42 The Genetic Bases of Brain Lateralization

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1. Lateralizations of Brain and Behavior

Lateralization of the human central nervous system begins early in development (figure 42.1). In a study of 72 fetuses at 10 weeks' gestational age, using in utero ultrasound scanning, Hepper, McCartney, and Shannon (1998) reported that the majority (85%) moved their right arms more than their left arms. This is consistent with the adult predominance of right-handedness and points to an embryonic precursor of this landmark behavioral lateralization (Hepper, 2013; Hepper et al., 1998). At 11 weeks of gestation, the choroid plexuses, which are highly vascularized structures that control the composition of cerebrospinal fluid in the brain's lateral ventricles, show an average leftward asymmetry of size (Abu-Rustum, Ziade, & Abu-Rustum, 2013), again based on in utero ultrasound scanning. This asymmetry may affect broader lateralized development of the brain via the secretion of diffusible signaling molecules into the ventricles (Corballis, 2013; Lehtinen et al., 2013). Slightly later in development, in utero ultrasound scanning of 274 human fetuses aged from 15 weeks of gestation showed a population-level preference for sucking of the right thumb (Hepper, Shahidullah, & White, 1991). In fact, the individual preference for fetal thumb sucking was also shown to be predictive of handedness aged 12 years, in follow-up analysis of 75 of the same subjects (Hepper, 2013; Hepper, Wells, & Lynch, 2005). Furthermore, anatomical brain lateralizations, including of perisylvian regions of the cerebral cortex that are important for language, have been reported from the second trimester and onward through fetal and infant development, with methodologies that have included ultrasound, *postmortem* analysis, and MRI (Chi, Dooling, & Gilles, 1977; Dubois et al., 2008; Fagard, 2013; Hering-Hanit, Achiron, Lipitz, & Achiron, 2001; Holland et al., 2014; Kasprian et al., 2011; G. Li et al., 2013; Y. Liu et al., 2010; Wada, Clarke, & Hamm, 1975; Witelson & Pallie, 1973).

These lateralizations of central nervous system (CNS) and limb activity in utero point strongly to a lateralized genetic-developmental program. In addition, varying degrees of lateralized brain activity have been recorded in adults during the performance of diverse cognitive tasks, including those related to language (figure 42.2), visuospatial cognition, and hand motor control (Gotts

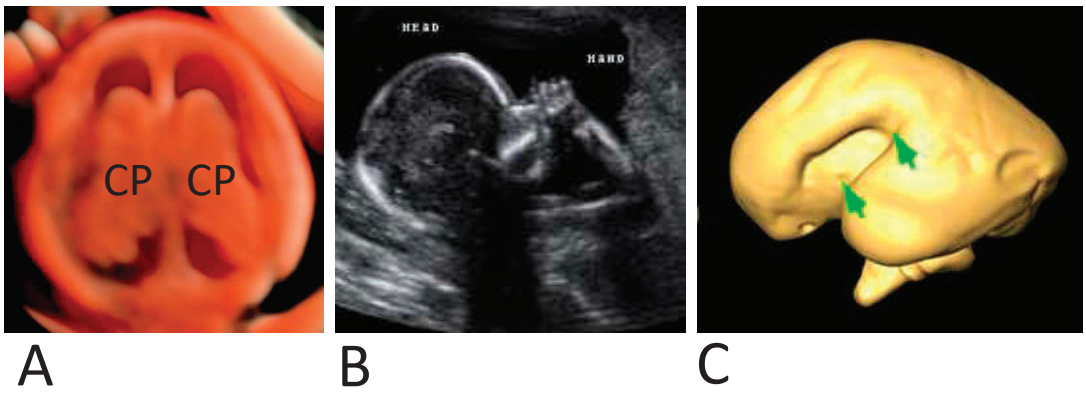

FIGURE 42.1 Asymmetrical development of the human brain and behavior in utero. (A) The left choroid plexus (CP) is 8% larger than the right one, on average, in fetuses at gestational age of 11 weeks. (B) At 15 weeks, most fetuses perform a right-handed "thumb sucking" behavior. (C) By mid-gestation, the anatomy around the sylvian fissure (highlighted by green arrows) has become left-right asymmetrical. See text for references. (A) adapted from Corballis (2013), (B) retrieved from https://www.pregmed.org/pregnancy-week-by-week/15-weeks-pregnant, (C) adapted from https://embryology.med.unsw.edu.au/embryology/index.php/Human_Sylvian_Fissure_Movie.

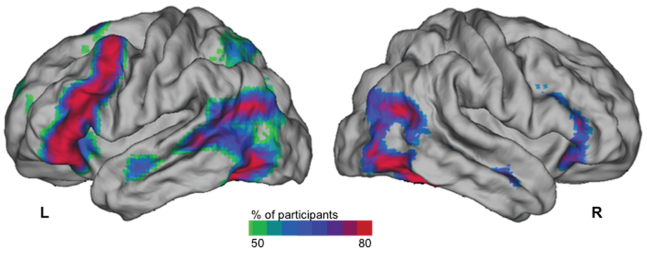

FIGURE 42.2 Laterality of brain activation during language production, based on 144 right-handed adults. Activation is more extensive in the left hemisphere. The task contrast used in this fMRI experiment was covert sentence-level versus word-list production. Figure reproduced, under the Creative Commons Attribution (CC BY) license, from Mazoyer et al. (2014).

et al., 2013; Hervé, Zago, Petit, Mazoyer, & Tzourio-Mazoyer, 2013; Rentería, 2012; Tomasi & Volkow, 2012). Lateralized functions imply left-right differences in the activity of proteins that modify the information-processing properties of neural circuits. Furthermore, syllabic speech rhythms have been reported to correspond to left-hemispheric neural oscillatory frequencies, in a manner that may preferentially support auditory and language processing in the left hemisphere (Morillon et al., 2010). Such neurophysiological lateralization is presumably supported at the molecular-genetic level by genes whose abundances determine the signaling properties of neuronal circuitry, including classes of genes involved in synaptogenesis, neurotransmission, and synaptic cell adhesion (Francks, 2011; Margeta & Shen, 2010). It has also been observed, by postmortem analysis of the auditory and other regions of the adult temporal lobe, that left superficial layers of the cortex contain a greater number of large pyramidal cells than right layers do (Hutsler, 2003). Pyramidal cells are large neurons involved in synaptic integration and plasticity (Spruston, 2008). Such left-right differences of microanatomy are a further indication that lateralization of gene activity is to be expected, since different neuronal classes are known to have their own signature profiles of gene expression (Zeisel et al., 2015).

In fact CNS lateralization is not unique to humans, being a feature of many vertebrate clades (Ocklenburg & Güntürkün, 2012; Rogers & Andrew, 2002; Rogers, Vallortigara, & Andrew, 2013). Population-level lateralization manifests, for example, in direction-biased turning behavior of schooling fish and reactions to visual stimuli in chicks (Ocklenburg & Güntürkün, 2012). Some crucial developmental events underlying lateralization have been elucidated in bird and fish species (Concha, Bianco, & Wilson, 2012; Concha, Signore, & Colombo, 2009; Ocklenburg & Güntürkün, 2012), and in zebrafish, in particular, characterization of CNS lateralized development at the molecular level is at a relatively advanced state (Concha et al., 2012). Asymmetrical development of the zebrafish forebrain involves the epithalamus, a structure of the dorsal posterior diencephalon, which migrates away from its embryonic origin at the midline, toward the left side (Concha et al., 2012). The epithalamus then innervates asymmetrically and influences broader CNS development in a lateralized manner (Concha et al., 2012). The genetic-developmental program that controls this process is linked to the same molecular factors that set up left-right lateralization of the viscera (e.g., heart, lungs), which include the Nodal signaling molecule (Concha et al., 2012). In *Xenopus* too, lateralization of tadpole swimming behavior is linked to visceral organ lateralization (Blackiston & Levin, 2013).

However, it is not clear how closely the mechanisms of lateralized brain development in fish, birds, and amphibians are related to those in humans. Humans with the rare genetic condition *situs inversus*, involving a mirror reversal of visceral asymmetries on the left-right axis, have shown normal population rates of right-handedness and left-lateralized language dominance, in the largest studies of these kinds to have been performed (McManus, Martin, Stubbings, Chung, & Mitchison, 2004; Tanaka, Kanzaki, Yoshibayashi, Kamiya, & Sugishita, 1999). Therefore an early developmental dissociation is suggested between visceral and brain asymmetries in humans, at least as regards handedness and language lateralization. This contrasts with the process of epithalamus-driven lateralized development of the zebrafish forebrain and means that the earliest developmental origins of human brain asymmetry remain mysterious. Regardless, the studies of zebrafish have clearly illustrated the principle that lateralized genetic-developmental programs can create brain structural and functional asymmetries, and therefore the search for such mechanisms in humans is strongly motivated. Note that here we are concerned with mechanisms of population-level lateralization, whereas there are many examples of lateralities that occur within species equally frequently in their leftward and rightward forms (Rogers et al., 2013; Vallortigara & Rogers, 2005). Individual-level lateralities presumably occur when asymmetry is advantageous for the organism but the direction is not important (Rogers et al., 2013; Vallortigara & Rogers, 2005).

Some mammalian species may prove to be useful models for understanding aspects of the genetics and development of human brain lateralization. Mice have not been widely reported to have population-level asymmetries of brain structure or function, but lateralization has

recently been reported using imaging in vivo (Apostolova et al., 2012; Spring, Lerch, Wetzel, Evans, & Henkelman, 2010), as well as molecular-level asymmetries in the hippocampus, which affect learning and memory (Goto et al., 2010; Kawakami et al., 2003). Weak population-level paw preference has also been observed in inbred mice during reaching tasks, although these lateralizations required large samples to detect them, and they varied in leftward versus rightward direction depending on the task (Waters & Denenberg, 1994). Rats have been reported to show a stronger population-level bias (73% right paw preference) (Güven, Elalmis, Binokay, & Tan, 2003) than mice, as well as hemispheric differences in spatial cognition (LaMendola & Bever, 1997) and proteomic lateralization in the hippocampus (Samara et al., 2011). Great apes have also shown evidence for population-level handedness, albeit at levels much weaker than for humans, and also some structural brain lateralizations similar to those found in regions important for language in humans (Cantalupo et al., 2009; Hopkins, 2013; Lyn et al., 2011; Meguerditchian, Vauclair, & Hopkins, 2013). However, research with nonhuman primates, particularly apes, is restricted ethically and legally, while human brain lateralizations linked closely to language may not manifest sufficiently, or at all, in rodents. Therefore, genetic studies that have a direct focus on human tissues and traits are critical for making progress in this field.

2. Asymmetrical Gene Expression in Human Brain Development

The most well-studied lateralizations of the human brain involve the cerebral cortex, and several attempts have been made to identify genes that are asymmetrically active in this tissue, either during development or in adulthood (Hawrylycz et al., 2012; Johnson et al., 2009; Lambert et al., 2011; Pletikos et al., 2014; Sun et al., 2005). For these studies, postmortem tissue samples have been carefully dissected shortly after donor death, and the levels of messenger RNA (mRNA) of thousands of genes was measured simultaneously, using an approach called *transcriptomic profiling*. The level of mRNA of any specific gene within a tissue is an imperfect indication of the amount of protein encoded by that gene. Sun et al. (2005) studied the cerebral cortices of human fetuses at 12–19 weeks, using a transcriptomic technique called *serial analysis of gene expression*, and found higher right-than-left mRNA levels of the transcription factor *LMO4*[1] at the earlier developmental stages, which was not detected at 19 weeks. Transcription factors are proteins that regulate the mRNA expression of other genes and can influence many cellular and developmental processes. *LMO4* was more recently shown to affect neurogenesis and axonal projection (Q. Li et al., 2013). Induced unilateral knockdown of the *Lmo4* mRNA level in one embryonic mouse brain hemisphere, *in utero,* caused suppression of neurogenesis in that hemisphere, which resulted in asymmetries of neuronal production, functional area formation, and axonal projection (Q. Li et al., 2013). Later, 12-week-old mice that had been treated in this way as embryos showed behavioral lateralizations, including of turning during swimming, and paw preference (Q. Li et al., 2013). Nontreated mice showed no population-level lateralization of these behaviors, as well as little individual-level lateralization (Q. Li et al., 2013). However, asymmetrical developmental outcomes would seem likely to arise from unilateral manipulation of a cortically expressed transcription factor that affects processes such as neurogenesis and functional area formation, even if that transcription factor is not naturally important for lateralized development. Furthermore, lateralization of *LMO4* mRNA in the human fetus was statistically tentative in the original study and has yet to be replicated in the literature. This therefore remains a key finding that is in need of confirmation.

Using a more up-to-date technology, that is, microarray transcriptomics, Lambert et al. (2011) did not identify significant asymmetries of gene expression in frontal or temporal cortical tissue from human fetuses aged 17 and 19 gestational weeks. Pletikos et al. (2014) also used microarrays to study postmortem neocortical regions, this time all across the human life span from embryo to old age, but again they did not find significant evidence for differential left-right gene expression, either at the level of individual genes or in terms of the changes observed in gene expression over time. Another microarray-based postmortem study, by Johnson et al. (2009), also did not identify significant lateralization of cortical mRNA expression in tissue taken from mid-fetal human brains aged between 18 and 23 weeks of gestation. A recent expression-profiling study from adult brain tissue also did not identify asymmetrically expressed genes (Hawrylycz et al., 2012).

However, each of these transcriptomic studies was based on only tiny numbers of postmortem samples from any given stage of development. Such studies are severely limited by the availability of tissue samples, as well as the expense of transcriptomic profiling techniques. For the transcriptomic-screening stage of their study, Sun et al. (2005) used tissue from only two fetuses at 12 weeks, two at 14 weeks, and one at 19 weeks; Lambert et al. (2011) analyzed one fetus at 17 weeks and one fetus at 19 weeks; Johnson et al. (2009) analyzed four mid-fetal brains; and Hawrylycz et al. (2012) analyzed two adult brains for which data from both hemispheres

Table 42.1
Studies of gene expression in human embryonic and fetal cerebral cortex

Study	Age range (gestational weeks)	Sample size	Technology	Asymmetrical gene expression
Sun et al. (2005)	12–19*	5	SAGE	LMO4 and others
Lambert et al. (2011)	17–19	2	Microarray	None found
Johnson et al. (2009)	18–23	4	Microarray	None found
Pletikos et al. (2014)	14–40	20†	Microarray	None found

*It was not stated in the study whether the age range referred to postconception or gestational weeks (gestational weeks are measured from the last reported menstruation and therefore roughly two weeks prior to conception).
†Left-right differential expression analysis was performed within age-restricted subsets of samples.
SAGE = serial analysis of gene expression.

were available. The study by Pletikos et al. (2014) was the most substantial in terms of sample size, being based on 57 brains spanning the life span, but again the number of brains at any given stage of development averaged less than one for the prenatal material and was similarly low for the infant, childhood, and teenage samples. In addition, for testing lateralized gene expression, Pletikos et al. (2014) used a maximum sample size of four brains that were grouped by consecutive ages, including for the adult samples (see table 42.1).

It follows that none of these transcriptomic studies was well powered, in statistical terms, to detect subtle contrasts of left-right gene expression. In addition, these studies involved individually testing thousands of genes and performing false-discovery-rate correction, which necessarily meant that they were not powered to detect asymmetries of less than 1.5-fold expression level for a given gene, in the small sample sizes that were used. Yet, expression differences of 1.5-fold magnitude may be functionally relevant, especially when considered over multiple genes interacting together in networks to influence neuronal and circuit properties.

3. Lateralization of Cerebral Cortical Gene Expression in Adult Brains

In light of the limited power of previous studies of asymmetrical gene expression, Karlebach and Francks (2015) recently reanalyzed some of the adult cerebral cortical gene expression data of Pletikos et al. (2014) and Hawrylycz et al. (2012), using various techniques to increase the statistical power to detect left-right differences, which had not been previously applied. First, data from the posterior superior temporal cortex (corresponding to Brodmann's area [BA] 22), as well as from the primary auditory cortex (BA41) (see figure 42.3), were specifically targeted, as lateralizations of these regions have been reported in terms of function, neurophysiology, gross anatomy, and histological microanatomy (as discussed in section 1). Data from Pletikos et al. (2014) for all 13 adults within the age range 18–55 years were entered into a single analysis without subdividing by age, followed by meta-analysis with the data of Hawrylycz et al. (2012). Bayesian smoothing of gene expression variance estimates was used to aid statistical testing in these small data sets. Lateralization was tested at the level of individual genes, but also at the level of functional gene sets defined according to Gene Ontology classifications, by which gene products are grouped hierarchically according to molecular functions, biological processes, and cellular components (Ashburner et al., 2000). Through applying these data-analytic approaches, robust evidence for left-right differences were found for BA22, which manifested most strongly at the level of sets of genes that are involved in synaptic transmission,

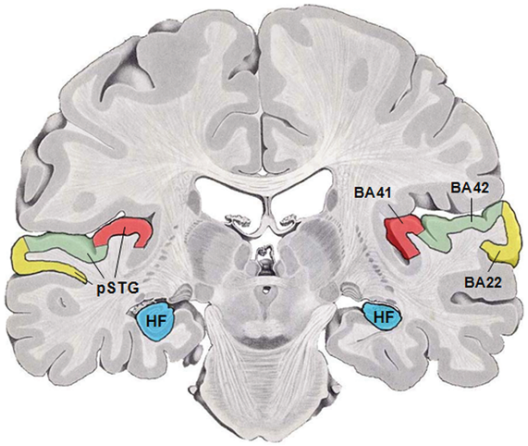

Figure 42.3 Regions of the posterior superior temporal gyrus (pSTG) of the adult human cerebral cortex, including BA22, which showed lateralization of gene expression levels in the study by Karlebach and Francks (2015). Lateralization was detected for genes involved in membrane receptor activity and synaptic functions (among others). A coronal section of the brain is shown. HF = hippocampal formation. Figure reproduced, under the Creative Commons Attribution 2.5 Generic license, from Talbot et al. (2011).

signal transduction, glutamate receptor activity, and transmission of nerve impulses, all showing relative upregulation in the left-hemispheric region (Karlebach & Francks, 2015). The genes involved have neuronal functions that are likely to affect signaling, learning, and information-processing properties of circuitry. Interestingly, even though these data were from adult brains, there was also lateralization of gene sets that are defined for their developmental roles, which suggests that transcription factors and other developmentally important proteins have roles in maintaining lateralized function in the adult brain. Overall, the findings of Karlebach and Francks (2015) indicate that the combinatorial effects of subtle, quantitative left-right differences, over many genes, are likely to fine-tune neurophysiological outcomes differently in the two hemispheres and underpin lateralized cortical functions.

4. Heritability of Brain and Behavioral Asymmetries

A very different approach to identify genes involved in human brain lateralization is to correlate genetic polymorphisms in the population with interindividual differences in structural or functional brain asymmetries or lateralized behaviors. The summed effects of all such polymorphisms in the genome indicate the heritability, that is, the proportion of population variation in a trait that is caused by genetic differences. Heritability can be measured through studies of twins, in which monozygotic pairs of twins show how similar individuals are when they are genetically identical, by contrast with dizygotic pairs of twins who share, on average, half of their chromosomes identical-by-descent.

So far there have only been a small number of twin studies of asymmetries of human brain structure, function, or behavior, and they have generally shown evidence for zero-to-modest heritability (Badzakova-Trajkov, Häberling, & Corballis, 2010; Bishop, 2013; Häberling, Badzakova-Trajkov, & Corballis, 2013; Jahanshad et al., 2010; Medland et al., 2009; Steinmetz, Herzog, Schlaug, Huang, & Jäncke, 1995). The heritability of left-handedness, for example, was estimated at close to 24%, in a large meta-analysis study that involved data from more than 25,000 families with twins (Medland et al., 2009). In other words, when one twin in a pair was left-handed, the other twin was significantly (but only slightly) more likely also to be left-handed when the pair was monozygotic than when the pair was dizygotic. The large sample size of this study meant that the weak heritability was accurately measured, with a tight confidence interval. It is therefore clear that genomic variation has a weak effect on the probability of becoming left-handed, while it is also clear that environmental effects and/or random effects during development are largely responsible (additionally there was no evidence that shared rearing environments for given pairs of twins have an effect).

By contrast with handedness, heritability studies of brain structural and functional asymmetries have only been performed in low hundreds of twin pairs, rather than thousands, and therefore the heritability estimates have been much less accurately measured. In addition, a large number of different imaging-based measures of asymmetry have sometimes been derived within individual studies, leading to the issue of multiple testing, which is difficult to control adequately in smaller samples. Eyler et al. (2013) found significant heritabilities of regional cortical areas and thicknesses in a study of 130 monozygotic twin pairs, 97 dizygotic pairs, and 61 unpaired twins, using automated segmentation of MRI images. However, their data indicated that left-right homologous regions of the two hemispheres share most or all of the genetic contributions to their variances, and there was little evidence for genetic effects that were different between the hemispheres and that would contribute to asymmetry (Eyler et al., 2013). In a study of 374 human twins, Jahanshad et al. (2010) used diffusion tensor imaging (DTI) to study nerve fiber bundles. They found the heritability of asymmetry indexes to range from 0% to 47%, depending on the particular fiber tract and DTI-based metric of white matter integrity. Frontal and temporal regions showed the most significant population-level asymmetries (Jahanshad et al., 2010), and genetic factors accounted for 33% of the variance in asymmetry in the inferior fronto-occipital fasciculus, 37% of the variance in the anterior thalamic radiation, and 20% of the variance in the forceps major and the uncinate fasciculus (Jahanshad et al., 2010).

As regards measures of brain function, hemispheric language lateralization was shown to have a heritability of 31% using functional transcranial Doppler in families from the Netherlands (Somers et al., 2015). This study used families rather than monozygotic versus dizygotic twins, and it therefore remains possible in principle that part of the apparent heritability was driven by shared environmental influences on relatives from the same family, although this seems unlikely since shared environmental effects did not prove significant in the studies of handedness or brain asymmetries that we have discussed.

In general, large nonshared environmental or random effects on brain asymmetries are indicated by these studies, in addition to low-to-moderate heritabilities, as is the case for handedness. Larger imaging

studies of twins will be required to more accurately assess the degree to which brain structural and functional asymmetries are heritable.

5. Viscera and the Principle of Randomization on the Left-Right Axis

Visceral lateralization (of the heart, lungs, and such) illustrates some important principles of asymmetrical development that are likely to be informative for studies of brain asymmetry. When early developmental mechanisms underlying visceral asymmetry are disrupted by certain genetic mutations, the direction of asymmetrical development can become randomized: half of mutation carriers develop visceral asymmetry in the normal orientation, and half develop the mirrored form situs inversus (Sharma, Berbari, & Yoder, 2008) (see figure 42.4). In humans this condition has a population frequency of roughly 1 in 10,000, and it can be induced by mutagenesis or gene knockouts in various vertebrate species. The typical pattern of lateralized visceral development likely has its origins in asymmetrical motions of protein cilia located on the ventral surface of very early mammalian embryos (Shinohara et al., 2012). Cilia rotate predominantly in only one of two theoretically possible orientations, due to their protein components being constructed by chiral amino acid molecules (Shinohara et al., 2012). Beating of the cilia apparently causes a unidirectional flow of fluid within a pitted embryonic structure called the node, resulting in mechanical and/or chemical differences between the left and right sides (Yoshiba et al., 2012) that are thought to trigger differential gene expression. Lateralization may even be initiated earlier than this, by molecular chirality of subcellular components such as cytoskeletal elements (Burdine & Caspary, 2013; Levin & Palmer, 2007). Primordial left-right differences are then amplified by differential gene activity into distinct developmental fates for the left and right sides of the embryonic viscera (Levin, 2005; Shinohara et al., 2012). In situs inversus with primary ciliary dyskinesia, mutations in genes encoding protein components of the nodal cilia, or other genes functionally related to these, result in a loss of unidirectional fluid flow or its detection, and thus a lack of consistency in the direction of asymmetrical development. Left-right differentiation of the viscera still proceeds in the embryo, but it is triggered with an equal probability in either orientation, probably by random and slight asymmetrical fluctuations of key developmental gene activities (Concha et al., 2009; Levin, 2005).

Randomization that results from the genetic loss of consistent, direction-giving mechanisms early in development has also been considered in relation to left-handedness and other aspects of human brain lateralization (Annett, 1985; Klar, 1999; McManus & Bryden, 1992; McManus, Davison, & Armour, 2013). However, there is no direct evidence for this, since core genes and mechanisms that give rise to human brain lateralization are unknown. As mentioned, people with situs inversus and primary ciliary dyskinesia have normal population proportions of left-handedness and left-lateralized language dominance, which suggests a dissociation of visceral lateralization from at least some aspects of cerebral lateralization, in terms of their embryonic development. Regardless, the concept of randomization in the direction of brain asymmetry, which arises from disruption of normally lateralized genetic-developmental programs, is consistent with the weak heritability estimates for brain asymmetries and lateralized behaviors that have been measured in studies of twins and families. In these studies, any random contribution to trait variability is confounded with the nonshared environmental component of variance that is estimated.

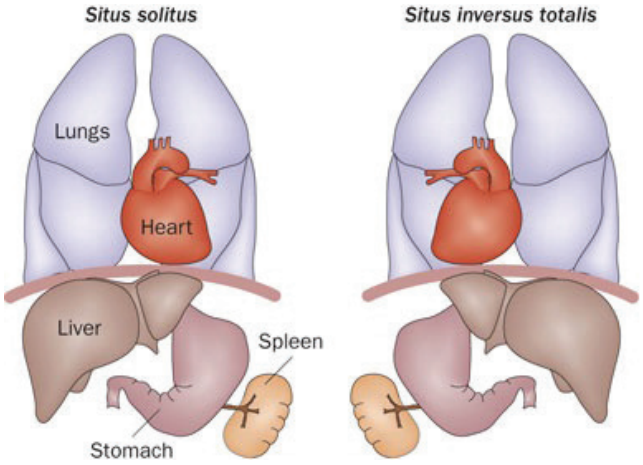

FIGURE 42.4 Mirror reversal of the viscera (situs inversus) can result from genetic mutations that disrupt the functions of cilia in the very early embryo. It is unclear whether the same fundamental mechanisms of left-right patterning are involved in all brain lateralizations, since people with situs inversus due to ciliary mutations appear to have similar proportions of right-handedness and left-hemisphere auditory language dominance as the general population (see text). Picture reproduced from Patel and Honoré (2010).

6. Cognitive Performance and Plasticity

Variability in lateralized brain structures, functions, or behaviors has been shown to weakly associate with cognitive or behavioral performance in some studies, including with verbal ability and scholastic achievement

(Badzakova-Trajkov, Häberling, & Corballis, 2011; Björk, Brus, Osika, & Montgomery, 2012; Boles, Barth, & Merrill, 2008; Catani et al., 2007; Gotts et al., 2013; Groen, Whitehouse, Badcock, & Bishop, 2013; Kikuchi et al., 2011; Leask & Crow, 2001; Mellet et al., 2013; Prichard, Propper, & Christman, 2013). For example, Björk et al. (2012) observed an association between mixed-handedness and slightly reduced performance on school tests, including tests of verbal ability and mathematics, in a British birth cohort of 10,612 children. This effect was limited to those children who scored within the lower third on a measure of right-hand motor performance, suggesting interactions between variances in motor skill, lateralization, and cognition. Catani et al. (2007) found that individuals with more symmetric patterns of white matter connections in the perisylvian language network were better at remembering words using semantic association, although this was a DTI-based study of only 50 participants. If such findings are correct, it appears that some specific aspects of cognition can benefit from relatively more bilateral organization, while general academic performance may benefit from relatively stronger lateralization. In general, however, reorganizations of lateralized brain structure and function, such as left-handedness and reversed language lateralization, can obviously occur developmentally without major consequences for cognitive or behavioral performance (Mazoyer et al., 2014; Mellet et al., 2013; Willems, der Haegen, Fisher, & Francks, 2014).

It has also become clear in recent years that the variances in different aspects of brain-asymmetrical structure and function are often largely uncorrelated with each other (Badzakova-Trajkov, Häberling, Roberts, & Corballis, 2010; Bishop, 2013; Guadalupe, Willems, et al., 2014; Guadalupe, Zwiers, et al., 2014; Knecht et al., 2002; Liu, Stufflebeam, Sepulcre, Hedden, & Buckner, 2009; Mazoyer et al., 2014; Rentería, 2012). For example, handedness and lateralized language dominance are only weakly related, which has been found using both functional MRI (fMRI) and functional transcranial Doppler sonography (Knecht et al., 2000; Mazoyer et al., 2014). Liu et al. (2009) analyzed intersubject variance in lateralized brain activity using resting-state fMRI in 300 participants and found four separately lateralized factors: systems involved in vision, internal thought, attention, and language. These observations, together with the generally weak associations of altered lateralization with cognitive performance, imply a high degree of developmental plasticity of lateralization on a brain-regional and process-specific basis. Either hemisphere is apparently able to become dominant for any given function, especially if the requirement to do so is initiated early enough in development. This plasticity is consistent with the data on lateralized gene expression that were already discussed, which indicated only subtle, quantitative variations on what are bilaterally homologous themes at the molecular level and which are likely to be developmentally readjustable.

At the same time, many studies have found cognitive and psychiatric disorders to be modestly associated with alterations of brain asymmetry and/or lateralized behavior (Eyler, Pierce, & Courchesne, 2012; Floris et al., 2013; Herbert et al., 2002; Herbert et al., 2005; Kawasaki et al., 2008; Lindell & Hudry, 2013; McCarley et al., 2002; Mock et al., 2012; Preslar, Kushner, Marino, & Pearce, 2014; Seidman et al., 2002; Shenton, Dickey, Frumin, & McCarley, 2001; Somers, Sommer, Boks, & Kahn, 2009; Sommer, Ramsey, Kahn, Aleman, & Bouma, 2001; Tsuang, Chen, Kuo, & Hsiao, 2013), including schizophrenia, autism, dyslexia, and language impairment, although not in all populations affected with these disorders (Deep-Soboslay et al., 2010; Preslar et al., 2013). A comprehensive meta-analysis study published in 2001 found that schizophrenia was associated with mixed- and left-handedness and also with reductions of structural lateralization of the planum temporale and sylvian fissure (Sommer et al., 2001). Both findings have subsequently received further support (Kawasaki et al., 2008; Somers et al., 2009; Tsuang et al., 2012). People with autism spectrum disorders have been reported to show changes of cortical structure, handedness, and functional lateralization for language (Lindell & Hudry, 2013). Genetic variations and environmental influences that contribute to these disorders may therefore affect brain lateralized development and function, although cause-effect relationships between altered lateralization and disorders are not currently understood.

7. Genetic Association Studies

Genetic association studies have identified individual polymorphisms within certain genes and genetic networks that may have modifying effects on brain or behavioral asymmetries (Arning et al., 2013; Brandler et al., 2013; Francks et al., 2002; Francks et al., 2003; Francks et al., 2007; Medland et al., 2005; Ocklenburg et al., 2013a, 2013b; Ocklenburg et al., 2011; Ocklenburg, Beste, & Güntürkün, 2013; Scerri et al., 2011). Measures used in these studies have included indices of lateralized hand motor skill (Francks et al., 2007), binary-trait hand preference (Medland et al., 2005), and lateralization of auditory language dominance as assessed by dichotic listening (Ocklenburg et al., 2011). The implicated genes have functions including steroid

hormone biology (*AR*) (Medland et al., 2005), synaptic adhesion (*LRRTM1*) (Francks, 2011), glutamatergic neurotransmission (*GRIN2B*) (Ocklenburg et al., 2011), transcriptional regulation (*FOXP2*) (Ocklenburg et al., 2013b), dopamine release (*CCKAR*) (Ocklenburg et al., 2013a), and left-right lateralization of the viscera (*PCSK6*) (Brandler et al., 2013; Scerri et al., 2011). However, these studies were based on data sets of hundreds of individuals and were therefore not well powered to establish effects of individual, common polymorphisms on etiologically heterogeneous and complex traits (Altshuler, Daly, & Lander, 2008; Sham & Purcell, 2014). Each of the findings therefore remains tentative. Studies using thousands of participants will be required (Sham & Purcell, 2014) to reliably pinpoint individual, common genetic effects on brain asymmetry measures, especially given the generally low heritabilities of these traits (see section 4). Recent success has been achieved for various multifactorial human traits through the use of genetic association studies in tens of thousands of participants, including for human height and body mass index, and complex diseases such as diabetes and schizophrenia (J. Z. Liu et al., 2010; Welter et al., 2014). However, the only genetic studies of brain asymmetries performed at something approaching this scale were two recent genome-wide association study meta-analyses, which were both based on just over 3,000 subjects (Guadalupe, Zwiers, et al., 2014; Guadalupe et al., 2015) (see figure 42.5). One of these studies found that structural lateralization within and around the planum temporale is sexually dimorphic and associated with genes involved in steroid hormone biology (Guadalupe et al., 2015). The other study analyzed volume asymmetry of the caudate nucleus but did not find genetic polymorphisms associated with individual differences in this measure (Guadalupe, Zwiers, et al., 2014).

It is not clear how a reported association between hand motor skill asymmetry and polymorphisms within visceral asymmetry genes (Brandler et al., 2013) is consistent with the dissociation of situs inversus from handedness that was discussed in section 5. Some elements of visceral asymmetrical development may in fact be shared with those that set up human brain asymmetries, and indeed, situs inversus in mice has been reported to affect molecular lateralization in the hippocampus (Kawakami, Dobi, Shigemoto, & Ito, 2008). However, the human genetic association data still require replication in independent data sets.

When associations are discovered between common genetic polymorphisms and brain-asymmetrical traits or lateralized behaviors, the genes that are implicated can, in principle, be either slight modifiers of asymmetrical outcomes or else essential for patterning developmental lateralization. Genetic association studies using common polymorphisms, in which effects are expected to be small, should also be complemented by investigating families that show unusually high rates of atypical lateralization of structure, function, or behavior, for example, an unusually high rate of left-handedness (Willems et al., 2014). Such families may carry genetic

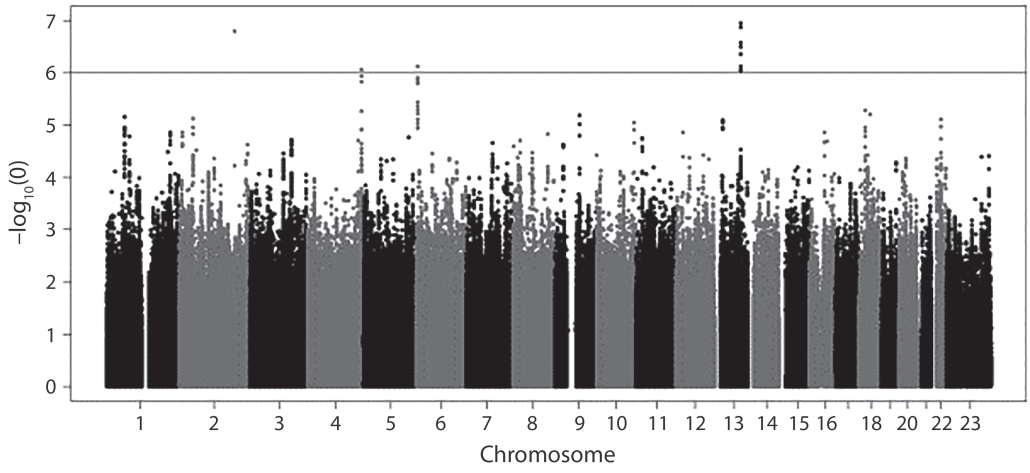

Figure 42.5 Genome-wide scan for polymorphisms associated with an index of gray matter asymmetry, measured within and around the planum temporale (cerebral cortical region). The *x*-axis represents the chromosomes laid end-to-end, from short to long arms, in ascending numerical order from left to right. The *y*-axis shows the significance of association for each of over 2.5 million individual polymorphisms located at unique points in the genome. Shading represents the different chromosomes. The horizontal line represents the threshold used for defining suggestive association ($P = 1 \times 10^{-6}$). No result reached genome-wide significance ($P = 5 \times 10^{-8}$), but genes involved in steroid hormone biology were found to have an enrichment of low association *P* values, within the overall distribution of signals. Figure reproduced from Guadalupe et al. (2015).

mutations that are rare in the population but that have large effects on lateralized brain development when they occur (McManus et al., 2013; Willems et al., 2014). Genes identified through studying such families would be likely to have key roles in setting up brain lateralization, rather than having downstream, modifying effects on lateralized traits. Epigenetic effects on brain lateralization, owing to variation in the structure and function of chromosomes that is not attributable to DNA polymorphisms, are also a possibility (Brucato, DeLisi, Fisher, & Francks, 2014). Epigenetic variation involves chromosomal properties such as DNA methylation (Gordon et al., 2012) or chemical modifications of proteins that associate with DNA in the cell nucleus (Gräff & Mansuy, 2008), and this variation can be caused heritably, environmentally, or randomly.

8. Reconciling Theme with Variations: Are Strong Genetic Effects on Lateralization Compatible with Weak Heritabilities?

As we've discussed, lateralization at the population level is characteristic of many aspects of human brain structure, function, microanatomy, neurophysiology, and behavior, right across the life span. For example, handedness and language dominance are lateralized at the population level at a rate of 90% or more. Lateralized genetic-developmental programs are required to create differently adjusted properties of neural circuitry in the two hemispheres. Such molecular programs have been described for the brains of fish and for the viscera of humans and other species. Furthermore, hemispheric differences in adult gene expression that involve multiple individual genes, such as those identified by Karlebach and Francks (2015), are likely to underlie functional lateralization for language and other aspects of cognition. It is therefore clear that genes have a major role in setting up and maintaining the brain lateralizations that are found in the majority of people.

A strong genetic effect on a lateralized trait's asymmetric mean in the population can be reconciled with a weak genetic effect on its variance (i.e., low heritability) if lateralized developmental programs become randomized in their directions in response to environmental or genetic disruptions. The notion of randomization in response to disruption is supported by the known effects of certain genetic mutations that cause situs inversus of the viscera with 50% probability. The picture can be further complicated by genetic mutations that affect processes downstream in development from the primary direction-setting mechanisms. Again the viscera can illustrate the various genetic mutations affecting visceral asymmetry that cause complex and partial disruptions of laterality known as *heterotaxias* (Peeters & Devriendt, 2006). In these conditions, specific organs or clusters of organs become located abnormally on the left-right axis and are sometimes malformed (Peeters & Devriendt, 2006). While the mirror reversal in situs inversus can have no direct medical consequences, misplacement or malformation of organs in heterotaxias often has health implications (Peeters & Devriendt, 2006). In terms of brain lateralization, although the key developmental mechanisms have not been identified, genetic variation is likely to affect the degree of lateralization in addition to its direction on the left-right axis (Arning et al., 2013). As for the viscera, functional consequences in the brain (for cognitive performance) are most likely to occur when lateralization is incomplete, or when certain functions become dissociated with respect to each other, rather than when lateralization develops completely in the reverse direction to the typical form. Observations regarding academic performance and mixed hand dominance support this notion (see section 6). Again by analogy with heterotaxias, distinct lateralized traits such as language dominance and hand preference, which develop consistently with respect to each other in the typical brain, might become dissociated as a result of disruptions of a lateralized genetic-developmental program. Such traits would then appear to be largely uncorrelated in the population, even though they may stem from overlapping mechanisms in typically developing people. Furthermore, it seems likely that some early developmental disruptions, whether they are environmentally mediated, genetic, or random in nature, might be localized to specific brain regions or networks. This could then give rise to an array of different outcomes, depending on how early or late they occur during development.

9. Future Research and Implications

For the reasons discussed herein, further research on the genetic bases of brain lateralization will require complementary approaches that are focused on both the *majority average form* and also on lateralized *trait variances*. A powerful method to study the mean form is transcriptomic analysis of left and right CNS regions in postmortem human tissue from a necessarily limited number of donors, whereas trait variance can best be studied in data sets of thousands of participants, using, for example, genome-wide association scanning and brain imaging.

Improved transcriptomic and proteomic studies will be required to measure lateralized gene activity more accurately than has been achieved to date. Given the findings of Karlebach and Francks (2015) on

lateralization of gene expression in the adult cerebral cortex, the study of embryonic, fetal, and developing cerebral cortices should also benefit greatly from further studies that make use of larger numbers of postmortem samples than used previously, as well as methods such as functional gene set analysis and meta-analysis. Furthermore, new studies will ideally be based on the most accurate and up-to-date method of transcriptome analysis, which is currently RNA sequencing (Külahoglu & Bräutigam, 2014). This method has not yet been used to investigate lateralization of gene expression in the human brain.

Beyond the cerebral cortex, other regions of the brain have been less well investigated for genetic lateralization. Only the study by Johnson et al. (2009), which was based on four postmortem fetal brains, included cerebellar, subcortical, and hippocampal tissue in addition to cerebral cortical tissue. As noted, the epithalamus (subcortical) is a crucial site of CNS asymmetrical development in zebrafish, and the human dorsal thalamus is therefore worth investigating in this regard. The reported lateralization of human embryonic arm movements at 10 weeks of gestation, which occurs before most or all neural connections between the arms and forebrain are in place (Clowry, 2007), also suggests that more caudal regions of the CNS are functionally lateralized at early developmental stages. Future studies of asymmetrical gene activity in the human brain should therefore investigate brain regions beyond the cerebral cortex.

Through genetic studies of lateralization it may become possible to understand some of the properties of cerebral cortical regions that are especially suited to language perception (Morillon et al., 2010) by contrasting left-sided regions at the genetic level against their "natural control" homologue regions on the right. This approach can identify molecular profiles that are likely to specify the fine-tuning of neuronal circuitry for particular types of information processing. Genetic networks arising from this work may then be manipulated in animal models: for example, genetically modified rodents with more *human left-type* cortices may be compared to those with more *human right-type* cortices. Multilevel neurobiological analyses in model organisms may then deliver a new understanding of how one human hemisphere is preferentially adapted for carrying out particular functions. The data of Karlebach and Francks (2015) suggest that this will be challenging, however, because lateralization of gene expression in the adult superior temporal cortex involved subtle left-right differences over many genes. To model these effects in cell and animal models would therefore require the simultaneous and precise manipulation of many genes, and this may not be feasible with current technology. Lateralization of gene expression will also need to be studied at the level of individual neuronal and glial subtypes, rather than at the level of mRNA derived from whole tissue excisions.

As we've already discussed, psychiatric and cognitive disorders including schizophrenia and dyslexia have been associated with alterations of brain structural and/or functional asymmetries. Genes involved in brain lateralization may therefore influence these diseases, in terms of both individual susceptibility and disorder progression. Further progress toward understanding the genetic basis of human brain lateralization is needed in order to assess the relevance to these disorders.

Lateralization is also of considerable interest with respect to human evolution. Many of our higher cognitive functions show cerebral hemispheric dominance, while our language faculty is likely to have co-opted aspects of our motor circuitry (French & Fisher, 2014), perhaps even involving a hand-gestural component in its origins (Corballis, 2003). Genes that are found to be involved in human brain lateralization may therefore be analyzed informatively with respect to their comparative genomics: whether they show evidence for having undergone positive selection in human or primate evolution.

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NOTE

1. Following standard nomenclature, genes are denoted in italics, proteins in regular font. Uppercase letters denote the human version of the gene (i.e., *FOXP2*), lowercase the mouse version of the gene (i.e., *Foxp2*).

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