MAPPING BRAIN ASYMMETRY

Arthur W. Toga and Paul M. Thompson

Brain asymmetry has been observed in animals and humans in terms of structure, function and behaviour. This lateralization is thought to reflect evolutionary, hereditary, developmental, experiential and pathological factors. Here, we review the diverse literature describing brain asymmetries, focusing primarily on anatomical differences between the hemispheres and on the methods that have been used to detect them. Brain-mapping approaches, in particular, can identify and visualize patterns of asymmetry in whole populations, including subtle alterations that occur 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.

PLANUM TEMPORALE
An auditory processing structure that is located in the posterior temporal lobe.

BRODMANN AREA
(BA). Korbinian Brodmann (1868–1918) was an anatomist who divided the cerebral cortex into numbered subdivisions on the basis of cell arrangements, types and staining properties (for example, the dorsolateral prefrontal cortex contains several subdivisions, including BA 46, BA 9 and others). Modern derivatives of his maps are commonly used as the reference system for analysis of brain-imaging findings.

Laboratory of Neuro Imaging, Department of Neurology, Room 4238, Reed Neurological Research Center, UCLA School of Medicine, 710 Westwood Plaza, Los Angeles, California 90095-1769, USA. Correspondence to A.W.T. e-mail: toga@loni.ucla.edu

Most biological systems show some degree of asymmetry[1]. 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 asymmetry[2]. In humans and many other mammals, the two brain hemispheres differ in their anatomy and function. Although a cursory examination of the gross features of the human brain fails to expose profound left–right differences, a careful examination of its structure reveals a variety of asymmetrical 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, might have led to marked volume asymmetries in Broca's speech area, the PLANUM TEMPORALE, and in other structures that are crucial for speech production, perception and motor dominance. Asymmetries in the brain's functional layout, cytoarchitecture and neurochemistry have also been correlated with asymmetrical behavioural traits, such as handedness, auditory perception, motor preferences and sensory acuity. Here, we provide an overview of structural and functional asymmetries of the brain, focusing on anatomical differences between the hemispheres and the methods that have been used to detect them. We begin with a brief consideration of language and handedness, two well-known behaviours that provide clues to the asymmetrical organization of the human brain.

Early models of brain asymmetry

Language. The specialization of the left hemisphere for language was one of the earliest observations of brain asymmetry. Reported in the nineteenth century by Broca[3] and Wernicke[4], language was found to be more severely impaired in response to tumours 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 FIG. 1). By contrast, language comprehension, such as understanding spoken words[7], is confined primarily to the posterior temporal–parietal region, including Wernicke's area (BRODMANN AREA (BA) 39 and BA 40, posterior BA 21 and BA 22, and part of BA 37). Numerous behavioural tasks have further elucidated language circuits, including tests of grammatical processing, semantic knowledge and syntax[5,6,8,9].

Handedness. The relationship between brain asymmetry and handedness has, for some time, sparked considerable interest and debate[10–12]. 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 subtle[13]. Intriguingly, hand preference correlates more strongly with structural and functional asymmetries in language-processing structures, such as the planum temporale and other primary
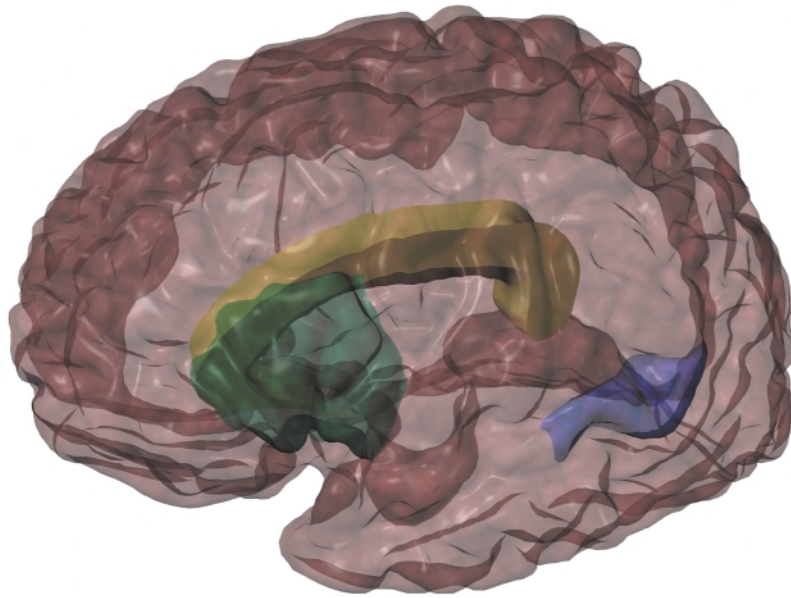
Figure 1 | **Language areas with anatomical and functional asymmetries.** Broca's speech area (green) and Wernicke's language-comprehension area (blue) are identified on a transparent surface model of the human cerebral cortex. All cortical regions are heavily interconnected with corresponding systems in the opposite brain hemisphere, through the corpus callosum (yellow). The language areas show profound asymmetries, both structurally and functionally, the left hemisphere being dominant for language in most right-handed individuals.

auditory and ASSOCIATION CORTICES that surround the Sylvian fissure. Language dominance and handedness are not perfectly correlated either. Right-handers (but not left-handers) typically show a strong leftward specialization for speech and language comprehension[14]. Approximately 97% of right-handers show left-hemisphere speech and language localization, whereas only 3% show right-hemisphere lateralization or bilateral language representation. These relationships shift to 70% and 30%, respectively, in left-handed individuals[15]. So, some right-handed patients have a right-hemisphere dominance for language, whereas left-handers can display a leftward dominance[16].

Clearly, brain asymmetry, language laterality and handedness are interrelated, but in a complex way[17–19]. Many factors affect these gradients, including genetics[20,21], developmental events[22], neurochemical asymmetries[23] (BOX 1), experience and disease.

Macroscopic anatomical asymmetries

Petalia and Yakovlevian torque. Gross anatomical asymmetries in the brain have been observed for over a century[24]. More recently, many structural magnetic resonance imaging (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, and their analysis has even been extended to the microscopic domain (BOX 2).

Among the most prominent observations of brain asymmetry are the right frontal and left occipital PETALIA[25]. These impressions on the inner surface of the skull provide a negative of the brain's surface topology and a signature of regional hemispheric asymmetries. Computed tomography and MRI studies have shown that these petalia are more prominent in right-handers[26,27]. Similar but less pronounced asymmetries have been observed in phylogenetically older primates (and in other species), as evidenced by endocasts from fossilized cranial bones (K. Zilles, personal communication). Asymmetries seen in comparative studies provide strong evidence for phylogenetic origins of brain lateralization. The massive evolutionary expansion of the prefrontal cortex might reflect, in part, its role in speech production.

Although the two hemispheres of the brain are similar in weight and volume, the distribution of tissue differs markedly between them. 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 these frontal and occipital protrusions, is that the right frontal region is often wider than the left, and the left occipital lobe wider than the right. These features of overall brain shape reflect volume differences in frontal

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ASSOCIATION CORTICES
The neocortical regions that are not involved in primary sensory or motor processing. They include frontal areas subserving executive functions, and temporoparietal areas supporting visuospatial processing.

PETALIA
Impressions left on the inner surface of the skull by protrusions of one hemisphere relative to the other. In humans, for example, the right frontal lobe often extends beyond the left anteriorly, and the left occipital lobe beyond the right posteriorly. These asymmetries can be detected in endocasts of fossilized cranial bones.

Box 1 | **Neurochemical asymmetries**

Some investigators have linked chemical asymmetries with the specialized functional roles of the two hemispheres. Tucker and Williamson[131] argued that the left and right hemispheres are relatively rich in processes that depend on dopamine and noradrenaline, respectively. Postmortem studies show a leftward asymmetry in dopamine levels in the globus pallidus[23], as do radioligand positron emission tomography (PET) scans of the basal ganglia[132]. Noradrenergic neurons are also strongly lateralized in the thalamus, being relatively abundant in the right ventrolateral nuclei[133].

Glick *et al.*[23] also noted behavioural asymmetries that mirrored these neurotransmitter differences: dopaminergic drugs, when injected systemically, induced motor changes in rats that caused them to circle strongly in one direction. This behavioural asymmetry was proportional to the asymmetry in dopaminergic activity, and to nigrostriatal dopamine sensitivity. Tucker and Williamson[131] 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 debated[19]. Nonetheless, the idea that specific neurochemical asymmetries lead to cognitive specialization is readily testable. It also leads to tantalizing links between molecular and behavioural asymmetries. Other models of laterality[2,119] indicate that the left hemisphere is specialized for specific types of motor function — verbal and non-verbal — and that the lateralization of language emerged from a leftward dominance over motor function.

Box 2 | **Asymmetries of microscopic anatomy**

Cytoarchitecture

Asymmetries in brain organization are also found at the cellular level. Cytoarchitectural studies by Galaburda *et al.*[134] 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 temporale. This cellular field is implicated in higher-order auditory functions. Similar asymmetries were found for parietal architectonic regions (for example, language area PG[135]). The magnitude of planum temporale asymmetries also correlates negatively with the total size of the planum temporale (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.*[136] found that there were no subsequent hemispheric differences in labelling ratios between left and right sides, regardless of the degree of asymmetry. Cortical area asymmetries were therefore thought to result from earlier asymmetries, before cell labelling, in progenitor cell proliferation (and/or early cell death), rather than from differences in post-migrational cell death (which would have led to subsequent differences in cell labelling). Such studies, tracking cellular changes in cortical development, implicate early developmental events in the formation of asymmetrical cortical areas; specifically, events that occur during progenitor cell proliferation and/or death (that is, before the birth of the first neuron), rather than during later neuroblast division[136].
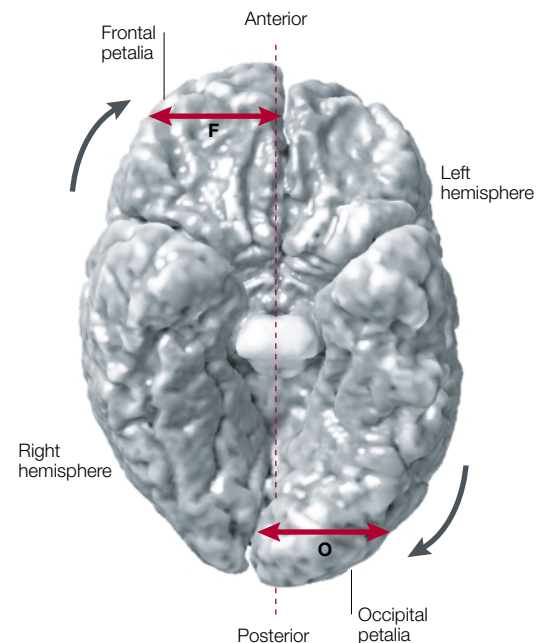
Dendritic arborization

A further provocative finding came in 1985 when Scheibel *et al.*[137] reported that the extent of high-order dendritic branching (high-order branches are thin branches that lie far away from the main dendrite) was greater in the left-hemisphere speech areas (including Broca's area) than in their homologues on the right. However, lower-order dendrites were longer in the right hemisphere. The authors also noted that 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 homologues in their state of development, perhaps to await speech development[138]. The hemispheres might follow separate developmental programmes[86], with a variety of physical asymmetries emerging *in utero*, in childhood and in the teenage years.

Figure 2 | **Petalia and Yakovlevian torque.** This three-dimensional rendering of the inferior surface of a human brain is derived from an *in vivo* magnetic resonance imaging (MRI) scan that has been 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 produce imprints on the inner skull surface, known as petalia. 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 the 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).

(right greater than left) and occipital (left greater than right) regions. Another prominent geometric distortion of the hemispheres is known as YAKOVLEVIAN ANTICLOCKWISE TORQUE[25]. 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, which is established prenatally, is illustrated in FIG. 2.

Perisylvian asymmetry. The asymmetrical trajectory of the Sylvian fissure was one of the first anatomical asymmetries to be described[24,28]. At its posterior limit, the right Sylvian fissure curves upwards more anteriorly than the left, and the left has a gentler slope[10] (FIG. 3). The height of the end-point of the Sylvian fissure is also negatively correlated with the volume of the planum temporale[25]. This region, in the posterior superior temporal lobe, is important for phonological encoding and speech perception, and is the epicentre of a mosaic of left-hemisphere language regions. It analyses the amplitude and frequency of sounds, as well as other acoustic information involved in speech perception. The planum temporale shows a marked leftward volume asymmetry[29] that is related to the

degree of right-handedness[30]. Using an asymmetry index (AI) that corrects for total planum temporale size (AI = (right – left)/0.5(right + left)), Steinmetz[31] analysed 154 MRI scans, and found that right-handers have greater planum temporale asymmetry (mean AI = −0.30 ± 0.28; n = 121), whereas left-handers show a weaker but still leftward asymmetry (mean AI = −0.16 ± 0.31; n = 33). In this study, no gender effects or gender-by-handedness interactions were found, indicating that these are probably subtle, if present[32,33].

Although the left planum temporale is an extension of Wernicke's posterior receptive language area, the planum temporale asymmetry also appears in higher non-human primates (including chimpanzees[34]). Its marked increase in humans points to a link with the evolution of language. In humans, the left planum temporale is up to ten times larger than its right-hemisphere counterpart; this is perhaps the most prominent and functionally significant human brain asymmetry[31]. Broca's speech area is also larger in volume than its homologue in the right hemisphere[35,36].
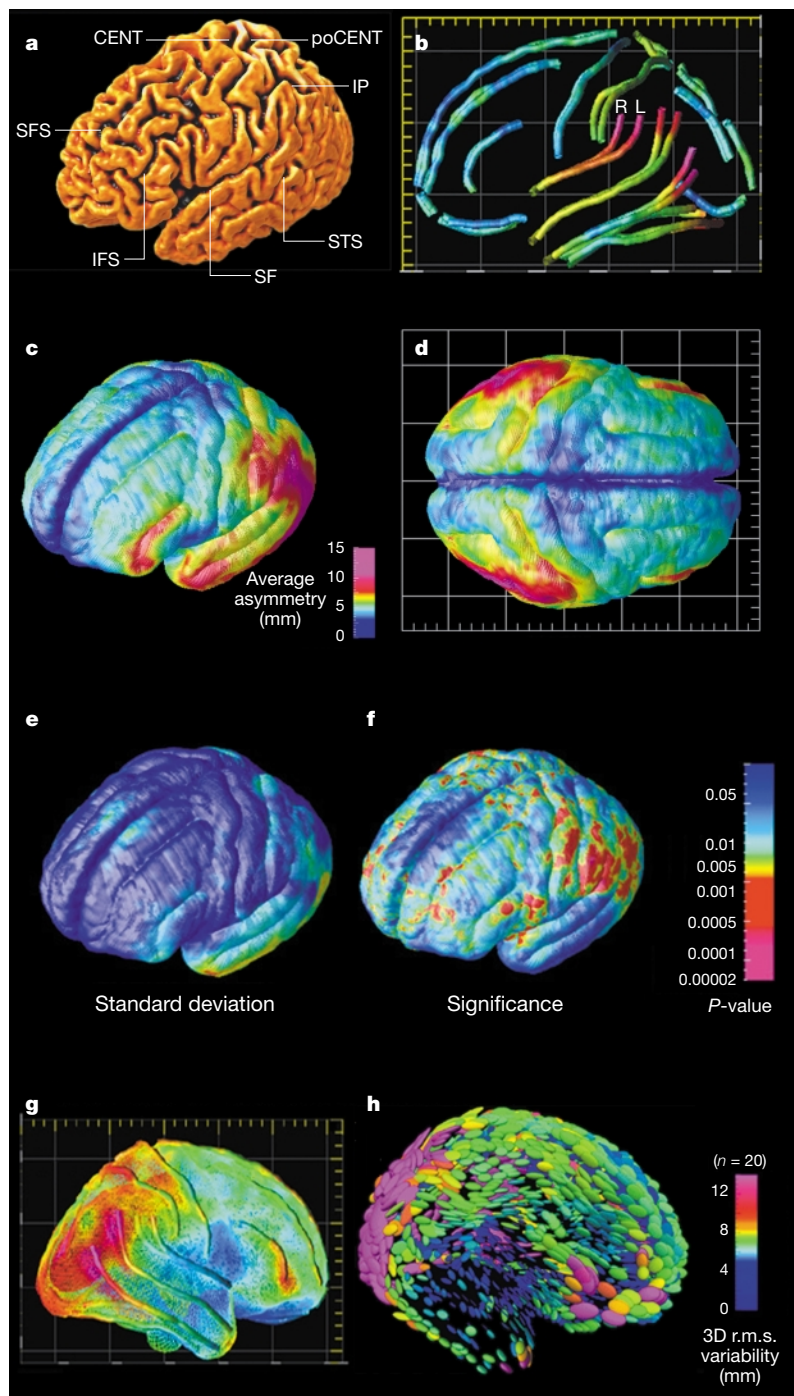
YAKOVLEVIAN ANTICLOCKWISE TORQUE
A double asymmetry of the normal human brain in which the right frontal lobe extends across the midline, over the left, and the left occipital lobe protrudes over the right. The brain thus has the appearance of having been exposed to an anticlockwise twisting force, or torque.

Figure 3 | **Multi-subject maps of brain asymmetry.** Image-analysis techniques make it possible to distinguish systematic asymmetries in a population, or in a specific group of subjects, from random fluctuations in anatomy. **a** | After aligning and scaling individual magnetic resonance imaging (MRI) scans into a standard three-dimensional (3D) space, 3D curves representing the primary sulcal pattern are digitized. Sulci include the central (CENT), postcentral (poCENT), intraparietal (IP), superior frontal (SFS), inferior frontal (IFS) and superior temporal sulci, and the Sylvian fissures (SF). **b** | By averaging these curves across 20 normal subjects, the magnitude of asymmetry in the average anatomy is shown in colour (red colours denote greater asymmetry). R, right; L, left. **c,d** | Extension of these methods to surfaces reveals prominent asymmetries in Broca's anterior speech area and in language regions surrounding the Sylvian fissure. **f** | By comparing the average magnitude of these asymmetries with their standard error — derived from the standard deviation (**e**) — regions of significant asymmetry are identified. **g,h** | Asymmetries are greatest in brain regions with the greatest gyral pattern variability across subjects. The TENSOR MAP (**h**) shows that the preferred directions of intersubject anatomical variability are also approximately aligned with the direction of interhemispheric asymmetry.

The greatest asymmetries of structure are clearly localized to the perisylvian language area. Hochberg and LeMay[37] studied the location of the posterior tip of the Sylvian fissure; they found that it was higher on the right in 67 of the 100 right-handers that they studied, but in only 6 of 28 non-right-handers (21%). HESCHL'S GYRUS is also larger on the left side[38], a feature that can be attributed to greater amounts of underlying white matter on the left[39]. These asymmetries are also found in children[40,41]. Their magnitude increases throughout childhood and the teenage years, even after adjusting for developmental increases in brain volume[42]. This indicates that there might be hemispheric differences in white matter maturation, perhaps during the many regional growth spurts in myelination that occur in childhood[43]. In addition, exposure to gonadal steroid hormones during critical developmental periods might 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 hemisphere[44].

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 females[45]. Positional asymmetries were gender specific, observed only in males. These measures remain controversial, as Amunts *et al.*[46] found the central sulcus to be deeper on the left, in males. Methodological differences and age effects could explain the inconsistencies. Nonetheless, clear motor asymmetries are found in regions that are more proximal to the motor effectors. The right corticospinal 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 subjects[47]. In physiological studies of squirrel monkeys[48], 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 (BOX 3). It is not known at present how extensive these asymmetries are cytoarchitecturally.

Composite brain maps. More recently, digital brain maps have been used to visualize the profile of cortical asymmetries[13,49,50]. FIGURE 3 shows an average representation of the primary sulcal pattern derived from MRI scans of 20 right-handers[51]. Using computational methods, three-dimensional (3D) models of cortical sulci can be reflected in the inter-hemispheric 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 colour-coded map. The degree of asymmetry

Box 3 | **Why is the brain asymmetrical?**

Functional asymmetries in the brain were initially thought to be uniquely human, reflecting unique processing demands required to produce and comprehend language. However, functional and structural asymmetries have been identified in non-human primates and in many other species[139]. Passerine birds produce song primarily under left-hemisphere control[140], and Japanese Macaques have a right-ear advantage for processing auditory stimuli[141]. 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 might be more efficient to transfer language information between a collection of focal areas in a single hemisphere. Asymmetrical brains, for example, have a corpus callosum with a reduced midsagittal area relative to more symmetrical ones[142]. This might reflect fewer and/or thinner fibres connecting the two hemispheres, perhaps owing to differences in axonal pruning. The massive evolutionary expansion of the brain might have resulted in a level of complexity in which the duplication of structures was no longer efficient compared with the specialization of functions within a hemisphere. Time limits in callosal transfer of information between the brain hemispheres, in larger brains, might also have favoured the 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, is also common. In addition, leftward dominance does not, in general, provide a cognitive advantage[143].

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 might have evolved to encompass control of the motor systems involved in speech[2]. 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 Brodmann area 44 (part of Broca's area). This area controls muscles of the face and vocal tract, although it is not as extensively interconnected with the homologue of Wernicke's area as in humans[144]. Cantalupo and Hopkins[145] suggest that non-human primates developed a homologue of Broca's area because of a link between primate vocalization and gesture: captive apes usually gesture with the right hand as they vocalize. Lieberman[146] proposes that language is a relatively recent evolutionary adaptation (not more than 200,000 years old), and 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 Taiwan[147] and in Nicaragua[148] provides some evidence for the innate relationship between gesture and language. Functional neuroimaging studies also indicate that deaf subjects using a gestural sign language might activate many of the systems involved in verbal language production[149]. These congruences in functional anatomy seem to support the hypothesis that verbal language evolved from gestural language as an outgrowth of the already asymmetrical motor control system[150].

differs between 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 can be readily identified (FIG. 3f).

As these maps indicate, the Sylvian fissure is, in general, longer in the left hemisphere. 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 (see above). Nonetheless, the effect is comparatively localized, and perisylvian structures show 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 coordinates[52]. Paus et al.[53] 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 hemisphere[53], a feature that is thought to be linked to the participation of the left anterior cingulate cortex in language tasks. Subsequent functional MRI (fMRI) 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; however, if no paracingulate sulcus was present, these activations spread

into the cingulate sulcus[54]. Group studies of functional anatomy rarely stratify their samples into groups with different normal anatomical variations, but such studies are needed to elucidate how these normal variants affect functional organization and cerebral asymmetries.

Statistical maps. Apart from examining sulci or other features of the brain's surface, VOXEL-based morphometric analyses have further characterized the extent of cerebral asymmetry[55,56]. In this type of study, 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, these approaches are automated and allow studies to be carried out efficiently with large sample numbers. Good et al.[55] found significant asymmetries in the distribution of grey and white matter in the occipital, frontal and temporal lobes, including Heschl's gyrus, the planum temporale and the hippocampus, and Watkins et al.[56] discovered previously undetected volume asymmetries, in both sexes, in the anterior insular cortex (right greater than left). In the largest MRI study to date, Good et al.[55] did not find a relationship between asymmetry and handedness, but did find several gender-related differences. Males had a greater leftward asymmetry in the planum temporale and Heschl's gyrus compared with females, consistent with the idea that brain structure is more lateralized in males than in females[57].

HESCHL'S GYRUS
A division of the superior temporal gyrus that corresponds to the primary auditory cortex.

TENSOR MAP
A map illustrating the principal directions of some multidimensional quantity at each point in space, such as the preferred directions of anatomical variation in a population, or the principal directions of water diffusion in the brain (measured using diffusion tensor imaging).

VOXEL
A volume element: the smallest distinguishable, box-shaped part of a three-dimensional space.
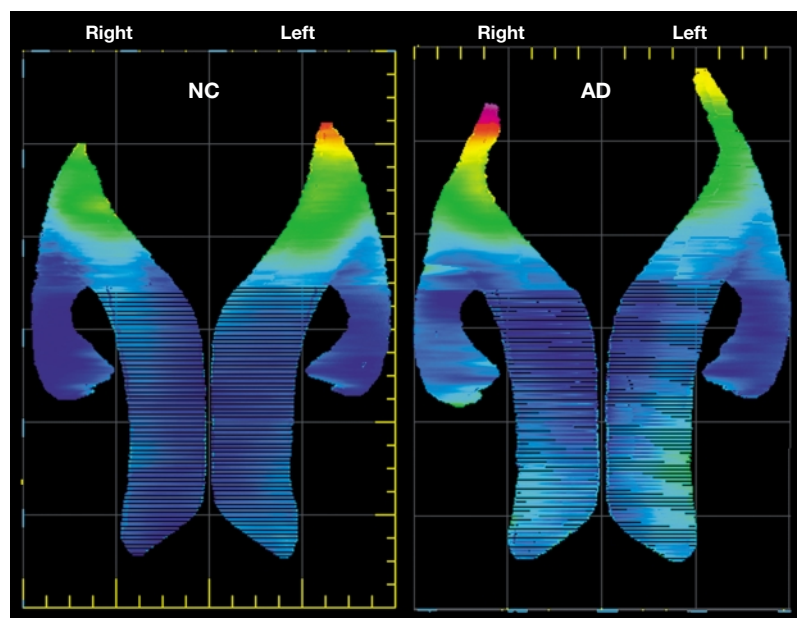
Figure 4 | **Ventricular asymmetry.** The three-dimensional anatomy of the lateral ventricles is combined across subjects to create an average anatomical model. Separate averages are shown, in this case for a group of normal elderly control subjects (NC; n = 20) and a group of age-matched patients with 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 reflects volumetric asymmetries in the overlying language cortices. It could go unnoticed in individual subjects owing to the high intersubject variability of anatomy. Local anatomical variability is shown as a three-dimensional measure of deviation from the group average model (red colours denote regions with greatest anatomical variability).

Mapping asymmetry with brain atlases. Building on these automated methods, digital brain atlases now compile brain data from hundreds or even thousands of subjects[58,59]. These tools empower large-scale studies of brain asymmetry, revealing how factors such as age[42], gender[33] and disease[50] modulate these asymmetries (see below).

Brain structure is so complex and variable that systematic asymmetries can be difficult to localize and to distinguish from random fluctuations. Population-based brain atlases surmount this problem by averaging 3D models of anatomy across subjects, while storing statistics on anatomical variation. FIGURE 4 shows average 3D shape models for the lateral ventricles in two groups of subjects: 26 individuals with Alzheimer's disease and 20 elderly controls. In the average brain maps, a marked ventricular asymmetry emerges in both groups, the left ventricle being visibly larger than the right. (As expected, the ventricles are also significantly enlarged in dementia.) The anatomical asymmetry is clearly localized to the occipital horn, which extends (on average) 5.1 mm posteriorly on the left relative to the right. This is consistent with the petalia and torque effects described above (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 (see, for example, Shenton *et al.*[60]). In normal subjects, occipital horns are (on average) about 17%

larger on the left (4,070 ± 480 mm^3 compared with 3,475 ± 334 mm^3; $P < 0.05$), but no significant asymmetry is observed in the superior or inferior horns ($P > 0.19$ and $P > 0.37$, respectively). This ventricular asymmetry might reflect rapid, asymmetrical growth in the overlying language systems; it can occasionally be seen in the embryonic brain, by ultrasound, as early as 29–31 weeks post conception[61].

Factors that affect anatomical asymmetries

Fetal orientation. Previc[62] suggests that asymmetrical influences in the prenatal environment, even due to fetal posture, might 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 might result from asymmetries in their auditory experience. The right ear might even be better positioned to discriminate high-frequency speech sounds. In an elaborate model of motor dominance, Previc[62] also argues that asymmetrical vestibular stimulation *in utero* might produce behavioural asymmetries later in life. In an intriguing epidemiological study, Kieler *et al.*[63] 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 childhood malignancy or behavioural sequelae.

Heredity and the environment. Embryonic processes that lead to functional and structural asymmetry of the language cortex are the focus of intense study, as their failure might lead to decreased functional specialization of the cortex. Schlaug *et al.*[64] also studied musicians with PERFECT PITCH. In musicians, planar asymmetry was twice as great as in non-musicians, and greatest of all in those with perfect pitch. Exaggerated asymmetries might, therefore, indicate increased capabilities in processing certain auditory features[31]. A follow-up study[65] revealed that the pronounced asymmetry in the perfect-pitch group was attributable to a smaller right (rather than an enlarged left) planum temporale compared with non-musician controls or musicians without perfect pitch. The absolute size of the right planum temporale (not the left) predicted group membership, perhaps indicating neurodevelopmental 'pruning' of the right planum temporale in musicians with perfect pitch. The authors highlighted the possibility of a genetic determination of increased planum temporale asymmetry.

Recent genetic brain-mapping techniques, applied to MRI scan data from identical and fraternal twins, indicate that heredity has an important role in structuring the perisylvian cortex. Grey matter volumes in perisylvian areas are under tight genetic control and are highly heritable[66,67]. Gyral–sulcal patterns appear to be much less heritable[68,69]. Studies of monozygotic

PERFECT PITCH
The ability to identify any musical note without comparing it to a reference note.

twins (who are genetically identical) have yielded low intraclass correlations for the planum temporale AI[31] ($r \leq 0.2$). However, low statistical power might have precluded the detection of these genetic effects[66,70].

Laterality cannot be influenced exclusively by an individual's genotype, as many identical twins are discordant for handedness and differ considerably in planum temporale asymmetry[71]. A recent study of twins who were 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 the genetic control of cerebral volumes in the non-right-handed pairs supports the idea of a 'right shift' genotype[11] that is lost in non-right-handers, resulting in decreased cerebral asymmetry[72]. Whatever the genetic determinants of laterality, many pre- and postnatal (but non-genetic) factors modulate anatomical and functional asymmetries. These include asymmetrical brain damage[73], embryonic position *in utero*[62], chemical and genetic gradients[74], and fetal testosterone effects[75]. Laland *et al.*[76] proposed a population-genetics model of handedness that incorporated 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 a 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 indicating that the male brain might be (on average) more lateralized or asymmetrical than the female brain[77]. In tests designed to assess perceptual asymmetries (see below), some studies report a greater lateralization of auditory or visual processing skills in men than in women[78,79]. Kimura[80] proposes that this might mean either that the functions of the hemispheres are not as sharply differentiated in women as they are in men, or that larger commissural systems in women can act to reduce the difference in response scores between the 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 lesions[80]. Sex differences have also been reported in the structural asymmetry of the planum temporale, with greater asymmetries in males[81], but these findings have been contested. A more robust sex difference appears in the anatomy of the PLANUM PARIETALE, another asymmetrical structure in the parietal lobe, at the posterior end of the Sylvian fissure. This structure is typically larger in the right hemisphere; in right-handers, this asymmetry is greater in men, whereas in left-handers, the asymmetry is greater in women[81]. How these asymmetries relate to differences in visuospatial processing is not yet understood.

PLANUM PARIETALE
An asymmetrical cortical area in the inferior parietal lobule, buried deep in the posterior ascending ramus of the Sylvian fissure. It is anatomicaly adjacent to the planum temporale, an asymmetrical auditory processing structure.

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 show a (statistically nonsignificant) trend towards the opposite pattern[82]. The male asymmetry is established, 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 18 (REF. 83). These findings indicate that levels of androgenic and ovarian sex steroids, before and after birth, have 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 specific[84]. Finally, the masculinizing effect of androgens on male cortical asymmetry seems to be mediated by their conversion to oestrogen, rather than by testosterone acting directly, as the effect is blocked by 1,4,6-androstatriene-3,17-dione, an inhibitor of aromatase, which catalyses the production of oestrogen from androgens[85].

However, it is less clear 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 adults[80]. In their widely cited theory of cerebral lateralization, Geschwind and Galaburda[41] suggested that elevated testosterone effects might be responsible for deviations from the normal dominance pattern (that is, right-handed with 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, owing to a delay of left-hemisphere growth. This model was posited to explain the different maturational rates of the sexes (with females generally maturing faster[86]), the relative male superiority in right-hemisphere visuospatial tasks, and the superior performance of females in left-hemisphere linguistic tasks[87]. It might also explain the greater incidence of left-handedness in males[88]. 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[89,90].

Functional adaptation. Experience-dependent plasticity and asymmetrical behaviours might also induce different neuronal changes in the two hemispheres. In rats, the asymmetrical use of only one forelimb in the post-weaning period induces an asymmetrically larger neuropil volume and lower cell packing density in the motor cortex[91]. In mice with a hereditary asymmetry in their whisker pads, a dominant right whisker pad has been associated with left paw preference[92]. So, limb
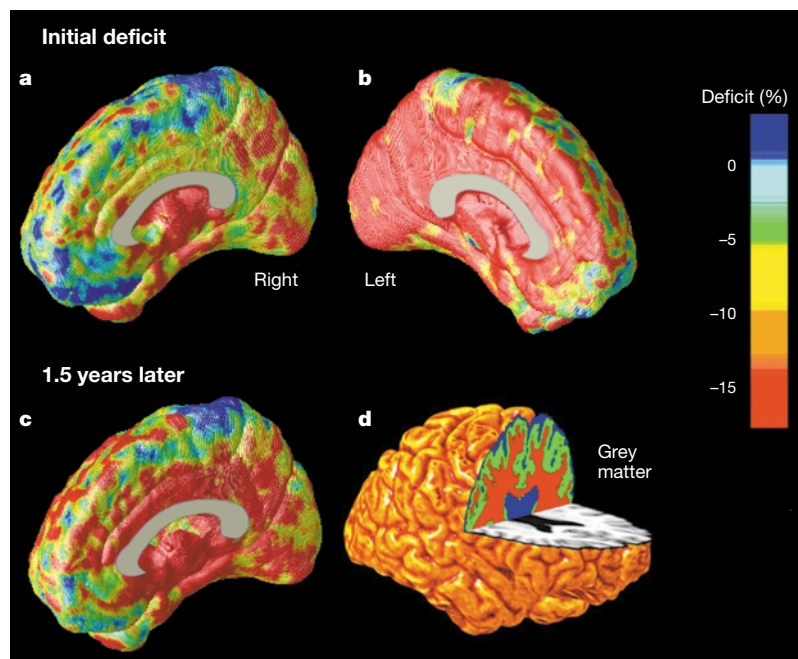
Figure 5 | **Asymmetrical progression of Alzheimer's disease.** These maps show the average profile of grey matter loss in a group of 17 patients with mild to moderate Alzheimer's disease[103]. Average percentage reductions in the local amount of grey matter are plotted, relative to the average values in a group of 14 healthy age- and gender-matched elderly controls. **a–c** | 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**). **d** | Maps of regional grey matter (green) are here computed from magnetic resonance imaging (MRI) brain scans that were acquired longitudinally over a 1.5 year period from both patients and controls.

preference might be associated with asymmetries in sensory input, although it is not known whether this relationship is causal. These findings indicate that some brain asymmetries are not necessarily genetically determined, and could result from lateralized sensory stimulation in pre- and postnatal development.

Aberrant asymmetries and disease. Reduced planum temporale volume asymmetries have been reported in some subjects with reading disorders or developmental dyslexia[93–95], and in people with an unusual right-hemisphere dominance for speech. Hynd *et al.*[93] reported reversed planar asymmetry (that is, a larger right planum temporale) in nine out of ten right-handed dyslexic children who were studied with MRI. Dyslexic individuals with phonological processing deficits also show reduced planum temporale asymmetry[94]. Analogously, fMRI studies have revealed a pattern of brain activation in stutterers that is shifted towards the right in both motor and auditory language areas. This might reflect an inherent difference in the way in which normal subjects and stutterers process language[96]. Controversy surrounds reports of reduced or altered planar asymmetry in schizophrenia[33,97,98]. At the same time, there is great interest in the perisylvian region in schizophrenic patients, as this area houses the primary auditory cortex, which has been implicated in auditory hallucinations[99].

Disease processes might also interact with existing brain asymmetries or exacerbate them. An increased asymmetry of cerebral function in males is thought to

WADA TEST
A test used in surgical patients to determine which brain hemisphere is dominant for language. Intracarotid injection of sodium amytal produces transient anaesthesia in the ipsilateral hemisphere, as well as blockage of speech function if it is the dominant hemisphere.

underlie the greater male incidence of language impairments after stroke, and possibly also the increased incidence of learning disorders in males. The right hemisphere has a larger blood supply overall than the left[100], and there is a higher mortality in cases of similar but right-sided hemispheric lesions[101].

Some diseases also progress asymmetrically. Patients with semantic dementia generally show asymmetrical anterolateral temporal atrophy (typically worse on the left side) with relative sparing of the hippocampal formation. In Alzheimer's disease, a spreading wave of grey matter loss emerges initially in entorhinal and temporal–parietal cortices, sweeping into frontal and ultimately sensorimotor territory as the disease progresses[102,103]. This sequence occurs in both hemispheres, but left-hemisphere regions are affected earlier and more severely. The right hemisphere follows a similar pattern roughly two years later (FIG. 5). Sylvian fissure cerebrospinal fluid volumes also rise more sharply on the left than the right in dementia (32% higher than controls on the left, but only 20% higher on the right[104]). Positron emission tomography (PET) studies also show left-greater-than-right metabolic dysfunction in early dementia[105]. These asymmetries indicate that the left hemisphere might be more susceptible than the right to neurodegeneration in Alzheimer's disease, or that left-hemisphere pathology results in greater structural change and lobar metabolic deficits[105].

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 haemodynamic changes during lateralized behaviours. 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 anaesthesia and recording of the cortex) that are 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 colleagues[106,107] revealed that speech was blocked by electrical stimulation of the left hemisphere, but rarely by that of the right (but see Ojemann *et al.*[108]). 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 TEST[109]. This procedure makes use of an intracarotid injection of sodium amytal to locate speech areas[110]. Transient anaesthesia occurs in the hemisphere ipsilateral to the injection. In the dominant hemisphere, this anaesthesia transiently blocks speech. Aphasic errors occur until speech function is fully recovered. In left-dominant subjects, injection into the right hemisphere affects speech only minimally, but it can affect singing, causing it to become monotone[111]. Language dominance, ascertained by the Wada test,

is also correlated with planum temporale asymmetry[112]. However, even in highly lateralized subjects, some aspects of linguistic function, such as processing the prosodic, 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 humour and metaphor, as well as hesitations and tone of voice.

Split-brain patients. Cognitive tests in split-brain patients have also yielded important information on hemispheric specialization. In these patients, the corpus callosum was surgically resected to control intractable seizures[113]. This also disrupts the communication of perceptual, cognitive, mnemonic, learned and volitional information between the two brain hemispheres[114]. As a result, unique tests can be performed, presenting auditory or visual stimuli selectively to a single, isolated hemisphere[115,116]. While fixating on a central spot on a screen, patients could verbally report words flashed on the right side of the screen (that is, those processed by the left hemisphere). Patients could not repeat verbally words flashed on the left side of the screen (those processed by the right hemisphere), but they could identify them by picking up with the left hand a physical item that matched a word. So, 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 be used to assess functional asymmetries in normal subjects who have not undergone surgery. Typically, these include auditory or visual stimuli that are presented asymmetrically. DICHOTIC LISTENING studies[80,117,118] show that verbal material is more readily analysed if presented to the right ear (which has preferential access to the left hemisphere). Musical material, by contrast, is more effectively analysed if presented to the left ear (right hemisphere). Using dichotic listening to study laterality in auditory processing, Kimura[119] presented digit pairs (1–2, 5–3, and so on) over stereo headsets, sending one digit to one ear and the second digit 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 PET and, more recently, fMRI — have been widely applied to the study of functional asymmetries. With different tracer compounds, PET scans can map rates of regional blood flow, as well as oxygen and glucose use. fMRI can be used to monitor blood flow in real time during cognitive tasks, drawing on the paramagnetic effect of deoxygenated haemoglobin. Statistical mapping techniques[120] can then process these functional images and map task-related fluctuations (in both PET and fMRI), identifying 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 allows brain data to be pooled from multiple studies, and assists in computing group differences and hemispheric asymmetries in cortical activation.

In PET studies of language comprehension (listening to a story), Tzourio *et al.*[121,122] 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 and the temporal poles. The percentage increase in regional cerebral blood flow in the left superior temporal gyrus 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.*[123] 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 temporale asymmetry. These and other brain-mapping studies indicate that widely reported anatomical asymmetries in this region might 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 Shepard–Metzler 'mental rotation' task[124], subjects are shown pairs of perspective drawings of various 3D 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 have found a right-hemisphere laterality effect, with faster reaction times to shapes presented in the left visual field[125,126], indicating dominance of the right-hemisphere. More recent neuroimaging studies[127,128] have implicated mainly the right parietal lobule in this task, in keeping with right-hemisphere dominance, although this is not entirely consistent across subjects (for a review, see REF. 129).

Conclusion

We have surveyed a variety of studies that have examined asymmetries of brain structure and function. In humans, 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 at around 29–31 weeks of gestation. 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 and age, and with a variety of genetic factors and hormonal influences.

DICHOTIC LISTENING
A technique for studying brain asymmetry in auditory processing. The subject is presented simultaneously with different sounds to the right and left ears, and is later tested to determine which, if any, auditory stimulus was more accurately analysed.

Although brain asymmetries have also been identified in animal studies, it might prove difficult to extrapolate from other animals to humans in terms of the lateralization of brain structure and function (BOX 3). For example, it is not yet clear whether precursors of language-related asymmetries in humans are present in other animals, and it is possible that the mechanisms that underlie the development of at least some asymmetrical features of the human brain differ substantially from those that underpin brain asymmetries in other animals. In future studies, it will be important to compare data, where possible, from human neuroimaging, cognitive and animal studies.

Studies of the molecular mechanisms that are involved in the formation of brain asymmetries are in their infancy[130]. Future investigations 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 allow us to measure and visualize asymmetrical patterns of structure and function, revealing how they vary in entire populations. Large-scale neuroimaging analyses can also be carried out to optimize the detection of asymmetrical 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 could ultimately be used to discover and explore genetic, demographic and maturational events that have a role in the determination of brain asymmetry.

1. Geschwind, N. & Galaburda, A. M. Cerebral lateralization. Biological mechanisms, associations, and pathology. *Arch. Neurol.* **42**, 428–459 (1985).
2. Kimura, D. The asymmetry of the human brain. *Sci. Am.* **228**, 70–78 (1973).
3. Broca, P. Remarques sur le siège de la faculté du langage articulé, suivies d'une observation d'aphémie (perte de la parole). *Bull. Soc. Anthropol.* **6**, (1861).
4. Wernicke, C. Der aphasische Symptomenkomplex: eine psychologische Studie auf anatomischer Basis (Cohn und Welgert, Breslau, 1874).
5. Dapretto, M. & Bookheimer, S. Y. Form and content: dissociating syntax and semantics in sentence comprehension. *Neuron* **24**, 427–432 (1999).
6. Binder, J. The new neuroanatomy of speech perception. *Brain* **123**, 2371–2372 (2000).
7. Price, C. J. The anatomy of language: contributions from functional neuroimaging. *J. Anat.* **197**, 335–359 (2000).
8. Zatorre, R. J. On the representation of multiple languages in the brain: old problems and new directions. *Brain Lang.* **36**, 127–147 (1989).
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**, 21–32 (2002).
10. Geschwind, N. & Levitsky, W. Human brain: left–right asymmetries in temporal speech region. *Science* **161**, 186–187 (1968).
    This seminal report observed anatomical asymmetries in perisylvian brain structures that are involved in language. It ignited the interest in anatomical asymmetry, using post-mortem and imaging methods.
11. Annett, M. *Left, Right, Hand and Brain: the Right Shift Theory* (Lawrence Erlbaum, London, 1985).
    This book proposed the influential 'right shift' theory of handedness and cerebral dominance. This theory proposes that handedness is determined by a single 'right-shift' gene, the dominant allele of which produces a bias towards right-handedness and left-hemisphere dominance for language.
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 Lang.* **60**, 255–322 (1997).
13. Zilles, K. *et al.* Structural asymmetries in the human forebrain and the forebrain of non-human primates and rats. *Neurosci. Biobehav. Rev.* **20**, 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. *The Left-Hander Syndrome: the Causes and Consequences of Left-Handedness* (Free Press, New York, 1992).
16. Desmond, J. E. *et al.* Functional MRI measurement of language lateralization in Wada-tested patients. *Brain* **118**, 1411–1419 (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**, 487–491 (1986).

18. Davidson, R. J. & Hugdahl, K. (eds) *Brain Asymmetry* (MIT Press, Cambridge, Massachusetts, 1995).
19. Hellige, J. B. *Hemispheric Asymmetry: What's Right and What's Left* (Harvard Univ. Press, Cambridge, Massachusetts, 2001).
    This book provides an overview of hemispheric asymmetry. Surveying extensive data in the cognitive sciences, it explores whether hemispheric asymmetry is unique to humans, and discusses models of brain lateralization and how it might have evolved.
20. Annett, M. Genetic and nongenetic influences on handedness. *Behav. Genet.* **8**, 227–249 (1978).
21. McManus, I. C. & Bryden, M. P. in *Handbook of Neuropsychology* Vol. 6 (eds Rapin, I. & Segalowitz, S. J.) 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**, 53–63 (1982).
24. Eberstaller, O. Zür Oberflachen Anatomie der Grosshirn Hemisphaeren. *Wien. Med.* **7**, 479, 642, 644 (1884).
25. LeMay, M. Morphological cerebral asymmetries of modern man, fossil man, and nonhuman primate. *Ann. NY Acad. Sci.* **280**, 349–366 (1976).
26. LeMay, M. & Kido, D. K. Asymmetries of the cerebral hemispheres on computed tomograms. *J. Comput. Assist. Tomogr.* **2**, 471–476 (1978).
27. Kertesz, A., Black, S. E., Polk, M. & Howell, J. Cerebral asymmetries on magnetic resonance imaging. *Cortex* **22**, 117–127 (1986).
28. Cunningham, D. J. Contribution to the surface anatomy of the cerebral hemispheres. *Cunningham Mem. (R. Ir. Acad.)* **7**, 372 (1892).
29. Fleschig, P. Bemerkungen über die Hörsphare des menschlichen Gehirns. *Neurol. Zent. Bl.* **27**, 2–7 (1908).
30. 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**, 238–258 (1995).
31. Steinmetz, H. Structure, functional and cerebral asymmetry: *in vivo* morphometry of the planum temporale. *Neurosci. Biobehav. Rev.* **20**, 587–591 (1996).
32. Kulynych, J., Vladar, K., Jones, D. & Weinberger, D. A 3D surface rendering in MRI morphometry: a study of the planum temporale. *J. Comput. Assist. Tomogr.* **17**, 529–535 (1993).
33. Narr, K. L. *et al.* 3D mapping of gyral shape and cortical surface asymmetries in schizophrenia: gender effects. *Am. J. Psychiatry* **158**, 244–255 (2001).
34. Yeni-Komshian, G. H. & Benson, D. A. Anatomical study of cerebral asymmetry in humans, chimpanzees and rhesus monkeys. *Science* **192**, 387–389 (1976).
35. Falzi, G., Perrone, P. & Vignolo, L. Right–left asymmetry in anterior speech region. *Arch. Neurol.* **39**, 239–240 (1982).
36. Amunts, K. *et al.* Broca's region revisited: cytoarchitecture and intersubject variability. *J. Comp. Neurol.* **412**, 319–341 (1999).
37. Hochberg, F. & LeMay, M. Arteriographic correlates of handedness. *Neurology* **25**, 218–222 (1975).

38. 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. *Cereb. Cortex* **3**, 313–329 (1993).
39. 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**, 661–672 (1996).
40. Galaburda, A. M. & Geschwind, N. Anatomical asymmetries in the adult and developing brain and their implications for function. *Adv. Pediatr.* **28**, 271–292 (1981).
41. Geschwind, N. & Galaburda, A. M. *Cerebral Lateralization* (MIT Press, Cambridge, Massachusetts, 1987).
42. Sowell, E. R. *et al.* Mapping sulcal pattern asymmetry and local cortical surface gray matter distribution *in vivo*: maturation in perisylvian cortices. *Cereb. Cortex* **12**, 17–26 (2002).
43. Thompson, P. M. *et al.* Growth patterns in the developing brain detected by using continuum-mechanical tensor maps. *Nature* **404**, 190–193 (2000).
44. 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**, 1218–1224 (2002).
45. Davatzikos, C. & Bryan, R. N. Morphometric analysis of cortical sulci using parametric ribbons: a study of the central sulcus. *J. Comput. Assist. Tomogr.* **26**, 298–307 (2002).
46. Amunts, K. *et al.* Asymmetry in the human motor cortex and handedness. *Neuroimage* **4**, 216–222 (1996).
47. 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).
48. 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**, 2918–2947 (1992).
49. Steinmetz, H., Furst, G. & Freund, H. J. Variation of perisylvian and calcarine anatomic landmarks within stereotaxic proportional coordinates. *Am. J. Neuroradiol.* **11**, 1123–1130 (1990).
50. Thompson, P. M. *et al.* Cortical variability and asymmetry in normal aging and Alzheimer's disease. *Cereb. Cortex* **8**, 492–509 (1998).
51. 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. *Proc. IEEE Conf. Inf. Process. Med. Imaging (IPMI)* (Univ. California, Davis, 2001).
52. Westbury, C. F., Zatorre, R. J. & Evans, A. C. Quantifying variability in the planum temporale: a probability map. *Cereb. Cortex* **9**, 392–405 (1999).
53. Paus, T. *et al.* Human cingulate and paracingulate sulci: pattern, variability, asymmetry, and probabilistic map. *Cereb. Cortex* **6**, 207–214 (1996).
54. Crosson, B. *et al.* Activity in the paracingulate and cingulate sulci during word generation: an fMRI study of functional anatomy. *Cereb. Cortex* **9**, 307–316 (1999).
55. Good, C. D. *et al.* A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* **14**, 21–36 (2001).

56. Watkins, K. E. *et al.* Structural asymmetries in the human brain: a voxel-based statistical analysis of 142 MRI scans. *Cereb. Cortex* **11**, 868–877 (2001).

57. 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**, 423–435 (1994).

58. Mazziotta, J. C. *et al.* A probabilistic atlas and reference system for the human brain. *Phil. Trans. R. Soc. Lond. B* **356**, 1293–1322 (2001).
This paper describes the efforts of an international consortium to build an image database of the human brain that encodes statistical information on anatomical and functional variation. The resulting reference system stores brain maps from multiple imaging devices, and can be used to assess group differences in brain structure and function, as well as hemispheric asymmetries in these measures.

59. Thompson, P. M. & Toga, A. W. A framework for computational anatomy. *Comput. Vis. Sci.* **5**, 1–12 (2002).

60. Shenton, M. E. *et al.* Application of automated MRI volumetric measurement techniques to the ventricular system in schizophrenics and normal controls. *Schizophr. Res.* **5**, 103–113 (1991).

61. Chi, G. J., Doaling, E. G. & Gilles, F. H. Left–right asymmetries of the temporal speech areas of the human fetus. *Arch. Neurol.* **34**, 346–348 (1977).

62. Previc, F. H. A general theory concerning the prenatal origins of cerebral lateralization in humans. *Psychol. Rev.* **98**, 299–334 (1991).

63. 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**, 618–623 (2001).

64. Schlaug, G., Jäncke, L., Huang, Y., Staiger, J. F. & Steinmetz, H. Increased corpus callosum size in musicians. *Neuropsychologia* **33**, 1047–1055 (1995).

65. Keenan, J. P., Thangaraj, V., Halpern, A. R. & Schlaug, G. Absolute pitch and planum temporale. *Neuroimage* **14**, 1402–1408 (2001).

66. Thompson, P. M. *et al.* Genetic influences on brain structure. *Nature Neurosci.* **4**, 1253–1258 (2001).
This paper was the first to create maps of genetic influences on human brain structure. It showed that the amount of grey matter in the frontal cortex was highly heritable and correlated with IQ. It discusses hemispheric asymmetries in these heritability patterns.

67. Posthuma, D. *et al.* The association between brain volume and intelligence is of genetic origin. *Nature Neurosci.* **5**, 83–84 (2002).

68. Lohmann, G., von Cramon, D. Y. & Steinmetz, H. Sulcal variability of twins. *Cereb. Cortex* **9**, 754–763 (1999).

69. Thompson, P. M. *et al.* Detecting dynamic and genetic effects on brain structure using high-dimensional cortical pattern matching. *Proc. Int. Symp. Biomed. Imaging (ISBI2002)* (Washington DC, 2002).

70. Plomin, R. & Kosslyn, S. M. Genes, brain and cognition. *Nature Neurosci.* **4**, 1153–1154 (2001).

71. Steinmetz, H., Herzog, A., Huang, Y. & Hacklander, T. Discordant brain-surface anatomy in monozygotic twins. *N. Engl. J. Med.* **331**, 951–952 (1994).

72. 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**, 3176–3181 (2002).

73. Satz, P., Orsini, D. L., Saslow, E. & Henry, R. The pathological left-handedness syndrome. *Brain Cogn.* **4**, 27–46 (1985).

74. Corballis, M. C. & Morgan, M. J. On the biological basis of human laterality: I. Evidence for a maturational left–right gradient. *Behav. Brain Sci.* **2**, 261–336 (1978).

75. Geschwind, N. & Behan, P. Left-handedness: association with immune disease, migraine, and developmental learning disorder. *Proc. Natl Acad. Sci. USA* **79**, 5097–6100 (1982).

76. Laland, K. N., Kumm, J., Van Horn, J. D. & Feldman, M. W. A gene-culture model of human handedness. *Behav. Genet.* **25**, 433–445 (1995).

77. Shaywitz, B. A. *et al.* Sex differences in the functional organization of the brain for language. *Nature* **373**, 607–609 (1995).

78. Lake, D. A. & Bryden, M. P. Handedness and sex differences in hemispheric asymmetry. *Brain Lang.* **3**, 266–282 (1976).

79. 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).

80. Kimura, D. *Sex and Cognition* (MIT Press, Cambridge, Massachusetts, 2000).
This book provides an overview of studies that assess sex differences in brain structure and function.

81. Jäncke, L., Schlaug, G., Huang, Y. & Steinmetz, H. Asymmetry of the planum parietale. *Neuroreport* **5**, 1161–1163 (1994).

82. 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**, 163–174 (1975).

83. 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**, 395–398 (1986).

84. Witelson, S. F. Neural sexual mosaicism: sexual differentiation of the human temporo-parietal region for functional asymmetry. *Psychoneuroendocrinology* **16**, 131–153 (1991).

85. Diamond, M. C. Hormonal effects on the development of cerebral lateralization. *Psychoneuroendocrinology* **16**, 121–129 (1991).

86. Taylor, D. C. Different rates of cerebral maturation between sexes and between hemispheres. *Lancet* **2**, 140–142 (1969).

87. Benbow, C. P. & Stanley, J. C. Sex differences in mathematical reasoning ability: more facts. *Science* **222**, 1029–1031 (1983).

88. Oldfield, R. C. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* **9**, 97–113 (1971).

89. 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**, 529–539 (1980).

90. Arnold, A. P. Sexual differentiation of the zebra finch song system: positive evidence, negative evidence, null hypotheses, and a paradigm shift. *J. Neurobiol.* **33**, 572–584 (1997).

91. 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**, 1235–1238 (1994).

92. Barneoud, P. & Van der Loos, H. Direction of handedness linked to hereditary asymmetry of a sensory system. *Proc. Natl Acad. Sci. USA* **90**, 3246–3250 (1993).

93. Hynd, G. W., Semrud-Clikeman, M., Lorys, A. R., Novey, E. S. & Eliopulos, D. Brain morphology in developmental dyslexia and attention deficit–hyperactivity disorder (ADHD): morphometric analysis of MRI. *Arch. Neurol.* **47**, 919–926 (1990).

94. Larsen, J. P., Hoien, T., Lundberg, I. & Odegaard, H. MRI evaluation of the size and symmetry of the planum temporale in adolescents with developmental dyslexia. *Brain Lang.* **39**, 289–301 (1990).

95. Galaburda, A. M. in *Brain Asymmetry* (eds Davidson, R. J. & Hugdahl, K.) 51–73 (MIT Press, Cambridge, Massachusetts, 1995).

96. Barinaga, M. Brain researchers speak a common language. *Science* **270**, 1437–1438 (1995).

97. Crow, T. J. *et al.* Schizophrenia as an anomaly of development of cerebral asymmetry. *Arch. Gen. Psychiatry* **46**, 1145–1150 (1989).
This paper describes a theory that suggests that the symptoms of people with schizophrenia might result, in part, from disturbances of cerebral lateralization.

98. Bilder, R. M. *et al.* Cerebral volume asymmetries in schizophrenia and mood disorders: a quantitative magnetic resonance imaging study. *Int. J. Psychophysiol.* **34**, 197–205 (1999).

99. 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**, 644 (1999).

100. 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**, 511–524 (1975).

101. Gerendai, I. in *Cerebral Dominance: the Biological Foundations* (eds Geschwind, N. & Galaburda, A. M.) 167–178 (Harvard Univ. Press, Cambridge, Massachusetts, 1984).

102. Thompson, P. M. *et al.* Cortical change in Alzheimer's disease detected with a disease-specific population-based brain atlas. *Cereb. Cortex* **11**, 1–16 (2001).

103. Thompson, P. M. *et al.* Dynamics of gray matter loss in Alzheimer's disease. *J. Neurosci.* (in the press).

104. Wahlund, L. O. *et al.* Cognitive functions and brain structures: a quantitative study of CSF volumes on Alzheimer patients and healthy control subjects. *Magn. Reson. Imaging* **11**, 169–174 (1993).

105. Loewenstein, D. A. *et al.* Predominant left hemisphere metabolic dysfunction in dementia. *Arch. Neurol.* **46**, 146–152 (1989).

106. Penfield, W. & Jasper, H. *Epilepsy and the Functional Anatomy of the Human Brain* (Little, Brown & Co., Boston, 1954).

107. Penfield, W. The electrode, the brain and the mind. *Z. Neurol.* **201**, 297–307 (1972).

108. 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**, 33–38 (2002).

109. 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).
This paper describes the sodium amytal test (also known as the Wada test), which determines cerebral dominance in surgical patients by using selective anaesthesia of one brain hemisphere.

110. Zatorre, R. J. Perceptual asymmetry on the dichotic fused words test and cerebral speech lateralization determined by the carotid sodium amytal test. *Neuropsychologia* **27**, 1207–1219 (1989).

111. Gordon, H. W. & Bogen, J. E. Hemispheric lateralization of singing after intracarotid sodium amylobarbitone. *J. Neurol. Neurosurg. Psychiatry* **37**, 727–738 (1974).

112. Foundas, A. L., Leonard, C. M. & Heilman, K. M. Morphological cerebral asymmetries and handedness. The pars triangularis and planum temporale. *Arch. Neurol.* **52**, 1137–1138 (1995).

113. Sperry, R. Consciousness, personal identity and the divided brain. *Neuropsychologia* **22**, 661–673 (1984).

114. Bogen, J. E., Fisher, E. D. & Vogel, P. J. Cerebral commissurotomy: a second case report. *J. Am. Med. Assoc.* **194**, 1328–1329 (1965).

115. Gazzaniga, M. S. *et al.* Collaboration between the hemispheres of a callosotomy patient. Emerging right hemisphere speech and the left hemisphere interpreter. *Brain* **119**, 1255–1262 (1996).

116. Zaidel, E. & Iacoboni, M. *The Parallel Brain: the Cognitive Neuroscience of the Corpus Callosum* (MIT Press, Cambridge, Massachusetts, 2002).

117. Deutsch, D. Dichotic listening to melodic patterns and its relation to hemispheric specialization of functions. *Music Percept.* **3**, 127–154 (1985).

118. Jäncke, L., Steinmetz, H. & Volkmann, J. Dichotic listening: what does it measure? *Neuropsychologia* **30**, 941–950 (1992).

119. Kimura, D. Cerebral dominance and the perception of verbal stimuli. *Can. J. Psychol.* **15**, 156–165 (1961).

120. Friston, K. J. *et al.* Statistical parametric maps in functional imaging: a general linear approach. *Hum. Brain Mapp.* **2**, 189–210 (1995).

121. Tzourio, N., Nkanga-Ngila, B. & Mazoyer, B. Left planum temporale surface correlates with functional dominance during story listening. *Neuroreport* **9**, 829–833 (1998).

122. 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**, 1–16 (1998).

123. Karbe, H. *et al.* Planum temporale and Brodmann's area 22. Magnetic resonance imaging and high-resolution positron emission tomography demonstrate functional left–right asymmetry. *Arch. Neurol.* **52**, 869–874 (1995).

124. Shepard, R. N. & Metzler, J. Mental rotation of three-dimensional objects. *Science* **171**, 701–703 (1971).

125. Corballis, M. C. & Sergent, J. Imagery in a commissurotomized patient. *Neuropsychologia* **26**, 13–26 (1988).

126. Ditunno, P. L. & Mann, V. A. Right hemisphere specialization for mental rotation in normals and brain damaged subjects. *Cortex* **26**, 177–188 (1990).

127. Cohen, M. S. *et al.* Changes in cortical activity during mental rotation. A mapping study using functional MRI. *Brain* **119**, 89–100 (1996).

128. Richter, W., Ugurbil, K., Georgopoulos, A. & Kim, S. G. Time-resolved fMRI of mental rotation. *Neuroreport* **8**, 3697–3702 (1997).

129. Hugdahl, K. Lateralization of cognitive processes in the brain. *Acta. Psychol.* **105**, 211–235 (2000).

130. Geschwind, D. H. & Miller, B. L. Molecular approaches to cerebral laterality: development and neurodegeneration. *Am. J. Med. Genet.* **101**, 370–381 (2001).
This paper reviews molecular biological techniques to investigate the genetic and epigenetic mechanisms that underlie brain asymmetry.

131. Tucker, D. M. & Williamson, P. A. Asymmetric neural control systems in human self-regulation. *Psychol. Rev.* **91**, 185–215 (1984).

132. Wagner, H. N. Jr *et al.* Imaging dopamine receptors in the human brain by positron emission tomography. *Science* **221**, 1264–1266 (1983).

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133. Oke, A., Keller, R., Mefford, I. & Adams, R. N. Lateralization of norepinephrine in human thalamus. *Science* **200**, 1411–1413 (1978).
134. Galaburda, A. *et al.* Left–right asymmetries in the brain. *Science* **199**, 852–856 (1978).
135. Eidelberg, D. & Galaburda, A. M. Symmetry and asymmetry in the human posterior thalamus: I. Cytoarchitectonic analysis in normal persons. *Arch. Neurol.* **39**, 325–332 (1982).
136. Rosen, G. D. Cellular, morphometric, ontogenetic and connectional substrates of anatomical asymmetry. *Neurosci. Biobehav. Rev.* **20**, 607–615 (1996).
    In this paper, the developmental processes that result in anatomical asymmetries are assessed by labelling migrating cells during cortical neurogenesis.
137. Scheibel, A. B. *et al.* Dendritic organization of the anterior speech area. *Exp. Neurol.* **87**, 109–117 (1985).
138. Stromswold, K. in *The Cognitive Neurosciences* (ed. Gazzaniga, M. S.) 855–870 (MIT Press, Cambridge, Massachusetts, 1995).
139. 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**, 239–244 (1985).
140. Nottebohm, F. Neural lateralization of vocal control in a passerine bird. I. Song. *J. Exp. Zool.* **177**, 229–261 (1971).
141. 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**, 324–327 (1978).
142. Witelson, S. F. The brain connection: the corpus callosum is larger in left-handers. *Science* **229**, 665–668 (1985).
143. Hardyck, C., Petrinovich, L. F. & Goldman, R. D. Left-handedness and cognitive deficit. *Cortex* **12**, 266–279 (1976).
144. Aboitiz, F. & Garcia, R. The anatomy of language revisited. *Biol. Res.* **30**, 171–183 (1997).
145. Cantalupo, C. & Hopkins, W. D. Asymmetric Broca's area in great apes. *Nature* **414**, 505 (2001).
146. Lieberman, P. *The Biology and Evolution of Language* (Harvard Univ. Press, Cambridge, Massachusetts, 1984).
147. Goldin-Meadow, S. & McNeill, D. in *The Descent of Mind: Psychological Perspectives on Hominid Evolution* (eds Corballis, M. C. & Lea, S.) 155–172 (Oxford Univ. Press, New York, 1999).
148. Kegl, J. & McWhortner, J. Perspectives on an emerging language. *Proc. Stanford Child Lang. Res. Form* (ed. Clark, E.) 15–36 (Center for the Study of Language and Information, Palo Alto, California, 1997).
149. Emmorey, K. *et al.* Neural systems underlying spatial language in American sign language. *Neuroimage* **17**, 812–824 (2002).
150. Corballis, M. C. The gestural origins of language. *Am. Sci.* **87**, 138–145 (1999).

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