

Review

How Asymmetries Evolved: Hearts, Brains, and Molecules

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Abstract: Humans belong to the vast clade of species known as the bilateria, with a bilaterally symmetrical body plan. Over the course of evolution, exceptions to symmetry have arisen. Among chordates, the internal organs have been arranged asymmetrically in order to create more efficient functioning and packaging. The brain has also assumed asymmetries, although these generally trade off against the pressure toward symmetry, itself a reflection of the symmetry of limbs and sense organs. In humans, at least, brain asymmetries occur in independent networks, including those involved in language and manual manipulation biased to the left hemisphere, and emotion and face perception biased to the right. Similar asymmetries occur in other species, notably the great apes. A number of asymmetries are correlated with conditions such as dyslexia, autism, and schizophrenia, and have largely independent genetic associations. The origin of asymmetry itself, though, appears to be unitary, and in the case of the internal organs, at least, may depend ultimately on asymmetry at the molecular level.

Keywords: bilateria; cerebral asymmetry; handedness; language; molecular asymmetry; situs



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1. The Symmetrical Background

The evolution of asymmetry should be understood in relation to its opposite, the overwhelming bilateral symmetry which characterises the vast clade of organisms to which we belong. These are the bilateria. They go back at least to the Cambrian, beginning some 541 million years ago, and probably slightly earlier into the late Protozoic [1]. Bilateral symmetry emerged in species that move in space, and depends on the prior establishment of two bodily axes. The antero–posterior axis may have arisen first in relation to feeding, involving openings at head and tail separated by a through-gut [2], as in worms that burrow. The demands of locomotion led further to sense organs, such as eyes and nose, oriented toward the direction of motion, and the limbs were shaped to facilitate linear motion in a consistent direction, further defining the antero–posterior axis. The dorsal–ventral axis evolved later through the influence of gravity and the demands of locomotion, creating consistent differences between top and bottom, such as eyes placed high for distance vision and feet touching the ground. The formation of these two axes, with their distinctive asymmetries, appears to be highly conserved genetically, at least across vertebrates and arthropods [3].

Only when these two axes are established can the left–right axis be defined, and the body remains highly symmetrical along this axis. The great British scientist Sir Isaac Newton remarked that this symmetry, with the exception only of the bowels, proved “the counsel and contrivance of an Author.” There is no need, though, to appeal to a deity; bilateral symmetry can be understood in evolutionary terms. As an animal moves around, the environment it encounters is largely indifferent to whether things are on the left or right. Predators and prey and obstructions to movement can occur on either side. With respect to movement and orientation in space, there seem to be no contingencies favouring differences between the left and right sides of animals.

Bilateral symmetry, though, is not merely a matter of default; it also enhances biological fitness. In animals that move freely, locomotion is almost universally dependent

on paired limbs, be they legs, flippers, or wings, and symmetry ensures linear movement, which provides the most efficient way to journey between two points. Having one leg longer than the other, or functionally more efficient, might leave an animal moving in circles, or at least making multiple corrections. Animals also need to be as sensitive to features on their left as on the right if they are to respond optimally to danger or to exploit what the environment has to offer. This means that sense organs, such as eyes, ears, and skin receptors, are symmetrically placed.

Much of behaviour is a matter of programming movement or processing information provided by the senses, creating evolutionary pressure for the brain itself to be symmetrical. Indeed, for much of human history the two sides of the brain were considered duplicates, albeit mirror images. Descartes [4], for example, observed “the brain to be double” (p. 275). In terms of gross anatomy, at least, the left and right sides did seem to be mirror images, causing the French physician Marie Francois Xavier Bichat (1771–1802) to formulate the “law of symmetry.” Bichat died at the age of 30 and was not widely known at the time, but his law of symmetry gained wide currency in the 19th century, especially through the influence of Franz Joseph Gall (1758–1828) [5].

There is even pressure for the brain to preserve its bilateral symmetry in the face of asymmetrical experience. It is well established that animals have more difficulty learning to distinguish left–right mirror images than up–down mirror images, and tend to treat left–right mirror images as though they were the same [6]. In one classic experiment, people shown 2500 pictures were later able to recognise them with surprising accuracy, except that they were as likely to report a picture as familiar when it was the left–right reverse of the original as when it was the original itself [7]. So-called left–right equivalence is especially evident in young children learning to read; up until the age of six or so, they frequently write letters or words backwards, despite being shown them only in correct orientation [8]. Animals, too, have much more difficulty discriminating left–right mirror images than in discriminating up–down mirror images. Left–right equivalence is adaptive in the natural world, where objects or animals can occur in opposite profiles, and events on one side of the body might next time occur on the other side.

The equivalence of left–right mirror images can be attributed to a process of inter-hemispheric reversal in the formation of memories, so that memories are held both in the veridical format and the mirrored one [9]. Logothetis et al. [10] found that some single cells in the inferotemporal cortex of two adult rhesus monkeys responded equivalently to meaningless mirror-image shapes, and remarked that “Distinguishing mirror images has no apparent usefulness to any animal” (p. 360). It can be an impediment, though, in some human activities, notably in learning to read and write scripts written in a consistent left–right direction. With specific training, it can be overcome. Torres et al. [11] found that three weeks of training first-grade children to discriminate mirror-image letters, such as b and d, led to a doubling of reading speed: “a simple and cost-effective way to unleash the reading fluency potential of millions of children worldwide” (p. 742).

2. Emerging Asymmetries

2.1. Internal Organs

Bilateral symmetry, then, is a striking feature of nearly all animals, but there are also longstanding asymmetries. The most extreme example is *situs solitus*, the asymmetrical placement of thoracic and abdominal organs. In the vast majority of humans, for example, the heart is displaced to the left, along with the stomach, spleen, and aorta, while the liver, gall bladder and trilobed lung are displaced to the right. Approximately one in 10,000 individuals have *situs inversus totalis*, in which these asymmetries are reversed [12] and where it does occur, it seems to arise as a matter of chance when the normal directional influence is lacking [13,14]. The asymmetries are fundamentally the same in all vertebrates [15], and more generally in chordates, suggesting that they have a common origin and go far back in evolution [16].

In vertebrates, at least, imposing asymmetry on internal organs is adaptive. For example, a mass of muscle such as the heart, achieves much greater efficiency of pumping from a spirally coiled form than from a simple tube [17]. Beyond that, it is probably essentially a matter of efficient packaging in the human body. Just as it would be inefficient to pack a suitcase while maintaining perfect symmetry of the contents, so it is that the internal organs are arranged asymmetrically in the body. Similarly, design of an automobile abandons symmetry in its internal engine and controls, while largely maintaining symmetry of external body shape. Manufacturing has adopted a design long evident in biological evolution.

Deviations from bilateral symmetry can occur through random influences—no animal is perfectly symmetrical, even discounting the asymmetries of the internal organs. However, reliance on random or fluctuating asymmetry for internal organs would run the risk of error, so consistent asymmetry was stamped in early in evolution. *Situs solitus*, is clearly an ancestral condition, and is all but universal. Bilateral symmetry and asymmetry therefore coexist in a trade off, with pressure toward one vying with pressure toward the other.

2.2. Handedness

The clearest evidence of a trade off comes from use of the hands or forelimbs, which in some species is symmetrical while in others there seems a clear species-wide preference for one or the other in certain actions. For most animals, bilateral symmetry of the limbs is adaptive, especially in movement, but in bipedal animals the forelimbs are freed from locomotion and are potentially open to specialization. Symmetry of action can still be adaptive in reaching and grasping with the hands, but in more complex actions, biological fitness may benefit if the hands adopt complementary roles, such as one hand holding an object while the other operates on it. In some cases, one hand assumes a dominant role. For example, bipedal marsupials, such as kangaroos, show a 90 percent preference for the left hand when feeding, whereas quadrupedal marsupials, such as the sugar glider or grey short-tailed opossum, show no preference at the population level [18]. Cats and dogs, too, show no bias at the population level, but individual animals often show a consistent preference for one or other paw in activities such as reaching [19]. (For a more general review of limb preferences in non-human vertebrates, see [20].) Our closest non-human relatives, chimpanzees, are less consistently bipedal than are we humans, and correspondingly show lower right-hand preference, at approximately 65–70 percent, in intricate manual actions [21]. Gorillas are predominantly right-handed in bimanual actions, where the non-dominant hand holds a food-related object and the dominant hand performs actions on it, such as dipping, stripping, or extracting [22].

At least one study has shown a slight right-hand advantage for rhesus monkeys but no bias in capuchins [23]. It is not restricted to primates; for example, some 77% of walrus display a preference for the right flipper when feeding [24]. Some creatures, though, are clearly left-handed—or left-“limbed.” In some species of parrot, approximately 90% of individuals show a preference for using the left foot when picking up pieces of food [25], and as we have seen bipedal kangaroos are predominantly left-handed. The preference for one or other limb being dominant is seldom if ever absolute, with the dominance ranging from approximately 65 to approximately 90 percent [26].

In humans, bipedalism is obligate and the hands are correspondingly less involved in locomotion and more available for asymmetrical activities such as tool manufacture, throwing, and writing, in all of which the right hand is dominant in some 90 percent of the population. Yet, the symmetry between the hands is largely preserved in their basic anatomy as well as in simple operations, such as reaching and grasping, and even catching. People can intercept a moving object equally well with either hand, but throw much more efficiently with just one hand, usually the right [27]. Most cricketers or baseball players, for example, can make one-handed catches with either hand, but few can throw even adequately with the non-preferred hand. The trade off between symmetry and asymmetry is therefore well illustrated in the way we use our hands.

2.3. Cerebral Asymmetry in Humans

Perhaps the first intimation of an exception to the law of symmetry as applied to the brain arose at a meeting in Montpellier in 1836, when an obscure French physician called Marc Dax produced evidence that speech was localised in the left hemisphere. This was largely disregarded, but some twenty-five years later, a more eminent physician called Paul Broca [28,29] showed that speech was disrupted following damage to the portion of the left prefrontal cortex since labelled as Broca's area, confirming the left-hemispheric dominance for speech. At that point, Dax's son recognised the significance of his father's work and arranged to have the early manuscript published, along with further evidence from 140 patients [30]. Evidence also emerged that comprehension of speech was impaired after damage in the left superior temporal gyrus, in the area since known as Wernicke's area. [31]. By the late 19th century, then, the brain was understood to exhibit some fundamental asymmetries, at least in function, in spite of its seeming anatomical symmetry. At this point, it was recognised that handedness itself was due to brain asymmetry, adding to the notion that the left hemisphere was the dominant or major hemisphere, with the right relegated to minor status. With some hesitation from the French medical establishment [32], the law of symmetry was overturned.

These developments also led to the view that the two sides of the brain were not simply uneven, but functioned in some ways as complementary opposites. In the most extreme versions, the left hemisphere was said to harness humanity, volition, masculinity, and reason, while animality, instinct, femininity, and madness were closeted in the right. This phase of speculation is well described by the historian Anne Harrington [33], who observed that it probably owed more to the social prejudices of the time than to the neurological facts. She wrote, "It is interesting that, once one has given the two hemispheres sexual identities, the idea of cerebral dominance becomes a rather apt metaphor for the social and economic domination of men over women in 19th-century Europe" (p. 624).

These extreme notions seemed to subside after the turn of the 20th century, but a second wave of speculation followed the split-brain research of the 1960s, when a series of patients underwent section of the forebrain commissures for the relief of intractable epilepsy. Again, the left hemisphere was shown to be dominant for language [34], and in 1981, Roger W. Sperry belatedly received the Nobel Prize in Physiology or Medicine "for his discoveries concerning the functional specialization of the cerebral hemispheres." There again followed a barrage of speculation about the duality of mind, with the left brain described as logical, rational and mechanistic, and the right brain intuitive, emotional and creative [35]. The social and political pressures of the time were different from those of the previous century, and the protests against the war in Vietnam, feminism, and anti-establishment movements seemed generally to anoint the right brain as favoured over the militaristic left. In his Nobel address, Sperry [36] himself noted, "The left-right dichotomy in cognitive mode is an idea with which it is very easy to run wild" (p. 1226). The dichotomy is still with us in popular culture—and indeed often runs wild.

Brain asymmetry, then, was a comparatively recent discovery in human history, and a revelation against the general assumption of bilateral symmetry. It was linked, moreover, to specifically human aspects of thought. This has led to a tendency to regard it as uniquely human (e.g., [37]), and perhaps even a species-defining feature [38]. This is also implicit in the view that language itself is unique to our species (e.g., [39]). The idea that brain asymmetry emerged only in *Homo sapiens* has no doubt dampened efforts to understand its evolutionary origins, although this has begun to change with the realisation that asymmetries are ubiquitous in biology.

It is also commonly assumed that brain asymmetry is unidimensional, to the extent that individuals are often described as being either left- or right-brained, implying that the dominance of one or other hemisphere operates as a whole. It has become clear, though, that there are several, perhaps many, dimensions of laterality. Handedness, too, is effectively a cerebral asymmetry, not a manual one, and is commonly associated with the left-hemispheric dominance for speech. The correlation is in fact much weaker than

previously assumed [40]. Some 95 percent of right-handers are left-cerebrally dominant for language, but so are 70–80 percent of left-handers [41]. Situs inversus totalis does not seem to reverse normal handedness or functional brain asymmetry, with the exception of the Yakovlevian torque—an anatomical asymmetry normally characterised as a protrusion of the frontal lobe on the right and occipital lobe on the left. This is reversed in cases of situs inversus [42].

Overall, the brain shows multiple anatomical asymmetries. In a study of 171,141 brains scans derived from 99 data sets worldwide, Kong et al. [43] divided the brain into 34 distinct regions, with overall thickness of the cortex larger on the left and overall surface area larger on the right. On both measures, as many regions showed leftward as showed rightward asymmetry, with only a small minority showing no measurable asymmetry. The two measures, though, showed different associations. The frontal regions tended to be thicker on the left while the posterior one tended to be thicker on the right, a pattern which the authors suggest may derive from the Yakovlevian torque. It was surface area, though, which showed greater association with functional asymmetries. The largest asymmetries in surface area were within language-related areas, including a leftward advantage in a posterior region of Broca's area and the transverse temporal gyrus (part of Wernicke's area), and a rightward advantage in an anterior region of Broca's area. The opposite asymmetries within Broca's area suggest two different circuits involved in language, with the leftward circuit connecting Broca's and Wernicke's areas involved in phonology and syntax. The role of the rightward circuit is not so clear.

Functionally, too, it is becoming increasingly evident that there are several, perhaps many, independent dimensions of laterality. Liu et al. [44] factor analysed laterality indices derived from intrinsic brain activity in the resting brain, revealing four independent factors. Two were left-lateralized, one corresponding to the language network and the other the default-mode network, and the other two were right-lateralized corresponding to a visual network and an attentional one. Badzakova-Trajkov et al. [45] similarly carried out a factor analysis of functional asymmetries while participants undertook language tasks, an attentional task, and a face-recognition task, which yielded three independent factors, a left-lateralized one corresponding to the language network and two right-lateralized networks corresponding to the face-processing network and the attentional network. The right-lateralized face-processing network was largely homologous with the left-lateralized language network, yet uncorrelated with it.

Häberling et al. [46] undertook a further factor analysis of laterality indices while participants performed various left-lateralized tasks, and found three independent factors, representing a language circuit, a gesture-related circuit associated with handedness, and another gesture-related circuit independent of handedness. These findings raised speculation as to how the mirror-neuron system might have lateralized and fissioned into separate subcircuits in the process of hominin evolution.

Orthogonal factor analysis provides a convenient way to identify lateralized networks that are independent of one another and, at least as a first approximation, provide a useful means of determining just how many dimensions of laterality there are.

2.4. Cerebral Asymmetry in Animals

Evidence for cerebral asymmetries in a wide variety of animals is now abundant (see [47] for review). One general finding is a right-hemisphere dominance for emotion, which seems to be present in all primates so far investigated, including humans [48]. It seems to be true of other animals as well, including dogs [49], horses [50], and birds [51], and probably goes far back in the evolution of vertebrates. Right-hemisphere biases also appear to be unrelated to handedness or motor asymmetries [51]. From an evolutionary perspective, it may reflect a left-hemispheric disposition to approach and the right hemisphere to avoidance [52].

In humans, the planum temporale overlaps with Wernicke's area, one of the major language areas, and is larger on the left than on the right [53], but the same asymmetry

is present in great apes [54–56], and in both adult [57] and infant baboons [58]. This asymmetry may therefore date back at least to the common ancestor of humans, great apes and Old World monkeys, 30–40 million years ago, and is not specifically connected to language.

The other major cortical language area, Broca's area, is more complex. Its anterior portion, area 44 (*pars opercularis*) is part of the language network in humans, and is larger on the left [59] (According to Kong et al. [43] the other portion, area 45 (*pars triangularis*) is larger on the right, while Keller et al. [59] find no asymmetry). Cantalupo and Hopkins [60] report that the homolog of Broca's area in chimpanzees is also larger on the left. Graic et al. [61] report a structural asymmetry in area 44 of the chimpanzee characterised by smaller neurons, perhaps suggesting increased computational capacity. In this and other respects, the cyto-architectural structure of area 44 seems to resemble closely that in humans.

The emergence of language in humans, though, may be not so much a question of the size of Broca's or Wernicke's areas as of their connectivity. Berwick and Chomsky [39] suggest that two circuits connecting these areas, both present in the chimpanzee, are connected ("a slight rewiring") in the human brain to create a loop that gave us syntax. This occurred, they say, uniquely in humans within the last 100,000 years, "in barely a flick of an eye in evolutionary time" (p. 67). This seems to be more or less pure conjecture. Friederici [62] has suggested similarly but more cautiously that humans evolved a stronger left dorsal connection between these areas than in non-human primates, and that it was this left-sided circuit that enabled the hierarchical structure of language.

From a functional perspective, Friederici's analysis is based on studies showing that humans can detect the hierarchical embedding in sequences of the form $(A_3(A_2(A_1B_1)B_2)B_3)$ (double embedding of this type, when applied to sentences, can be very difficult even for humans to process—an example is *The cat that the dog that the man kicked chased miaowed*), whereas non-human primates cannot [63], and that human processing of such sequences activates area 44. A difficulty with this analysis is that processing sequences of this kind need not involve any understanding of embedding at all; one might simply note that three As are followed by three Bs [64,65]. It is not yet entirely clear how seemingly similar fronto-temporal circuits can give rise to language in humans but not in non-human primates, or whether there is indeed a critical difference between apes and humans in this circuitry.

2.5. Cerebellar Asymmetries

The cerebellum is often neglected in accounts of brain asymmetry, but it too shows functional and structural asymmetries, which tend to mirror asymmetries of the cerebrum; that is, leftward activity accompanies rightward activity in the cortex, and vice versa. In a follow up from the study by Liu et al. [44] of cortical asymmetries in the resting brain, activity on each side of the cerebellum correlated with activity in the association cortex on the opposite side [66]. This implied large-scale circuits combining cerebellum and cortex, with the cerebellum mapping in roughly homotopic fashion onto the association cortex. Cerebellar asymmetry also mirrored cortical asymmetry during a language task, but did not map onto asymmetries of the motor cortex itself. In a similar follow up from the study by Badzakova-Trajkov et al. [45], factor analysis of asymmetrical brain activity induced by language tasks and observations of manual gestures revealed two independent networks, one right lateralized in the cerebellum and left lateralized in the language areas of the brain, and the other associated with handedness and gesture but with no cerebellar involvement [67].

The role of the cerebellum in the hemispheric asymmetry for language gains further support from a recent study showing a correlation between left-hemispheric dominance for perception of dichotically presented syllables, and a rightward asymmetry in the number of voxels in lobule VI of the cerebellum [68]. The dichotic asymmetry also correlated with a leftward asymmetry of the number of voxels in the amygdala, and to a lesser extent with a leftward voxel asymmetry posterior superior temporal cortex. Although dichotic

listening provides a less reliable index of functional asymmetry than does brain imaging itself, the results suggest that subcortical areas contribute more to brain asymmetries than is commonly realised. The authors also note that the human cerebellum has a surface area approximately four-fifths of the neocortex, whereas the proportion in the macaque is only about one-third [69]. This invites the speculation that the cerebellum, generally considered to have its primary role in motor coordination, may have expanded in the course of hominin evolution to play a part in the emergence of language.

In chimpanzees, the cerebellum generally follows the pattern of the Yakovlevian torque observed in the human brain [70]. In a sample of chimpanzees studied by Phillips and Hopkins [71] this pattern was reversed, and there was a rightward bias in the volume of the posterior cerebellum in chimpanzees. This was unrelated to handedness as measured in a coordinated manual task. (Curiously, using the same measures, the authors did find that a leftward bias of the posterior cerebellum was associated with right-handedness in capuchins. Unlike chimpanzees, though, capuchins do not appear to show species-wide handedness, nor do they show the Yakovlevian torque.) A subsequent analysis, though, showed an association of this asymmetry with handedness determined from a tool-using task designed to simulate termite fishing [72]. The authors speculate that the asymmetry associated with tool use may have served as the foundation for the emergence of language.

Aside from the question of asymmetry, a recent study reports epigenetic modifications of DNA in the human cerebellum that sets it apart from that in the chimpanzee or macaque, and may suggest a role in the development of language and cognition [73]. GPS methylation at genes known to be involved in neurodevelopment and synaptic plasticity was even more distinctively human in the cerebellum than in the prefrontal cortex. The authors suggest that their results “highlight the value of tissue-specific species comparisons of methylation and are consistent with an important role for the cerebellum in human brain evolution.

3. The Genetics of Laterality

3.1. Handedness

Historically, attempts to discover the genetic basis of functional laterality have focused largely on handedness, presumably because it is easier to measure than brain asymmetry. Although left-handedness is associated with cultural influences, it is also highly polygenic, as indicated by genome-wide studies of the association between handedness and genetic loci, e.g., [74–76]. These studies clearly rule out single-gene models that have hitherto been popular, e.g., [77,78]. The largest study to date examined individuals from 1,766,671 individuals, combined from the UK Biobank [79] and the International Handedness Consortium, found 41 loci associated with left-handedness, and 7 different loci associated with ambidexterity [80]. A total of 11.9 percent of males were left-handed or ambidextrous, compared with only 9.3 percent of females, a difference comparable to that found in other large-scale studies. Left-handedness was also associated with genetic loci implicated in a number of phenotypical conditions, including schizophrenia, autism, bipolar disorder, neuroticism, mood swings, and educational attainment.

Using an additive model, the authors estimated that genetic effects accounted for 11.9 percent of the variance, shared environment accounted for 4.6 percent, but the largest portion, 83.6 percent, came from individual environmental effects. Dropping shared environment from the model raised the genetic component to 19.7 percent, closer to the 25 percent estimated from twin studies [75,81]. There appears to be still some uncertainty as to how to assess the genetic contribution.

Ambidexterity has often been lumped together with left-handedness, but the two were unrelated genetically. Ambidexterity also showed a different profile of associations with other traits, including a negative genetic correlation with educational attainment. Earlier studies had shown decrements in educational attainment among the ambidextrous relative to left- or right-handers [82,83].

In an overlapping analysis of 501,730 individuals from the UK Biobank, de Kovel et al. [84] revealed that left-handedness was higher in those with lower birth-

weight, among multiple births, those born in certain seasons of birth, children with lower incidence of breastfeeding, and males, with each of these effects being significant independently of all the others. Others have reported an association of left-handedness with schizophrenia [85], autism [86] and dyslexia [87]. De Kovel et al. refer to a similar analysis based on a large US cohort showing similar association, with the addition of increased left-handedness, among African Americans and those with an older mother [88]. As in the larger study described above, a genome-wide association analysis showed left-handedness to be significantly but only weakly heritable genetically. The bias toward right-handedness, then, may be universal, but subject to variation and possible reversal through extraneous influences, some cultural, some pathological, and some genetic.

This idea of a universal bias is not without precedent. Laland [89,90] suggested that all humans are born with a biological bias to be right-handed, but that deviations result from external pressures. The primary pressure comes from parents, consistent with evidence that the incidence of left-handedness is increased if one parent is left-handed, and more so if both are left-handed. This association has also been taken to support a genetic basis for left-handedness (or the absence of right-handedness), but may equally be due to parental influence. Given the evidence summarised above, though, there are probably additional influences. As a first approximation, then, there may be a universal bias toward right-handedness, but malleable enough to permit variations without undue disadvantage.

Although genetic studies show multiple genetic associations with handedness, these genes may represent different conditions that influence handedness, rather than being intrinsic to handedness itself. An example is the LRRTM1 gene, a maternally suppressed gene associated paternally with handedness and dyslexia; when inherited through the father a particular haplotype consisting of minor alleles at three locations significantly shifted handedness toward the left [91]—a finding partially confirmed elsewhere [92]. This same haplotype was over-transmitted paternally in those with schizophrenia. These effects were discovered in dyslexic samples, and were not evident in a Chinese sample or in other samples from the general population, including the large-scale study described above [79].

3.2. Cerebral Asymmetry

Estimates of cerebral asymmetry based on brain imaging paint a similar picture. In a brain-wide genome-wide analysis in 32,256 individuals, Sha et al. [93] found 41 locations for cerebral asymmetry, parcellated into 34 cortical regions per hemisphere and 7 subcortical regions. Among these, they found 21 distinct, highly significant genomic loci for the different aspects of brain asymmetry. Ten of these were associated with cytoskeletal development, while the remaining 11 were mostly with brain development. These included significant genetic overlaps with autism, schizophrenia, and educational achievement. Earlier studies had shown direct associations of cerebral asymmetry with dyslexia [94], Alzheimer's disease (e.g., [95], ADHD [96], and depression [97]. In all cases, the negative aspects were associated with deviations away from normal asymmetries. Although some of these variables also correlated with handedness in Sha et al.'s study, there was no significant genetic overlap between handedness and structural brain asymmetries, although five individual markers (SNPs) were associated with both. Many of the asymmetries were strong, but their heritabilities were low. As mentioned earlier, situs inversus does not systematically reverse handedness or the normal cerebral asymmetries, with the exception of the Yakovlevian torque.

Again, these findings concur with those based on handedness in suggesting a fundamental but universal bias, with variations imposed by environmental and other conditions, some of possibly genetic origin. Sha et al. conclude from their findings that the development of brain asymmetry is “tightly constrained and largely genetically invariant in the population.” The most parsimonious conclusion is that this universal bias also underlies the situs of the internal organs; Brandler and Paracchini [98] suggest that “the mechanisms for establishing LR asymmetry in the body are reused for brain midline development, which in turn influences traits such as handedness and reading ability” (p. 88).

This scenario need not contradict the evidence of relative independence among handedness, different dimensions of cerebral asymmetry, and situs of internal organs. The fundamental asymmetry is invoked where it proves adaptive, even though against the pressure toward symmetry in the bilateria. This is especially true of situs, but less so in handedness and or the various aspects of brain asymmetry where there may be some advantage to maintaining variation—a possibility explored by Ghirlanda and Vallortigara [26]. Evolution itself depends on variation, and within social species such as our own, variations in demeanour, cognition, skill, and personality provide for effective social living, allowing individuals to take multiple specialized roles. Száthmary [99] writes that language, itself strongly lateralized and subject to individual variation, was one of the seven major transitions in evolution, offering something unprecedented—the “negotiated division of labour” (p. 10,109). Whether it was indeed a major transition, or simply a result of progressive evolution is a moot point, and the evolution of complex societies depends not only on language but also on individual differences in other domains as well, including spatial abilities, creativity, athleticism, and computational abilities. We need, or have needed, butchers, bakers, candlestick makers, and software engineers. Genetically, such diversity need not be construed as group selection, but rather as a loosening of genetic determinism.

The universal bias toward asymmetry, then, appears to be most strongly expressed in the situs of internal organs, where deviations from asymmetry are maladaptive. It is also strongly expressed in cerebral asymmetry for language, where deviations may result in language disorders. The bias itself may be universal with deviations only due to extraneous conditions, some pathological, some cultural, and some themselves genetic. For example, a mutation of the FOXP2 gene results in a severe speech impediment, and brain imaging showed that members of an extended family affected by the mutation, unlike their unaffected relatives, showed no activation in Broca’s area while covertly generating verbs [100]; the activation seemed to be scattered and to exhibit no consistent asymmetry. Handedness, though, seems to be largely unaffected, with one study showing 12 of the 15 members of the family to be right-handed [101].

The universal bias seems to be less strongly expressed in handedness, where deviations may be adaptive if maintained in a minority. It probably varies across species, but is absent in most animals, where there is no species-wide difference in dominance or preference between left and right forelimbs. That is, the ratio is approximately 0.5, with variations from around equality due only to chance. Laland [89] estimates a bias of 0.78 in humans, so that in the absence of extraneous influences 78 percent of the population would be right-handed, but parental or cultural influences increase it to approximately 90 percent overall. He suggests ratios of 0.8 to 0.9 in Neanderthals, 0.61 in Middle Pleistocene hominins, 0.57 in Lower Pleistocene hominids, and 0.56 in chimpanzees. The bias may be overestimated in Neanderthals, who may have been sufficiently human-like for a cultural influence increasing the overall incidence of right-handedness itself. The bias runs counter to the otherwise general bilateral symmetry of the limbs, and may be largely restricted to bipedal species.

If there is indeed a fundamental bias underling situs as well as handedness and cerebral asymmetries, what is its origin? Morgan and I [102] (readers tempted to consult this article should ignore the Abstract, which was inadvertently substituted from another article) once suggested that it was coded in the oocyte rather than in the genes themselves, and favoured development on the left. It may even depend on the chirality (left–right asymmetry) at the molecular level [103–105]. The asymmetries of the internal organs are governed at the earliest stages by an asymmetry of the cilia, hair-like organelles on the surface of cells, and this directs the asymmetry of a genetic sequence (the Nodal–Lefty–Pitx2 cascade) [106]. Cooke [107] outlines a scenario whereby the asymmetry of the cilia themselves is governed by the alignment of chiral molecules, creating a leftward flow of morphogenes across the embryo, which in turn guides the asymmetrical morphogenes of internal organs through a cascade of genetic influences. These ideas remain speculative,

but imply that asymmetry—or symmetry breaking—is not restricted to humans, or even to vertebrates, but is a fundamental property of living matter.

Whether the asymmetry of the cilia can account for right-handedness, though, remains uncertain. Afzelius and Stenram [108] report on 239 cases of immotile-cilia syndrome, a rare condition in which the cilia are either absent or stationary. In these cases, one might expect random asymmetry, such that 50 percent would have situs inversus and be left-handed. In fact the figures were 44 percent and 14 percent, respectively. This suggests a bias other than that due to ciliary motility, especially in the case of handedness, where the bias was only slightly above the 10–12 percent found in the normal population. Cultural or familial influences may be strong even in the absence of a biological bias.

That said, asymmetries of the hands and brain are clearly more variable than that of situs, where departures from normal asymmetry are often maladaptive. Immotile cilia syndrome, with its high incidence of situs inversus, is accompanied by disorders of the respiratory tract, including sinusitis, rhinitis and bronchitis, and the combination of these with situs inversus is known as Kartagener syndrome, afflicting approximately one in 22,000 [108]. Departures from right-handedness and left-cerebral representation of language are far less drastic, and may even be adaptive in giving rise to special minority talents, as suggested earlier.

This raises the question as to whether disorders associated with lateralization are truly “disorders,” or simply part of the fabric of human existence. Dyslexia is often associated with creativity, and even a number of well-known authors, such as Agatha Christie, Gustave Flaubert, and Evelyn Waugh, are said to have been dyslexic. Normal reading depends on an area known as the visual word form area usurping the left side of the occipito-temporal region of the brain concerned with visual shape analysis. This implies that visual processing can be diminished, or at least altered, when children learn to read [109]. This might explain the special talents of artists, such as Andy Warhol, Pablo Picasso and Robert Rauschenberg, who are also said to have been dyslexic. Leonardo da Vinci is often mentioned as another example, although his mirror writing might have been not so much a disability as a disguise. He was, however, left-handed, at least when writing.

Even mental illnesses may be adaptive, or once were so. Kauffman [110] points out that hallucinations were at one time considered normal, and played a part in the lives of visionaries, such as Jesus of Nazareth, St Paul of Tarsus, and even Socrates, and suggests that it was through the writing of Voltaire, Darwin, and Freud that they began to be associated with psychiatric illness. Creativity, too, has long been associated with schizophrenia and bipolar disorders, and research also suggests a genetic link [111]. Nature and culture may have combined to maintain a diversity and creativity of benefit to the species.

4. Conclusions

The emergence of animals that move created pressure toward bilateral symmetry, and the establishment of the vast clade of animals known as the bilateria. This pressure was due largely to the absence of asymmetrical influences from the natural environment—or what physicists call the conservation of parity. Departures from bilateral symmetry in movement or sensory input could be perilous; Martin Gardner [112] once put it like this:

The slightest loss of bilateral symmetry, such as the loss of a right eye, would have immediate negative value for the survival of any animal. An enemy could sneak up unobserved on the right!

(p. 70).

Nevertheless, bodily asymmetry is ubiquitous, especially in the placement of internal organs. It applies to all chordates and presumably far goes back in evolution. Its fundamental basis may even go back close to the origins of life itself, with the emergence of chiral molecules. At the molecular level, we are steeped in asymmetry.

The brain has largely retained its bilaterian symmetry. Over the course of evolution, though, it has also evolved computational functions not directly constrained by inputs from, or outputs to, the immediate environment. This may include emotion, which seems

to be universally characterised by a bias toward the right hemisphere. Operations on the environment seem more likely to be asymmetrically programmed than are reactions to it, and generally favour the left hemisphere. Examples include throwing, the manufacture and use of tools, and language, whether in the form of speech, gesture, or writing. Again, there may be packaging constraints, with face recognition and perhaps music shifted to the right as compensation for the left-sided representation of language. In the large-scale brain-imaging study by Kong et al. [43], the great majority of the 34 regions examined were asymmetrical one way or the other, yet each region was identifiable on either side, and they were all packaged in such a way as to retain an overall symmetry. Indeed for most of the history of medicine the brain was thought to conform to the law of symmetry.

The genetic orchestration of the asymmetries remains elusive. The most parsimonious solution is that they are ultimately dependent on the same fundamental bias that underlies situs of the bodily organs, but are then expressed by the genetic cascades that create the various specializations, each of which may be expressed or perturbed independently. Even if the various cerebral asymmetries so far identified are not dependent on a single underlying event, they may still hark back to the chirality of biological molecules.

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References

1. Carroll, S.B. Chance and necessity: The evolution of morphological complexity and diversity. *Nature* **2001**, *409*, 1102–1109. [[CrossRef](#)] [[PubMed](#)]
2. Evans, S.D.; Hughes, I.V.; Gehling, J.G.; Droser, M.L. Discovery of the oldest bilaterian from the Ediacaran of South Australia. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 7845–7850. [[CrossRef](#)] [[PubMed](#)]
3. Bridi, J.C.; Ludlow, Z.N.; Kottler, B.; Hartmann, B.; Broeck, L.V.; Dearlove, J.; Göker, M.; Strausfeld, N.J.; Callaerts, P.; Hirth, F. Ancestral regulatory mechanisms specify conserved midbrain circuitry in arthropods and vertebrates. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 19544–19555. [[CrossRef](#)]
4. Descartes, R. Treatise on the Passions of the Soul. In *Descartes: Philosophical Writings*; Trans. N. K. Smith; Modern Library: New York, NY, USA, 1649/1958.
5. Eling, P.; Finger, S. Franz Joseph Gall on hemispheric symmetries. *J. Hist. Neurosci.* **2020**, *29*, 325–338. [[CrossRef](#)]
6. Corballis, M.C.; Beale, I.L. Bilateral symmetry and behavior. *Psychol. Rev.* **1970**, *77*, 451–464. [[CrossRef](#)]
7. Standing, L.; Conezio, J.; Haber, R.N. Perception and memory for pictures: Single-trial learning of 2500 visual stimuli. *Psychon. Sci.* **1970**, *19*, 73–74. [[CrossRef](#)]
8. Fischer, J.-P.; Koch, A.-M. Mirror writing in typically developing children: A first longitudinal study. *Cogn. Dev.* **2016**, *38*, 114–124. [[CrossRef](#)]
9. Corballis, M.C. Mirror-image equivalence and interhemispheric mirror-image reversal. *Front. Hum. Neurosci.* **2018**, *12*, 140. [[CrossRef](#)] [[PubMed](#)]
10. Logothetis, N.K.; Pauls, J.; Poggio, T. Shape representation in the inferior temporal cortex of monkeys. *Curr. Biol.* **1995**, *5*, 552–563. [[CrossRef](#)]
11. Torres, A.R.; Mota, N.B.; Adamy, N.; Naschold, A.; Lima, T.; Copelli, M.; Weissheimer, J.; Pegado, F.; Ribeiro, S. Selective inhibition of mirror invariance for letters consolidated by sleep doubles reading fluency. *Curr. Biol.* **2021**, *31*, 742–752. [[CrossRef](#)]
12. Torgersen, J. Situs inversus, asymmetry, and twinning. *Am. J. Hum. Genet.* **1950**, *2*, 361–370. [[PubMed](#)]
13. Douard, R.; Feldman, A.; Bargy, F.; Loric, S.; Delmas, V. Anomalies of lateralization in man a case of total situs inversus. *Surg. Radiol. Anat.* **2000**, *22*, 293–297. [[CrossRef](#)] [[PubMed](#)]
14. Layton, W.M., Jr. Random determination of a developmental process. *J. Hered.* **1976**, *67*, 336–338. [[CrossRef](#)]
15. Patten, B.M. The formation of the cardiac loop in the chick. *Am. J. Anat.* **1922**, *30*, 373–379. [[CrossRef](#)]
16. Boorman, C.J.; Shimeld, S.M. Pitx homeobox genes in *Ciona* and amphioxus show left–right asymmetry is a conserved chordate character and define the ascidian adenohypophysis. *Evol. Dev.* **2002**, *4*, 354–365. [[CrossRef](#)]
17. Kilner, P.J.; Yang, G.-Z.; Wilkes, A.J.; Mohiaddin, R.H.; Firmin, D.N.; Yacoub, M.H. Asymmetric redirection of flow through the heart. *Nature* **2000**, *404*, 759–761. [[CrossRef](#)] [[PubMed](#)]
18. Giljov, A.; Karenina, K.; Ingram, J.; Malashichev, Y. Parallel emergence of true handedness in the evolution of marsupials and placentals. *Curr. Biol.* **2015**, *14*, 1778–1884. [[CrossRef](#)] [[PubMed](#)]

19. Ocklenburg, S.; Isparta, S.; Peterburs, J.; Papadatou-Pastou, M. Paw preferences in cats and dogs: Meta-analysis. *Laterality* **2019**, *24*, 647–677. [[CrossRef](#)] [[PubMed](#)]
20. Ströckens, F.; Güntürkün, O.; Ocklenburg, S. Limb preferences in non-human vertebrates. *Laterality* **2013**, *18*, 536–575. [[CrossRef](#)]
21. Hopkins, W.D.; Wesley, M.J.; Izard, M.K.; Hook, M.; Schapiro, S.J. Chimpanzees (*Pan troglodytes*) are predominantly right-handed: Replication in three populations of apes. *Behav. Neurosci.* **2004**, *118*, 659–663. [[CrossRef](#)]
22. Tabiowo, E.; Forrester, G.S. Structured bimanual actions and hand transfers reveal population-level right-handedness in captive gorillas. *Anim. Behav.* **2013**, *86*, 1049–1057. [[CrossRef](#)]
23. Westergaard, G.C.; Suomi, S.J. Hand preference for a bimanual task in tufted capuchins (*Cebus apella*) and rhesus macaques (*Macaca mulatta*). *J. Comp. Psychol.* **1996**, *110*, 406–411. [[CrossRef](#)] [[PubMed](#)]
24. Levermann, N.; Galatius, A.; Ehlme, G.; Rysgaard, S.; Born, E.W. Feeding behaviour of free-ranging walrus with notes on apparent dexterity of flipper use. *BMC Ecol.* **2003**, *3*, 9. [[CrossRef](#)] [[PubMed](#)]
25. Friedman, H.; Davis, M. “Left-handedness” in parrots. *Auk* **1938**, *35*, 478–480. [[CrossRef](#)]
26. Ghirlanda, S.; Vallortigara, G. The evolution of brain lateralization: A game-theoretical analysis of population structure. *Proc. Biol. Sci.* **2004**, *271*, 853–857. [[CrossRef](#)]
27. Watson, N.V.; Kimura, D. Right-hand superiority for throwing but not for intercepting. *Neuropsychologia* **1989**, *27*, 1399–1414. [[CrossRef](#)]
28. Broca, P. Remarques sur le siège de la faculté du langage articulé, suivies d’une observation d’aphémie (perte de la parole). *Bull. Société Anatomique* **1861**, *36*, 330–357.
29. Broca, P. Sur le siège de la faculté du langage articulé. *Bull. Société d’Anthropol.* **1865**, *63*, 77–93. [[CrossRef](#)]
30. Dax, M. Lésions de la moitié gauche de l’encéphale coïncident avec l’oubli des signes de la pensée (lu à Montpellier en 1836). *Bull. Hebdomadaire Médecine Chirurgie, 2me Série* **1865**, *2*, 259–262.
31. Wernicke, K. *Der Aphasische Symptomencomplex. Eine Psychologische Studie auf Anatomischer Basis*; M. Cohn U. Weigart: Breslau, Poland, 1874.
32. Leblanc, R. *Fearful asymmetry: Bouillaud, Dax, Broca, and the Localization of Language, Paris, 1825–1879*; McGill-Queen’s University Press: Kingston, ON, Canada, 2017.
33. Harrington, A. Nineteenth-century ideas on hemisphere differences and duality of mind. *Behav. Brain Sci.* **1985**, *8*, 617–634. [[CrossRef](#)]
34. Gazzaniga, M.S.; Sperry, R.W. Language after section of the cerebral commissures. *Brain* **1967**, *90*, 131–148. [[CrossRef](#)] [[PubMed](#)]
35. Ornstein, R.E. *The Psychology of Consciousness*; Freeman: San Francisco, CA, USA, 1972.
36. Sperry, R.W. Some effects of disconnecting the cerebral hemisphere. *Science* **1982**, *217*, 1223–1226. [[CrossRef](#)] [[PubMed](#)]
37. Corballis, M.C. *The Lopsided Ape*; Oxford University Press: New York, NY, USA, 1991.
38. Crow, T.J. Why cerebral asymmetry is the key to the origin of *Homo sapiens*: How to find the gene or eliminate the theory. *Curr. Psychol. Cogn.* **1998**, *17*, 1237–1277.
39. Berwick, R.C.; Chomsky, N. *Why Only Us? Language and Evolution*; The MIT Press: Cambridge, MA, USA, 2016.
40. Packheiser, J.; Schmidt, J.; Arning, L.; Beste, C.; Güntürkün, O.; Ocklenburg, S. A large-scale estimate on the relationship between language and motor lateralization. *Sci. Rep.* **2020**, *10*, 13027. [[CrossRef](#)] [[PubMed](#)]
41. Badzakova-Trajkov, G.; Häberling, I.S.; Roberts, R.P.; Corballis, M.C. Cerebral asymmetries: Complementary and independent processes. *PLoS ONE* **2010**, *5*, e9682. [[CrossRef](#)] [[PubMed](#)]
42. Vingerhoets, G.; Li, X.; Hou, L.; Bogaert, S.; Verhelst, H.; Gerrits, R.; Siugzdaite, R.; Roberts, N. Brain structural and functional asymmetry in human situs inversus totalis. *Brain Struct. Funct.* **2018**, *223*, 1937–1952. [[CrossRef](#)]
43. Kong, X.Z.; Mathias, S.R.; Guadalupe, T.; Group, E.L.W.; Glahn, D.C.; Franke, B.; Crivello, F.; Tzourio-Mazoyer, N.; Fisher, S.E.; Thompson, P.M.; et al. Mapping cortical brain asymmetry in 17,141 healthy individuals worldwide via the ENIGMA Consortium. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, E1154–E1163. [[CrossRef](#)]
44. Liu, H.; Stufflebeam, S.M.; Sepulcre, J.; Hedden, T.; Buckner, R.L. Evidence from intrinsic activity that asymmetry of the human brain is controlled by multiple factors. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 20499–20503. [[CrossRef](#)] [[PubMed](#)]
45. Badzakova-Trajkov, G.; Corballis, M.C.; Häberling, I.S. Complementarity or independence of hemispheric specializations? A brief review. *Neuropsychologia* **2016**, *93*, 386–393. [[CrossRef](#)]
46. Häberling, I.S.; Corballis, P.M.; Corballis, M.C. Language, gesture, and handedness: Evidence for independent lateralized networks. *Cortex* **2016**, *82*, 72–85. [[CrossRef](#)]
47. Rogers, L.J.; Vallortigara, G.; Andrew, R.J. *Divided Brains: The Biology and Behaviour of Brain Asymmetries*; Cambridge University Press: New York, NY, USA, 2013.
48. Lindell, A.K. Continuities in emotion lateralization in human and nonhuman primates. *Front. Hum. Neurosci.* **2013**, *7*, 464. [[CrossRef](#)] [[PubMed](#)]
49. Siniscalchi, M.; Quaranta, A.; Rogers, L.J. Hemispheric specialization in dogs for processing different acoustic stimuli. *PLoS ONE* **2008**, *3*, e3349. [[CrossRef](#)] [[PubMed](#)]
50. Smith, A.V.; Proops, L.; Grounds, K.; Wathan, J.; Scott, S.K.; McComb, K. Domestic horses (*Equus caballus*) discriminate between negative and positive human nonverbal vocalisations. *Sci. Rep.* **2018**, *8*, 13052. [[CrossRef](#)] [[PubMed](#)]
51. Rogers, L.J. Asymmetry of motor behavior and sensory perception: Which comes first? *Symmetry* **2020**, *12*, 690. [[CrossRef](#)]

52. Rutherford, H.J.V.; Lindell, A.K. Thriving and surviving: Approach and avoidance motivation and lateralization. *Emotion Rev.* **2011**, *3*, 333–343. [\[CrossRef\]](#)
53. Geschwind, N.; Levitsky, W. Human brain: Left-right asymmetries in temporal speech region. *Science* **1968**, *161*, 186–187. [\[CrossRef\]](#)
54. 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* **1998**, *279*, 220–222. [\[CrossRef\]](#)
55. Hopkins, W.D.; Nir, T.M. Planum temporale surface area and grey matter asymmetries in chimpanzees (*Pan troglodytes*): The effect of handedness and comparison with findings in humans. *Behav. Brain Res.* **2010**, *208*, 436–443. [\[CrossRef\]](#)
56. Spocter, M.A.; Sherwood, C.C.; Schapiro, S.J.; Hopkins, W.D. Reproducibility of leftward planum temporale asymmetries in two genetically isolated populations of chimpanzees (*pan troglodytes*). *Proc. Royal Soc. B* **2020**, *287*, 20201320. [\[CrossRef\]](#)
57. Marie, D.; Roth, M.; Lacoste, R.; Nazarian, B.; Bertello, A.; Anton, J.-L.; Meguerditchian, A. left brain asymmetry of the planum temporale in a nonhominid primate: Redefining the origin of brain specialization for language. *Cereb. Cort.* **2018**, *28*, 1808–1815. [\[CrossRef\]](#)
58. Becker, Y.; Sein, J.; Velly, L.; Giacomino, L.; Renaud, L.; Lacoste, R.; Anton, J.-L.; Nazarian, B.; Berne, C.; Meguerditchian, A. Early left-planum temporale asymmetry in newborn monkeys (*Papio anubis*): A longitudinal structural MRI study at two stages of development. *NeuroImage* **2021**, *227*, 117575. [\[CrossRef\]](#) [\[PubMed\]](#)
59. Keller, S.S.; Highley, J.R.; Garcia-Finana, M.; Sluming, V.; Rezaie, R.; Roberts, N. Sulcal variability, stereological measurement and asymmetry of Broca's area on MR images. *J. Anat.* **2007**, *211*, 534–555. [\[CrossRef\]](#) [\[PubMed\]](#)
60. Cantalupo, C.; Hopkins, W.D. Asymmetric Broca's area in great apes. *Nature* **2001**, *414*, 505. [\[CrossRef\]](#) [\[PubMed\]](#)
61. Graic, J.-M.; Peruffo, A.; Corain, L.; Centelleghes, C.; Granato, A.; Zanellato, E.; Cozzi, B. Asymmetry in the cytoarchitecture of the area 44 homolog of the brain of the chimpanzee *pan troglodytes*. *Front. Neuroanat.* **2020**, *14*, 56. [\[CrossRef\]](#)
62. Friederici, A.D. Hierarchy processing in human neurobiology: How specific is it? *Phil. Trans. R. Soc. B* **2019**, *375*, 20180391. [\[CrossRef\]](#)
63. Fitch, W.T.; Hauser, M.D. Computational constraints on syntactic processing in a nonhuman primate. *Science* **2004**, *303*, 377–380. [\[CrossRef\]](#)
64. Corballis, M.C. On phrase-structure and brain responses: A comment on Bahlmann, Gunter, and Friederici (2006). *J. Cogn. Neurosci.* **2007**, *19*, 1581–1583. [\[CrossRef\]](#)
65. Corballis, M.C. Recursion, language, and starlings. *Cogn. Sci.* **2007**, *31*, 697–704. [\[CrossRef\]](#)
66. Wang, D.; Buckner, R.L.; Liu, H. Cerebellar asymmetry and its relation to cerebral asymmetry estimated by intrinsic functional connectivity. *J. Neurophysiol.* **2013**, *109*, 46–57. [\[CrossRef\]](#)
67. Häberling, I.S.; Corballis, M.C. Cerebellar asymmetry, cortical asymmetry and handedness: Two independent networks. *Laterality Asymmetries Body Brain Cogn.* **2016**, *21*, 397–414. [\[CrossRef\]](#)
68. Guadalupe, T.; Kong, T.; Kong, X.-Z.; Akkermans, S.E.A.; Fisher, S.E.; Francks, C. Relations between hemispheric asymmetries of grey matter and auditory processing of spoken syllables in 281 healthy adults. *Brain Struct. Funct.* **2021**. [\[CrossRef\]](#)
69. Sereno, M.I.; Diedrichsen, J.; Tachrount, M.; Testa-Silva, G.; d'Arceuil, H.; De Zeeuw, C. The human cerebellum has almost 80% of the surface area of the neocortex. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 19538–19543. [\[CrossRef\]](#) [\[PubMed\]](#)
70. Pilcher, D.; Hammock, L.; Hopkins, W.D. Cerebral volume asymmetries in non-human primates as revealed by magnetic resonance imaging. *Laterality* **2001**, *6*, 165–180. [\[CrossRef\]](#) [\[PubMed\]](#)
71. Phillips, K.A.; Hopkins, W.D. Exploring the relationship between cerebellar asymmetry and handedness in chimpanzees (*Pan troglodytes*) and capuchins (*Cebus paella*). *Neuropsychologia* **2007**, *45*, 2333–2339. [\[CrossRef\]](#) [\[PubMed\]](#)
72. Cantalupo, C.; Freeman, H.; Rodes, W.; Hopkins, W.D. Handedness for Tool Use Correlates with Cerebellar Asymmetries in Chimpanzees (*Pan troglodytes*). *Behav. Neurosci.* **2008**, *122*, 191–198. [\[CrossRef\]](#) [\[PubMed\]](#)
73. Guevara, E.E.; Hopkins, W.D.; Hof, P.R.; Ely, J.J.; Bradley, B.J.; Sherwood, C.C. Comparative analysis reveals distinctive epigenetic features of the human cerebellum. *PLoS Genet.* **2021**, *17*, e1009506. [\[CrossRef\]](#) [\[PubMed\]](#)
74. McManus, I.C.; Davison, A.; Armour, J.A.L. Multilocus genetic models of handedness closely resemble single-locus models in explaining family data and are compatible with genome-wide association studies. *Ann. N. Y. Acad. Sci.* **2013**, *1288*, 48–58. [\[CrossRef\]](#) [\[PubMed\]](#)
75. Medland, S.E.; Duffy, D.L.; Wright, M.J.; Geffen, G.M.; Hay, D.A.; Levy, F.; Van-Beijsterveldt, C.E.; Willemsen, G.; Townsend, G.C.; White, V.; et al. Genetic influences on handedness: Data from 25,732 Australian and Dutch twin families. *Neuropsychologia* **2009**, *47*, 330–337. [\[CrossRef\]](#) [\[PubMed\]](#)
76. De Kovel, C.G.F.; Francks, C. The molecular genetics of hand preference revisited. *Sci. Rep.* **2019**, *9*, 5986. [\[CrossRef\]](#)
77. Annett, M. *Handedness and Brain Asymmetry: The Right Shift Theory*; Psychology Press: Hove, UK, 2002.
78. McManus, C. *Right Hand, Left Hand*; Weidenfeld & Nicolson: London, UK, 2002.
79. Sudlow, C.; Gallacher, J.; Allen, N.; Beral, V.; Burton, P.; Danesh, J.; Downey, P.; Elliott, P.; Green, J.; Landray, M.; et al. UK Biobank: An open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med.* **2015**, *12*, e1001779. [\[CrossRef\]](#)
80. Cuellar-Partida, G.; Tung, J.Y.; Eriksson, N.; Albrecht, E.; Aliev, F.; Andreassen, O.A.; Barroso, I.; Beckmann, J.S.; Boks, M.P.; Boomsma, D.I.; et al. Genome-wide association study identifies 48 common genetic variants associated with handedness. *Nature Hum. Behav.* **2021**, *5*, 59–70. [\[CrossRef\]](#) [\[PubMed\]](#)

81. Medland, S.E.; Duffy, D.L.; Wright, M.J.; Geffen, G.M.; Martin, N.G. Handedness in twins: Joint analysis of data from 35 samples. *Twin Res. Human Genet.* **2006**, *9*, 46–53. [\[CrossRef\]](#)
82. Corballis, M.C.; Hattie, J.; Fletcher, R. Handedness and intellectual achievement: An even-handed look. *Neuropsychologia* **2008**, *46*, 374–378. [\[CrossRef\]](#)
83. Crow, T.J.; Crow, L.R.; Done, D.J.; Leask, S. Relative hand skill predicts academic ability: Global deficits at the point of hemispheric indecision. *Neuropsychologia* **1998**, *36*, 1275–1282. [\[CrossRef\]](#)
84. De Kovel, C.G.F.; Carrión-Castillo, A.; Francks, C. A large-scale population study of early life factors influencing left-handedness. *Sci. Rep.* **2019**, *9*, 584. [\[CrossRef\]](#)
85. Deep-Soboslay, T.M.; Calicott, J.P.; Lener, M.S.; Verchinski, B.A.; Apud, J.A.; Weinberger, D.R.; Apud, J.A.; Weinberger, D.R.; Elvevåg, B. Handedness, heritability, neurocognition and brain asymmetry in schizophrenia. *Brain* **2010**, *133*, 3113–3122. [\[CrossRef\]](#)
86. Markou, P.; Ahtam, B.; Papadatou-Pastou, M. Elevated levels of atypical handedness in autism: Meta-analyses. *Neuropsychol. Rev.* **2017**, *27*, 258–283. [\[CrossRef\]](#)
87. Scerri, T.S.; Brandler, W.M.; Paraccini, S.; Morris, A.P.; Ring, S.M.; Richardson, A.J.; Talcott, J.B.; Stein, J.; Monaco, A.P. PCSK6 is associated with handedness in individuals with dyslexia. *Hum. Mol. Genet.* **2011**, *20*, 608–614. [\[CrossRef\]](#)
88. Johnston, D.W.; Nicholls, M.E.R.; Shah, M.A.; Shields, M.A. *Handedness, Health and Cognitive Development: Evidence from Children in the NLSY*; Forschungsinstitut zur Zukunft der Arbeit: Bonn, Germany, 2010.
89. Laland, K.N. Exploring gene–culture interactions: Insights from handedness, sexual selection and niche-construction case studies. *Phil. Trans. R. Soc. B* **2008**, *363*, 3577–3589. [\[CrossRef\]](#)
90. Laland, K.N.; Kumm, J.; Van Horn, J.D.; Feldman, M.W. A gene-culture model of handedness. *Behav. Genet.* **1995**, *25*, 433–445. [\[CrossRef\]](#)
91. Francks, C.; Maegawa, S.; Lauren, J.; Abrahams, B.S.; Velayos-Baeza, A.; Medland, S.E.; Colella, S.; Groszer, M.; McAuley, E.Z.; Caffrey, T.M.; et al. LRRMT1 on chromosome 2p12 is a maternally suppressed gene that is associated paternally with handedness and schizophrenia. *Mol. Psychiat.* **2007**, *12*, 1129–1139. [\[CrossRef\]](#) [\[PubMed\]](#)
92. Ludwig, K.U.; Mattheisen, M.; Muhleisen, T.W.; Roeske, D.; Schmal, C.; Breuer, R.; Schulte-Körne, G.; Müller-Myhsok, B.; Nöthen, N.N.; Hoffmann, P.; et al. Supporting evidence for LRRMT1 imprinting in schizophrenia. *Mol. Psychiat.* **2009**, *14*, 743–745. [\[CrossRef\]](#) [\[PubMed\]](#)
93. Sha, Z.; Schijven, D.; Carrion-Castillo, A.; Joliot, M.; Mazoyer, B.; Fisher, S.E.; Crivello, F.; Francks, C. The genetic architecture of structural left-right asymmetry of the human brain. *Nat. Hum. Behav.* **2021**. [\[CrossRef\]](#)
94. Altarelli, I.; Leroy, F.; Monzalvo, K.; Fluss, J.; Billard, C.; Dehaene-Lambertz, G.; Galaburda, A.M.; Ramus, F. Planum temporale asymmetry in developmental dyslexia: Revisiting an old question. *Hum. Brain Mapp.* **2014**, *35*, 5717–5735. [\[CrossRef\]](#) [\[PubMed\]](#)
95. Thompson, P.M.; Moussai, J.; Zohoori, S.; Goldkorn, A.; Khan, A.A.; Mega, M.S.; Small, G.W.; Cummings, J.L.; Toga, A.W. Cortical variability and asymmetry in normal aging and Alzheimer’s disease. *Cereb. Cort.* **1998**, *8*, 492–509. [\[CrossRef\]](#)
96. Shaw, P.; Lalonde, F.; LePage, C.; Rabin, C.; Eckstrand, K.; Sharp, W.; Greenstein, D.; Evans, A.; Giedd, J.N.; Rapoport, J. Development of cortical asymmetry in typically developing children and its disruption in attention-deficit/hyperactivity disorder. *Arch. Gen. Psychiat.* **2009**, *66*, 888–896. [\[CrossRef\]](#)
97. Tomarkenand, A.J.; Keener, A.D. Frontal brain asymmetry and depression: A self-regulatory perspective. *Cognit. Emot.* **1998**, *12*, 387–420. [\[CrossRef\]](#)
98. Brandler, W.M.; Paracchini, S. The genetic relationship between handedness and neurodevelopmental disorders. *Trends Mol. Genet.* **2014**, *20*, 83–90. [\[CrossRef\]](#)
99. Szathmáry, E. Toward major evolutionary transitions theory 2.0. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 10104–10111. [\[CrossRef\]](#) [\[PubMed\]](#)
100. Liègeois, F.; Baldeweg, T.; Connelly, A.; Gadian, D.G.; Mishkin, M.; Vargha-Khadem, V. fMRI abnormalities associated with FOXP2 gene mutation. *Nat. Neurosci.* **2003**, *6*, 1230–1237. [\[CrossRef\]](#)
101. Alcock, K.J.; Passingham, R.E.; Watkins, K.E.; Vargha-Khadem, F. Oral dyspraxia in inherited speech and language impairment. *Brain Lang.* **2000**, *75*, 17–33. [\[CrossRef\]](#)
102. Morgan, M.J.; Corballis, M.C. On the biological basis of human laterality: II. The mechanisms of inheritance. *Behav. Brain Sci.* **1978**, *2*, 269–277. [\[CrossRef\]](#)
103. Afzelius, B.A. A human syndrome caused by immotile cilia. *Science* **1976**, *193*, 317–319. [\[CrossRef\]](#) [\[PubMed\]](#)
104. Almirantis, V. Left-right asymmetry in vertebrates. *Bioessays* **1995**, *17*, 79–83. [\[CrossRef\]](#) [\[PubMed\]](#)
105. Brown, N.A.; Wolpert, L. The development of handedness in left/right asymmetry. *Development* **1990**, *109*, 1–9. [\[CrossRef\]](#) [\[PubMed\]](#)
106. Dasgupta, A.; Amack, J.D. Cilia in vertebrate left-right patterning. *Philosoph. Transact. Royal Soc. B-Biol. Sci.* **2016**, *371*, 20150410. [\[CrossRef\]](#)
107. Cooke, J. The evolutionary origins and significance of vertebrate left–right organisation. *BioEssays* **2004**, *26*, 413–421. [\[CrossRef\]](#)
108. Afzelius, B.A.; Stenram, U. Prevalence and genetics of immotile-cilia syndrome and left-handedness. *Int. J. Dev. Biol.* **2006**, *50*, 571–573. [\[CrossRef\]](#) [\[PubMed\]](#)
109. Dehaene, S.; Pegado, F.; Braga, L.W.; Ventura, P.; Nunes Filho, G.; Jobert, A.; Dehaene-Lambertz, G.; Kolinsky, R.; Morais, J.; Cohen, L. How learning to read changes the cortical networks for vision and language. *Science* **2010**, *330*, 1359–1364. [\[CrossRef\]](#)

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110. Kauffman, P.R. Might hallucinations have social utility? A proposal for scientific study. *J. Nerv. Ment. Dis.* **2016**, *204*, 702–712. [[CrossRef](#)]
 111. Power, R.A.; Steinberg, S.; Bjornsdottir, G.; Rietveld, C.A.; Abdellaoui, A.; Nivard, M.M.; Johannesson, M.; Galesloot, T.E.; Hottenga, J.J.; Willemsen, G.; et al. Polygenic risk scores for schizophrenia and bipolar disorder predict creativity. *Nat. Neurosci.* **2015**, *18*, 953–955. [[CrossRef](#)] [[PubMed](#)]
 112. Gardner, M. *The Ambidextrous Universe*; Allen Lane, The Penguin Press: London, UK, 1967.