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The Evolution of Evolutionary Neuroscience

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2.1 The Evolution of "Evolution"

The history of evolution is as long as the history of the Earth—and yet, "evolution" hasn't always been there. Before "evolution," naturalists framed their thoughts on the assumption of a fixed *scala naturae* as conceived by Aristotle: a strict hierarchical structure of all that is, descending from God down to minerals ("the great chain of being"; Lovejoy, 1964), with animals arranged in between "according to the degree of perfection of their souls" (Bunnin & Yu, 2004).

Once it appeared, the concept of evolution itself evolved—that is, changed over time—and along with it have evolved the questions and interpretations posed by neuroscientists. In the 19th century, the uncovering of growing numbers of particular fossils in different geological strata led to the concept of the mutability over time of the panoply of beings that had lived, and evolution came to be conceptualized by Charles Darwin (Darwin, 1859).

In the light of evolution, the *scala naturae* became a phylogenetic scale that organisms supposedly ascended as they evolved, over time, from simple to complex. Thus reasoned Ludwig Edinger, by many considered the father of comparative neuroanatomy, when he formulated at the end of the 19th century a unified theory of brain evolution that combined Charles Darwin's 1859 concept of evolution with the then current version of Aristotle's *scala naturae*. Edinger viewed evolution as progressive and linear: from fish to amphibians, reptiles, birds, then mammals—culminating with humans, naturally, in an ascent from "lower" to "higher" intelligence. In the process, the brains of extant vertebrates supposedly retained ancestral structures; for that reason, and in the face of progressive evolution, the comparison of the brain anatomy of extant species would reveal the origin of more recent structures. This supposed evidence of "past lives" in modern brain structures resonated with the Law of Recapitulation proposed by Étienne Serres, supported by Étienne Geoffroy Saint-Hilaire (1830), and formulated by Ernst Haeckel in the aphorism "ontogeny recapitulates phylogeny" (1866). Haeckel claimed that the development of more recent ("advanced") species passes through successive stages represented by adult forms of older (more "primitive") species.

The Wiley Handbook of Evolutionary Neuroscience, First Edition. Edited by Stephen V. Shepherd.

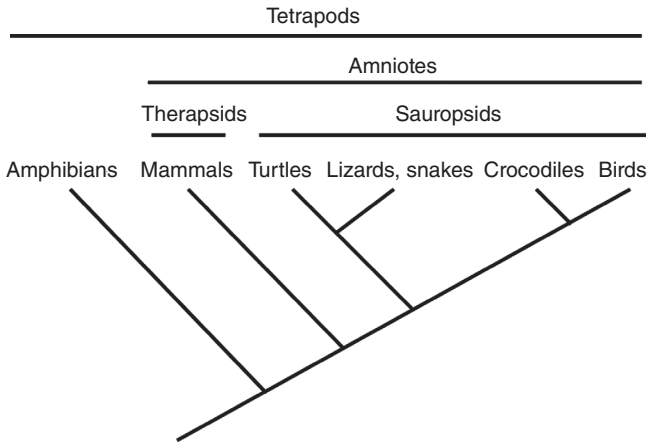

Figure 2.1 Phylogeny of Tetrapods.
Phylogeny of tetrapods places modern reptiles (including birds), the living descendants of sauropsids, as a sister group to modern mammals, the living descendants of therapsids.

Recapitulation was refuted both at the level of embryogenesis and of brain evolution in the 20th century (reviewed in Gould, 1977). Darwin himself acknowledged that early embryonic stages may be similar across related species, but are not similar to the adult forms of those species—a view that is shared by modern evolutionary developmental biology (see below). In 1922, Walter Garstang advanced the idea that differences among adult animal species arise because of evolutionary modifications in their development program—that is, that phylogeny occurs through changes in ontogeny. This amounted to the exact opposite of what Haeckel had advocated in 1866. More recent evidence against recapitulation was the recognition that mammals and birds/reptiles are sister groups—that is, that mammals don't derive from reptiles as they are today, just as humans don't derive from modern monkeys, and also that the last common ancestral form to all mammals was not a reptile (Carroll, 1988). Rather, mammals arose from ancestral therapsids, while reptiles (including the later birds) arose from ancestral sauropsids, and both therapsids and sauropsids were sister branches of the ancestral stem amniote (see Figure 2.1; see also Carroll, 1988; Evans, 2000). The notion of an ancestral "reptilian" brain has been hard to shake off, however (see below).

Modern evolutionary biologists also realize that phylogenetic trees are actually not trees, much less ladders, but rather erratic bushes with branches growing here and there in divergent directions (Gould, 1989), only some of which last through the ages. Edinger's phylogenetic scale also fails in the face of secondary simplification: the fact that species do not always "progress" into more complex beings in evolution (Jenner, 2004). Regardless, however, *scala naturae* thinking persisted in the neurosciences (Hodos and Campbell, 1969), reflecting a lack of proper training in evolutionary biology (Striedter, 2009).

Other inversions in the evolutionary tree have been driven by discoveries made by molecular phylogenetics: the use of differences and similarities in the coding and

noncoding sequences of particular genes to establish likely evolutionary relationships amongst them. Hence, the categorization of modern animals went from division into acoelomates, pseudocoelomates, and coelomates to, instead, division of Bilateria into protostomes (Lophotrochozoa and Ecdysozoa) and deuterostomes (echinoderms, hemichordates, urochordates, cephalochordates, and chordates) (Halanych et al., 1995; Hervé, Lartillot, & Brinkmann, 2005). The modern grouping is based on phylogenetic relationships unsuspected from simple morphological studies, upturning several popular theories on the evolution of the nervous system, and leads to the proposition of the Urbilateria as an ancestral group (De Robertis and Sasai, 1996).

Now disabused of the idea that ontogeny recapitulates phylogeny, modern evo-devo (evolutionary developmental biology) views animal evolution as the result of changes in the developmental process, as envisioned by Garstang (1922). The study of comparative neurobiology thus still fuels the modern search for the origins of nervous system diversity—no longer through the search for successive, progressive steps in development, but, instead, by looking for those evolved modifications in development that gave rise to different adult life forms.

2.2 Evolution of "the Nervous System"

The nervous system is a characteristic of animals—although not of all animals, as Placozoa and sponges lack any semblance of a nervous system. Cnidaria and Ctenophora have a distributed network of nerve cells throughout their bodies. It is only in bilaterians that the nervous system assumes a cord-like structure, although one that is arranged differently in protostomes and deuterostomes: It is situated ventrally in the former, and dorsally in the latter, raising the issue of how the nervous system was arranged in the common ancestor of bilaterians. One popular view was that this ancestor had a ventral nerve cord which became inverted in deuterostomes, as proposed by Geoffroy Saint-Hilaire and by Anton Dorhn (Gerhart, 2000)—a view in line with the mistaken but popular concept of progressive phylogenesis, in which the "simpler" protostomes arose before deuterostomes instead of simultaneously. The remaining—and then apparently less likely—possibility was that a nerve cord was formed twice independently: once (ventrally) in protostomes and again (dorsally) in deuterostomes (see Figure 2.2).

Comparing the expression of genes in *Drosophila* and mouse for extracellular signals that provide positional information in embryonic development, Eric de Robertis and Yoshiki Sasai showed in 1996 that the ventral cord of the insect and the dorsal cord of the vertebrate express similar genes, and are thus putatively homologous on molecular bases. Dorsal-ventral patterning in insects and vertebrates therefore appears to be controlled by homologous morphogens with mutually antagonistic actions. As a consequence, they argued that the position of the mouth (which is also homologous in protostomes and deuterostomes) changed between lineages, causing "dorsal" and "ventral" surfaces to become inverted (that is, "the animal lies on its back"). De Robertis and Sasai (1996) coined the term Urbilateria for the earliest bilaterally symmetrical animals. They proposed Urbilateria had a ventral nerve cord, but "turned over" by changing the location of the mouth in deuterostomes. This was based on the (incorrect) assumption that the protostome form would have been ancestral, in line

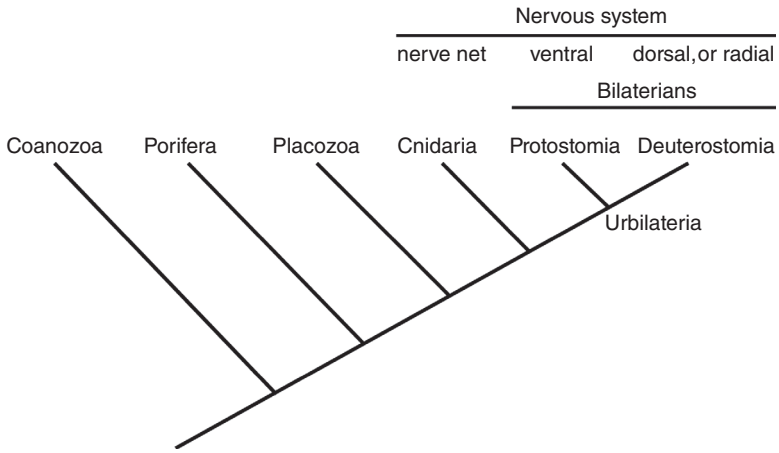

Figure 2.2 Organization of Nervous Systems.
Amongst animals, only Cnidaria, Protostomia, and Deuterostomia have a nervous system, which is organized in cords only in the latter two groups (the bilaterians).

with Geoffroy Saint-Hilaire's idea of an inversion of the dorsal-ventral axis in deuterostomes.

The origin of the bilateral nervous system thus goes back at least to the Urbilateria. Based on the simple comparison between mammals and *Drosophila*, Hirth and Reichert proposed a single, monophyletic brain origin, with a tripartite brain (comprising the hindbrain, forebrain/midbrain, and an intervening boundary region) and extended central nervous system already evident in the last common bilaterian ancestor (Hirth et al., 2003; Hirth & Reichert, 2007). But how to reconcile this monophyletic origin of all bilaterally symmetric animals with the many different shapes and types of nervous systems represented by extant Bilateria, which include insects, cephalopods, tunicates, mammals, and even the radially organized adult nervous systems of echinoderms?

The tripartite brain of bilaterians is supposed to have arisen after the diversion of the cnidarian and protostome/deuterostome lineages (Hirth, 2010), circa 630 million years ago (Erwin, 2009; Peterson et al., 2004). Alternately, cladistic analysis suggests that neurons, centralized nervous systems, and brains arose independently as many as seven times amongst Bilateria (Moroz, 2009). This analysis indicates that Urbilateria did not possess a tripartite brain, and probably no brain at all, but rather an uncentralized nerve net, similar to that maintained by Cnidarians today. In this scenario, modular mechanisms of development are invoked to explain why homologous genes might organize brains that are not, themselves, homologous (Moroz, 2009). Importantly, positing that the ancestral Urbilaterian nervous system was a neural net turns the otherwise improbable dual independent origins of ventral (protostome) and dorsal (deuterostome) nervous systems into the most parsimonious scenario, in which homologous molecular modules acted independently to form the two nonhomologous nervous systems (Northcutt, 2010).

Along the same lines, the similar patterns of Hox gene expression in the vertebral spinal cord and ventral nerve cord of insects, and of Pax-related genes in forebrain, eye, and hindbrain (Halder, Callaerts, & Gehring, 1995; Harris, 1997) in vertebrates and invertebrates do not necessarily make these structures homologous across the two clades. Rather, these are other instances in which the same genes may be used independently in the evolution of brain structures (Northcutt, 2010). In this case, the tripartite urbilaterian brain—considered by Heinrich Reichert, Frank Hirth, and Antonio Simeone to have had paired eyes, forebrain, a midbrain–hindbrain boundary (equivalent to the deuto–tritocerebrum boundary of invertebrates), and a hindbrain, with the telencephalon and most of the modern midbrain absent—would not have existed, and tripartite brains would have arisen independently, but from the same genetic modules, in vertebrates and invertebrates at the Ur/Bilateria branching (Northcutt, 2010).

A similar conceptual reorganization has taken place in our understanding of the evolution of the vertebrate brain. Amongst deuterostomes, the vertebrate brain was previously considered to be an invention exclusive of extant cephalochordates, given that urochordates (tunicates) lack a well-organized brain. Recently, however, Pani et al. (2012) found that genes involved in patterning the neurectoderm in vertebrates are also expressed in a hemichordate. This finding suggests that the genetic programs that were eventually modified into patterning the vertebrate brain already existed in an ancestral creature that lived over 600 million years ago and survived into Cambrian times, but then degenerated in amphioxus and tunicates, remaining (but patterning divergent structures) in hemichordates and vertebrates.

Besides having a well-organized brain, vertebrates differ from other chordates in that only the former are active, mobile predators, directed by an array of specialized sense organs, most of which are concentrated in the head. These sense organs are formed in development from neurogenic epidermal placodes, or thickenings of the ectoderm. The neural crest also contributes to the formation of vertebrate sense organs and other structures, and it was on this basis that Carl Gans and Glenn Northcutt proposed in 1983 that the elaboration of neural crest and neurogenic placodes was the seminal event in the origin of vertebrates, producing an enlarged brain and paired eyes and so leading to the formation of the new vertebrate head (Gans & Northcutt, 1983). Obviously, however, the head is not a vertebrate invention, as many protostome invertebrates also exhibit a well-defined head. It will be interesting to watch as continued research unveils the similarities and differences that go into building protostome and deuterostome heads.

Finally, proteomic studies of the molecular components of mammalian synapses, and their homologous proteins in other species, point to ancestral molecular machinery in unicellular organisms that existed well before the evolution of metazoans and neurons (the protosynapse; Ryan & Grant, 2009). For example, cadherins and ephrin receptors are also found in choanoflagellates, GABA and metabotropic glutamate receptors are found in Poriferans, and several synaptic proteins are found in Fungi (Ryan and Grant, 2009). Thus, regardless of when tripartite brains, a CNS, or even a neuron first appeared in evolution, the ursynapse most likely predated it, appearing sometime after the branching of Poriferans but before the branching of Cnidarians. Tomás Ryan and Seth Grant (2009) propose that, in this "synapses first" scenario, it may have been the evolution of the synapse that led to the evolution of the neuron.

2.3 New Understandings of Brain Structure

The main divisions of the human central nervous system—spinal cord, medulla, pons, cerebellum, diencephalon, mesencephalon, and telencephalon—are recognizable in all vertebrates. Amongst these structures, however, the telencephalon differs the most across species. Ludwig Edinger proposed in 1908 that the preeminence of the telencephalon in mammals, and particularly in humans, was a sign of the human evolutionary status as "highest" amongst animals. At that time, evolutionary relationships among vertebrates placed mammals as the most recently evolved group. That, however, was to change later in the 20th century, as mammals (the only remaining Therapsids) came to be recognized as a sister group to reptiles/birds (Sauropsids), rather than as their descendants (see Figure 2.1; Carroll, 1988).

But at the beginning of the 20th century, and in line with the idea of progressive evolution through gradual increases in complexity and size from fish to amphibians, to reptiles, to birds, to mammals—culminating with humans, of course—Edinger suggested that each new vertebrate group in evolution acquired a more advanced cerebral subdivision, much as the earth's geological strata formed over time. He thus proposed that an ancestral brain (the palaeoencephalon, or "striatum") controlled instinctive behavior, and had been followed by the addition of a newer brain (the neoencephalon, or pallium, or "cortex"), which controlled learned and intelligent behavior (Edinger, 1908). The ensuing view was to become dominant in neuroscience, codified in an important comparative neuroanatomy text (Kappers, Huber, & Crosby, 1936): that the primordial telencephalon of fishes had a small pallium (a palaeocortex) and a larger subpallium (the palaeostriatum), to which an archistriatum and archicortex were added in reptiles. Birds would have evolved a hypertrophied striatum, but not any further pallial regions; in contrast, mammals were thought to have evolved the latest and greatest achievement, on top of the primitive palaeo- and archicortices: the "neocortex." Thus, the striatal structures in fish, reptiles, and avians would correspond to the mammalian striatum, and their limited pallium would be a mostly olfactory version of what would become the mammalian neocortex (reviewed in Jarvis et al., 2005).

The (mistaken) idea that the neocortex was a recent mammalian invention gained popularity when neuroanatomist Paul MacLean evoked them in his view of a "triune brain" (MacLean, 1964, 1990), consisting of a reptilian complex (from the medulla to the basal ganglia) which evolved first, to which was added a "paleomammalian" complex (the limbic system), and finally a neomammalian complex (the neocortex). The intuitive (but incorrect) equation of evolution with progress, along with the alluring notion of a primitive reptilian brain, supposedly incapable of anything as complex as what a mammalian neocortex can achieve, attracted much attention from the popular media once it was used in Carl Sagan's popular book, *The Dragons of Eden* (Sagan, 1977). Building on the "evolutionary" version of the *scala naturae*, Edinger thus established the basis of a nomenclature that was used for an entire century to define the cerebral subdivisions of all vertebrates—and one that, through the words of MacLean, to this day influences popular concepts of brain evolution.

In parallel to changing views on vertebrate evolution, neuroanatomy slowly accumulated evidence against Edinger's progressive school of telencephalic advancement. Path-tracing and behavioral studies in the mid-1960s found that, like the mammalian neocortex, the neostriatum and hyperstriatum of the avian dorsal ventricular ridge

(DVR) receive sensory input from the thalamus, and carry out the same type of information processing as is performed by cortical layers. The archistriatum and hyperstriatum give rise to descending projections to premotor and motor neurons, like the mammalian cortico-bulbar and cortico-spinal pathways. Moreover, also like the mammalian neocortex, the avian DVR is crucial in motor control and sensorimotor learning (reviewed in Jarvis et al., 2005).

These functional similarities were captured in the nuclear-to-layered hypothesis formulated by Harvey Karten in 1969 (Karten, 196[illegible]hat proposed that the striatum of birds and the neocortex of mammals[illegible]gous. According to this hypothesis, the common ancestor of birds, repti[illegible]mals had cells organized into a globular structure, the DVR (the ensemb[illegible]rstriatum, neostriatum, and archistriatum). ~~According to the hypothesis,~~ this structure was reorganized into a laminar pallium early in the mammalian lineage, while maintaining the functional connectivity that determines distinct functional areas and relationships.

With the advent of studies of patterns of the expression of Hox genes and related early transcription factors, the homology between the avian DVR and the mammalian cortex gained increasing support. In a series of comparative studies, Luis Puelles, John Rubinstein, and their colleagues found similar expression patterns in developing mammalian and avian brains (Puelles et al., 2000; Puelles & Rubenstein, 2003). For instance, EMX1 and PAX6 are expressed both in the avian DVR and in the mammalian dorsal claustrum and basolateral amygdala. The bird "striatum," or DVR, is therefore equivalent in gene expression to the mammalian pallium—although not to the dorsal pallium, as originally proposed by Harvey Karten. While the expression of similar genes in morphologically different structures of bird and mammalian brains is considered by many as evidence of the homology of these structures, it must again be kept in mind that these may be genetic modules co-opted in evolutionarily independent ways in birds and mammals, as in protostomes and deuterostomes.

More recently, the nuclear-to-laminar hypothesis was tested directly and supported by the finding that genetic markers expressed in cells in mammalian cortical layers 4 and 5 are indeed expressed in thalamic input and brainstem output nuclei of the avian DVR (Dugas-Ford et al., 2012). Thus, the neuronal circuitry of the avian DVR (now "pallium"; see below) does feature cell types with the connectional and molecular properties of neocortical input and output neurons.

In 2004, in the face of this new wealth of neurochemical, anatomical, and functional data, and in an attempt to expunge neuroscience of *scala naturae* thinking, a consortium of comparative neurobiologists revised the neuroanatomical nomenclature in avians to replace the terms neostriatum, archistriatum, and paleostriatum (which suggested that brains evolved by the sequential addition of newbrain regions) with neutral terms (Jarvis et al., 2005; Reiner et al., 2004a, 2004b). The 2004 Avian Brain Nomenclature Consortium concluded that "the avian telencephalon is organized into three main, developmentally distinct domains that are homologous in fish, amphibians, reptiles, birds and mammals: pallial, striatal and pallidal domains" (Jarvis et al., 2005, p. 155). Subdivisions were then named within each domain with terms based on homologies, topology, and other recognizable roots, eliminating all phylogeny-alluding prefixes (palaeo-, archi-, and neo-) that erroneously implied the relative age, or evolutionary order, of each subdivision. Thus, the avian hyperstriatum, neostriatum, and archistriatum were renamed hyperpallium and mesopallium; nidopallium; and arcopallium, with a neighboring amygdaloid complex. The similarly corrected

terms for mammalian pallium (isocortex and allocortex) have, however, not been universally accepted. The Consortium notes that "neocortex" is still an appropriate term only if used to refer to the uniqueness of the six-layered pallium in mammals, and not to imply that it evolved from an older cortex, nor that it is the newest-evolved pallial organization.

Indeed, now that birds are recognized as a branch off sauropsids, which arose much later than the branching between therapsids and sauropsids that separated future reptiles from future mammals, the avian hyperpallium (a nuclear structure) is considered to have evolved more recently than the mammalian six-layered cortex (Evans, 2000). Because the six-layered cortex is shared by all living descendants of the therapsids (the mammals), it was presumably inherited from the common therapsid ancestor over 200 million years ago. In parallel, the nuclear pallium of birds and reptiles was presumably present in the common sauropsid ancestor equally long ago. Thus, the reptilian structure formerly known as the DVR is just as derived a structure as the mammalian layered pallium. Notably, the presence of a recognizable DVR in fish strongly suggests a nuclear organization of the ancestral pallium in the stem amniotes that gave rise to sauropsids (and then reptiles, and then birds) and therapsids (and then mammals), implying a nuclear-to-layered mechanism is indeed necessary to account for the evolution of the mammalian cortex. In turn, the true basal ganglia of birds (with which the DVR has often been confused) has been found to be organized in a similar, conserved way comparable to the basal ganglia of mammals and other vertebrates (Reiner, Medina, & Veenman, 1998).

2.4 New Understandings of Brain Size

Larger animals, be they vertebrate or invertebrate, tend to have larger brains. This relationship was recognized and formulated as early as in 1762, when Albrecht von Haller proposed what became known as Haller's rule: that larger animal species have larger brains, which are, however, *relatively* smaller in proportion to body size (von Haller, 1762). This rule was later confirmed by Georges Cuvier (1801). In 1867, Johann Friedrich von Brandt linked this reduction in the ratio between brain mass and body mass to the changing ratio between body volume and surface area in larger animals (Rensch, 1960). The relationship gained mathematical treatment in 1937, when von Bonin used linear regression of log values of brain mass and body mass to describe that the former varies as a power law of the latter, with an allometric exponent of 2/3, consistent with von Brandt's suggestion. Von Bonin was building on the concept of allometry, newly coined by Julian Huxley, which acknowledged that the mass of body parts scales as a power function of body mass (that it, it scales with body mass raised to an exponent, called the allometric exponent), a relationship that can be turned linear by plotting log values of each variable. Von Bonin (1937) has since often been credited with the introduction of objective mathematical and statistical methods to studies of brain evolution.

Harry Jerison also became interested in allometry from the point of view of Huxley's "Theory of Growth" (Huxley, 1932), through the calculation of allometric exponents that relate the scaling of body parts such as the brain to overall body mass. In the framework of the Theory of Growth, the finding of such an allometric exponent indicates that the growth pattern during the development of an individual species predicts

not only relationships between body parts in that species, but also among adults of different species. Working with a sample of mammalian species, Jerison reported an allometric exponent of 0.73 (Jerison, 1955), closer to the value of 0.75 that later became more accepted for mammals as a whole (Martin, 1990), although more recent work has pointed out that this allometric exponent is particular to each mammalian order (Martin & Harvey, 1985). Moreover, it is now recognized that the growth exponents that apply within a species do not necessarily apply across species, for instance depending on whether significant body growth happens after brain growth is over (Riska & Atchley, 1985).

Regardless of the flawed assumption of similar growth patterns within and across species, the recognition of an allometric exponent that described brain mass allowed a new concept to emerge: that of brain enlargement *relative to the size expected for a given body mass.* This is a measurement of how large a species' brain is compared to how large it was predicted to be from the species' body size, or, put in mathematical terms, the residual value of the brain x body mass allometric function. One of these new calculations was based on a wealth of new data collected and published between the 1960s and 1980s by Heinz Stephan's group in Ludwig Edinger's laboratory in Frankfurt, Germany (reviewed in Stephan et al., 1981a). In 1969, by assuming (in good Edingerian tradition) that primates and most if not all modern placental mammals had their phylogenetic origin in insectivore-like animals, Stephan and Andy calculated what they called "progression indices": that is, a measure of how much modern species would have distanced themselves from the "primitive" state. True to their advisor's "progressive" spirit, Stephan and Andy consider that "a fairly reliable and characteristic feature of directed progressive evolution is the concentration, enlargement and differentiation of the nervous system …. This development culminated in mammals, and especially in primates" (Stephan & Andy, 1969, p. 372). Their "progression indices" use the allometric relationship between brain volume (or the volume of each particular structure) and body mass pertaining to "basal insectivores" to then measure "how many times larger a given brain structure of a certain species is than the corresponding structure in a typical basal insectivore of the same body weight" (Stephan & Andy, 1969, p. 373).

As they expected, they found that the neocortex shows the stro sion," in an "ascending primate scale," while the olfactory bulb was the found to regress. Progression was particularly high, and actually highe neocortex. In exemplary circular logic, they conclude that the size of the neocortex "represents the best cerebral criterion presently available for the classification of a given species in a scale of increasing evolutionary stages" (p. 375). Since the progression indices of all other structures are very low compared to the neocortex, they further conclude that "the uncommonly large neocortex of the human represents indubitably the morphological substrate for the very high and complex functional capacity of his central nervous system" (Stephan & Andy, 1969, p. 376).

The same concept of progression indices was formulated independently as the encephalization quotient (EQ) by Harry Jerison (1973), though with the explicit purpose of serving as an indicator of intelligence both in human evolution and across primate and nonprimate species. Over time, the EQ became widely accepted as a standard for comparing species, with the expectation that it served as a better proxy for cognitive capacity than absolute brain size (for instance, Marino, 1998; Sol, Duncan, Blackburn, Cassey, & Lefebvre, 2005), as this excess brain mass, in Jerison's view, should be available for

functions other than those related to bodily demands. This expectation, however, was not founded on correlation with actual measures of behavioral capacity, but rather on the fact that for four decades, it was only in EQ, and not in absolute or relative brain size, that the human species stood out in comparison to all others (Herculano-Houzel, 2011; Marino, 1998). A recent analysis based on measures of behavioral capacity indicated that, among primates, simple brain size is a much better correlate of general cognitive abilities than EQ (Deaner, Isler, Burkart, & van Schaik, 2007).

The mid-1900s saw many other attempts at comparative studies of brain volumes (e.g. Count, 1947; Finlay & Darlington, 1995; Hofman, 1985; Haug, 1987; Rockel, Hiorns, & Powell, 1980; Tower, 1954; Zhang & Sejnowski, 2000). However, those were based on motley crews of ~~assorted~~ species as different as ferret, cow, opossum, elephant, insectivore, and human, all put together in one package, with no respect for phylogenetic relationships, and actually with the unstated but clear assumption that all mammalian brains scaled in the same way (Count, 1947; Haug, 1987). In this respect, the comparative analysis of brain volumes initiated by Stephan's group had the enormous advantage of being systematic and clade-specific. The group organized their wealth of data on volumes of brain structures of 76 mammalian species (28 insectivores, 21 prosimians, and 27 simians) into tables made available to all scientists for comparison and analysis (Stephan et al., 1981a). The large dataset fulfilled its purpose time and again, as more and more independent groups used their data on brain volumes in insectivores, primates, and also chiropterans (Stephan et al., 1981a,1981b) for analysis. One of the most influential external analyses of their dataset was published by Barbara Finlay and Richard Darlington (1995) and suggested a regular pattern of linked changes in volume across brain structures in evolution, which they attributed to a highly conserved order of neurogenesis across mammals, in correlation with the relative enlargement of structures as brain size increases (see Chapter 13). However, later analyses of the same dataset by different groups also revealed strong evidence of mosaic evolution, in which structures with major anatomical and functional links evolve together independently of evolutionary changes in other structures (Barton & Harvey, 2000).

2.5 Comparative Brain Mapping: Wally Welker's School of Cortical Cartography

In its 19th-century origins, neuroscience had known comparative studies of various mammalian brains by the hands of anatomists such as Fra[illegible] François Leuret, and Louis Pierre Gratiolet, who mapped the folds and fi[illegible]ral cortex, and physiologists like David Ferrier, who used electric[illegible], domesticated [illegible]ap the motor cortex in primates and dogs.

In the 20th century, however, neurobiology ap[illegible] its relationship to behavior were largely confined to a single ~~(domesticated)~~ species—the rat—while the occasionally studied locusts and pigeons were dismissed as not "real animals" in the case of the former, or an evolutionary dead-end in the case of the latter (Zeigler, 2011, p. 1). However, comparative neuroanatomy and neurophysiology was to gain a new impulse in the 1960s and 1970s, when Wally Welker put the newly available microelectrodes to use to map the cerebral cortex and other brain structures of different mammalian species.

By systematically studying the somatosensory system of as many mammalian species as he could, Welker showed that behavioral specializations across species correlate with differentially enlarged sensory representations of the behaviorally important appendages and other body parts throughout the sensory pathway leading to the apparently distorted "raccunculus," "hyraxunculus," "llamunculus," or "simiunculus" representation of the body in the somatosensory cortex (Welker & Campos, 1963; Welker & Carlson, 1976; Welker et al., 1976).

Besides the concept of a direct relationship between functional neuroanatomy and behavior, Welker's legacy also includes the brains of the dozens of species he collected and processed and which have since been the subject of investigations by many independent researchers. These brains are still available for study in the Comparative Mammalian Brain Collection (www.brainmuseum.org).

Wally Welker also made history by influencing several other neuroscientists interested in the evolution of the nervous system. One of these was Jon Kaas, who overlapped with Welker in Clinton Woolsey's lab at the University of Wisconsin. Moving further the combined neuroanatomical and physiological approach, Kaas developed the flattened preparation of the cerebral cortex (lovingly nicknamed the "roadkill preparation") which allowed the visualization of the cortex as a whole, including functional areas otherwise buried within sulci and the analysis of their characteristics, such as borders, distribution of neurochemical markers, and patterns of connectivity as well as their comparison across species (Gould & Kaas, 1981). A similar flattened preparation was later developed for the analysis of images obtained with PET and MRI (reviewed in Fischl, Sereno, & Dale, 1999). Kaas's former students Kenneth Catania and Leah Krubitzer continue to perpetuate the field of comparative functional neuroanatomy through their studies of specialized sensory systems such as the tactile appendages of the star-nosed mole (Catania, 1995) and of the evolution of cortical areas (Krubitzer, 2000).

2.6 The Human's Place in Nature: All Brains Are Not Made the Same

In regard to the human brain, much of comparative and evolutionary neuroscience has been based on two contradictory assumptions. On the one hand, it has been assumed that all brains, including the human brain, are built with the same basic cellular constitution, with a similar relationship between brain size, number of neurons, and neuronal density (the inverse of average neuronal size) that would not have changed over the course of mammalian brain evolution. Along the same lines, influential models of mammalian brain evolution have been built on assumptions of cortical uniformity across regions and species (e.g., Rockel et al., 1980), with cortical expansion occuring through the lateral addition of modules sharing identical numbers of cells (e.g., Rakic, 1988) and with a constant fraction of cortical neurons connected through the white matter (e.g., Zhang & Sejnowski, 2000).

On the other hand, it has been tacitly agreed that evolutionary rules, while applying to every other species, might not apply to humans. Hence the frequency with which the human brain has been considered "special," an outlier: in having the largest brain size relative to what it "should" have for the human body mass (Jerison, 1973; Marino, 1998), in having an unusually large prefrontal cortex (Smaers et al., 2011),

or in having a particular type of spindle-shaped neuron in its cerebral cortex (which many others species are now known to share; Nimchinsky et al., 1999).

Harry Jerison's concept of encephalization, which put humans on top—at last—created a trend in the field of adjusting brain size (and densities, and glia/neuron ratios, and cognitive measurements, and everything else) for body mass. Absolute values became more and more disregarded, as if body mass were a determinant variable on which even the most basic aspects of brain morphology and function depended, and to which they should be normalized. Similarly, the relative size of the cerebral cortex within the brain became a standard for comparisons across species, as if it provided a proxy for the relative functional importance of the structure. This emphasis creates paradoxes, such as expecting very large and small cerebral cortices with similar relative sizes to have the same "relative importance" across species. Recently, a meta-analysis showed that relative sizes are not meaningful, at least amongst primates: the best correlate of cognitive ability across non-human primates is absolute brain size, not encephalization or relative size of the cerebral cortex (Deaner et al., 2007).

Our recent finding that not all brains are made the same, with different relationships between brain size and number of neurons across mammalian orders, has provided a new conceptual basis for comparative neuroanatomy: One that regards brain size as a consequence of developmental programs that generate brains according to different scaling rules across clades (Herculano-Houzel, 2011; Herculano-Houzel, Manger, & Kaas, 2014). Our systematic analysis of the numbers of neurons and other cells that compose the brain of dozens of mammalian species has shown, for instance, that primate brains hold many more neurons than rodent brains of a similar size—and the human brain is no outlier, having the number of neurons that is expected for a generic primate of its brain size (Herculano-Houzel, 2012). We thus view the human brain as remarkable, yet not extraordinary, with notable cognitive abilities that can be attributed to the enormous number of neurons in its cerebral cortex, regardless of its relative size, its degree of encephalization, or the relative volume of the prefrontal area (Barton & Venditti, 2013; Semendeferi et al., 2001)—a number of neurons that is shared by no other animal, primate or otherwise, possibly due to a change in diet that allowed our direct ancestors to circumvent the metabolic limitation imposed by a raw foods diet (Fonseca-Azevedo & Herculano-Houzel, 2012). This new framework paves the way to studies of the genetic and nongenetic mechanisms that relate numbers of neurons to average neuronal cell size, and to the changes in those mechanisms that generate diversity in evolution, all the while constrained by a set of scaling rules (Herculano-Houzel et al., 2014).

2.7 Conclusions and Perspectives

The evolution of evolutionary neuroscience is a story as much of scientific achievements as it is of conceptual revolutions: from *scala naturae* to branched evolution, from homologies as evidence of conserved development to evidence of independent use of the same genes in different evolutionary branches, from veiled or explicit anthropocentricism to the analysis of humans as just another species. While some extrapolations have been informative, neuroscientists have learned that some are not.

Vertebrate and invertebrate brains may seem equally tripartite, but may not be homologous, just like bird and mammalian brain structures may not be homologous, despite expressing similar genes; body size may correlate with brain size, but probably does not determine it; and the human brain is not an enlarged mouse brain, although it is, in many senses, an enlarged primate brain. While there is still a lot to be learned from comparing turtle, frog, chicken, opossum, mouse, monkey, and human brains, modern comparative neuroanatomy has yet to shed the *scala naturae* bias of progression and embrace evolution more systematically: not as the means to the human brain, but as the way to diversity.

Acknowledgments

The author is grateful to Jon Kaas for ten years of informal guidance in the field of neuroanatomy. Supported by CNPq, FAPERJ, MCT/INCT and the James S. McDonnell Foundation.

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