Neocortex: Origins

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Introduction

The origin of the mammalian neocortex is probably one of the most controversial themes in modern comparative neurobiology. There have been long-standing arguments on this issue (dating from early last century), and still there is no general consensus about it. This is partly due to the enormous anatomical diversification that is observed in the cerebral hemispheres of distinct vertebrate groups. Starting from a relatively conserved embryonic plan that divides the hemispheres into a dorsal pallium and a ventral subpallium, different brain components have expanded in each vertebrate class, producing profound distortions of the ancestral adult condition. For example, cartilaginous fishes are characterized by the development of a central pallial nucleus located at the dorsal midline, while bony fish develop a brain in which the ventricular region everts to the outside, separating the medial hemispheres in the dorsal aspect. Amphibians possess quite a simple brain with little neuronal migration outside the internal ventricular zone, and almost no expansion of cell masses. Their pallium has been subdivided into medial, dorsal, and lateral components. On the other hand, the pallium of reptiles and birds (sauropsida) displays a cortical, laminated architecture containing a medial/dorsomedial (hippocampal) cortex, a lateral (olfactory) cortex, and a small dorsal cortex interposed between these two (in birds, the region corresponding to the dorsal cortex has been termed the Wulst, or more recently, the hyperpallium). These components correspond to the different pallial subdivisions in amphibians. In addition, the brains of sauropsids display a conspicuous nuclear structure that bulges into the ventricle, the dorsal ventricular ridge (DVR), which receives many thalamic sensory projections (Figure 1).

Mammals are characterized by the presence of a neocortex (Figure 1). This structure is bound medially by the medial cortex or hippocampus, and laterally by the lateral or olfactory cortex. Deep to some cortical areas like the insular region there are structures such as the claustral complex. These and other dorsal structures make up the pallium, while the ventral subpallium includes the basal ganglia and related nuclei. The neocortex of mammals is indeed a unique structure, consisting of six laminae that remain somewhat conserved across species and cortical regions. Furthermore, it is subdivided into several distinct areas in the tangential domain, some of them being sensory, others motor, and still others receiving multimodal input. In several mammalian groups there is a clear trend of tangential neocortical expansion that results in the increase of both surface area (leading to the formation of fissures and convolutions) and the number of cortical areas. The neocortex receives most of its extrinsic input from dorsal thalamic nuclei, many of them conveying sensory information from somatosensory, auditory, or visual modalities, and projects back to the thalamus, to the amygdala, to the entorhinal cortex (which in turn projects to the hippocampus), and to several subcortical structures, including the spinal cord.

Historical Background

Early in the last century, concepts on the evolution of the amniote brain (i.e., reptiles, birds, and mammals) were dominated by Elliot Smith's interpretation that sauropsids were characterized by the expansion of subpallial structures like the basal ganglia, leading to the development of the DVR. On the other hand, mammals would have expanded the pallial region, producing the neocortex. Interestingly, other authors, such as Nils Holmgren and Bengt Källén, proposed a pallial origin for the reptilian DVR, which they described as arising from a deep proliferative region that overlaps with the lateral cortex. Holmgren termed this region as the hypopallium, and considered it to be related to deep-brain mammalian structures like the claustrum or parts of the amygdalar complex. However, these views were eclipsed by Elliot Smith's claim for a subpallial origin of the DVR.

Subsequent analyses performed in the 1970s, taking advantage of newly developed histochemical procedures, revealed that the reptilian DVR does not contain acetylcholinesterase activity as the basal ganglia do, and is therefore a pallial structure. Furthermore, tract-tracing experiments performed by Harvey Karten and collaborators, showed that the avian DVR (more specifically, its anterior part, ADVR, or nidopallium) received thalamic sensory projections similar to those reaching some parts of the mammalian neocortex. More precisely, collothalamic nuclei (i.e., thalamic nuclei receiving input from mesencephalic sensory centers, conveying visual and auditory information) project to the ADVR/nidopallium of birds, and to the lateral neocortex of mammals (visual extrastriate and

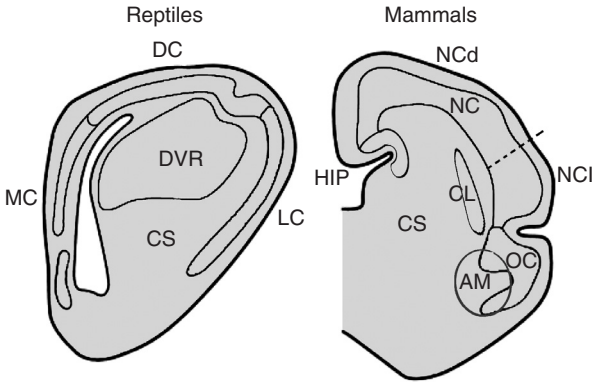

Figure 1 The cerebral hemispheres of reptiles and mammals. In the dorsal aspect of the hemisphere, reptiles display a cortex, with medial/dorsomedial (MC), dorsal (DC), and lateral (LC) components, and a dorsal ventricular ridge (DVR) consisting of an anterior part and a posterior part (not shown). The anterior DVR receives most sensory projections from mesencephalic-receiving thalamic nuclei. The medial and dorsomedial cortices of reptiles (MC) have been compared to the hippocampal formation (HIP) of mammals, and the lateral cortex (LC) is considered homologous to the mammalian olfactory cortex (OC). The dorsal cortex (DC) of reptiles has characteristics of both the entorhinal cortex (adjacent to the hippocampal formation; not shown) and the neocortex (NC) of mammals. The latter appears subdivided into a dorsal aspect, NCd, and a lateral aspect, NCl. There is no consensus regarding the homology of the anterior DVR. According to some authors, this structure corresponds to the mammalian lateral neocortex (NCl), while others consider that it relates to the claustroamygdaloid complex (AM, CL). Reproduced from Northcutt RG and Kaas JH (1995) The emergence and evolution of mammalian neocortex. *Trends in Neuroscience* 18: 373–379, with permission from Elsevier.

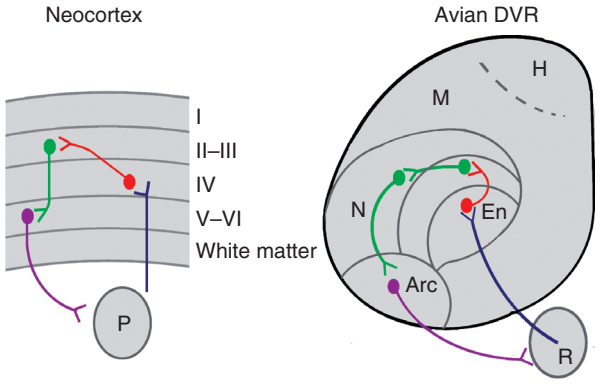

Figure 2 Harvey Karten's original cell-equivalent hypothesis, in which visual processing circuits of the avian nidopallium (N) and arcopallium (Arc) are homologous to those of the different layers in the mammalian extrastriate visual cortex. En, entopallium (a component of the nidopallium); H, hyperpallium; M, mesopallium; P, pulvinar nucleus; R, rotundus nucleus.

auditory cortices). On the other hand, lemnothalamic nuclei (receiving direct sensory input from ascending lemniscal systems, carrying visual or somatosensory input) project to the avian hyperpallium, and to the dorsal neocortex of mammals (primary visual and somatosensory cortices). Thus, Karten proposed that the avian hyperpallium (dorsal cortex of reptiles) was homologous to the dorsal neocortex of mammals (both receiving lemnothalamic input), while the ADVR/nidopallium of birds and reptiles was homologous to the mammalian lateral neocortex (both receiving collothalamic input). Furthermore, relying on similarities in intrinsic connectivity, it was proposed that different components of the avian ADVR corresponded to specific neocortical layers in mammals (Figure 2).

This hypothesis dominated the views of early mammalian brain evolution and neocortical origins for several years. Nevertheless, there were always some dissenters, backed by the early embryological studies and by the different topographical position of the mammalian neocortex and the reptilian DVR. In these alternative views, the most likely homolog of the whole mammalian neocortex was the reptilian dorsal cortex, which is located in a similar relative position as the neocortex: interposed between the lateral (olfactory) and the medial (hippocampal) cortices. Thus, in the origin of mammals, collothalamic projections originally destined to the ADVR or its equivalent region might have deviated or sent collaterals toward an expanding dorsal pallium or dorsal cortex. This change was considered to be more likely to occur than a transformation of the topographic positions of the embryonic proliferative zones and the adult structures. Supporting this view, the mammalian neocortex bears other patterns of connectivity that are not found in sauropsids, like the interhemispheric connections and the corticospinal tract. This is to be expected from a structure that increases in size and consequently increases its connectivity domains. Additional considerations on the topography, development, and connectivity of the sauropsidian ADVR led to the revival of Holmgren's hypothesis of homology between this structure and either the dorsal claustral complex or the basolateral amygdala of mammals.

Developmental and Genetic Evidence

An important breakthrough in this controversy was provided by the analysis of regulatory gene expression patterns in the developing telencephalon, which identified three main compartments during the specification of the cerebral vesicles: the subpallium, being positive for regulatory genes such as *Dlx1* and *Dlx2*; the medial, dorsal, and lateral pallia (or medial, dorsal, and lateral cortices), expressing genes such as *Emx1*, *Tbr1*, and *Pax6*; and the intermediate territory or ventral pallium located between these two, expressing *Tbr1* and *Pax6* but not *Emx1* (Figure 3).

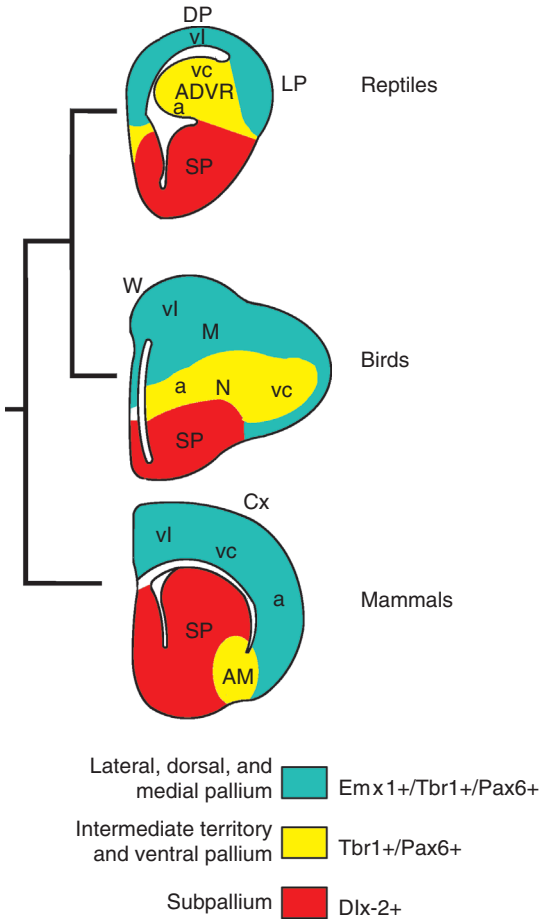

Figure 3 Patterns of regulatory gene expression in the developing telencephalon of sauropsids and mammals. All pallial components (medial, dorsal, and lateral; blue) express the markers Emx1, Tbr1, and Pax6, with the exception of the ventral pallium (yellow), which is positive for Tbr1 and Pax6 but not for Emx1. The subpallium (SP, red) expresses *Dlx* genes. According to this evidence, the ventral pallium gives rise to the reptilian anterior dorsal ventricular ridge (ADVR), to the avian nidopallium (N), and to the claustroamygdalar complex (AM) of mammals. a, vc, termination of auditory and visual collothalamic pathways, respectively; vl, termination of visual lemniscal pathways; DP, dorsal pallium; LP, lateral pallium; Cx, cortex; M, mesopallium; W, Wulst or hyperpallium. Adapted from Aboitiz F, Morales D, and Montiel J (2003) The evolutionary origin of the mammalian isocortex: Towards an integrated developmental and functional approach. *Behavioral and Brain Sciences* 26: 535–586, with permission from Cambridge University press.

Interestingly, the ventral pallium maps into parts of the claustrum and the amygdala of mammals and into the DVR of sauropsids, indicating a common developmental origin for these structures, and supporting embryonic homology between the territories producing the reptilian ADVR and parts of the claustroamygdalar complex of mammals. Nevertheless, it is not clear that in the adult state there is any precise homology between the different ventral pallial derivatives in sauropsids and mammals, as both structures are likely to have undergone distinct evolutionary histories. In fact, fossil evidence indicates that the lineage of mammal-like reptiles diverged quite early from the reptilian line, and that their brains were extremely simple in their gross morphology, resembling more the brains of modern amphibians than those of modern reptiles.

In an attempt to accommodate these data to Karten's original hypothesis, it has been proposed that the lateral neocortex of mammals arose by virtue of a transformation of a ventral pallial structure into a dorsal pallial phenotype. This may have resulted either from the acquisition of dorsal characteristics of a yet unspecified territory, or from duplication of the ventral pallium and subsequent transformation of its dorsal moiety. Nevertheless, these hypotheses might be difficult to refute, as any dorsal pallial feature in the lateral neocortex could be considered to result from the transformation from a ventral to a dorsal pallial structure. Instead, these proposals require positive evidence, such as a direct sign of ventral pallial origin in the lateral neocortex.

Reptilian Dorsal Cortex: Neocortical and Entorhinal/Subicular Features

Furthermore, the presumed homology – between visual and somatosensory areas in the reptilian dorsal cortex, and primary visual and somatosensory areas of the mammalian neocortex – has been questioned by some authors. For example, somatosensory projections to the dorsal cortex have not been observed in either lizards or turtles, and thus may not represent an ancestral character of sauropsids. In addition, visual projections to the dorsal pallium reach a region that in turtles includes the dorsal cortex and the pallial thickening, and in lizards, are restricted to the pallial thickening. The pallial thickening is located in the lateral aspect of the pallium of some reptiles and its homologies and embryonic origins are unclear. Moreover, the multimodal dorsomedial pallium of amphibians and reptiles has several features reminiscent of the mammalian entorhinal cortex. Like the latter, the reptilian dorsal cortex has important connections with the medial/dorsomedial or hippocampal cortices. In addition, the reptilian dorsal cortex does not participate in vision but rather in spatial learning and memory. Thus, the dorsal cortex of reptiles shares features with the entorhinal/subicular cortex of mammals, but also contains a direct visual (and sometimes somatosensory) sensory input that, if perhaps not being strictly equivalent to the mammalian visual (or somatosensory) cortex, may serve to feed sensory information to the hippocampus for establishing sensory associations during learning.

The Dorsalization Hypothesis

Considering the evidence discussed herein, Aboitiz and collaborators proposed that the mammalian neocortex arose as an expansion of an ancestral pallial region with dorsal characteristics, which acquired a massive lemnothalamic and collothalamic input. This may be conceived as a dorsalization effect, in which the activity of genes (*FGFs*, *Wnts*, *Emxs*, *Lhx2*, *Pax6*, and others) or signaling pathways involved in dorsal pallial specification was enhanced, thus producing an increase in proliferative activity leading to the expansion of a primitive dorsal cortex into a neocortex. More precisely, the embryonic dorsal pallium represents a transitional zone that receives influence from several signaling sources, including the anterior forebrain expressing FGF8; the medially located cortical hem expressing Wnts and BMPs, and regulating other genes like *Emxs* (these signals specify both the medial pallium and the neocortex); and the *Pax6*-dependent antihem that specifies the lateral and ventral pallium. The expansion of this transitional tissue may have somehow resulted from the interaction between these three morphogenetic fields.

This process was not only the result of a developmental transformation; probably it was also favored for functional reasons. As nocturnal animals, early mammals probably had refined senses of smell and hearing, which was reflected in the development of a large olfactory bulb, a middle ear, and external outer ears. Strong associative networks involving olfaction and other senses developed in the dorsal pallium and the hippocampus, which participated in the establishment of learned maps of space. These networks benefited from the expansion of the dorsal pallium, which in turn facilitated the projection of collothalamic pathways that were originally directed to the ventral pallium or to the subpallium into this structure.

Lamination of the Neocortex: The Preplate

The neocortex is not only the result of the tangential expansion of the dorsal pallium. There is also a dramatic increase in radial thickness, as the reptilian cortex is only a few cells deep while the mammalian neocortex is organized in vertical columns about 100 cells in depth. As mentioned, the adult neocortex consists of six laminae, the most superficial (layer I) being a cell-poor layer in which tangential axons from Martinotti cells and other axons run along various distances. The development of the neocortex is quite a conspicuous one, in which the first cells to arrive make up a transient embryonic structure termed the preplate, consisting of Cajal–Retzius cells and pioneer neurons. The former derive in large part from the medially located cortical hem and migrate laterally into the neocortex, while pioneer neurons derive mainly from the subpallium. Reelin-secreting Cajal–Retzius cells are involved in radial glia maintenance and in controlling the latest steps of neuronal migration to the cortex, and pioneer neurons display an axon directed subcortically that acts as a guide for growing thalamocortical axons. Subsequently, radially migrating neurons that make up the true neocortical plate arrive from the cortical ventricular zone and split the preplate into two layers: a superficial marginal zone, containing the Cajal–Retzius cells and other cells, and a deep subplate below the emerging cortical plate, containing most pioneer neurons and other cells such as excitatory neurons (**Figure 4**). The latter receive transient contacts from arriving thalamic axons before they enter into the mature cortex. Most of the cells in the marginal zone and the subplate die during development or dilute with cortical expansion, while cells of the cortical plate remain in adulthood. Interestingly, the development of the cortical plate occurs in an inside-out sequence in which the earliest-produced cells end up in the deepest cortical layers, and the latest-produced cells

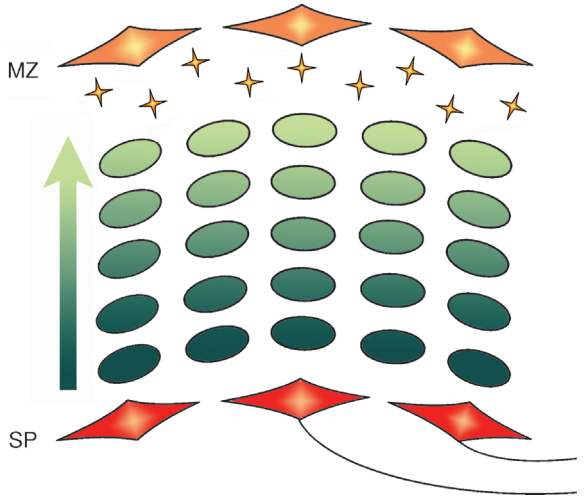

Figure 4 Lamination of the mammalian neocortex. The earliest cells to arrive at the embryonic cortex make up a preplate (not shown). The preplate becomes divided into two layers: a superficial marginal zone (MZ, future layer I), containing Cajal–Retzius cells (diamond-shaped cells above, brown) that secrete reelin (yellow stars), and a deep subplate (SP), containing pioneer neurons (diamond-shaped cells below, red) whose axon serves as a guide for growing thalamocortical axons. Cells that locate between these layers make up the cortical plate (green ovals) and arrange in five laminae (VI–II in the mature neocortex). These laminae are generated in an inside-out sequence in which early-produced neurons locate above late-produced ones (arrow represents progressively later neurogenetic times).

end up in the more superficial layers. This implies that late-produced neurons have to cross the layers of early-produced neurons and locate above them. Additionally, inhibitory neurons originating in the subpallium populate the developing cortical plate, also following an inside-out gradient in which early-produced cells arrive at deeper layers and late-produced cells arrive at superficial layers. This whole process contrasts with the situation of the much thinner reptilian cortex, where cells migrate in an outside-in sequence, early layers locating more superficially than late-produced layers.

Is there any correspondence between the reptilian cortical cells and the different layers making up the mammalian neocortex? Miguel Marín-Padilla originally proposed that neurons of the mammalian preplate (more specifically, those making up the subplate) were homologous to the reptilian cortex, the cortical plate being a developmental addition to the mammalian brain. However, other authors proposed that the mammalian preplate and the subplate emerged as devices to support the development of corticocortical connectivity in mammals. Instead of corresponding to the mammalian preplate, the reptilian cortex was claimed to be homologous to the deep neocortical layers V and (especially) VI of the mammalian cortical plate.

There are reports of a subplate-like structure in reptiles consisting of tangentially migrating interneurons, but no excitatory neurons have yet been described in it. On the other hand, in a marsupial, no subplate was detected and corticothalamic axons were seen directly penetrating the cortical plate, instead of establishing transient contacts below it as they do in placental mammals. If this observation is correct and true for all marsupials, it would imply that at least part of the subplate (its excitatory component, which receives arriving thalamic axons) is an acquisition of placental mammals. Moreover, in some mammals, including some marsupials, there is an adult cortical layer inferior to layer VI, termed layer VIb or VII, which contains persisting subplate cells. These cells have been considered to be closely related to the deepest neurons in the cortical plate. Furthermore, there is molecular evidence for an intimate relation between the inferior layers of the cortical plate and the subplate. The gene *Tbr1* marks both subplate neurons and the earliest cortical plate neurons, and mutations in this gene cause defects in both structures. Thus, in the origin of mammals (or of placental mammals), a subplate-like structure containing tangentially migrating neurons might have incorporated excitatory cells that originally belonged to the cortical plate, that aided in the guidance of thalamocortical axons.

Origin of the Superficial Neocortical Layers and the Inside-Out Neurogenetic Gradient

Additional molecular evidence supports the concept of the superficial neocortical layers IV–II as developmentally distinct from the inferior layers VI and V. Among other features, mutants for the gene *Pax6* exhibit cortical migration defects, consisting of the inability to migrate and differentiate supragranular neocortical neurons belonging to layers IV to II. Furthermore, early-produced cortical plate neurons destined to neocortical layers VI and V are produced in the embryonic ventricular zone and express the marker gene *Otx1*. On the other hand, late-produced neurons, which depend on *Pax6* for their development and are destined to superficial layers IV–II, are produced in the subventricular zone surrounding the ventricular zone, and express the marker gene *Svet1*. Thus, *Pax6* may be involved in the origin of the superficial neocortical layers by recruiting the subventricular zone in the neurogenetic process. Further findings indicate that the proneural genes *Ngn1* and *Ngn2* specify the laminar characteristics of early-born cortical neurons, but upper-layer cortical neurons are specified in an *Ngn*-independent manner, requiring instead the synergistic activities of *Pax6* and *Tlx*. There is also comparative evidence indicating a progressive development of the subventricular zone in large-brained mammals, its near absence in the reptilian embryonic dorsal cortex, and its independent development in the avian nidopallium. It will be of interest to determine what, if any, is the contribution of the subventricular zone and of the genes *Pax6*, *Svet1*, and *Tlx* to dorsal cortical development in reptiles.

In this context, the effect of mutations in some genes involved in the regulation of cortical cell migration has provided further clues to the development of the laminar organization of the neocortex. For example, the reeler mutant mouse, deficient in the extracellular protein reelin, shows a striking inversion of the developmental gradient in the cortical plate, in which early-produced neurons become located superficially and late-produced neurons arrange in the inferior layers. Furthermore, in this mutant the preplate is not split and is compressed above the cortical plate. In the adult, no cell-poor layer I is detectable, as the cortical plate cells are observed immediately below the subpial layer. Electron microscopy analyses indicate abnormal attachments between the neurons and the radial glia, suggesting that these neurons did not detach correctly from the latter. There have been several hypotheses for the participation of reelin in the control of neuronal migration, including a role as

a stop signal, as a glial detachment signal, or as an attractor for migrating neurons. Overall, the evidence indicates that reelin has a role in the final stages of neuronal migration and, more important to our purposes, in detaching migrating neurons from the radial glia, and in the generation of a cell-free superficial marginal zone. Reelin is present in several other brain regions besides the cerebral cortex, and its patterns of expression reflect an evolutionarily stable framework. However, reelin expression is strongly amplified in the mammalian cortical marginal zone in relation to the reptilian marginal zone, indicating that this molecule has been one key element in the origin of the neocortex. Furthermore, the level of reelin expression correlates with the degree of columnarity present in the dorsal cortex of different reptiles, suggesting that it may have contributed to the radial organization of the mammalian neocortex.

Another molecule of interest is the cyclin-dependant kinase cdk5; cdk5 and its activator, p35, are fundamental for the adequate lamination of the neocortex. Recently, two modes of radial migration have been characterized: nuclear translocation, in which the leading process of the neuron is attached to the subpial layer and the cell body is dragged toward the periphery as a consequence of the shortening of this process; and cellular locomotion, in which cells migrate along the radial glia in their pathway to the cortex. Interestingly, early-produced, deep-layer cortical neurons migrate mainly by translocation, while late-produced, superficial neurons use glial-guided locomotion to reach the cortical plate. Mutants for the enzyme cdk5 show strong deficits in locomotion, and therefore the superficial layers of the cortex fail to form. In these animals, neurons are not able to reach the cortical plate by birth and remain in the subcortical intermediate zone. However, early-produced layer VI cells which migrate by translocation do so correctly and are able to split the preplate normally. Moreover, mutants for the cdk5 activator p35 display milder defects in locomotion, and neurons from all layers are able to reach the cortical plate by birth. However, within the cortical plate, cells arrange in an inverted outside-in gradient reminiscent of the reeler mouse, but with the difference that the preplate has been partially split and there is a normal marginal zone. *N*-Cadherin-mediated cell aggregation in migrating neurons is inhibited by cdk5/p35, which provides a possible mechanism by which normally migrating cells may use this cascade to bypass a migration-suppressing signal (*N*-cadherin or a related molecule) present in postmigratory neurons, to move above them. Considering that early-produced cortical plate cells are more likely to correspond to reptilian cortical cells, it is conceivable that the cdk5-independent mechanism of translocation represents an ancestral condition, while the activation of the cdk5 pathway represents an evolutionary innovation of the mammalian brain, associated with new modes of neuronal migration and, by virtue of the activator p35, contributing to the generation of the inside-out neurogenetic gradient that is characteristic of the neocortex.

A Scenario for the Origin of Neocortical Lamination

Based on this evidence, a possible scenario for the evolution of cortical lamination is that initially there was a radial expansion of the primitive mammalian cortex, producing late-born, phylogenetically new neurons which participated in local processing circuits, as opposed to the older neurons that function as an output layer. These new elements originated in an expanded subventricular zone, by virtue of the action of the gene *Pax6*, among others. The acquisition of an inside-out neurogenetic gradient was possibly related to the ancestral organization of afferents to the primitive cortex. The neocortex differs from other structures, including the hippocampus, the olfactory cortex, and the reptilian cortex, in the strong radial organization of its inputs, in which afferents penetrate the cortical plate from the underlying white matter (aided by subplate cells and pioneer neurons); in these other structures the afferents arrange tangentially in the superficial marginal zone (**Figure 5**). Radial expansion of the primitive cortex in the context of a primitive outside-in developmental pattern would have left the new, local processing neurons located below the early-produced output neuronal layer, separating them from the superficially located afferents. In such context, there would be a benefit to those individuals in which late-produced neurons were able to cross the layer of early-produced cells, generating an intermediate layer between the input axons and the output cells. In other words, the inside-out neurogenetic gradient was produced in order to maximize synaptic contacts between the new, late-born neurons, and the superficially located cortical afferents. In this process, the cdk5 signaling pathway facilitated new mechanisms of radial migration, and especially its activator p35 was important in permitting late-born neurons to cross the barrier formed by previously migrated cells. Finally, an important increase in the expression of reelin by Cajal–Retzius cells permitted the preservation of a neuron-free marginal zone. Reelin also contributed to stop radial migration by detaching migrating neurons from the radial glia, thus facilitating the migration of young neurons past old ones.

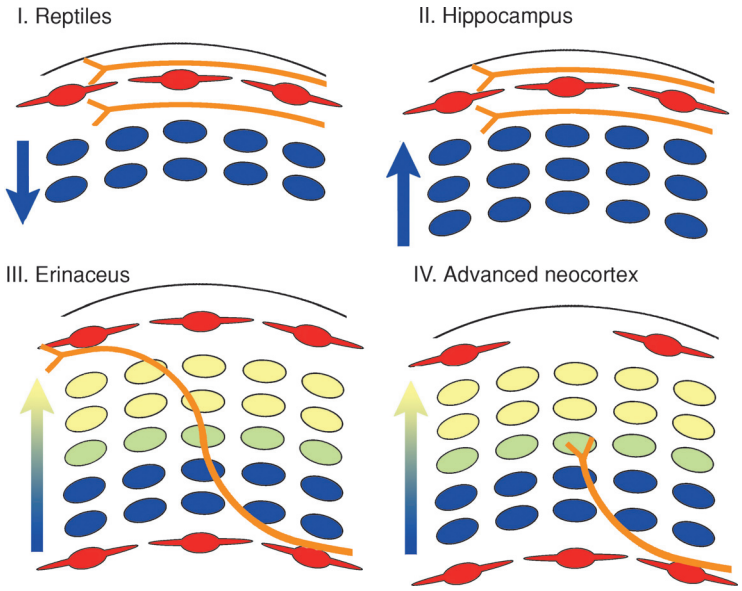

Figure 5 Postulated sequence in the evolution of neocortical lamination. In a primitive state (I) like that of reptilian cortex, with an outside-in neurogenetic gradient (arrow downwards), pioneer neurons (pointed ovals, red) locate in the superficial marginal zone and guide thalamocortical axons (Y-shaped lines) tangentially above the cortex (ovals, blue, green, and yellow). A second stage (II) may be exemplified by the hippocampus, which already displays an inside-out gradient (arrow upwards) while its afferents are located superficially. The neocortex of the hedgehog (Insectivora) represents a third stage (III), where axons enter the cortical plate from below but many run obliquely and end tangentially in the marginal zone. Finally (IV), the primary sensory cortex of advanced mammals displays axons radially entering the cortex and synapsing with neurons in layer IV, and a large proportion of pioneer neurons locate in the subplate below the cortex.

As the neocortex expanded tangentially, however, the distance traveled by tangential afferent axons became increasingly longer, with a consequent impairment in transmission time. A solution to this problem was provided by the rerouting of these axons via the subcortical white matter, making a shortcut to their final targets. This was possible by virtue of the displacement of the pioneer neurons attracting the thalamic afferents, from a superficial position in the marginal zone of reptiles, to a deeper position in the subplate of mammals. Thus, there were several steps in the acquisition of a neocortex, including the increase in cortical thickness, the origin of the inside-out gradient, and the displacement of axonal trajectories from a superficial to a subcortical position. Interestingly, intermediate stages may be found between the reptilian cortex, displaying superficial, tangential inputs, and the advanced mammalian neocortex, with radially organized inputs. For example, like the neocortex, the hippocampus has an inside-out developmental gradient, but also a superficial localization of afferents, indicating a step above the reptilian cortex. A subsequent stage may be represented by the neocortex of the primitive insectivore *Erinaceus*, in which axons penetrate the cortex radially from the underlying white matter, cross obliquely to the marginal zone, and run tangentially there for some distance. Finally, in the sensory neocortex of advanced mammals, afferents enter the cortex radially and synapse in spiny stellate neurons of layer IV (Figure 5).

Final Comments

Summarizing the views presented here, the mammalian neocortex displays several unique characteristics and therefore the term 'neocortex' is indeed appropriate. One main dicussion in relation to its origins concerns the ancestral structure that gave rise to it. There are two main proposals in this regard, one that claims that the neocortex partly arose from the DVR of reptiles, and the other that prescribes that it originated as an expansion of the dorsal pallium. Current developmental evidence tends to favor the latter, as the reptilian DVR has embryonic origins similar to those of the mammalian claustroamygdalar complex in the ventral pallium. The neocortex is also unique in its laminar structure. Recent genetic and developmental analyses have provided important insights as to the mechanisms and possible sequence of events that gave rise to the neocortex, producing its characteristic inside-out neurogenetic gradient and the rerouting of thalamic afferents from a superficial to a deep, subcortical position. All this evidence strengthens the view that development may not only give clues to evolutionary processes, but also that variations in the developmental processes are the main events in the generation of new structures in evolution.

See also: Cerebral Cortex; Evolution of Vertebrate Brains; Homology and Homoplasy.

Further Reading

Aboitiz F, Montiel J, and García RR (2005) Ancestry of the mammalian preplate and its derivatives: Relicts or embryonic adaptations. *Reviews in the Neurosciences* 16: 359–376.

Aboitiz F, Morales D, and Montiel J (2003) The evolutionary origin of the mammalian isocortex: Towards an integrated developmental and functional approach. *Behavioral and Brain Sciences* 26: 535–586.

Bar I, Lambert de Rouvroit C, and Goffinet A (2000) The evolution of cortical development. An hypothesis based on the reelin signaling pathway. *Trends in Neuroscience* 23: 633–638.

Bruce LL and Neary TJ (1995) The limbic system of tetrapods: A comparative analysis of cortical and amygdalar populations. *Brain, Behavior and Evolution* 46: 224–234.

Butler AB and Hodos W (1996) *Comparative Vertebrate Neuroanatomy. Evolution and Adaptation.* New York: Wiley-Liss.

Caviness VS, Crandall JE, and Edwards MA (1988) The reeler malformation. Implications for neocortical histogenesis. In: Peters A and Jones EG (eds.) *Cerebral Cortex, Vol. 7. Development and Maturation of the Cerebral Cortex*, pp. 59–89. New York: Plenum.

Doron NN and LeDoux JE (1999) Organization of projections to the lateral amygdala from auditory and visual areas of the thalamus in the rat. *Journal of Comparative Neurology* 412: 383–409.

Goffinet AM, Daumerie C, Langerwerf B, and Pieau C (1986) Neurogenesis in reptilian cortical structures: ^{3}H-thymidine autoradiographic analysis. *Journal of Comparative Neurology* 243: 106–116.

Karten HJ (1997) Evolutionary developmental biology meets the brain: The origins of mammalian neocortex. *Proceedings of the National Academy of Sciences of the United States of America* 94: 2800–2804.

Kriegstein AR and Noctor SC (2004) Patterns of neuronal migration in the embryonic cortex. *Trends in Neuroscience* 27: 392–399.

Marín-Padilla M (1978) Dual origin of the mammalian neocortex and evolution of the cortical plate. *Anatomy and Embryology* 152: 109–126.

Molnár Z, Métin C, Stoykova A, et al. (2006) Comparative aspects of cerebral cortical development. *European Journal of Neuroscience* 23: 921–934.

Nadarajah B and Parnavelas JG (2002) Modes of neuronal migration in the developing cerebral cortex. *Nature Reviews Neuroscience* 3: 423–432.

Northcutt RG and Kaas JH (1995) The emergence and evolution of mammalian neocortex. *Trends in Neuroscience* 18: 373–379.

Powers AS (1990) Brain mechanisms of learning in reptiles. In: Kesner RP and Olton DS (eds.) *Neurobiology of Comparative Cognition*, pp. 75–87. New York: Erlbaum Press.

Puelles L, Kuwana E, Puelles E, et al. (2000) Pallial and subpallial derivatives in the embryonic chick and mouse telencephalon, traced by the expression of the genes Dlx-2, Emx-1, Nkx-2.1, Pax-6 and Tbr-1. *Journal of Comparative Neurology* 424: 409–438.

Schuurmans C, Armant O, Nieto M, et al. (2004) Sequential phases of cortical specification involve neurogenin-dependent and -independent pathways. *EMBO Journal* 23: 2892–2902.

SmithFernández A, Pieau C, Repérant J, et al. (1998) Expression of the Emx-1 and Dlx-1 homeobox genes defines three molecularly distinct domains in the telencephalon of mouse, chick, turtle and frog embryos: Implications for the evolution of telencephalic subdivisions in amniotes. *Development* 125: 2099–2111.

Striedter GF (2005) *Principles of Brain Evolution.* Sunderland, MA: Sinauer Associates.

Supèr H and Uylings HB (2001) The early differentiation of the neocortex: A hypothesis on neocortical evolution. *Cerebral Cortex* 11: 1101–1109.

Sur M and Rubenstein JL (2005) Patterning and plasticity of the cerebral cortex. *Science* 310: 805–810.

Voogd J, Nieuwenhuys R, and VanDongen PAM (1998) Mammals. In: Nieuwenhuys R, Ten Donkelaar HJ, and Nicholson C (eds.) *The Central Nervous System of Vertebrates,* vol. 3, pp. 1637–2098. Berlin: Springer.