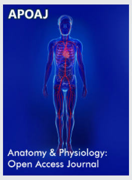

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Review article

Symmetry and Asymmetry, Crossing and Polarity: The Avian Synthesis

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Abstract

"Two things commonly escape notice in considering the ingenuity of symmetrical patterning, a) being co-equal, each half of a nervous system is potentially an independent entity; and thus, b) the necessity arises for one or the other side to decide which of two possible behaviours, that of the left or of the right, the organism will follow [1]". This article contains three parts. Part 1 relates crossings to symmetry by treating three hypothesis Cajal's, stereometric and double twist explanations, while part two discusses planar polarity and asymmetry. Part 3 directs to symmetry and asymmetry in the avian "split" brain since no corpus callosum is present.

Keywords: Invariant asymmetry; placodes; avian song; planar polarity; hubs

Part 1: Crossings

Introduction

Wherefore should fibre systems in the brain cross to the other side or decussate at the same side in vertebrates? A series of hypotheses have been published on this topic by various scientists. Treated are three of them: The oldest is the explanation of the Nobel Prize winner and father of the neurosciences Ramon y Cajal [2]. The second is called the topological-stereometric explanation [3]. The third is the axial twist hypothesis [4,5]. (Two nearly identical axial twist explanations were independently published, see [6]). After Cajal's explanation, using the visual system, several other clarifications have been published with emphasize on the optic system. The main six (1976 to 2005), briefly mentioned below, belong to the top of the iceberg of explanations of the crossings in the vertebrate nervous system. However, our attention goes to the noteworthy first three mentioned also for the sake of brevity.

The three-dimensional predictive approach of brain wiring or topological-stereometric explanation [3] also establishes the rules governing storage of brain connections. The start is with Cajal's laws of neuronal optimization:

a) Neuronal arrangements have to minimize space,

b) They have to maintain sufficient size and

c) They must minimize conduction time.

These are simple rules to store neurons and connections effectively within the brain, since the skull has restricted brain space and the brain has to cope economically with the various organ demands of the body. Thus, crossings have to fulfil applied conditions of the general laws:

a) Crossings should be minimized,

b) Crossings must be tightly regulated and

c) Information is needed to plan the crossings during development

These rules are the consequences of the general laws [7]. In principle, crossing does not induce asymmetry (see part 2), although asymmetry can be the cause for symmetric crossings (see axial twist hypothesis). Most crossings are symmetric.

Cajal's Explanation of Crossing

The eye will cast reverse images on the retina, the camera obscura effect present in boxes with a small opening, but also using a lens. In (Figure 1), the arrow should be depicted head to pin-tail, without crossing this visual information (see Figure 1 red block). The projection of the correct image can only be obtained by crossed information transport, and its uncrossed tectum (C), projecting to cortical areas, should be reached. The shortest way (O in Figure 1 thus minimizing space and conduction time) is the crossing of the axons from the eye to both tectal structures (C). In consequence, somatosensory and motor information also need to be crossed to reach areas belonging to and matching with it (M and S). This explanation is eloquent and graceful. Nevertheless, critics argue that the difficulty of real alignment is due to eye movements and the resulting movement of images.

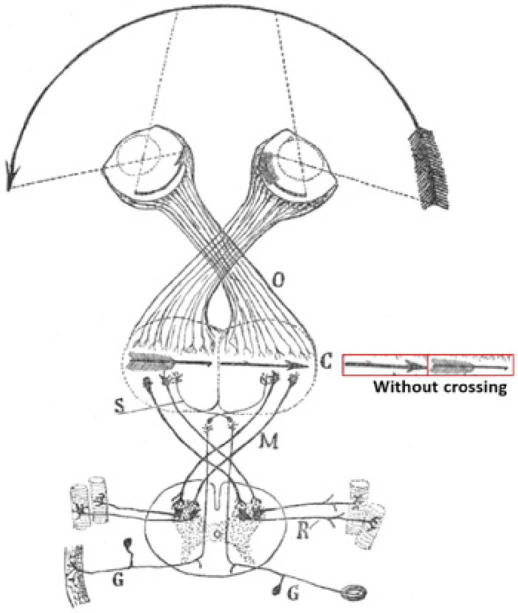

Figure 1: Ramón y Cajal's explanation for the crossed organisation of the forebrain (see text). The contralateral somatosensory and motor representations are consequences of the crossed visual system. O, optic tract; C, primary and secondary visual centres; M, decussating motor pathways; S, decussating sensory pathways; R, motor efferent of the spine; G, spinal ganglions and sensory afferents. Cajal pictured the spinal section reversed to its cord position and the tecti (C) are fused [2].

The visual forebrain areas are poorly interconnected in various vertebrates. Cajal thought that all vertebrates used the corpus callosum for this purpose. In birds, the rather small anterior commissure (decussatio supraoptica, related to the principal optic and rotundus nucleus; [8-10]) takes over, since the corpus callosum is absent in birds. Nevertheless, avian commissures are present but restrictedly connect left and right cortical areas, e.g., the anterior and posterior commissure and supraoptic connections (part 3; [11]). Moreover, there is no direct connection between the avian visual cortex and the motor cortex. Directly related to Cajal's explanation are several other propositions: image-forming eye hypothesis, the binocular vision hypothesis and, on other grounds, the bilateral symmetrical hypothesis, the avoidance behaviour hypothesis and the limb evolution hypothesis. All are put to the optic system test with more or less success ([12-14] for criticism and more references).

The Topological-Stereometric Explanation

On the condition that brain and body could be represented as being a two-dimensional flat structure crossings are absent (Figure 2a). However, brain and body both are three dimensional. Thus, folding the flat structures into a three-dimensional structure directly produces the crossing of connections (Figure 2b). A real crossing is determined by its mirror image (Figure 2c): "a mirror reflection about a symmetry plane generates an inseparable link if and only if the connections cross in that projection". Even in the case of a two-dimensional structure connected with a three-dimensional structure crossing occurs (Figure 2d). For the avian brain (Figure 2) this means: the cortical plates can be considered two dimensional (somewhat bent) structures, while the brainstem is three dimensional. Thus, connections between both cortices don't need crossings, in fact the situation in Figure 2a. However, the connections from cortex into the brainstem lead to crossings as represented in Figure 2d. Crossing of systems can happen ipsilateral of the structures involved or contralateral.

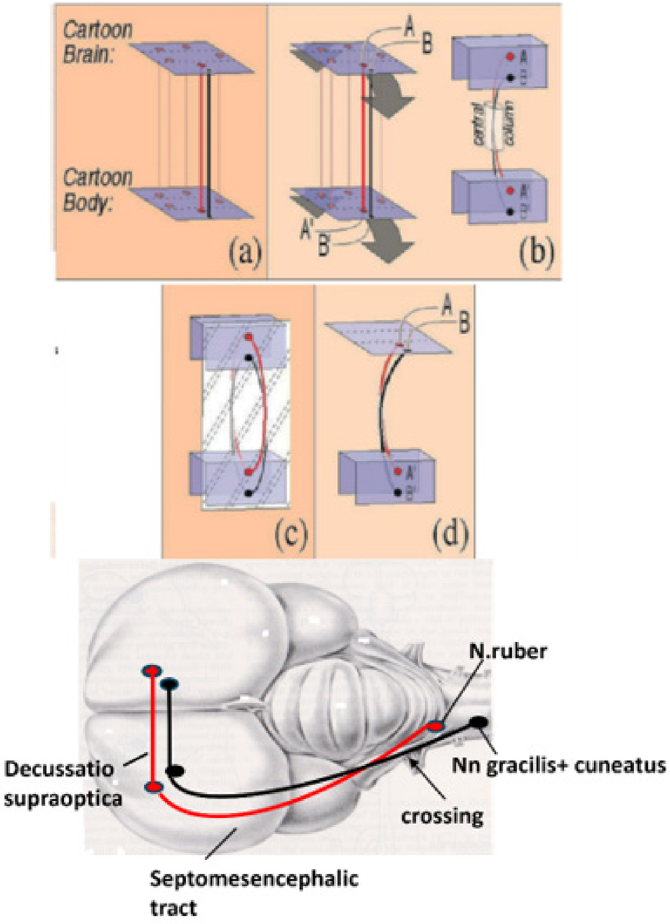

Figure 2: Upper parts are cartoon pictures between brain and body in 2D (a) and folded into 3D (b). Point to point connections is made without crossing in 2D. Body and brain connections that travel through a central column (3D), must cross (b). Formal descriptions (c) are given for a mirror reflection. Crossings can appear only if the body is extended into 3D, while the other plane stays 2D (d) [Figure 2a-2d are taken from 3]. Lower part shows the bird's brain with the connections of the Wulst (eminentia sagittalis) to the contralateral side and downwards to the ruber and gracile-cuneate nuclei. Pallium to pallium (decussatio supraoptica) is two dimensional (2D) and thus without crossing, Nucleus ruber and gracile with cuneate differ in localisation, a 3D situation within crossing is the consequence (the septomesencephalic tract is a central connection).

The topological-stereometric approach states:

a) Crossings are a mathematical necessity in 3D structures. In simple connections these decussations can be within a tract (see septomesencephalic tract in Figure 2). In complex systems contralateral tract crossings are preferred.

b) Large numbers of neurons ask for a contralaterally wired system to be stable.

c) Large systems need the decussation mechanism otherwise an enormous number of genes are needed to organize identical connections.

The Axial Double Twist Hypothesis

The double twist hypothesis is considered valid by the authors for all vertebrates and its rotation effects started with their common ancestors living presumably 450 million years ago. The double twist hypothesis is based on the compensation for embryological axial rotations present during morphogenesis. This should explain the decussations and decussation-absences in the central nervous system. Moreover, the consequence of the embryological axial rotations is the formation of an optic chiasm. All vertebrates do have an optic chiasm, although with different organisation types [15]. (In the course of the description of this rotation see Figure 3). All through its earliest development the embryo changes position and turns to the left. This is anti-clockwise to the position of the embryo. Thus, finally the embryo is located on its left side (see also part 2). The symmetry of the midsagittal vertico-dorsal plane has vanished (in Figures 3a&3b). This is unfavourable for organisms that need bilateral symmetric locomotor systems, e.g., fish. It does not matter for asymmetrical visceral organs (heart, digestive tract) in general. By compensatory mechanisms the bilateral symmetry can be restored.

This happens both clockwise and anticlockwise. The front of the embryo's head goes on with the anticlockwise movement restoring symmetry in the head region. The body part restores symmetry by turning clockwise (Figures 3b&3c). The embryo undergoes a double twist: anticlockwise in the head region and clockwise in the rest of the body. The consequences are that the

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optic axons have to reach its brain parts in an inverted position. The eyes and forebrain are inverted, so the target area, the optic tectum, which is not inverted, can only be reached by the optic axon bundles if they cross to the other side (Figure 3d&3e). After crossing they reach the optic thalamus nucleus (lateral geniculate body, LNG, Figure 3d). This explanation for crossings is supported by results of the development of zebrafish and chickens [16]. Consequences are: Optic thalamus (LGN, anticlockwise turned) projects without crossing to the visual cortex (also anticlockwise turned), but the received thalamus information was already crossed.

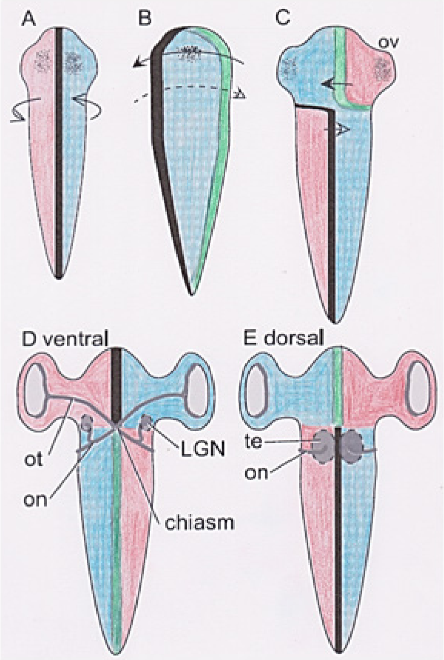

Figure 3: "Model of the compensations to an axial turn in the early vertebrate development (shark); (A-C) The embryo viewed from above, with rostral (head) up. Black zone: dorsal midline; green zone: ventral midline; spotted blue: right side; red, left side, black dotted: prospective eye region. The embryo turns anti-clockwise, towards and finally on its left side, as indicate by the arrows in (A). The turn is compensated by anti-clockwise (filled arrows) and clockwise (dashed arrows) movements (B). Consequently, the rostral region is inverted with respect to the rest of the body (C). The optic vesicles (ov) emerge and evaginate. (D-E) Development of the optic tract is given in ventral view (D) and dorsal view (E). The optic tracts (ot) originate from the retinas and grow medially towards the inverted "dorsal" of the forebrain region (black zone in ventral view, D). After the chiasm the optic nerves (on) project toward the dorsal optic tectum (te) of the opposite side (panel E). Note that the optic nerves also target the lateral geniculate nucleus of the thalamus (LGN)" (Figure is colour adapted from [6]).

The visual cortex gets information from the contralateral eye. In sharks the visual input crosses twice: in the chiasm and later in the mesencephalon: in the chiasm due to the anticlockwise rotation and back due to the clockwise rotation in the mesencephalon, which is no forebrain structure. This is because the shark anterior cortex contains a large visual central nucleus. This nucleus represents the ipsilateral eye. This visual central nucleus gets its input from the optic tectum (te in Figure 3e) via the thalamus. The nerve fibres decussate again between tectum and the thalamus to give ipsilateral eye information. "Thus, in accordance with our hypothesis, the visual information crosses the midline twice: first in the optic chiasm [to bring contralateral eye information to tectum, remark ours] and again in the ventral mesencephalic tegmentum [to bring back ipsilateral eye information to the central nucleus, remark ours]". By the way, one could consider the shark system as a violation of Cajal's laws.

Synopsis 1

The kick-off of the discussion on crossings in the nervous system was given by Ramon y Cajal. Applying the simple laws of Cajal in a stereo-metric approach for the explanation of brain wiring reveals the necessity for crossing of the fibre systems in the brain. Small connections of 500- 1000 neurons can organize crossings within the tract, while large connections force contralateral decussations. Developmental rotations within the embryo support contralateral decussations as exemplified in the optic system. Therefore, without internal decussations of tracts and contralateral crossings no "stable" wired 3D brain can exist.

Part 2: Asymmetry and Polarity: The Avian Song System

Introduction

Why is asymmetry present in the vertebrate body, as, for example, in birds? The exterior of humans is characterized by bilateral symmetry with respect to the midline. Nevertheless, asymmetry, also called lateralisation in the brain, in humans is well known for function and form. It goes from right-handedness to left

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sided speech localization in the human brain. The human heart (apex and aorta) and spleen are localized on the left and the liver is more placed on the right. Both form and function in the human body have internal asymmetry. Asymmetry is also present in the bird's exterior e.g.: the wry bill (Anarhynchus frontalis) has a beak that is bent sideways and the crossbill (Loxia curvirostra) has an upper and lower bill tip that cross each other (Figure 4). Owls have asymmetrically placed ears. The asymmetry found in the avian exterior is generally in contrast to the mammalian appearance. The hyo-branchial system of the woodpecker's tongue is related to the right nostril or the right eye [17]. In the bird's connections of visual and song systems, lateralization of hemispheres is clearly present.

Figure 4: Wry bill and crossbill with asymmetries of the beak ((Figures, courtesy BBC and R. Crossley respectively).

Moreover, kidneys and gizzard together induce an asymmetrical location and consequently right and left testes are different. In various bird species only, a left ovary is present, best known are the chicken and quail that have recently been studied at the single-cell level [18]. The bird's right and left liver and lungs have different lobes. Bird's right eye-left hemisphere function is often found dominant, for example in migration and in food collection in various birds. Food collection asymmetry is strongly variable in birds, left eye-right hemisphere is also often encountered, and it is frequently food-type dependent [19]. Functional food asymmetry is clearly present. This external and internal located asymmetry, already produced in the early embryo, is genetically determined and is affected by a roll to one side. King and Brown [20] even noted in their article on asymmetry: "The left side gets all the best genes", and over 30 genes are detected to be involved in the avian asymmetry production [21]. Important contributions to the unravelling of asymmetry have been possible due to the chick embryo model [22].

Development of Invariant Asymmetry

Two types of asymmetry are discerned: invariant and fluctuating asymmetry [23]. Ontogenetic plasticity will refine the asymmetry. Best known example is the light effects on the visual system of chickens and pigeons [24]. Moreover, environmental and stochastic determination of asymmetry directions are also recognized [25]. A more common origin of animal asymmetry has been discussed by [26] in relation to MMP21, a (matrix) metallo-proteinase breaking the symmetry [27]. However, this MMP21 is absent in the genome of birds and reptiles and induces genetic research (e.g.: gonadal differentiation of chickens [28]).

Morphological invariant asymmetry is found earliest on day 23 of the human development (looping of the heart), on embryonic day 8.5 in the mouse and after 33-45 hrs of development in the chick. The initial cells of the embryonic disc are produced by its primitive node responsible for asymmetry [29], and its primitive streak, responsible for bilateral symmetry ([30]; Figure 6). These intra-embryonic cells make the mesoderm (precursors for bone and muscles) located in between ectoderm and endoderm of the embryonic disc.

The disc will form the primitive embryo (Figure 6). Before the closure of the neural groove into a neural tube (see [31] for cascades), by the ascend of the bilateral symmetric neural walls, meso-ectoderm cells are already deposited into the embryo. These early neural crest cells, produce symmetrically mesodermal bone and muscles and their bilateral symmetric neuronal structures (spinal ganglia; Figure 6). The ectoderm cells also contribute and produce placodes. Placodes are specialized transient parts of ectoderm adding cells to the mesoderm compartment. Placodes also produce neuronal structures and contribute to the sense organs in the head, e.g., olfactory structures [32,33], cranial nerve parts and the lens of the eye (Figure 5) [34]. Placodes are mostly seen as symmetric structures, but do possess an internal asymmetry [35,36]. The first embryonic disc cells will multiply and grow in three directions called axes. The anterior-posterior axis, dorsal-ventral axis and the left-right axis. The left-right axis is strongly involved in the production of asymmetries. A series of protein cascades is needed that are genetically induced to produce asymmetry in the embryonic disc, the blastoderm.

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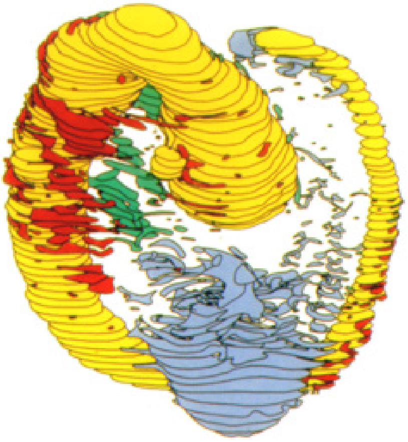

Figure 5: Placodes (in different colours) around the rat nervous system (yellow). (Reconstruction from the results of [33,34&37]).

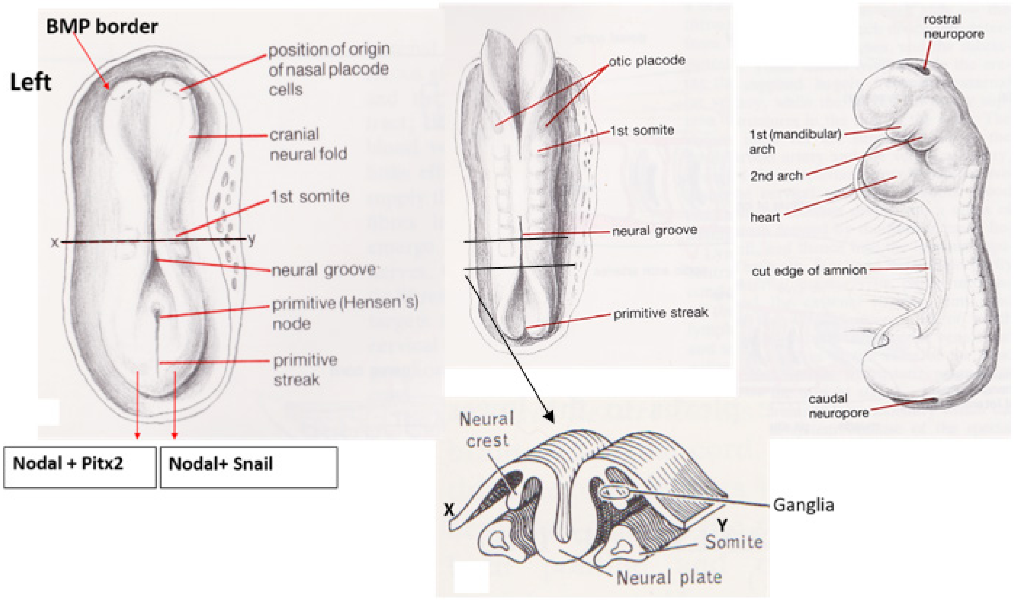

Figure 6: The embryonic disk in the two-somite stage with the neural plate, primitive node, and primitive streak. The first picture shows a view from above with the BMP border of the neural plate. Left is determined by the factor combination Nodal and Pitx2 and Nodal while Snail organizes the right side. All cells and structures above the primitive node have already be gone through the asymmetry process. Retinoic acid maintains the left side, especially in the primitive streak. Finally head and body are constituted by various types of mesoderm in the anterior posterior axis, together with the neural plate derivatives and the addition of placode cells. The heart in vertebrates takes a position partially on the left after uptake in the thorax, because it develops in front of the neck. Note that head and pelvis are differently, structurally developed and already express in the embryo anterior-posterior polarity (Figures. adapted and extended from [42]).

The avian blastoderm is floating and drifting on the egg yolk. Only some of the classic protein cascades involved are treated here at large. Within the blastoderm a neural part and an epidermal, surrounding part can be seen. The boundaries of the neural plate within the rest of the embryonic disc are determined by the Bone Morphogenetic Protein (BMP). Together with other substances such as Wnts ("wingless-related integration"), fibroblast growth factor and retinoic acid this border determines the change towards neuronal plate cells or towards epidermal cells [37,38]. While the anterior-posterior axis develops, followed by the dorsal-ventral axis and, with some delay, finally the left-right axis is added with its node and streak activity, operating consistent by three distinct asymmetric phases (denoted 1, 2, and 3 below). These three phases are based on polarity present within the organism (see part below, Figure 8) and asymmetries are genetically based. Fibroblast growth factors are a family of cell signalling proteins that are involved in embryonic development, specifically in cell proliferation and differentiation.

These fibroblast growth factors induce the initial neuronal symmetry break (1) together with other substances. It is important for the direction or side of the asymmetry: left side is initiated by fibroblast growth factor-8 with lefty-1 (left-right determination factor-1), which holds for all species studied [39], the right side is instigated by fibroblast growth factor-8 and activing (which also regulates morphogenesis of the prostate, lung, and kidney). To it inhibition and activations of other cascades of proteins are needed but not treated here. In this manner disc plate cells are produced in an “asymmetric” environment. The chick embryo shows nodal expression in the primitive or Hensen’s node that is a pit-shaped embryonic plate structure (Figure 6). The nodal pathway imposes the structural direction of the asymmetry (2), which is in most cases to the left, due to the transcription factor Pitx2. Right side structures are determined by the combination nodal and snail (Figure 6). In such cases, here Pitx2 versus snail, the asymmetry is exclusively headed on the left side of the embryonic plate [40].

The nodal signalling protein belongs to the transforming growth factor-β family of proteins. The nodal cascade needs stimulation of the Notch signalling pathway to be asymmetrically effective (3). The nodal-notch cascade finally organizes the asymmetry (see recent and classic overviews [41,42]). The zebrafish (Danio rerio) is the main experimental animal in the study of asymmetries. A series of brain asymmetries are known. One concerns the epithalamus, placed above the thalamus at the end of the brainstem. Its dorsal part, the habenula needs attention. The fish epithalamus is related to freeze behaviour: “the primary function of the zebrafish habenula could be to suppress motor activity under adverse conditions (something unpredictable and potentially dangerous that happens to fish). Indeed, the lateral habenula parts (thus one-sided) can inhibit dopaminergic neurons, which are key modulators of movement and motivation in this fish. This function of the habenula possibly dates back to very early evolutionary times. Presumably this pathway worked like “a circadian system of ancient vertebrates” [43].

Asymmetry is regarded as evolutionary old [44]. The asymmetry of the thalamo-fugal connections for the bird optic system has to be considered. Learning and action-reaction in birds is right eye-left hemisphere dominant. Bird memory seemingly needs an asymmetric organisation. “Visual imprinting in chicks and song-learning in songbirds are prominent model systems for the study of the neural mechanisms of memory. In both systems, neural asymmetry or lateralisation has been found to be involved in memory formation” [45]. While in mammals, except hominids, it remains difficult to investigate, both external and internal, asymmetries [46], a rather large series of studies in birds support asymmetries. A remarkable functional asymmetry concerns bird-song and the neural aspects of the syrinx needs explanation, especially the tracheosyringeal nerve branch of the hypoglossal nerve will be discussed.

The Syrinx

The air that circulates through the bird’s lungs, originates in the so-called air sacs and passes through air tubes into the bronchi. The Bernoulli effect states that increasing speed of the air passing through a tube will produce altered lower pressure within this air. Flexible walls will be drawn into the lumen of the tubes as also happens with the tympaniform membranes in the bird’s bronchi (Figure 7). Together with the external labia position and air-sac pressure regulation, membrane oscillations occur. These vibrations are determined in amplitude and frequency by intrinsic and extrinsic muscle groups. Each of the bronchi contains tympaniform membranes, has its own air supply by the left or right bronchus, and has its own muscles. Together with the bilateral innervation of the hypoglossal nerves, each bronchus could be considered a separate sound well.

Tracheosyringeal Nerve: Avian Functional and Dimorphic Asymmetries

First to notice is the larger muscle mass at the left side of the syrinx of the canary (Serinus canaria). Cutting the left or right branch of the hypoglossal nerve, the tracheosyringeal nerve, produce different results (Figure 7). Surgery of the right tracheosyringeal nerve does not change the song of the male canary as pictured by the two upper sound spectrograms. However, surgery of the left tracheosyringeal nerve destroys the main repertoire of the song (lower two spectrograms, Figure 7). The song is replaced by silent gaps, clicking sounds or distorted modulations. “Such birds sing vigorously, as judged by their posture and motion, yet look like actors in a silent cinema film” [47]. The conclusion of these surgical result of 49 male canaries is that the left tracheosyringeal nerve, branch of the left hypoglossus (Figure 7), is dominant for song control. Extra results show that this dominance is not related to auditory processing but is a syringeal bilateral innervated motor phenomenon [48].

The Zebra finch (Taeniopygia guttata) shows the contrary. In this bird species the right hypoglossus nerve is dominant for song control with right side dominance for its hemisphere [49]. There is a song difference between male and female, the male sings and the female is mostly silent. Research showed that the female hypoglossal nucleus volume was 63% of the male, the female neuron somata within this nucleus were 86% of the male, the total number of female neurons was 90% of the male and the female syrinx musculature weight was 51% of the male [50]. Females masculinized by hormones do start singing. The part of the hyperstriatum that respond to sounds and normally induces song in the males, can stimulate the song in males, but not in the females. Although the same stimulation has been applied no response passes over the tracheosynringeal nerve of the female [51]. The question now is whether the female has the same neuronal connections [52].

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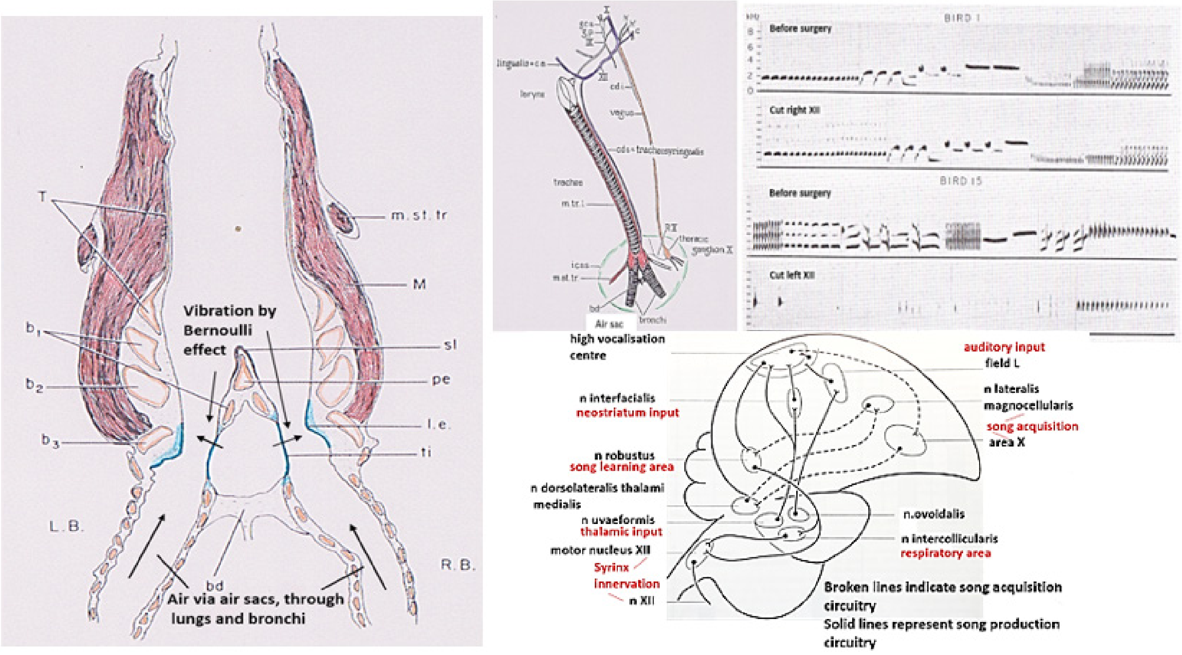

Figure 7: Left upper part: longitudinal section through the syrinx of the adult canary: R.B. and L.B. right and left bronchi; M section through intrinsic syringeal muscles; left syringeal muscle mass is heavier than right counterpart. T, tympanum; b1-b3 bronchial half rings; bd, bronchidesmus; pe, pessulus; sl, semilunar membrane, l.e. labium externum; ti, internal tympaniform membrane; m. st.tr, sterno-tracheal muscle. Middle upper part: topography of the left XII cranial nerve around trachea and syrinx: The sternotracheal muscle (m. st.tr) and the syrinx muscle mass (red). In green is the interclavicle air sac's position indicated (i.c.a.s.). Right upper part: effects on the song of the canary before and after surgery of the right and the left tracheosyringeal nerve (branch of the XII). Lower Figure: Left hemisphere is dominant for song production and song learning in the canary (Figures, are colour adapted and extended from [47]; see also [11,48]).

Three Levels of Planar Polarity: Subcellular, Cellular and Tissue Polarity

Attention to asymmetry induces the awareness of polarity. The initial step is the breaking of the symmetry, followed by the generation of polarity in the axes. Polarity has a clear structural basis producing functional consequences in: the anterior-posterior (by animal poles), dorsal-ventral (by gravity) and the right-left (by asymmetry) axes. Polarity is considered: "The most fundamental characteristic of any pluricellular structure. The organism has at least two dissimilar poles, ends or surfaces" [53]. The term planar polarity [54] causes problems, since various definitions and approaches are current. In general, planar polarization is determined by one surface or one layer of cells in which cell to cell interaction organizes those two or more cells accept coordinated divergence, called cellular polarity [55], which is also important to establish 3D configuration of morphogenetic structures. For this interaction between cells special proteins are needed to mediate this act [56]. Planar cell polarity was first studied in the fruit fly Drosophila melanogaster [57] and later it has been applied to other experimental animals, especially in the cochlea of the mouse. The study of polarity in a two-dimensional plane and in the anterior–posterior patterning system has been useful due to the detection of the Frizzled/planar cell polarity.

Its directional signals are based on the same underlying mechanism in various organisms. A cellular interaction between receptor and its protein generates the polarity. In the Frizzled polarity system, its Frizzled transmembrane receptor act independently in the planar cell polarity system. This receptor is present in various cell types, including the otic-cochlear cells. Essential proteins needed are cell surface and cytoplasmic ones, names in brackets are the mammalian homologues: Frizzled (Fz, 1, 2, 3, 6), Strabismus (Vang 1, 2), Flamingo (Celsr 1, 2, 3) and the cytoplasmic Dishevelled (Dvl 1, 2, 3), Prickle (prickle-like 1, 2) and Diego (Diversin) proteins (Figure 8a-8c). These proteins after their production in the rough endoplasmic reticulum are released in the cytoplasm. Like a submarine that comes to the surface, these proteins reach the luminal (cochlea) or apical (Drosophila) surface of the cell involved. Microtubules are involved and required in this process to bring the Frizzled protein to the surface. Two groups are formed, a proximal and a distal one by activity of all six proteins (Figure 8c). Description of this gathering process has been omitted here [58].

The induced local polarity by these proteins is not restricted to that special cell, but will have effect on cell–cell interaction levels and/or on the tissue level (Figure 8) [59]. Another polarity cascade is the Fat/Dachsous pathway important in the placing of

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actin-rich hairs in animal fur (Figure 8d). Hair cells of the cochlea contain cilia that are organized in a V or W form on top of the luminal surface (Figure 8e). The height increases towards the point of the V and is called the staircase pattern. The V top is made by one large kinocilium (Figure 8 left). This structure "repeats" itself on all hair cell groupings. All the V bundles are directed away from the cochlear neural side that is ab-neural. (By the way, within the cochlea the Prickle protein act differently as explained in Figure 8a-8c). In rat and mouse cochlea, the Dishevelled 1, 2, 3 accumulate abneural, while Strabismus (Vang 1, 2) and Frizzled (Fz 3, 6) group at the neural side and presumably organize the polarity within the hair cell rows [60-62]. The relation of kinocilium polarity and the influence of the other ciliary polarity are still under discussion. These interactions at the cellular level do have analogues at the tissue level.

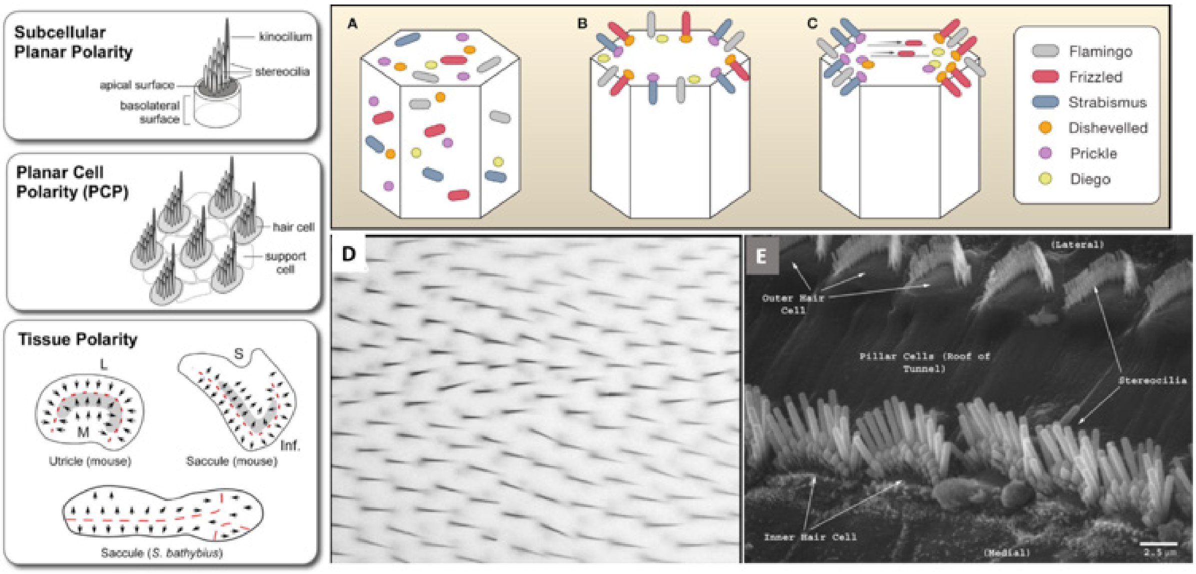

Figure 8: Left figures of planar polarity diagrams (see [59]) showing the three levels of planar polarity, i.e., subcellular, cell and tissue. A, B, C The planar cell polarity pathway as known from Drosophila wing epithelial cell. The proteins are present in the cytoplasm (A) proceed to the cell surface (B) and all six proteins (see column colour indication) reorganize on the surface in proximal and distal domains with the help of organized microtubules (C). D is an example of planar polarity of the hairs of the fruit fly wing, and E shows planar polarity of the stereocilia of the cochlea. A, B, C and D are from [58]); E is taken from [60]. (Lateral (L), medial (M), superior (S) and inferior (Inf.) see [34] for figure and its text).

The vestibular maculae contain within the mature sensory epithelium opposite polarities. Within utricle and saccule maculae, the ciliary hair cell groups contain luminal opposite bundle orientations. The so-called Line of Polarity Reversal is the border between these opposite cilium distributions. While in the utricle, the polarity of the ciliary bundles is towards this line, in the saccule the ciliary bundles point away Figure 8 left diagrams, red line). Polarity is needed for the whole-body composition, e.g., during growth to maturation along the anterior–posterior axis. Normally, these various planar polarities for body development are combined. The antero-posterior body polarity with its dorso-ventral body polarity is converted into a bilateral symmetry of the mammalian body. Cell sociology already hypothesized the laws needed to understand this automation in animal development at cellular and tissue levels. Birds have been studied for planar cell polarity. It plays a role in skin feather implant, in the cochlear apparatus and in the lagena.

The lagena in pigeons showed that "hair cell planar polarities were oriented away from a central reversal line that ran nearly the length of the epithelium" [63], which is completely comparable to the cochlea results depicted in fig. 8 left.

Several more models, still under discussion, explain the breaking of the symmetry:

a) The nodal flow model; the cilia in the node move into one direction, bringing fluid with its substances to the left side of the embryo [64],

b) The two-cilia model; two populations of cilia are present in the node, the central population produces the left flow, while the immobile ones are the mechano-sensors that induce intracellular influx of calcium at the flow side [65].

c) The Gap-junction model; in birds the asymmetry is already present before the node's existence. Due to the electric coupling of these early cells by Gap-junctions asymmetry is induced, since several substances (e.g., serotonin) can move one sided to other cells [66-68].

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Synopsis 2

The conclusion of part 2 is that total symmetry is not present at the subcellular-, cellular-, tissue- and body levels whether by planar polarity or by left-right asymmetry.

Part 3. Symmetry and Asymmetry of The Avian Brain: Its Synthesis

The Absence of The Avian Corpus Callosum: The Consequences

All placental mammals have the corpus callosum, which establishes the mutual functional hemispherical connections (Figure 9, left). The human corpus callosum contains ± 170 million fibres [69,70]. The diameter of the myelinated fibres counted can vary and beside myelinated fibres also unmyelinated ones are present, but hardly measured. Sperry [71] studied the total commissurotomy of the corpus callosum, known as "split brain". He concluded: "We can now demonstrate with appropriate tests a whole of distinct impairments [72] that are most simply summarized by saying that the left and right hemispheres, following their disconnection, function independently in most conscious mental activities. Each hemisphere, that is, has its own private sensations, perceptions, thoughts and ideas all of which are cut off from the corresponding experiences in the opposite hemisphere. Each left and right hemisphere has its own private chain of memories and learning experiences that are inaccessible to recall by the other hemisphere. In many respects each disconnected hemisphere appears to have a separate "mind of its own".

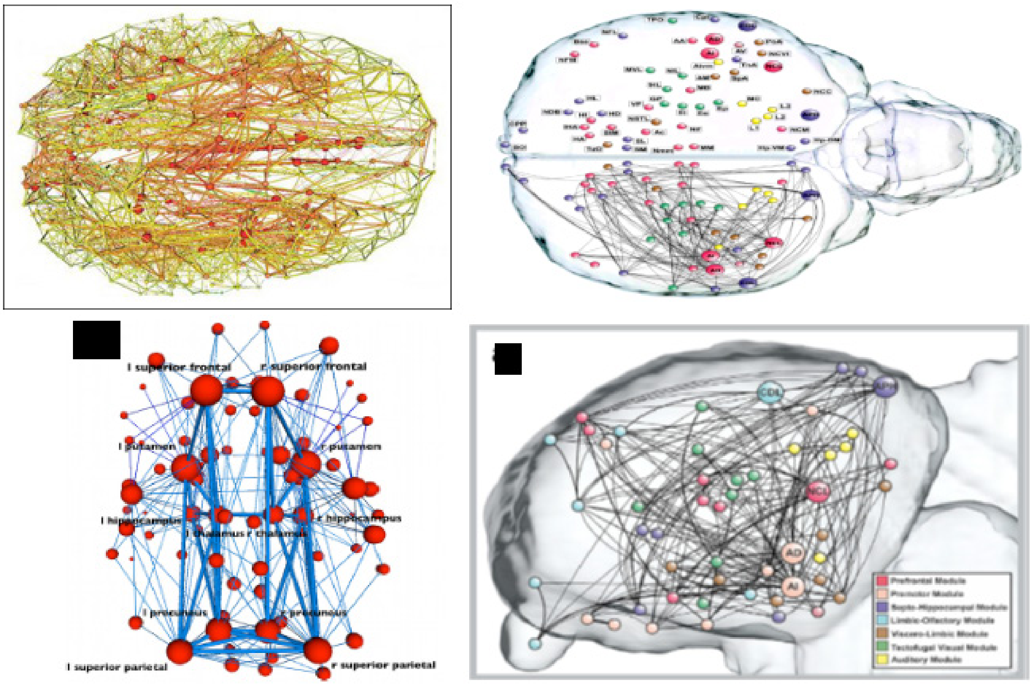
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Figure 9: Connective matrix (hubs) studied in humans left and pigeon right. The human hubs are extremely well connected between the two brain halves. In the pigeon these hub connections are clearly absent between both hemispheres. The "intensity" of the connections over the corpus callosum belong to the strongest ones (thickness of the blue lines indicates the intensity of the inter-hemispherical connections) (with permission; [67, 68]).

The avian brain halves are restrictedly interrelated by its commissura anterior, posterior and the commissura supraoptica, since the corpus callosum is absent in the avian brain. Interaction between both hemispheres is strongly reduced and is not comparable to the hemispherical communication of mammals as studied by hubs. The cortex structure of birds is also different. The avian pallium is based on nucleated clusters, while the mammalian cortex is known by its laminated neuronal organisation (Figure 10) [73]. The storage of neurons in the avian forebrain is different, resulting in more neurons/volume [74]. Information towards avian "split brain" hemispheres asks for symmetrical relay groupings, of which eight main connections are discerned: Lateral and intermediate thalamofrontal, striotegmental, medial thalamo-frontal, medial strio-hypothalamic, quinto frontal, supraoptic and septo-mesencephalic tract [75,76] (Figure 10). The functional asymmetry as common in the human brain is also present in the avian brain, but in its own hemispherical separated way.

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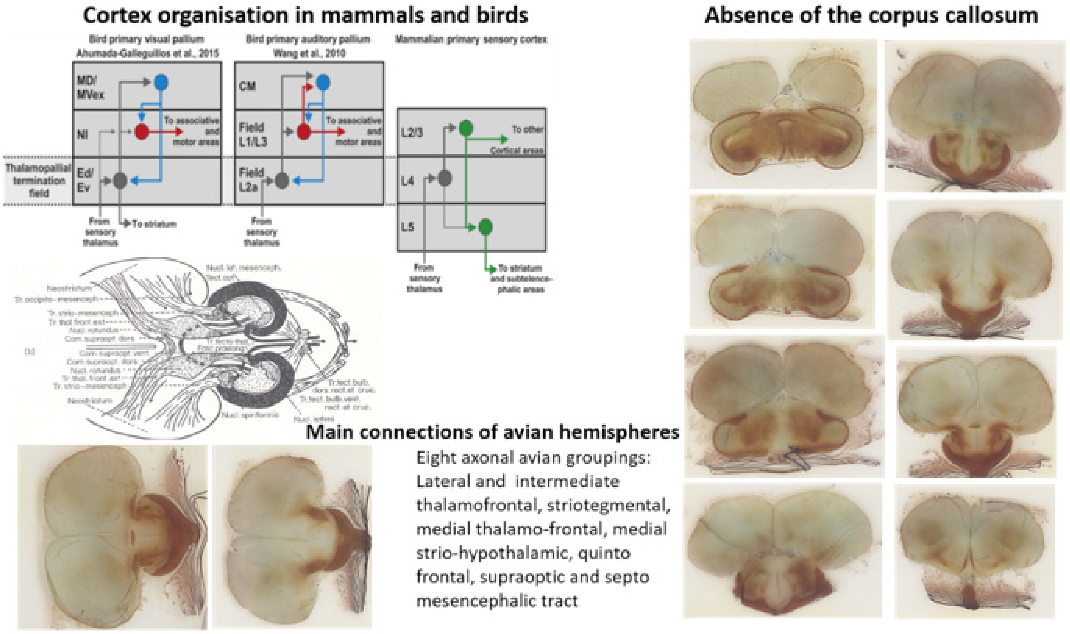

Cortex organisation in mammals and birds

Absence of the corpus callosum

Main connections of avian hemispheres

Eight axonal avian groupings: Lateral and intermediate thalamofrontal, striotegmental, medial thalamo-frontal, medial strio-hypothalamic, quinto frontal, supraoptic and septo mesencephalic tract

Figure 10: Three aspects of the differences between mammalian and avian brains. Cortex organisation is altered in its laminar (mammals) and cluster-like (birds) construct [68]; Scheme [77], with permission). Both avian hemispheres lack a “corpus callosum”, as demonstrated for the pigeon by silver colouration (Nauta-Gygax, 1951; Series H7135). To serve information to these separated hemispheres several and unique axonal tracts are present [8,11,75,76], Figure from [11].

Lateralisation comprises several of the functional asymmetries in the avian brain, which clearly can differ in various bird species. Generally, the right eye-left hemisphere is dominant for mate recognition, category distinction, vocalisation, olfactory cues, while the left eye- right hemisphere knows dominance for spatial abilities, predator recognition, fear expression and aggression, and in various birds for food. The establishment of asymmetry in bird’s brains, we owe to Nottebohm [77,78]. In the canary the left hemisphere is exclusively the location for both song and song learning (Figure 7). Small and large lesions targeted to the nuclei involved in song production showed that in the canary the left hemispheric lesions disturbed song production heavily, while analogous lesions to the right hemisphere had clearly less effect on song production.

Synopsis 1-3

Part 1 on symmetry states: without internal tract decussations and contralateral crossings no stable wired brain can exist.

Part 2 on asymmetry concludes: deviations of symmetry are a necessary prerequisite to structure and to let the organism function.

Part 3 on symmetry and asymmetry shows that absence of avian symmetrical hemispherical crossing favours functional asymmetry.

Conflict of Interest

The author declares that he has no competing interests.

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