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Exploring human brain lateralization with molecular genetics and genomics

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Lateralizations of brain structure and motor behavior have been observed in humans as early as the first trimester of gestation, and are likely to arise from asymmetrical genetic–developmental programs, as in other animals. Studies of gene expression levels in postmortem tissue samples, comparing the left and right sides of the human cerebral cortex, have generally not revealed striking transcriptional differences between the hemispheres. This is likely due to lateralization of gene expression being subtle and quantitative. However, a recent re-analysis and meta-analysis of gene expression data from the adult superior temporal and auditory cortex found lateralization of transcription of genes involved in synaptic transmission and neuronal electrophysiology. Meanwhile, human subcortical mid- and hindbrain structures have not been well studied in relation to lateralization of gene activity, despite being potentially important developmental origins of asymmetry. Genetic polymorphisms with small effects on adult brain and behavioral asymmetries are beginning to be identified through studies of large datasets, but the core genetic mechanisms of lateralized human brain development remain unknown. Identifying subtly lateralized genetic networks in the brain will lead to a new understanding of how neuronal circuits on the left and right are differently fine-tuned to preferentially support particular cognitive and behavioral functions.

Keywords: genomics; genetics; transcriptome; neurodevelopment; lateralization; asymmetry; brain

Introduction

Functional lateralization for language and other cognitive processes is an intriguing aspect of the human brain, which is often disrupted in cognitive disorders and neuropsychiatric diseases, including dyslexia and schizophrenia.[1,2] Despite the importance of lateralization for many aspects of human cognition, the genetic basis has remained largely mysterious, both with reference to the genetic–developmental program and the molecular basis of lateralized neurophysiology in the adult brain. Characterizing the genetic basis of brain lateralization may eventually have important clinical and educational implications.

In this perspective paper, I first discuss lateralization with reference to its early appearance in human brain and behavioral development, and how animal models and visceral lateralization may inform us about human brain lateralization. I then discuss what is known about the genetic basis of human brain lateralization, first from postmortem studies that have contrasted gene expression levels in the left and right hemispheres during development and adulthood, and then from studies of human genetic polymorphisms and their associations with variance in adult brain and behavioral lateralization. Finally, I discuss more generally how genetic analysis can influence our understanding of brain lateralization, disorders, and healthy cognition.

Population-level asymmetry

Lateralization of human brain and behavior begins early in development. Already at 10 weeks gestational age, 85% of 72 human fetuses studied with *in utero* ultrasound scanning by Hepper *et al.*[3] moved their right arms more than their left arms. This percentage is similar to the adult rate of right-handedness and indicates an embryonic precursor

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of this landmark human behavioral lateralization.[3,4] At 11 weeks of gestation, the choroid plexuses of the human embryonic brain show an average leftward asymmetry of size,[5] again based on *in utero* ultrasound scanning. The choroid plexuses are highly vascularized structures that control the composition of cerebrospinal fluid in the lateral ventricles, and may affect broader lateralized development of the brain via the secretion of diffusible signaling molecules into the ventricles.[6,7] 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, rather than the left.[8] The preference for fetal thumb sucking at the individual level was also strongly predictive of handedness aged 12 years in longitudinal follow-up analysis of 75 of the same subjects.[4,9] Furthermore, various population-level structural brain lateralizations, including those of cerebral cortical regions important for speech and language, have been studied from the second trimester and onward throughout fetal and infant development using methodologies, including ultrasound, postmortem analysis, and magnetic resonance imaging (MRI).[10–19]

The appearance *in utero* of lateralization of brain and limb activity indicates a genetically mediated program of central nervous system (CNS) development, which is inherently lateralized to a degree. In addition, well-described lateralizations of adult brain functions, such as those related to language, visuospatial cognition, and hand motor control,[2,20–22] even if of degree rather than absolute, imply left–right differences in the activity of genes whose products modify information-processing properties of neuronal circuitry. For example, left-hemispheric neural oscillatory frequencies have been reported to correspond to syllabic speech rhythms in a manner that may preferentially support auditory and language processing.[23] It is to be expected that such neurophysiological lateralization is reflected at the molecular genetic level, such as lateralization of protein activities that modulate the signaling properties of neural networks. Genes affecting the signaling properties of neuronal circuitry include those involved in synaptogenesis, neurotransmission, and synaptic cell adhesion;[24,25] these classes of genes are therefore good candidates to study in relation to brain asymmetrical function in the adult. Lateralization of gene activity in the brain is also suggested by left–right differences of microanatomy within auditory and language regions of the adult temporal lobe. For example, it has been observed by postmortem analysis that left superficial layers of the cortex contain a greater number of large pyramidal cells than the right layers;[26] large neurons with a pyramidal-shaped cell body and two types of dendritic trees, pyramidal cells are involved in synaptic integration and plasticity.[27]

Lateralization of central nervous system structure and function is a feature of many vertebrate clades.[1,28,29] Lateralization manifests, for example, in direction-biased turning behavior of schooling fish and in reactions to visual stimuli in chicks.[29] Indeed, some of the crucial developmental events underlying CNS lateralization have been elucidated in bird and fish species.[29–31] In zebrafish, in particular, molecular characterization of CNS lateralized development is at a relatively advanced state.[30] 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.[30] The epithalamus then innervates asymmetrically and influences broader CNS development in a lateralized manner.[30] The lateralized 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 and lungs), which include the Nodal signaling molecule.[30] In *Xenopus*, lateralization of tadpole swimming behavior (in terms of clockwise versus anticlockwise turning preference) is also linked to visceral organ lateralization.[32]

However, it is not clear how closely mechanisms of lateralized brain development in fish, birds, and amphibians are related to those in humans. Crucially, humans with the rare genetic condition situs inversus, involving a mirror reversal of visceral asymmetries on the left–right axis, were found, in the largest studies of this issue, to have normal population rates of right-handedness and left-lateralized language dominance (assessed with dichotic listening).[33,34] These findings suggest an early developmental dissociation between visceral and, at least some, brain asymmetries in humans, which contrasts with the process of epithalamus-driven lateralized development of the zebrafish forebrain. Nonetheless, studies of zebrafish have

clearly indicated crucial roles of lateralized genetic–developmental programs in creating brain structural and functional asymmetries, motivating the search for such mechanisms in humans. Furthermore, as alterations of visceral lateralization can occur as a consequence of heterogeneous mutations in various different genes with diverse molecular functions (discussed further later), it may be that at least some of the molecular pathways involved can also affect brain lateralization.

Although mice have not been widely reported to show population-level asymmetries of brain structure and function, lateralization has recently been reported using imaging *in vivo*,[35,36] and hippocampal lateralization has been studied at the molecular level in relation to learning and memory.[37,38] In addition, subtle population-level paw preference in reaching tests has been observed in inbred mice.[39] However, the subtlety of these lateralizations required large samples to detect them, and they varied in leftward versus rightward direction depending on the specific task.[39] Rats have shown a stronger population-level bias (73% right paw preference)[40] than mice, as well as hemispheric differences in spatial cognition[41] and proteomic lateralization in the hippocampus.[42] Apes have also shown evidence for population-level handedness, and some structural brain lateralizations similar to those found in regions important for language in humans.[43–46]

Various mammalian species may therefore prove to be useful models for understanding aspects of the genetics and development of human brain lateralization. Research with nonhuman primates, particularly apes, is severely restricted practically and ethically, however, and human brain lateralizations linked closely to language may not manifest sufficiently, or at all, in rodents. Therefore, genetic studies with a direct focus on human tissues and traits will remain important for making progress in this field.

Lateralized gene expression

Many of the most prominent neuroanatomical and functional lateralizations of the human brain involve the cerebral cortex, and several studies have attempted to identify genes that are asymmetrically active in this tissue during development or in adulthood.[47–51] These studies used postmortem samples and measured the levels of messenger RNA (mRNA) of thousands of genes simultaneously, an approach known as *transcriptomic profiling*. The level of mRNA of a given gene within a tissue is correlated with the abundance of protein that is encoded by that gene, and therefore a higher mRNA level generally indicates relatively higher activity of the corresponding protein. Sun *et al.*[47] studied human fetuses at 12–19 weeks of gestation, using a transcriptomic technique known as *serial analysis of gene expression* (SAGE), and identified quantitatively higher right-than-left cortical mRNA levels of the transcription factor LMO4 at 12–14 weeks gestation, which was not evident at 19 weeks gestation. Gene products that regulate the mRNA expression of multiple other genes, transcription factors can therefore influence many cellular and developmental processes. LMO4 has since been shown to affect neurogenesis and axonal projection in mice.[52] Unilateral manipulation of the LMO4 gene (*Lmo4*) in developing mice, which involved the specific knockdown of *Lmo4* mRNA in one embryonic hemisphere *in utero*, was shown to result in suppressed early neurogenesis in that hemisphere, causing asymmetries of functional area formation, neuronal production, and axonal projection.[52] Ultimately, 12-week-old mice that had been treated in this way as embryos showed lateralization of some behaviors, including paw preference and turning during swimming.[52] In contrast, nontreated mice showed no population-level lateralization of these behaviors, and mostly no individual-level lateralization either.[52] However, unilateral manipulation of a cortically expressed transcription factor might be expected to give rise to asymmetrical developmental outcomes, owing to its effects on processes such as neurogenesis and functional area formation, even if that transcription factor is not naturally important for lateralized development. Asymmetry of LMO4 cortical expression in the human fetus has yet to be replicated by additional researchers, and therefore remains a landmark finding in need of further confirmation.

Using a more modern technology for transcriptomic profiling based on microarrays, Lambert *et al.*,[51] did not identify significant asymmetries of gene expression in frontal or temporal cortical tissue from human fetuses aged 17 and 19 weeks (i.e., later in gestation than the LMO4 lateralization observed by Sun *et al.*[47]). Pletikos *et al.*[50] used microarray technology to study postmortem neocortical regions across the human life span from embryo

to old age, which included the fetal age range studied by Sun *et al.*,[47] and again did not find significant evidence for differential left–right gene expression either at the level of individual genes or in the context of global trajectories of changes in gene expression over time. Another microarray-based study by Johnson *et al.*[49] also did not identify significant lateralization of cortical mRNA expression in postmortem tissue samples taken from mid-fetal human brains aged between 18 and 23 weeks of gestation. A recent expression-profiling study from adult brain tissue also failed to identify significantly asymmetrically expressed genes.[48]

However, all of these transcriptomic studies were based on only small numbers of postmortem samples from any particular developmental stage. Human postmortem tissue samples that are suitable for transcriptomic studies are not easily available to researchers. For the transcriptomic-screening stage of their study, Sun *et al.*[47] used tissue from two fetuses at 12 weeks gestation, two at 14 weeks, and one at 19 weeks; Lambert *et al.*[51] analyzed one fetus at 17 weeks and one fetus at 19 weeks; Johnson *et al.*[49] analyzed four mid-fetal brains; and Hawlyrycz *et al.*[48] analyzed two adult brains for which data from both hemispheres were available. The study by Pletikos *et al.*[50] was the most substantial in relation to sample size, being based on 57 brains spanning the life span, from embryonic material to adult old age, but the number of brains at any given stage was again low, averaging less than one brain per embryonic/fetal stage for the prenatal material and, similarly, throughout infancy, childhood, and the teenage years. In addition, for analyzing lateralized expression, Pletikos *et al.*[50] grouped brains within each set of four consecutive ages, thus limiting the number of samples within any single analysis, including for adult samples.

None of these transcriptomic studies were well powered in statistical terms to detect subtle contrasts of gene expression between the left and right sides that may be developmentally transient in nature, in the context of testing thousands of genes and performing appropriate false-discovery correction. The studies were generally poorly powered to detect functionally relevant asymmetries if, for example, they involved left–right differences of less than 1.5-fold expression for a given gene. Yet, lateralized expression differences of this limited magnitude may still be biologically and functionally significant, especially when considered over multiple genes that are functionally related or interacting to influence neuronal and circuit properties. Accordingly, Karlebach and Francks[53] applied several unutilized approaches in a recent re-analysis of the data of Pletikos *et al.*[50] and Hawlyrycz *et al.*[48] to increase the power to detect lateralized gene expression in adult cerebral cortex. First, data from the superior temporal and primary auditory cortex were specifically selected out of all cortical regions available on the basis of reported lateralization of these regions in relation to function, neurophysiology, gross anatomy, and histological microanatomy (see above). Data from Pletikos *et al.*[50] for all 13 adults within the age range 18–55 years were then entered into a single analysis without further subdividing by age, followed by a meta-analysis with the data of Hawlyrycz *et al.*[48] Bayesian smoothing of gene expression variance estimates was used to aid statistical testing in these relatively 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 (GO) classifications, by which gene products are grouped hierarchically according to molecular functions, biological processes, and cellular components.[54] Robust evidence for lateralization was found, particularly at the level of gene sets for synaptic transmission, signal transduction, glutamate receptor activity, nervous system development, and transmission of nerve impulses.[53] Lateralization within these gene sets was consistent between the datasets of Pletikos *et al.*[50] and Hawlyrycz *et al.*,[48] and the findings arose despite having tested all GO sets without reference to their neuronal relevance, while performing false-discovery rate (FDR) correction for multiple testing.[53] The genes involved have clear neuronal functions likely to affect signaling, learning, and information-processing properties of circuitry differently in the two hemispheres.[53] Furthermore, lateralization within gene sets that are defined for their developmental roles indicated that transcriptional factors and other developmentally important proteins continue to have roles in maintaining lateralized function in the adult brain.[53] Overall, the findings of Karlebach and Francks[53] indicate a broad-based, lateralized fine-tuning of gene expression at the genomic level, which may have wide-ranging but unpredictable implications for diverse

neurophysiological mechanisms and properties. It is therefore likely that the combinatorial effects of small quantitative differences over many genes determine neurophysiological outcomes that underlie lateralized function in the superior temporal and auditory cortex.

In light of the detection of lateralized gene expression in postmortem adult brain data,[53] the study of embryonic, fetal, and developing cerebral cortex would probably also benefit from more studies using greater numbers of samples and the application of methods such as GO analysis and meta-analysis. Furthermore, new studies will ideally be based on the most accurate method of transcriptome quantification possible, which is currently RNA sequencing.[55] This method has not yet been used to investigate lateralization of gene expression in the brain.

In comparison to the cerebral cortex, other regions of the brain, including the subcortical structures, mid brain, and hindbrain, have been less well investigated for molecular lateralization, despite being potentially important developmental origins of brain asymmetries. Only the study by Johnson *et al.*,[49] based on four postmortem fetal brains, included cerebellar, subcortical, and hippocampal tissue. As noted earlier, the epithalamus (subcortical) is a crucial site of CNS asymmetrical development in zebrafish, and the human dorsal thalamus is therefore worth investigating in relation to lateralization. The lateralization of embryonic arm movements at 10 weeks of human gestation, occurring before most or all neural connections between the arms and forebrain have been established,[56] also suggests that more caudal regions of the CNS are functionally lateralized at early developmental stages in humans. Future studies assessing lateralization of gene activity in the human brain should therefore be targeted more broadly than the cerebral cortex. Left–right differences of mRNA expression may be more detectable in other structures, particularly during embryonic development.

Variations of asymmetry

Another potential avenue for identifying genes involved in brain lateralization is to correlate genetic polymorphisms in the population with inter-individual variation in asymmetries of human brain structure, function, and behavior. To what extent are variations in asymmetries attributable to the combined effects of genetic polymorphisms overall? Heritability can be measured through studies of twins, in which monozygotic pairs indicate how similar individuals are when they are genetically identical, in contrast to dizygotic pairs who share on average only half of their chromosomes. On the basis of a limited number of studies thus far, population variances in asymmetries of human brain structure, function, and behavior have shown evidence for zero to modest heritability.[57–62] For example, the heritability of left-handedness was accurately estimated at close to 24% in a large meta-analysis study that involved data from more than 25,000 families with twins.[57] 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. A weak effect of genomic variation on the probability of becoming left-handed is therefore indicated; but it is also clear that environmental effects and/or random effects during development play a substantial role.

In a study of 374 human twins using diffusion tensor imaging (DTI) to study white matter tracts in the brain, the heritability of asymmetry indexes ranged from 0% to 47%, depending on the particular fiber tract and DTI-based metric of its white matter integrity.[60] Frontal and temporal regions showed the most significant mean asymmetries,[60] and genetic factors were estimated to account 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.[60] Again, substantial environmental or random effects on asymmetry are therefore indicated by these data, in addition to low-to-moderate genetic influences.

Eyler *et al.*[63] analyzed asymmetries of adult regional cerebral 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. They found significant heritabilities of regional cortical areas and thicknesses, but the data also indicated that left–right homologous regions of the two hemispheres shared most or all of the genetic contributions to their variances. In other words, heritability was mostly bilateral, and there was little evidence for genetic effects that were different between the hemispheres

and that would therefore contribute to asymmetry.[63] Larger imaging studies of twins are required to more accurately assess the degree to which brain structural asymmetries may be heritable, but it is likely, given current evidence, that such heritabilities are generally low to moderate.

Interestingly, when developmental mechanisms underlying visceral lateralization (of the heart and lungs, for example) 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.[64] This has been observed in various vertebrate species in the laboratory, and in humans the naturally occurring condition has a population frequency of roughly 1 in 10,000. The normal pattern of lateralized visceral development (e.g., heart toward the left) has its origins in asymmetrical motions of protein cilia located within a pitted structure called the *node*, on the ventral surface of very early mammalian embryos.[65] Cilia rotate in only one of two theoretically possible orientations, because of their protein components being constructed by inherently chiral amino acids[65] (all life on Earth uses L-form amino acids rather than mirror image D-forms). Beating of the cilia causes a unidirectional flow of fluid within the node, causing mechanical and/or chemical differences between the left and right sides[66] that are thought to trigger differential gene expression. Even before this, lateralization may be initiated by molecular chirality of subcellular components, such as cytoskeletal elements.[67,68] Downstream genetic cascades then elaborate these primordial left–right differences into different developmental fates for the left and right of the embryonic viscera.[65,69] 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 in the embryo. Left–right differentiation of the viscera still proceeds, but it is triggered with an equal likelihood in either orientation by random and slight asymmetrical fluctuations of key developmental gene activities in the early embryo.[31,69]

The concept of randomization resulting from a genetic loss of consistent, direction-giving mechanisms early in development has also been considered extensively in relation to left handedness,[70–73] and may be relevant to other aspects of human brain lateralization. However, direct evidence is lacking because core genes and mechanisms involved in human brain lateralization are unknown. As mentioned earlier, people with situs inversus have normal population proportions of left-handedness and left-lateralized language dominance, suggesting a developmental dissociation of visceral lateralization from at least some aspects of cerebral lateralization in humans. Nonetheless, the concept of a random contribution to brain asymmetry, occurring when a normally lateralized genetic–developmental program is disrupted, is broadly consistent with the weak heritability estimates for brain-asymmetrical traits and behaviors that have been measured in studies of twins. In twin studies, a random component to trait variability is assigned to the nonshared environmental component of variance.

Some studies have found that variability in lateralized brain structures, functions, or behaviors is weakly associated with cognitive or behavioral performance, including verbal ability and scholastic achievement.[74–83] For example, Bjork *et al.*[79] analyzed data on 10,612 children from a British birth cohort and observed an association between mixed-handedness and slightly reduced performance on school tests, including tests of verbal ability and mathematics. This effect was seen only in those children who also scored within the lower third on a measure of right hand motor performance, suggesting complex interactions between variances in motor skill, lateralization, and cognition. Catani *et al.*[81] studied 50 subjects with DTI and found that individuals with more symmetric patterns of white matter connections in the perisylvian language network were better at remembering words using semantic association. Some specific aspects of cognition might therefore benefit from relatively more bilateral organization, whereas general academic performance may benefit from relatively more lateralization. Nonetheless, despite these intriguing findings, it is clear that reorganizations of lateralized structure and function, such as left-handedness and atypical language lateralization, can occur developmentally without major consequences for many aspects of cognitive or behavioral performance.[76,84,85]

It is also increasingly clear that the variances in different aspects of brain-asymmetrical structure and function can be largely dissociated from each other.[2,62,85–89] 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 (fTCD) to assess language dominance.[85,90] Furthermore, Liu *et al.*[89] analyzed intersubject variance in lateralized intrinsic brain activity during rest, using fMRI in 300 participants, and found the variance in lateralization to be composed of four separate 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. In other words, either side is able to take on a dominant role for a particular lateralized function, if the requirement to do so is initiated early enough in development. This plasticity underscores again that lateralization of gene activity is likely to involve only subtle, quantitative, and developmentally re-adjustable variations on what are bilaterally homologous themes at the molecular level.

Specific polymorphisms within some individual genes and genetic networks have been associated with modifying effects on human brain or behavioral lateralization.[91–101] Measures of lateralization used in these genetic association studies have included quantitative indices of lateralized hand motor skill,[92] binary measurement of hand preference,[98] and lateralization of auditory language dominance as assessed by dichotic listening.[99] The implicated genes have functions including transcriptional regulation (*FOXP2*),[97] synaptic adhesion (*LRRTM1*),[92,102] steroid hormone biology (*AR*),[98] dopamine release (*CCKAR*),[91] glutamatergic neurotransmission (*GRIN2B*),[99] and left–right lateralization of the viscera (*PCSK6*).[93,94] However, all of these findings remain tentative and require further validation. All were based on samples of hundreds rather than thousands of individuals, and were therefore too small to reliably establish effects of individual, common polymorphisms on what are likely to be complex and etiologically heterogeneous traits.[103,104] Studies using thousands of participants will be required[104] to unequivocally identify individual, common genetic effects on traits such as cerebral cortical asymmetries, white matter asymmetries, and handedness, especially in light of the generally low heritabilities of these traits. Such large-scale genetic studies have recently been performed for various multifactorial human traits including human height and body mass index, and complex diseases such as diabetes and schizophrenia, resulting in statistically robust findings.[105,106] However, the only genetic studies of brain asymmetries performed on this scale were two recent genome-wide association study meta-analyses, which were both based on just over 3000 subjects.[107,108] 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.[108] The other study focused on asymmetry of the caudate nucleus and did not find significantly associated genetic polymorphisms.[107]

It is not clear how a reported association between handedness and polymorphisms within visceral asymmetry genes[93] might be consistent with the reported dissociation of situs inversus from handedness that was mentioned earlier.[33] It may be that some elements of visceral asymmetrical molecular cascades are indeed shared with those affecting human brain asymmetries. Consistent with this, situs inversus in mice may influence subtle molecular lateralization in the hippocampus.[109] However, confirmation of the human genetic association data is required.

In general, studies that test for associations of common genetic polymorphisms with brain-asymmetrical traits or lateralized behaviors have the potential to identify genes that either slightly modify asymmetrical outcomes or are essential for setting up early developmental lateralization in the embryo. Such genetic studies should also be complemented by investigating unusual families that show particularly high rates of altered lateralization in one or more domain, for example, a markedly elevated rate of left-handedness.[84] These families may be affected by individually infrequent genetic mutations with relatively large effects on lateralized brain development.[71,84] Genes identified in such families would be more likely to have key roles in establishing brain lateralization, rather than having secondary or modifying effects on lateralized outcomes. Epigenetic effects on brain lateralization, owing to variation in the structure and function

of chromosomes that is not attributable to DNA polymorphisms, should also be investigated.[110] Epigenetic variation, not necessarily linked to DNA sequence variation, involves chromosomal properties such as DNA methylation[111] or chemical modifications of histones and other proteins that associate with DNA in the cell nucleus,[112] variation that can be caused environmentally, randomly, or heritably.

Asymmetry more apparent than real?

As outlined above, population-level lateralization has been widely reported for various aspects of human brain structure, function, neurophysiology, microanatomy, and behavior, as assessed with numerous different approaches and technologies, and at various points throughout the life span. Lateralized genetic–developmental programs, strongly implied by this wealth of evidence, are probably required to specify differently fine-tuned properties of neural circuitry in the two hemispheres. Lateralization at the genetic level is therefore likely to be real—-both with reference to developmental processes and adult function. At the developmental level, lateralized molecular programs have been elucidated for the brains of some vertebrate species (not humans), and for the viscera of humans and other species. For the human brain, improved transcriptomic and proteomic studies are required to detect, and more accurately measure, lateralized gene activity. Hemispheric differences in adult gene expression, which involve multiple individual genes, such as those identified by Karlebach and Francks,[53] are likely to underlie functional lateralization for language and other aspects of cognition.

A clear genetic effect on a lateralized trait's asymmetric mean in the population and a weak genetic effect on its variance (i.e., low heritability) can be reconciled if normally lateralized developmental programs lose their consistent directional biases by becoming randomized in response to environmental or genetic disruptions. This concept is supported by the known effects of genetic mutations in nodal ciliary genes that underlie visceral lateralization, causing situs inversus with 50% probability. However, it is also important to note that various genetic mutations affecting visceral asymmetry pathways can cause complex and partial disruptions of laterality.[113] In these conditions, known as *heterotaxias*, specific organs or groups of organs are misplaced on the left–right axis and may also be malformed.[113] In contrast to the complete mirror reversal in situs inversus, which has no direct medical consequences, the disruption and misplacement of organs in heterotaxias often has clinical implications.[113] By analogy, genetic variation is likely to influence the degree of lateralization of brain systems in addition to the direction of lateralized development on the left–right axis.[96] Functional consequences for cognitive or behavioral performance may be most apparent when lateralization is incomplete, or when closely interdependent functions become relatively dissociated compared to the typical organization, rather than when lateralization of a system develops fully but in the atypical direction. The findings mentioned above regarding academic performance and mixed hand dominance support this concept. Furthermore, different lateralized traits such as language dominance and hand motor control, which develop in a consistent fashion with respect to one another in the typically organized brain, may become dissociated in the event of early disruptions of a subtly lateralized genetic–developmental program, again by analogy with heterotaxias. This is expected if environmentally mediated, genetic, or random effects can be locally restricted to individual regions or networks of the developing brain. However, different aspects of human brain lateralization may also have relatively or completely distinct genetic and developmental bases, for example, with some linked to visceral lateralization and others not. Understanding the genetic basis of brain lateralization will benefit from approaches that are focused both on the typical *majority mean form* and on lateralized *trait variances*. Comparative transcriptomic analysis of left and right CNS regions in postmortem human tissue provides one way of studying the typical form, whereas association studies correlating genetic variation with quantitative measures derived from brain imaging provide one way to study variance.

Alterations of the average pattern of human brain lateralization are orders of magnitude more common than those of the viscera, and it has been suggested that minority forms of brain lateralization may sometimes have survival and selective evolutionary advantages.[114,115] For example, as noted earlier, certain aspects of cognitive performance may benefit from relatively bilateral representation. However, compared to the viscera, brain lateralization may have greater developmental plasticity and

therefore may be better able to respond to and tolerate early reorganization. In addition, brain lateralization is more anatomically subtle than visceral lateralization, and may be more easily perturbed without severely disrupting function. It may therefore be unnecessary to invoke advantages of having forms of human brain lateralization that are divergent from the average pattern in order to explain their relatively high frequency in the population. The genetic study of human brain lateralization is likely to affect our evolutionary understanding, through pinpointing specific genes and genetic networks that can be analyzed in relation to genomic signals of positive or negative selection.

The genetic study of lateralization also has the potential to pinpoint subtle molecular differences in homologous left–right regions of the brain, which control the fine-tuning of neuronal circuitry for particular types of information processing, as many cognitive processes are lateralized to a degree. For example, it may be possible to understand some of the properties of cerebral cortical regions that are especially suited to language perception[23] by contrasting left-sided regions at the genetic level against their natural control homologous regions on the right. The relevant genetic networks might then be manipulated informatively in animal models. The generation of genetically-modified mice with more *human left-type* cortices compared to mice with more *human right-type* cortices may facilitate contrasting of left–right neuronal circuit properties at multiple levels, possibly yielding insights into how one hemisphere becomes slightly preferentially adapted for carrying out a particular function. However, given that lateralization of gene expression in the adult superior temporal cortex apparently involves quantitative left–right differences over multiple genes, the future modeling of these effects in cell and animal models may require the simultaneous manipulation of many genes, which will probably depend on significant improvements in technology. Lateralization of gene expression will also need to be studied at the level of individual neuronal and glial subtypes.

Many studies have found cognitive and psychiatric disorders to be modestly associated with alterations of brain asymmetry and/or lateralized behavior,[116–129] including schizophrenia, autism, and language impairment, although not in all populations affected with these disorders.[124,130] 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.[128] Both findings have subsequently received further support.[120,127,129] People with autism spectrum disorders have been reported to show changes of cortical structure, handedness, and functional lateralization for language.[121] Genetic variations and environmental influences that contribute to these psychiatric disorders may therefore affect brain lateralized development and function. It follows that identifying genes involved in brain lateralization may elucidate some of the developmental pathways and processes affecting susceptibility to psychiatric disorders.[131] Similarly, neurological conditions including Alzheimer's disease and semantic dementia can involve lateralized neuropathology and might therefore sometimes involve dysregulation of lateralized molecular processes. In principle, genes involved in lateralization may influence these neurological diseases in relation to both individual susceptibility and patient progression. However, further progress toward understanding the genetic basis of human brain lateralization is needed in order to assess the importance of CNS molecular lateralization in the clinical setting. In particular, an understanding of lateralization at the genetic level may help to reveal why some asymmetries, which can clearly be reconfigured early in development without major consequences for performance, become less plastic throughout the lifetime in response to disease or injury.

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Conflicts of interest

The author declares no conflicts of interest.

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