

Review

When and Why Did Brains Break Symmetry?

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Abstract: Asymmetry of brain function is known to be widespread amongst vertebrates, and it seems to have appeared very early in their evolution. In fact, recent evidence of functional asymmetry in invertebrates suggests that even small brains benefit from the allocation of different functions to the left and right sides. This paper discusses the differing functions of the left and right sides of the brain, including the roles of the left and right antennae of bees (several species) in both short- and long-term recall of olfactory memories and in social behaviour. It considers the likely advantages of functional asymmetry in small and large brains and whether functional asymmetry in vertebrates and invertebrates is analogous or homologous. Neural or cognitive capacity can be enhanced both by the evolution of a larger brain and by lateralization of brain function: a possible reason why both processes occur side-by-side is offered.

Keywords: brain asymmetry; invertebrates; vertebrates; evolution; memory; social interactions

1. Asymmetry in the Brains of Vertebrates

Despite its superficial appearance of symmetry, the vertebrate brain is functionally asymmetrical, and there are structural asymmetries in its substructure (e.g., in neuronal connections and neurotransmitters). It has been long known that the left hemisphere of the human brain is specialized to produce speech and process language and that this asymmetry is manifested in structural asymmetry in the planum temporale region of the cortex [1,2]. However, over the last three to four decades, it has become clear that

asymmetry of brain function is a characteristic of a wide range of vertebrate species [3–5] and may possibly be present in all vertebrate species. In a few cases, this asymmetry of function has been linked to structural asymmetry, at least at the cellular or subcellular level [6–9], but, as far as we know, in the majority of species, behavioural asymmetry is clearly present without any obvious, or known, structural asymmetry.

Lateralization of visual processing has been investigated most widely in vertebrate species, and it can be demonstrated easily in vertebrates with their eyes positioned on the sides of their head and, hence, with large monocular visual fields. They show left-right eye differences in response to stimuli (Figure 1). Birds, for example, process information in different ways in the left and right hemispheres, and this is evident as differences in behaviour according to whether the left or right eye is used [10,11]. Input from the right eye is processed primarily in the left hemisphere, and this hemisphere is specialized to categorise stimuli according to previously-established (learnt) criteria and to focus attention on the pursuit of prey [3,12]. Input from the left eye is processed primarily in the right hemisphere, which is specialized to control behaviour in emergency situations, as in the detection of and escape from predators [13], and is used in the expression of attack and copulation behaviour [10], spatial behaviour using geometric cues [14] and social recognition [15–17], as well as other aspects of social behaviour [18].

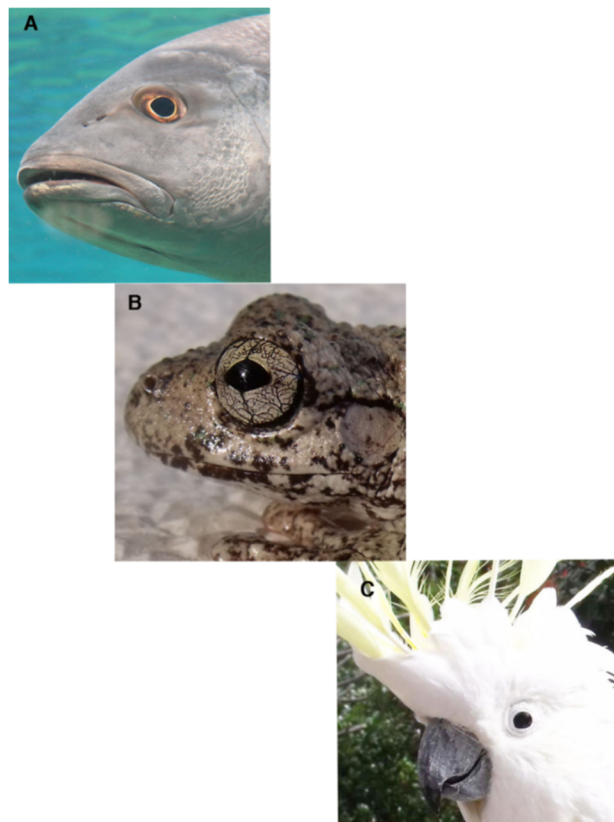


Figure 1. Representative species with eyes positioned laterally: (A) fish; (B) frog; (C) bird. Although these species have a binocular visual field to some extent, the monocular visual field of each eye is much larger. As stated in the text, it is relatively easy to test such species for lateralization of visual function. However, this does not mean that species with frontally-positioned eyes and large binocular visual fields lack visual lateralization.

Many mammalian species also have their eyes positioned laterally on the sides of their head, and the inputs from one eye cross the midline to be processed by the contralateral hemisphere, as in birds. Research on horses, for instance, has shown that, similar to birds, they are more likely to use the left eye before they attack a conspecific, and they react more strongly to stimuli seen on their left side [19,20].

Here, we have mentioned just some of the differential functions of the left and right hemisphere of the vertebrate brain. It is notable that the same fundamental pattern of lateralization is present across species, including humans (summarized in Figure 2).

Left hemisphere	Right hemisphere
Focused attention	Broad attention (easily distracted)
Established (learnt) behaviour	Response to unexpected stimuli
Categorises stimuli	Face recognition
Pursuit of prey	Social behaviour
Attention to landmarks	Geometric spatial processing
Long-term memory	Short-term memory
	Expression of strong emotions (aggression)

Figure 2. A summary of the general pattern of lateralization in vertebrate species.

2. Midline Crossing of Sensory Inputs and Motor Outputs

Perhaps strangely, these functional asymmetries of visual and other sensory processing, apart from olfaction, occur in brains that receive their input from sensory receptors on the opposite side of the body and, in turn, send output controls to that same, opposite side. Why this complexity has evolved has yet to be explained convincingly. The idea, attributed to Santiago Ramón y Cajal, that the crossing over of visual projections is a way of accounting for the inversion of the visual image caused by the lens of the eye, has received little support. Together with Richard Andrew [3], we have tried to relate the decussation (crossing) of the optic nerves to the evolutionary history of brain asymmetries. Briefly, on the basis of evidence provided by the current-living *Amphioxus* (now called *Branchiostoma*), particularly its larval form, it can be argued that in the earliest vertebrates, the mouth was located on the left side of the head. When, during the evolution of vertebrates, two eyes replaced the single eye (of the lancelet), the visual control of mouth (still on the left) opening in preparation for capture of prey forced the crossing over of the optic nerve fibres from the right eye, which was used to detect prey (for a summary see [3], Chapter 2).

3. Asymmetry in the Brains of Invertebrates

Over very recent years, bees have provided us with the clearest evidence of lateralization in the invertebrate brain. Discovery of asymmetry in honeybee behaviour was made by Letzkus *et al.* [21], who found that bees tethered in a holder could learn to associate an odour, such as that of lemon, with a sugar reward when they could use their right antenna during training, the left antenna being covered in

a silicone coating, which prevents this antenna from sensing odours. With the right antenna covered with the silicone coating, the bees were unable to learn the association between the odour and the sugar reward. In these tasks, a second odour (vanilla) was used in association with saline, which acted as a punishment. In other words, the bees learned to respond positively (*i.e.*, extend their proboscis) to lemon odour and not to vanilla odour.

Memory recall of the learnt association of a specific odour with a sugar reward is also asymmetrical. Immediately after training and up to some three hours afterwards, the bee will extend its proboscis on detecting the lemon odour provided that it can use its right antenna, but after a longer delay between training and testing of recall (six or 24 hours), the extension of the proboscis occurs only when the bee can use its left antenna [22]. Hence, short- and long-term memory recall is allocated to opposite antennae and to different brain locations. This is a clear example of a small brain breaking symmetry. The same antennal differences in recall of olfactory memories have been shown in other species of bees, three species of Australian stingless bees [23]. One assumes that it must be beneficial to separate short- and long-term memories in this way, perhaps in order to avoid confusion between immediate behaviour and longer-term past experience (e.g., separating learning from that which has already been learnt). This might also serve to avoid making mistakes in memory recall.

In a completely different species of insect, the fruit fly *Drosophila melanogaster*, an asymmetrically-positioned brain structure has been found; interestingly, the small proportion of fruit flies that have symmetrical brains with two such structures lack the ability to form normal long-term memory, although their short-term memory is intact [24].

Honeybees also show asymmetry of antennal use when they interact with each other [25]. This was shown by removing either the left or right antenna and looking at the behaviour of pairs of bees in petri dishes. Pairs of bees with their right antenna in use (left antenna removed) showed appropriate social behaviour, in that they interacted by extending and touching each other with their proboscis provided that both bees were from the same hive (Figure 3A). If they were from different hives, they showed aggressive behaviour; *viz.*, the C-response, in which one bee arches its body and attempts to sting the other (Figure 3B). Pairs of bees using their left antennae showed inappropriate social behaviour, exemplified by performing more C-responses when both bees were from the same hive and fewer C-responses when the bees were from different hives.



Figure 3. (A) A positive interaction involving proboscis extension with antennal contact between bees from the same hive. (B) A negative interaction involving one bee mounting the other and adopting the C-response in preparation for stinging.

Lateralized behaviour has been reported also in other invertebrate species [26], including ants [27] and spiders [28,29]. Even octopuses display eye preferences, despite their radial symmetry, but in their case, individuals can be biased either left or right, and there is no population bias [30,31]. Cuttlefish, however, do show a population bias to escape leftwards when they detect the odour of a predator, and this asymmetry results from a preference to look for escape routes using the left eye [32].

Although more research on lateralization in invertebrate species is needed, it is now clear that to think of these species as symmetrical, either bilaterally or radially, is incorrect.

4. What Is the Relationship between Asymmetry in Invertebrates and Vertebrates?

Brain asymmetry has had a long history. For over a hundred years, it was seen as a defining characteristic of the human brain. At first, scientists, especially those studying humans, were most reluctant to accept the findings of lateralization in non-human species. Then, in time, they slowly relinquished this human-centred view in the face of increasing evidence of lateralization in vertebrate species (e.g., Corballis [33]). Now, it must be rather unsettling to traditional thinkers to learn that functional lateralization is also present in invertebrate species. Indeed, in response to the recent reports of lateralized behaviour in invertebrate species, the assumption has been made that vertebrate and invertebrate laterality are analogous and not homologous. As no genetic evidence, so far, supports this claim, this idea may reflect threads of past thinking that linger in our minds.

Since the vertebrates, or chordates to be precise, evolved via life forms with radial symmetry (echinoderms, star fish), the argument that lateralization has arisen separately in invertebrates and vertebrates may have some substance. However, species with radially-symmetrical body plans can exhibit asymmetry of perceptual processing and motor output of escape responses, as for cuttlefish mentioned above. The deep-sea squid, *Histioteuthis*, has obvious structural differences between its eyes, and this asymmetry is biased in the same direction within the population: the left eye is larger than the right and looks upward, whereas the smaller right eye looks downward [34]. Most likely, these structural differences between the eyes are associated with lateralized differences in the optic pathways or, at least, lateral differences in neural processing.

Considering that laterality is, indeed, present even in species with radially-symmetrical body forms, it seems possible that there was continuity of gene expression from invertebrates to vertebrates and that the same genes involved in the expression of lateralization in invertebrates might have roles important in the lateralization of vertebrates. In other words, it is possible that the same genes influencing lateralization are present in both protostomes and deuterostomes (Figure 4).

The signaling molecule, Nodal, is involved in the development of asymmetry in vertebrates [35–38]. Grande and Patel [39] discovered that an orthologue of Nodal is also present in a non-deuterostome, a snail. This finding suggests that the Nodal pathway may be involved quite generally in bringing about asymmetry in the Bilateria, which includes nematodes, flies, snails and annelid worms. Nodal also has a role during later embryogenesis of sea urchins, where it breaks symmetry even though adult sea urchins are radially-symmetrical [40]. In fact, recent research by Watanabe *et al.* [41] has shown that a Nodal-related gene has a role in determining a structural axis in the radially-symmetrical Cnidarian, *Hydra*: it establishes a body axis for a new bud distinct from that of the parent. Given these roles of Nodal in the development of structural asymmetry [42], asymmetry in invertebrates and vertebrates may

have at least some homologous aspects. As known from research on the zebrafish, the Nodal signaling pathway has a role in the development of both visceral and neural asymmetry [43,44]. In fact, it could well be that Nodal is an ancestral mechanism for the development of left/right asymmetry in several organs or tissues [42].

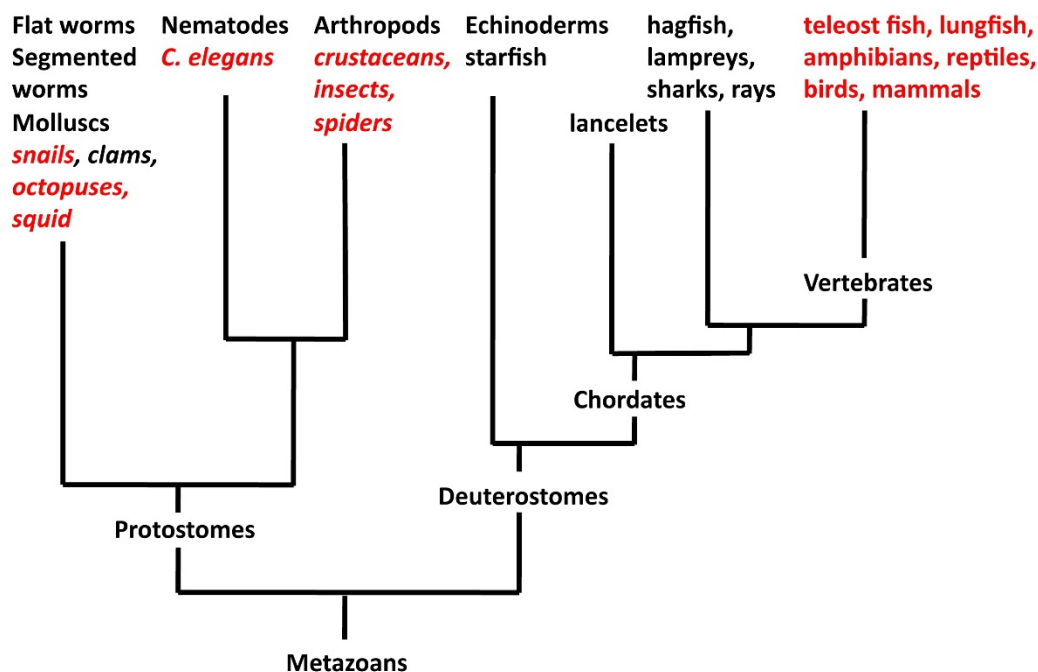


Figure 4. A simplified representation of the evolutionary links of animal species. Red font indicates known classes/orders/species in which lateralized brain function has been found as a population bias.

Research on the genes involved in symmetry and breaking symmetry in invertebrates is in its infancy, but, although is still debated, other genes (e.g., the Hox gene [45]) have emerged as potentially similar determinants of gut asymmetry in invertebrates and vertebrates [46]. Whether the same or similar genes are involved in the genesis of neural asymmetry remains to be investigated, and the nematode, *C. elegans*, and the zebrafish are proving to be useful models for this research [47,48]. In fact, genes expressed in left-right asymmetry in *C. elegans* are known to have homologs in vertebrates [49]. This does not necessarily mean that these genes have the same role in species so distantly separated in evolution, but we are now in a position to test this.

5. Genes as the Foundation, Experience as the Decider

Although genes are important in the genesis of functional asymmetry, it is important to stress the role played by experience. In birds, lateralization of some types of visual behaviour is generated by exposing the developing embryos to light just before they hatch (in chicks [50]; in pigeons [51]). Chicks hatched from eggs incubated in the dark lack asymmetry of visual behaviour in categorisation of food items and in responding to predators (summarized in Rogers [12]). Light exposure during embryonic development also affects the development of lateralized behaviour in zebrafish [52].

In the chick, we know that the role of light in generating lateralization of visual behaviour depends on the orientation of the embryo within the egg, such that the right eye only can be stimulated by light during the sensitive period before hatching [50]. The orientation of the embryo is determined by the expression of genes, including Nodal, from the beginning stages of embryonic development. These genes determine the physical positioning of the embryo on the egg sac and in the egg before hatching. The question to ask now is whether asymmetry in the visual pathways and in visual processing also relies on genetic expression at the neural level or whether the asymmetry in vision simply comes about as a consequence of the body asymmetry. The latter seems to apply, since experiments demonstrate that the direction of asymmetry in visual behaviour can be reversed by occluding the embryo's right eye while exposing its left eye to light. Such experience-dependent functional asymmetry may not apply to other sensory systems, but, so far, no research has tackled this issue.

It has been suggested that light stimulation during the initial stages of embryonic development may act directly on gene expression [53], rather than by the asymmetrical stimulation of the eyes by light, as occurs during a later stage of embryonic development. In chicks, at least, such early effects of light affect asymmetry in different aspects of visual behaviour than those discussed above [54] (further consideration by Rogers [55]).

Using micro-array analyses, it has recently been reported that several genes are differentially expressed in the left/right hemispheres of the fruit fly, *Drosophila*, brain. Some of these genes encode proteins that serve functions, such as neural gene expression, memory, ion channel number and membrane receptor number or sensitivity. Intriguingly, they all have their peak expression during early embryonic stages, which suggests that, as in vertebrates, they may play a role in the development of brain lateralization [56].

There has also been an elegant demonstration of experience affecting lateralization in an invertebrate species, the cuttlefish [57]. Exposure of cuttlefish to the odour of a predator throughout the incubation period prior to hatching leads to the development of a left-turning preference, even when the cuttlefish are tested in water that has no odour of a predator present. One could say that the experience during early development has strengthened the left-turning bias or caused it to generalize to contexts in which no predator is detected.

Perhaps the important consideration here is that the asymmetry of brain function is flexible and can vary within a species according to experience in different environments. We should conceive of lateralization as flexible and dynamic. Although genes definitely act during embryonic stages to generate brain asymmetries, experience in embryonic and later stages may modulate the strength of lateralization, its presence or absence to such an extent that it is context that “decides” the outcome.

6. Advantages of Having an Asymmetrical Brain

Given that brains break symmetry of processing regardless of their size, to do so must be advantageous. One immediately assumes, and perhaps rightly, that to break asymmetry increases the cognitive capacity of a brain by decreasing duplication of neural processes. However, breaking asymmetry may provide more than this: it may avoid confusion by segregating different types of neural processing. Some time ago, Bianki [58], working on rats, provided some evidence of the separation of serial processing to the left hemisphere and parallel processing to the right hemisphere. Such separation

of computational processes might prevent mistakes that could arise from confusion. An experiment comparing lateralized with non-lateralized chicks supports this, in principle at least.

If the lateralized and non-lateralized chicks are tested in a task requiring them to search for grains of food scattered on a background of small pebbles and, at the same time, monitor overhead for a model predator, those that have been exposed to light and are lateralized can conduct both aspects of this task efficiently [59]. By contrast, chicks that have been kept in the dark for the last few days before hatching and that are not lateralized perform poorly on both aspects of the task. They are very likely to miss seeing the predator, but, when they do see it, they are so disturbed, that their ability to avoid pecking at the pebbles is impaired [59]. Other studies have also shown that breaking symmetry increases performance efficiency: in pigeons finding grain mixed amongst grit [60] and in chimpanzees fishing for termites using a tool [61].

In honeybees, Rigosi *et al.* [62] have recently found evidence for left-right differences in the types of neural coding in the antennal lobes, the primary brain region for processing olfactory information. Using *in vivo* functional imaging of bee brains when both antennae were exposed to odours, they found that the inter-odour distances between neural response patterns were higher in the right than the left antennal lobe. This, they said, would allow the bee to use simultaneously different coding schemes on the left and right and, so, would increase computational capacity. This, of course, could simply be a deduction based on the proposed advantage of lateralization in vertebrates, but, in the case of the bees, some empirical evidence supports the hypothesis. Therefore, it seems possible that the same computational differences between left and right may underlie functional lateralization in both small and large brains. In zebrafish, Dreosti *et al.* [7] have shown that lateralization in the epithalamic region of the brain enables visual and olfactory processing. Wild-type zebrafish with structural asymmetry of the epithalamic region process visual inputs mainly on the left side and olfactory inputs mainly on the right side. Zebrafish with symmetry of the epithalamus have impaired ability to respond to either visual or olfactory stimuli depending, respectively, on whether their symmetry is due to having two right sides or two left sides.

7. Disadvantages in Having an Asymmetrical Brain

The lateralities that we have discussed are present at a population level, meaning that they are in the same direction in the majority of individual animals in the species. In fact, the asymmetries recorded in our experiments on recall of odour memory in honeybees were present in the same direction in almost all bees tested [22]. This strong bias could, of course, be coincidental, but it could be worth exploring further. In vertebrates, the population bias tends to be around 70%, although in sulphur crested cockatoos, the preference to hold food items in the left foot is above 90% and, hence, is equivalent to right handedness in humans (for a comparison of asymmetries in the use of limbs in human and non-human species, see Versace and Vallortigara [63] and Hopkins *et al.* [64]).

One assumes that to have some individuals with weak, absent or reversed laterality in a population is insurance for coping with changes in environmental demands. Although individuals without lateralization of visual behaviour are unable to perform more than one task in parallel, as in the case of chicks discussed above, they may have other attributes that serve them well in different environments. They are more competitive and less likely to be at the bottom of a hierarchy without access to food, for example [65]. Hence, their presence in a population may enhance survival in conditions of resource

scarcity. In such situations, cognitive capacity may be sacrificed for social competition: “brawn over brain”, as the saying goes. Such demands are, however, likely to be transient for a species.

Another view explaining the polymorphism of brain/behaviour asymmetries (*i.e.*, the fact that it usually shows up with a majority of individuals having one direction and a minority having the other direction) is to imagine that the minority with reversed laterality has an advantage that is frequency dependent [66]. Mathematical models of prey-predator interaction [67] and intraspecific competition and coordination [68] have revealed that population-level lateralization represents an evolutionarily stable strategy for organisms that display asymmetric behaviour and some degree of social interaction. Maintenance of left-handedness in the human population would be easily explained by the hypothesis that different directions of lateralization are held in balance through frequency-dependent selection (evidence in Raymond *et al.* [69], and see Hori [70]). A corollary of this hypothesis is that population-level, rather than individual-level, lateralization would be expected when animals deal with tasks involving some degree of interaction for which the direction of asymmetry matters (for evidence, see the comparison between shoaling and non-shoaling fish [71], and see Vallortigara and Rogers [72] for a full description of this theory and the supporting evidence).

8. Why Lateralize Rather than Grow Larger?

If a certain degree of asymmetry of brain function increases cognitive capacity, why lateralize rather than grow a larger brain, which also increases cognitive capacity? Within a species, a number of factors constrain brain size: (1) the brain is a heavy “organ” and must be supported by bone and muscle structures; and (2) the brain is metabolically expensive, because neurons in particular demand a high supply of energy and nutrients [73]. The “expensive brain” hypothesis predicts that larger brains can evolve only when energy input increases or there is a trade-off between one area of the brain and another [74], or a trade-off between brain size and gut size, as supported by selection experiments in fish [75].

Certainly, evolutionary selection has led to larger and larger brains, but within a specific class or order, brain size relative to body size is held rather constant. In birds, for example, there appears to be a trade-off between the tectofugal visual system and the trigeminal/somatosensory system or between the tectofugal visual system and the thalamofugal visual system (discussed in Wylie *et al.* [74]). Perhaps, therefore, within a species-specific constraint, neural capacity can be enhanced by lateralization of different types of processing to the left *versus* right hemisphere. In a sense, to lateralize a brain regardless of its size appears to be a “cheap” way of increasing neural capacity and efficiency. Note, however, that the relationship between the degree of functional brain asymmetry and cognitive abilities may not be linear, since very pronounced asymmetry does not seem to confer any particular cognitive advantage (see Rogers *et al.* [3] for a discussion). Note, also, that research in humans suggests that increased cognitive abilities may be associated with the way hemispheres interact (e.g., more within-hemisphere interactions for the left hemisphere, more bilateral interactions between hemispheres for the right hemisphere; see Gotts *et al.* [76]). However, given the huge differences among species in the patterns of inter-hemispheric connections (*viz.*, absence of a corpus callosum in non-mammalian species), it is difficult to say how general this hypothesis may be.

Time/place considerations must be most important. Asymmetry of brain function is often discussed as if it were a fixed characteristic of individuals comprising a species. This is unlikely to be the case. As

mentioned above, sensory stimulation during development can influence the development of lateralization. Although a particular type of lateralized function may be common to the majority of individuals within a species, this is in a given set of environmental conditions. Should the latter change, individuals with weaker lateralization or no lateralization might develop. We can say that functional lateralization is flexible and responds to external demands. It may even be flexible within a much shorter timeframe. Consider the processing in a serial manner by the left hemisphere and in a parallel fashion in the right hemisphere. The brain as a whole needs to integrate outcomes of both kinds of processing. Is there a part of the brain, some structure, where the endpoints of both of these processes come together and which determines the final output? This could be unlikely. Instead, the brain, as a whole, may move between states of serial and parallel processing and between lateralization and non-lateralization (or different lateralization), in order to generate a single solution to control performance (e.g., by hemispheric switching [77]). If so, in the final analysis, brain lateralization must be flexible in a moment-to-moment sense. Of course, the evolution of a larger brain is entirely different from this, and it follows that it could not replace the function of lateralization.

Some have argued that lateralization of brain function increased as the size of the brain increased across species and even that behavioural and anatomical asymmetry emerged merely as a by-product of evolutionary selection for a larger brain (discussed in Hopkins *et al.* [64]). As far as some structural asymmetries go, there is support for this hypothesis within the primate line of evolution [64], but, as we have outlined, no such support comes from evidence of behavioural lateralization across a broad range of species. To put it simply, the small brains of insects are just as functionally lateralized as the large brains of vertebrates, even those of the apes. Lateralized processing is clearly not dependent on brain size, but, rather, is a fundamental feature of all species regardless of their brain size.

9. Concluding Remarks

Two notable aspects of the brain still stand out in their need for further explanation: (1) the crossed sensory input and neural output; and (2) the presence of laterality in brains of all sizes. Perhaps both have come about as a consequence of genetic constraints on development, but, of course, different ones in each case. We hope that this paper has gone some of the way in explaining why lateralization may be present in brains of widely varying size and brains designed to function in widely different habitats and social settings. The hypotheses outlined need empirical support. However, recognizing that it was only little more than three decades ago that evidence of lateralization in species other than humans came to light and that evidence for lateralization in invertebrates is a discovery made within the last decade, one could be impressed by the progress made in understanding how and why brains are not symmetrical.

Author Contributions

L.J. Rogers prepared the first draft and submitted the manuscript, but both authors made equal contributions to the final copy.

Conflicts of Interest

The authors declare no conflict of interest.

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