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Vertebrate brains and evolutionary connectomics: on the origins of the mammalian ‘neocortex’

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The organization of the non-mammalian forebrain had long puzzled neurobiologists. Unlike typical mammalian brains, the telencephalon is not organized in a laminated ‘cortical’ manner, with distinct cortical areas dedicated to individual sensory modalities or motor functions. The two major regions of the telencephalon, the basal ventricular ridge (BVR) and the dorsal ventricular ridge (DVR), were loosely referred to as being akin to the mammalian basal ganglia. The telencephalon of non-mammalian vertebrates appears to consist of multiple ‘subcortical’ groups of cells. Analysis of the nuclear organization of the avian brain, its connections, molecular properties and physiology, and organization of its pattern of circuitry and function relative to that of mammals, collectively referred to as ‘evolutionary connectomics’, revealed that only a restricted portion of the BVR is homologous to the basal ganglia of mammals. The remaining dorsal regions of the DVR, wulst and arcopallium of the avian brain contain telencephalic inputs and outputs remarkably similar to those of the individual layers of the mammalian ‘neocortex’, hippocampus and amygdala, with instances of internuclear connections strikingly similar to those found between cortical layers and within radial ‘columns’ in the mammalian sensory and motor cortices. The molecular properties of these ‘nuclei’ in birds and reptiles are similar to those of the corresponding layers of the mammalian neocortex. The fundamental pathways and cell groups of the auditory, visual and somatosensory systems of the thalamus and telencephalon are homologous at the cellular, circuit, network and gene levels, and are of great antiquity. A proposed altered migration of these homologous neurons and circuits during development is offered as a mechanism that may account for the altered configuration of mammalian telencephalae.

1. What is the history of the origin of the mammalian thalamus and telencephalon?

The evolution of the brain was of central concern to Darwin. He had long recognized its importance in relationship to his interests in instincts, social interactions, morality, motor–sensory control, origins of consciousness and cognition. By the late 1800s, particularly in the light of Darwin’s *On the origin of species by means of natural selection* [1] and his *Descent of man* [2], there was increasing appreciation within the biological community of the importance of the brain in all of these functions. However, by the time of Darwin’s death in 1882, there were few studies of the brains of various mammals or non-mammalian vertebrates. Prompted by the impact of Darwin’s *Origin of species*, Herrick, Retzius, Cajal, Edinger, Brodmann and other founders of modern neurobiology, expanded their studies of the nervous system to a broad range of mammals as well as non-mammalian vertebrates [3]. However, largely owing to the greater interest in medical implications, studies of the mammalian brain continued to be the dominant focus of neurobiologists for more than 140 years. Reflecting the widespread medical interest in understanding the consequences of injuries to the human brain with its associated loss of cognitive and refined sensory–motor performance, studies of the brains of

non-mammalian vertebrates attracted far less interest. Studies of the brains of non-mammalian vertebrates were limited in number, though Herrick, Edinger, Brodmann and others in the late 1800s and the first one-third of the 1900s relied heavily on comparative studies in their evolutionary formulations of the broad principles of the organization and development of properties common to the brains of all vertebrates. However, the evolutionary origins of the mammalian neocortex evoked widespread interest, and prompted many formulations regarding the evolutionary uniqueness of mammalian neocortex. Indeed, the traditional classification of cortical domains into paleocortex, archicortex and neocortex, conveyed the impression of the temporal phylogeny of the cortex. The prevailing notion was that the so-called neocortex was a structure unique to mammals, possibly emerging from the 'older cortices'. There was little information regarding the possible phylogenetic origins of the neocortex in non-mammalia.

2. Are our brains unique?

Darwin's 'Origin of the species' [1] released a firestorm within society. The notion that we share a common heritage with other mammals, and even non-mammalian vertebrates, had long been entertained, but the unavoidable implication of Darwin's 'Origin of species' and the 'Descent of Man' [2] left little room for doubt as to where Darwin stood in regards to humans as social, intellectual and moral creatures. He repeatedly emphasized the importance of understanding the brain, and evolutionary changes in the brain in relationship to behaviour, and once again, as a consequence of natural selection.

Was Darwin's notion that man shared common neural features with apes and dogs so novel? Certainly, the work of many of his predecessors, as well as his strongest contemporary opponents, such as Owens, demonstrated the similarities and conservation of skeletal features across phylogeny. The explicit and unavoidable conclusion of Darwin's writings was that these shared origins also pertained to their cognitive skills, behaviour, and social traits including ethical and sexual behaviour. As Darwin frequently pointed out, those are qualities that are all directly a result of the operations of our brains. That was surely the major source of outrage upon reading Darwin's works. Our brains! No longer unique, but a consequence of the long, slow process of natural selection. Many opponents argued, and continue to argue, that there are some brain structures unique to humans, and that must explain man's special status on this planet.

Strangely, for much of the past century, many contemporary neurobiologists have taken an intermediate position, arguing that even if the neocortex is common to all mammals, it is distinct and restricted to mammals, with special elaborations unique to humans. Even in this year of 2015, there are many scientists, as well as laypersons, who would comfortably advance the notion that consciousness and morality are properties that are independent of our brains, but there are also many neuroscientists who consider these qualities limited and fully dependent upon the cortex—a structure seemingly found only in mammals.

Traditionally, the structure and capabilities of the neocortex have long been considered unique to mammals, and many authors have considered the cortex, with its diverse and massive numbers of cells and its varied and complex specific sensory and motor connections, to have arisen abruptly with

the origin of mammals. It also provoked notions that animals lacking the structure of the neocortex were incapable of equally complex behaviours. However, the past 50 years have been witness to increasing evidence that birds, cephalopods and probably many other taxa, show all the qualities of consciousness, intelligent behaviour, social altruism and tool use, as well as a variety of skills that, in mammals, require an intact functioning corticobasal ganglionic circuit.

What are the evolutionary origins of the cells and circuitry that constitute the mammalian neocortex? Modern evolutionary biology rests firmly on the notion that there is historical precedence for those complex systems that are present in the skeleton, immune system, digestive system, sensory receptors and even brainstem in all vertebrates. If non-mammalian vertebrates share common behavioural capabilities with mammals, and such behaviours in mammals require an intact cortex, what is the neurobiological substrate of this common behaviour? Can we find equivalent cells and circuits in non-mammalian vertebrates, perhaps even evidence of precursors of the cortex among non-mammalia? Or have mammals actually generated a novel neurobiological solution to deal with complex cognitive and sensory–motor challenges? If so, what mechanisms are operational among non-mammalia to achieve similar performance?

3. Why fossils are of so little help in understanding evolutionary connectomics?

Contemporary methods for recognizing evolutionary changes of homologous regions and systems such as skeletal features or the external morphology of the brain in different classes of vertebrates relied heavily on endocasts of the cranium of fossils. Fossils and endocasts, however, are of little help in understanding the evolutionary changes in cells, circuits, transmitters or molecular modifications leading to novel qualities in the brain. These properties generally leave no trace in fossils, and cannot be identified in fossil material. The essence of the operations and evolution of the brain can most explicitly be understood in terms of the connections, physiology, transmitters and circuitry in their contributions to behaviour and the evolutionary advantages of subtle changes in the function of the brain.

The cells, connections and circuits within the brain are vital to the effective functioning of the nervous system. The general macroscopic to microscopic level of connections are loosely referred to as the 'connectomics' within the brain, spanning several orders of resolution, from several centimetres to the level of the synaptic microcircuitry. Contemporary neurobiology focuses on connections from the level of major regions to individual cells and axons to synapses, with particular emphasis on the cell types, transmitters, receptors and the multineuronal microcircuitry of the brain. Examples of such microcircuitry may include circuits within the retina, spinal cord, long ascending paths (e.g. from spinal cord to cerebellum), data processing circuits within the radial processing units of the tectum, cortex, etc. Each of these regions has exquisitely detailed and refined features in their anatomical, physiological and molecular organization and often display unique evolutionary histories, dependent upon a specific species and its modes of adaptation to its environment.

How old are each of these important circuits? When did they first evolve, and how much do they vary over the course

of phylogeny? Are they shared between widely differing species and classes of vertebrates? In what ways have they changed over course of evolution in different species? To varying degrees of precision, these questions have been a recurrent theme among students of the evolution of brains for more than a century. These questions obviously cannot be addressed in even the most detailed analysis of endocasts of fossil brains. Although gross anatomical regions may be sufficiently well preserved to allow comparison between major anatomical components of the brain, such as midbrain, hindbrain, cerebellum or forebrain, or between fossils and extant vertebrates, the cells and connections that constitute the microcircuitry of the brain are beyond detection in fossil brains.

Deciphering the microcircuitry of neural tissue in order to clarify the phylogenetic history of a microcircuit requires the study of living, viable, tissue. Furthermore, effective and credible comparison demands slow and meticulous experimental studies on a par with all other current contemporary neurobiological research.

4. The early period of evolutionary neurobiology

From the 1890s, and extending into the mid-1930s, workers in the field of comparative evolutionary neurobiology attempted to sample and compare a wide range of non-mammalian vertebrates. But most workers during the nineteenth and early-twentieth centuries relied almost completely upon non-experimental descriptive studies which severely limited the prospect of deciphering the wiring diagram of the non-mammalian brain, much less the physiological operations of these animals. It was largely based on examination of various animals that had died in accidents or of natural causes, and the brains extracted, fixed and stained with methods that showed neurons and some of the heavily myelinated tracts. These methods did not allow the viewer to identify most of the tortuous finer connections within the brain. In the late 1800s, the development of the Golgi method for studying the morphology of single neurons and of axons, and the Marchi method for tracking heavily myelinated axons, and their use in the skilled hands of scientists such as S. Ramon y Cajal, Edinger, Wallenberg and others, greatly advanced our knowledge of the structure and major connections of the brain. The Golgi method was effectively applied to the brains of a wide variety of vertebrates and invertebrates. The Golgi method, however, was ill suited to the study of long-range connections in the brain. However, connectional methods, such as the Marchi method, were only rarely applied to non-mammalian vertebrates. The lack of connectional information about circuits in non-mammalian brains resulted in limited concepts of brain organization in non-mammalia, particularly at the level of the thalamus and telencephalon.

5. Progressive telencephalization of function

By the end of the nineteenth century, Herrick [4] and others had demonstrated that the brainstem of all vertebrates shared a profound level of similarity. However, the thalamus and telencephalon, with the exception of the olfactory bulbs, seemed to show few commonalities between mammals and non-mammalian vertebrates. This led to the prevailing view that the forebrain of most non-mammalian vertebrates was related to olfactory inputs. The mammalian forebrain,

particularly the cortex of the telencephalon, was increasingly thought to be novel and unique to mammals. There was no structure in the non-mammalian forebrain that could readily be compared with the mammalian cortex. The belief in the uniqueness of the mammalian forebrain was particularly emphasized in the writings of Sir Hughlings Jackson (1835–1911) [5], and his co-worker, David Ferrier (1843–1928), who suggested that over the course of evolution, functions of the brainstem were transferred to the forebrain. This was referred to as the *progressive telencephalization* of complex functions. Examples of such functions included the ability to decode auditory inputs generated by vocal communication, visual pattern recognition, visual stereopsis, deciphering complex somatosensory inputs and most notably, so-called *higher* cognitive functions. The level of analysis performed was judged to be that requiring the participation of the neocortex in mammals.

But how could non-mammalia perform such operations in the absence of modal-specific thalamic nuclei and cortical regions? Structures within the forebrain, such as the specific sensory relay nuclei of the thalamus and the ‘neocortex’ of the telencephalon, were largely considered unique to mammalian brains. The telencephalae of non-mammalia were considered to consist almost exclusively of olfactory centres and basal ganglia. This directly implied the lack of refined lemniscal visual, vestibular, gustatory, auditory or somatosensory inputs to the telencephalon, and certainly no prospect of ability to deal with discrete stimuli from any of these sources. It also posed a paradox among birds, as many species of birds with large telencephalae have only very limited, or no olfactory capabilities, particularly when compared with many non-avian reptiles and mammals. What might be the possible function of the large avian telencephalon?

However, the notion of the uniqueness of mammals with a distinct thalamus and neocortex was based on painfully sparse information. The afferent connections to the thalamus in non-mammalian brains, their projections upon the telencephalon and the various discrete populations of the telencephalon were almost totally unexplored. This led to the erroneous notions that the thalamic and cortical populations of the mammalian brain were unique to mammals, and arose abruptly with the evolutionary origin of mammals.

6. The revival of comparative neurobiology in the 1960s

Prior to the 1960s, knowledge of the connectional features of brains, particularly at the levels of the thalamus and telencephalon, was largely limited to studies centred on cats, monkeys and rats. It was only beginning in the early 1960s, that modern experimental methods, initially reliant on the use of small lesions in the brains and selective staining for the resultant axonal degeneration, became available and that a small group of neuroanatomists began to use these same methods in application to the analysis of the brains of various non-mammalian vertebrates. A group of young neuroanatomists at the Walter Reed Army Institute of Research, under the leadership of Walle J. H. Nauta and William Mehler, initiated a broad reaching series of studies in marsupials, birds, non-avian reptiles, amphibia, teleosts and elasmobranchs. These included William Hodos, Ford Ebner, Sven Olaf Ebbe Ebbesson and C. Boyd Campbell, as well as myself. Although the impact of this group was limited, their enthusiasm and breadth of interest

launched the new era of comparative evolutionary neurobiology. They, as well as other groups, such as that at SUNY-Downstate under the leadership of Walter Riss, Max Cowan of Oxford and J. Reperant in Paris, were willing to challenge the ensconced dogmata about non-mammalian vertebrates.

It is also helpful to point out that for the first half of the twentieth century, tracing neuroanatomical pathways was a prominent part of neurobiological research. What is presently referred to as 'connectomics' is perhaps best thought of as a modern 're-badging' of neuroanatomical tract tracing. By the end of the twentieth century, morphological analysis was being done at an ever more refined level, combining tract tracing with single cell morphology, synaptic localization, identification of the molecular profiles, transmitter characterization, receptor identification, second messenger systems and elegant electrophysiology. When such analyses are applied in pursuit of clarifying differences in various classes and species, we may refer to this as 'evolutionary connectomics'. Such comparisons provide us with unique insights into the changes that occur in the circuitry and molecular characteristics in the course of evolution. Most notably, they have demonstrated that many of the long- and short-range connections within the lemniscal sensory and motor pathways have been highly conserved in the course of evolution. Thus, evolutionary connectomics may be considered to be both an experimental strategy as well as a discrete field of intellectual pursuit.

7. Natural selection and connectomics

I have called this principle, by which each slight variation, if useful, is preserved, by the term Natural Selection.

Charles Darwin (1809–1882) [1, p. 61]

How does the concept of natural selection pertain to the evolution of the nervous system of vertebrates and connectomics? Natural selection implies that changes often tend to be fairly subtle, highly conserved and cumulative, rather than strikingly novel. Seemingly, dramatic changes, as in the instance of avian wings compared with non-avian anterior appendages in tetrapods, may initially appear to constitute marked novelties. However, they are both anterior pentadactyl appendages, with morphologically differing end results, but with clearly similar and homologous skeletal components, muscles, developmentally regulated expression of transcription factors, homeotic genes, etc. I suggest that highly conserved and complex multi-synaptic neural connections, cellular molecular expression patterns and dendritic morphologies are also subject to natural selection. Such multidimensional properties are conserved across vertebrate classes as widely noted in the published literature of comparative neuroanatomy. The extent of this conservation, however, is far more pervasive than generally appreciated.

Analysis of the vertebrate brain requires a detailed examination of the constituents at the cellular and molecular levels. This requires application of technically demanding histological, histochemical and molecular methods, preferably in conjunction with physiological and behavioural methods. In many regions of the brain, particularly the spinal cord, brainstem, cerebellum, mesencephalon, hypothalamus and olfactory bulb, the similarities are easily recognized, and homologous relationships generally agreed upon with minimal dispute. The cell types and their connections within the brain are highly conserved across phylogeny as evident in the

morphology, circuitry and physiological properties of, for example, Purkinje cells of the cerebellum. Although for most of the past 150 years, the validity of the conservation of organization and connections at levels of the spinal cord, cerebellum and brainstem was generally accepted, this idea did not extend to the conservation of cells and circuits to the thalamus and telencephalon (i.e. 'forebrain'). In fact, similarities in organization or connections within the thalamus and telencephalon between mammals and non-mammalian vertebrates had little support in the published literature.

In an attempt to directly explore the validity of these assumptions, I concentrated on studies of birds, with easily observed behaviours, and large and well differentiated thalamic and telencephalic regions. Although unsure as to what I might uncover (is not that a definition of what research is all about?), I was impressed by the richness of avian behaviour, and the occasional reports of their visual, auditory and cognitive abilities. How did they manage to perform tasks that, in mammals, required the presence of an intact neocortex? The most common proposal was that they performed the refined sensorimotor operations at the level of the brainstem, and that the massive telencephalon was largely dedicated to generating instinctually determined stereotyped responses. This implied that mammals had evolved a truly novel way of dealing with the external world, mediated via the thalamus and neocortex, whereas all other vertebrates must have developed a very different neural strategy of responding to the external world. What might that imply about natural selection as consequent to many small cumulative beneficial changes? Although the prospect of uncovering the mechanisms of so unique a neural basis of a rich behavioural repertoire was fascinating, the actual findings led us into a very different set of conclusions. We found that birds and other reptiles processed discrete sensory inputs in the same manner as do mammals. The thalamus, the doorway to the cortex, contained cell groups homologous to those mediating auditory, visual and somatosensory inputs. Once we uncovered the homologies within the thalamus between birds and mammals, it was only a short step to discovering several obviously similar circuits that were homologous to those contained within the mammalian cortex [6–8].

8. The organization of the forebrain of non-mammalian amniotes

I will present only brief summaries of some of the critical studies leading to the current, rapidly expanding information about the avian brain, and by extension, to reptilian, teleost and agnathan brains. Birds display highly complex and skilled levels of cognitive performance. Their auditory and visual systems are capable of refined discrimination, and are used to control complex motor behaviours, often at skill levels equal to or exceeding that of the large apes. How do they do this? What circuits do they have in their brains that allow them to indulge in such 'complex' behaviour?

When this project began, in the early 1960s, the prevailing notion was that birds lacked any notable representation of a cortex or cortex-like circuitry (figure 1a, 'classic view'). The greater portion of the avian telencephalon was considered to be vaguely comparable to the mammalian basal ganglia. The interpretation was that birds were only capable of highly stereotyped behaviour, and because the prevailing (and largely

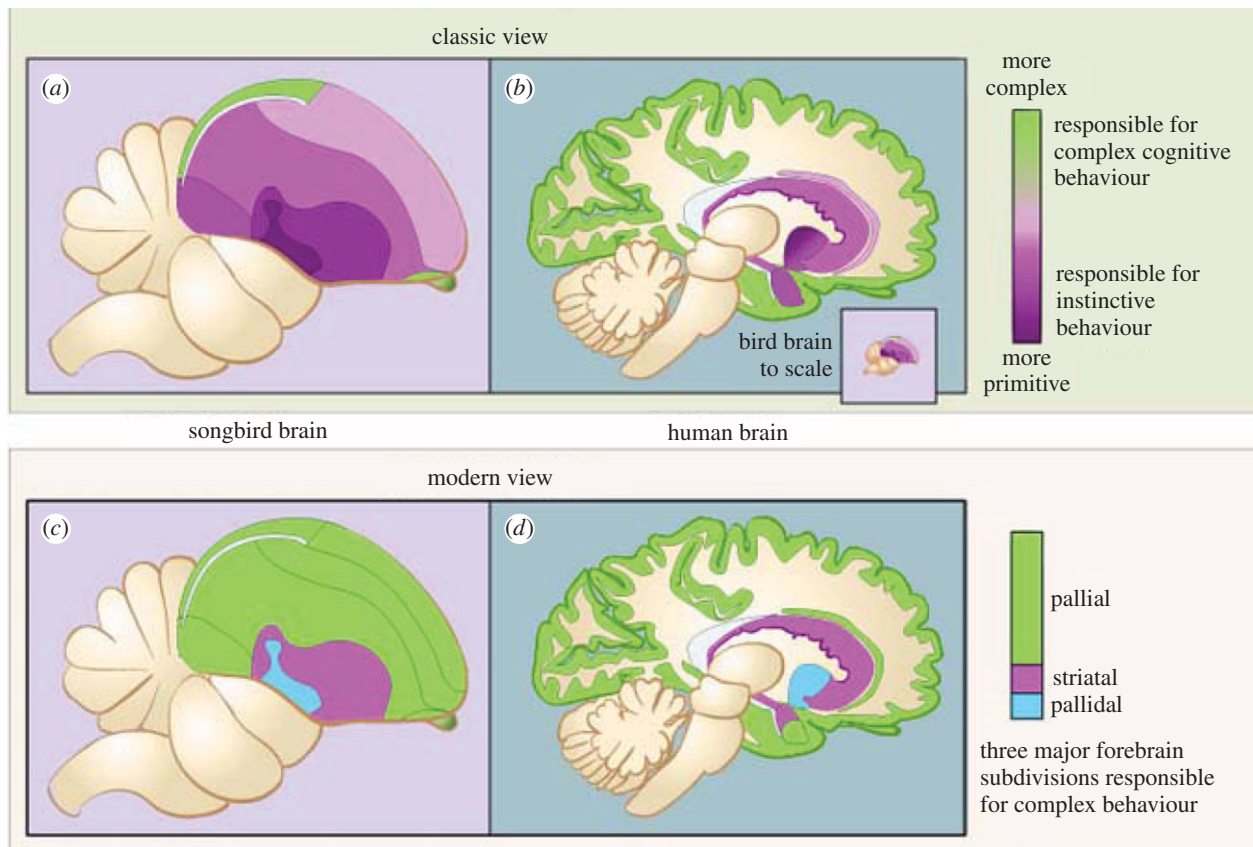


Figure 1. Pre-1969 ‘classic view’ of avian (a) and mammalian (b) brain relationships. Individual brain regions are coloured according to the earlier concepts of the homologous relationships of each general brain regions. Note that the vast majority of the avian telencephalon was considered to be homologous to the mammalian basal ganglia and claustrum. This concept was based exclusively on studies of non-experimental material. There was no information regarding regions of the avian forebrain that were involved in processing clearly defined sensory/motor information in a manner comparable to that performed by the mammalian cortices. (c,d) ‘Modern view’ of avian and mammalian brain relationships according to the proposal of the Avian Brain Nomenclature Forum, largely based on the formulation proposed by Karten [6]. Note that based on an expanding body of experimental material, only a limited portion of the telencephalon is now considered to be homologous to the mammalian basal ganglia. As in mammals, the major portion of the dorsal telencephalon contains discrete components to various pallial derivatives, including those homologous to cortex, hippocampus, claustrum and amygdala. Well-defined auditory, visual and somatosensory fields are now well recognized in birds and non-avian reptiles (modified from [9]). (Online version in colour.)

erroneous) notion was that stereotyped behaviour reflected operations of the basal ganglia—*ergo*, the avian telencephalon was an elaborated version of the basal ganglia.

This is represented in figure 1*a,b*, reflecting the pre-1969 [6] concept of homological comparisons of birds and mammals. This shows the prevailing view of the avian brain suggesting that only a very small portion of the avian telencephalon was homologous to the mammalian hippocampus. A slightly rostral division of this region, called the ‘Wulst’ or dorsal bump, was referred to as ‘vicarious cortex’ [3], but without explicit justification for this designation. The vast majority of the telencephalon of birds and non-avian reptiles was considered ‘comparable’ to the mammalian basal ganglia.

9. What are the boundaries of the basal ganglia in birds?

This prompted us to ask about the extent of similarity and boundaries of cell groups that might reasonably match the properties of the mammalian basal ganglia. Karten [6,10], Reiner *et al.* [11], Kuenzel *et al.* [12] using various connectional and histochemical methods, demonstrated that only a limited portion of the avian telencephalon shared common properties with the mammalian basal ganglia. This was confined to the basal ventricular ridge (BVR) of the telencephalon. This constituted less than 20–25%

of the total volume of the avian telencephalon (H.J. Karten 1969, unpublished data). The remaining region, the dorsal ventricular ridge (DVR), lying dorsal to the BVR and protruding into the telencephalic ventricle, constituted a much larger percentage of the volume of the telencephalon. There is also a thin pallial zone lying on the external surface of the hemisphere. The volume of the BVR relative to the DVR is about the same ratio as represented by the basal ganglia to remainder of the telencephalon in mammals—i.e. thus including the cortex and amygdala of mammals. Studies of the connections of the basal ganglia of birds revealed long descending connections that were largely identical to those of the mammalian basal ganglia [10]. This is shown schematically in figure 1*c*. Subsequent studies of the organization of the basal ganglia summarized in a detailed review by Kuenzel *et al.* [12] further consolidated the information, justifying the conclusion that only the components of the BVR conformed to the properties of the basal ganglia of mammals.

10. If only 25% of the avian telencephalon is homologous to the basal ganglia, what is the nature of the remaining 75%?

The major region of the telencephalon dorsal to the basal ganglia is referred to as the DVR. In a series of studies over

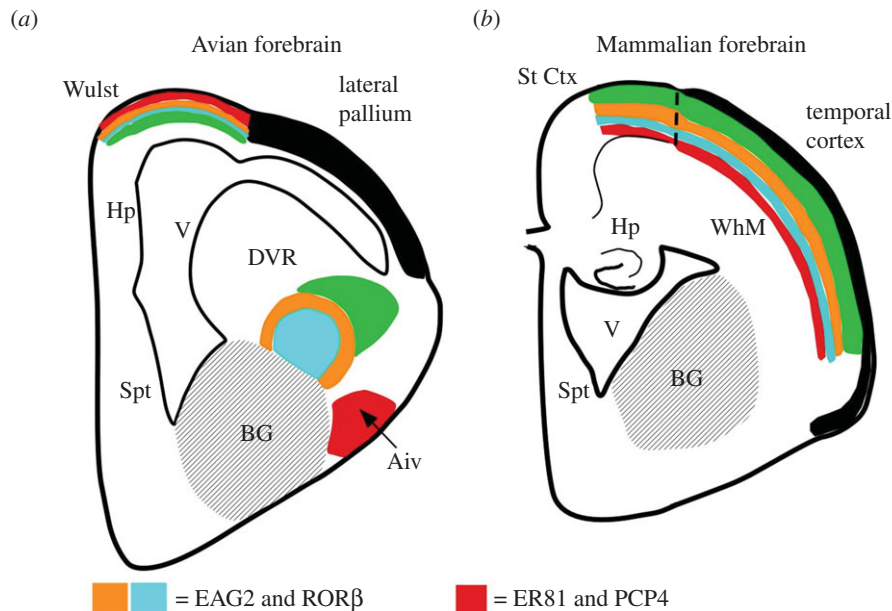


Figure 2. Neurons in the nuclei of the avian DVR are homologous to neurons in layers of mammalian cortex. Although differing in macroarchitecture, the basic cell types and connections of sensory input and output neurons of (a) avian/reptilian and (b) mammalian telencephalon are nearly identical, most notably lacking the familiar pyramidal cell morphology. The populations receiving sensory input and the output neurons of both regions express the same genes found in the sensory recipient and output laminae of mammalian neocortex as indicated by the colour code of genes and layers [13]. In birds and other non-mammalian vertebrates, individual laminae were often disposed as distinct nuclei, particularly within the large intraventricular expansion of the dorsal ventricular ridge (DVR). The cell clusters share properties with individual layers of the mammalian sensory cortex, particularly the auditory and tectofugal visual sensory cortex of the temporal lobe. In mammals, the homologous neurons are found in laminae, a characteristic feature of mammalian neocortex. The major change that may have occurred with the evolution of mammals is an altered pattern of migration of these cell groups from the DVR into laminae in the dorsolateral pallium. In birds, a separate pallial region, the dorsomedial ‘wulst’ or ‘bump’ shares many properties with the mammalian striate cortex, though with the output layer lying most externally. In contrast, the basal ganglia occupy similar location, connections, relative volume and molecular properties in all classes of vertebrates and appear to have experienced few changes over the past 535 million years. Aiv, arcopallium intermedium; BG, basal ganglia; DVR, dorsal ventricular ridge; Hp, hippocampus; Spt, septum; St Ctx, striate cortex; V, ventricle; Wulst, ‘bump’ homologous to mammalian striate cortex; WhM, white matter; EAG2 and RORbeta, genes commonly expressed in sensory neurons of layer 4; ER81 and PCP4, genes commonly express in output neurons of layers 5b-6 of cortex. (Online version in colour.)

the following 40 years, we were able to uncover auditory, visual and somatosensory pathways through the thalamus upon the DVR. These pathways consistently matched the patterns of afferents and efferents so familiar to students of the mammalian cortical system. We discovered that there were large numbers of dense clusters of cells of regionally specific nature, with thalamic inputs of sensory nature, populations of interneurons, and well-defined groups with long descending efferent connections with remarkable similarities to the regionally localized cortical areal efferents. This led me to the proposal that despite the absence of prominent lamination typical of mammalian neocortex, the avian brain contained nuclear clusters homologous to lamina-specific populations of mammalian neocortex, as shown in figure 2 [6,8]. This has been referred to as the ‘nuclei to laminae’ equivalency hypothesis. The most detailed cytological analysis centred on the prominent auditory pathway of birds. Other studies discovered the presence of visual pathways virtually identical in inputs, interneuronal connections, outputs and physiological properties to the mammalian visual ‘striate’ cortex. Yet still other pathways corresponding to mammalian ascending visual tectal outputs upon thalamus (nucleus rotundus of birds and caudal pulvinar of mammals such as tree shrews and squirrels) and then upon a well-delineated region of the telencephalon in birds presently designated the entopallium.

Yet other efferent pathways descending from the telencephalon were discovered in birds, that exactly matched the projections of the sensory, auditory, visual and motor cortices

of mammals, and other delimited zones directly comparable to the amygdala in its projections upon the hypothalamus of mammals [14].

Much to our delight, we discovered that all the major components of the mammalian telencephalon, including the cortex, amygdala, hippocampus and striatal complex, were found to have corresponding cell groups in birds.

In 1970 [15], we proposed that a more parsimonious formulation of the problem of the nature of the avian brain would be to consider the problem as one of ‘homology at the cellular level’, rather than at the level of nuclear clusters. At about that time, we embarked on an extensive series of immunohistochemical studies, which largely confirmed the localization of various transmitters, receptors and neuropeptides to subpopulations of neurons in manner of distribution that was virtually identical to the matching subsets of cells of the mammalian cortex. However, for reasons that seem to reflect a preference for a more simplistic regional-based model, many people continue to refer to the avian brain as containing ‘nuclear to laminar’ correspondences. Contemporary neurobiology is increasingly concerned with homologies at the cellular level.

These findings led us to propose that the origins of mammalian cortex should best be viewed as a two-step process: (i) evolutionary origins of the cells and circuits found in all vertebrates, and (ii) macroarchitectural modification of these cells and circuits into the more familiar pattern of lamination so ubiquitous among mammals. This led me to propose that

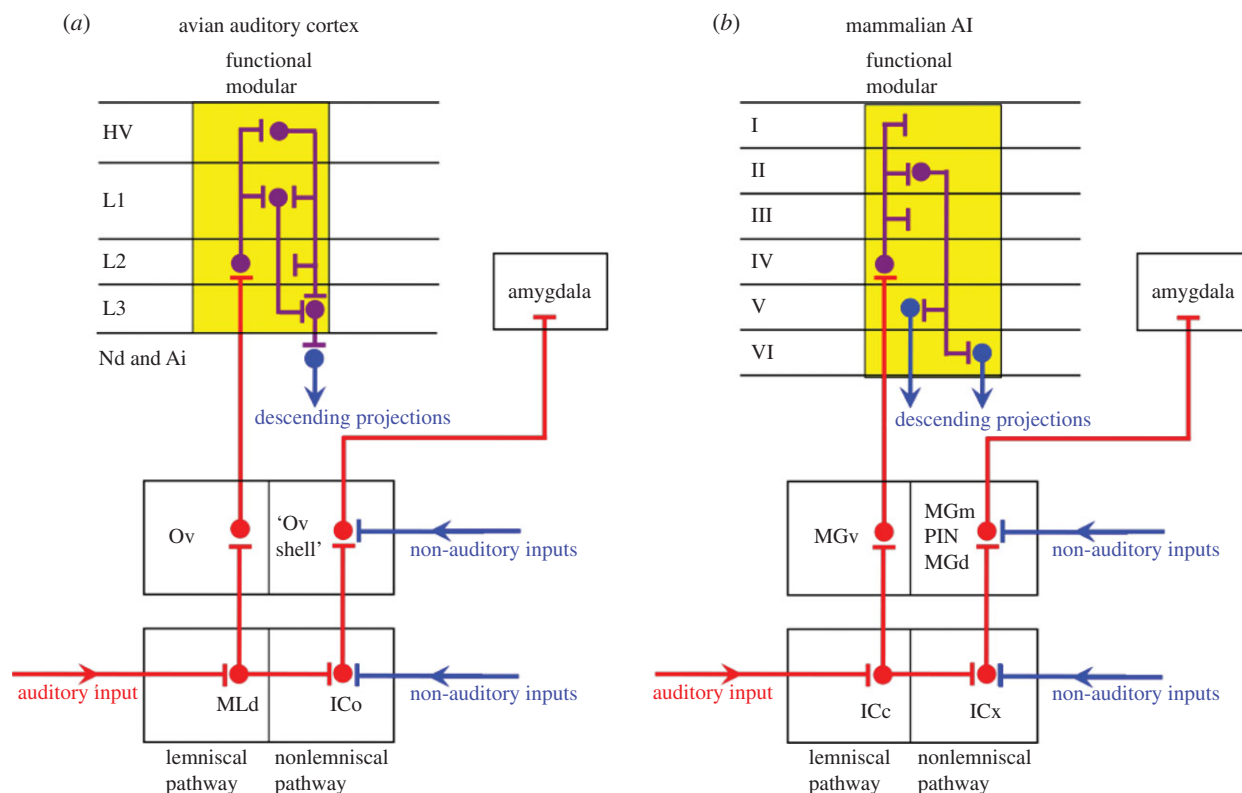


Figure 3. Comparable laminar and columnar organization of the avian auditory pallium (a) and the mammalian AI auditory cortex (b). Note that this schematic drawing illustrates only the major components of this intricate network. The microanatomy is now also supported by recent molecular analyses of the profiles of the corresponding populations, as well as electrophysiological studies by Calabrese and Woolley [21] (Illustration based on [20]). (Online version in colour.)

the cells and microcircuits, so characteristic of the mammalian neocortex, had evolved early in vertebrate evolution and independently of lamination [6,8,16]. Under the leadership of Erich Jarvis, a community of comparative neurobiologists joined together and proposed a revised nomenclature of the avian brain reflecting the similarities of many of the components of the DVR and wulst of birds with the various pallial derivatives of mammals [8]. This resulted in a revision of terminologies of several of the divisions of the DVR, within the framework of the pathways and nuclear clusters discovered during the preceding 30 years. Several of the schematic diagrams displayed in this current publication were drawn from the series of publications consequent to the revised nomenclature and/or the works of [7,8,17–19].

11. Microcircuitry of the avian telencephalon revealed radial/columnar organization

One major area of particular interest, consequent to the dramatic expansion of research in the neurosciences, has been the growing focus on the underlying microcircuitry that provides the computational mechanisms of operation of the brain. In 2010, Wang *et al.* [20] provided one of the more dramatic demonstrations of the similarities in cells and microcircuits of mammalian and avian brains. Using slice preparation, and single cell filling, we examined the microcircuitry of the auditory fields of the telencephalon. We discovered that the auditory telencephalic field, in extension of our findings regarding the presence of homologous neurons within nuclear clusters matching several of the layers of the auditory cortex of mammals, also were organized in radial arrays, with recurrent loops and re-entrant pathways. These findings are

summarized in figure 3. These properties are virtually identical to the circuitry that is now believed to be the hallmark of mammalian cortex. Radial column-like features with defined network connections were found between specific subsets of neurons within each layer of the auditory telencephalic regions of birds. This led us to conclude that even so seemingly specific a property of mammalian cortex as radial/columnar organization, with recurrence and re-entrant loops, had probably evolved long before the evolutionary appearance of mammals.

Further support for this proposal is provided in a recent paper by Ahumada-Galleguillos *et al.* [13] wherein the authors demonstrated a radial/columnar pattern of organization in a visual field of the avian DVR, the entopallial core, belt and overlying domain within the mesopallium. The similarities to the findings of Wang *et al.* [20] are quite remarkable and further support the hypothesis of the antiquity of radial microcircuitry and the shared cell and circuit properties of avian and mammalian brains. Recent studies by Maler and co-workers [22] have revealed the presence of similar radially organized microcircuits, mediating electroreception, in the telencephalon of teleost fish. Further studies of the DVR telencephalic circuitry of non-avian reptiles as well as amphibia are clearly needed.

The prevailing and recurrent theme that emerged was that the microcircuits of the mammalian thalamus and cortex had evolved long prior to and independently of the developmental processes that led to the more notable cortical lamination in mammals. We suggested that this radial recurrent type of microcircuit, so characteristic of mammalian cortex, was probably common to all amniotes, and represented an antiquity of more than 200 million years. The above-mentioned studies in teleost fish by Trinh *et al.* [22]

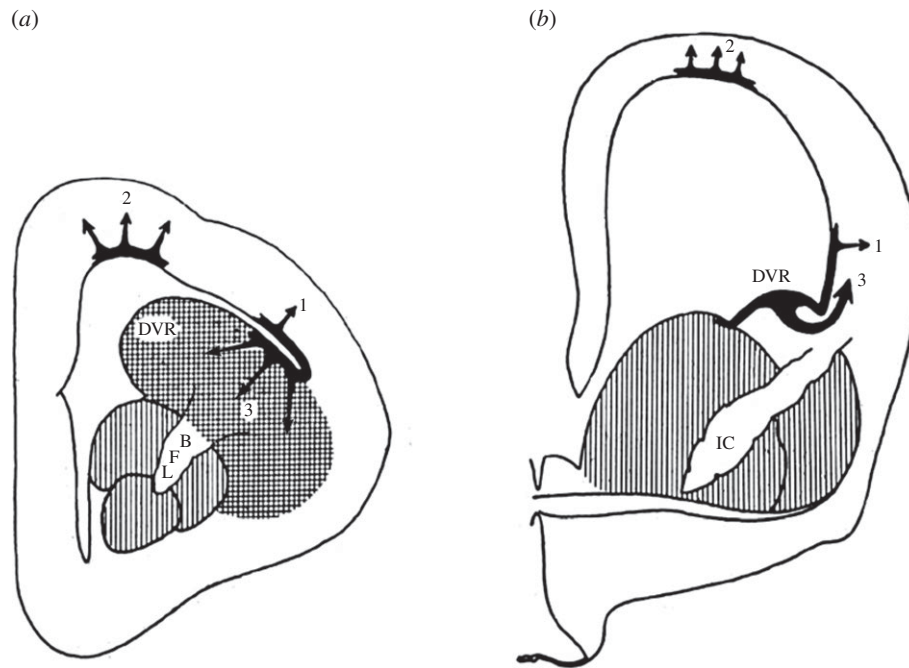


Figure 4. Schematic of the postulated difference between non-mammalian (*a*) and mammalian (*b*) forms with respect to the ontogenetic derivation of neurons composing the pallial mantle. In both forms, numerous pallial neurons are proliferated in embryonic development by the ependyma of the mantle proper (arrows 1 and 2). Only short stretches of the continuous ependymal lining of the cerebral ventricle have been indicated (in black). It is suggested in the text that the mammalian neocortex results from an augmentation of the intrinsic pallial cell population by neuroblasts proliferated by the ependyma of the dorsal ventricular ridge (DVR, arrow 3 in *b*); the corresponding proliferation in non-mammalian forms produces the DVR (arrows 3, in *a*). The striatal complex of the non-mammalian brain and the caudoputamen-globus pallidus of the mammal are indicated by vertical shading; the non-mammalian external striatum is shown by cross-hatching. DVR, dorsal ventricular ridge; IC, internal capsule; LFB, lateral forebrain bundle [15].

in Leonard Maler's laboratory may suggest an even greater antiquity of such telencephalic radial microcircuits.

The original hypothesis published in 1969 [6] appeared ever more justified. It appears to be highly consistent with a concept of natural selection that uncovers multiple small features, presumably beneficial and of great antiquity, and were thus retained across phylogeny. Identification of the number of congruent features that overlap between mammalian and avian circuitry keeps increasing, and adds to the confidence that we are dealing with homologous cells and circuits across phylogeny.

12. Recent developments in dissecting the cellular and 'laminar' components of the avian brain

The studies through 2010 largely relied on connectional, electrophysiological, immunohistochemical and behavioural data. In 2012, Dugas-Ford *et al.* [23] demonstrated that each of the distinct 'nuclei' of the avian telencephalon also expressed various genetic molecular features that very closely match those of layers of the mammalian neocortex to which they were speculatively linked [6,8,24]. Their paper strongly supported the proposed 'nucleus to layer' hypothesis, though did not explore the more rigorous 'homology at the cellular level' of [15], Stell *et al.* [25] and Major *et al.* [26], as discussed in Dugas-Ford & Ragsdale [27]. Similar results have recently been reported by Jarvis *et al.* [28,29], and are described in further detail in the accompanying paper in this issue by Jarvis & Chakraborty [30]. The so-called claustramygdaloid hypothesis, proposing that the majority of the DVR, is homologous

to the claustrum, and amygdala is discussed in detail in [7]. Although a distinct region that appears homologous to the amygdala was first confirmed by Zeier & Karten [14], it constitutes only a relatively limited portion of the arcopallium (previously designated as the medial archistriatum), and fails to account for the extensive similarities of the connectomics of the components of the DVR and those of the mammalian neocortex.

Most recently, Calabrese & Woolley [21] demonstrated that the electrophysiological properties of the different laminae of the auditory 'cortex' of birds share an amazing degree of similarity to lamina-specific properties of mammalian cortex in regard to the manner of signal and information processing. This similarity was noted in a strongly supportive commentary by Harris [31] published to accompany the Calabrese and Woolley paper.

The one major portion of the original [6] paper that has not yet been tested pertains to mechanisms of proposed transformation of the reptilian/avian DVR type of organization to the macroarchitecturally laminated pattern of mammals. My 1969 paper postulated that the transformation would require an altered pattern of tangential migration from the region of the ganglionic eminences to the overlying dorsolateral cortical anlage (figure 4). This was first directly demonstrated with O'Rourke *et al.*'s [32] discovery of tangential migration in the formation of the neocortex in rat embryos. The occurrence of tangential migration of neurons from the ganglionic eminences during embryogenesis was reported by Anderson *et al.* [33]. They demonstrated that the GABAergic neurons of the mammalian cortex arise from the medial ganglionic eminence and migrate tangentially into the neocortex. Their analysis was not concerned with migration of the neuronal population of glutamatergic neurons of the DVR; thus direct support for

the migration of DVR neurons during mammalian embryogenesis, in a manner consistent with Karten [5], is still wanting of direct demonstration.

The original 1969 model explicitly proposed that many of the glutamatergic thalamorecipient neurons of cortex found in the temporal lobe (auditory and visual tectofugal) also enter the cortex from the dorsolateral part of the DVR. The migration of glutamatergic neurons has not been adequately demonstrated in mammals. However, the recent report by Jarvis *et al.* [28] is consistent with the notion that the nidopallium and mesopallium contribute to the formation of tangentially migrating glutamatergic neurons. Butler *et al.* [7] offer an alternative possible means of reconciling the relationship during development of the DVR of reptiles and ancestral mammals.

What are the molecular and cellular mechanisms mediating the altered pattern of migration of neurons and the postulated model of actual transformation of the brain of the shared ancestral brain into the mammalian configuration? As pointed out by Karten [24], earlier models of cortical development in mammals presented a major obstacle in the postulated alternative migration of cells as a mechanism of this transformation. The still dominant model of cortical development relies heavily on the radial migration of dividing cells within the pallial ependyma to form cortex in an 'inside-out' pattern of lamination. This model also assumed that all the layers were generated from a single 'grandmother' cell. Recent studies by Franco *et al.* [34] indicate that in the elaboration of the neocortex in mice, the cells of layers 2, 3 and 4 appear to be derived from different neuroglial anlagen than the cells of layer 5 and 6. Layers 2, 3 and 4 (and probably layer 5a) are the major contributors to the radial/'columns' of the neocortex, and constitute the primary initial phases of information processing of thalamic inputs. In contrast, the cells of layers 5b and 6 are major cortical efferent populations, most commonly projecting upon the brainstem and thalamus, respectively. As noted in Zeier & Karten [14], the region of the arcopallium in birds resembles an isolated zone of cells corresponding to those of layers 5 and 6 of mammalian cortex. These cells are clearly connected to the populations of cells of layers 2, 3 and 4, but rely on axonal recurrence over moderately lengthy distances, with only scant prospects of the complex dendrodendritic connections of the mammalian cortex. While this might imply a longer time delay in feedback loops owing to axonal conduction times, there is no evidence that it results in laggardly behavioural performance within the auditory or visual systems of birds when compared with comparable pathways in mammals.

13. Evo-devo problems—what might the avian brain teach us about the development of the mammalian neocortex?

The traditional goals of those in the field of comparative neurobiology are to uncover universal patterns of organization, and to reveal novelties in the course of evolution. The field of evo-devo promises to address both of those issues in a developmental framework. A fundamental underlying question in the present story is what molecular and genetic changes occur in the course of development that produce so drastically

different an outcome, if my proposals about homologies at the cell and circuit levels are correct. The single most notable challenge is how to reconcile the traditional story of the development of the neocortex as a laminated structure with the markedly different organization of the DVR. The mammalian cortex is believed to arise by a process of radial migration of cells from the pallial ependyma. The DVR model implies that the otherwise homologous cells and circuits arise from a markedly different anlagen population of cell. It clearly suggests that the long-standing concept of cortical development in mammals needs revision. I continue to harbour the suspicion that one of the underlying problems I was confronted with was not only the 'transformation' problem, but my uncertainty that the analysis of how the mammalian cortex developed was necessarily correct. I still do not quite know how to deal with these two inter-related problems. Such a conclusion appears to challenge the long held beliefs that mammalian cortex develops by a single mechanism and from a common pool of anlagen cells across the complex extent of the so-called neocortex. This was also part of the rationale for the alternative term of 'isocortex' used for this complex sheet of laminated cells. The implication of my proposal is that there is fundamental flaw in our notion of how the cortex develops. Perhaps the origins of the cortex are not by a single common mechanism across the full span of the neocortex, nor from a uniform population of cells. This notion was implicit in my original 1969 paper [6], but seemed so outrageous that I chose to concentrate my efforts on the circuitry and nature of the DVR. How the development of the DVR as a region of homologous cells and circuits may be comparable to those of the temporal cortical regions remains a puzzle. Perhaps that is best dealt with in a separate review, or perhaps I will leave it to the next generation to struggle with the issue! I recognize that this challenges many of our generally accepted classifications of cortex and cortical organization. But my time is running out as I reach the limits of my grasp in dealing with this problem.

14. A unified model of telencephalic organization in vertebrates

Within the past 3 years, there have been several dramatic advances in our knowledge that may allow us to offer a possible unified model of the telencephalon that encompasses all classes of vertebrates from agnathans to mammals (figure 5).

One of the first of these remarkable findings pertains to the demonstration that the basal ganglia of all vertebrates share a large set of detailed similarities. Grillner and co-workers [35] and Ganz *et al.* [36] have now established that in agnathan lampreys, and in teleost zebrafish, respectively, many of the unique connections, molecular features of transmitters and receptors of the basal ganglia are virtually identical to those defining features of the mammalian and avian basal ganglia.

A growing number of experimental studies in teleost brains by the Finger, Ito, Yamamoto and Maler laboratories have discovered the existence of well-defined ascending monosensory (lemniscal) sensory pathways to the thalamus and thence to the telencephalon. These convey auditory and electrosensory information from the periphery to various regions within the 'dorsal ridge' of the teleost brain, with striking resemblances to corresponding pathways in mammals and birds. Yamamoto *et al.* [37] and Maler *et al.* [38]

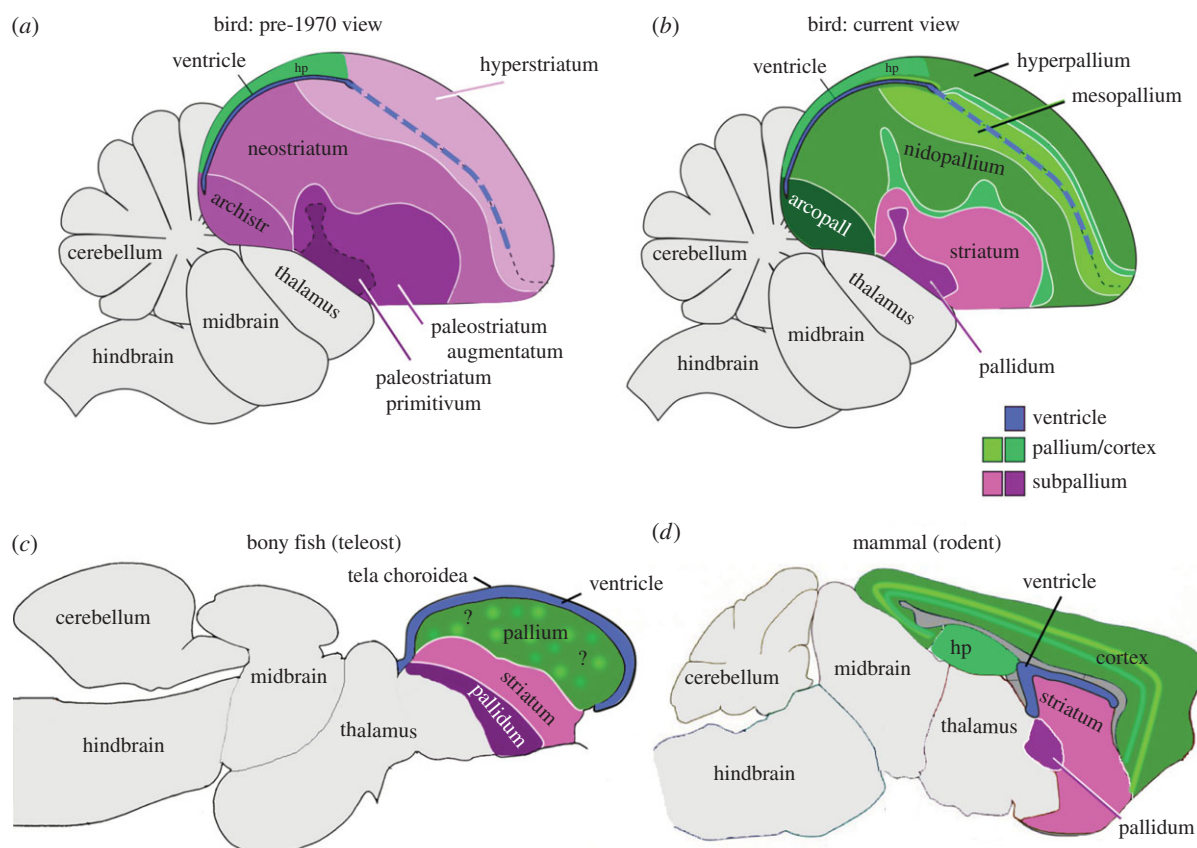


Figure 5. Schematic of a parasagittal section through the brains of birds (*a,b*), a teleost fish (*c*), and a rodent (*d*), showing the relative location of the lateral ventricle (blue) in relation to neural populations homologous to the mammalian cortex (green) and subpallial domains (magenta). In mammals (*d*), the cortex (pallium) lies entirely above the ventricle, which led early anatomists to consider the entire region below the ventricle in birds to be subpallial (*a*). Studies since 1969 [5] have shown that cortical-equivalent cell groups lie both above and below the lateral ventricle (*b*) and its extension (blue dotted line) suggesting that the lateral ventricle is not a useful demarcation between pallial (cortex) and subpallial (striatopallidal) fields. The situation in teleosts (*c*) is even more extreme where the telencephalic ventricle is covered by the membranous tela choroidea and lies entirely dorsal of the telencephalic neuronal populations. The detailed organization and homologies of pallial cell groups in teleosts remains to be elucidated. More extensive arrays of gene expression data and details of connectivity are necessary in order to discern the full organization of the forebrain in ray-finned fishes. Panels (*a,b*) are adapted from Jarvis *et al.* [28]; panel (*c*) is adapted from [34]; panel (*d*) is based on the Allen Brain Atlas (<http://mouse.brain-map.org>). (Adapted from [17].) (Online version in colour.)

have now shown that the dorsocentral region of the teleost telencephalon emits modality-specific projections upon the brainstem with patterns explicitly similar to those in mammals and birds, from the cortical and cortical-equivalent regions, respectively. Most recently, Ocaña *et al.* [39] have reported that a similar pattern of projections arise from the dorsal region of the telencephalon in lampreys, and terminate in a manner similar to those projections derived from the neocortex of mammals.

Reflecting this rapidly changing concept of the organization of the telencephalon common to all vertebrates, Finger *et al.* [19] have suggested a unified pattern of organization shown in figure 5, that attempts to reconcile the seemingly diverse telencephalic features of the different classes of vertebrates. Much research will still be required to flesh out this latest model and confirm its general validity, but the consequences of this unified model may have a profound influence on our concepts of the evolution of the vertebrate brain. This new model is actually very conservative, and argues for only minor differences in organization across all vertebrates, with largely quantitative changes in the relative numbers of subpopulations of neurons, but with surprisingly few instances of the introduction of truly novel features at the cellular or microcircuitry level. In the past, when confronted with unfamiliar cell populations or macro-architecture, there was frequently a rush to declare novelty. A

more thorough assessment of the phylogeny of cells and circuits will better enable us to identify those instances where such interpretations are more likely to prove valid.

As noted with great succinctness by Darwin, 'natura non facit saltum' [1, p. 460], it may be wiser to assume a posture of caution, and consider that recently discovered does not mean recently evolved!

15. Where to from here?

A brief perspective of where we started, and where we yet have to travel is in order. I have tried to recount the history of comparative neurobiology of the avian brain. That was the initial goal, and comparison with mammals emerged largely thanks to the weekly laboratory discussions, initially at the Walter Reed Army Institute of Research, where I presented my findings to the group of enthusiastic experimental neuroanatomists, including Walle Nauta, William Mehler and Enrique Ramon Moliner. None of this would have happened without the collaborative support of my colleagues, particularly Professor William Hodos. Vague similarities rapidly became consolidated into postulated homologies between structures as we came to recognize the remarkable identity in patterns of connection, organization and behavioural contributions

between the ascending spinal projections upon the brainstem of the avian brain and that found in the various mammalian brains under study in the laboratory. The spinal studies were soon expanded to include the connections of the cerebellum, inferior colliculus and optic tectum. The exploration of the auditory and visual pathways led us into the thalamus, and from there, we followed our nose into the telencephalon. This inevitably led to attempts to compare the sensory lemniscal pathways within the cortex of mammals in relationship to the telencephalon of non-mammalian vertebrates. The journey was not linear, and the goals kept shifting from trying to characterize the cell groups in the avian telencephalon to trying to compare them with ill-defined groups in mammals. After a bit of a struggle, the central question—at least for a while—was concerned with homologies between telencephalic clusters in birds and laminae of cortex mammals. The redirection of our focus upon homologies at the cellular level in 1970 [15] was a singularly important step [27].

Despite my early success in defining the auditory system in birds, I concentrated heavily on trying to sort out the visual pathways. I have not discussed the large body of information on the organization of the visual pathways in non-mammalia, particularly birds, over the past 50 years. In briefest terms, the more diligently we examined the avian visual system, the ever greater the similarities with mammalian visual pathways that emerged. This was true not only at the level of retinal organization, as first shown by Cajal [40], but in every other part of the multiple visual pathways that form the complexity of the visual system. These included striking similarities in retinal projections, but also in second-, third- and fourth-order connections within each of the diverse targets of the retina. Space does not permit me to review these in detail, but these included discoveries of the existence of the geniculostriate pathway in birds [41], novel discoveries of pathways in the accessory optic system that were subsequently found to also pertain to mammalian structures and connections, and a major ascending tectofugal projection upon the thalamus of birds and mammals involved in motion detection.

16. Do birds reflect an early stage of pre-mammalian reptiles?

Demonstration of the existence of homologous populations of cells and microcircuits common to birds and mammals poses the obvious need to postulate similar populations in a reptile ancestral to both birds and mammals. Lacking the prospect of being able to do that, can similar cells and circuits be found in reptiles other than birds? There is a growing body of information about the forebrain circuitry in various non-avian reptiles. Hall & Ebner [42] identified an ascending auditory projection from the nucleus reuniens posterior upon the caudomedial telencephalon, and the two visual pathways we had previously identified in birds. Topologically, this appears similar to the pathways in birds. Pritz [43] has studied the organization of the thalamus and telencephalon in crocodylians and pointed out the many similarities in organization between birds and non-avian reptiles. Ulinski [44] has extensively studied the organization of the thalamo-cortical system in turtles, a pathway that may be more directly comparable to the retino-thalamo-wulst pathway of birds [10].

17. Turing test in comparative neurobiology

Our meeting was held at the Royal Society/Kavli Centre near the famous Bletchley Park, location of the code breaking efforts of Alan Turing. In his writings about computers and artificial intelligence, Turing [45] raised the challenge of how closely we might approximate human performance by a computer, and asked the question ‘Can computers *think?*’ Turing suggested that this might be tested by placing a computer behind one screen and a human being behind the second screen. Responses presumably were posted on a computer monitor in order to avoid obvious hints provided by the spoken human voice. Various challenges were posed to the human and to the computer. A third party was to judge if the responses were generated by the computer or by the human being. If a ‘smart observer’ could not differentiate the computer’s responses from those of the human being, then we were possibly approaching the ability to build computers that could accomplish tasks associated with human consciousness, as well as human cognition. It has often been said to be the ‘touchstone’ of artificial intelligence. Turing referred to this as ‘the imitation game’, a phrase used in the name of a recent motion picture about the life of Alan Turing. Turing discussed several variants of the imitation game, including the version where the judge is asked to determine if a man or a woman is hidden behind the two screens. The ‘game’ was rendered still more challenging by having one player intentionally try to deceive the judge, and the second player trying to aid the judge in the correct determination. He then substituted a computer in place of either the man or the woman, and the judge was to determine the identity of the two players.

18. Can we compare cognitive function across phylogeny?

The Turing test has been proposed to compare machine versus humans and humans versus humans (male versus female). But can it also be applied to evolutionary neurobiology?

Evolutionary neurobiology is concerned with comparison of cells, circuits, genomes and behaviour of any organisms of varying phylogenetic distances. Thus, I would suggest that a Turing test can be used to compare cognitive skills of an octopus and a chimpanzee, mechanisms of stereopsis of primates and owls, transmitters in proposed homologous regions of different organisms such as the basal ganglia of tree shrews and cichlid fish. The list of items compared and the list of species to be compared is virtually infinite. The Turing test is thus merely a specific application of comparative testing applied to a defined pair of subjects. The appealing part of the Turing test is that it defines the ‘judge’ as the arbiter of equivalent performance or set of properties. In comparative neurobiology, we have been concerned with which brain cells and circuits mediate a particular behaviour in, for example, mammals. The notion that homologous structures mediate ‘homologous behaviours’ is widely accepted, but poorly formulated. To what extent are ‘homologous behaviours’ mediated by anatomically homologous structures?

It has often been a foregone conclusion that mammalian brains are the ‘best’ of brains, and humans the best among mammals. Perhaps both of these concepts are in need of re-evaluation.

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