

# Ontogenesis of Lateralization

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The brains of humans and other animals are asymmetrically organized, but we still know little about the ontogenetic and neural fundamentals of lateralizations. Here, we review the current state of understanding about the role of genetic and non-genetic factors for the development of neural and behavioral asymmetries in vertebrates. At the genetic level, the Nodal signaling cascade is of central importance, but several other genetic pathways have been discovered to also shape the lateralized embryonic brain. Studies in humans identified several relevant genes with mostly small effect sizes but also highlight the extreme importance of non-genetic factors for asymmetry development. This is also visible in visual asymmetry in birds, in which genes only affect embryonic body position, while the resulting left-right difference of visual stimulation shapes visual pathways in a lateralized way. These and further studies in zebrafish and humans highlight that the many routes from genes to asymmetries of function run through left-right differences of neural pathways. They constitute the lateralized blueprints of our perception, cognition, and action.

## How It All Starts

We all start as a ball of cells. How the spherically symmetric vertebrate zygote develops into an organism with the heart and pancreas on the left side and the gallbladder and many more organs on the right side has fascinated developmental biologists for decades (Hirokawa et al., 2006). During mammalian embryogenesis, determination of three body axes takes place. First, the embryo assumes an anterior-posterior axis, soon to be followed by the development of the dorsal-ventral axis. Then, after quite a delay, the third and final symmetry break happens: that between left and right (Hackett, 2002). Determination of the left-right body axis is coordinated by a midline structure called the node and critically depends on the Nodal signaling cascade. This asymmetric event is initiated during neurulation in the left lateral plate mesoderm (Blum et al., 2014). Within this cascade, the transforming growth factor beta (TGF- $\beta$ ) Nodal determines the left side, while the feedback inhibitor Lefty restricts Nodal activity to the left (Shiratori and Hamada, 2014). Other factors within the Nodal signaling cascade that are important for left-right determination include the proprotein convertase PCSK6 that cleaves the Nodal proprotein into its biologically active form (Brandler et al., 2013) and Pitx2, a homeodomain protein that acts as transcription factor (Ji et al., 2016). Moreover, several other convertases, microRNAs, TGF- $\beta$  signals, trafficking factors, and co-receptors that have been reviewed elsewhere (Schier, 2009) regulate the Nodal signaling cascade.

Leftward expression of Nodal genes in the lateral plate mesoderm is induced by expression in the node and leftward movement of gene products by leftward flow of extracellular fluid (Blum et al., 2014). This leftward flow is caused by a pit of cilia that is located on the ventral surface of the node. Cilia are a type of cell organelles that are formed by protuberances projecting from the apical surface of the cell into the extracellular space. The ventral node cilia move vigorously, creating a unidirectional leftward flow of extracellular fluid that causes the left-

ward move of Nodal pathway gene products that ultimately causes left-right determination (Hirokawa et al., 2006). The importance of normal cilia functioning for left-right body axis determination is highlighted by primary ciliary dyskinesia, a rare autosomal recessive disorder that defects the ability of cilia to rotate (Honoré and Burgel, 2016). Thus, no leftward flow of extracellular fluid is generated, and as a consequence, 50% of patients show situs inversus, a mirrored placement of laterally located internal organs. These patients are, however, mostly right-handed and have left hemispheric control of language (Kennedy et al., 1999; Torgersen, 1950). Thus, molecular asymmetries induced by the Nodal pathway cannot be the only determining factor of all asymmetries in brain and behavior. Instead, left-right differences of the brain in diverse systems and species may have their own routes to lateralization.

Hemispheric asymmetries (e.g., structural or functional differences between the left and the right cortical hemisphere), pervade practically all major neural systems of the human brain. On the structural level, they can be observed in region-specific left-right expression asymmetries of certain genes (Karlebach and Francks, 2015), microstructural asymmetries such as in the columnar and connectional structure within auditory and language-related cortical areas (Hutsler and Galuske, 2003), as well as at the macrostructural level. Here, asymmetries have been reported in size and shape of brain areas (Amunts, 2010) or white matter tracts (Ocklenburg et al., 2016). Moreover, structural asymmetries have also been reported on the level of structural and functional network properties of the left and right hemisphere (Caeyenberghs and Leemans, 2014; Gotts et al., 2013), as well as in shape and structure of the hemispheres itself (Amunts, 2010). On the functional level, neuroimaging studies indicate that the most pronounced asymmetries in brain activity exist in the language system (Corballis, 2012). Other prominent asymmetrically organized cognitive systems include visual-spatial processing (Vogel et al., 2003), auditory processing

(Tervaniemi and Hugdahl, 2003), memory (Cabeza, 2002), the motor system (Goodale, 1988), emotional processing (Grimshaw and Carmel, 2014), and attention (Brooks et al., 2014). Last but not least, our behavior is also asymmetrically organized. We have a favorite hand to write with (Papadatou-Pastou and Tomprou, 2015), a favorite foot to kick a ball with (Carey et al., 2001), and even a favorite direction in which to turn the head when kissing (Güntürkün, 2003).

Despite this ubiquity of hemispheric asymmetries in the human nervous system and their high relevance for behavior and cognition, they are among the least understood organizational principles of the brain. Therefore, the aim of the present review is to analyze and systematically integrate recent breakthrough findings that have been made regarding the mechanisms of their ontogeny in humans and non-human model species.

### A General Principle of Nature

It is rare that the starting point of a scientific area can be traced down to a specific day and a certain place. For asymmetry research, this is possible. On June 15, 1865, the young physician Pierre Paul Broca presented a large number of carefully analyzed medical cases before the members of the Société d'Anthropologie in the Rue René Panhard No. 1 in Paris. All of the collected cases had lesions of the left hemisphere in a region that was later to be called Broca's area. In all cases, the patients had suffered from a deficit of language production. Such deficits did not occur after right hemisphere damage. Broca concluded his insights with the sentence "Nous parlons avec l'hémisphère gauche" ("We speak with the left hemisphere"; Broca, 1865, p. 384). This was the start signal of brain asymmetry research.

Although Broca's discovery is seen as the official beginning, decades before Broca's talk, anatomists had reported that not only the human cortex but also that of other mammals displays asymmetrical convolutions (Leuret and Gratiolet, 1839). However, the arrangement of cortical gyri seemed to become more asymmetric with phylogenetic proximity to humans. These observations fostered the view that brain asymmetry represents an advanced organizational pattern and is thus typical of the human brain. Because only humans have a language system, and because anything resembling human handedness was in those days never observed in animals, the conclusion was clear: brain lateralization had to be a unique human trait that could even be the key evolutionary event that fostered our cognitive superiority. This assumption held for more than a century.

The change came in the 1970s, when several publications about chaffinches (Nottebohm, 1970), rats (Denenberg et al., 1978), and chicks (Rogers and Anson, 1979) reported in quick succession that asymmetries of brain and function also exist in non-human animals. Asymmetries could even be traced back more than 500 million years to the Cambrian: Babcock and Robison (1989) showed that fossilized trilobites had a 3:1 distribution of right-to-left bite marks at their rear. Either the animals were taking a skewed position in Paleozoic rivers when being attacked from the back, or their predators had a tendency to bite the right side.

Hundreds of publications could meanwhile show diverse asymmetries of brain and behavior in all kinds of species. One of them is the nematode *Caenorhabditis elegans*, with a nervous

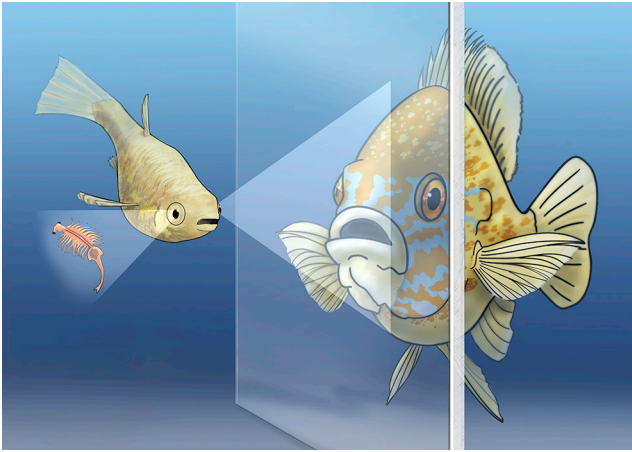
system that consists of just 302 neurons. This little worm lives in moist soil and moves in a film of water, constantly smelling or tasting particles that signal food, danger, or mates. Some neuron pairs of *C. elegans* express their chemoreceptors with left-right differences (Hobert et al., 2002). This asymmetry provides the worm the ability to discriminate between distinct sensory cues (Ortiz et al., 2009; Wes and Bargmann, 2001). The slug *Limax* memorizes food odors asymmetrically in its procerebral brain divisions (Matsuo et al., 2010), and honeybees also show left-right asymmetries in odor-driven sensory processing, behavior, and neural representation (Rigosi et al., 2015). These are just few examples of the dozens of different invertebrate and vertebrate species that demonstrated asymmetries of brain and behavior in the animal kingdom (Frasnelli, 2013; Ocklenburg et al., 2013d; Ströckens et al., 2013).

If asymmetry is so widespread, could it have a common origin? The answer to this question depends on the level of comparison. If common genetic factors that determine left-right body axis are compared, the signaling cascade of Nodal genes constitutes a homolog in vertebrates (Blum et al., 2014). Orthologs of Nodal were also discovered in sea urchins (Duboc et al., 2004) and snails (Grande and Patel, 2009), thus opening the possibility that the Nodal pathway in left-right asymmetry could represent an ancestral feature for the induction of lateralization in bilateria. The situation is different when we try to identify possible common origins at the neural and behavioral level. Ocklenburg et al. (2013d) and Ströckens et al. (2013) conducted a cladistics analysis on limb and vocalization asymmetries in vertebrates, thereby collecting all available publications on these topics. They could show that left-right differences are widespread and occur in all classes of vertebrates. In some clades, such as primates, there also was evidence that the left hemispheric dominance for vocalization was shared and could be traced to common ancestry. However, the overall picture made it likely that most species differences in lateralization are not explained by phylogenetic relations but rather are shaped by local ecological adaptations. If this is the case, left-right differences were repeatedly selected in various neural systems and species. So what then is the advantage of a lateralized brain?

### Asymmetry Pays

If animals from nematodes to humans show asymmetries of brain and behavior, we should expect that left-right differences provide some important fitness benefits. The brain represents only about 2% of the body weight of an adult human but accounts for about 20% of the calories consumed by the body (Raichle and Gusnard, 2002). Thus, making efficient use of brain tissue should underlie strong evolutionary pressure. Vallortigara (2006) suggested that the major fitness benefit of lateralization is to increase neural capacity, because specialization of one hemisphere for a cognitive function avoids useless duplication of cognitive functions between the two hemispheres. Another factor that might enhance the evolutionary pressure to make efficient use of neural tissue is the fact the human skull is limited in size by the restrictions of the birth canal.

One way to test these benefits is to exploit the individual variation in the degree of lateralization and to correlate this with task performance. These studies showed that chimpanzees with



**Figure 1. Schematic Overview of an Experiment in which the Superiority of Brain Asymmetry for Multitasking Is Tested in Fish**

While small fish (*Girardinus falcatus*) caught live *Artemia*, they were observed by a large predatory fish in an adjacent tank. Thus, this task required attention sharing between two parallel tasks: prey capture and predator vigilance. When comparing lateralized and non-lateralized *Girardinus falcatus*, lateralized individuals were twice as fast as non-lateralized ones at catching prey with their preferred eye for foraging while simultaneously monitoring the predator with the other eye. This is based on [Dadda and Bisazza \(2006\)](#). Drawing by Oliver Wrobel.

stronger individual handedness were more successful when fishing for termites using a tool ([McGrew and Marchant, 1999](#)). Similarly, pigeons with stronger visual asymmetry were more successful when foraging for grain scattered among pebbles ([Güntürkün et al., 2000](#)). Similarly, individuals with pronounced language lateralization have higher verbal IQs ([Everts et al., 2009](#)) and better reading skills ([Chiarello et al., 2009](#)).

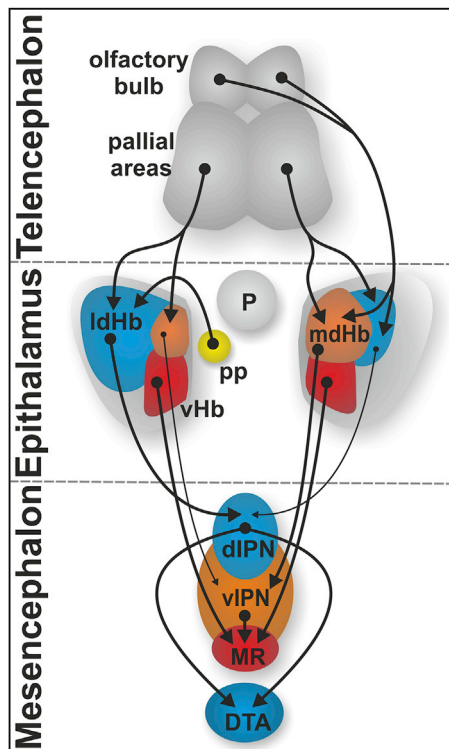
However, further analyses cast doubt on the simple assumption that increasing asymmetry levels increase perceptual and cognitive functions. [Boles et al. \(2008\)](#) searched for possible benefits from high degrees of asymmetry in linguistic and spatial tasks and found positive effects for only some tasks. The most sobering news came from a meta-analysis, including 100,000 subjects, of the possible effects of handedness on verbal and spatial tasks ([Somers et al., 2015a](#)). No positive effect of right-handedness on overall verbal ability and only a very moderate effect for spatial ability could be shown. Similar negative reports came also from studies in non-human animals ([Agrillo et al., 2009](#)). So why do some studies reveal a benefit of being asymmetric while others do not find this relation?

There are several possible reasons for these inconsistent findings. First, asymmetrically organized neural systems represent independent entities of which the degree of left-right difference in one system can be different from that of the other ([Badzakov-Trajkov et al., 2010, 2016](#); [Häberling et al., 2016](#); [Liu et al., 2009](#)). Therefore, asymmetries in one system should be relevant only for this specific function. The second problem concerns the question of how performance on a cognitive task is measured. In some studies, performance and lateralization are derived from the same task such that these values are not independent or are at least confounded. [Hirnstein et al. \(2014\)](#) took all these points into account and examined in 1,839 participants the relationship between language lateralization and performance

on a verbal dichotic listening task. The results revealed a U-shaped relationship between degree of lateralization and overall accuracy: the stronger the left or right ear advantage, the better the overall accuracy. Thus, strength of lateralization was a predictor of high performance, while direction (right, left) was not. This is identical to the finding of [Güntürkün et al. \(2000\)](#) in 108 pigeons in which more visually lateralized individuals found more grain in shorter time, irrespective if they were right- or left-eye dominant.

These findings do not clarify the mechanism by which brain asymmetries increase performance. According to numerous studies, three such mechanisms are likely. First, asymmetry could selectively increase the perceptual or motor learning effect in one hemisphere. In birds, the eyes are so laterally placed that most of the visual input derives from monocular vision. Thus, increased perceptual training of one eye should ensure higher discrimination ability with this side. This is what was repeatedly found ([Güntürkün et al., 2000](#); [Ventolini et al., 2005](#)). The situation is similar for the motor system in primates, in which some tasks are executed by only one hand or leg. A small ontogenetic advantage of one extremity can result with further lateralized practice in a higher performance level with the preferred limb in conjunction with a higher likelihood to use this hand ([Annett, 1970](#); [McGrew and Marchant, 1999](#)) or leg ([Teixeira and Teixeira, 2008](#)). The second mechanism for an advantage of asymmetry is directly related: increased learning with one perceptual or motor system also decreases reaction times, resulting in a time advantage of the dominant side ([Gülbetkin et al., 2009](#); [Vallortigara et al., 2011](#)). The third mechanism of advantage is parallel and complementary processing during task execution. If, for example, lateralized and non-lateralized chicks are tested in a foraging task that requires them to find grains scattered among grit and, at the same time, monitor overhead for a flying model predator, the lateralized birds can conduct both tasks efficiently and in parallel ([Rogers et al., 2004](#)). By contrast, non-lateralized chicks perform poorly, because they often miss seeing the predator but, when seeing it, suddenly start mistaking grit for grains. Similarly, in some poeciliid fish that were artificially selected for a high degree of visual lateralization, asymmetric individuals were twice as fast as non-lateralized ones at catching live prey when the animals had to simultaneously monitor for predators ([Dadda and Bisazza, 2006](#)). Both lateralized birds and fish could attain this result by attending the feeding task with one eye while monitoring the predators with the other. Thus, hemispheric specialization seems to increase parallel processing by enabling separate processing of complementary information into the two hemispheres ([Figure 1](#)).

These mechanisms, however, do not explain why for all types of vertebrate lateralization, there is a majority of individuals in which one side is dominant and a minority of individuals in which the other side is dominant. This fact has been explained by frequency-dependent fitness benefits (e.g., adaptive advantages associated with belonging to a minority) ([Vallortigara and Rogers, 2005](#)). For example, in a predator-prey relationship, the predator could learn to anticipate prey movements to one side. If all individuals in a prey population would always escape to the same side and the predator would start to expect a movement to this side, a mutant showing reverse lateralization would



**Figure 2. Schematic Depiction of the Zebrafish Epithalamic System, Its Asymmetrical Pallial Input, and Its Lateralized Projection to the Mesencephalon**

The habenula of zebrafish is divided into a dorsal and a ventral component (vHb), with the dorsal habenula being constituted by lateral (IdHb) and medial (mdHb) subnuclei of unequal sizes. Further components of the zebrafish epithalamus are the photosensitive pineal (P) and the asymmetrically organized parapineal organ (PP). IdHb and mdHb project to dorsal (dIPN) and ventral (vIPN) n. interpeduncularis, respectively. Dorsal and ventral IPN project differentially to the dorsal tegmental area (DTA) and the serotonergic median raphe (MR), respectively.

have a fitness benefit. However, if individuals with reverse lateralization would become the majority, they would lose this benefit (Vallortigara and Rogers, 2005). Similar mechanisms have also been suggested for combat sports in humans. Loffing and Hagemann (2015) reported greater fighting strength in left- compared with right-oriented boxers, an advantage that could be explained by negative frequency-dependent selection mechanisms. As long as left-handed boxers are a minority, most opponents would expect them to fight right-oriented. This would result in an advantage for left-handed boxers, as they could surprise their opponents. However, if all boxers were left-handed, they would lose this benefit.

If certain functions are lateralized to one hemisphere or the other, efficient gating via commissural systems becomes essential. This inter-hemispheric interaction can be both inhibitory as well as excitatory. Inhibitory interactions are possibly crucial when only one function for which one hemisphere is dominant has to be executed (Hirnstein et al., 2014; Genç et al., 2015). In lateralized systems such as handedness or language in humans or visual object discrimination in birds, there is strong evidence for an asymmetrical inhibition from the dominant to the subdom-

inant hemisphere (Keyes et al., 2000; Genç et al., 2015). In contrast, facilitation of inter-hemispheric transfer is essential when complementary hemispheric specializations are to be integrated. In the human motor domain, this is often relevant during complex bimanual tasks or during learning of new movements (Serrien et al., 2006) while birds need transfer when combining hemisphere-specific memories (Manns and Römling, 2012) or differential left- and right-hemispheric specializations during difficult discrimination and categorization tasks (Yamazaki et al., 2007; Prior and Wilzeck, 2008).

### The Asymmetrical Brain of Zebrafish

Hemispheric asymmetries can be observed in all vertebrate classes, but one species in particular has been established as the leading model species for the reconstruction of the genetic, functional, and neuronal pathways that lead to asymmetric brain development: the zebrafish (*Danio rerio*). This tropical freshwater fish shows a pronounced structural asymmetry in the epithalamus that can be genetically manipulated, allowing insights into the ontogenesis of structural asymmetries. The epithalamus constitutes the dorsal part of the diencephalon and comprises an ancient structural asymmetry of vertebrates. It contains the unpaired pineal complex and the bilateral habenular nuclei. The habenula and its associated fiber tracts form part of a conserved limbic conduction system linking the forebrain with the ventral midbrain. In mammals, the habenula is constituted by a medial and a lateral component that project to the interpeduncular nucleus (IPN) and a complex of serotonergic and dopaminergic midbrain nuclei, respectively (Herkenham and Nauta, 1977). The general outline of the system is similar in zebrafish. However, genetic, structural, and functional asymmetries of the epithalamus could be identified in this animal with more details than in any other vertebrate. We will first review the general structural and connective outline of the system before discussing the ontogeny, genetics, and behavioral relevance of its asymmetries.

The habenula of mammals and fish are homologous but anti-clockwise rotated by 90°: the dorsal habenula of zebrafish is homologous to the mammalian medial habenula and can be divided into medial and lateral subnuclei (Amo et al., 2010). These structures are bilaterally innervated by the anterior pallium, while a subgroup of olfactory bulb fibers selectively innervate the right habenula (Miyasaka et al., 2009). A similar connective asymmetry is visible in the zebrafish pineal complex: this system is photosensitive and comprised by the pineal (P) and the parapineal organ (PP). The pineal serves as a photosensitive clock that secretes melatonin, a hormone that synchronizes physiological functions with the circadian cycle. The parapineal is situated left to the midline and projects only to the lateral subnucleus of the dorsal habenula on the left side (Gamse et al., 2005). Thus, the left and the right habenula receive different input patterns (Figure 2).

The lateralized input patterns also reflect physiological properties of habenular neurons. Left-sided neurons are mostly responsive to visual stimuli, while right habenular neurons are predominantly activated by olfactory cues (Dreosti et al., 2014). If brain asymmetry is reversed, this kind of functional asymmetry follows. Loss of asymmetry results in a loss of responsibility to



visual and olfactory stimuli. Thus, functional properties of sensory processing (Dreosti et al., 2014) and fear-related behavior (Facchin et al., 2015) depend in zebrafish on the presence of epithalamic neural asymmetries.

Because both pineal and parapineal are photosensitive, it is conceivable that light can modify functional asymmetries during ontogeny. This is especially relevant for the period that starts at about 24 hr after fertilization, when parapineal precursor cells condense in the epithalamic midline and thence migrate within the next hours to the left side to innervate the left habenula (Roussigné et al., 2012). This unilateral migration is required for the establishment of epithalamic asymmetry (Concha et al., 2012). Indeed, Budaev and Andrew (2009) demonstrated that absence of light on day 1 after fertilization changes the preferred eye for predator inspection from left to right. Dadda et al. (2010) used the fact that about 10% of zebrafish larvae have a parapineal that aberrantly migrates to the right. They tested if animals with aberrant or normal epithalamic asymmetries display different visual lateralized behavior. Indeed, in all three laterality tests (mirror viewing, predator inspection, and rotational direction) groups of fish with opposite parapineal positions differed significantly. Thus, epithalamic asymmetry is directly linked to lateralized behavior.

The development of epithalamic asymmetries in the zebrafish is regulated by at least four major genetic signaling cascades: the FGF, Nodal, Notch, and Wnt/beta-catenin pathways (Hüsken and Carl, 2013). The Nodal signaling pathway is central to the regulation of neuroanatomical asymmetries in the zebrafish forebrain, but the first steps are FGF mediated. Initial migration of the parapineal from the midline to a lateralized position in the brain is controlled by the fibroblast growth factor Fgf8. Zebrafish Fgf8 mutants do not develop epithalamic asymmetries (Regan et al., 2009). FGF signaling controls expression of six3b and six7, two transcription factors that mediate repression of lefty1 in the brain. Reduced FGF signaling leads to bilateral lefty1 expression and increased cell boundary formation in the midline of the brain (Neugebauer and Yost, 2014). Although these data show a clear contribution of FGF, the Nodal pathway and not FGF signaling is essential for the direction of asymmetry. If Nodal signaling is removed in fgf8 mutant zebrafish, local provision of Fgf8 leads to asymmetric migration of parapineal cells, but not to the left, but toward the source of Fgf8 asymmetries (Regan et al., 2009).

Interestingly, absence of Nodal pathway gene expression does not lead to neuroanatomical symmetry in the epithalamus. Epithalamic asymmetries are still established, but instead of the pronounced 90% leftward asymmetry found on the population level in wild-type fish, their direction is determined at random (Concha et al., 2000). Taken together, these findings show that FGF signaling breaks symmetry, but Nodal signaling determines direction of asymmetry. This shows that Nodal genes only determine the direction of asymmetries.

Within the Nodal signaling cascade, leftward asymmetry of the parapineal is initiated by ndr2 (also called cyclops), which is required for expression of the feedback inhibitor Lefty1, and the homeodomain transcription factor Pitx2c (Duboc et al., 2015; Roussigné et al., 2012; Snelson and Gamse, 2009). In addition, it has been found that early diencephalic left-right

asymmetries also requires activity of Southpaw, a gene encoding for a Nodal-related protein. Southpaw is expressed in the left lateral plate mesoderm and controls asymmetries of heart, pancreas, and brain. Southpaw deficient embryos show severe downregulation of left-sided expression of cyclops, pitx2, lefty1, and lefty2 (Long et al., 2003).

Successful Nodal-mediated left-right asymmetry induction critically depends on the Notch pathway, a signaling pathway that controls cilia length (Lopes et al., 2010; Takeuchi et al., 2007). Raya et al. (2003) showed that in zebrafish, activity of the Notch pathway is necessary for Nodal expression and left-right asymmetries: bilateral injection of Notch mRNA led to bilateral expression of ndr2 and pitx2, which normally are only expressed in the left lateral plate mesoderm.

The last major signaling pathway that has been related to the establishment of neuroanatomical asymmetries in the zebrafish is the Wnt/beta-catenin pathway. Similar to the Notch pathway, this cascade is active in the lateral plate mesoderm before the first Nodal pathway genes are expressed. Wnt signaling regulates ciliogenesis in zebrafish via Foxj1a, a ciliogenic transcription factor, and later contributes to proper left-sided Nodal gene expression by repressing repression of Nodal (Hüsken and Carl, 2013). Inhibition of Foxj1a transcription leads to a reduction of cilia length and number and randomized asymmetry (Zhu et al., 2015).

After these genetic events have unfolded, the young zebrafish has an asymmetrically organized epithalamic system with a habenula that is constituted by a dorsal and a ventral part. The dorsal habenula consists of a lateral (ldHb) and a medial subnucleus (mdHb) that are grossly asymmetric with respect to their sizes: although the left dorsal habenula has a large lateral and a small medial subnucleus, the situation is inverted on the right (Roussigné et al., 2012). Although the lateral subnucleus of the habenula targets the dorsal component of the n. interpeduncularis (dIPN) in the ventral mesencephalon, the medial habenula innervates the ventral component (vIPN). Because of the size asymmetry of lateral and medial habenular subnuclei, dIPN is mostly innervated from the left side, while vIPN receives input predominantly from the right habenula. By this arrangement, left-right size asymmetries of the dorsal habenula are converted to dorsoventral differences in the interpeduncular nuclei (Aizawa et al., 2005). Because dorsal and ventral IPN project differentially to the dorsal tegmental area (DTA) and the serotonergic median raphe (MR), respectively (Beretta et al., 2012), asymmetries of the habenula can modulate distinct downstream circuits with distinct roles in emotional behavior (Concha et al., 2012; Chou et al., 2016). Some of these findings also shed new light on asymmetries in humans.

As had been outlined above, patients with primary ciliary dyskinesia have a 50% chance of situs inversus, possibly because of an absence of cilia movements and a subsequent lack of embryonal leftward flow of extracellular fluid at the node. Because these patients are mostly right-handed with left hemispheric language dominance, it was concluded that Nodal pathway asymmetries cannot be the key factor for left-right differences of the human brain (Kennedy et al., 1999). As shown by Barth et al. (2005), this is different in zebrafish. Here, the *frequent-situs-inversus* line of zebrafish show a coupling of

visceral, habenulo-interpeduncular, and visual behavioral asymmetries. Thus, Nodal seems to orchestrate both visceral and some of the neural and behavioral asymmetries in zebrafish but not in humans. But also in zebrafish, two of the tested behavioral asymmetries do not reverse, suggesting that there are different parallel genetic routes that influence functional lateralization during ontogeny (Barth et al., 2005).

Specific manipulation of the lateralized epithalamic circuitry could meanwhile reveal further insights into behavioral lateralizations. Inactivation of the *IdHb* induces freezing instead of flight when the animal is confronted with a fear stimulus (Agetsuma et al., 2010). Chou et al. (2016) went a step further by using agonistic encounters between dyads of male zebrafish as a behavioral model. When male zebrafish are placed in one tank, they first start with display behavior and then start with biting attacks, until one of the individual surrenders. When a zebrafish had won the fight, Chou et al. (2016) observed higher activity levels in the *IdHb* → *dIPN* → *DTA* pathway (Figure 2). In losing fish, there was a tendency for increased activation in *vIPN*. When the *IdHb* → *dIPN* pathway was experimentally silenced, the animals mostly lost fight encounters. When the same manipulation was done with the *mdHb* → *vIPN* pathway, the animals turned into winners. This differential effect was not due to fatigue or any other obvious behavioral difference between the two types of manipulation but possibly resulted from a differential resilience to the agonistic situation. Indeed, the *DTA* is known to play a key role in the binary switch between fight and flight (Siegel et al., 2007).

The reconstruction of these genetic, functional, and neuronal pathways in zebrafish, as well as their interactions with non-genetic factors, starts to offer insights into the principles underlying variant and invariant ontogenetic mechanisms for brain asymmetries controlling handedness and language in humans.

### The Riddle of Handedness: The Ontogenesis of Human Lateralization

In humans, a hereditary basis for handedness was suggested as early as in the 1930s (Wilson and Jones, 1932). From the 1960s onward, the dominant view was that handedness and language lateralization were determined genetically, with a single gene controlling both phenotypes (Annett, 1964; McManus, 1985). However, after sequencing of the human genome in the early 2000s made it possible to investigate the molecular genetics of handedness, single-gene models were refuted by empirical evidence. Findings from genome-wide associations studies (GWAS) (Armour et al., 2014; Eriksson et al., 2010; McManus et al., 2013) as well as from linkage analysis (Somers et al., 2015b) and whole-exome sequencing in genetic bottleneck populations with an over-representation of left-handedness (Kavalioglu et al., 2015) all clearly indicated that there is no single gene controlling handedness and language lateralization. Today, most investigators agree that handedness and language lateralization are complex phenotypes determined by several, possibly interacting, genetic and non-genetic influences (Francks et al., 2007; McManus et al., 2013; Ocklenburg et al., 2013c, 2014; Somers et al., 2015b). Regarding genetic influences, a recent estimation based on existing GWAS data indicated that at least 40 loci are involved in determining handedness (McManus et al.,

2013). Because of the typically very small effect sizes yielded by genetic variation in a single locus for multifactorially determined phenotypes, reliable and replicable identification of relevant genes has proved to be notoriously difficult. At the present moment, three functional gene groups have been associated with handedness and language lateralization by more than one research group in independent studies.

The first functional gene group relevant for functional lateralization are genes involved in left-right body axis formation. Within this group, *PCSK6* in particular has been a focus of research. *PCSK6* encodes for a proprotein convertase that cleaves the *NODAL* proprotein into its biologically active form, thus regulating left-right body axis formation during embryogenesis (Shore et al., 2016). Mice lacking *PCSK6* show deficits of left-right body axis formation, such as *situs ambiguus* (Constam and Robertson, 2000). *PCSK6* was first linked to handedness by Scerri et al. (2011) in a study investigating the genetics of hand skill measured with the pegboard test. In that study, a SNP within *PCSK6* (rs7182874) reached genome-wide significance in a sample of 728 dyslexic patients, but not in a healthy cohort. A dyslexia-specific relation of *PCSK6* and hand skill was also reported by Brandler et al. (2013) for another SNP (rs7182874). However, there is also evidence for a role of this gene for handedness in healthy cohorts. Arning et al. (2013) found a significant association between genetic variation in a variable-number tandem repeat polymorphism in *PCSK6* (rs10523972) and degree of handedness (e.g., to which extent one hand is preferred over the other, independent of whether it is the left or the right hand). This finding was partially replicated by Robinson et al. (2016), who found a relation of *PCSK6* variation and handedness predominantly in female but not male subjects.

In addition to these studies focusing on *PCSK6*, Brandler et al. (2013) also investigated the contribution of genes involved in left-right body axis formation to handedness with a pathway-based approach. These authors used gene set enrichment analysis in order to test for over-representation of highly associated variants within genes that are involved in left-right body axis formation. Over-representation of genes annotated to 15 different morphological asymmetry phenotypes was tested. Three phenotypes associated with disruption in 116 unique genes showed enrichment at a false discovery rate (FDR) < 5% (double outlet right ventricle, heterotaxia, and *situs inversus*). Interestingly, four of the five genes that were most highly associated with handedness were involved in ciliogenesis (*RFX3*, *MNS1*, *GLI3*, and *PKD2*). Cilia rotation is a crucial process in creating bodily asymmetry (Hirokawa et al., 2006). This accumulation of genes involved in the same biological process highlights the importance of taking biological pathways, not only individual genes, into account when investigating the ontogenesis of handedness (Karlebach and Francks, 2015).

Because there are no substantial nervous, muscular or other differences between the left and right hand, handedness is thought to be a brain phenotype (Ocklenburg et al., 2013c). Therefore, genes involved in CNS function are the second group of candidate genes within the focus of handedness research. In particular, *LRRTM1*, an imprinted gene encoding for a transmembrane protein that functions as a synaptic organizer in

glutamatergic neurons (Linhoff et al., 2009), has been investigated in relation to handedness. Comparable with *PCSK6*, the first evidence linking *LRRTM1* and handedness was obtained in a dyslexic cohort. Francks et al. (2007) identified a three-SNP haplotype within *LRRTM1* that was associated with relative hand skill. Individuals with the minor allele on each of these three SNPs show a significant shift of 1.1 SDs toward left-handedness within the overall handedness distribution of the sample. Although Leach et al. (2014) did not find this association in a healthy cohort, they reported a significant negative correlation between levels of methylation in a block of CpG sites in the putative promoter region of *LRRTM1* and strength of handedness. Thus, in healthy subjects, epigenetic variation in *LRRTM1* seems to be more relevant for handedness development than genetic variation. Handedness is not the only phenotype *LRRTM1* has been related to, as several studies have linked this gene to schizophrenia (Brucato et al., 2014; Francks et al., 2007; Ludwig et al., 2009). Schizophrenia, in turn, has been linked to non-right-handedness and atypical language lateralization (Sommer et al., 2001), suggesting that the ontogenetic bases of schizophrenia and handedness might overlap to a certain extent.

Genes involved in CNS function have also been a focus of candidate gene studies that focused on language lateralization rather than handedness. The relevance of glutamatergic neurotransmission for the development of functional hemispheric asymmetries indicated by the *LRRTM1* data (Francks et al., 2007) is further corroborated by a study by Ocklenburg et al. (2011). These investigators found that genetic variation in *GRIN2B*, a gene that encodes for a subunit of ionotropic glutamate receptors, was associated with dichotic listening performance, a common behavioral measure of functional hemispheric asymmetries in speech perception. Glutamate is not the only excitatory neurotransmitter that has been linked to development of hemispheric asymmetries. Using the dichotic listening task, Ocklenburg et al. (2013b) found an association of language lateralization and genetic variation in *CCKAR*, a schizophrenia-related gene encoding for a G protein-coupled receptor that regulates dopamine release. Additionally, *FOXP2* has been linked to language lateralization. This gene is expressed in fetal and adult brain tissue. It encodes for a transcription factor that is essential for proper development of language-related brain regions during embryogenesis. Pinel et al. (2012) reported that genetic variability in two *FOXP2* SNPs (rs6980093 and rs7799109) was associated with variability in brain activation in the left frontal cortex as assessed with fMRI. Moreover they found one SNP (rs17243157) on *KIAA0319*, a dyslexia-associated gene that encodes for a transmembrane protein that plays a role in cortical development by regulation of cell adhesion and neuronal migration, to be linked to activation asymmetries in the superior temporal sulcus. A relation of *FOXP2* and language lateralization was later confirmed by Ocklenburg et al. (2013a), who found two SNPs within *FOXP2* (rs2396753 and rs12533005) to be associated with language lateralization.

One intriguing finding in handedness research is the fact that a subtle but significant sex difference exists in the distribution of left- and right-handedness. Papadatou-Pastou et al. (2008) found the odds ratio between men and women to be 1.23; that is, for 10 female left-handers there would be 12 male ones.

This led several researchers to assume that factors related to sex determination, such as sex hormones, might be relevant for handedness too. For example, the classic Geschwind-Galaburda hypothesis assumes that high intrauterine levels of testosterone and/or enhanced sensitivity to testosterone disrupt neural development in the fetus, causing a higher probability for atypical functional lateralization (such as left-handedness) in male fetuses (Geschwind and Galaburda, 1985). The genetic base for such a relation of intrauterine testosterone levels and handedness might lie in the androgen receptor gene, *AR*, which encodes a transcription factor that mediates the actions of testosterone. *AR* comprises a polymorphic CAG repeat in exon 1, and increasing CAG repeat block size has been linked to decreased *AR* function (Buchanan et al., 2004). Medland et al. (2005) reported that in women, greater CAG repeat block size was linked to increased left-handedness, whereas in men, it was linked to decreased left-handedness. Hampson and Sankar (2012) subsequently reported that mixed-handers showed greater *AR* CAG repeat block size than left- and right-handers. Both of these findings were later replicated by Arning et al. (2015), who found that mixed-handed men had longer CAG repeat blocks, and women who were homozygous for longer CAG repeats showed a tendency for stronger left-handedness. In relation to the sex chromosomes, it has also been suggested that protocadherin gene *PCDH11* might play a role for both hemispheric asymmetries and the development of psychosis in humans (Crow, 2013), but this idea so far has not been supported by molecular evidence.

One group of genes that might be of particular interest for the ontogenesis of functional lateralization are genes that are expressed asymmetrically in the two hemispheres (Karlebach and Francks 2015; Sun and Walsh, 2006). Although direct association between these genes and behavioral lateralization in humans has not been shown at the present point, a recent knockout study in mice indicated a relevance of asymmetrically expressed genes for mammalian limb preferences. Li et al. (2013) reported that knocking out *LMO4*, a rightward asymmetrically expressed transcriptional regulator, in the embryonic cortex of mice induced a stronger preference to use the right paw in the knockout mice compared with the wild-type.

Taken together, molecular genetic studies indicate a substantial influence of genetic factors on the ontogenesis of functional lateralization but fall short of constituting a full explanation, as a substantial amount of variance in handedness data remains unexplained, even when taking all known genetic factors into account. Indeed, a recent twin study indicated that genetic effects account for only about 25% of the variance in handedness data, with the remaining 75% being accounted for by non-shared environmental influence (Medland et al., 2009). This finding highlights the importance to investigate the molecular epigenetics of asymmetry development. However, with the exception of the aforementioned study by Leach et al. (2014), there has been no molecular study in human subjects on this question so far. Additional indirect evidence comes from a study linking genetic variation in the methyltransferase gene *SETDB2* to handedness (Ocklenburg et al., 2015), as the protein encoded by *SETDB2* regulates gene expression epigenetically by histone H3 methylation.

One mechanism that has been suggested in humans is a relation of asymmetric perceptual input triggered by perinatal asymmetries. As outlined further below, this is a key factor in the ontogeny of visual lateralization in birds but could also contribute to behavioral asymmetries in humans. Human embryos preferentially turn their heads to the right and suck at their right thumbs already at 14 weeks after conception (Hepper et al., 1990). This behavioral asymmetry strongly correlates with later handedness at school age (Hepper et al., 2005). After delivery and when in a supine position, most newborn infants prefer to lie with their heads turned to the right, resulting in greater perceptual experience related to the right hand. This head-turning preference predicts handedness in later life and thus has been suggested to contribute to handedness development (Michel, 1981).

Interestingly, adults also show a preference to turn their heads to the right: when kissing, about 64.5% of couples preferentially turn their heads to the right, while only 35.5% prefer to turn their heads to the left, indicating that the rightward head-turning motor bias persists into adulthood (Güntürkün, 2003). Moreover, right-kissers are significantly more right-handed than left-kissers (Ocklenburg and Güntürkün, 2009), suggesting that the relation between head-turning and handedness might be linked, as in birds, by experience-dependent factors. However, from these studies it is unclear, whether there is any causal relationship, as they might also simply share a common genetic background. In order to causally test the influence of a skewed visual experience of the hands on the development of handedness, it would be necessary to test children born with a permanent motor bias of the head, which would increase the probability of visual experiences of one hand. Such a cohort was tested in a recent study investigating handedness in children with congenital muscular torticollis (Ocklenburg et al., 2010). These patients display a permanently tilted asymmetric head posture to the left or to the right in combination with a contralateral rotation of face and chin, leading to an increased visual experience of the hand contralateral to the head tilt. The results indicated that increased visual experience of one hand affects human handedness to some extent: right-handedness had a prevalence of 100% in patients with left-sided torticollis (and more visual experience directed toward the right hand) but of only 78% in patients with right-sided torticollis (and more visual experience directed toward the left hand). Thus, visual experience, as well as other potential non-genetic influence factors on functional lateralization, such as birth stress (Coren and Porac, 1980), cultural pressures (Zverev, 2006), seasonal anisotropy (Jones and Martin, 2008), and many more, could interact with the genetic mechanisms of handedness. To uncover the mechanisms of these interactions will be the great challenge in laterality research in the next decade. Because the methodological repertoire available to investigate this in humans is limited, animal models are of utmost importance in this quest.

### Avian Asymmetry: From Stimulation Asymmetry to Lateralized Cognition

The previous section showed that the ontogeny of handedness has a genetic background but that the relevant genes can establish the adult phenotype only by interaction with environmental input. Can we identify the non-genetic factors that are relevant

for asymmetry and discern their ways of interaction with the genotype? In the visual system of birds, this is to some extent possible.





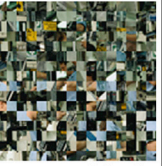
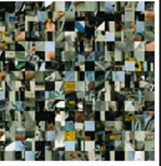
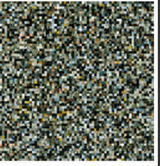
Studies of diverse avian species have revealed prominent lateralizations of visual processing. The left hemisphere excels in categorization, discrimination, and memorization of visual patterns (chicks: Rogers, 2014; quails: Valenti et al., 2003; pigeons: von Fersen and Güntürkün, 1990; Yamazaki et al., 2007), while the right hemisphere dominates visually guided interactions with emotionally charged stimuli (black-winged stilts: Ventolini et al., 2005; quails: Gülbetekin et al., 2009; chicks: Vallortigara et al., 2011), attentional shifts (chicks and pigeons: Diekamp et al., 2005), social interactions (chicks: Vallortigara and Andrew, 1994), as well as relational analysis of pictorial and spatial information (chicks: Vallortigara et al., 2004; pigeons: Yamazaki et al., 2007).

The complementary specialization of the two hemispheres was nicely illustrated in a categorization task with pigeons (Yamazaki et al., 2007). Here, the birds were confronted with hundreds of photographs that depicted everyday scenes with or without humans. Pigeons were rewarded to peck on the pictures showing humans, while being punished when pecking on stimuli without humans. Soon the pigeons started to properly discriminate between the two photograph sets. Then the birds were confronted with novel pictures and had to apply their discrimination strategy to these new instances. As predicted, the pigeons spontaneously differentiated between the two new picture sets. Thus, the animals had acquired a general ability to categorize humans.








But did the hemispheres use different strategies to solve the task? To approach this question, the stimuli were modified in two different ways. In the first test, the stimuli were fractioned into increasingly smaller squares that were arbitrarily scrambled (Figure 3). This was done in six increasing degrees. In degree 1, the pictures were divided into 64 squares, and only 8 of them were displaced. In degree 6, the pictures were cut into 4,096 squares that were all randomly rearranged. This procedure ensured that the animals had to use increasingly smaller features to decide between the presence or absence of humans. The pigeons worked on this task with eye caps that covered either the left or the right eye. Because of the complete crossover of the optic nerves, this ensures that only one hemisphere receives direct visual input. The result was clear-cut: pigeons could tolerate increasing degrees of scrambling with the right eye (left hemisphere), while they quickly fell to chance level when having to categorize even mildly scrambled picture with the left eye (right hemisphere) (Figure 3). Thus, the left hemisphere could discern diagnostic visual features in considerably smaller fragments than the right hemisphere. Because there are no acuity differences between the eyes, this difference must result from a differential specialization of the left and the right visual systems (Güntürkün and Hahmann, 1994). In the second test, the pigeons were confronted with pictures in which the depicted humans were distorted in different ways such that the usual configuration of the human body was no longer given. In this test, the performance of the left hemisphere was not affected, while the right hemisphere did not accept the dismembered humans as positive stimuli. Thus, the right hemisphere used



## Is there a human?

LH / RE	yes	yes	yes	yes	yes	no	no
RH / LE	yes	yes	yes	no	no	no	no
Scramble-Test							
	original	scramble 1	scramble 2	scramble 3	scramble 4	scramble 5	scramble 6

LH / RE	yes	yes	yes	yes	yes	yes	yes
RH / LE	yes	no	no	no	no	no	no
Distortion-Test							
	original	attached	detached	horizontal	vertical	inverted	square irregul.

**Figure 3. Hemispheric Differences of Visual Categorization in Pigeons**

Pigeons had learned to discriminate pictures with and without humans. When confronted with novel photographs, stimuli were altered either by increasingly scrambling them in six steps or by distorting the human image by six different procedures. The birds conducted this test either with the left hemisphere/right eye seeing (LH/RE) or with the right hemisphere/left eye (RH/LE). Scrambling affected LH/RE less, making it likely that the left hemisphere uses small pictorial features to solve the task. Every kind of distortion resulted in the RH/LE opting against the possibility that a human was depicted. Thus, the right hemisphere seems to rely on a configurational strategy to identify categorized objects. This is based on Yamazaki et al. (2007).

a configurational strategy to recognize humans. Taken together, visual asymmetry in birds reveals a parallel and complementary specialization of the two hemispheres. But how does this lateralization develop?

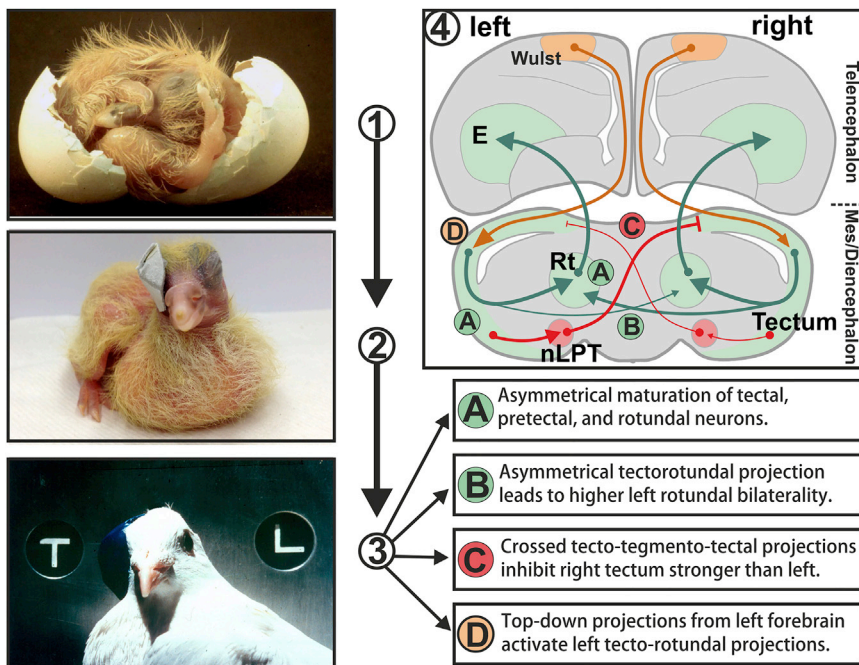
As early as 1932, Zing Yang Kuo reported that birds assume an asymmetrical position in the egg. The embryo is curled such the right eye is turned to the semi-translucent eggshell, while the left eye is covered by the embryo's body (Kuo, 1932). Because of this position, the right eye is stimulated by incident light, whereas the left one is mostly light deprived. During breeding, parental birds regularly turn their eggs and leave the nest for short periods (Buschmann et al., 2006). Thus, the embryo's right eye is repeatedly stimulated by light. The lateralized curled position of the bird embryo is very likely mediated by the Nodal cascade, as the processes underlying the asymmetrical positioning of the viscera are always accompanied by torsion of the embryo and a turn of the head to the right (Ramsdell and Yost, 1998). This occurs in all amniotes, including humans (Dunsirn et al., 2016).

The lateralized position of the avian embryo has an unexpected consequence: if chicken or pigeon eggs are incubated in darkness, the development of a functional lateralization in object discrimination with a dominance of the left hemisphere is prevented (Deng and Rogers, 2002; Skiba et al., 2002). Embryonic (Rogers, 1990) or posthatch (Manns and Güntürkün, 1999a) visual stimulation of the left eye can even reverse behavioral asymmetry in chicks and pigeons, respectively. Thus, normal rearing conditions correspond to right eye stimulation, resulting in left hemisphere superiority for visual object discrimination. This population bias is not genetically determined by fac-

tors within the visual system but by the lateralized environmental factor light input that results from the genetically determined body position.

The resulting asymmetry in visual object discrimination is mediated through activity differences between left and right retinal ganglion cells. Synaptic maturation of visual pathways is regulated by retinal activity and transiently blocking right eye retinal activity in pigeons reverses visual lateralization for the entire life (Prior et al., 2004). The lateralized retinal activation asymmetrically regulates tectal neurons in the midbrain, which in turn seem to release brain derived neurotrophic factor (BDNF) differentially on the left and the right side (Manns et al., 2005). As a result, BDNF and the signaling cascade of its high-affinity receptor TrkB are asymmetrically activated in response to embryonic light stimulation (Manns et al., 2005). It is likely that BDNF is just one out of many biochemical pathways that translate a transient embryonic visual stimulation asymmetry into structural left-right differences of the ascending visual system that then determine lateralized visually guided behavior (Figure 4).

Visual information reaches the avian forebrain by two parallel ascending systems, the thalamofugal and the tectofugal pathways which are homologous to the mammalian geniculocortical and extrageniculocortical systems, respectively. In pigeons, the tectofugal system is the most important pathway for visually guided behavior (Figure 4). It runs from the retina via the optic tectum to the thalamic n. rotundus, which in turn projects to the entopallium in the telencephalon. Lesions of the n. rotundus or its telencephalic target, the entopallium, result in deficits of a



**Figure 4. Ontogeny of Visual Asymmetry in Pigeons**

(1) Asymmetrical position of a pigeon hatchling. The animal points with its right eye toward the eggshell while the left eye is covered by the body. As a result, the right eye is stimulated by incident light in the days before hatch, resulting in higher right retinal activity and a lateralized release of BDNF in the developing visual system. (2) Two-day-old pigeon that undergoes right eye light deprivation. This procedure can reverse asymmetry in brain and behavior. (3) Adult pigeon with eye cap during a pattern discrimination task. Its behavioral asymmetry is related to four asymmetrical properties of the tectofugal system and associated pathways (A–D). (4) Schematic diagram of a frontal section through the pigeon brain depicting the tectofugal visual system (in green). nLPT, n. of the lateral ponto-mesencephalic tegmentum. (1) and (3) are reproductions from Ocklenburg and Güntürkün (2012), published open-access under the terms of the Creative Commons Attribution Non Commercial License. (2) is a reproduction from Ströckens et al. (2013), used with permission of the author and the publisher.

large number of visual psychophysical and visuocognitive functions (Güntürkün, 2000).

How does this neural pathway enable visual asymmetries of object discrimination? Anatomical studies demonstrated that the tectofugal system is characterized by morphological asymmetries at tectal (Güntürkün, 1997; Manns and Güntürkün, 2003; Manns et al., 2005) and rotundal level (Manns and Güntürkün, 1999b). In addition, commissural fibers are asymmetrically organized such that the left tectum is less inhibited through a tegmental link by its counterpart (Keysers et al., 2000; Stacho et al., 2016), while the left entopallium integrates input from both eyes to a larger extent than the right one (Güntürkün et al., 1998; Ströckens et al., 2013). In addition, left tectofugal neurons are able to discern rewarded and non-rewarded stimuli at a higher level (Verhaal et al., 2012). Consequently, left-sided tectofugal lesions result in more severe visual deficits than right-sided ones (Güntürkün and Hahmann, 1999; Valencia-Alfonso et al., 2009). Dark incubation abolishes these anatomical tectofugal asymmetries (Manns and Güntürkün, 1999a, 1999b, 2003) and alters inter-hemispheric transfer (Manns and Römling, 2012; Letzner et al., 2014). Thus, lateralized light input before hatch induces both structural and behavioral asymmetries.

These studies focused only on the ascending pathways from retina to telencephalon. Top-down signals from the forebrain can in addition activate neural templates, which then enable fast recognition and categorization of the incoming input (Ullman, 2007). Similarly, descending projections from visual areas in the left telencephalon of pigeons selectively amplify incoming visual stimuli within the left but not the right thalamic n. rotundus (Folta et al., 2004; Freund et al., 2016). Blocking this top-down system on the left side abolishes the superiority of the pigeons' left hemisphere in visual decision tasks (Freund et al., 2016).

Up to now we have presented the ontogenetic events as starting with a biased embryonic visual input, proceeding with activity-dependent asymmetrical changes of the structure of the tectofugal visual system, and finally giving rise to functional asymmetries in object discrimination. But at the very beginning of this section, it was stressed that avian visual lateralization has a complementary organization, with the left and right hemispheres being specialized for different processes. As it turns out, the biased embryonic photic input only activates object discrimination asymmetries but does not affect right hemispheric superiorities that mediate visual reactions to novelty (Chiandetti et al., 2005) and social recognition (Andrew et al., 2004). Thus, the neuronal effects of lateralized embryonic visual stimulation mediate only some of the left hemispheric visually guided functions. This makes it clear that there must be multiple modes of interactions between genetic and environmental factors that differentially shape the diverse lateralized systems of the brain.

### Conclusions

Although humans and other vertebrates show a fundamentally symmetrical body plan, their brain organization is shaped by hemispheric asymmetries. There is hardly any perceptual, cognitive, or motor system that is not affected by left-right differences of at least some of its subcomponents. Despite this importance, the ontogenetic mechanisms and neural fundamentals of lateralization are still mostly enigmatic. To some extent, this lack of proper knowledge results from a century-old assumption that lateralization is a human-only trait, which resulted in the conviction that animal models do not make sense. Only for about two decades have most comparative scientists realized that asymmetries of brain and behavior are not the exception but the norm and can be discovered in practically all taxa of the animal kingdom.

When a trait is so widespread, it is conceivable that it represents a phylogenetically old system of common origin. Indeed, asymmetries seem to have started early in phylogenetic time. However, species differences in brain lateralization cannot easily be explained by phylogenetic relations but rather seem to represent local ecological adaptations that were shaped by natural selection. Thus, asymmetries pay, possibly by increasing task performance, decreasing reaction times, and by the possibility to run parallel and complementary neural processes. The diversity of lateralizations is reflected in the observation that asymmetries of brain and behavior are constituted by diverse subsystems that can have different organizations and different ontogenetic backgrounds.

Despite these vast differences at the level of the phenotype, there are more commonalities at the genetic level. In vertebrates, determination of the left and right sides can be traced back to a midline structure called the node and the ensuing Nodal signaling cascade during neurulation. Nodal could even constitute an ancestral feature for the induction of lateralization in bilateria. However, the genetic cascades that then shape the developing brain into its species-typical lateralized organization are diverse and work in parallel at different system levels. In particular, studies on the epithalamus of zebrafish have unraveled at least four different and parallel genetic signaling pathways that shape the lateralization of the brain as early as the first 24 hr after fertilization.

Although the FGF signaling pathway orchestrates the first symmetry break, the Nodal pathway in interaction with the Notch and the Wnt/beta-catenin pathways manages the direction of brain asymmetry. This shows that genes that are involved in left-right body axis formation also are relevant for hemispheric asymmetries of brain and behavior. This assumption is also supported by data in human subjects, where this gene group as well as genes involved in CNS function and genes related to sex determination have been shown to influence behavioral asymmetries. In general, single genes or gene networks explain only small amounts of variance in behavioral data, arguing for a multifactorial origin of human asymmetries and a substantial role of non-genetic factors.

The complexity and diversity of lateralized pathways even within a single neural system is nicely exemplified by the finding that in zebrafish, lateralized behavior depends on multiple asymmetrical connections that reach from the forebrain via the diencephalon up to the tegmentum. The key relevance of asymmetrical wiring of ascending and descending pathways is also visible when studying visual lateralization in birds. These studies reveal that lateralized visual connections can emerge from a genetically determined motor asymmetry that then subsequently shapes visual experience in a lateralized way. Thus, although starting by purely genetic means, the subsequently unfolding lateralized events are then mostly shaped by non-genetic mechanisms. This resembles discoveries in the field of development of sensory systems: although genes settle the initial architecture of embryonic sensory pathways, most of their adult phenotype emerges from interactions with the environment. As always for brains, no neural system develops by genetic pre-determination only but is constantly molded during ontogeny by a close interaction of genetic and non-genetic mechanisms. Thanks to

animal models, these translations from gene-environment interactions into lateralized neural structure and function are beginning to be visible. It is clear, however, that there are still many unresolved questions regarding the ontogenesis of hemispheric asymmetries. In particular, the molecular mechanisms by which non-genetic factors influence hemispheric asymmetries are still far from being understood. DNA methylation, histone modification, and post-transcriptional regulation by microRNA's represent epigenetic modifications of gene expression that need to be investigated in the context of hemispheric asymmetries. In addition, it is also still completely unclear why so many psychiatric and neurodevelopmental disorders have been linked to atypical lateralization and what the ontogenetic basis of this link is. Combining molecular, behavioral, and neuroimaging research in humans and non-human model species to answer these questions represents the major challenge in research on hemispheric asymmetries for the next decade.

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