

# The Epigenetic Control of Asymmetry Formation: Lessons from the Avian Visual System

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Although lateralization is a core feature of information processing of vertebrate brains, there is no model which can explain how ontogenetic mechanisms lead to an adult asymmetric functional architecture. While the very early appearance of embryonic asymmetries and the heritability of specific lateralization patterns suggest a genetic foundation, a high degree of plasticity highlights the critical role of environmental factors. The avian visual system demonstrates that the formation of neuronal asymmetries can be caused by sensory stimulation that is asymmetrically experienced. Monocular deprivation or intraocular applications of tetrodotoxin or BDNF suggest that lateralization develops via activity-dependent differentiation of brain circuits. A brief period of visual asymmetry in prehatch birds, resulting from a genetically determined head turning bias, triggers asymmetric differentiation processes in both hemispheres which gain significance during posthatch maturation. During this time, functional dominance of the right eye/ left hemisphere for visual feature analysis develops, and morphological asymmetries in the tectofugal pathway differentiate into an adult phenotype.

In sum, asymmetry formation in pigeons can be used as a general model to examine how biased peripheral stimulation establishes cerebral lateralization. It can explain how both epigenetic influences and genetically determined left-right differences contribute to the development of laterality.

## Lateralization Is a Core Feature of Information Processing in the Vertebrate Brain

As we all know from common experience, humans prefer one - mostly the right - hand for unimanual manipulations. Less well known is the fact that several other cortical functions are also lateralized. For example, language is mainly processed in the left hemisphere while spatial skills or emotional behaviour are generally under control of the right hemisphere. Some of these functional asymmetries are associated with left-right differences of gross anatomical landmarks and/or architectonic cortical subdivisions.

Cerebral lateralization originally was considered to be a unique characteristic of the human brain, and it is likely that evolutionary pressures associated with upright body position, tool use and speech may have selected out asymmetries that favour survival. Recent research demonstrates the existence of lateralization in all vertebrate species, placing lateralization as an ancient feature of the vertebrate brain.<sup>1,2</sup> Although animal models provide the opportunity to

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examine phylogenetic and developmental foundations of cerebral lateralization, the functional and ontogenetic interplay between neuronal substrate and behavioural lateralization is still an unsolved problem. This ambiguity results at least partly from the uncertainty regarding the relative contribution of genetically versus environmentally determined lateralization.

### **Unsolved Riddle: The Ontogenetic Foundations of Cerebral Lateralization**

The presence of a population bias for cerebral asymmetries like handedness or speech processing in humans provoked genetic models to explain the ontogenetic foundations of lateralization.<sup>3</sup> In humans, twin studies support a genetic basis of cortical volume and handedness.<sup>4,5</sup> In fish, data supports the role of genetic factors as the source of a turning bias.<sup>6,7</sup>

The neuronal mechanisms that mediate genetic regulation of asymmetrical brain development are still unclear, but asymmetry formation within the dorsal diencephalon of vertebrates provides some hints.<sup>8,9</sup> The alignment of anatomical asymmetries in the epithalamus is controlled by the Nodal signaling pathway, a gene cascade that is also involved in biasing laterality of the visceral organs.<sup>10,11</sup>

Additionally, early embryonic emergence of behavioural and morphological asymmetries may have a genetic basis. Human fetuses in uterus exhibit lateralized motor behavior,<sup>12-14</sup> display a functional hemispheric asymmetry in auditory evoked cortical activity,<sup>15</sup> and develop asymmetry of the planum temporale, which is regarded as the anatomical basis for lateralized language dominance.<sup>16,17</sup>

Since anatomical left-right differences represent the structural basis for cerebral lateralization they should precede the appearance of behavioral lateralization. Similarly, the direction of anatomical left-right differences should be correlated with functional ones. Such a relationship is found between right-handers and their language dominant left-hemisphere, where a leftward asymmetry in planum temporale exists. But this asymmetry is less pronounced in sinistrals.<sup>5,18</sup> Moreover, pre and postnatal events can affect asymmetry during development of the planum temporale and disrupt twin concordance.<sup>19,20</sup> This plasticity indicates the critical role of environmental factors. At least in some systems, environmental influences are actually essential for the establishment of cerebral lateralization. The interplay between gene-dependent prespecifications and epigenetic control is exemplified in the adoption of face expertise in human brains. Visual input is necessary to gain face recognition competence but affects only the right hemisphere suggesting that this brain side is predetermined to achieve face recognition competence.<sup>21</sup>

Genetic models cannot explain such plasticity in structure-function bias because the underlying neurobiology that controls this process is unknown. Here, we propose that lateralized environmental experiences during embryonic<sup>22</sup> or postnatal<sup>23</sup> development are crucially involved in the establishment of stable cerebral lateralization patterns.

Although cerebral asymmetries are assumed to control handedness, asymmetric motor behaviour arises earlier than structural left-right differences within the cerebral cortex. Asymmetry of the planum temporale develops during the third gestational trimester,<sup>16,17</sup> but human embryos perform more arm movements with their right arm and exhibit a preference for sucking their right thumb from the first trimester gestation onwards.<sup>12-14</sup> The early appearance of lateralized motor behavior suggests a muscular or spinal control because a functional corticospinal tract has not been developed at this timepoint. Such lateralized motor behavior might represent left-right differences in maturational speed e.g., of controlling GABAergic systems within the spinal cord.<sup>13,14</sup> These motor asymmetries are related to postnatal handedness.<sup>24</sup> From the final weeks of gestation to the first six months after birth, neonates develop a preference for turning their head to the right.<sup>25</sup> This positional bias correlates with the preference of the fetus to suck the right thumb.<sup>12</sup> Michel and Harkin<sup>23</sup> propose that the neonatal rightward bias in the direction of head orientation is the starting point in developing a stable hand preference. A turning bias leads to a greater amount of ipsilateral hand and arm movement that, in turn, results in an ipsilateral prehensile grasping preference. This creates differences between the hands in their experience of object

manipulation and, hence, a bias in unimanual manipulation. Finally, this unimanual preference may develop into a role-differentiated bimanual manipulation preference.<sup>26</sup> These studies describe developmental steps determining handedness preference by lateralized sensorimotor experience, but they, like earlier cited studies, are not able to clarify the mechanisms by which this occurs.<sup>14</sup>

A deeper understanding of the mechanisms that cause these developmental asymmetries can only be gained by experimental manipulations in animal models. Here, new insight comes from the avian visual system where behavioral lateralization can be associated with morphological left-right differences at the individual as well as the population level. This system suggests that epigenetic factors play a critical role in inducing cerebral lateralization and, in our laboratory, we have undertaken a number of studies to unravel the neuronal mechanisms that cause this asymmetrical development.

### Visual Lateralization in the Avian Brain: A Model System for the Neuronal Foundations of Cerebral Asymmetries

An increasing number of cognitive studies shows that the left and right hemisphere of the avian brain analyze different aspects of visual stimuli.<sup>27,28</sup> While the left hemisphere is specialized for detailed visual object analysis allowing rapid categorization of food objects or use of local aspects for spatial encoding,<sup>30-32</sup> the right hemisphere extracts relational or global (geometric) properties of visual stimuli.<sup>33-35</sup> These hemispheric specializations can be easily tested by occluding one eye, as the optic nerves in birds completely cross to the contralateral hemisphere. Specifically, the right eye is connected with the left hemisphere and vice versa while the absence of major commissures in the avian brain allows a restricted information transfer between the two hemispheres.<sup>28,29</sup>

The observed behavioral lateralization is associated with morphological asymmetries in the ascending visual systems.<sup>27,29</sup> Chicks exhibit transient left-right differences in the

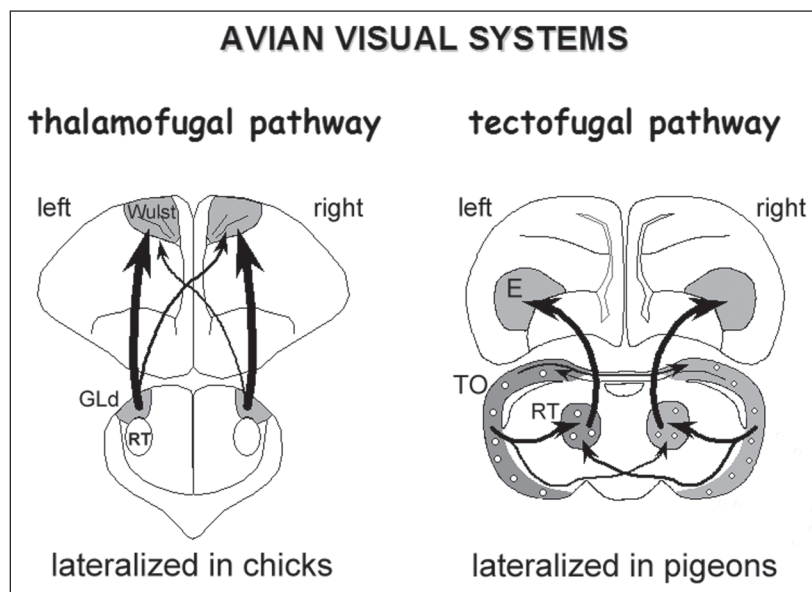


Figure 1. Asymmetries in the avian visual system. Chicks display asymmetries in the thalamofugal pathway with asymmetric projections from the GLd to the Wulst. In pigeons, asymmetries are implemented in the tectofugal pathway with cell size asymmetries in the optic tectum (TO) and nucleus rotundus (RT), and asymmetric ascending and intertectal projections. Abbreviations: E = entopallium, GLd = dorsal lateral geniculate complex, RT = nucleus rotundus; TO = optic tectum.

thalamofugal pathway. This system corresponds to the mammalian geniculostriatal system and transfers retinal information via the contralateral geniculate complex (GLd) bilaterally onto the telencephalic visual Wulst (Fig. 1A).<sup>36</sup> The left GLd gives rise to more projections to the right Wulst than the right GLd to the left Wulst.<sup>37-40</sup> In contrast, in pigeons visual lateralization is related to morphological asymmetries in the tectofugal pathway. This system corresponds to the mammalian extrageniculocortical system which projects via the contralateral mesencephalic optic tectum and the diencephalic nucleus rotundus to the forebrain (Fig. 1B).<sup>36</sup> Apart from tectal<sup>41-43</sup> and rotundal<sup>44</sup> cell size differences, the tectorotundal projection is asymmetrically organized with more fibers ascending from the right tectum to the left rotundus than vice versa.<sup>45</sup> Thus, the left hemisphere receives a stronger bilateral input from both visual hemifields. All recent studies indicate that the control of visuomotor processing is critically dependent on activity of the left hemisphere. This is supported by drastically reduced visual discrimination capabilities after left-sided forebrain lesions or by biochemical manipulations,<sup>27,28</sup> and by studies showing that the left hemispheric regulates bilateral tectofugal processing.<sup>46</sup>

### **Visual Lateralization Is Actually Induced during Embryonic Development but Consolidated during the Posthatching Phase**

The left hemispheric dominance for visual object analysis depends on asymmetric light stimulation during embryonic development.<sup>27,47,48</sup> Prior to hatching, avian embryos keep their head turned to the right such that the right eye is close to the egg shell and the left eye is occluded by the body.<sup>49</sup> Thus, light shining through the translucent shell stimulates the right eye while the left eye is visually deprived. It is likely that this asymmetric position is genetically determined because torsion of the embryo axis is controlled by left-/right-specific cascades of gene expressions which also determine heart looping bias.<sup>50</sup> Consequently, incubation of embryos in complete darkness prevents the formation of behavioral as well as anatomical asymmetries.<sup>42,51</sup> In chicks, the normal lateralization pattern can be reversed by occluding the embryo's right eye and exposing its left eye to light for 24 hours.<sup>37,52</sup>

However, chicks hatch as precocial birds with a fully mature visual system, able to forage and follow their mother. In contrast, the altricial pigeon hatches with closed eyes and a highly immature visual system staying three weeks in the nest fed with crop milk by their parents.<sup>53</sup> Therefore, it is possible to alter the final lateralization pattern in pigeons by modulating the visual experience post hatch. Comparable to chicks, occlusion of the right eye in pigeons reverses visual lateralization by inducing a functional dominance of the left eye and by modulating tectofugal left-right differences. Conversely, left eye deprivation enhances right eye dominance.<sup>44,54</sup> Thus, the vulnerable period for the development of visual asymmetries extends into the posthatching period, thus delineating two developmental phases critically involved in the establishment of a lateralized architecture of the pigeon's visual system (Fig. 2).

### **Asymmetries Develop According to Mechanisms Well Known to Be Involved in Ontogenetic Plasticity**

In general, neuronal plasticity which exists during the development of the nervous system allows the maturing brain to respond to environmental experiences during critical periods of development.<sup>55</sup> The visual pathways, in particular, have been established as model systems to examine how sensory input controls the activity-dependent development of neurons. As described earlier, the asymmetric head turning in avian embryos causes the amount of incoming light to differ between the left and right eye. In pigeons, this biased photic stimulation causes anatomical left-right differences in the development of the tectofugal pathway. The optic tectum is the first station of the processing stream where morphological asymmetries are visible, with a majority of retinorecipient neurons displaying larger cell bodies in the left tectum.<sup>41</sup> Since the soma size of a neuron is an indicator for the extent of the axo-/dendritic

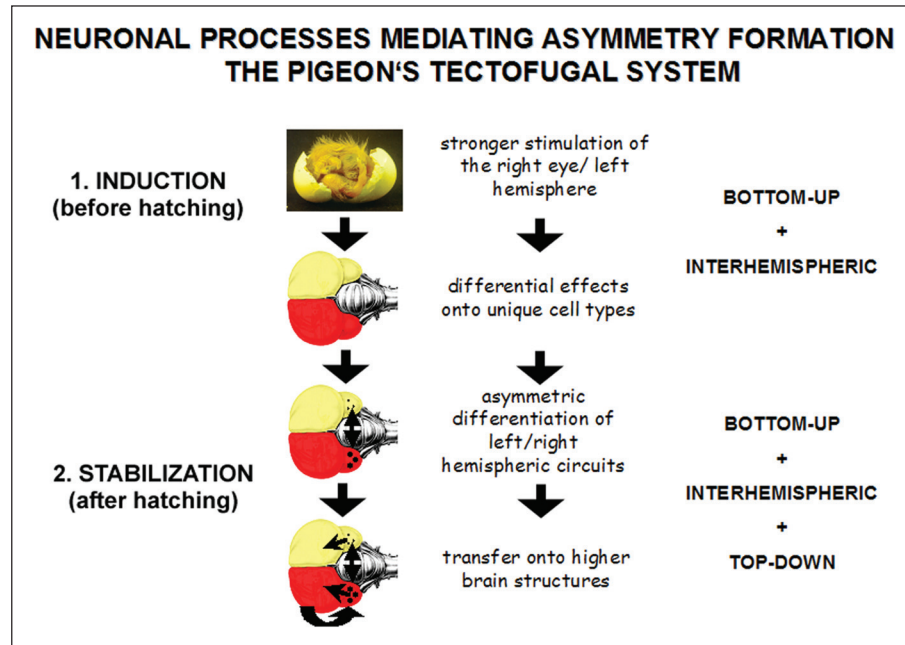


Figure 2. Two phases are critically involved in the development of a lateralized architecture of the pigeon's visual system. In a first step, the visual stimulation of the right eye/left hemisphere during embryonic development induces tectofugal asymmetries by differential effects on unique cell types. Bottom-up and interhemispheric interactions regulate asymmetric differentiation of left and right hemispheric visual circuits. In a second step that occurs post hatch, the induced asymmetries are transferred to higher brain structures by interactions of bottom-up, top-down and interhemispheric projections.

arborization pattern, tectal soma size asymmetries indicate differences in the complexity of left and right tectal circuits.

Since the maturation of the retinotectal pathway is regulated by photic stimulation,<sup>56,57</sup> it is likely that retinal activity differences constitute the first step in the initiation of asymmetric anatomical development. In fact, the transient inhibition of retinal activity by intraocular injections of the sodium channel blocker tetrodotoxin (TTX) leads to a dominance of the ipsilateral nondeprived hemisphere.<sup>58</sup> This activity-dependence suggests that lateralization develops according to mechanisms well known to be involved in activity-dependent maturation of the nervous system.

Brain derived neurotrophic factor (BDNF) may serve as a key player in ontogenetic plasticity.<sup>59-62</sup> Many of the effects of light on the asymmetrical development of the avian visual pathways are mediated by BDNF. For example, light regulates BDNF expression and secretion,<sup>63,64</sup> while BDNF rescues dark rearing effects<sup>65</sup> and affects axo-dendritic dynamics within the retinotectal system.<sup>66-69</sup> Since BDNF is present in the developing retinotectal system of pigeons,<sup>70</sup> it is conceivable that retinal activity differences are mediated by asymmetric BDNF supply. Hence, BDNF application should be able to mimic the effects of a light pulse. This hypothesis was tested by intraocular BDNF injections into the right eye of newly hatched pigeons which were incubated in complete darkness. These injections caused the animals to display a modified adult functional and morphological asymmetry pattern (Manns and Gütürkün in preparation).<sup>71</sup>

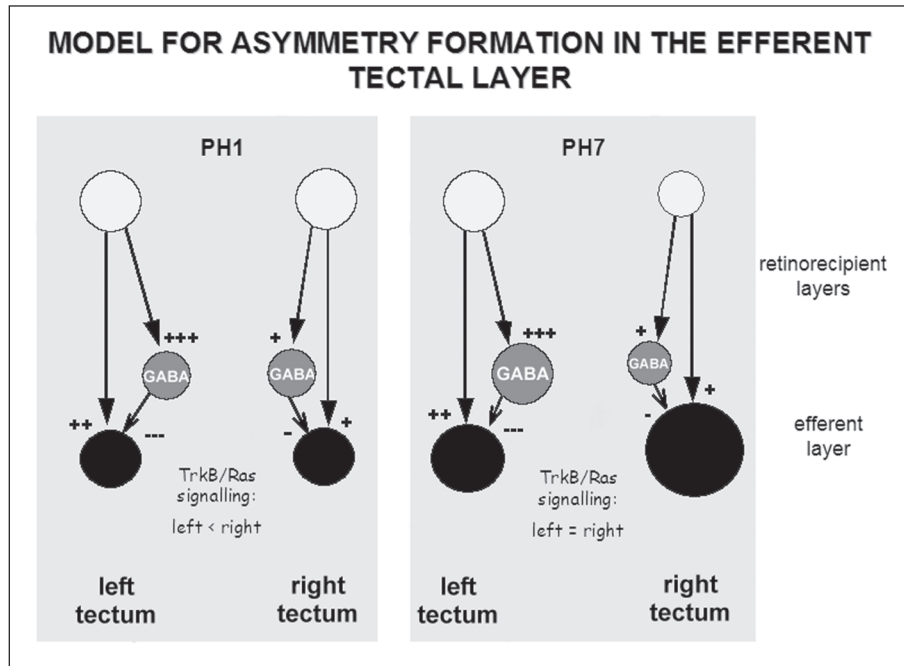


Figure 3. Model for asymmetry formation in the efferent tectal cell layer. Efferent tectal cells receive direct as well as indirect visual input from the outer retinorecipient lamina. Due to the stronger photic stimulation of the right retina, left retinorecipient tectal cells experience greater activation, in turn leading to their enhanced differentiation after hatching (PH1). In particular, maturation and/or synaptic activity of GABAergic interneurons is enhanced within the left tectum. Greater inhibition of efferent cells leads to reduced TrkB/Ras signaling within these cells. This, in turn, develops smaller cell bodies in the left tectum during the first week after hatching (PH7).

BDNF exerts its physiological role by binding to its specific neurotrophic tyrosine kinase (TrkB) receptor. Ligand bound TrkB receptors activate intracellular signaling cascades which, in turn, affect activity and/or differentiation of the responding cells.<sup>72,73</sup> The small intracellular membrane anchored GTPase Ras is a critical molecular switch by which BDNF induces its neurotrophic actions. BDNF/Ras induction thus may signal enhanced cell sizes and axo-dendritic complexity.<sup>74-76</sup> Asymmetric BDNF supply should lead to the asymmetric activation of the TrkB/Ras-signalling cascade. In fact, light incubation during embryonic development leads to a transient inhibition of the TrkB/Ras signalling within the stronger stimulated left optic tectum, but only after hatching.<sup>77</sup> These data verify posthatch consequences of biased embryonic visual experience at the cellular level.

It is very likely that posthatch effects are mediated by inhibitory interactions within the optic tectum.<sup>54</sup> Experience-dependent plasticity in the developing visual cortex is critically regulated by local GABA circuits<sup>78</sup> and GABAergic cells are enlarged in the stronger stimulated left tectum.<sup>43</sup> The critical roles of intratectal inhibitory effects are exemplified at the tectal level (Fig. 3). While the majority of tectal cells display enlarged cell bodies on the left side, supporting a growth promoting effect of light, the efferent cells in the deeper lamina (giving rise to the ascending forebrain projections) are larger in the right tectum.<sup>41</sup> This soma size asymmetry pattern develops within the first week after hatching in response to reduced TrkB/Ras signaling.<sup>77</sup> It is conceivable that the light-dependent stimulation of left-tectal GABAergic input exerts enhanced inhibitory control onto the efferent cells in the



left tectum, thus leading to smaller cell bodies and to fewer contralaterally ascending projections arising from the left tectum.<sup>45,54</sup>

### **Visual Lateralization Results from the Balance of Left- and Right-Hemispheric Differentiation Processes**

The consequences of asymmetric light stimulation are not confined to an enhanced trophic support of the left brain. A detailed analysis of light- and dark-incubated animals reveals that light induces a left-hemispheric increase in visuoperceptual skills. Conversely, light simultaneously decreases visuomotor speed within the right hemisphere. Thus, specialized visual circuits are differentially adjusted in both hemispheres.<sup>42</sup> These complex effects may be caused by a differential sensitivity of distinct cell types to retinal input. Evidence for such differential effects can be observed in immunohistochemically characterized tectal cells. Unique cell populations express different calcium-binding proteins like calbindin, calretinin or parvalbumin. In light-incubated animals, parvalbumin-positive cells display smaller cell bodies in the left, light stimulated tectum, indicating a suppressive effect of light on this cell type.<sup>43</sup> Accordingly, intraocular BDNF injection reduces parvalbumin-positive neuron size in both tectal halves. In contrast, calbindin-positive (presumably GABAergic) cells in the retinorecipient tectal laminae are enlarged only in the BDNF-enriched tectum. Calbindin-positive but nonGABAergic neurons in the efferent cell layer are not affected at all.<sup>71</sup>

The complex bihemispheric effects that occur at the behavioral as well as cellular level require control over the balance between left- and right hemispheric circuits. Even subtle retinal modulations are able to interrupt this balance. This conclusion is supported by the transient inhibition of retinal activity with TTX. Dominance of the nonsuppressed ipsilateral eye/contralateral hemisphere can be attributed to a performance increase conveyed by this brain side while performance, when tested with the TTX-injected eyes, does not differ from that of saline-injected controls. The transient silencing of one visual input does not simply suppress the deprived hemisphere but alters the activity balance between the left and right eye, enhancing visuoperceptive skills in the activated hemisphere.<sup>58</sup> A corresponding effect can be observed at the cellular level. Although GABAergic tectal cells are smaller in light-incubated animals compared to dark-incubated ones, this suppressive effect is less pronounced in the stronger stimulated left tectum of light incubated birds which bears larger GABAergic cell bodies.<sup>43</sup>

The necessary integration of activity from the left and the right side might be mediated by inter- and/or intrahemispheric influences.<sup>54</sup> On the one hand, the two tectal hemispheres are connected by mainly inhibitory commissures.<sup>79,80</sup> In pigeons, this interaction is asymmetrically organized with a stronger influence of the left tectum onto the right one than vice versa.<sup>81</sup> After transection of these commissures, lateralization of visually controlled behaviour is reversed.<sup>82</sup> On the other hand, tectofugal processing is controlled by afferents from the forebrain and this influence is presumably lateralized. Only left hemispheric lesions of the descending fibre tracts disrupt lateralization,<sup>83</sup> and only the left visual Wulst controls tectofugal processing.<sup>46</sup> This raises the possibility that top-down influences are involved in the final establishment and/or maintenance of cerebral lateralization.

### **Synopsis: Lateralization Develops within the Scope of Developmental Plasticity**

In sum, in the avian visual system the formation of neuronal asymmetries may occur as a result of an unbalanced sensory stimulation. This, in turn, may lead to a functional lateralization by bottom-up processes that are mediated by mechanisms known to be involved in developmental plasticity.

In avian species, lateralized brain functions start with an asymmetric light trigger. This trigger induces asymmetric differentiation in the tectofugal system. This, in turn, leads to asymmetric interactions with intra- and/or inter-hemispheric developing circuitries, causing functional lateralization. This process requires a phase during which induced asymmetries must be stabilized

and, hence, can be easily modulated. It is likely that inhibitory interactions regulate these processes. Since motor asymmetries in human embryos also precede cerebral lateralization, it is conceivable that human cerebral lateralization develops according to similar developmental principles. For example, the ability of spinally controlled asymmetries to influence the cerebral cortex may represent a human corollary to the avian system.<sup>12-14,25</sup>

The presence of light-independent asymmetries in chicks suggests that some aspects of forebrain control may be independent from visual input. Dark incubated chicks display higher ability to assess and respond to novelty seeing with their left eye,<sup>85</sup> and endogenous asymmetries in receptor binding were demonstrated in telencephalic imprinting areas.<sup>84</sup> However, visual experience can modify these endogenous left-right differences.<sup>84,85</sup> Thus, even when genetically determined asymmetries are present, their direction can be modulated by environmental factors. This supports a role for bottom-up processes in the determination of cerebral lateralization and suggests that genetic factors do not directly lead to a functional lateralization pattern. Rather, it is the interaction between genetically determined and environmental factors that cause asymmetrical regulation by the brain. Inherited asymmetries can provoke left-right differences in a variety of areas, including: (a) the rate in which left-right differences in maturation,<sup>86</sup> growth or susceptibility to epigenetic factors like hormones, sensory input, or motor activity occur, (b) morphogenesis leading to asymmetric body positions or craniofacial asymmetries,<sup>22</sup> each of which results in biased environmental experience, or (c) neuronal substrate like asymmetries in cell number<sup>4</sup> or receptor densities,<sup>84</sup> which cause a differential sensitivity to epigenetic factors.

In summary, lateralization develops as the result of the interplay between genetically determined and epigenetically controlled factors, findings which suggest that lateralization can be explained by mechanisms mediating ontogenetic plasticity. This plasticity may explain why very early peripheral asymmetries or developmental disturbances have such a great impact on the final pattern of cerebral lateralization.

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