

Review

It Is Not Just in the Genes

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Abstract: Asymmetries in the functional and structural organization of the nervous system are widespread in the animal kingdom and especially characterize the human brain. Although there is little doubt that asymmetries arise through genetic and nongenetic factors, an overarching model to explain the development of functional lateralization patterns is still lacking. Current genetic psychology collects data on genes relevant to brain lateralizations, while animal research provides information on the cellular mechanisms mediating the effects of not only genetic but also environmental factors. This review combines data from human and animal research (especially on birds) and outlines a multi-level model for asymmetry formation. The relative impact of genetic and nongenetic factors varies between different developmental phases and neuronal structures. The basic lateralized organization of a brain is already established through genetically controlled embryonic events. During ongoing development, hemispheric specialization increases for specific functions and subsystems interact to shape the final functional organization of a brain. In particular, these developmental steps are influenced by environmental experiences, which regulate the fine-tuning of neural networks via processes that are referred to as ontogenetic plasticity. The plastic potential of the nervous system could be decisive for the evolutionary success of lateralized brains.

Keywords: avian brain; brain asymmetries; hemispheric lateralization; ontogeny; epigenetic; neuronal plasticity; visual system



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1. The Functional Organization of Brain Asymmetries and Its Development

“A number of embryonic events make up an integrated overture to the post-hatching expression of lateralization” Lesley Rogers [1]

1.1. Lateralization Patterns of Neuronal Systems across the Animal Kingdom

A fundamental organizational principle of our brain is its asymmetries, which encompass both structural and functional differences between the two hemispheres. This characteristic has led to numerous hypotheses and research projects, which have attempted to elucidate the evolutionary and developmental origins of this specific trait [2,3]. However, lateralization of the brain is not specific to humans, but is present in many species across the animal kingdom. Not only vertebrates, but also many invertebrates, such as flies, bees, octopuses or nematodes, show left–right differences in neural organization and behavior [3–9], which suggests that lateralization is a common feature of metazoan nervous systems [10]. Neuronal asymmetries can be observed in all areas of information processing, including perception, cognition, emotion, homeostatic regulation or motor control and are based on neuroanatomical as well as physiological left–right differences [7,11,12]. Lateralization can be present at the individual level, with left-sided dominance for a certain function in half of a population and right-sided dominance in the other half. In other cases, the direction of a lateralized function within a population is aligned, so that lateralization is present at population level [2,11,13]. Comparative studies indicate that some aspects of functional brain lateralizations share a common evolutionary history [3,7,8,14]. It has been suggested that the vertebrate brain is characterized by specific functional dichotomy, with the left

hemisphere more strongly involved in routine and approach behavior, while the right hemisphere dominates detection and response to unexpected, novel and potentially pivotal stimuli [15–17]. For example, several species of fish, amphibians and birds react faster when a predator approaches from the left, indicating that right-hemispheric networks are specialized for the detection of potential dangers, while foraging is controlled by the left hemisphere [3,7,8,18]. The processing of social stimuli, such as faces, is also dominated by the right hemisphere [19] in humans [20], sheep [21,22] and chicks [23]. On the other hand, at least in mammals, communicative signals, such as spoken language in humans [24] or other forms of conspecific vocalizations [25,26], are typically processed within the left hemisphere. A widespread behavioral indicator of hemispheric lateralization is the preferred use of one extremity, which has been documented in a variety of vertebrate and invertebrate species at individual and population levels [5,27–31]. In humans, handedness is the most obvious asymmetry with about 90% of individual preferring to use their right hand for complex manual tasks like fine-tuned object manipulation or writing [32]. Handedness is related to other behavioral asymmetries, like preferential foot use [33] or cradling bias [34], while deviations from the typical pattern are associated with psychiatric or developmental disorders [2,35–37]. Therefore, handedness is used as the favorite measure for correlating functional lateralization with structural left–right differences and genetic variations (e.g., [12,32,36,38]).

1.2. Understanding Ontogeny of Neuronal Asymmetries—An Unfinished Business

Despite increasing knowledge about the relationships between different functional lateralizations and their structural foundations, our understanding of the underlying ontogenetic mechanisms is still limited. The presence of population-level lateralizations and cross-species similarities makes it likely that neuronal asymmetries have developed under phylogenetic pressure and, therefore, have a genetic basis [7,8,39,40]. However, human and animal research currently differ in the approaches and methods used in investigating the mechanisms guiding the development of a functional lateralized brain and, therefore, there has only been limited integration of knowledge between research approaches [41]. In some animal models, the genetically controlled events that drive the development of neuronal asymmetries have been studied in detail. In the nervous system of the nematode *Caenorhabditis elegans*, for example, there are pairs of chemoperceptive neurons, which are characterized by molecular left–right differences and different connectivity patterns that are related to their differential functional embedding [42,43]. Molecular genetic studies identified a complex regulation network comprising transcription factors, microRNAs, chromatin regulators and intercellular signals, which determine the asymmetric features of these specific neurons [44]. A second well-studied example is the epithalamus of vertebrate brains, which connects limbic regions of the forebrain with hindbrain motor circuits and which is characterized by evolutionarily conserved asymmetries within the pineal complex and the adjacent habenular nuclei. The molecular pathways that control these asymmetries have mainly been elucidated in studies with larvae of the zebrafish. Here, too, it is a chain of gene expression cascades that underlie the development of lateralization in this area [42,45,46]. Other genes are persistently expressed asymmetrically within the adult forebrain of zebrafish [47].

In human research, however, the first popular models, such as the right shift [48] or dextral chance [49] theory, suggested a single gene origin for human brain lateralization and attributed the left-hemispheric dominance for language processing and hand use to a common genetic factor. Their predictions fit data on the prevalence of handedness and language lateralization, but they did not explain the nature, as well as the action, of such a factor. However, recent meta-analysis studies have shown that the associations between language lateralization and motor asymmetries are much weaker than previously assumed [50]. Currently, research concentrates on the identification of genes that regulate functional and structural lateralization using large-scale heritability and genome-wide association (GWAS), or single nucleotide (SNP) variation studies to find associations between gene variants and

phenotypic lateralizations. These studies have reported an increasing number of genes and their variants related to lateralization pattern. One recent study even identified multifaceted gene networks associated with different aspects of anatomical brain asymmetries [51]. It has also been suggested that the impact of single genes is small and functional lateralizations are polygenic traits [38,52–56]. A recent study, for instance, detected 41 gene loci associated with left-handedness and seven associated with ambidexterity [52]. This also suggests that different manifestations of a trait can be controlled by different types of genes, which are either relevant during different phases of development or which influence discrete differentiation processes of the underlying neural networks.

In general, additive genetic effects account for less than one quarter of the variance in human handedness data, while nonshared environmental factors explain the remaining variance [52,57]. This is not surprising since neuronal systems always differentiate in close interactions with environmental experiences and genes alone do not explain the functional organization of neuronal systems [58]. This implies that the emergence of a functional lateralization pattern can only be understood by elucidating how genes and the environment interact to shape the functional organization of a lateralized brain [2,3,14,59–63]. It must also be considered how noncoding microRNA [64], or epigenetic mechanisms, which affect gene activity and expression by modifying DNA accessibility or chromatin structure, mediate long-term effects of gene–environment interactions [37,63].

Research has reported a potpourri of environmental factors influencing lateralization patterns in humans, including sex hormones [65], stress experience [66], sensory input, learning, birthweight, location and season of birth, breast feeding and cultural constraints [32,53]. These influences underline, on the one hand, the general role of environmental factors, while on the other hand, the lack of specificity of some factors suggests that deviations from genetically controlled patterns simply reflect random stochastic asymmetry [67].

1.3. Structural Foundations of Functional Asymmetries

Since neuronal functions are based on the organization of specific neuronal networks or cells, it is necessary to clarify how exactly structural and functional asymmetries are related. An increasing number studies have reported structure–function associations, but have also provided an inconsistent pattern. However, it is important to differentiate that left–right differences in the structure of neural circuits can be realized on different organizational levels, from the cellular to the macroscopic level.

An obvious global shape asymmetry of the human brain is the so called “cerebral torque”, which refers to a counter-clockwise twist of the whole brain along the anterior–posterior axis [68,69]. At macroscopic level, the left hemisphere has a thicker cortex but a smaller surface area relative to the right hemisphere [70]. Region-specific left–right differences are reported in size and shape [70–72] and connectivity [73,74], as well the cellular and molecular organization [75,76]. Similar cortical asymmetries are also present in chimpanzees [77–79]. The left-hemispheric dominance of language processing is related to left–right differences in the microcircuitry of cortical columns in the posterior part of the superior temporal gyrus [80]. Moreover, there are function-related asymmetries in the hippocampus and subcortical structures in humans [71] and other mammals [81]. Handedness for instance is related to asymmetries within the nigrostriatal dopaminergic system in humans [82] and rodents [83–85].

Cortical left–right differences emerge early during development in humans [86,87], but also in nonhuman primates [88]. The cortical torque can be detected by the second trimester of gestation [68,89], while asymmetry of perisylvian language-related cortical regions appears during the third trimester [90–92]. Motor asymmetries can be observed even earlier. Human fetuses tend to make more movements with their right arms and preferentially suck the right thumb from the 12th gestational week onwards [93]. These motor asymmetries are related to postnatal handedness [94]. In relation to this behavioral lateralization, the fetal spinal cord segments innervating hands and arms display asymmetries in gene expression and DNA methylation at the end of the first trimester [95].

In sum, average left–right differences of global brain anatomy, which emerge early during development, suggest a developmental program that is genetically determined [96]. However, when analyzing specific cognitive functions, gene–structure interrelations are less detectable. Twin studies, for instance, indicate that pre- and postnatal events can affect asymmetry during development of the planum temporal [97,98]. Accordingly, a recent large-scale study did not find significant associations between cortical asymmetries and language lateralization [99]. There is also no significant relation between cortical asymmetries and handedness [70]. The lack of correlations may not come as a surprise since the macroscopic cortical features do not necessarily represent the internal microscopic organization. It is conceivable that functional asymmetries only emerge on the cellular, synaptic or neurophysiological level. This means that it is necessary to understand how neuronal asymmetries arise at precisely this cellular level. To this end, findings from developmental neurosciences have to be integrated into models of asymmetry formation. Experiments with animal models have shown that activity-dependent processes triggered by internal or external signals are decisive for the functional maturation of neural networks [100–103]. In the following, I will, therefore, first summarize what is known about the role of genetic factors for asymmetry formation during different developmental phases. I then illustrate the possible effects of environmental factors as suggested by the light-dependent development of visual asymmetries in birds.

2. Potential Roles of Genetic Factors for Asymmetry Formation

The relative importance of genes and the environment depends on the species examined, the specific neuronal function and their developmental trajectories, as well as the level of analysis [61]. This means that we have to differentiate the action of gene–environment interactions depending on the development phase. The development of the nervous system can be roughly divided into three phases, during which the degree of hemispheric specialization increases (Figure 1). The first phase comprises the earliest embryological steps, in which the axes of the body plan are determined. The second phase includes the differentiation of neural systems and networks, while processes mediating the refinement of neural connections dominate the third phase. During these phases, different cellular processes dominate development and genes can influence the action of epigenetic factors in different ways, which affect the developing organism (Figure 1):

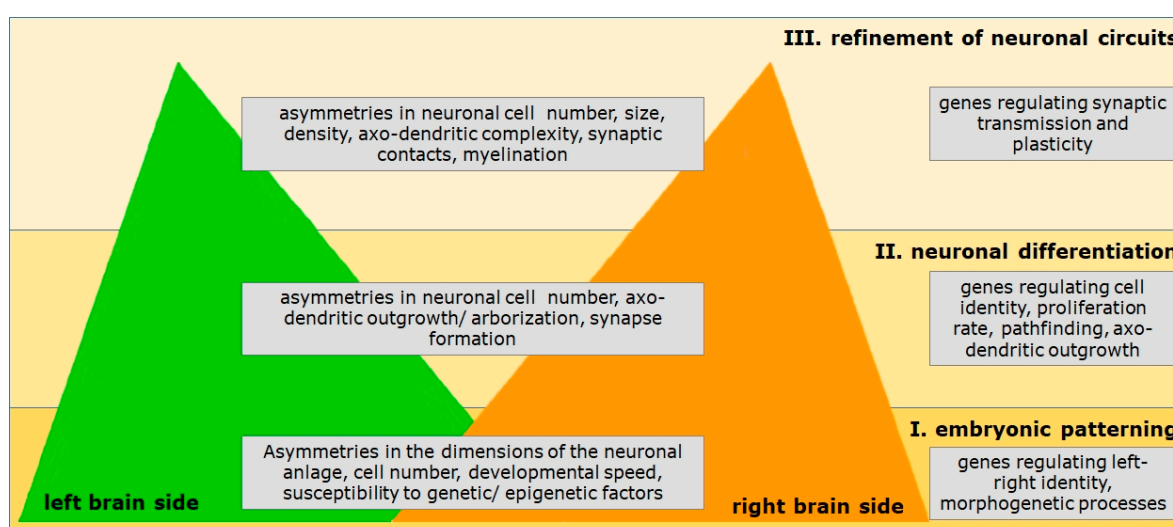


Figure 1. Model of the hierarchical development of brain lateralization—the three main phases of neuronal development are dominated by different cellular processes, which lead to an increasingly lateralized functional organization of the two hemispheres (indicated by the green and orange triangles). In each phase, certain types of genes regulate differentiation and, thus, asymmetry formation.

- I. Specific genes can account for left–right differences in the amount of neuronal substrate. An asymmetrical number of neuronal and/or glial precursor cells can result in gross morphological asymmetries and can be related to differences in cellular identity or cell-type-specific proteins.
- II. Specific genes can control left–right differences in developmental dynamics. Differences in the maturation of left- or right-hemispheric neurons or networks could lead to asymmetries in the susceptibility to epigenetic factors like hormones, sensory input or motor activity.
- III. Specific genes can regulate asymmetrical morphogenetic events leading to asymmetric body positions or craniofacial asymmetries, which bias sensory experiences.
- IV. Specific genes can control asymmetrical differentiation of neuronal elements like growth or arborization of axons and dendrites or development of synapses.
- V. Specific genes involved in synaptogenesis or signal transmission can lead to left–right differences in the degree of neuronal plasticity.

In the meantime, a number of genes have been discovered that mediate at least one of these actions during asymmetry formation:

2.1. Embryonic Patterning

Asymmetry formation within neuronal systems starts with breaking the symmetry of the body plan during early embryogenesis in all bilaterian animals, when the primary axes and tissue layers form. Complex cascades of genetic and epigenetic interactions lead to an asymmetrical placement of internal organs, but also induce asymmetries of paired organs like the lungs or the nervous system [104–109]. Determination of the left–right body axis is coordinated by a midline structure called the node. In several species, including humans, symmetry is broken by the rotation of motile cilia, which generate a directed flow that acts as a signal for the asymmetrical expression of a gene cascade, the Nodal signaling pathway. This pathway is remarkably conserved within bilaterian evolution [10,106,108].

This implies that asymmetry formation of body and brain starts with the action of cilia and, therefore, genes controlling generation and motility of cilia could play an early role in the development of neuronal asymmetries [38,110]. Some studies have actually provided evidence for the involvement of ciliary genes for handedness—however, only in specific humans populations [38,54,111].

A second critical mechanism during this early phase is the lateralized action of the Nodal pathway. One key player in this signaling cascade is PCSK6, which cleaves the Nodal protoprotein into its biologically active form [10,110,112]. PCSK6 polymorphism has been associated with human handedness [38,113], but also with structural asymmetries in temporal cortical areas, indicating a potential role of PCSK6 not only for motoric but also language networks [114].

However, when symmetry breaking processes of visceral and neuronal structures share the same developmental route, one should assume that individuals with reversed visceral organization also display reversed brain asymmetries. A test case involves individuals with situs inversus, where the visceral organs are organized as a mirror image of the default organ position. Situs inversus can occur in, but does not depend on, ciliary dyskinesia [115]. While the typical gross morphological asymmetry of the human brain–cerebral torque is actually reversed in situs inversus, functional and cortical lateralizations are not [115–119], although atypical functional segregation can be more frequent in participants with visceral reversal [115,120]. Similarly, in less complex animals, such as the nematode *C. elegans*, motor lateralization is independent from left–right body asymmetry [121] and zebrafish with situs inversus develop reversed lateralization of some but not all structural and behavioral lateralizations [122]. This suggests that early embryonic patterning processes regulate, to some degree, the establishment of basic brain asymmetries, but lateralization of specific functional modules are presumably shaped by specific cellular mechanisms later during development [119,123].

2.2. Regionalization of Neuronal Substrate

When the neuronal anlage starts to differentiate region-specific differences, genes playing a role in symmetry breaking of the embryo are also involved in the generation of specific brain asymmetries. The best known example is the Nodal pathway, whereby asymmetrical left-sided Nodal signaling within the developing dorsal diencephalon is required for determining the direction of epithalamic asymmetries [42,45,112,124]. It is conceivable that laterality signals result in asymmetrical expression of neuron-type-specific gene batteries, which are responsible for cell-type-specific structural and functional properties [125].

2.3. Differential Developmental Dynamics

One consequence of the early left–right patterning is that the left and right hemispheres develop at different speeds. In human embryos, the right hemisphere tends to develop a little earlier than the left one [86] and the lateralized gradient of brain development might contribute to the development of the cerebral torque [69]. Differences in developmental speed of cortical subareas are indicated by specific lateralized gene expression profiles from the fifth week postconception onwards [126]. The early appearance of asymmetrical arm movements in human fetuses can be explained by left–right differences in the differentiation of spinal neurons, since the cortex and spinal cord are not connected at this age [127,128]. As a result of the asymmetrical developmental gradients of the two hemispheres, it is possible that a nongenetic factor, which acts on the developing organism at a certain point in time, differentially influences left- and right-hemispherical neuronal structures. There is, for instance, some evidence that the right hemisphere of human fetuses is generally less subject to external influences than the left one [86].

2.4. Differentiation of Hemisphere-Specific Neuronal Elements

When the nervous tissue starts to differentiate region-specific neurons and connections, specific genes regulate proliferation, migration and growth of axonal and/or dendritic fibers. Therefore, asymmetrical expression of these genes can account for the asymmetrical differentiation of specific brain regions.

Sun et al. [129,130] identified a couple of genes in perisylvian regions of the human cortex, which are asymmetrically expressed at the end of the first trimester and, therefore, before a neuroanatomical asymmetry of this area can be detected [90,91]. Intriguingly, most of these asymmetrically expressed genes function in signal transduction and gene expression regulation [129,130].

One of these genes is the transcription factor *LMO4*, which is consistently more highly expressed in the right perisylvian cortex of 12–16-week human fetuses and, hence, during a period of high proliferation and migration rate [129,130]. *LMO4* displays higher expression level also in the right forebrain of zebrafish [47], while in the mouse cortex, *LMO4* expression is not constantly lateralized to one side [129,130]. Expression of *LMO4* is confined to postmitotic neurons [131] and regulates key aspects of neuronal differentiation, radial migration of newborn nerve cells and acquisition of neuronal identities [132,133].

Another example is the transcription factor forkhead box P2 gene *FOXP2*, which is involved in neural development and, in particular, in regulating neurogenesis of the embryonal cortex. It is expressed in distinct brain areas from gestational week six onwards and is related to speech development [134]. Intriguingly, *FOXP2* polymorphism is associated with the interindividual variability in hemispheric asymmetries for speech perception [135].

2.5. Ontogenetic Plasticity

After the establishment of the basic brain organization, neuronal networks typically sharpen their functional efficiency. Growth, stabilization or reduction of synaptic contacts or cell death occur in an activity-dependent manner and are triggered by sensory experience [100,136]. This critical period is likely to amplify expression of genes and proteins that mediate synaptic plasticity. Accordingly, genes that are involved in regulating ontoge-

netic plasticity can affect the asymmetrical development during specific sensitive phases. Asymmetrical expression of these genes can result in a differential sensitivity of left- and right-hemispheric circuits towards stimulation. Karlebach and Francks [137], for instance, identified several asymmetrically expressed genes in the human cortex that are likely to fine-tune electrophysiological and neurotransmission properties of cortical circuits during different phases of development. Additionally, in the rat hippocampus, a dynamic pattern of asymmetrically expressed genes has been identified during the first postnatal weeks, with a large percentage of genes being associated with synaptic function [138]. One example could be the transmembrane molecule LRRTM1 (leucine-rich repeat transmembrane neuronal 1). It interacts at synapses with the extracellular matrix as a regulator of neuronal plasticity [139]. Gene variations have been associated with handedness [53,140,141].

Crucial mediators of ontogenetic plasticity are neurotrophic factors like BDNF (brain-derived neurotrophic factor), which mediates activity-dependent synaptic stabilization, axo-dendritic growth, arborization and cell survival [142,143]. It is, therefore, intriguing that BDNF is asymmetrically expressed in the hippocampus of rats, specifically during the first two weeks after birth when neurogenesis rate is high [144]. BDNF might also mediate stress effects in the brain and could, therefore, regulate the well-known action of stress hormones onto brain lateralization [145].

To sum it up, neuronal development is controlled at very different levels of differentiation by genes that are either asymmetrically expressed or whose variants are associated with specific phenotypes. The same function (e.g., handedness) can, therefore, be regulated during different developmental phases by different types of genes. Asymmetrical expression of single genes can be confined to specific developmental phases, while other genes are lateralized up until adulthood. At all levels, nongenetic factors can modulate genetic effect and thereby change the direction and/or degree of lateralization. However, little is yet understood about the neuronal processes through which environmental factors can influence the differentiation of the complex functional organization of lateralized brains. One of the few models in which the influence of a specific environmental factor has been examined in more detail is the visual system of birds. Research on chicks and pigeons has delineated a chain of events that begins with asymmetrical photic stimulation of the embryo in the egg and ends in a lateralized organization of visual processing and cognition [1–3,14,40,59–61,146,147]. This model suggests critical steps for the formation of asymmetries that can serve as a blueprint for a better understanding of the ontogenesis of brain asymmetries in general. These developmental steps are summarized below (Figure 2) and are complemented by findings in other species, especially in humans.

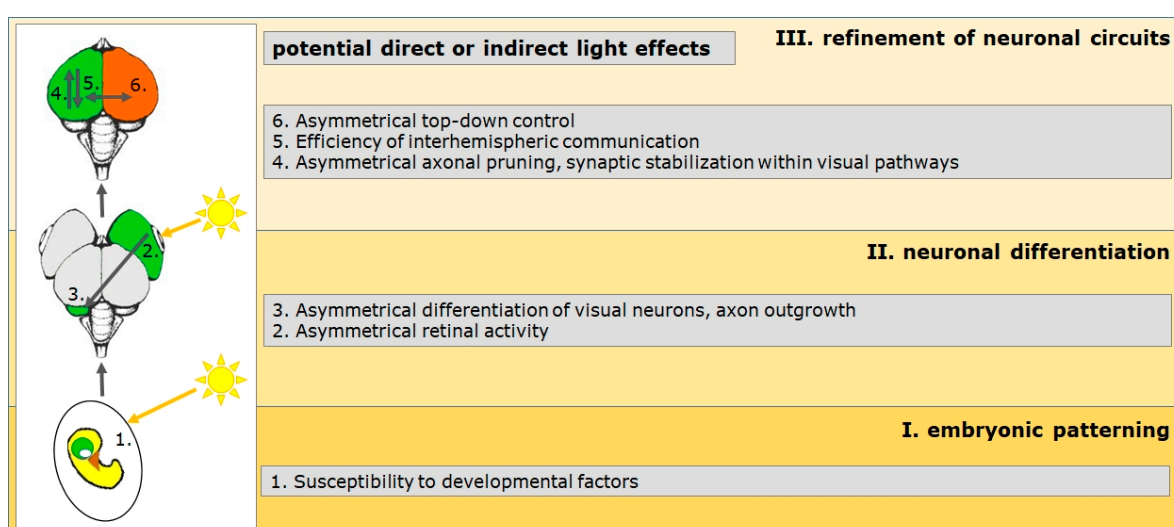


Figure 2. The developing visual systems of chicks and pigeons exemplifies how one environmental factor—in this case light—affects the development of brain asymmetries during the three main phases of neuronal development (see text for details).

3. The Avian Visual System as a Model for Ontogenetic Plasticity

The visual system of chicks and pigeons is lateralized with a pattern that is similar to the lateralization of the human brain. The left hemisphere dominates the discrimination of small optic details, rule learning, categorization and visuomotor control [59–61,147–149]. The right hemisphere on the contrary, is in charge of spatial attention [150] and aspects of social cognition [23]. These hemispherical specializations can be identified very easily by temporarily occluding one eye with an opaque cap. Since the optic nerves cross virtually completely in birds, information from the left eye is primarily directed to the right hemisphere and vice versa. A comparison of monocular and binocular testing, therefore, enables the investigation of hemispherical differences in performances or analysis strategies. Behavioral asymmetries are accompanied by anatomical left–right differences within the ascending visual pathways. In both pigeons and chicks, for example, differences in the projection strength between the two hemispheres can be observed. Major aspects of these asymmetries develop in response to asymmetrical visual stimulation during development. Therefore, light deprivation before and after hatching prevents or modifies visual lateralizations. The comparison of structural and behavioral lateralizations of light-exposed or light-deprived birds makes it possible to unravel critical neuronal processes that mediate light-dependent development (Figure 2) [1–3,14,40,59–61,146,147,151,152].

3.1. Mechanisms during Embryonic Patterning (Phase I)

As in all vertebrates, asymmetry formation in birds starts during embryonic body patterning [153,154], whereby symmetry breaking is independent from motile cilia [105,106]. At this point of development, light cannot directly affect visual lateralization patterns but there are at least three routes serving as starting points for the induction of asymmetries in the visual system:

1. Differences in left–right identity presumably determine asymmetries in the developing nervous system, which result in functional lateralizations when no other factors modify these predetermined ones. Early asymmetrical differentiation is indicated by a rightward torsion of the neuronal tube. Some evidence suggests that bending is caused by differential growth of the left and right neuronal tube side but physical mechanisms in relation to asymmetrical heart bending might also play a role [154]. This bending also occurs in mammalian embryos [155] and could contribute to the emergence of the cortical torque in the human brain. Presumably dependent on these early asymmetrical developmental processes, some visual lateralization develops independent from asymmetrical light stimulation. In chicks, visual choice to approach a social partner [156,157], uni-hemispheric sleep [158] or structural asymmetries of forebrain areas [159–162] are present in birds that are not exposed to biased visual stimulation. Interocular transfer of conditioned information [163] or lateralized visuospatial attention [164] emerge without embryonic light stimulation in pigeons but, interestingly, not in chicks [165,166]. It is currently unknown which genetic factors and which neuronal processes control the emergence of these visual asymmetries. However, endogenous asymmetries can be modulated by later visual experience [159,163,164,167].
2. As a consequence of the primarily Nodal-dependent left–right determination of the body, morphogenetic processes lead to bending of the head region, which turns to the left so that the beak points to the right and the right side of the head is facing the egg [168]. Due to the fact that the size of the embryo during the last embryonic phase does not allow free head rotations anymore, the left eye arrests on the body while the right eye is close to the egg shell and can be stimulated by light shining through the egg shell (Figure 2). This biased environmental stimulation triggers the second step in asymmetry formation, inducing asymmetrical differentiation processes, which involve neuronal mechanisms well known for ontogenetic plasticity [59,60,152] (see phase II). Such a rightward torsion occurs in all amniotes [168] including human embryos, which display a right-turn of their head during the last gestational phase

from week 38 onwards [169]. During this time, human fetuses are already responsive to sensory stimulation. They are able to memorize auditory stimuli from the external world by the last trimester of pregnancy, with a particular sensitivity to melody contour in both music and language [170,171]. Differential auditory input to the left and right ear because of postural asymmetries, therefore, might affect the development of language lateralizations [172–174].

3. Although visual systems are not developed, there is some evidence that during this phase, light stimulation already affects the establishment of some aspects of lateralization in both chickens and zebrafish [166,175–177] (Figure 2). Transduction mechanisms mediating these light effects are unknown but might include epigenetic mechanisms [166,177]. It is also possible that some genes unfold their actions only after photostimulation [178].

3.2. Mechanisms during Neuronal Differentiation (Phase II)

It is well known that the differentiation of visual networks is critically influenced by visual stimulation (e.g., [100]), and it is therefore not surprising that unbalanced light stimulation differentially affects left- and right-hemispheric developmental processes during species-specific sensitive phases [61,179]. Some behaviors and anatomical asymmetries only develop after embryonic light stimulation [180–182] and can be reversed by altered visual experience before (chicks, [183]) or after (pigeons [184,185]) hatching. In chicks, the outgrowth of visual fibers is influenced by light stimulation, resulting in a transiently stronger innervation of the right visual forebrain. Thereby, the action of light is modified by corticosterone, testosterone and estradiol [1,14,146,147,149,186]. The modulatory action of steroid hormones is in line with the often described sex- and stress-effects on human and nonhuman lateralization patterns [66,187,188]. In pigeons, left–right differences in cell size and projection strength differentiate in response to asymmetric photic stimulation [180,182,184,185,189]. Posthatch experimental manipulations have shown that starting with asymmetrical retinal activity [190], asymmetrical differentiation within the ascending visual system is mediated partly by BDNF-dependent processes [191,192].

The avian models exemplify how an environmental factor shapes the generation of neuronal asymmetries by modifying specific bottom-up systems. In a similar way, left–right differences in spectrotemporal selectivity of neurons in the auditory cortex of mice develop depending on hearing experience, which is related to the left-hemispheric dominance for the analysis of vocalization features [193]. In humans, visual experience can affect handedness [173], head turning preference [194] or lateralized face-processing competence [195,196].

However, an asymmetrical sensory trigger, such as light, not only enhances differentiation of the stronger stimulated hemisphere but also modifies the balance of left- and right-hemispheric development. A detailed analysis of light- and dark-incubated pigeons, for instance, revealed that light induces a left-hemispheric increase in visuoperceptual skills but simultaneously decreases visuomotor speed within the right hemisphere [182]. At the neuroanatomical level, embryonic light stimulation does not increase the bilateral innervation of the more strongly stimulated left brain side, but rather decreases input to the right side [180].

Presumably, interdependent left- and right-hemispheric developmental processes also play a role in the experience-dependent specialization of the human cortex, as indicated by the distribution of hemispheric language and face recognition processing. While the visual word form area in the left hemisphere becomes specialized while learning to read, the right hemisphere develops face recognition dominance. This suggests that the hemispheric organization of face recognition and of word recognition does not develop independently, and that word lateralization may precede and drive later face lateralization [196,197].

3.3. Consolidation of Functional Asymmetries (Phase III)

The ontogeny of visual asymmetries in birds is profoundly triggered within the developing ascending visual pathways but cognitive asymmetries emerge only at a higher (forebrain) processing level [60,148]. This means that asymmetries, which are induced within bottom-up systems, have to be transferred onto higher brain structures. At this level, they might interact with inherent or light-independent asymmetries (see above) and thereby sculpt and stabilize the final functional organization of the visual brain. In the pigeon, these processes mainly take place after hatching, when light input is normally symmetrical. During this phase, lateralization can still be modified by manipulating the visual experience [59,60,152,184,190]. It is likely that top-down as well as commissural mechanisms play a critical role in these stabilization processes [59,60,185,189,198,199]. As a consequence, relevant top-down and/or commissural systems develop their own asymmetrical properties for controlling asymmetrical decision-making and behaviors, but also for determining the degree of interhemispheric crosstalk. For example, left-hemispheric dominance for conflict choices is related to the asymmetrical action of top-down projections from the forebrain [198]. Light-dependent efficiency of interhemispheric integration has been shown in chicks, where only light-stimulated individuals can efficiently allocate food searching to the left and predator vigilance to the right hemisphere [200]. Also, only light-exposed chicks can use object (left-hemisphere)- as well as position (right-hemispheric)-dependent cues in food searching tasks [201,202]. A study with pigeons showed that only light-stimulated birds integrate hemispheric-specific knowledge for solving a task that cannot be correctly answered with information of one hemisphere alone [199]. Relevance of interhemispheric mechanisms for the generation and modulation of hemispheric-specific functions is in line with studies exploring the role of the corpus callosum for brain lateralizations [203,204]. The avian model suggests that top-down and commissural systems unfold their effects mainly at the end of asymmetry formation and modulate the interaction of more or less strongly lateralized neuronal networks in the left and right hemispheres [148]. To this regard, these processes shape the final functional organization of lateralized cognitive modules.

4. Conclusions

Studies on the genetic basis and/or environmental influences on the formation of asymmetries in humans and other animals have shown that the development of a lateralized functional architecture of the brain is to be understood as an example of ontogenetic plasticity. Genes and environmental factors play different but intertwined and complementary roles that can be specific to certain processing modules. The final functional lateralization pattern is then the result of hierarchical processes that build on one another. Genetically controlled early embryonic developmental steps set the framework for hemispherical differences and can be indicated by gross morphological asymmetries in volume and/or shape of gray and white matter. Epigenetic processes lead to increasing hemispherical specialization and control dynamics of interhemispheric communication. This means that no factor alone can explain the variance of lateralization patterns in a population; it is the sum of individual experiences, which shape individual brain lateralization. It is possible to identify general roles of single genes or environmental factors, but only their interplay within a specific environment determines the functional outcome. Consequently, single factors can only explain limited variance in the lateralization pattern within a population.

This flexibility enables fluctuating lateralization patterns within a population depending on the ecological requirements. Recent field studies showed, for instance, that factors such as predator pressure, environmental pollutants or seasonal conditions can modify brain asymmetries [205–207]. Humans have cultural constraints affecting, for example, the prevalence of left-handedness [208]. It is conceivable that the specific ecological or social conditions account for population-level lateralization in humans, which is absent in other animal species [208]. Ontogenetic plasticity, however, can be a general mechanism that enhances the evolutionary benefit of brain asymmetries [61,208].

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