalupo, C. & Hopkins, W. D. Asymmetric Broca's area in great apes. *Nature.* **414(6863)**, 505 (2001).
66. Lieberman, P. in *The biology and evolution of language* (Harvard University Press, 1984).
67. Goldin-Meadow, S. & McNeill, D. The role of gesture and mimetic representation in making language the province of speech (eds Corballis, M. C. & Lea, S.) *The Descent of Mind.* (Oxford UP, New York, NY, 1999).
68. Kegl, J. & McWhortner, J. Perspectives on an emerging language (ed Clark, E.) Proceedings of the Stanford Child Language Research Form, 15-36 (Palo Alto: Center for the Study of Language and Information, 1997).
69. Emmorey, K., Damasio, H., McCullough, S., Grabowski, T., Ponto, L. L., Hichwa, R. D. & Bellugi, U. Neural systems underlying spatial language in American Sign Language. *Neuroimage.* **17(2)**, 812-24 (2002).
70. Corballis, M. C. *The Gestural Origins of Language.* *American Scientist.* **87**, 138-145 (1999).
71. Steinmetz, H., Furst, G. & Freund, H. J. Variation of Perisylvian and Calcarine Anatomic Landmarks within Stereotaxic Proportional Coordinates. *Amer. J. Neuroradiol.* **11(6)**, 1123-30 (1990).
72. Thompson, P. M., Moussai, J., Zohoori, S., Goldkorn, A., Khan, A. A., Mega, M. D., Small, G. W., Cummings, J. L. & Toga, A. W. Cortical variability and asymmetry in normal aging and Alzheimer's Disease. *Cereb. Cortex.* **8**, 492-509 (1998).
73. Thompson, P. M., Mega, M. S., Vidal, C., Rapoport, J. L. & Toga, A. W. Detecting Disease-Specific Patterns of Brain Structure using Cortical Pattern Matching and a Population-Based Probabilistic Brain Atlas, IEEE Conference on Information Processing in Medical Imaging (IPMI), UC Davis (2001a).
74. Westbury, C. F., Zatorre, R. J. & Evans, A.C. Quantifying variability in the planum temporale: a probability map. *Cereb Cortex.* **9(4)**, 392-405 (1999).
75. Paus, T., Tomaiuolo, F., Otaky, N., MacDonald, D., Petrides, M., Atlas, J., Morris, R. & Evans, A. C. Human cingulate and paracingulate sulci: pattern, variability, asymmetry, and probabilistic map. *Cereb Cortex.* **6(2)**, 207-14 (1996).
76. Crosson, B., Sadek, J. R., Bobholz, J. A., Gokcay, D., Mohr, C. M., Leonard, C. M., Maron, L., Auerbach, E. J., Browd, S. R., Freeman, A. J., Briggs, R. W. Activity in the paracingulate and cingulate sulci during word generation: an fMRI study of functional anatomy. *Cereb Cortex.* **9(4)**, 307-16 (1999).
77. Good, C. D., Johnsrude, I. S., Ashburner, J., Henson, R. N., Friston, K. J. & Frackowiak, R. S. J. A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage.* **14(1 Pt 1)**, 21-36 (2001).
78. Watkins, K. E., Paus, T., Lerch, J. P., Zijdenbos, A., Collins, D. L., Neelin, P., Taylor, J., Worsley, K. J. & Evans, A. C. Structural asymmetries in the human brain: a voxel-based statistical analysis of 142 MRI scans. *Cereb Cortex.* **11(9)**, 868-77 (2001).
79. Hiscock, M., Inch, R., Jacek, C., Hiscock-Kalil, C., & Kalil, K. M. Is there a sex difference in human laterality? I. An exhaustive survey of auditory laterality studies from six neuropsychology journals. *J Clin Exp Neuropsychol.* **16(3)**, 423-35 (1994).
80. Mazziotta, J. C., Toga, A. W., Evans, A. C., Fox, P. T., Lancaster, J., Zilles, K., Woods, R. P., Paus, T., Simpson, G., Pike, B., Holmes, C. J., Collins, D. L., Thompson, P. M., MacDonald, D., Schormann, T., Amunts, K., Palomero-Gallagher, N., Parsons, L., Narr, K. L., Kabani, N., Le, Goualher, G., Boomsma, D., Cannon, T., Kawashima, R. & Mazoyer, B. A Probabilistic Atlas and Reference System for the Human Brain. *Journal of the Royal Society.* **356(1412)**, 1293-1322 (2001).
81. Thompson, P. M. & Toga, A. W. A Framework for Computational Anatomy [Invited Paper]. *Computing and Visualization in Science.* **5**, 1-12 (2002).
82. Shenton, M. E., Kikinis, R., McCarley, R. W., Metcalf, D., Tieman, J. & Jolesz, F. A. Application of automated MRI volumetric measurement techniques to the ventricular system in schizophrenics and normal controls. *Schizophr Res.* **5(2)**, 103-13 (1991).

83. Chi, G. J., Doaling, E. G. & Gilles, F. H. Left-right asymmetries of the temporal speech areas of the human fetus. *Arch Neurol.* **34**, 346-8 (1977).
84. Previc, F. H. A general theory concerning the prenatal origins of cerebral lateralization in humans. *Psychological Review.* **98(3)**, 299-334 (1991).
85. Kieler, H., Cnattingius, S., Haglund, B., Palmgren, J. & Axelsson, O. Sinistrality--a side-effect of prenatal sonography: a comparative study of young men. *Epidemiology.* **12(6)**, 618-23 (2001).
86. Schlaug, G., Jancke, L., Huang, Y., Staiger, J. F. & Steinmetz, H. Increased corpus callosum size in musicians. *Neuropsychologia.* **33(8)**, 1047-1055 (1995).
87. Keenan, J. P., Thangaraj, V., Halpern, A. R., Schlaug, G. Absolute pitch and planum temporale. *Neuroimage.* **14(6)**, 1402-8 (2001).
88. Thompson, P. M., Cannon, T. D., Narr, K. L., van Erp, T., Khaledy, M., Poutanen, V. P., Huttunen, M., Lönnqvist, J., Standertskjöld-Nordenstam, C. G., Kaprio, J., Dail, R., Zoumalan, C. I. & Toga, A. W. Genetic Influences on Brain Structure. *Nature Neuroscience.* **4(12)**, 1253-8 (2001b).
89. Posthuma, D., De Geus, E. J., Baare, W. F., Hulshoff Pol, H. E., Kahn, R. S. & Boomsma, D. I. The association between brain volume and intelligence is of genetic origin. *Nat Neurosci.* **5(2)**, 83-4 (2002).
90. Lohmann, G., von Cramon, D. Y. & Steinmetz, H. Sulcal variability of twins, *Cereb Cortex.* **9(7)**, 754-63 (1999).
91. Thompson, P. M., Hayashi, K. M., de Zubicaray, G., Janke, A. L., Rose, S. E., Semple, J., Doddrell, D. M., Cannon, T. D. & Toga, A. W. Detecting Dynamic and Genetic Effects on Brain Structure using High-Dimensional Cortical Pattern Matching, *Proc. International Symposium on Biomedical Imaging (ISBI2002)* (Washington, DC, 2002).
92. Plomin, R. & Kosslyn, S. M. Genes, brain and cognition. *Nature Neuroscience.* **4(12)**, 1153-4 (2001).
93. Steinmetz, H., Herzog, A., Huang, Y. & Hacklander, T. Discordant brain-surface anatomy in monozygotic twins. *N Engl J Med.* **331(14)**, 951-2 (1994).
94. Geschwind, D. H., Miller, B. L., DeCarli, C. & Carmelli, D. Heritability of lobar brain volumes in twins supports genetic models of cerebral laterality and handedness. *Proc Natl Acad Sci USA.* **99(5)**, 3176-81 (2002).
95. Satz, P., Orsini, D. L., Saslow, E. & Henry, R. The pathological left-handedness syndrome. *Brain Cogn.* **4(1)**, 27-46 (1985).
96. Corballis, M. C. & Morgan, M. J. On the biological basis of human laterality: I. Evidence for a maturational left-right gradient. *Behavioral and Brain Sciences.* **2**, 261-336 (1978).
97. Geschwind, N., & Behan, P. Left-handedness: association with immune disease, migraine, and developmental learning disorder. *Proceedings of the National Academy of Sciences USA.* **79(16)**, 5097-100 (1982).
98. Laland, K. N., Kumm, J., Van Horn, J. D., Feldman, M. W. A gene-culture model of human handedness. *Behav Genet.* **25(5)**, 433-45 (1995).
99. Shaywitz, B. A., Shaywitz, S. E., Pugh, K. R., Constable, R. T., Skudlarski, P., Fulbright, R. K., Bronen, R. A., Fletcher, J. M., Shankweiler, D. P. & Katz, L., et al. Sex differences in the functional organization of the brain for language. *Nature.* **373(6515)**, 607-9 (1995).
100. Lake, D. A. & Bryden, M. P. Handedness and sex differences in hemispheric asymmetry. *Brain and Language.* **3**, 266-282 (1976).
101. Weekes, N. Y., Zaidel, D. W. & Zaidel, E. The effects of sex and sex role attribution on the right ear advantage in dichotic listening. *Neuropsychology.* **9**, 62-67 (1976).
102. Kimura, D. in *Sex and Cognition* (MIT Press, 2000).
103. Jancke, L., Schlaug, G., Huang, Y. & Steinmetz, H. Asymmetry of the planum parietale. *Neuroreport.* **5(9)**, 1161-3 (1994).
104. Diamond, M. C., Johnson, R. E. & Ingham, C. A. Morphological changes in the young, adult and aging rate cerebral cortex, hippocampus, and diencephalon. *Behav Biol.* **14(2)**, 163-74 (1975).
105. Fleming, D. E., Anderson, R. H., Rhees, R. W., Kinghorn, E. & Bakaitis, J. Effects of prenatal stress on sexually dimorphic asymmetries in the cerebral cortex of the male rat. *Brain Res Bull.* **16(3)**, 395-8 (1986).
106. Witelson, S. F. Neural sexual mosaicism: sexual differentiation of the human temporo-parietal region for functional asymmetry. *Psychoneuroendocrinology.* **16(1-3)**, 131-53 (1991).
107. Diamond, M. C. Hormonal effects on the development of cerebral lateralization. *Psychoneuroendocrinology.* **16**, 121-129 (1991).
108. Benbow, C. P. & Stanley, J. C. Sex differences in mathematical reasoning ability: more facts. *Science.* **222(4627)**, 1029-31 (1983).
109. Oldfield, R. C. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia.* **9(1)**, 97-113 (1971).
110. Gorski, R. A., Harlan, R. E., Jacobson, C. D., Shryne, J. E. & Southam, A. M. Evidence for the existence of a sexually dimorphic nucleus in the preoptic area of the rat. *J Comp Neurol.* **193(2)**, 529-39 (1980).

111. Arnold, A.P. Sexual differentiation of the zebra finch song system: positive evidence, negative evidence, null hypotheses, and a paradigm shift. *J Neurobiol.* **33(5)**, 572-84 (1997).
112. Diaz, E., Pinto-Hamuy, T. & Fernandez, V.. Interhemispheric structural asymmetry induced by a lateralized reaching task in the rat motor cortex. *Eur J Neurosci.* **6(7)**, 1235-8 (1994).
113. Barneoud, P. & Van der Loos, H. Direction of handedness linked to hereditary asymmetry of a sensory system. *Proc Natl Acad Sci U S A.* **90(8)**, 3246-50 (1993).
114. Hynd, G. W., Semrud-Clikeman, M., Lorys, A. R., Novey, E. S. & Eliopoulos, D. Brain morphology in developmental dyslexia and attention deficit-hyperactivity disorder (ADHD): Morphometric analysis of MRI. *Archives of Neurology.* **47**, 919-926 (1990).
115. Larsen, J. P., Hoiem, T., Lundberg, I. & Odegaard, H. MRI evaluation of the size and symmetry of the planum temporale in adolescents with developmental dyslexia. *Brain Lang.* **39(2)**, 289-301 (1990).
116. Galaburda, A. M. *Anatomic Basis of Cerebral Dominance*, in: *Brain Asymmetry* (eds Davidson, R. J., Hugdahl, K.) 51-73 (MIT Press, Boston, 1995).
117. Barinaga, M. Brain researchers speak a common language. *Science.* **270(5241)**, 1437-8 (1995).
118. Crow, T. J., Ball, J. & Bloom, S. R., et al. Schizophrenia as an anomaly of development of cerebral asymmetry. *Arch Gen Psychiatry.* **46**, 1145-1150 (1989).
119. Bilder, R. M., Wu, H., Bogerts, B., Ashtari, M., Robinson, D., Woerner, M., Lieberman, J. A. & Degreef, G. Cerebral volume asymmetries in schizophrenia and mood disorders: a quantitative magnetic resonance imaging study. *Int J Psychophysiol.* **34(3)**, 197-205 (1999).
120. Lennox, B. R., Park, S. B., Jones, P. B., Morris, P. G. & Park, G. Spatial and temporal mapping of neural activity associated with auditory hallucinations. *Lancet.* **353(9153)**, 644 (1999).
121. Risberg, J., Halsey, J. H., Wills, E. L. & Wilson, E. M. Hemispheric specialization in normal man studied by bilateral measurements of the regional cerebral blood flow. A study with the 133-Xe inhalation technique. *Brain.* **98(3)**, 511-24 (1975).
122. Gerendai, I. Lateralization of neuroendocrine control (eds Geschwind, N. & A Galaburda, A. M.) *Cerebral dominance. The biological foundations.* 167-178 (Harvard University Press, Cambridge, Massachusetts, 1984).
123. Thompson, P. M., Mega, M. S., Woods, R. P., Blanton, R. E., Moussai, J., Zoumalan, C. I., Aron, J., Cummings, J. L. & Toga, A. W. Cortical Change in Alzheimer's Disease Detected with a Disease-Specific Population-Based Brain Atlas. *Cerebral Cortex.* **11(1)**, 1-16 (2001c).
124. Thompson, P. M., Hayashi, K. M., de Zubicaray, G., Janke, A. L., Rose, S. E., Semple, J., Dittmer, S., Herman, D., Hong, M. S., Doddrell, D. M. & Toga, A. W. Dynamics of Gray Matter Loss in Alzheimer's Disease. *Journal of Neuroscience* [in press] (2003).
125. Wahlund, L. O., Andersson-Lundman, G., Basun, H., Almkvist, O., Bjorksten, K. S., Saaf, J. & Wetterberg, L. Cognitive functions and brain structures: a quantitative study of CSF volumes on Alzheimer patients and healthy control subjects. *Magnetic Resonance Imaging.* **11(2)**, 169-74 (1993).
126. Loewenstein, D. A., Barker, W. W., Chang, J. Y., Apicella, A., Yoshii, F., Kothari, P., Levin, B. & Duara, R. Predominant left hemisphere metabolic dysfunction in dementia. *Arch. Neurol.* **46**, 146-152 (1989).
127. Penfield, W. & Jasper, H. in *Epilepsy and the Functional Anatomy of the Human Brain* (Boston: Little, Brown, 1954).
128. Ojemann, J. G., Ojemann, G. A. & Lettich, E. Cortical stimulation mapping of language cortex by using a verb generation task: effects of learning and comparison to mapping based on object naming. *J Neurosurg.* **97(1)**, 33-8 (2002).
129. Wada, J. A., Clarke, R. J. & Hamm, A. E. Control speech zones in 100 adult and 100 infant brains. *Arch. Neurol.* **32**, 239-246 (1975).
130. Zatorre, R. J. Perceptual asymmetry on the dichotic fused words test and cerebral speech lateralization determined by the carotid sodium amytal test. *Neuropsychologia.* **27(10)**, 1207-19 (1989).
131. Gordon, H. W. & Bogen, J. E. Hemispheric lateralization of singing after intracarotid sodium amylobarbitone. *J Neurol Neurosurg Psychiatry.* **37(6)**, 727-38 (1974).
132. Foundas, A. L., Leonard, C. M. & Heilman, K. M. Morphologic cerebral asymmetries and handedness. The pars triangularis and planum temporale. Comment in: *Arch Neurol.* **52**, 1137-8 (1995).
133. Bogen, J. E., Fisher, E. D. & Vogel, P. J. Cerebral commissurotomy. *A second case report JAMA.* **194(12)**, 1328-1329 (1965).
134. Gazzaniga, M. S., Eliassen, J. C., Nisenson, L., Wessinger, C. M., Fendrich, R. & Baynes, K. Collaboration between the hemispheres of a callosotomy patient. Emerging right hemisphere speech and the left hemisphere interpreter. *Brain.* **119 (Pt 4)**, 1255-62 (1996).
135. Zaidel, E. & Iacoboni, M. *The Corpus Callosum* (MIT Press, 2002).

136. Deutsch, D. Dichotic listening to melodic patterns and its relation to hemispheric specialization of functions. *Music Perception*. **3**, 127-154 (1985).
137. Jancke, L., Steinmetz, H., & Volkman, J. Dichotic listening: what does it measure? *Neuropsychologia*. **30(11)**, 941-50 (1992).
138. Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J. P., Frith, C. D. & Frackowiak, R. S. J. Statistical Parametric Maps in Functional Imaging: A General Linear Approach. *Human Brain Mapping*. **2**, 189-210 (1995).
139. Tzourio, N., Nkanga-Ngila, B. & Mazoyer, B. Left planum temporale surface correlates with functional dominance during story listening. *Neuroreport*. **9(5)**, 829-33 (1998a).
140. Tzourio, N., Crivello, F., Mellet, E., Nkanga-Ngila, B. & Mazoyer, B. Functional anatomy of dominance for speech comprehension in left handers vs right handers. *Neuroimage*. **8(1)**, 1-16 (1998b).
141. Karbe, H., Wurker, M., Herholz, K., Ghaemi, M., Pietrzyk, U., Kessler, J. & Heiss, W. D. Planum temporale and Brodmann's area 22. Magnetic resonance imaging and high-resolution positron emission tomography demonstrate functional left-right asymmetry. *Arch Neurol*. **52(9)**, 869-74 (1995).
142. Shepard, R. N. & Metzler, J. Mental rotation of three-dimensional objects. *Science*. **171(972)**, 701-3 (1971).
143. Corballis, M. C. & Sergent, J. Imagery in a commissurotomy patient. *Neuropsychologia*. **26(1)**, 13-26 (1988).
144. Dittus, P. L. & Mann, V. A. (1990). Right hemisphere specialization for mental rotation in normals and brain damaged subjects. *Cortex*. **26(2)**, 177-88 (1990).
145. Cohen, M. S., Kosslyn, S. M., Breiter, H. C., DiGirolamo, G. J., Thompson, W. L., Anderson, A. K., Brookheimer, S. Y., Rosen, B. R. & Belliveau, J. W. Changes in cortical activity during mental rotation. A mapping study using functional MRI. *Brain*. **119(1)**, 89-100 (1996).
146. Richter, W., Ugurbil, K., Georgopoulos, A. & Kim, S. G. Time-resolved fMRI of mental rotation. *Neuroreport*. **8(17)**, 3697-702 (1997).
147. Hugdahl, K. Lateralization of cognitive processes in the brain. *Acta Psychol (Amst)*. **105(2-3)**, 211-35. Review (2000).
148. Geschwind, D. H. & Miller, B. L. Molecular approaches to cerebral laterality: development and neurodegeneration. *Am J Med Genet*. **101(4)**, 370-81 (2001).