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193
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Origin and Evolution of the Vertebrate Telencephalon, with Special Reference to the Mammalian Neocortex

With 15 Figures

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List of Contents

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1
Introduction

There is little doubt that the vertebrate brain is the most complex structure we know. As with any complex structure, there is the immediate question about its origins. How could such a complex design develop from the simplest multicellular animals? This problem has pervaded the study of evolutionary biology since its beginnings. Although Darwin (1859, 1871) proposed an impeccable mechanism (natural selection) for the gradual transformation of species including human origins, even he sometimes expressed certain doubts about the origin of highly complex structures. This issue has been highly debated both within science and outside it. For instance, a rebirth of the old religious argument of intelligent design has gained unexpected strength in the last few years. In essence, this argument follows Paley's (1802) claim that if we find a clock that has been thrown away we cannot consider that it was created on its own, but rather has to be the consequence of conscious design. Today, creationists have developed a modern version of this argument, that of "intelligent information" (Denton 2002). For example, after sequencing the human genome in 2001, one of Celera Genomics top computer scientists claimed that this complexity suggested design. Although he clarified not to be thinking of God, he asserted that "there's a huge intelligence there" (quoted in Witham 2002, p 9). As Witham (2002) says, modern computer-literate believers may soon ask the question of whether the universe is self-running or functioning on DOS, a Divine Operating System.

In this volume, we have decided to tackle the problem of the origin and evolution of the vertebrate brain, from the simplest nervous system-like elements that we can observe in nature. In doing so, we expect to establish a continuity between the simplest stages and the elaboration of the highly intricate neuronal network that is the mammalian cerebral cortex. For lack of space, we will have to leave aside several other brain structures such as the basal ganglia or the cerebellum, as well as components perhaps comparable to the mammalian cerebral cortex in other vertebrates; as will be seen, the cerebral cortex alone is sufficient to fill up quite an extensive review. Our main point will be to present a case for continuous evolutionary transformation of the central nervous system, from its very origins to the elaboration of the most complex structure that exists on earth.

In order to pursue our goal, we will have to discuss some basic concepts of neuroanatomy, embryology, and developmental genetics. This knowledge was unavailable in Darwin's time, which further emphasizes his genius. We will follow an approach that has been termed developmental evolutionary genetics, which seeks to establish a correspondence between embryological processes and the phylogenetic history of an organism. In other words, if we observe continuity in development between a fertilized egg and an adult brain, we should also expect continuity in its evolutionary history. This approach is not new; its roots can be found in Von Baer's biogenetic law (Von Baer 1828; see also Gould 1977), stating that embryos start from a general condition (the unicellular egg), shared by all

animals, and during development they progressively acquire characters that include them in successively restricted taxonomical groups. That is, if at early stages all embryos are similar among them, they subsequently develop characters that define them as say, vertebrates, then mammals, then primates and then as humans. This view was further expressed in a more extreme version by Haeckel (1892), who considered both evolution and development as a linear chain, embryology recapitulating the phylogenetic history of the animal. Thus, the human embryo passed through stages in which it was first a unicellular organism, then an undifferentiated metazoan (morula), then a jellyfish (gastrula), then a fish, then a tailed reptile and so on until he or she became a human. Modern understanding of these hypotheses acknowledges that in fact, early embryos are readily distinguishable among them, and that human embryos are human embryos during all development; they do not pass from a jellyfish stage to a fish stage and so on (Garstang 1922; Gould 1977; Richardson et al. 1997). However, it is also recognized that embryos pass through successive stages in which they acquire the characteristics proper to each of the nested phylogenetic categories to which they belong. Thus, there is a general concordance between embryonic stages and the phylogenetic history.

Recent expressions of this approach have taken the name of "evo-devo" (from evolution and development) and have been particularly fruitful after the rise of molecular embryology. This discipline has revealed an exquisite correspondence in the molecular mechanisms underlying similar embryonic processes in a wide group of animals, which nevertheless appear quite diverse in their superficial morphology (McGinnis and Krumlauf 1992; Gerhart and Kirschner 1997; Martindale 2005; Pearson et al. 2005). Furthermore, the bulk of comparative molecular and embryological evidence strongly points toward a relatively conserved embryonic stage (the zootype) that corresponds to the establishment of the taxonomic group's body plan (Slack et al. 1993). In the case of vertebrates, this corresponds to the point in which the embryo develops the pharyngeal pouches: the pharyngula stage. Thus, there is high diversity in early developmental processes (mainly due to species differences in yolk content and early embryonic adaptations), followed by a convergence in structure at mid-developmental stages, in order to diverge again as development proceeds toward the adult state. Interestingly, the expression of specific and highly conserved regulatory genes (homeobox and related genes) takes place in this converging embryonic stage and participates in patterning the embryo's body plan. Homeobox *(Hox)* and related genes have been found to be fundamental in anteroposterior patterning in vertebrates, in the fruit fly *Drosophila* and in other animal groups, indicating that they represent quite an ancient developmental regulatory system (McGinnis and Krumlauf 1992; Krumlauf 1992; García-Fernández and Holland 1994; Martindale 2005; Pearson et al. 2005; García-Fernández 2005).

In a way, this evidence has produced a turn back to the times of the preevolutionary concepts of Transcendental Anatomy, in which the architectural body plans were considered to be established by divine intervention; diversity in design was only the result of variations within a theme, due to adaptations to contingent

circumstances. This perspective considered adaptation as a constant, universal feature of living beings. The advent of evolutionary theory, putting its focus on diversity rather than on common organization and emphasizing that adaptation was variable, related to successful reproduction, relegated this perspective to a second plane for quite a long time (Desmond 1982). As said, the discovery of a common genetic organization in the body of most animals has produced a strong shift of emphasis into the commonality of type again, this time observed under the light of evolutionary theory. We will pursue an evo-devo view to the phylogenetic history of the brain, showing which genetic processes are shared with other, nonvertebrate animals to underline the genetic conservatism of morphological evolution; but will also put emphasis on the dramatic morphological diversification that has taken place during evolution. It appears that, even given a relatively fixed genetic battery, developmental morphology has taken quite different courses in the different lineages, possibly related to the specific circumstances in which characters have been acquired. Thus, we also intend to emphasize the behavior and way of living of the ancestral organisms, in order to provide an integrated view of the specific conditions that led to the divergence of the distinct lineages.

An important theme to be discussed in this section relates to the concept of homology. We will need to compare structures in different species and will have to determine whether they are or not comparable structures. There are many (perhaps too many) criteria to determine the homology between two organs, and as expected they do not always agree. In one particular instance, the origin of the neocortex from a reptilian-like brain, this issue has been highly controversial in the last few years. As the evidence to date indicates strong genetic conservatism with morphological diversification, we have relied on genetic criteria to determine the structure that most likely gave rise to the mammalian neocortex.

In general, we will address this issue in the context of a conserved structural organization of the vertebrate brain. As in the concept of the zootype expressed above, in vertebrate brains there is a stage of convergence at about the same developmental stage. For example, a proposal for a neuronal zootype has been recently outlined, considering the basic embryonic elements that determine the organization of the vertebrate brain (Deutsch and le Guyader 1998). However, long before these authors, Bergquist and Källén (1953a,b; 1954) established in the mid-1900s that all vertebrate brains at the pharyngula stage have a similarly organized brain, divisible into a series of transverse domains visible as periodic thickenings of the anterior neural tube, which they termed neuromeres. These thickenings were proposed to be centers of proliferative activity, separated by regions where cell division occurs more slowly. Although this view was neglected for a long time, recent studies have confirmed the presence of seven neuromeres in the hindbrain or rhombencephalon (rhombomeres), one in the midbrain (mesomere) and six in the forebrain (prosomeres) (Shimamura et al. 1997; Wilkinson et al. 1989; Fraser et al. 1990; Lumsden 1990; Rubenstein et al. 1994; Puelles and Rubenstein 1993, 2003; Puelles 1995). Furthermore, it was found that the expression boundaries of different *Hox* genes were largely coincident with the rhombomeric segmentation pattern

and were highly conserved across vertebrate species (Wilkinson and Krumlauf 1990; Nieto et al. 1991; Kimmel 1993).

In the more anterior prosencephalon, which is of more immediate interest to us, evidence for segmentation was for some time difficult to obtain. However, analyzing the expression domains of several transcription factors that were activated in the developing forebrain, Puelles and Rubenstein (1993, 2003) determined that there was a nice fit with Bergquist and Källén's description of prosomeric segments, which is again largely conserved across vertebrates. While in the prosomeres there is no expression of *Hox* genes, several homeodomain proteins are expressed, which perform a similar role to that of *Hox* gene clusters in more caudal segments. For example, genes of the *Dlx* and the *Emx* (*Emx1* and *Emx2*) families are respectively expressed in the ventral telencephalon (subpallium) and the dorsal telencephalon (pallium). *Dlx* genes are closely related to *Hox* genes (they appear to belong to the same cluster) and are homologs to the *Drosophila* gene *distal-less* (*Dll*), expressed in the embryonic imaginal disks (Panganiban 2000). The linkage between *Dlx* and *Hox* genes also exists in invertebrates such as the nematode, suggesting that the primordial *Dlx* and *Hox* genes were similarly linked. Importantly, in vertebrate origins there were two duplications of the *Dlx-Hox* cluster (Digregorio et al. 1995; Stock et al. 1996). On the other hand, *Emx* genes are orthologs of the *Drosophila* gene *empty spiracles* (*ems*), responsible for the formation of head segments (Dalton et al. 1989; Walldorf and Gehring 1992; Hirth et al. 1995).

Puelles and Rubenstein's (1993, 2003) prosomeric model has faced some criticisms such as the evidence of cell migration across prosomere borders (but not across rhombomere borders), the fact that early patterns of gene expression may be quite dynamic and a static picture like the one presented does not capture this dimension, or the possibility that the authors have disregarded evidence that does not support the model (for review see Striedter 2005). However, comparative evidence has determined that this pattern is highly conserved across vertebrates (it is observed not only in mammals and birds, where it was first reported, but also in teleosts and agnathans; Wulllimann and Puelles 1999; Pombal and Puelles 1999), which strongly suggests that it reflects a phylogenetically stable framework that can be of great utility in species comparisons.

Before starting with our analysis, it will be useful to recall some basic concepts of neuroanatomy and embryology. In the early embryo, the central nervous system (CNS) originates from a flat neural plate in the dorsal aspect of the animal, after the action of inductive signals from the mesoderm. In a process called neurulation, this plate develops into a hollow neural tube. Eventually, this tube widens in the cephalic region, forming three main vesicles, from caudal to rostral, the rhombencephalon or hindbrain, the mesencephalon or midbrain, and the prosencephalon or forebrain (Fig. 1). The latter subdivides into a diencephalon and two telencephalic vesicles (the cerebral hemispheres) that contain the future olfactory bulbs, the cerebral cortex and the basal ganglia, among other structures. The cerebral hemispheres have been classically subdivided into a pallium located dorsally and a ventral subpallium (basal ganglia), both separated by the corticostriatal sulcus

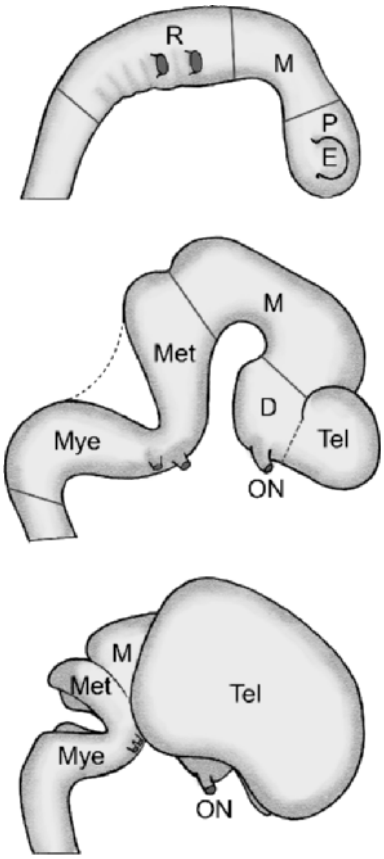

Fig. 1 Early development of the mammalian forebrain. Initially, the forebrain is subdivided into three main components, the segmented rhombencephalon (*R*); the mesencephalon (*M*) that contains the main sensory structures in nonmammals; and the prosencephalon, which is later partitioned into a diencephalon (*D*) and a telencephalon (*Tel*). *E*, eye; *ON*, optic nerve

or pallial-subpallial boundary in the ventricle at the equatorial level of the vesicle (Fig. 2). In the subpallium, the basal ganglia (involved in motor functions) develop in the lateral side from two structures that protrude into the ventricle: the medial and the lateral ganglionic eminences. On the other hand, the pallium has been subdivided into a medial part (giving rise to the hippocampal formation), a dorsal part (giving rise to the neocortex or isocortex), and a lateral part (giving rise to the olfactory cortex), which is connected anteriorly to the olfactory bulb. Although in the adult stage all these are cortical layered structures, the neocortex is different from the olfactory or lateral cortex and from the hippocampus or medial cortex in having six cellular laminae composing it, while the other two structures bear only three laminae. In the border between pallium and subpallium, several structures

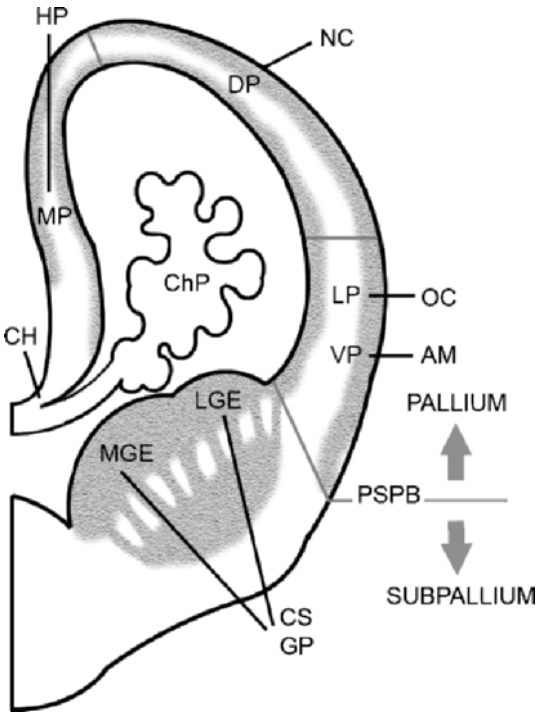

Fig. 2 Main components of the developing mammalian telencephalon. The telencephalic hemispheres consist of a ventral part or subpallium, separated from the pallium by a pallial–subpallial boundary (*PSPB*). The medial ganglionic eminence (*MGE*) and the lateral ganglionic eminence (*LGE*) differentiate in the subpallium and give rise to the globus pallidus (*GP*) and corpus striatum (*CS*), respectively. These structures produce inhibitory interneurons for most pallial regions. The pallium consists of a medial pallium (*MP*) that gives rise to the hippocampal formation (*HP*), a dorsal pallium (*DP*) giving rise to the neocortex (*NC*), a lateral pallium (*LP*) giving rise to the olfactory cortex (*OC*), and finally a ventral pallial (*VP*) territory producing part of the claustroamygdalar complex (*AM*). In its medialmost aspect, the pallium is bordered by an embryonic structure termed the cortical hem (*CH*), which separates the medial pallium from the choroid plexus (*ChP*) that differentiates from the roof plate

develop that collectively make up the so-called cerebral amygdala and other structures, containing both pallial and subpallial elements. Recent analyses have shown that in this region an additional embryonic pallial element is distinguishable (the ventral pallium). In the developing brain vesicle, as in the rest of the neural tube, cell proliferation takes place in the inner walls, lining the ventricular cavity (the ventricular and subventricular zones). Then, immature neurons migrate radially out to make up distinct brain nuclei. In the cerebral cortex, this migration process makes a long journey to establish a mantle of gray matter in the periphery of the pallium. However, there is also migration of some cells in the tangential direction,