Molecular approaches to brain asymmetry and handedness

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Abstract | In the human brain, distinct functions tend to be localized in the left or right hemispheres, with language ability usually localized predominantly in the left and spatial recognition in the right. Furthermore, humans are perhaps the only mammals who have preferential handedness, with more than 90% of the population more skilful at using the right hand, which is controlled by the left hemisphere. How is a distinct function consistently localized in one side of the human brain? Because of the convergence of molecular and neurological analysis, we are beginning to consider the puzzle of brain asymmetry and handedness at a molecular level.

Protomap model
Proposed by Pasko Rakic. He suggested that regionalization is mainly controlled by molecular determinants that are intrinsic to the proliferative zone of the neocortex. The 'proliferative units' in the ventricular zone form a protomap of prospective cortical regions. Postmitotic neurons migrating from the ventricular zone maintain the regional properties of the proliferative units.

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The human brain is a complex structure that controls sophisticated cognitive behaviour. Anatomically, the cerebral cortex is divided into frontal, temporal, parietal and occipital lobes, and these regions control thinking, language, movement, sensation, vision and other functions. The formation of these distinct functional regions during cortical development is called regionalization (or arealization)[1–4]. Two models for the formation of cortical functional regions have been proposed[5–7]. The protomap model suggests that intrinsic signals from the 'proliferative units' in the ventricular zone regulate functional regionalization, whereas the protocortex model argues the importance of extrinsic influences, such as the thalamocortical inputs[5–7]. Accumulating evidence indicates that both models are applicable to the regulation of cortical patterning and the establishment of cortical regionalization[2–4].

The cerebral cortex is also divided into left and right hemispheres. The left hemisphere is normally dominant for language and logical processing, whereas the right hemisphere is specified for spatial recognition[8,9]. Additionally, the segregation of human brain functions between the left and right hemispheres is associated with asymmetries of anatomical structures, such as the Sylvian fissures and the planum temporale[10,11]. One of the striking features of motor control in humans is that more than 90% of the population is more skilful with the right hand, which is controlled by the left hemisphere[12]. Similar to the left-hemisphere dominance of handedness, language ability is dominant in the left hemisphere in more than 95% of the right-handed population but in only 70% of the left-handed population[12].

Is it coincidental that both language ability and hand use are dominant in the left hemisphere in most of humans? Is there genetic control of both brain asymmetry and handedness? Using molecular and neurological approaches, we are beginning to tackle these questions and discover the neurological circuitries that regulate brain asymmetry. Here, we describe brain asymmetries that have been measured using modern imaging techniques and discuss the genetic correlation between brain asymmetry and preferential hand use. Furthermore, we propose evolutionary and molecular mechanisms that might regulate brain asymmetry and handedness.

Functional and anatomical brain asymmetries

The first detailed description of functional asymmetry in the human brain was made in the 1860s by a French doctor named Paul Broca. He found that there was a lesion in the left hemisphere of the post-mortem brain of a patient with a one-word vocabulary. Broca claimed that language ability in the human brain is lateralized and supplied perhaps the first strong evidence of functional asymmetry in the brain[13]. This brain region, which controls speech, is called Broca's area in honour of his discovery. In 1874, a German neurologist named Carl Wernicke discovered that damage to a region of the left hemisphere could cause a type of aphasia that resulted in an impairment of language comprehension[14]. This area is called Wernicke's area.

Brain functional asymmetry is not limited to language ability. Whereas the right cerebral cortex regulates movement of the left side of the body (and the left cerebral cortex regulates movement of the right side),

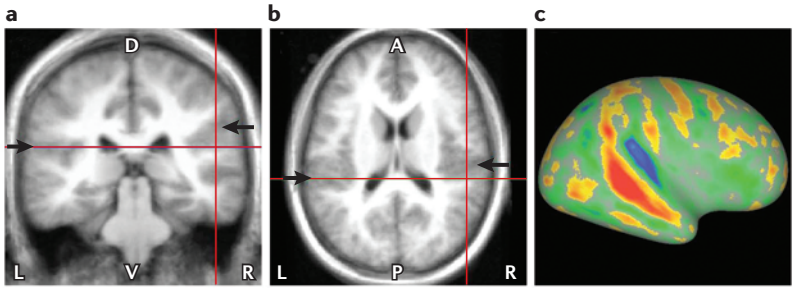

Figure 1 | **Anatomical asymmetries in the human cerebral cortex.** Coronal (**a**) and horizontal (**b**) MRI of the Sylvian fissures (red arrows) in the human brain. The Sylvian fissures separate the frontal lobes and temporal lobes in both hemispheres. The left (L) fissure is more ventral (V) and extends further towards the posterior (P) than does the right (R). Illustration of differences of sulcal depth between the left and right hemispheres (**c**). Cortical regions that are deeper in the right hemisphere are shown in red and yellow, whereas regions that are deeper in the left are shown in blue and green. A, anterior; D, dorsal. Modified, with permission, from REF. 11 © (2005) Elsevier Science.

more than 90% of the human population is naturally more skilled with the right hand than with the left[12]. Cognitive studies on patients with unilateral lesions and on patients with split-brain surgery have revealed many other differences between the left and right cerebral cortex[15]. For example, the left hemisphere is dominant for mathematical and logical reasoning, whereas the right hemisphere excels at shape recognition, spatial attention, emotion processing and musical and artistic functions[15–17].

Using modern imaging techniques, particularly MRI, scientists can map the asymmetries of anatomical structures in the human brain. Among the most studied regions are the Sylvian fissures, which separate the frontal and temporal lobes. For example, the posterior end of the Sylvian fissure in the right hemisphere is higher than in the left, whereas the left fissure has a more gentle slope[10,11,18] (FIG. 1a,b). The planum temporale, a region in the posterior portion of the superior temporal sulcus, is larger in the left hemisphere than in the right in more than 65% of adult brains and 56–79% of fetal or infant brains examined[19–22]. More recently, digital brain maps have generated three-dimensional images of human brains and further revealed cortical asymmetries[10]. Moreover, a new population average, landmark- and surface-based (PALS) atlas approach has shown the most consistent asymmetries to be in and near the Sylvian fissures (FIG. 1a,b) and the superior temporal sulcus[11] (FIG. 1c).

The differences in neuronal cell type or cell organization that might underlie these gross anatomical differences are unclear. Studies have shown that language-related areas of the left cortex might contain more and larger layer 3 pyramidal cells than corresponding areas in the right hemisphere[23]. Rosen[24] and Galaburda[25] used histological studies to suggest that the asymmetrical regions in the cortex might be the results of differences in neuron numbers but not packing density. However, the tremendous size of the human cortex and its extensive and variable folding pattern make corresponding areas difficult to compare with certainty.

In addition to the asymmetries related to language abilities, such as those of the Sylvian fissures and the planum temporale, anatomical asymmetries associated with hand use have also been detected in other regions in the human cerebral cortex. In the primary somatosensory cortex (S1), studies using magnetic source imaging have shown that the cortical representation of the right hand is larger than the one of the left hand in right-handers, and vice versa in left-handers[26]. Moreover, the left central sulcus, a large inward fold marking the division between the frontal and parietal lobes, is deeper than the right central sulcus in right-handers[27]. Inter-hemispheric comparison has further revealed a significant increase of the hand and finger movement representation in the primary motor cortex opposite to the preferred hand[28].

In contrast to these findings, other reports have shown no obvious correlation of handedness and brain asymmetries. For example, using voxel-based morphometry, Good *et al.*[29] did not detect effects of hand use on asymmetrical morphology in sensorimotor regions of more than 465 normal adult brains. Although different methodologies used in these studies could lead to opposite conclusions, the analyses of anatomical asymmetries associated with handedness in the primary sensory and motor cortices are compelling.

Handedness and language ability are two of the most obvious lateralized behaviours in humans. Taking note of the convergence of functional and anatomical studies, the asymmetrical cortical controls that regulate handedness are tightly correlated with those for language ability. But how are these controls established in humans?

Correlation of hand use and language ability

That most humans (more than 90%) prefer to use their right hand has been observed in almost all cultures and ethnicities throughout history[12,30]. Statistical studies suggest that handedness might be under genetic control. There are at least two well-known genetic models of handedness[31,32] (BOX 1), and although these models seem to reflect genetic mechanisms of cortical asymmetry and handedness, genes that regulate these asymmetries have not been identified. Furthermore, the question of whether a single gene can control such complex processes in the CNS is still unanswered[31]. Nevertheless, the single-gene models proposed by Annett[33] and McManus[34] fit statistical data of cerebral dominance for handedness in humans. Identifying the gene(s) that regulates brain asymmetry and handedness remains an appealing but challenging task.

Why is there a left-hemisphere bias for handedness and language ability? Preferred hand use has been observed even at embryonic and fetal stages in humans, long before language ability is developed. For example, in most human embryos, the right hand is more developed than the left at 7 weeks[35]. Using ultrasound, it has been observed that at 15 weeks most fetuses prefer to suck their right thumb, hinting that handedness is present prior to birth[36]. Interestingly, Hepper *et al.*[37] followed up this study of 75 individuals. They found that the 60 fetuses that preferred to suck their right thumb were indeed right-handed as teenagers, and of the 15 fetuses that

Protocortex model
Proposed by Dennis O'Leary. He suggested that regionalization is controlled in large part by extrinsic influences, such as thalamocortical inputs.

Sylvian fissures
The deepest and most prominent of the cortical fissures (clefts). They separate the frontal lobes and temporal lobes in both hemispheres.

Broca's area
The left inferior frontal gyrus of the frontal lobe of the human cortex. This area is responsible for speech and for understanding language. Injuries to this area can cause Broca's aphasia, which is characterized by non-fluent speech, few words, short sentences and many pauses. Patients normally lose the ability to understand or produce grammatically complex sentences.

Wernicke's area
The left posterior section of the superior temporal gyrus, where the temporal lobe and parietal lobe meet. It is involved in the comprehension of written or spoken language. People with damage in this area speak fluently, but often using words or jumbled syllables that make no sense; this is known as Wernicke's aphasia.

Box 1 | Genetic models of human handedness

Marian Annett[33] has proposed that the inheritance of the right-shift (*RS*) gene shifts the manual skills in favour of the right hand instead of the left. She emphasizes that *RS* influences left cerebral dominance rather than handedness; the effect of RS is to impair the control of speech systems in the right hemisphere, allowing language abilities to function in the left side. Handedness is just the secondary consequence of the left-cerebral cortical dominance[93].

The other model was proposed by Chris McManus[34]. He suggests that handedness is controlled by two alleles: *D* (dextral) and *C* (chance). According to his model, the homozygous *DD* genotype produces only right-handers, whereas the homozygous *CC* genotype produces a random mixture of 50% right-handers and 50% left-handers. Furthermore, the heterozygote, *DC*, produces 25% left-handers and 75% right-handers. This model reflects the Mendelian model of genotype and phenotype distribution.

preferred to suck their left thumb, 5 were right-handed and 10 were left-handed. Moreover, several early studies have shown that some cortical sulci and gyri, such as the temporal gyri, are asymmetrical in human fetal brains from 10–44 weeks[22,38,39]. Using the measurement of cerebral blood flow, Chiron *et al.*[40] found that the maturation of the right hemisphere precedes the left in the brains of human infants between 1 and 3 years of age. This asymmetrical pattern shifts towards the left hemisphere during the process of development of language abilities at about the age of 3 (REF. 40). Additionally, Trevarthen[41] observed that expressive gestures, such as communicative hand movement, were asymmetrical in infants.

These results imply that anatomical and functional brain asymmetry precedes uptake of information from the environment and cognitive development. This in turn suggests the existence of intrinsic controls that regulate brain asymmetries at early stages. Although these kinds of study are interesting, one has to keep in mind whether this early right-hand preference is controlled by high-level regulation in the left hemisphere of the cortex, or by spontaneous movement regulation in the spinal cord. Furthermore, whether early brain asymmetries contribute more to handedness or to language ability still remains an intriguing and challenging question[12].

Because anatomical asymmetries of certain areas in the human brain are associated with language ability, several researchers have made efforts to map asymmetries of the planum temporale and Broca's area in the brains of chimpanzees and great apes[42–44]. They found that simian brains also have asymmetries, which resemble those of humans. These studies suggest that brain structures associated with language ability might have existed before humans evolved. However, it is not clear whether vocal communication is asymmetrical in non-human primate brains or how these asymmetrical structures are involved in vocal processing[45]. Furthermore, because of the complex structure of the cerebral cortex, the mapping of areas that correspond in human and primate brains is difficult[46].

Which hemispheric asymmetry (for handedness or for language ability) appeared first in evolution still remains a puzzle. Further comparative studies of brain asymmetry and handedness in non-human primates will help us to understand the relationship between handedness and language ability in humans[47].

Magnetic source imaging
The detection of the changing magnetic fields that are associated with brain activity and their subsequent overlaying on magnetic resonance images to identify the precise source of the signal.

Paw preference
In a food-reaching task, paw preference measures the frequency of using either the left or the right front paw to reach food. It has been observed in mice, rats, cats and dogs.

Evolutionary mechanisms of biased hand use

More than 90% of the human population is right-handed, and biased hand use is also observed in non-human primates and other mammals. But whether there is a dominant preference for one hand at a population level is still debatable. What has made most humans right-handed during evolution is still unknown.

Handedness in non-human primates. There are many contradictory reports about hand use in non-human primates, such as chimpanzees. A broad range of manual tasks have been observed in chimpanzees, including simple reaching, bimanual feeding, coordinated bimanual actions, throwing, manual gestures and so on[48,49]. Although these observations have led to the argument that, for some measures, chimpanzees are right-handed, most of these findings are from captive great apes; evidence of population-level handedness in wild apes is extremely sparse[48,49]. Therefore, these studies do not conclude that there is a dominant preference for hand use in non-human primates at the population level.

A recent report of hand preferences during termite-fishing/probing actions of chimpanzees is interesting. First, Lonsdorf and Hopkins[50] studied wild chimpanzees living in the Gombe National Park, Tanzania, but not captive chimpanzees. Second, they observed termite-fishing actions, which require fine motor skill. They claimed that directional biases in hand use vary depending on the type of tool use. Therefore, the question of whether there is strong handedness in non-human primates might be confounded by biases in the types of motor skill required. Tests that better discriminate behavioural biases in wild primates are needed before any definitive conclusions can be drawn.

Paw preference in other mammals. A well-studied lateralized manual behaviour of many mammals is the food-reaching task, defined by paw preference. Although paw preference has been observed and studied in mice, rats, cats and dogs, it does not seem biased to either the left or the right front paw at a population level[51–56]. For example, paw preference was observed among domestic cats, but no significant bias in preference was found at the level of the group[53]. In mice, although there is paw preference in each individual mouse, approximately half of the mice studied preferred to use the left paw and half preferred to use the right[57,58]. There are also differences in the strength and direction of paw preference between mouse strains, indicating that genetic background is an important influence on this behaviour[55].

Paw preference in mice has encouraged scientists to find the genetic causes of this manual lateralization. Collins[59] attempted to breed left- or right-handed mice, and although he was unable, by inbreeding, to create a mouse strain that prefers to use only the left or the right front paw, he did succeed in generating mice that show a strong lateralization. For example, the HI strain was bred using mice that showed consistent right or left paw use in a food-reaching task, and the LO strain was bred using mice with little overall paw preference[59].

Box 2 | Molecular regulation of visceral organ asymmetry

Several studies have elegantly addressed the molecular regulation of the left–right asymmetry of internal organs, such as the heart, stomach, lungs and intestines of vertebrate bodies[94,95]. Three signalling pathways (SHH, FGF8 and NODAL) have crucial roles in left–right body determination[96,97]. In the chick embryo, sonic hedgehog (SHH) and its target gene caronte (*CAR*) are expressed to the left of the chick node (a structure of the body organizer in chicks) , whereas FGF8 is expressed to the right of the chick node[98–100]. Misexpression of SHH on the right side of the node is sufficient to induce heart formation on the right[98]. In the mouse embryo, neither SHH nor FGF8 is expressed asymmetrically[97]. Instead, the unidirectional rotation of monocilia on the surface of the mouse node directs the NODAL molecule to the left and activates its downstream genes, such as *Lefty2* and *Pitx*[101–103]. Moreover, early differential ion flux, such as that driven by the H^+ and K^+ ATPase transporter, was shown to cause early body asymmetry[104]. The neurotransmitter serotonin was recently reported upstream of asymmetrically expressed genes (such as *SHH*) in chick and frog embryos, and has a role in early patterning of the left–right body axis[105,106].

Is paw preference associated with lateralized brain anatomy and/or function in mice? The direction of paw preference seems to correlate with the dominance of dopamine expression levels in the brain: a mouse that prefers to use the left front paw has a higher dopamine level in the left hemisphere than in the right, although the physiological implications of this correlation are unknown[60,61]. Selectively bred mice (the O/AP strain) with supernumerary whiskers on the right side of the face and corresponding supernumerary barrels in the left barrel field showed a higher preference for using the left front paw. Likewise, mice with supernumerary whiskers on the left side of the face preferred to use the right front paw[62]. This biased front-paw use might be the result of competition for cortical representation between the size of the motor cortex and the somatosensory barrel field in which the whiskers are represented. A larger S1 (the barrel field) in the left hemisphere, for example, might make the size of the left motor cortex smaller, and lead to biased left front-paw use controlled by the right hemisphere.

Moreover, the areas of whisker-pad representation in the S1 between the left and right hemispheres of adult rats have shown striking variations (that is, asymmetries) in individuals. However, these asymmetries are not biased to either the left or the right hemispheres[63,64]. Does the asymmetry of the S1 provide a hint that paw preference has corresponding and asymmetrical cortical structures that control it? It will be interesting to map the sizes of the S1 regions and the direction of paw preference in mice.

In terms of the distribution of hand use, there is a consistent 9:1 ratio of right/left hand preference reported in humans, higher than has been reported for any other mammal[12,50]. The directional manual task in mice, like paw preference, might be regulated by the formation of stable neural circuits, but it has a random distribution at the population level. Given these examples of low or no bias in chimpanzees and mice, it is an intriguing puzzle as to how consistent right-hand dominance evolved in humans. Corballis[31] has proposed that there was a genetic mutation in hominid evolution that promoted preferential use of the right hand and is now seen in modern humans. This evolutionary bias might be advantageous as it could increase brain capacity and social cohesion[65]. Applying genomic approaches, particularly the complete sequencing of the human and chimpanzee genomes, will provide a considerable insight into the evolutionary mechanisms of lateralized human behaviours and human brain development and asymmetry[47,66–69].

Box 3 | Molecular regulation of zebrafish brain asymmetry

The asymmetries of the epithalamus, which are exemplified by the habenula and the pineal complex, are well studied in zebrafish[71]. Although the functional consequences of epithalamus asymmetry are still unclear, it seems to be involved in regulating sexual activities, photoreception and communication[71,107]. Both the habenula and the pineal complex show asymmetries on the left side in zebrafish. Interestingly, genes involved in the Nodal pathway, such as the Nodal-related gene *cyclops* and Nodal downstream genes *lefty1* and *pitx2*, were shown to control the laterality of the asymmetry, suggesting that a conserved signalling pathway that regulates visceral laterality also underlies an anatomical asymmetry of the zebrafish brain[72,108–110]. Moreover, a recent report has shown that the *frequent situs inversus* (*fsi*) line of zebrafish displayed concordant reversal of visceral organ and neuroanatomical asymmetries in the diencephalons[111]. Interestingly, *fsi* zebrafish also showed a reversal of some behavioural responses, which has not been detected in mammals with *situs inversus*[111]. These results indicate that the molecular regulation of brain and body asymmetries can be species specific.

Body and brain asymmetries

Little is known about the genetic causes of brain anatomical and functional asymmetries[70]. By contrast, studies of molecular regulation of asymmetries in the visceral organs, such as the heart and lungs, have made encouraging progress (BOX 2). Inspired by the identification of molecules that have essential roles in visceral organ asymmetry, researchers have succeeded in identifying molecules that regulate brain asymmetry in zebrafish, perhaps the only species that has been well studied with respect to brain asymmetry (BOX 3). Conserved molecules that regulate body asymmetry, such as Nodal and ion channel related gene products, are also essential for regulating asymmetry of the epithalamus, a small structure of the diencephalons[71,72].

Do the same molecular mechanisms that regulate body asymmetry also cause human brain asymmetry? The complete reversal of normal organ position, such as heart and lungs, is called *situs inversus*. With the exception of the reversed frontal and occipital petalia observed using anatomical and functional MRI techniques, the left-hemisphere dominance for language was still found to be similar in individuals with *situs inversus* and in normal subjects[73]. Nor did lateralization of auditory processing show any differences between individuals with *situs inversus* and normal subjects[74]. Moreover, 50% of individuals with Kartagener's syndrome, a disorder caused by cilia with a decreased or total absence of motility, have been found to have *situs inversus*[75]. This disorder might confirm the function of cilia in regulating visceral organ asymmetry, as defects in cilia mobility might result in the random distribution of NODAL molecules (BOX 2). However, the *situs inversus* patients with Kartagener's syndrome developed normal handedness[76]. Therefore, it seems reasonable that the molecules and mechanisms that regulate visceral organ asymmetries might be distinct from those that regulate brain asymmetries and handedness[70,77].

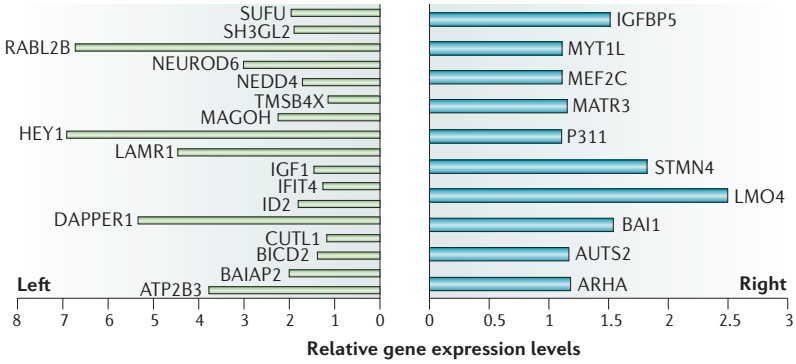

Figure 2 | **Asymmetrically expressed genes in 12-week-old human fetal brains, detected by serial analysis of gene expression and real-time reverse transcription (RT)-PCR.** The cDNA made from the perisylvian regions of the left and right hemispheres of two 12-week-old human fetal cortices were used as templates for real-time RT-PCR. The relative gene expression levels are average ratios of gene expression detected by RT-PCR between the left and right hemispheres of two brains. These differential gene expression levels also match those measured by serial analysis of gene expression (SAGE)[78]. 27 genes showing consistent differential expression are listed. Among them, 17 genes were highly expressed in the left perisylvian regions, whereas 10 genes were highly expressed in the right.

Serial analysis of gene expression
(SAGE). A method for comprehensive analysis of gene expression levels and patterns using PCR amplification and generating SAGE libraries.

Our recent studies, using a genomic screening approach, further support this idea. Using a serial analysis of gene expression (SAGE) technique, we measured gene expression levels in the left and right hemispheres of human fetal brains[78]. We verified 27 genes that are differentially expressed in the hemispheres of 12-week-old human fetal brains by using either real-time reverse transcription (RT)-PCR or *in situ* hybridization (FIG. 2). Most genes identified using SAGE analyses function in signal transduction and gene expression regulation[47]. Among them, the transcription factor Lim domain only 4 (*LMO4*) showed consistent asymmetry of expression in human fetal brains at 12 weeks and 14 weeks, and less so at 16 and 17 weeks[78]. However, we did not detect genes that have essential roles in visceral organ asymmetry, such as genes involved in the sonic hedgehog (SHH) or NODAL pathways, which are also differentially expressed in human fetal brains[78]. Because the earliest stage analysed was in the human fetus at 12 weeks, it cannot be ruled out that molecules regulating body asymmetry might also be differentially expressed in human embryonic brains (for example, at 8–10 weeks). It will be interesting to measure gene expression levels in the left and right hemispheres in human embryonic brains (8–10 weeks) using SAGE or cDNA microarray approaches.

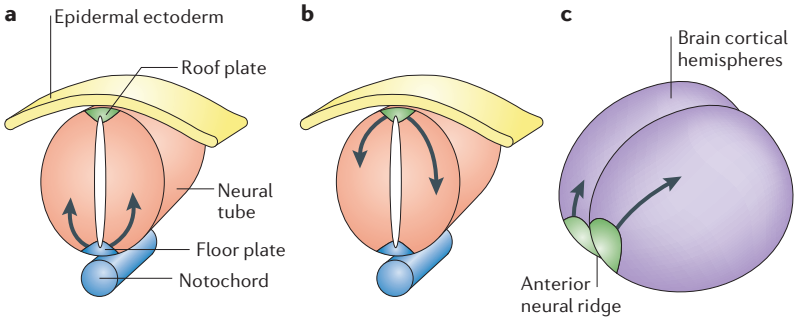

Figure 3 | **Three models of molecular induction of brain asymmetry. a** | Whereas the neural tube (red) is derived from the ectoderm, the notochord (blue) is derived from the mesoderm and accompanies the neural tube formation. During neural tube development, the most dorsal part of the neural tube becomes the roof plate (green), whereas the most ventral part of the neural tube becomes the floor plate (blue). The forebrain is developed from the most rostral region in the neural tube. In the forebrain, the morphogens secreted from the notochord or the prechordal plate (not shown) might be differentially distributed between the left and right neural tube. **b** | Similarly, uneven secretion of molecules might also occur in the roof plate. Different morphogen expression levels in the left and right neural tube might break the symmetry of brain patterning and induce asymmetrical expression of downstream genes. **c** | Anterior signals might also induce cortical asymmetry. The patterning centre in the most rostral neural tube — for example, the anterior neural ridge (green) — could be a source for cortical asymmetrical patterning. The distribution of molecules secreted from this area might be different in the left and right hemispheres.

Molecular regulation of brain asymmetry

An essential step leading towards asymmetry is to break symmetry[79]. Although the initiation mechanisms of breaking symmetry are still unknown, an uneven distribution of molecules that are essential for left–right body axis patterning could be important for this biological event.

How, then, is symmetry broken in the CNS? Neuroepithelial cells divide vigorously, fold dorsally and form a neural groove during early embryonic development[80]. The neural groove continues to grow, and the dorsal parts meet at the midline and fuse to form a neural tube[80]. Neural tube development is accompanied by the formation of the notochord and the induction of the floor plate[81]. Numerous studies have shown that the notochord is a patterning centre for the ventral neural tube[82]. In the forebrain, a structure anterior to the notochord is called the prechordal plate[83]. Molecules secreted from the notochord, such as SHH, function as morphogens to induce and maintain the ventral property and neural cell types in the spinal cord[82]. Similar morphogens also induce and pattern the forebrain, and are probably secreted from the notochord or the prechordal plate[84]. Moreover, the patterning centres are not limited to the notochord and the ventral neural tube. Morphogens, such as bone morphogenetic proteins and WNTs, are secreted from the roof plate in the neural tube[85].

One possible mechanism for breaking symmetry in the brain is that the morphogens secreted from the ventral (floor plate or prechordal plate) and/or dorsal (roof plate) midlines are distributed differently between the left and right (FIG. 3a,b). The different expression levels of morphogens induce differential expression of downstream transcription factors, such as LMO4 (REF. 78), and eventually lead to brain asymmetry.

Recent studies of the molecular regulation of cortical regionalization have identified a patterning centre in the anterior cortex[2–4]. An important molecule that is secreted from the anterior cortical region is fibroblast growth factor 8 (FGF8)[86]. The ectopic expression of FGF8 can expand the motor cortex and shift the functional regions of the cortex caudally[86]. It is possible that the expression levels of morphogens secreted from the anterior cortical region might be different in the left and right hemispheres (FIG. 3c). The asymmetrical expression

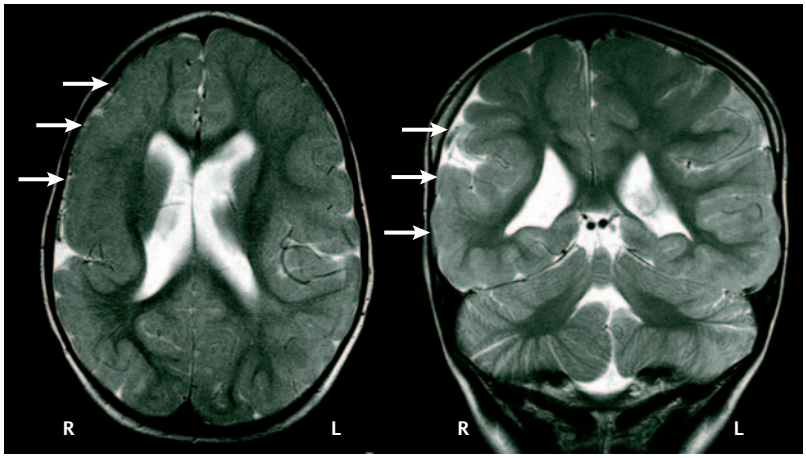

Figure 4 | **Unilateral polymicrogyria detected using MRI.** Polymicrogyria (indicated by arrows) is detectable in the right hemispheres in both brains shown. An apparent increase in cortical thickness is observed in the right (R) hemispheres, whereas the cortices of the left (L) hemispheres appear entirely normal. Modified, with permission, from REF. 92 © (2006) Lippincott Williams & Wilkins.

of regional markers, such as LMO4, could reflect asymmetrical topographic mapping of functional regions along the anterior–posterior axis in the cortex[78].

Future work will include the identification of more of the morphogens that pattern the early cortex and their downstream targets. Consistent with regionalization in the cortex, which involves complex gene expression and regulation[4], brain asymmetry and handedness are a conjugated result of molecular regulation, neural connections and plasticity.

Conclusions and future perspectives

The challenge of studying brain asymmetry is that because the obvious anatomical and functional asymmetries have been identified largely in humans, we cannot carry out direct experiments. The recent behavioural studies in non-human primates, such as the investigation of handedness in chimpanzees, might help us to better understand how human handedness has evolved[50]. In particular, the comparison of human and chimpanzee genomes has enriched our knowledge of the evolutionary mechanisms of human brain development[47,66–69]. Similar studies might help us to understand the evolutionary regulation of human brain asymmetry.

Several human neurological disorders show disrupted normal brain asymmetry. For example, reduced and reversed anatomical brain asymmetry has been reported in individuals with schizophrenia, autism or dyslexia[87–90], suggesting a potential indirect relationship between the causes of these disorders and the asymmetrical development of the human cerebral cortex. Recently, several studies have reported clinical cases of polymicrogyria — a malformation of cortical development that is characterized by many small gyri in the cortex — that occurs only on one side of the cortex; this is known as unilateral polymicrogyria[91,92] (FIG. 4). Patients have seizures, motor dysfunction and mental retardation. A genetic cause of unilateral right-sided polymicrogyria is suggested by the existence of several pedigrees in which the disorder is present in more than one individual of an affected family[92]. These studies indicate that unilateral polymicrogyria can be inherited as a Mendelian trait, suggesting that there might be a gene that is required for the development of the right perisylvian region[92]. Using forward genetic approaches to map genes that cause disrupted brain asymmetry might reveal their normal function in asymmetrical development of the brain.

Faster development and improvement of large-scale screening approaches at the genomic level could make the identification of asymmetrically expressed genes in human and mouse brains easier and quicker. Generating genetically engineered mice can help us to understand the functions of these genes in brain development. Using these mouse models can also help to reveal the neural circuitries that regulate brain asymmetry and lateralized behaviours. However, unlike visceral organ asymmetries, which are easy to detect, brain asymmetry relies largely on fine brain mapping and reliable behavioural tests. Therefore, the development of molecular imaging techniques and an improved understanding of lateralized behaviours in rodents will be extremely useful for studies of brain asymmetry.

Notochord
A structure composed of cells derived from the mesoderm and defines the primitive axis of the embryo. It lies between the neural tube (spinal cord) and the gut.

Morphogen
A diffusible substance that carries information influencing the movement and organization of cells during morphogenesis. It normally forms a concentration gradient.

1. Levitt, P., Barbe, M. F. & Eagleson, K. L. Patterning and specification of the cerebral cortex. *Annu. Rev. Neurosci.* **20**, 1–24 (1997).
2. O'Leary, D. D. & Nakagawa, Y. Patterning centers, regulatory genes and extrinsic mechanisms controlling arealization of the neocortex. *Curr. Opin. Neurobiol.* **12**, 14–25 (2002).
3. Grove, E. A. & Fukuchi-Shimogori, T. Generating the cerebral cortical area map. *Annu. Rev. Neurosci.* **26**, 355–380 (2003).
4. Sur, M. & Rubenstein, J. L. Patterning and plasticity of the cerebral cortex. *Science* **310**, 805–810 (2005).
5. Rakic, P. Neuronal migration and contact guidance in primate telencephalon. *Postgrad. Med. J.* **54**, 25–40 (1978).
6. O'Leary, D. D. Do cortical areas emerge from a protocortex? *Trends Neurosci.* **12**, 400–406 (1989).
7. Rakic, P. Specification of cerebral cortical areas. *Science* **241**, 170–176 (1988).
8. Geschwind, D. H. & Miller, B. L. Molecular approaches to cerebral laterality: development and neurodegeneration. *Am. J. Med. Genet.* **101**, 370–381 (2001).
Examines expression patterns of genes that regulate body asymmetries in human fetal brains and discusses molecular regulation of brain asymmetry.
9. Riss, W. Testing a theory of brain function by computer methods. III. Detecting cerebral asymmetry in normal adults. *Brain Behav. Evol.* **24**, 13–20 (1984).
10. Toga, A. W. & Thompson, P. M. Mapping brain asymmetry. *Nature Rev. Neurosci.* **4**, 37–48 (2003).
Overview of brain anatomical asymmetries mapped using modern imaging techniques.
11. Van Essen, D. C. A population-average, landmark- and surface-based (PALS) atlas of human cerebral cortex. *Neuroimage* **28**, 635–662 (2005).
Maps brain asymmetries and beautifully demonstrates consistent asymmetries in the Sylvian fissures and the superior temporal sulcus.
12. Corballis, M. C. From mouth to hand: gesture, speech, and the evolution of right-handedness. *Behav. Brain. Sci.* **26**, 199–208; discussion 208–260 (2003).
13. 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**, 330–357 (1861) (in French).
14. Wernicke, C. *Der Aphasische Symptomenkomplex: Eine Psychologische Studie auf Anatomischer Basis* (Cohn und Welgert, Breslau, 1874) (in German).
15. Gazzaniga, M. S. Forty-five years of split-brain research and still going strong. *Nature Rev. Neurosci.* **6**, 653–659 (2005).
16. Gazzaniga, M. S. Brain and conscious experience. *Adv. Neurol.* **77**, 181–192; discussion 192–193 (1998).
17. Borod, J. C., Bloom, R. L., Brickman, A. M., Nakhutina, L. & Curko, E. A. Emotional processing deficits in individuals with unilateral brain damage. *Appl. Neuropsychol.* **9**, 23–36 (2002).
18. Rubens, A. B., Mahowald, M. W. & Hutton, J. T. Asymmetry of the lateral (Sylvian) fissures in man. *Neurology* **26**, 620–624 (1976).
19. Shapleske, J., Rossell, S. L., Woodruff, P. W. & David, A. S. The planum temporale: a systematic, quantitative review of its structural, functional and clinical significance. *Brain Res. Brain Res. Rev.* **29**, 26–49 (1999).
20. Hirayasu, Y. *et al.* Planum temporale and Heschl gyrus volume reduction in schizophrenia: a magnetic

resonance imaging study of first-episode patients. *Arch. Gen. Psychiatry* **57**, 692–699 (2000).
21. Geschwind, N. & Levitsky, W. Human brain: left–right asymmetries in temporal speech region. *Science* **161**, 186–187 (1968).
22. Chi, J. G., Dooling, E. C. & Gilles, F. H. Left–right asymmetries of the temporal speech areas of the human fetus. *Arch. Neurol.* **34**, 346–348 (1977).
23. Hutsler, J. J. The specialized structure of human language cortex: pyramidal cell size asymmetries within auditory and language-associated regions of the temporal lobes. *Brain Lang.* **86**, 226–242 (2003).
24. Rosen, G. D. Cellular, morphometric, ontogenetic and connectional substrates of anatomical asymmetry. *Neurosci. Biobehav. Rev.* **20**, 607–615 (1996).
25. Galaburda, A. M., Rosen, G. D. & Sherman, G. F. Individual variability in cortical organization: its relationship to brain laterality and implications to function. *Neuropsychologia* **28**, 529–546 (1990).
26. Soros, P. *et al.* Cortical asymmetries of the human somatosensory hand representation in right- and left-handers. *Neurosci. Lett.* **271**, 89–92 (1999).
27. Amunts, K. *et al.* Asymmetry in the human motor cortex and handedness. *Neuroimage* **4**, 216–222 (1996).
28. Volkmann, J., Schnitzler, A., Witte, O. W. & Freund, H. Handedness and asymmetry of hand representation in human motor cortex. *J. Neurophysiol.* **79**, 2149–2154 (1998).
29. Good, C. D. *et al.* Cerebral asymmetry and the effects of sex and handedness on brain structure: a voxel-based morphometric analysis of 465 normal adult human brains. *Neuroimage* **14**, 685–700 (2001).
30. Coren, S. & Porac, C. Fifty centuries of right-handedness: the historical record. *Science* **198**, 631–632 (1977).
31. Corballis, M. C. The genetics and evolution of handedness. *Psychol. Rev.* **104**, 714–727 (1997).
32. Klar, A. J. Genetic models for handedness, brain lateralization, schizophrenia, and manic-depression. *Schizophr. Res.* **39**, 207–218 (1999).
33. Annett, M. The distribution of manual asymmetry. *Br. J. Psychol.* **63**, 343–358 (1972).
Proposes a genetic model for the regulation of cortical asymmetry and handedness.
34. McManus, I. C. Handedness, language dominance and aphasia: a genetic model. *Psychol. Med. Monogr. Suppl.* **8**, 1–40 (1985).
Proposes and discusses a genetic model that leads to preferential handedness in humans.
35. O'Rahilly, R. & Müller, F. *Developmental Stages in Human Embryos* (Carnegie Institute of Washington, Publication 637, Washington DC, 1987).
36. Hepper, P. G., Shahidullah, S. & White, R. Handedness in the human fetus. *Neuropsychologia* **29**, 1107–1111 (1991).
37. Hepper, P. G., Wells, D. L. & Lynch, C. Prenatal thumb sucking is related to postnatal handedness. *Neuropsychologia* **43**, 313–315 (2005).
38. Chi, J. G., Dooling, E. C. & Gilles, F. H. Gyral development of the human brain. *Ann. Neurol.* **1**, 86–93 (1977).
39. Galaburda, A. M., LeMay, M., Kemper, T. L. & Geschwind, N. Right–left asymmetrics in the brain. *Science* **199**, 852–856 (1978).
40. Chiron, C. *et al.* The right brain hemisphere is dominant in human infants. *Brain* **120**, 1057–1065 (1997).
41. Trevarthen, C. Lateral asymmetries in infancy: implications for the development of the hemispheres. *Neurosci. Biobehav. Rev.* **20**, 571–586 (1996).
42. Gannon, P. J., Holloway, R. L., Broadfield, D. C. & Braun, A. R. Asymmetry of chimpanzee planum temporale: humanlike pattern of Wernicke's brain language area homolog. *Science* **279**, 220–222 (1998).
43. Cantalupo, C. & Hopkins, W. D. Asymmetric Broca's area in great apes. *Nature* **414**, 505 (2001).
44. Hopkins, W. D., Marino, L., Rilling, J. K. & MacGregor, L. A. Planum temporale asymmetries in great apes as revealed by magnetic resonance imaging (MRI). *Neuroreport* **9**, 2913–2918 (1998).
45. Hutsler, J. & Galuske, R. A. Hemispheric asymmetries in cerebral cortical networks. *Trends Neurosci.* **26**, 429–435 (2003).
46. Sherwood, C. C., Broadfield, D. C., Holloway, R. L., Gannon, P. J. & Hof, P. R. Variability of Broca's area homologue in African great apes: implications for language evolution. *Anat. Rec. A Discov. Mol. Cell. Evol. Biol.* **271**, 276–285 (2003).
47. Sun, T., Collura, R. V., Ruvolo, M. & Walsh, C. A. Genomic and evolutionary analyses of asymmetrically expressed genes in human fetal left and right cerebral cortex. *Cereb. Cortex* **16**, i18–i25 (2006).
48. Hopkins, W. D. & Cantalupo, C. Individual and setting differences in the hand preferences of chimpanzees (*Pan troglodytes*): a critical analysis and some alternative explanations. *Laterality* **10**, 65–80 (2005).
49. McGrew, W. C., Marchant, L. F., Wrangham, R. W. & Klein, H. Manual laterality in anvil use: wild chimpanzees cracking *Strychnos* fruits. *Laterality* **4**, 79–87 (1999).
50. Lonsdorf, E. V. & Hopkins, W. D. Wild chimpanzees show population-level handedness for tool use. *Proc. Natl Acad. Sci. USA* **102**, 12634–12638 (2005).
Shows that preferential hand use in wild chimpanzees depends on the specific task.
51. Wells, D. L. Lateralised behaviour in the domestic dog, *Canis familiaris*. *Behav. Processes* **61**, 27–35 (2003).
52. Tan, U. Paw preferences in dogs. *Int. J. Neurosci.* **32**, 825–829 (1987).
53. Fabre-Thorpe, M., Fagot, J., Lorincz, E., Levesque, F. & Vauclair, J. Laterality in cats: paw preference and performance in a visuomotor activity. *Cortex* **29**, 15–24 (1993).
54. Bulman-Fleming, M. B., Bryden, M. P. & Rogers, T. T. Mouse paw preference: effects of variations in testing protocol. *Behav. Brain Res.* **86**, 79–87 (1997).
55. Waters, N. S. & Denenberg, V. H. Analysis of two measures of paw preference in a large population of inbred mice. *Behav. Brain Res.* **63**, 195–204 (1994).
56. Guven, M., Elalmis, D. D., Binokay, S. & Tan, U. Population-level right-paw preference in rats assessed by a new computerized food-reaching test. *Int. J. Neurosci.* **113**, 1675–1689 (2003).
57. Signore, P. *et al.* An assessment of handedness in mice. *Physiol. Behav.* **49**, 701–704 (1991).
58. Biddle, F. G., Coffaro, C. M., Ziehr, J. E. & Eales, B. A. Genetic variation in paw preference (handedness) in the mouse. *Genome* **36**, 935–943 (1993).
59. Collins, R. L. Reimpressed selective breeding for lateralization of handedness in mice. *Brain Res.* **564**, 194–202 (1991).
60. Cabib, S. *et al.* Paw preference and brain dopamine asymmetries. *Neuroscience* **64**, 427–432 (1995).
61. Barneoud, P., le Moal, M. & Neveu, P. J. Asymmetric distribution of brain monoamines in left- and right-handed mice. *Brain Res.* **520**, 317–321 (1990).
62. 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).
63. Riddle, D. R. & Purves, D. Individual variation and lateral asymmetry of the rat primary somatosensory cortex. *J. Neurosci.* **15**, 4184–4195 (1995).
64. Chen-Bee, C. H. & Frostig, R. D. Variability and interhemispheric asymmetry of single-whisker functional representations in rat barrel cortex. *J. Neurophysiol.* **76**, 884–894 (1996).
65. Halpern, M. E., Gunturkun, O., Hopkins, W. D. & Rogers, L. J. Lateralization of the vertebrate brain: taking the side of model systems. *J. Neurosci.* **25**, 10351–10357 (2005).
Summary of recent studies of vertebrate brain asymmetries, particularly brain asymmetries in zebrafish and chicks.
66. Hill, R. S. & Walsh, C. A. Molecular insights into human brain evolution. *Nature* **437**, 64–67 (2005).
67. Initial sequence of the chimpanzee genome and comparison with the human genome. *Nature* **437**, 69–87 (2005).
Accomplished the initial sequencing of the chimpanzee genome. This work will have a considerable impact on our understanding of the genomic regulation of human evolution.
68. Khaitovich, P. *et al.* Parallel patterns of evolution in the genomes and transcriptomes of humans and chimpanzees. *Science* **309**, 1850–1854 (2005).
69. Preuss, T. M., Caceres, M., Oldham, M. C. & Geschwind, D. H. Human brain evolution: insights from microarrays. *Nature Rev. Genet.* **5**, 850–860 (2004).
70. Hobert, O., Johnston, R. J. Jr & Chang, S. Left-right asymmetry in the nervous system: the *Caenorhabditis elegans* model. *Nature Rev. Neurosci.* **3**, 629–640 (2002).
Overview of the molecular mechanisms that regulate asymmetries in the *Caenorhabditis elegans* nervous system.
71. Concha, M. L. & Wilson, S. W. Asymmetry in the epithalamus of vertebrates. *J. Anat.* **199**, 63–84 (2001).
72. Halpern, M. E., Liang, J. O. & Gamse, J. T. Leaning to the left: laterality in the zebrafish forebrain. *Trends Neurosci.* **26**, 308–313 (2003).
73. Kennedy, D. N. *et al.* Structural and functional brain asymmetries in human *situs inversus totalis*. *Neurology* **53**, 1260–1265 (1999).
74. Tanaka, S., Kanzaki, R., Yoshibayashi, M., Kamiya, T. & Sugishita, M. Dichotic listening in patients with *situs inversus*: brain asymmetry and *situs* asymmetry. *Neuropsychologia* **37**, 869–874 (1999).
75. Carlen, B. & Stenram, U. Primary ciliary dyskinesia: a review. *Ultrastruct. Pathol.* **29**, 217–220 (2005).
76. McManus, I. C., Martin, N., Stubbings, G. F., Chung, E. M. & Mitchison, H. M. Handedness and *situs inversus* in primary ciliary dyskinesia. *Proc. Biol. Sci.* **271**, 2579–2582 (2004).
77. McManus, C. Reversed bodies, reversed brains, and (some) reversed behaviors: of zebrafish and men. *Dev. Cell* **8**, 796–797 (2005).
78. Sun, T. *et al.* Early asymmetry of gene transcription in embryonic human left and right cerebral cortex. *Science* **308**, 1794–1798 (2005).
Measured differential gene expression levels in the Sylvian fissures between the left and right human fetal brains and identified 27 asymmetrically expressed genes using SAGE, real-time reverse transcription (RT)-PCR and *in situ* hybridization.
79. Palmer, A. R. Symmetry breaking and the evolution of development. *Science* **306**, 828–833 (2004).
80. Tanabe, Y. & Jessell, T. M. Diversity and pattern in the developing spinal cord. *Science* **274**, 1115–1123 (1996).
81. Dodd, J., Jessell, T. M. & Placzek, M. The when and where of floor plate induction. *Science* **282**, 1654–1657 (1998).
82. Jessell, T. M. Neuronal specification in the spinal cord: inductive signals and transcriptional codes. *Nature Rev. Genet.* **1**, 20–29 (2000).
83. Rubenstein, J. L., Shimamura, K., Martinez, S. & Puelles, L. Regionalization of the prosencephalic neural plate. *Annu. Rev. Neurosci.* **21**, 445–477 (1998).
84. Tannahill, D., Harris, L. W. & Keynes, R. Role of morphogens in brain growth. *J. Neurobiol.* **64**, 367–375 (2005).
85. Chizhikov, V. V. & Millen, K. J. Roof plate-dependent patterning of the vertebrate dorsal central nervous system. *Dev. Biol.* **277**, 287–295 (2005).
86. Fukuchi-Shimogori, T. & Grove, E. A. Neocortex patterning by the secreted signaling molecule FGF8. *Science* **294**, 1071–1074 (2001).
87. Herbert, M. R. *et al.* Brain asymmetries in autism and developmental language disorder: a nested whole-brain analysis. *Brain* **128**, 213–226 (2005).
88. Hugdahl, K. *et al.* Central auditory processing, MRI morphometry and brain laterality: applications to dyslexia. *Scand. Audiol. Suppl.* **49**, 26–34 (1998).
89. Galaburda, A. M., Menard, M. T. & Rosen, G. D. Evidence for aberrant auditory anatomy in developmental dyslexia. *Proc. Natl Acad. Sci. USA* **91**, 8010–8013 (1994).
90. Falkai, P. *et al.* Loss of Sylvian fissure asymmetry in schizophrenia. A quantitative post mortem study. *Schizophr. Res.* **7**, 23–32 (1992).
91. Pascual-Castroviejo, I., Pascual-Pascual, S. I., Viano, J., Martinez, V. & Palencia, R. Unilateral polymicrogyria: a common cause of hemiplegia of prenatal origin. *Brain Dev.* **23**, 216–222 (2001).
92. Chang, B. S. *et al.* A familial syndrome of unilateral polymicrogyria affecting the right hemisphere. *Neurology* **66**, 133–135 (2006).
93. Annett, M. Handedness and cerebral dominance: the right shift theory. *J. Neuropsychiatry Clin. Neurosci.* **10**, 459–469 (1998).
94. Wright, C. V. Mechanisms of left–right asymmetry: what's right and what's left? *Dev. Cell* **1**, 179–186 (2001).
95. Levin, M. Left–right asymmetry in embryonic development: a comprehensive review. *Mech. Dev.* **122**, 3–25 (2005).
Gives a comprehensive summary of asymmetries in invertebrates and vertebrates and discusses molecular mechanisms that lead to these asymmetries.
96. Capdevila, J., Vogan, K. J., Tabin, C. J. & Izpisua Belmonte, J. C. Mechanisms of left–right determination in vertebrates. *Cell* **101**, 9–21 (2000).
97. Hamada, H., Meno, C., Watanabe, D. & Saijoh, Y. Establishment of vertebrate left–right asymmetry. *Nature Rev. Genet.* **3**, 103–113 (2002).

98. Levin, M., Johnson, R. L., Stern, C. D., Kuehn, M. & Tabin, C. A molecular pathway determining left-right asymmetry in chick embryogenesis. *Cell* **82**, 803–814 (1995).
99. Rodriguez Esteban, C. *et al.* The novel Cer-like protein Caronte mediates the establishment of embryonic left-right asymmetry. *Nature* **401**, 243–251 (1999).
100. Boettger, T., Wittler, L. & Kessel, M. FGF8 functions in the specification of the right body side of the chick. *Curr. Biol.* **9**, 277–280 (1999).
101. Nonaka, S., Shiratori, H., Saijoh, Y. & Hamada, H. Determination of left–right patterning of the mouse embryo by artificial nodal flow. *Nature* **418**, 96–99 (2002).
102. McGrath, J., Somlo, S., Makova, S., Tian, X. & Brueckner, M. Two populations of node monocilia initiate left–right asymmetry in the mouse. *Cell* **114**, 61–73 (2003).
103. Nonaka, S. *et al.* Randomization of left–right asymmetry due to loss of nodal cilia generating leftward flow of extraembryonic fluid in mice lacking KIF3B motor protein. *Cell* **95**, 829–837 (1998).
104. Levin, M., Thorlin, T., Robinson, K. R., Nogi, T. & Mercola, M. Asymmetries in H^+/K^+-ATPase and cell membrane potentials comprise a very early step in left–right patterning. *Cell* **111**, 77–89 (2002).
105. Fukumoto, T., Blakely, R. & Levin, M. Serotonin transporter function is an early step in left–right patterning in chick and frog embryos. *Dev. Neurosci.* **27**, 349–363 (2005).
106. Fukumoto, T., Kema, I. P. & Levin, M. Serotonin signaling is a very early step in patterning of the left–right axis in chick and frog embryos. *Curr. Biol.* **15**, 794–803 (2005).
References 96–106 are excellent studies of molecular regulation of body asymmetries.
107. Harris, J. A., Guglielmotti, V. & Bentivoglio, M. Diencephalic asymmetries. *Neurosci. Biobehav. Rev.* **20**, 637–643 (1996).
108. Concha, M. L., Burdine, R. D., Russell, C., Schier, A. F. & Wilson, S. W. A nodal signaling pathway regulates the laterality of neuroanatomical asymmetries in the zebrafish forebrain. *Neuron* **28**, 399–409 (2000).
109. Bisgrove, B. W., Essner, J. J. & Yost, H. J. Multiple pathways in the midline regulate concordant brain, heart and gut left–right asymmetry. *Development* **127**, 3567–3579 (2000).
110. Essner, J. J., Branford, W. W., Zhang, J. & Yost, H. J. Mesendoderm and left–right brain, heart and gut development are differentially regulated by pitx2 isoforms. *Development* **127**, 1081–1093 (2000).
111. Barth, K. A. *et al. fsi* zebrafish show concordant reversal of laterality of viscera, neuroanatomy, and a subset of behavioral responses. *Curr. Biol.* **15**, 844–850 (2005).

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Competing interests statement
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