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The evolutionary origin of the mammalian isocortex: Towards an integrated developmental and functional approach

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Abstract: The isocortex is a distinctive feature of mammalian brains, which has no clear counterpart in the cerebral hemispheres of other amniotes. This paper speculates on the evolutionary processes giving rise to the isocortex. As a first step, we intend to identify what structure may be ancestral to the isocortex in the reptilian brain. Then, it is necessary to account for the transformations (developmental, connectional, and functional) of this ancestral structure, which resulted in the origin of the isocortex. One long-held perspective argues that part of the isocortex derives from the ventral pallium of reptiles, whereas another view proposes that the isocortex originated mostly from the dorsal pallium. We consider that, at this point, evidence tends to favor correspondence of the isocortex with the dorsal cortex of reptiles. In any case, the isocortex may have originated partly as a consequence of an overall "dorsalizing" effect (that is, an expansion of the territories expressing dorsal-specific genes) during pallial development. Furthermore, expansion of the dorsal pallium may have been driven by selective pressures favoring the development of associative networks between the dorsal cortex, the olfactory cortex, and the hippocampus, which participated in spatial or episodic memory in the early mammals. In this context, sensory projections that in reptiles end in the ventral pallium, are observed to terminate in the isocortex (dorsal pallium) of mammals, perhaps owing to their participation in these associative networks.

Keywords: basolateral amygdala; claustrum; Emx-1; endopiriform nucleus; dorsal cortex; dorsal ventricular ridge; hippocampus; homology; olfactory cortex; Pax-6; ventral pallium

1. Introduction

The study of brain evolution has been hampered by difficulties related to the complexity of this organ, which makes difficult the comparisons among different taxa; and by the relative lack of plausible scenarios proposing specific mechanisms by which transformations of brain structure may have taken place. The first attempts in comparative neuroanatomy date from at least two centuries ago, and were mainly based on analyses of distinct cell masses from histological sections of developing and adult brains of different species (Ariëns Kappers et al. 1936; Ramón y Cajal 1995). With the advent of tract-tracing techniques in the mid-twentieth century, a new era appeared which permitted visualization of the connectivity between these brain components and identification of similarities and differences in network organization among species (Heimer 1970; Nauta & Gygax 1951; 1954; Nauta & Karten 1970). Powerful histochemical and immunochemical techniques subsequently have been applied to the nervous system. These procedures permitted identification of neurochemical markers (neurotransmitters, cell adhesion molecules, cytoskeletal components, and other elements) that labeled specific neuronal populations, thus providing finer-grained observations on the anatomical arrangements and development of different cell masses (Parent & Olivier 1970). More recently, molecular techniques based on the analysis of gene expression have proved to be particularly fruitful for determining genes involved in the development of distinct brain components and for making cross-species correspondences.

Although each of these different strategies has a value of its own, unfortunately some of these techniques have been used to validate discrepant interpretations of brain evolution. For example, when searching for homologue structures, one may look for nuclei with similarities in connectivity, or for nuclei with a common developmental origin. If these two criteria agree, there will obviously be no problem, but if they disagree, one has to think that only one (or neither) of these criteria is valid. Furthermore, if, say, connections are considered to be more reliable indicators of ho-

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mology, then one should explain how the structures acquired different developmental origins during evolution. Conversely, if developmental criteria are found to be stronger, then one should explain how the connectivity of these nuclei has changed in evolution. In this sense, when different criteria for homology disagree, one is forced to propose an explanation of how only some homology criteria are valid in that particular case, and must also offer a plausible mechanism (a scenario) to account for the observed differences.

In this target article, we address the issue of the evolutionary origin of the mammalian isocortex, which has been amply debated in recent years. We first discuss different proposals about this structure's homology with specific brain components in reptiles and birds (these two taxa together are called *sauropsida*), and provide arguments to validate the criteria that we will embrace. Next, we propose a scenario of isocortical origins, integrating both developmental and connectional/functional evidence, to account for some of the discrepancies in the homology criteria. In other words, we present an integrative hypothesis, combining different lines of evidence into a coherent proposal about the early evolution of the mammalian isocortex. Briefly, our suggestion is that the mammalian isocortex originated in large part as a consequence of a "dorsalizing" influence in pallial development. This means that (1) genes specifying the fate of dorsal territories in the embryonic pallium may have increased their domains of expression, perhaps at the expense of the expression of genes specifying lateral or ventral phenotypes; (2) cells from other brain compartments contributed to the developing dorsal pallium (although perhaps not massively); and (3) there may have been an increased production of progenitor cells in the dorsal pallium and other brain regions, leading to an increase in brain size. This may have occurred as a consequence of the development of olfactory-hippocampal associative networks in primitive mammals, and the progressive incorporation of the dorsal cortex into this network. This process was accompanied by major changes in the pattern of termination of some sensory afferents into the pallium, especially those sensory pathways that use the mesencephalon as a relay to access the thalamus.

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2. The problem of isocortical origins

The mammalian isocortex is a character unique to mammals in several respects. First, it has undergone an enormous expansion, especially in the tangential domain (Rakic 1988). Second, it has a six-layered architecture, which differs from the three-layered array of simpler telencephalic laminar structures such as the hippocampal formation, the olfactory cortex, and the reptilian cortices (Supèr et al. 1998b). Although in other vertebrates there are some expanding telencephalic structures that receive a similar sensory input, in no case has such a conspicuous laminar arrangement been observed (Striedter 1997).

There have been important disagreements as to which components of the non-mammalian telencephalon can be compared to the isocortex. This problem is complicated by the intricate topography of the hemispheres in some vertebrate classes and by the absence of a single criterion to establish the homology of neural structures. Commonly used criteria for similarity are connectivity (Bruce & Neary 1995; Butler 1994a; 1994b; Karten 1969; 1997; Medina & Reiner 2000; Reiner 2000), neurochemistry (Reiner 1991; 1993), and embryonic origins (Aboitiz 1992; 1995; Källén 1951; Puelles et al. 1999; 2000; Smith Fernández et al. 1998; Striedter 1997). Unfortunately, when intending to identify structures homologous to the isocortex, there have been discrepant conceptions derived from these different approaches.

In order to understand its origins, we first need to establish which structure gave rise to the isocortex. For this, we need to select some homology criteria as the most reliable, while rejecting other criteria. However, while doing this, we also need to address the fact that the rejected criteria may indicate important differences between the isocortex and its homologue. Below, we briefly outline some aspects of brain organization in vertebrates and discuss the different hypotheses of homology that have been proposed. After that, we offer a developmental and a connectional/behavioral scenario, which may account for early isocortical evolution. Finally, we review some evidence on fossil mammals which bears relation to isocortical origins.

3. The cerebral hemispheres of vertebrates

3.1. Taxonomical relations

Vertebrates – or craniates – are divided into *agnathans* (jawless vertebrates like the lamprey) and *gnathostomes* (jawed vertebrates like most fish and all terrestrial verte-

brates). Among gnathostomes, there are the *chondrychthian* fish (sharks, rays, and related cartilaginous fish) and the *osteichthies* or bony fish. *Sarcopterygians* are a group of bony fish that are considered related to the ancestors of terrestrial vertebrates. Terrestrial vertebrates are divided into anamniotes (amphibians) and amniotes (reptiles, birds, and mammals). Amniotes are those vertebrates whose embryological development occurs within an amniotic cavity (either within the egg as in reptiles, birds, and monotreme mammals, or inside the maternal uterus as in marsupials and placental mammals), and thus are able to reproduce outside the water (see Fig. 1). The basic stock of amniotes is considered to be represented by the stem reptiles, from which different groups diverged in the Paleozoic period. Reptiles have been usually classified on the basis of the pattern of openings in the dermal skull behind the orbits. In primitive amniotes (subclass *anapsida*), there are no openings and the roof of the skull is completely covered by bone. Members of this class include fossil reptiles, and some authors have placed turtles among them, based on the absence of cranial openings in this group (see Carroll 1988). For this reason, turtles have been considered in many instances to be the reptiles closest to the point of reptilian-mammalian divergence, and their brains have been considered as models of the ancestral amniote brain. However, some paleontologists have considered the inclusion of turtles into the subclass anapsida somewhat arbitrary, as it disregards many other aspects which strongly suggest that this group is rather a highly derived one (see Carroll 1988). Moreover, recent phylogenetic analyses based on morphology and on molecular evidence place turtles as a rather modified group of reptiles, with no direct relation to the ancestral anapsids (Mannen & Li 1999; Rieppel & Reisz 1999; Zardoya & Meyer 2001). Therefore, the absence of temporal openings in the skull of turtles may be secondary and not reflect an ancestral condition.

Another reptilian subclass is represented by the *synapsid* condition (with one cranial opening), which is exemplified by the mammal-like reptiles from which the first mammals emerged (Fig. 1). Synapsid reptiles were the first group of amniotes to be abundant and diversified, and their relations with the presumed ancestral anapsid stock are obscure. It is likely that the mammal-like reptiles emerged quite early from the ancestral amniote stock. The *diapsid* reptilian condition (Fig. 1), in which there are two postorbital openings, possibly originated from a group of anapsid reptiles. This subclass represents most living reptiles and includes two main groups: *lepidosaura,* with lizards, snakes, and a primitive New Zealand reptile called the tuatara; and *archosaura,* which includes crocodiles, dinosaurs, and birds. According to some phylogenetic analyses mentioned above, turtles may also belong to the diapsids. Finally, there is the subclass *parapsida,* represented by fossil ichthyosaurs and plesiosaurs (Carroll 1988).

3.2. A brief history of the pallium

The cerebral hemispheres can be subdivided into a dorsal part or pallium (divided into medial, dorsal, lateral, and ventral pallium; see below), and a ventral part or subpallium (see Fig. 2). In agnathans, the olfactory bulbs project heavily upon the whole pallial surface (Northcutt 1996a; Northcutt & Puzdrowski 1988; Wicht & Northcutt 1992; 1993; Wicht 1996), and there is evidence that a true dorsal pallium may be lacking at least in some species (Myojin et al. 2001). In gnathostomes, the olfactory projection occupies a

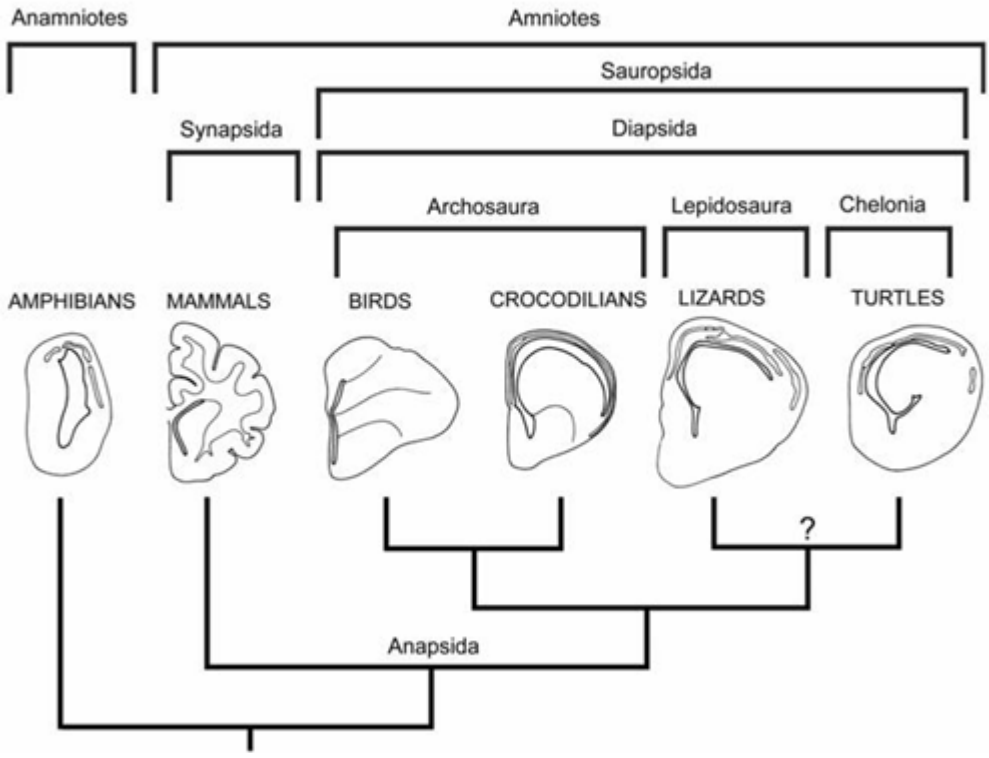

Figure 1. Cladogram indicating phylogenetic relationships in tetrapods. In each crown taxon, a figure of a coronal section of one cerebral hemisphere (only one hemisphere is shown; lateral is to the right and medial is to the left) of a representative species is included.

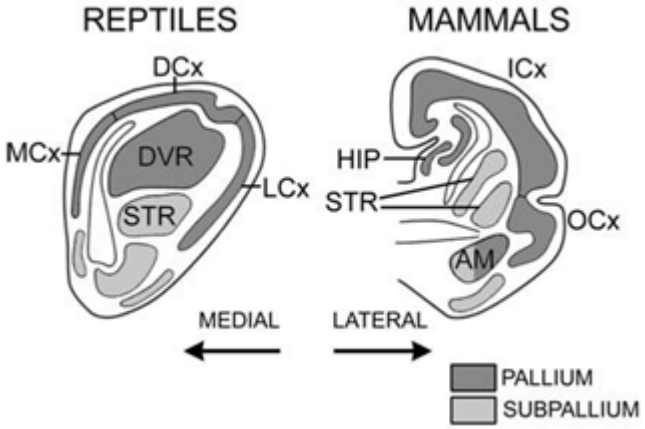

Figure 2. The main components of the amniote cerebral hemispheres (coronal sections of only one hemisphere are shown; lateral is to the right). The pallium of reptiles consists of a medial cortex (MCx), a dorsal cortex (DCx), a lateral cortex (LCx), and a large part of the periventricular dorsal ventricular ridge (DVR). Interposed between the medial and the dorsal cortex, a dorsomedial cortex is observed in many reptiles. In mammals, the pallium consists of the hippocampal formation (HIP, which is comparable to the MCx and the dorsomedial cortex), the isocortex (ICx), the olfactory cortex (OCx, comparable to the reptilian LCx), and part of the claustroamygdaloid complex (AM). The subpallium of both reptiles and mammals include the basal ganglia, of which a main component is the corpus striatum (STR). In reptiles, part of the posterior DVR may be of subpallial origin, while in mammals part of the amygdalar complex is also subpallial.

much more restricted portion of the pallium, being usually confined to the lateral aspect of this structure (Ebbesson & Heimer 1970; Northcutt & Kaas 1995; Smeets 1983). The acquisition of predatory lifestyles by the early gnathostome vertebrates, involving the further development of other sensory modalities, implied the progressive development of ascending visual, somatosensory, and lateral line afferents to the pallium (Northcutt & Puzdrowski 1988; Wicht 1996; Wicht & Northcutt 1992; 1993). The expansion of these sensory projections, which are relayed to the hemispheres via the diencephalon, was concomitant with the enlargement of the telencephalic components receiving the respective inputs (Northcutt 1981; Northcutt & Puzdrowski 1988; Striedter 1997; Wicht 1996; Wicht & Northcutt 1992; 1993). With the exception of amphibians, which are considered to have a secondarily simplified brain (Neary 1990; Northcutt 1981), this phenomenon is also evident among terrestrial vertebrates.

The pallium of amphibians consists in large part of periventricular cells that show a limited degree of radial migration, and do not make up a true cortical architecture. The amphibian pallium has been subdivided into lateral, dorsal, and medial components (Bruce & Neary 1995; Neary 1990). Based in large part on the relative absence of direct olfactory input and on the presence of at least thalamic visual and somatosensory projections, the medial pallium has been considered to be comparable to both the medial/dorsomedial cortex and the dorsal cortex of reptiles (or the hippocampus and the isocortex of mammals, respectively; Bruce & Neary 1995; see also Ten Donkelaar 1998a; 1998c). On the other hand, the dorsal pallium receives substantial input from the main olfactory bulb, and has been compared to parts of the lateral and olfactory cortices of reptiles and mammals. The lateral pallium of amphibians is subdivided into a dorsal component, also comparable to parts of the lateral cortex of amniotes, and a basal part which is comparable to the basolateral amygdalar complex of mammals and perhaps to the dorsal ventricular ridge (DVR) of birds and reptiles. In amphibians, there is also a caudal striatum (subpallial), which has been considered to be homologous to the striatal amygdala of reptiles and to the central amygdalar complex of mammals (Bruce & Neary 1995).

The reptilian pallium (Fig. 2) has a three-layered cortex, consisting of a medial and a dorsomedial moiety (both comparable to the mammalian hippocampal formation), plus a lateral (olfactory) cortex (Ulinski 1990), and finally a dorsal cortex (equivalent to the Wulst of birds) located between these two. Part of the dorsal cortex receives visual projections from the dorsal lateral geniculate nucleus, as well as some somatosensory input (Medina & Reiner 2000). In reptiles and birds, many non-olfactory sensory projections terminate in a prominent periventricular structure called the dorsal ventricular ridge (DVR; Fig. 2) (Ten Donkelaar 1998c; Ulinski 1983). The DVR is the most expansive telencephalic component of reptiles and birds, and is a main integratory center in their brains. It consists of an anterior part (ADVR) and a posterior or basal part (PDVR). The ADVR receives much of the sensory input, and its output is directed mainly to the subpallial corpus striatum and to the PDVR. The latter (corresponding to the archistriatum in birds) has been compared to parts of the mammalian amygdala and projects mainly to the hypothalamus (Lanuza et al. 1998; 1999; Ten Donkelaar 1998c).

Mammals are characterized by the possession of the isocortex (Fig. 2), which, during development, originates at least in large part from the dorsal pallium (Northcutt & Kaas 1995; Rakic 1988; 1995). Recent studies in mammals indicate that additionally, cells originating in the embryonic ganglionic eminences migrate tangentially in a dorsal direction and become incorporated into the isocortex, mostly as GABAergic interneurons (Anderson et al. 1997a; 1999; 2001; Lavdas et al. 1999; Marín & Rubenstein 2001; Nadarajah & Parnavelas 2002; Nery et al. 2002; Parnavelas 2000). The fact that tangentially migrating interneurons have also been observed migrating into the DVR and other pallial regions of birds (Cobos et al. 2001) suggests that the acquisition of this character predates the origin of mammals and the isocortex. The isocortex receives ascending sensory input from the thalamus and projects to the hippocampus and to the amygdala, as well as sending output to many lower brain centers including the thalamus, corpus striatum, various brainstem nuclei, and the spinal cord. Medial to the isocortex is the hippocampal formation, and lateral to it is the olfactory cortex. Finally, there is a claustroamygdaloid complex in the ventral pallium, containing both pallial and subpallial elements (Fig. 2).

3.3. The basal ganglia (subpallium)

A main component of the subpallium are the basal ganglia, which embryologically derive from the medial, lateral, and caudal ganglionic eminences (MGE, LGE, and CGE), which give rise to the corpus striatum, to the globus pallidus, and to some amygdalar components, respectively (see Fig. 2). The evolution of the basal ganglia has been rather conservative in the history of vertebrates (Marín et al. 1998; Medina & Reiner 1995; Smeets et al. 2000). However, a few changes in striatal output have taken place in mammals. One of these consists of the pathways connecting the basal ganglia with the mesencephalic optic tectum. There are

multiple pathways for this connection, of which the most important are a ventral route via the substantia nigra which is present in all tetrapods, and a dorsal route via the pretectal nuclei. The pretectal pathway is most developed in anurans, some lizards, turtles, crocodiles, and birds, although it is weak or absent in urodeles, some lizards, snakes, and mammals, suggesting that it is a highly variable trait (Marín et al. 1998). In addition, some authors have described in mammals an emphasis of projections from the basal ganglia to the dorsal thalamus, which in turn projects to the isocortex (Brauth 1990; Medina & Reiner 1995). This perhaps has some relation to the loss of the pretectal pathway from the basal ganglia to the optic tectum (in mammals, the optic tectum is significantly reduced in relative size), and may be concomitant with the development of the mammalian corticospinal tract. In reptiles, projections from the basal ganglia to the dorsal thalamus appear to be less developed, although there has been an independent development of pallido-thalamic connections in birds (Brauth 1990). Finally, one important difference between reptiles and mammals is that the corpus striatum, whose more prominent input may be from the ADVR in reptiles, receives a major projection from the isocortex in mammals.

4. Diverging concepts of homology in pallial organization

Two alternative hypotheses have been raised regarding the origins of the mammalian isocortex, which have been elegantly summarized by Northcutt and Kaas (1995) as the "recapitulation hypothesis" and the "out-group hypothesis" (Fig. 3). Proponents of the recapitulation hypothesis suggest that a dorsal ventricular ridge (DVR)-like structure existed in the common ancestor of mammals and reptiles, which became somehow transformed into parts of the isocortex in the origin of mammals. According to the outgroup hypothesis, the common ancestor of reptiles and mammals would have had a cerebral hemisphere similar in its topographic organization to that of present-day amphibians. In this case, the most likely candidate for homology with the isocortex is the reptilian dorsal cortex, which derives from the dorsal pallium. Proponents of the recapitulation hypothesis mostly focus on similarities of sensory projections between the DVR and the isocortex, while proponents of the outgroup hypothesis have usually put weight on developmental evidence. Below, we will consider some of the evidence argued in favor of each of these hypotheses.

4.1. Connectional and neurochemical similarities between reptilian pallial fields and the mammalian isocortex

The dorsal cortex of reptiles and its avian equivalent, the Wulst, are considered to be homologous to both the striate or primary visual cortex and the somatosensory cortex of mammals, as all these structures receive similar sensory projections (Karten 1997; Medina & Reiner 2000; Nauta & Karten 1970; Shimizu & Karten 1993). More precisely, the visual projections from the retina to the thalamic dorsal lateral geniculate nucleus (the so-called thalamofugal visual pathway; see Fig. 4) terminate in the posterior dorsal cortex/Wulst of sauropsids and in the striate cortex of mammals, respectively. In addition, the somatosensory spinothalamic and the dorsal column-medial lemniscus pathways project to the anterior dorsal cortex/Wulst of sauropsids and to the somatosensory cortex of mammals (Medina & Reiner 2000; Wild 1997).

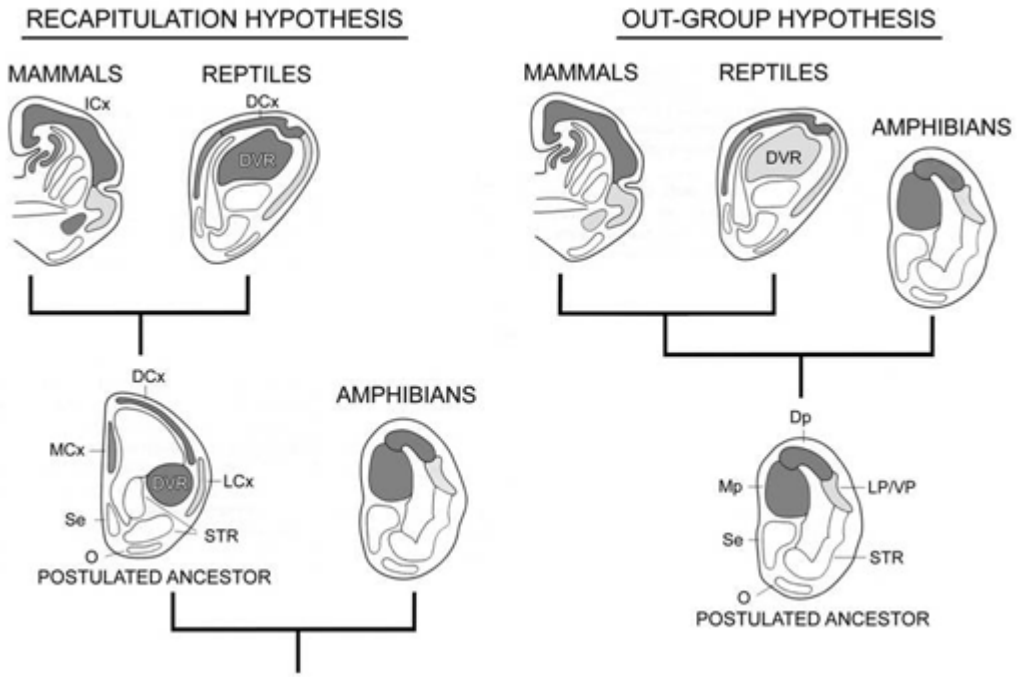

Figure 3. In the recapitulation hypothesis, the common ancestor of mammals and reptiles had a DVR-like structure which evolved into the isocortex in mammals and into the DVR of reptiles. In the out-group hypothesis, the DVR appears as a derived structure of reptiles and birds. O = olfactory tuberculum; Se = septum. Other abbreviations as in Figure 2.

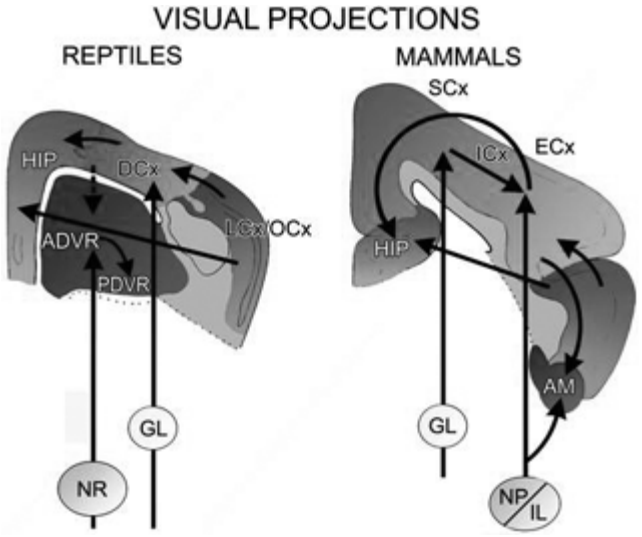

Figure 4. Diagrams summarizing some visual projections in mammals and in reptiles. Visual projections originate in the retina and project in two separate pathways: the thalamofugal or lemniscal path (LEM/TAF), which is directed to the dorsal lateral geniculate nucleus (GL), and from there to the dorsal cortex (DCx) in reptiles and to the primary or striate visual cortex (SCx) in mammals. The second visual route is the mesencephalic or tectofugal pathway (MES/TEF), that projects from the retina to the mesencephalic optic tectum (or superior colliculus). In reptiles, this pathway then synapses in the thalamic nucleus rotundus (NR) and from there projects to the reptilian anterior dorsal ventricular ridge (ADVR). In mammals, this pathway projects to the pulvinar nucleus (NP) and to the extrastriate visual cortex (ESt). There is some controversy as to whether the NR and the NP can be considered homologous (see text). Other two important sensory pathways (not shown) are the somatosensory pathways and the auditory pathway. In both mammals and reptiles, the somatosensory system contains a lemniscal component (spinothalamic and dorsal column pathways), that does not synapse in the mesencephalic colliculi before reaching the thalamus. These pathways end in the reptilian dorsal cortex and in the mammalian somatosensory cortex. On the other hand, the auditory pathway is a "mesencephalic" or collicular one that has an important mesencephalic relay (in the reptilian torus semicircularis or mammalian inferior colliculus) before reaching the thalamus. The auditory pathway ends in the reptilian ADVR and in the mammalian auditory cortex.

Additionally, the lateral cortex (LCx) or olfactory cortex (OCx) projects to the medial/dorsomedial cortex (MCx) in reptiles and to the hippocampus (HP) in mammals. The reptilian dorsal cortex (DCx) has connections with the MCx. In mammals, the primary visual cortex (SCx) exerts control over the extrastriate visual areas (ECx); all sensory isocortical areas indirectly project to the hippocampus (HIP). The reptilian posterior dorsal ventricular ridge (PDVR) is related to parts of the mammalian amygdalar system and receives projections from the ADVR. All other abbreviations as in Figure 2.

In addition to the thalamofugal visual pathway described above, there is a tectofugal visual pathway, which originates in the retina and projects to the mesencephalic optic tectum or superior colliculus. From there, this pathway is directed to the reptilian/avian thalamic nucleus rotundus and to the mammalian pulvinar nucleus, to end in the cerebral hemispheres (see Fig. 4). In the telencephalon, the tectofugal visual pathway ends in the avian/reptilian dorsolateral ADVR and in the mammalian extrastriate visual cortex. Furthermore, the auditory pathway terminates in the ventromedial ADVR of reptiles and in the mammalian auditory cortex. This similarity in sensory connectivity has been claimed to support the concept of homology between the DVR of reptiles and the visual extrastriate and auditory cortices of mammals (Karten 1968; 1997; Nauta & Karten 1970; Shimizu & Karten 1993). Furthermore, relying on similarities in intrinsic connectivity, it has been proposed that the avian ectostriatum (a component of the neostriatum), the rest of the neostriatum and the archistriatum correspond to the mammalian visual extrastriate cortical layers IV, II-III and V-VI, respectively (Karten 1997; Nauta & Karten 1970; Shimizu & Karten 1993; Veenman et al. 1995). Both the ectostriatum of birds and the isocortical layer IV of mammals receive thalamic afferents; these structures project to other parts of the avian neostriatum and to the layers II-III of the mammalian isocortex respectively, which themselves project to the archistriatum and to isocortical layers V-VI. Summarizing, this hypothesis (recapitulationist; Fig. 3) implies that the mammalian isocortex has a dual origin, one from the dorsal cortex of reptiles and corresponding to the striate visual cortex and the somatomotor cortex, the other from a structure homologous to the DVR of reptiles and corresponding to the auditory cortex (receiving the auditory projection) and to the extrastriate visual cortex (associated to the tectofugal visual pathway).

In agreement with this interpretation, Butler (1994a; 1994b) has classified dorsal thalamic nuclei as either *lemnothalamic* or *collothalamic. Lemnothalamic* nuclei receive projections from lemniscal systems, which do not synapse in the mesencephalic colliculi, like the visual thalamofugal pathway (which relays on the lateral geniculate nucleus), and the somatosensory, spinothalamic, and dorsal column pathways (see Fig. 4). *Collothalamic* nuclei receive sensory projections from the mesencephalic colliculi (like the visual tectofugal and the auditory pathways). Lemnothalamic nuclei project to the dorsal cortex of reptiles and birds, and to the more medial/dorsal aspects of the isocortex of mammals (such as the striate or primary visual cortex and the somatosensory cortex), whereas collothalamic nuclei project to the ADVR of reptiles and birds, and to more lateral/ventral regions of the mammalian isocortex (such as the extrastriate visual cortex and the auditory cortex).

In terms of neurotransmitter contents, the DVR resembles the reptilian dorsal cortex and the mammalian infragranular isocortical layers (Reiner 1993). The granular and supragranular isocortical layers differ from these structures in that some of their cells possess neurotransmitters (CCK8, VIP, and acetylcholine) that are absent in reptiles and in the infragranular isocortical layers.

4.2. Differences in connectivity between the DVR and the isocortex

Other connectional evidence points to important differences between the reptilian DVR and the mammalian isocortex. First, the mammalian extrastriate visual cortex receives an important input from the primary or striate visual cortex (Montero 1993; Rosa & Krubitzer 1999). Although in reptiles, projections from the dorsal cortex to the DVR have been described (Ten Donkelaar 1998b; Ulinski 1990), these projections do not exert a significant influence. Secondly, the mammalian isocortex projects reciprocally to the entorhinal cortex and from there to the hippocampus (Haberly 1990; Insausti 1993; Rosene & Van Hoesen 1987;

Van Hoesen 1982), while in reptiles few connections have been reported from the DVR to the medial/dorsomedial cortex or hippocampus (Ten Donkelaar 1998b; Ulinski 1983; 1990). Note that, in this regard, the mammalian isocortex resembles more the reptilian dorsal cortex, which has important connections with the medial/dorsomedial cortices (Ulinski 1990; Fig. 4). Finally, the main termination of sensory projections is not always in comparable structures. In amphibians, the auditory and tectal visual pathways terminate mainly in the corpus striatum, which is clearly not homologous to either the isocortex or the DVR (Ten Donkelaar 1998a; Wilczynski & Northcutt 1983).

Moreover, based on comparisons of connectivity, Bruce and Neary (1995) have argued that the reptilian DVR is most similar to the mammalian lateral amygdala, since both structures receive projections from collothalamic nuclei and both project to the corpus striatum, the striatal amygdala, and the ventromedial hypothalamus. (More precisely, the reptilian ADVR would correspond to the mammalian basolateral amygdala, while the whole DVR might correspond to the whole lateral amygdalar nucleus.) On the other hand, the isocortex projects to many other brain regions in the brainstem and spinal cord, and does not project to the hypothalamus. These authors claim that fewer changes in connectivity are required, by assuming homology between the lateral amygdala of mammals and the DVR of reptiles, than by considering homology between the isocortex and the DVR.

One particularly relevant aspect in this discussion concerns the thalamic pulvinar nucleus of mammals. This nucleus receives projections from the superior colliculus and projects to the extrastriate visual isocortex, and has been considered to be homologous to the reptilian or avian nucleus rotundus, which receives projections from the optic tectum and sends efferents to the ADVR (Fig. 4; Butler 1994b). Furthermore, Major et al. (2000) recently described marked similarities of the dendritic morphology of motion-sensitive tectopulvinar neurons in mammals and birds. In both groups, such neurons have dendritic arborizations that end in monostratified arrays of spiny terminal specializations called "bottlebrush" endings. The presumed homology between the pulvinar and the rotundus nuclei has been a strong element in the theory of homology between the lateral isocortex and the DVR, since these two nuclei have been considered to form part of the collothalamic, tectofugal visual pathway in mammals and reptiles, respectively. According to Bruce and Neary (1995), because in mammals the thalamic nuclei projecting to the lateral amygdala belong to the intralaminar complex, these nuclei and not the pulvinar nucleus should be considered homologous to the thalamic nucleus rotundus of reptiles and birds. Supporting this interpretation, recent reports have emphasized the fact that the mammalian pulvinar nucleus receives a different type of tectal projections than the reptilian rotundus; the pulvinar receives axons from late-born, superficial collicular layers, whereas the rotundus receives axons from early-born, deep collicular layers (Dávila et al. 2000; 2002; Guirado et al. 2000; Redies et al. 2000; Yoon et al. 2000). These authors subdivide the thalamic nuclei into three tiers: the intermediate and ventral tiers receive projections from the mesencephalic colliculi, and the dorsal tier receives projections from lemniscal systems. According to this view, the reptilian nucleus rotundus and the mammalian intralaminar nuclei might correspond to intermediate tier nuclei, while the mammalian pulvinar might be a dorsal tier nucleus which acquired a tectal input in the origin of mammals. Whichever interpretation of pulvinar homology is correct, the outgroup hypothesis implies that this nucleus must have undergone important changes in connectivity in the origin of mammals: either its efferents were re-routed to the dorsal pallium (Shimizu & Karten 1993), or it expanded from a subgroup of intralaminar nuclei and received invading afferents from the superior colliculus (Bruce & Neary 1995). On the other hand, the recapitulation hypothesis specifies little connectional changes for the origin of the pulvinar nucleus, as it assumes it to be the homologue of the reptilian nucleus rotundus.

4.3. Developmental criteria

Another criterion to establish homology is the comparison of the developmental origin of structures across taxa. Northcutt (1996b) has already pointed out the importance of the ontogenetic context in evolutionary considerations, as originally proposed by Garstang (1922). More precisely, in a lucid discussion of the different approaches to the problem of homology, Striedter (1997) quotes Russel's (1916/1982) considerations favoring similarity of development as a strong criterion for homology. In Russel's view, the generalized morphology and topographic relations are shown most clearly in early developmental stages; this view facilitates cross-species comparisons. This assumption is valid in cases in which there is cross-species conservation of embryonic processes, whereas adult morphology tends to diverge. Alternatively, in cases of embryological diversity with adult conservation, perhaps adult structures and relations may be a better criterion for homology (Aboitiz 1995; 1999b). In a similar line, Striedter and Northcutt (1991) and Striedter (1997) have called attention to the importance of combining embryological information with phylogenetic data in order to discern true homologies from instances of independent evolution or homoplasy, and emphasize phyletic continuity as a strong requirement for homology. In the case of the amniote telencephalon, phylogenetic evidence points to a notable conservation of early embryonic structure with adult diversification (Aboitiz 1995; 1999b; Striedter 1997), which adds weight to embryological comparisons as a reliable criterion for homology.

During embryogenesis, the DVR (especially its anterior part) develops from a position deep inside the olfactory cortex (Källén 1951; Striedter et al. 1998), whereas most of the isocortex originates from the dorsal pallium. This is supported by studies of expression patterns of regulatory homeobox-like genes in the embryonic forebrain, which have revealed a conserved mosaic organization in which the different compartments develop into specific brain components in the adult (Gellon & McGinnis 1998; Moens et al. 1998; Puelles & Rubenstein 1993; Seo et al. 1998). In the embryonic mammalian telencephalon, distinct markers for pallial and subpallial regions have been detected. The embryonic lateral and medial ganglionic eminences (GEs), which are located in the lateral subpallium, express the marker genes Dlx-1 and Dlx-2 (Anderson et al. 1997b). The cerebral cortex arises mostly from the embryonic pallium and is characterized by the expression of genes of the Emx and the Otx families (Acámpora & Simeone 1999; Mallamaci et al. 1998; Pannese et al. 1998; Puelles & Rubenstein 1993; Simeone et al. 1992; see Fig. 5). Smith Fernández et

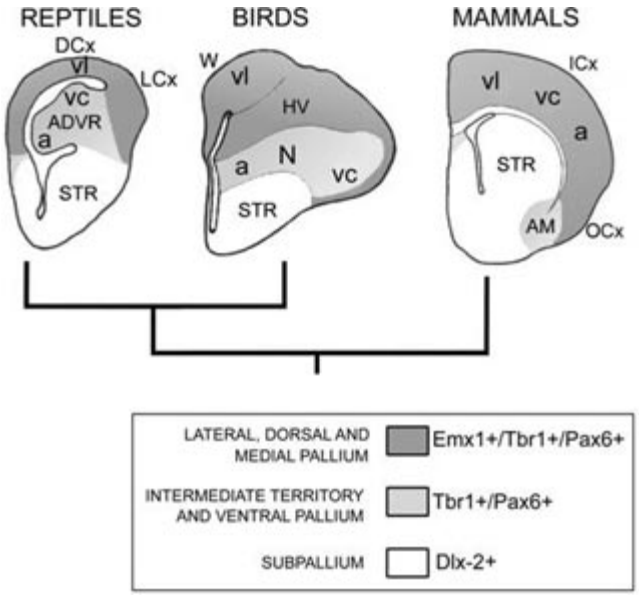

Figure 5. The cerebral hemispheres of reptiles, birds, and mammals, indicating the medial, dorsal and lateral pallium (dark grey), which, during development, expresses the marker genes Emx 1/2, Otx 1/2, Pax-6, and Tbr-1, and gives rise to the Wulst (W, equivalent to the reptilian DCx) and hyperstriatum ventrale (HV) of birds, and to cortical structures in reptiles and mammals. The subpallium (white) expresses Dlx-type genes during embryogenesis and gives rise to the corpus striatum (STR) among other structures. Light grey indicates the intermediate territory or ventral pallium, which is largely positive for the genes Emx-2, Pax-6 and Tbr-1 and gives rise to the anterior dorsal ventricular ridge (ADVR) of reptiles, to the neostriatum (N) of birds (which corresponds to a large part of the reptilian ADVR), and to the basolateral amygdala (AM) of mammals. In each vertebrate class, the projection sites of the auditory pathway (a) and the visual pathways via the lateral geniculate (vg, thalamofugal) and via the optic tectum (vt, tectofugal), are indicated. D, dorsal cortex; ISO ICx, isocortex. (Based on Smith Fernández et al. 1998 and Puelles et al. 1999.)

al. (1998) identified for the first time an intermediate territory (IT) in the equatorial region of the hemisphere, between the pallium and the subpallium of amphibians, reptiles, birds, and mammals, which does not express either the Emx-1 or Dlx-1 markers of the pallium and subpallium, respectively, but is largely positive for the gene Pax-6 (Smith-Fernández et al. 1998; see Fig. 5). More recent reports (Puelles et al. 1999; 2000) confirmed the existence of the IT (which has been termed ventral pallium, VP, by these authors), and extended the previous findings by showing that Pax-6 is expressed mainly near the ventricular zone of the whole pallium including the IT/VP; another gene, Tbr-1, is also expressed in both the pallium and the IT/VP but has a more superficial domain of expression. Thus, the medial, the dorsal, and part of the lateral pallium express Emx-1 and Tbr-1 superficially and Pax-6 more internally, whereas the IT/VP expresses Tbr-1 superficially and Pax-6 deeply, but not Emx-1 (Fig. 5).

In sauropsids, an important part of the ADVR (including the neostriatum and ectostriatum of birds) and part of the lateral cortex develop from the IT/VP (Fig. 5), whereas in mammals, the basolateral amygdalar complex, part of the claustral complex, the endopiriform nucleus, and parts of the lateral or olfactory cortex – among other structures – derive from this region (Puelles et al. 1999; 2000; Smith-Fernández et al. 1998). In this context, two mammalian structures have recently been proposed to be homologous to the ADVR: the basolateral amygdala (Bruce & Neary 1995; Puelles et al. 1999; Smith Fernández et al. 1998) and the endopiriform nucleus (Striedter 1997). Developmental evidence favors both the basolateral amygdala and the endopiriform nucleus as homologous to the ADVR (Puelles et al. 1999; Smith Fernández et al. 1998). On the other hand, connectional evidence indicates similarity between the ADVR and the basolateral amygdala (Bruce & Neary 1995), while the connections of the endopiriform nucleus parallel quite closely those of the olfactory cortex (Behan & Haberly 1999).

Smith-Fernández et al. (1998) have argued that, in reptiles and birds, the IT/VP remains as a distinct neuroepithelial zone until late development, the period in which it gives rise to most of the ADVR. On the contrary, in mammals, this territory has been described as producing only the above-mentioned, early-generated components, becoming obliterated between the Emx-1-positive and the Dlx-½-positive zones in later development (Smith-Fernández et al. 1998). Swanson (2000) and Künzle and Raddtke-Schuller (2001) suggest that the mammalian claustral complex has developmental timing similar to early-produced cortical elements, which in part agrees with the concept that the IT/VP gives rise mostly to early-produced brain components. This evidence may suggest that in mammals there are no structures comparable to those late-generated components in the avian/reptilian intermediate territory, which also agrees with the concept that in mammals there is no strict homology to the reptilian ADVR (Aboitiz 1992).

Puelles et al. (1999) seem to disagree with the concept of the IT/VP disappearing from the neuroepithelial surface in mammals, although they admit that this territory is considerably compressed between the lateral pallium and the developing striatum. Undoubtedly, further studies are urgently needed to clarify the developmental fate of the IT/VP in mammals. In any case, for this component to contribute to isocortical development as predicted by the recapitulation hypothesis, a massive tangential migration of Emx-1-negative neurons should take place from the IT/VP into the dorsal pallium, making up the visual extrastriate and the auditory cortices. There is evidence that many isocortical GABAergic cells originate in the subpallial GEs (ganglionic eminences) and migrate dorsally into the isocortex (Anderson et al. 1997a; 2001), which raises the possibility that some excitatory cells from the IT/VP also migrate to the dorsal pallium. Therefore, it cannot be discounted that the IT/VP becomes reduced as a consequence of cell emigration to the dorsal pallium during late development. Just as cells migrating from the GEs into the isocortex keep expressing their subpallial molecular markers (Anderson et al. 1997a), cells migrating from the IT/VP might make the visual extrastriate and auditory cortices largely Emx-1-negative (something that has not been observed), unless they somehow begin to express Emx-1 as they invade the dorsal pallium. Nevertheless, no evidence yet exists for a massive migration from the IT/VP into the isocortex.

5. The origin of the isocortex: I. Developmental aspects

Considering the evidence reviewed in the above sections, we have argued that the structure that most likely corresponds to a large part of the mammalian isocortex is the reptilian dorsal cortex, which expanded both tangentially (increase in area) and radially (increase in thickness) during the origin of mammals. As mentioned earlier, at this point we intend to propose some hints as to how this structure has changed from a small, three-layered structure in reptiles into a large, six-layered component in the mammalian brain.

5.1. Dorsoventral gradients and expansion of the dorsal pallium

During embryogenesis, telencephalic differentiation is patterned by dorsoventral gradients of regulatory genes such as sonic hedgehog (Shh), which specifies a ventral phenotype by inducing subpallial markers like Nkx-2.1, Gsh-2, and Dlx-2. On the other hand, dorsal pallial markers and phenotypes are at least partly determined by the gene Gli-3 (for review, see Monuki & Walsh 2001; Wilson & Rubenstein 2000). Furthermore, mutations in some genes can produce displacements in compartment boundaries during development. In mutants for the gene Nkx-2.1, the corpus striatum becomes enlarged at the expense of the more ventral globus pallidus (Sussel et al. 1999). In the Emx-2 −/− mutant mouse, presumptive cortical regions develop into a basal ganglia phenotype (Muzio et al. 2002a). Perhaps more interesting for our purposes, mutants of the gene Pax-6 show a dorsal expansion of the medial ganglionic eminence (MGE) into the territory of the lateral ganglionic eminence (LGE; Chapouton et al. 1999; Stoykova et al. 2000). In this mutant, the expression limits of marker genes such as Emx-1, Tbr-1, Shh, Dlx-1, and Nkx-2.1 become displaced dorsalwards, producing a dorsal shift in the pallial-subpallial boundary, which is associated with dysgenesis of the claustrum, endopiriform nucleus, insular cortex, and piriform cortex. This dorsal displacement of boundaries may be, in part, the consequence of an enhancement of ventro-dorsal migration of cells (mostly inhibitory interneurons) from the GEs into pallial territories. Normally, Pax-6 upregulates R-cadherin, which acts as a barrier for the migration of many cells from the MGE and the LGE into the cortex (Chapouton et al. 1999). The release of this barrier in the Pax-6 mutant may imply an increased number of cells migrating into the dorsal telencephalon. Another important possibility is that the boundaries expand by changing the identity of the cells previously belonging to neighboring compartments. That is, the lack of Pax-6 signal may transform future pallial cells into subpallial phenotypes. In this context, the gene Gsh-2, a marker for the GEs (Szucsik et al. 1997), has been proposed to play a complementary role with Pax-6 in the specification of the GEs and the IT/VP; in mutants for Gsh-2, part of the LGE may differentiate as IT/VP, whereas in Pax-6 mutants, the IT/VP is re-specified to become a LGE-like structure (Yun et al. 2001). More recently, Butler and Molnár (2002) reported the development of a DVR-like structure (termed the pallial "mound") in the Pax-6 −/− mutant, which they consider to consist of cells from the lateral migratory stream that failed to migrate into the lateral isocortex. However, in addition to not expressing Pax-6, this mutant has been described to lack, or express very poorly, other ventral pallial markers such as Dbx-1 (Osumi 2001; Yun et al. 2001), and its ventral pallial structures have been reported to be, in general, dysgenic. Therefore, it is not clear to what extent this pallial "mound" can be directly compared to the reptilian DVR. It could be that the mound is formed by the accumulation of cells in the ventricular and subventricular zones of the lateral and dorsal pallium, which depend on Pax-6 for proper migration (Heins et al. 2002; Tarabykin et al. 2001). In any case, we agree with Butler and Molnár (2002) in that the Pax-6 −/− mutant may represent a ventralized phenotype somehow similar to that of the reptilian brain, although not in some specific details.

Other gene systems have also been found to be expressed in gradients in the developing telencephalon. For example, the genes of the Wnt family are required for hippocampal development and are expressed strongly in the caudomedial margin of the cortical pallium (Kim et al. 2001). Wnt receptors of the Frizzled family are most concentrated in the isocortical neuroepithelium, while being sparse or entirely absent in the more medial hippocampal neuroepithelium (Kim et al. 2001). Similarly, two Wnt inhibitors (secreted Frizzled-related proteins 1 and 3) are expressed in opposing anterolateral to caudomedial gradients in the telencephalic ventricular zone. In addition, the gene Emx-2, which is similar to Emx-1 but has a more widespread domain of telencephalic expression (including pallium and subpallium; Gulisano et al. 1996), has been found to be arranged in a gradient with maximal concentrations in the posteromedial isocortex and minimal concentrations in the anterolateral isocortex (Mallamaci et al. 2000). Conversely, the gene Pax-6 is expressed in a complementary gradient, being maximally expressed in the anterolateral isocortex and minimally expressed in the posteromedial isocortex (Bishop et al. 2000). Interestingly, mutants of Emx-2 show reduction of the posteromedial cortical areas (i.e., visual), and, concomitantly, there is significant expansion of anterolateral cortical regions (i.e., somatosensory and frontal), whereas Pax-6 mutants evidence a reduction of anterolateral areas and expansion of posteromedial regions (Bishop et al. 2000; Mallamaci et al. 2000).

The above evidence suggests that the modulation of overall dorsoventral, frontocaudal, and/or mediolateral gradients of regulatory gene expression may have profound effects in the development of specific telencephalic components. It is therefore possible that the expansion of the dorsal pallium in primitive mammals occurred partly as a consequence of the enhancement of a dorsalizing signal in telencephalic development. Since the structure that expanded the most in mammalian evolution is the dorsal pallium (isocortex) rather than the medial pallium, the lateral pallium, and the IT/VP, there may be some yet unknown genes exclusively determining the fate of this structure, which increased their domains of expression and enhanced cell proliferation specifically in this region. In particular, genes involved in the regional specification of the cortical ventricular zone, like Wnt-3a, BMP, Neurogenin, and others, may have been fundamental in the expansion of this structure (Monuki & Walsh 2001). The expansion of the presumptive dorsal pallial territory may have produced a ventrolateral displacement of the lateral pallium, which perhaps differentiated in territory originally destined to the

IT/VP. In this way, through shifts in the boundaries of the territories of regulatory gene expression, cells that initially differentiated in one specific compartment may have acquired patterns of differentiation of other telencephalic areas. The obliteration or compression of the IT/VP that has been described in the mammalian telencephalon (Smith-Fernández et al. 1998), might result from tangential expansion of the expression domain of Emx-1 and related markers, from invasion of the IT/VP by tangentially migrating Emx-1 positive cells, or simply from its elimination by cell exhaustion or cell death. Of course, this may not be the whole story because, in addition to the displacement of pallial boundaries, there has also been an overall increase in brain size, which possibly was largely produced by an increase in proliferative activity within the dorsal pallium and other regions. In this context, a recent report indicates that transgenic mice expressing b-catenin in neural precursors develop an enlarged cortical surface area, while maintaining a normal cortical depth (Chenn & Walsh 2002). Another report indicates that ASPM, a gene essential for mitosis in embryonic neuroblasts, is required for attaining a normal cortical size (Bond et al. 2002). Perhaps these genes are downstream elements in the cascade triggered by the dorsalizing elements in early development. On the other hand, the pallium of reptiles may present an enlarged IT/VP because of a ventralizing pallial influence that maintains a restricted expression of Emx-1 and other dorsal pallial genes.

Another, not alternative possibility is that dorsalizing factors somehow triggered the tangential migration of excitatory neurons from the IT/VP into the dorsal pallium, thus contributing to the expansion of this brain region. As said, this mechanism might imply that these neurons acquired Emx-1 expression as they invaded the dorsal pallium. Increased tangential migration of inhibitory cells toward the dorsal pallium is observed in ventralized phenotypes like the Pax-6 mutant (Chapouton et al. 1999), but yet there are no observations on tangential migration of excitatory cells or their regulation.

Reiner (2000) has proposed that, in the common ancestor to reptiles and mammals, there was a structure that diverged into the lateral isocortex of mammals and into the ADVR of reptiles. This structure was either Emx-1 negative and acquired Emx-1 expression in mammals, or, alternatively, was Emx-1 positive and lost Emx-1 expression in reptiles and birds. This possibility is certainly consistent with the concept of a dorsalized pallium in mammals with respect to reptiles. However, in many reptiles the topographic relation between the IT/VP and the dorsal cortex is such that a large part of the olfactory cortex is interposed between them. Perhaps a mere shift in gene boundaries may not be sufficient to transform the IT/VP into an isocortical area, and a tangential migration of cells from the IT/VP through the lateral pallial territory into the dorsal cortex would also be needed. Exceptions to the topographic relations between DVR, lateral cortex, and dorsal cortex are found in turtles and in Sphenodon. In turtles, a structure termed the pallial thickening (a dorsal cortex-derivative located beneath the lateral cortex) bridges the ADVR with the dorsal cortex (Ten Donkelaar 1998b; Ulinski 1990); whereas in Sphenodon there is continuity between the ADVR and the dorsal cortex in the rostral hemisphere (Reiner & Northcutt 2000). It is not clear if cellular continuity between the ADVR and the dorsal cortex is an ancestral character of reptiles. If so, the possibility of a mechanism as proposed by Reiner (2000), might depend on the precise topographic relations between ADVR and dorsal cortex (recall that auditory and extrastriate visual cortices are located in the posterior hemisphere and that the continuity between ADVR and dorsal cortex tends to be found anteriorly).

Summarizing, two possibilities (not necessarily exclusive) may account for the relative growth of the mammalian dorsal pallium in relation to the IT/VP. The first is, that the dorsal pallium expanded tangentially, perhaps invading territory destined to the lateral pallium, and the latter was displaced into territory destined to the IT/VP. The second possibility is that of a massive migration of cells from the IT/VP into the dorsal cortex. This mechanism would make the visual extrastriate and auditory cortices largely negative for Emx-1 (and positive for Dbx-1; Yun et al. 2001), something that has not been observed. Still, there is the possibility that Emx-1-negative cells from the IT/VP migrate dorsally very early in development, and acquire Emx-1 expression after they arrive in the dorsal pallium. Unfortunately, at this point there is no evidence indicative of a migratory process from the ventral pallium into the dorsal pallium. Further studies oriented to identify regulatory genes specific for the dorsal pallium and their regulatory mechanisms, as well as analyses of cell migration into and out of the IT/VP, will help to determine to what extent each of these two possibilities accounts for the expansion of the isocortex.

5.2. Laminar development of the isocortex

The mammalian isocortex develops through successive waves of neuronal migration following the pathway imposed by radial glia from the ventricular zone of the hemisphere (as mentioned, there is also contribution of tangentially-migrating cells). The first migratory waves make up a transient, embryonic cell layer known as the preplate (Fig. 6). This is later split into a superficial marginal zone (future layer I) and a deep subplate by the arrival of older cells that make up the future cortical plate (cortical layers VI to II). That is, cells of the cortical plate become positioned within the preplate, dividing the latter into a superficial marginal zone and a deep subplate. Within the cortical plate, cells become arranged in an inside-out neurogenetic gradient, in which late-produced cells migrate past early-produced ones and locate above them. Thus, the more superficial layer II contains the youngest neurons of the cortical plate, and the deepest layer VI contains the oldest neurons of the cortical plate. In many species, cells of the preplate (subplate and marginal zone) die during late development (for full review, see Rakic 1988).

Marín-Padilla (1978) originally proposed that the mammalian preplate represented the ancestral reptilian cortex. In mammals, Swanson (2000) and Künzle and Radtke-Schuller (2001) have recently emphasized the developmental relation (in terms of similar timing of origin) between the subplate and other early-produced cell populations such as the claustrum. Considering that part of the claustral complex corresponds to the IT/VP and has been considered homologous to part of the reptilian ADVR, by extension the possibility is open that some subplate cells can be comparable to some reptilian embryonic or adult cortical cells.

However, there may be some problems comparing an embryonic structure like the mammalian preplate with an

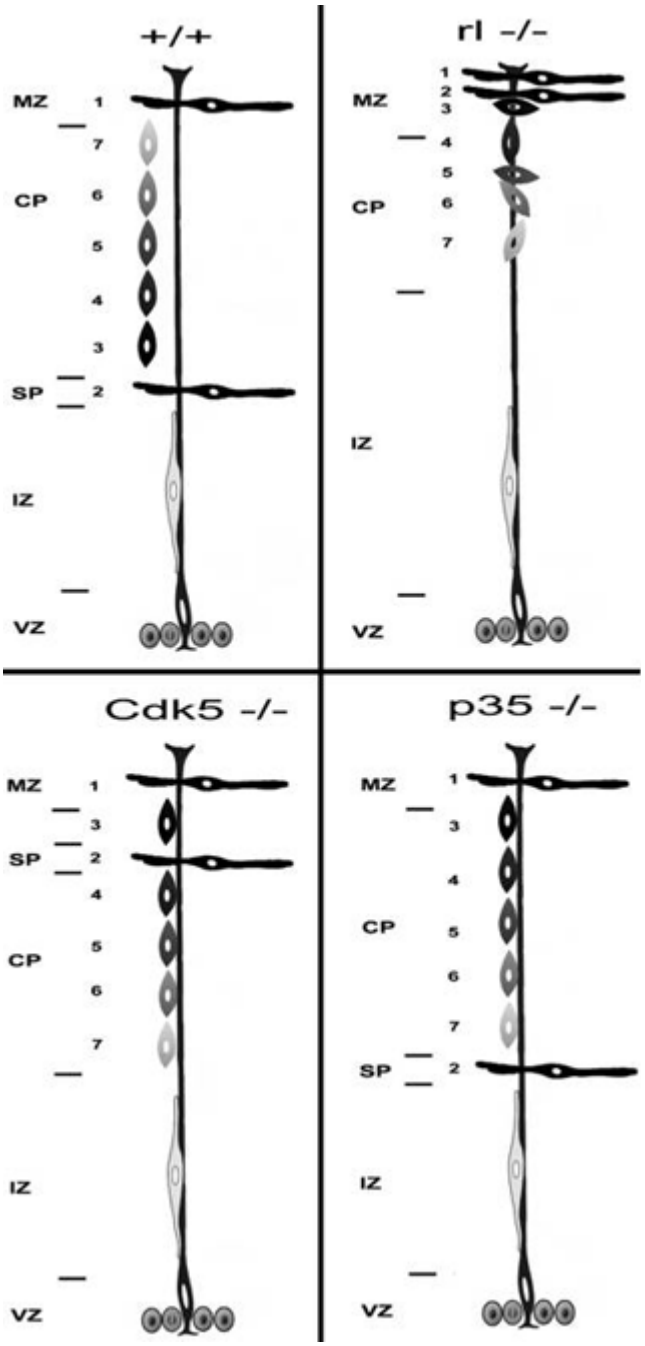

Figure 6. Laminar isocortical arrangement in normal and mutant mice. In the normal mouse (+/+), the preplate (consisting of the marginal zone, MZ, and the subplate, SP) is split by the cells of the younger cortical plate (CP), which cross the SP and remain between the latter and the MZ, in an inside-out gradient (where late-born cells become positioned above early-born cells). Numbers indicate order of origin of the different cell layers. In the reeler mouse (rl −/−), CP cells are unable to split the preplate and accumulate below it, invading layer I. In addition, CP layers are arranged in an abnormal outside-in gradient (where late-born cells become positioned below early-born cells). In the cdk5 −/− mutant, CP layers are arranged in an outside-in gradient. Furthermore, only the earliest-born CP cells are able to cross the SP and reach their normal position; subsequently born CP cells accumulate below the SP. In the p35 −/− mutant, all CP cells are able to cross the SP, but arrange in an outside-in gradient. The difference between the cdk5 −/− mutant and the p35 −/− mutant may be that in the latter, some other activator of cdk5 (perhaps p39) permits cortical plate neurons to migrate past the subplate. IZ, intermediate zone; VZ, ventricular zone.

adult one like the reptilian cortex. Perhaps it is more meaningful to compare the developing mammalian isocortex with the developing reptilian cortex. Supèr et al. (1998b) argue that an incipient preplate, including a subplate, may be already present in reptiles, and we have observed horizontal cells above and below the developing cortical plate of reptiles (cf. Aboitiz 1999a), suggesting a preplate-like arrangement. Nacher et al. (1996) described the presence of somatostatin-positive cells, appearing first in the inner plexiform layer and later in the outer plexiform layer of the medial and dorsal cortices of the developing lizard brain. Nevertheless, Cordery and Molnár (1999) argue that no simple homology can be found between the early cortical cells in the turtle and cells in the mammalian preplate, since the former have very low levels or simply lack the markers reelin and calbindin (which are present in the mammalian preplate). However, they also observed cells positive to neuropeptide-Y, scattered in all regions of the ventral and dorsal pallium of the turtle (Cordery & Molnár 1999). We also need to note that Kostovic and Rakic (1990) consider that much of the subplate is not ancestral; instead, this structure can be viewed as an acquisition of the mammalian brain, since it is most complex in those areas that appear later in mammalian evolution, and also is more complex in mammals with more complex brains.

Thus, there seem to be early cell populations in the developing reptilian cortex, which may appear before the development of the reptilian cortical plate. However, these early cells are not totally equivalent to the mammalian preplate cells. The question is to determine to what extent the reptilian early cells form a preplate-like structure that is split into a marginal zone and a subplate by the arrival of younger cortical neurons. It is important to note that, if in reptiles there is a subplate-like structure, cortical plate cells might have to migrate past these cells as they do in the mammalian brain.

Comparing the adult isocortex with the reptilian cortex, Ebner (1969) and Reiner (1991; 1993) proposed that the reptilian cortex mostly corresponds to the deep isocortical layers VI and V of the mammalian cortical plate. Cells in the superficial layers IV–II are morphologically and neurochemically different from reptilian cells, and can be considered as a derived character of the mammalian isocortex.

Summarizing the above points, some cells in the embryonic preplate and in layers VI–V of the adult mammalian isocortex may be comparable to the early-produced and late-produced cortical cells of reptiles. In the evolution of the mammalian isocortex, new cell types have appeared both in the preplate (including reelin- and calbindin-positive cells) and in the cortical plate. In particular, the late-born, superficial isocortical layers IV–II may have originated as an extension of the neurogenetic period in cortical development, and largely consist of phenotypically new cell types (Aboitiz 1999a; Aboitiz et al. 2001a; 2001b).

Note that, in mammals, the difference between the embryonic subplate and the deepest layers of the adult cortical plate are not absolutely clear-cut, and that these structures may be developmentally related. For example, mutations in the gene Tbr-1 cause defects in both the preplate and the deepest layer VI of isocortex (Hevner et al. 2001), suggesting similarities in genetic organization between these structures. Moreover, considering that in the rat and other mammals with a limited or moderate degree of isocortical expansion, many subplate cells survive into

adulthood, forming the layer VII (Reep 2000; Woo et al. 1991), it is also possible that in some reptiles there are early cortical cells that remain until adulthood.

Further molecular evidence supports the concept of the superficial isocortical layers IV–II as developmentally distinct from the inferior layers VI and V. In addition to specifying pallial territories, the gene Pax-6 participates in the laminar differentiation of the isocortex. Mutants for Pax-6 exhibit cortical migration defects – consisting of the inability to migrate and differentiate, on the part of superficial, late-generated isocortical neurons belonging to layers IV to II (Caric et al. 1997; Fukuda et al. 2000). It has been proposed that Pax-6 specifies a cellular environment that permits late-born cells to express their developmental potential. Furthermore, a recent report shows that early-produced cortical plate neurons destined to isocortical layers VI and V are produced in the embryonic ventricular zone and express the marker gene Otx-1. On the other hand, late-produced neurons, which depend on Pax-6 for their development and are destined to superficial layers IV–II, are produced in the subventricular zone and express the marker gene Svet-1 (Tarabykin et al. 2001). Thus, it is perhaps likely that Pax-6 somehow participated in the origin of the isocortical superficial layers (see Aboitiz et al. 2001b), and that this may have involved the recruitment of the subventricular zone in the neurogenetic process. In this context, the recent findings that radial glial cells can generate neurons, and that their neurogenic potential depends on Pax-6 expression (Heins et al. 2002) is of great interest. It will also be of interest to determine the contribution of the subventricular zone and of the genes Pax-6 and Svet-1 to dorsal cortical development in reptiles.

5.3. The inside-out neurogenetic gradient

Another feature that characterizes the isocortex is its inside-out neurogenetic gradient (Angevine & Sidman 1961; Rakic 1974), in which late-produced neurons migrate past layers of early-produced neurons and become located in more superficial layers. In the reptilian cortex, laminar development proceeds according to an outside-in neurogenetic gradient, where late-produced neurons become positioned below early-produced ones and thus are not able to migrate past older cells (Goffinet et al. 1986). In the mammalian isocortex, there are at least two signaling cascades (which may be related to some degree) involved in the generation of the inside-out neurogenetic gradient. Mutations in components of these two cascades produce an inversion of the normal inside-out neurogenetic gradient, positioning cells in an outside-in gradient reminiscent to that of reptilian cortex (Fig. 6). One of these signaling pathways is related to the extracellular protein reelin, to its receptors (which include the low density and the very low density lipoprotein receptors, integrin receptors, and N-cadherin) and to its downstream intracellular components such as Dab-1 (Curran & D'Arcangelo 1998; Dulabon et al. 2000; Frotscher 1998; Senzaki et al. 1999; Trommsdorff et al. 1999). Reelin, which is secreted by the Cajal-Retzius cells and related cell types in the embryonic marginal zone (future layer I), has been proposed to work by binding to its receptors in the surface of the migrating neurons, detaching them from the radial glia (Aboitiz et al. 2001b; Dulabon et al. 2000; Pinto-Lord et al. 1982). If reelin signaling is defective as in the reeler mutant, neurons do not separate from the radial glia and keep migrating into the marginal zone, compressing the preplate above them. Thus, in the reeler, cells might arrange in an abnormal outside-in pattern because the early-born cells remain attached to the radial glia and do not leave space for younger neurons to migrate past them (Pinto-Lord et al. 1982). Interestingly, the reelin gene is faintly expressed in the developing cortex of reptiles (Bar et al. 2000), indicating that early cells in the marginal zone have undergone important transformations in the origin of mammals, and that reelin may have been an important element in isocortical evolution. Recently, it has been observed that the role of reelin may be more complex than previously thought. For example, in organotypic cultures, neurons may migrate across the reelin-positive marginal zone to differentiate in a cortical plate at a distance from the cortical slice (Hedin-Pereira et al. 2000). Somehow, neurons in this preparation are prevented from arresting migration in their proper place; perhaps this results from blocking reelin function, the reelin cascade, or other factors which may be altered in the organotypic culture. A more recent study found that some of the wild characters – like the ability to split the preplate – were rescued by artificially expressing ectopic reelin in the ventricular zone of reeler mice (Magdaleno et al. 2002). However, in the cortical plate, many cells still show an inverted lamination and migrate into the marginal zone as in the standard reeler mutant. Likewise, in a mutant for Dab-1 (p45), a downstream component of the reelin cascade, late-born neurons are observed in the marginal zone (Herrick & Cooper 2002), suggesting that they are not prevented from migrating into it. Another study shows that migration of neural stem cells is impaired in the reeler mutant (Kim et al. 2002). Tabata and Nakajima (2002) found that abnormalities in the internal plexiform zone may cause some of the deficits observed in the reeler. Finally, in the olfactory bulb, Hack et al. (2002) observed that reelin acts as a detachment signal but not a stop or guidance clue. Despite these recent findings, we believe the evidence indicates, overall, that in natural conditions, reelin has a role in the final stages of neuronal migration, perhaps specifically in the generation of a cell-free marginal zone. Any proposed mechanism for reelin action must take into account the facts that in the reeler mouse migrating neurons invade the marginal zone, and remain abnormally attached to the radial glia (Pinto-Lord et al. 1982).

The other signaling cascade depends on the cyclin-dependent, serine-threonine protein kinase 5 (cdk5) and its neural-specific activator p35 (Chae et al. 1997; Ohshima et al. 1996; cf. Fig. 6). It has been suggested that cdk5/p35 permit cortical neurons to migrate through preexisting cell layers within the cortical plate (Kwon & Tsai 1998), since in the mutants (more specifically, in the p35 mutant) cortical cells apparently respond normally to reelin in the marginal zone and yet arrange in an abnormal outside-in gradient (in this mutant, the preplate is correctly split but the cortical plate arranges in an inverted sequence). Furthermore, cdk5/p35 inhibit N-cadherin cell aggregation in migrating neurons (Kwon et al. 2000). This provides a possible mechanism by which migrating cells may bypass a migratory-suppressing signal (N-cadherin or a related molecule) present in postmigratory neurons of the cortical plate, thus allowing them to migrate through the latter to reach the inferior border of the marginal zone (Aboitiz 2001; Aboitiz et al. 2001a; 2001b). In the present context, it is of interest to note that in cdk5 mutants, cells belonging to the deepest

cortical layer VI (which are also the earliest-produced of the cortical plate) are the only ones that can reach their proper position above the subplate (Fig. 6). Later-produced cells (destined to layers V–II) are not able to cross the embryonic subplate and arrange below it, in an outside-in gradient. This may be partly because mutant cells migrate very slowly, and since the cdk5 mutant dies perinatally, these cells may not have time to arrive to the cortical plate (Gupta et al. 2002; Nadarajah et al. 2001). Considering that early-produced cortical plate cells may represent an ancestral phenotype, while late-produced cells are considered to be an evolutionary acquisition, we have suggested that the cdk5/p35 pathway is somehow related to the migration of the phylogenetically new cell types of the mammalian isocortex and to the origin of the inside-out neurogenetic gradient of the isocortex (Aboitiz 1999a; 2001; Aboitiz et al. 2001a; 2001b). Cells in isocortical layer V might represent an intermediate condition between the ancestral phenotypes and the new ones, as they originate in the ventricular zone and are morphologically and neurochemically reptilian-like; but like younger cells, they depend on cdk5 to cross the subplate and layer VI. Again, the study of cdk5/p35 expression in the developing cortex of reptiles may provide substantial information on isocortical evolution.

Recently, two modes of cell migration have been observed in the developing cerebral cortex (Nadarajah et al. 2001). One is called *translocation,* and is observed in early-produced cells of the cerebral cortex, including those of layer VI, and also in the latest stages of migration of late-produced cells within the cortical plate. In this modality, the apical process of the cell contacts the subpial layer, and the cell body is dragged toward the surface while the apical process shortens. The other mode, *locomotion,* consists of the continuous lengthening and shortening of the apical process as the cell migrates along the radial glia. It is highly interesting that in the cdk5 and the p35 mutants, only cells that move by locomotion are affected, whereas cells in layer VI and other early-produced cells that migrate mainly by translocation are unaffected (Aboitiz 2001; Gilmore & Herrup 2001). This suggests that cdk5 and its activators p35 and p39 participate in helping migration by locomotion. It is then possible that cdk5, activated by p35, allows migrating neurons to move by locomotion within the cortical plate, thus allowing the generation of the inside-out gradient.

To summarize: in isocortical origins, the cdk5/p35 pathway may have facilitated the migration by locomotion of late-born, phylogenetically new neurons, and also (particularly by the activation of cdk5 by p35) permitted the migration across cells of the cortical plate, producing the inside-out gradient. At this stage, reelin may have become important in somehow preventing these migrating cells from penetrating into the marginal zone, and also in detaching neurons from the radial glia, thus allowing later-produced cells to use the same glial pathway to migrate across layers of older neurons. In reptiles, perhaps there are other factors different from reelin that maintain a cell-free marginal zone. Besides the reelin and the cdk5 cascades – which, although they are partly independent, may well have cross-talk among them (Gupta et al. 2002) – there are several other genes regulating radial migration (such as Lis-1), which may also have had important roles in isocortical origins. It is quite possible that several other genes are discovered that participate specifically in mammalian cortical cell migration and in the generation of the outside-in gradient. Our attempt has been to point out the (at this point) most likely genetic mechanisms involved in the generation of this unique structure and its developmental sequence.

Previously (cf. Aboitiz 1999a), we proposed a hypothesis for the origin of the inside-out neurogenetic gradient, based on the fact that, in the cortex of reptiles, cortical afferents are arranged in a tangential direction in layer I. In mammals, on the other hand, most isocortical afferents enter the cortex radially from the underlying white matter. In the mammalian isocortex, late-produced cells participate in cortico-cortical connections of large and short range, while the early-produced, deep layers are mostly output layers. Thus, the addition of late-produced cells may have provided the emerging isocortex with a tier of intracortical processing before the output was produced by the early-born neurons. However, a requisite for this function is to gain access to the axons providing input to the cortex, which were located in the most superficial layer I. Hence, the inside-out gradient may have originated as a strategy to gain synaptic contact with cortical afferents by the late-produced neurons. Eventually, cortical afferents may have found a "shortcut" to reach the cortex: traveling through the subcortical white matter and entering the cortex radially instead of running tangentially. In this process, the transient subplate may have become a fundamental element as it projects to the thalamus, and its axons serve as substrates for axonal growth toward the isocortex (Molnár & Blakemore 1995). Furthermore, the subplate serves as a "waiting compartment" for thalamocortical axons, which arrive before the maturation of the cortical plate. Once the cortical plate is mature, thalamocortical axons leave the subplate and enter radially into the cortical plate (Allendoerfer & Shatz 1994). Thus, the subplate may have been important to guide axons through the subcortical white matter and allowing them to enter the isocortex in the radial direction. In addition, the tangential expansion of the isocortex which resulted in an explosive increase in cortical area may have also put a constraint for the tangential growth of thalamocortical axons through the marginal zone, as fibers would have to run excessively long distances to reach the cortical fields on which they were supposed to synapse.

6. The origin of isocortex: II. Evolution of connectivity

As we have just discussed, developmental biology can provide important clues about the mechanisms involved in evolutionary transformations. However, we strongly consider that major evolutionary transitions have been a result of the process of natural selection, therefore, there must be a functional or behavioral context in which these developmental changes proved to be adaptive. In the following sections, we will argue that assuming that the mammalian isocortex originated largely from the reptilian dorsal cortex, implies that a major divergence in brain connectivity has occurred in the evolution of reptiles and mammals. More specifically, in mammals, the sensory pathways that relay in the mesencephalon (collothalamic) are directed to the dorsal pallium, whereas, in reptiles and birds, these pathways terminate in the ventral pallium. The dorsal and the ventral pallium have different domains of connectivity and are involved in different functions, which implies diverging strategies of sensory processing in sauropsids and mam-

mals. In the following sections, we will provide a hypothesis relating the expansion of the dorsal cortex in early mammals, with functional demands associated to the development of associative networks between the olfactory cortex, the dorsal cortex, and the hippocampus. This hypothesis intends to provide a partial account for the major difference in sensory connectivity in the major groups of amniotes.

6.1. Sensory processing in reptiles and mammals

In mammals, the primary visual cortex projects to the extrastriate cortical areas (which receive the tectofugal visual projection), and these, together with the auditory and somatosensory cortical areas, project (through a series of successive cortico-cortical projections) to the hippocampus and the amygdala, in order to process different types of mnemonic information (spatial/episodic and emotional, respectively; Lynch 1986; Maren 1999). In reptiles and birds, although a circuit exists associating the olfactory, the dorsal (visual thalamofugal), and the medial/dorsomedial (hippocampal) cortices, the more important projections from somatosensory, auditory, and visual tectal systems end in the ADVR, which is in turn connected primarily to the PDVR (comparable to parts of the mammalian amygdalar complex). In other words, in reptiles and birds, two relatively (but not totally) separate systems exist for processing thalamic sensory information. One receives thalamofugal visual information and somatosensory projections (lemniscal systems), which are connected primarily with the hippocampus. The other receives mesencephalic or collothalamic auditory and visual information, which is more related to the amygdalar system (see Fig. 4). Thus, in mammals, the hippocampus may receive a much heavier sensory projection than in reptiles and birds, who may rely more on amygdalar components (PDVR/archistriatum) than on the hippocampus to process certain types of sensory and mnemonic information. Further comparative behavioral studies on hippocampal function and spatial memory in mammals and reptiles are needed to verify this intriguing possibility. In this context, it has been found that, in homing pigeons, hippocampal lesions disrupt certain types of spatial learning such as using the sun for directional information, but the capacity to learn on the basis of landmark beacons remains intact (Gagliardo et al. 1996). This suggests that not all forms of spatial memory depend on the hippocampus in birds, as they do in mammals.

An additional difference between sauropsids and mammals is that the corpus striatum receives its major projection from the ADVR and from the isocortex, respectively. Nevertheless, the basolateral amygdala of mammals and the dorsal cortex of reptiles also project to the corpus striatum (Bruce & Neary 1995; Ten Donkelaar 1998b), thus implying similarity of connections between the ADVR and the mammalian basolateral amygdala, and between the dorsal cortex of reptiles and the mammalian isocortex. The fact that most collothalamic inputs terminate in the sauropsidian ADVR and in the mammalian isocortex may account for the quantitative differences in striatal input between these groups. In any case, the basal ganglia of reptiles receive their major input from the ADVR (related to collothalamic inputs), and project to the optic tectum or superior colliculus. On the other hand, in mammals the basal ganglia receive their major input from the isocortex (related to both lemnothalamic and collothalamic inputs), and possibly send an important projection back to it, via the dorsal thalamus (Brauth 1990).

6.2. Olfaction in early mammals

Although an explanation for the evolutionary development of the reptilian DVR is still needed, meanwhile, we will suggest a scenario for the behavioral context of isocortical origins. This proposal is based partly on Sagan's (1977) and Lynch's (1986) original hypotheses of the origin of the isocortex. We suggest that associative networks between the dorsal cortex and the olfactory system, via the hippocampus, became increasingly important to develop multisensorial maps of space and behavior. This may have triggered the expansion of the dorsal cortex as a recipient of not only the visual thalamofugal but also the auditory and visual tectofugal sensory projections.

It has been repeatedly proposed that, in ancestral mammals, olfaction was an important sensory modality (Jerison 1973; 1990; Kemp 1982). Endocasts of mesozoic mammals indicate relatively large olfactory bulbs and perhaps an elevated rhinal fissure (Jerison 1990), suggesting a large olfactory cortex in relation to the rest of the pallium. Likewise, in small-brained insectivores and in some marsupials, olfactory-related structures occupy a much larger proportion of the volume of the brain than is the case in larger-brained species with a well-developed isocortex (Finlay & Darlington 1995; Finlay et al. 1998; Stephan 1983; Voogd et al. 1998). Since early mammals were most likely nocturnal animals (Carroll 1988; Jerison 1973; Kemp 1982; Sagan 1977) the exploration of their environment may have depended heavily on the olfactory system.

6.3. Olfaction and the hippocampus

In amphibians, there are projections from both the lateral and dorsal pallium (receiving olfactory input) into the medial pallium (Ten Donkelaar 1998a; 1998c). These projections may have served as precursors for the development of olfactory-hippocampal circuits in amniotes. In reptiles, there is a well-defined circuit connecting the medial (hippocampal), the dorsal (receiving the lemnothalamic pathways), and the olfactory cortices (Lynch 1986; Ten Donkelaar 1998b; see Fig. 4). Furthermore, there is evidence that in reptiles and in other vertebrates, the medial and the dorsal cortices participate in spatial learning (Rodríguez et al. 2002). Active foraging lizards tend to have larger medial and dorsal cortices than species that hunt with a sit-and-wait strategy (Day et al. 1999). In addition, lesions in these regions impair spatial learning in these animals (Day et al. 2001; Rodríguez et al. 2002). These researchers further argue that these cortical areas use non-spatial clues for spatial navigation, which is important in relation to new concepts of hippocampal function described below.

The mammalian olfactory cortex (which is really a mosaic of areas, including the piriform cortex, the entorhinal cortex, and the perirhinal cortex, among others; Shipley & Ennis 1996) is reciprocally connected with the hippocampus through the entorhinal cortex (Haberly 1990), and has been postulated to engage in associative interactions with other sensory modalities which are mapped in the isocortex and project to the hippocampus (Lynch 1986; Shipley & Ennis

1996). Thus, hippocampal activity is strongly dependent on olfactory and other sensory information.

A classical understanding of hippocampal function is that this structure creates a Cartesian representation of space, in which the different places and coordinates are mapped onto the structure itself (O'Keefe & Nadel 1978). This concept was partly proposed on basis of the discovery of "place-cells" in the hippocamus of experimental animals, which are activated by specific positions of the animal in a given space (O'Keefe & Dostrowsky 1971). However, evidence has shown that many hippocampal cells fire in response to non-spatial determinants such as odors, and that the activity of the cells depends on the behavioral state of the animal (see Eichenbaum 1999; Eichenbaum et al. 1999; Frank et al. 2000). Hippocampal cells can recognize rewarded and non-rewarded cues, spatial configurations of odors, differences between odors, or fire at specific behavioral instances (Wiener et al. 1989; Wood et al. 1999; 2000). In addition, it has been found that spatial and non-spatial (olfactory) information are segregated in interleaved, oblique stripes along the hippocampus (Hampson et al. 1999).

The hippocampus has also been shown to be required for non-spatial olfactory tasks, such as tests of transitive inference, in which if A>B, B>C, C>D, and D>E, then B>D (Dusek & Eichenbaum 1997). If A–E are distinct olfactory cues, rats can be trained to prefer A over B, B over C, and so on. Furthermore, rats can also infer that B>D, but only if their hippocampus is intact (A>E can be learned by intact and lesioned rats, but this can be solved by noticing that A is always chosen and E is never chosen, and thus does not require transitive inference).

Another example of hippocampal-dependent, non-spatial learning is the social transmission of food preferences, in which rats in contact with other rats who have recently eaten some scented food will prefer this food over others. This is learned by an association between the scent of the food and a constituent of the rat's breath, carbon disulfide (Galef 1990). Again, hippocampal-lesioned rats perform poorly in this task (Bunsey & Eichenbaum 1996). (This latter finding was called into question; Burton et al. 2000; but see reply by Alvarez et al. 2001.)

In summary, there is substantial evidence that the hippocampus participates in olfactory memory. Although it may not be essential to memory for single odors, it seems to be critical for establishing the relations among odor memories, and for the expression of odor memory representations in novel situations (Eichenbaum 1998).

Partly based on this evidence and on the finding that place cells are more consistently controlled by local cues (see Eichenbaum et al. 1999), it has been proposed that the representation of space in the hippocampus consists of the specification of behaviorally-relevant spots. These spots are identified by cues such as odors and other (visual) characteristics of the environment, and include a collection of independent representations of places, linked among them by the behavioral context in which the animal explores its environment (Eichenbaum 1999; 2000b; Eichenbaum et al. 1999). For these authors, a fundamental function of the hippocampus is its participation in episodic memory, that is, memory of the events that take place during a particular behavioral action. Spatial memory emerges as a consequence of the integration of successive episodes during an exploration task, and involves associations between different sensory modalities, including vision and olfaction. This proposal could reconcile the apparently discrepant findings that, in animals, the hippocampus participates in spatial memory, whereas in humans, it participates in declarative memory. Instead of spatial memory, Eichenbaum prefers to speak of a "memory space," which is an organized representation of memory episodes linked by their common features (Eichenbaum 2000b; however, see alternative view by O'Keefe 1999). We suggest that, in the process of generating this memory space, olfaction (which is an important sense used to investigate the environment by many small mammals such as rodents and insectivores) may participate as a "glue" that helps to link many of these spots, creating a cohesive map of the behaviorally-relevant points. This may have been especially important in early mammals or mammaliaforms, which had not yet developed a strong cortical visual system. In present-day mammals such as the rat, visual input is necessary for the firing of a large number of hippocampal cells, while olfactory information can be used to compensate for the lack of visuospatial information (Save et al. 2000). Therefore, visual information may have progressively been involved in the associative hippocampal-olfactory networks during the origin of mammals, thus triggering the expansion of the dorsal cortex.

The olfactory-hippocampal-dorsal cortex circuit may have been put to use by the first mammals to make relatively elaborate, largely olfactory-based representations of space, in which specific odors labeled particular places and routes. Nevertheless, the contribution of the visual system undoubtedly became necessary in the elaboration of more precise maps of space, especially when mammals invaded diurnal niches after the decline of dinosaurs. The dorsal cortex, receiving visual information from the thalamofugal visual pathway, may have become an important sensory processing system in the early mammalian brain (Aboitiz 1992).

In this context, a dorsalizing effect on dorsal pallial development as we have suggested before, triggering an expansion of the dorsal cortex, may have been of great benefit for the development of olfactory-hippocampal-cortical networks. This expansion may have permitted the arrival of "mesencephalic" sensory routes to the dorsal pallium, originating the visual extrastriate and auditory cortices (Northcutt 1969; Northcutt & Kaas 1995). In addition, the auditory projection to the cerebral cortex may have benefited from the cortical representation of space by developing a more elaborate sound localization system. In reptiles, on the other hand, the thalamofugal/lemniscal visual pathway does not play a dominant role for processing visual information (Ulinski 1990). In this vertebrate class, the more important tectofugal pathway and the auditory system project into the DVR, which apparently does not participate in such extensive associative networks with the hippocampus.

Thus, we postulate that a major innovation in the origin of the mammalian brain has to do with the confluence of the lemnothalamic and the collothalamic pathways in the dorsal pallium, in order to process spatial information which, among other things, participated in spatial learning and episodic memory. In this process, the hippocampus may have become a fundamental component in which both types of sensory pathways eventually converged. Strictly, this particular proposal is consistent with both the recapitulation and the outgroup hypotheses, since the merging of the two pathways is independent of the embryonic origin of

the ventrolateral isocortex. However, it may be more parsimonious to consider that for this confluence to occur, only the axonal projections changed their route instead of producing a massive cellular migration that dragged the collothalamic axons to a more dorsal position.

6.4. Other circuits: Frontal cortex and basolateral amygdala

An additional olfactory pathway influencing isocortical activity consists of the projections from the piriform cortex to the dorsomedial thalamic nucleus – which then sends axons to the frontal cortex – and of direct projections from the piriform cortex to the frontal cortex (Haberly 1990; Haberly & Price 1978). It is interesting that these projections are better developed in so-called "primitive" mammals like the opossum, whose dorsomedial nucleus has much denser olfactory projections than placental mammals (Benjamin et al. 1982; Lynch 1986). Furthermore, the orbitofrontal cortex of the rat is reciprocally connected with perirhinal and entorhinal areas and participates in odor memory (Ramus & Eichenbaum 2000). In the rat there is also a hippocampo-prefrontal/orbitofrontal circuit, which is connected with the nucleus accumbens, a structure involved in motivation (Aboitiz & Montiel 2001; Thierry et al. 2000). Thus, the olfactory cortex and the hippocampus may have been connected with parts of the dorsal cortex through several routes, which may have also participated in motivational aspects of behavior.

In this context, the basolateral amygdala of mammals has important connections with orbitofrontal cortex (McDonald 1991) and participates in olfactory memory, perhaps by encoding the motivational significance of stimuli used to guide behavior. On the other hand, the orbitofrontal cortex may use this information to select an appropriate behavioral strategy (Schoenbaum et al. 1998; 1999). The basolateral amygdala of mammals, instead of receiving and processing collothalamic sensory information as the ADVR does in reptiles, acquired a perhaps more restricted, modulatory role over motivation and emotional behavior.

7. Fossil mammals and their brains

The first radiation of mammal-like reptiles (synapsids) gave rise to the *pelycosaurs,* which were relatively large, lizard-like reptiles. In the upper Permian, pelycosaurs were gradually replaced by their descendants, the *therapsids.* The hands and feet of these animals faced more directly forward instead of being oriented sidewards as in other reptiles, which gave those animals a more mammalian-like gait. Some therapsids grew to achieve large sizes, and they are classified into carnivorous and herbivorous therapsids. Most therapsids became extinct by the end of the Triassic, but one group of carnivorous therapsids, the *cynodonts,* survived well into the Jurassic (Carroll 1988; Kemp 1982).

Cynodonts had a more mammal-like jaw musculature, but the ear ossicles were still attached to the lower jaw, as they are in reptiles. From cynodonts arose the *eucynodonts* or *mammaliaforms,* which include Jurassic fossils like Sinoconodon and Morganucodon, whose gross morphology resembled that of some present-day insectivores (Rowe 1996a; 1996b). True mammals descend from eucynodonts, and are defined by the presence of a single dentary bone making up the inferior mandible and the complete detachment of the middle ear ossicles, as in the fossils Hadrocodium (Luo et al. 2001), Gobiconodon and Repenonamus (Wang et al. 2001; however, according to these authors, Hadrocodium is a juvenile form and it is not clear whether it had a fully mammalian middle ear). Further evolution of mammals includes the origin of monotremes, marsupials, and placental mammals. Triconodon is another interesting fossil, originally considered to be close to Morganucodon (Carroll 1988), but, according to newer analyses, this fossil has been classified as a true mammal, perhaps belonging to the *therians* (marsupials and placental mammals; Rowe 1996a; 1996b).

Endocasts are molds of the cranial cavity of fossil animals. Analysis of these casts indicates that early mammal-like reptiles (therapsids) had narrow, tubular hemispheres with no signs of telencephalic expansion (Hopson 1979; Kemp 1982; Quiroga 1980). Increase in brain size, resulting from a generalized growth of the isocortex, occurs in the recent fossil mammals Triconodon and Hadrocodium (Luo et al. 2001; Rowe 1996a; 1996b; Fig. 7). In these fossils, the detachment of the auditory bones from the mandible to form the mammalian middle ear coincides with enlargement of the brain (Rowe 1996a; 1996b). However, in other fossil mammals like Repenomanus and Gobiconodon, braincases are narrow despite detachment of the ear ossicles (Wang et al. 2001). Therefore, brain expansion may have occurred after the origin of the middle ear, more than the reverse, that is, brain enlargement triggering ossicle detachment for mechanical reasons (Wang et al. 2001). As we propose, the development of collothalamic sensory projections (including the auditory pathway) into the isocortex was an important factor in the expansion of the isocortex. Although this may have been related more to the develop-

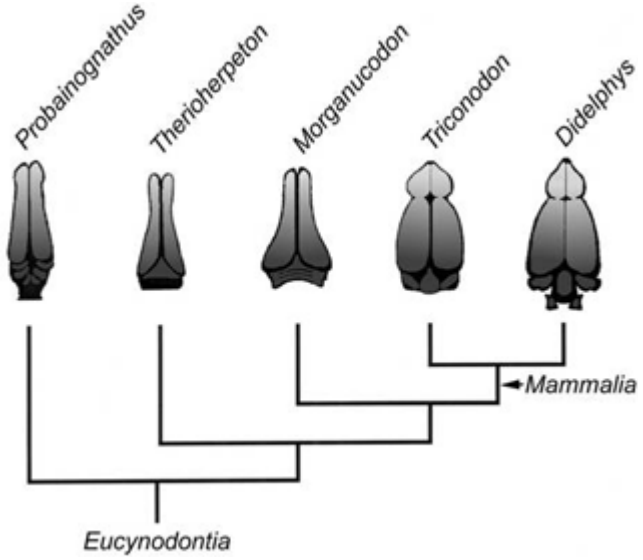

Figure 7. Endocasts of mammal-like reptiles and primitive mammals, indicating the progressive increase in brain size. Note that in Morganucodon, expansion of the posterior part of the hemisphere can be observed. More advanced mammals like Triconodon show a more complete expansion of the hemispheres. The first true mammals, possibly represented by Hadrocodium, Repenomanus, and Gobiconodon (not shown), are proposed to be in an intermediate position between Morganucodon and Triconodon. Based on Rowe (1996a; 1996b).

ment of the hippocampal, multimodal association circuits described above, it may have also contributed to enhanced hearing. In this context, the mammalian auditory cortex contains binaural cells, many of which are interconnected interhemispherically by fibers of the corpus callosum (Pallas 2001) and may participate in spatial localization of sounds. On the other hand, the DVR of birds and reptiles has few or no interhemispheric connections, which may limit telencephalic auditory spatial processing in these animals.

Interestingly, Morganucodon, a primitive mammaliaform taxonomically intermediate between Triconodon and smaller-brained, more primitive therapsids, shows only partial expansion of the brain. In this species, widening of the occipital parts of the hemispheres can be observed (Rowe 1996a; 1996b; Fig. 7). Admittedly, endocast information can be difficult to interpret, since there are few anatomical details to identify as landmarks. Nevertheless, this feature may perhaps be attributed to the early development of the dorsal cortex in Morganucodon.

8. Final comments

The main point of this article is that the origin of the mammalian isocortex may have been largely due to an overall dorsalizing effect during early pallial development in mammal-like reptiles. This may have implied (1) tangential expansion of the ventricular zone corresponding to the dorsal pallium, (2) increased duration of the neurogenetic period, and perhaps also (3) tangential migration of excitatory cells from the ventral pallium (although there is no evidence yet of such a process).

Current developmental evidence suggests separate origins of the mammalian isocortex and the reptilian DVR. The latter appears to be related to ventral pallial structures of mammals such as the basolateral amygdala and/or the endopiriform nucleus (ventral claustrum), while the isocortex originates largely from the dorsal pallium. There is a possibility that some cells that originally differentiated into the IT/VP, became part of the lateral or perhaps dorsal pallium, either by changing territorial identity or by undergoing tangential migration. In our view, this alternative is not to say that the lateral isocortex derives from an ancestral DVR. Rather, we consider that the two structures originated in parallel, in two different lineages (in mammal-like reptiles and in stem reptiles, respectively), neither of which is ancestral to the other. Evidence supporting this interpretation is the fossil endocasts of mammal-like reptiles, which indicate that brain expansion (and possibly the origin of the isocortex) was a late event in mammalian evolution.

Connectional evidence indicating similarity of sensory input in the reptilian ADVR and the mammalian auditory and extrastriate isocortex is contrasted with other hodological evidence showing important connectional differences between these structures. If the ADVR and the isocortex have different embryonic origins, this implies that the main mesencephalic sensory input has been directed to different targets in the lineages leading to sauropsids and to mammals. For example, the ectostriatum, a component of the avian ADVR, receives thalamic visual input from the thalamic nucleus rotundus, whereas layer IV of extrastriate visual cortex of mammals receives projections from the thalamic pulvinar nucleus. Furthermore, the intrinsic connections of the avian DVR (ectostriatum to neostriatum to hyperstriatum) are similar to the connections between the different isocortical laminae (layer IV to layers III-II to layers VI-V; Karten 1969). Many of these similarities in intrinsic connectivity may perhaps have been independently acquired in the evolution of birds and mammals. In fact, there may be strong parallelisms in sensory processing in the brains of birds and mammals, which does not imply that there cannot have been an important divergence earlier on. One important point in these considerations is that perhaps one of the major innovations in mammalian sensory processing was the confluence of the lemniscal and mesencephalic sensory pathways (especially visual) in the dorsal pallium, and their convergence in the amygdala and hippocampus. The concept that, in mammals, the collothalamic and the lemnothalamic processing routes merge in the telencephalon is compatible with both the recapitulation and the outgroup hypotheses. However, in terms of developmental mechanisms, it may be more parsimonious to consider that there has been a re-routing of the collothalamic inputs (outgroup hypothesis) rather than a migration of cells from the ventral to the dorsal pallium (recapitulation hypothesis).

One important problem concerns the issue of determining a strict homology to the isocortex in the reptilian brain. As we discussed, at least some cells in the superficial isocortical layers may have no counterpart in sauropsids. Likewise, if the outgroup hypothesis turns out to be correct, there may be many isocortical regions (i.e., extrastriate visual and auditory) that perhaps have no specific correspondence in the brains of sauropsids (although they may have emerged from some embryonic component present in the reptilian brain, like the dorsal cortex). One possibility is to consider the dorsal pallium of sauropsids and mammals as "field homologues." We consider that, although there may be a true homology in the embryonic structures, perhaps the best consideration is to assume that only some components of the adult isocortex may have homology in the adult reptilian brain, whereas others may be viewed as evolutionary innovations (see Northcutt 1999). Likewise, many parts of the sauropsidian ADVR may have no counterpart in the adult mammalian brain (Aboitiz 1992; 1999b).

The above proposals have been complemented with a scenario describing the origin of the isocortex from the dorsal pallium, based on the reciprocal relations of this structure and the hippocampus. The scenario proposed here is an attempt to describe the sequences of developmental and functional changes that may have led to this early separation of the reptilian and mammalian brain architectures. In our view, the main significance of these scenarios is that they provide an evolutionary framework which may guide future studies of the embryology and structure of the cerebral cortex.

Strictly speaking, our "hippocampal-olfactory" theory for the origin of isocortex might also agree with the recapitulation hypothesis. In this case, there would have been cell migration from the IT/VP into the dorsal cortex, and collothalamic afferents would have followed those cells; all this might have contributed to the development of associative networks with the olfactory cortex and hippocampus. In other words, cells originally from the IT/VP would have been transformed into dorsal pallial phenotypes. However, we consider that the outgroup hypothesis fits better with the concept of expansion of the dorsal cortex, in the sense

that it requires less and less dramatic developmental transformations. Furthermore, as mentioned, at this point there is no evidence indicative of the migratory process required by the recapitulation hypothesis.

Rejecting the recapitulation hypothesis and accepting the outgroup hypothesis implies the assumption that the reptilian and the mammalian brains diverged very early in their evolution, which would be consistent with the concept of therapsids diverging at the earliest points of the amniote radiation. An explanation of the expansion of the DVR in reptiles is still needed. However, we will preliminarily suggest that the reptilian solution was a more conservative outcome, in which emphasis in sensory processing was given by the mesencephalic projection systems (collothalamic), perhaps as it happens in other vertebrate classes. In mammals, the main innovation consisted of the early dominance of olfaction in sensory processing (possibly associated with nocturnal habits and with a new respiratory system; Carroll 1988; Kemp 1982), which triggered the development of olfactory-dorsal cortex-hippocampal associative networks, eventuallly facilitating the confluence of the lemnothalamic and collothalamic sensory streams in the dorsal pallium and hippocampus.

Finally, the present perspective raises questions that impinge directly on several lines of research. For example, the study of dorsoventral gradients in isocortical specification, the studies of tangential cell migration into the isocortex, and the role of Pax-6 in reptilian cortical lamination may have immediate relevance to the hypotheses proposed here. On the functional side, comparative studies on hippocampal and amygdalar functions in amphibians, reptiles, and mammals may be of special relevance in relation to the concept of isocortical expansion triggered by hippocampo-olfactory-cortical associative networks.

ACKNOWLEDGMENTS

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APPENDIX

Glossary of Abbreviations

A	termination site of the auditory projection
ADVR	anterior dorsal ventricular ridge
AM	amygdala; basolateral amygdala
cdk5	cyclin-dependant protein kinase 5
CP	cortical plate
DCx	dorsal cortex
Dp	dorsal pallium
DVR	dorsal ventricular ridge
GEs	ganglionic eminences
GL	thalamic dorsal lateral geniculate nucleus
HIP	hippocampus
ICx	isocortex
IL	thalamic intralaminar nucleus
IT	intermediate territory
IT/VP	intermediate territory/ventral pallium
IZ	intermediate zone
LCx	lateral cortex
LEM/TAF	lemniscal/thalamofugal visual pathway
LGE	lateral ganglionic eminence
Lp	lateral pallium
MCx	medial cortex
MES/TEL	mesencephalic/tectofugal visual pathway
MGE	medial ganglionic eminence
Mp	medial pallium
MZ	marginal zone
NP	thalamic pulvinar nucleus
NR	thalamic nucleus rotundus
O	olfactory tuberculum
OCx	olfactory cortex
PDVR	posterior dorsal ventricular ridge
Se	septum
SP	subplate
STR	corpus striatum
vl	termination site of the lemniscal, thalamofugal projection
vc	termination site of the collicular, tectofugal projection
VP	ventral pallium
VZ	ventricular zone
W	Wulst

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From axis to triangle: The role of orbital cortex

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Abstract: This commentary focuses on the "olfactory cortices–hippocampal formation" axis, proposed by Aboitiz et al. to be that network which allowed the first mammals to create elaborate representations of space. I argue here that this neural axis can be extended to a triangle of structures which also includes the orbital cortex.

Aboitiz et al. present compelling evidence that the mammalian isocortex appeared on account of a dorsalizing effect during the early development of the pallium of the first mammals. The authors argue that the olfactory-hippocampal-dorsal cortex circuit was needed to create complex olfactory-based representations of space.

Though the data cited by the authors support the olfactory cortex–hippocampus theory (OHT), I propose that this network is extendable to the orbital cortices and that these form a necessary component of the network of brain regions responsible for complex representations of space.

The orbital cortex in the rat receives connections from the subiculum (Canteras & Swanson 1992; Jay & Witter 1991), and a light projection from the CA1 field of the hippocampus (Jay & Witter). Unilateral ablations of the ventral lateral orbital cortices in rats lead to spatial neglect (King et al. 1989), and bilateral lesions of the same area impair rats performing tasks that require spatial maps of the environment (Corwin et al. 1994). The orbital cortex of the rat also receives connections from such olfactory-related structures as the perirhinal cortex (Ramus & Eichenbaum 2000a) and the entorhinal cortex (Deacon et al. 1983; Swanson &

Kohler 1986). Damage to the orbital cortex impairs animals in the odor version of the delayed nonmatch to sample (DNMS) task when the memory delay is minimal, which suggests that this region is important in perceptual processing or learning of rules (Eichenbaum 2000a).

Neurons in the rat orbital cortex recorded during an eight-odor discrimination task correlate their activity with recent past information and anticipate future events (Schoenbaum & Eichenbaum 1995). Physiological studies of orbital neurons in the rat showed that these fire either for single events or associations of events such as initiation of trials, sampling of odors, and reward consumption of odor-guided DNMS tasks (Ramus & Eichenbaum 2000). Rodent, monkey, and human experimental data show that the orbital cortex is the place where inputs from sensory and emotional and motivational information converge and it may be involved in representation of goals (Rolls 2000; Schultz et al. 2000). The orbital cortices can be considered to be part of the partially overlapping networks that are involved in the visual and nonvisual representations of space where sensory information is associated with reward and motivational-related information for rules formation.

The survival of animals depends on the creation and storage of complex representations of space. These are not only collections of places associated with visual or nonvisual cues or associations of stimuli, but also sets of rules for navigation and associations between stimuli and rewards. The orbital cortex appears to be a place involved both in the creation of the rules needed to construct and use spatial representations in lower mammalian species such as rodents, and for encoding more abstract rules in monkeys and humans. Therefore, the successful survival of animals also depends on the orbital cortices. The existence of the orbital cortex and the connections with olfactory regions in insectivore species (Radke-Schuller & Kunzle 2000) may be an indication that this region was present in the earliest mammals, and it may have similar functions across mammalian species.

The experimental findings presented above suggest that the olfactory cortex–hippocampal formation axis can be extended to a triangle of structures involved in olfactory representations of the environment, the "olfactory cortex–hippocampal formation–orbital cortex," and it may appear early in the mammalian speciation. Nonmammalian vertebrate species present homologous structures of the olfactory cortex and the hippocampal formation, but the orbital cortex appears to be characteristic only to mammals.

One can therefore hypothesize that the network of cortical regions made of the olfactory regions, hippocampal formation, and orbital cortices is that circuit which allowed early mammals to construct complex representations of space, first olfactory-based but which, following the hypothesis of Aboitiz et al., became more visual when diurnal mammalian species emerged.

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The third alternative: Duplication of collopallium in isocortical evolution

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Abstract: One hypothesis of isocortical evolution requires tangential migration of glutaminergic neurons. A second requires invasion of collothalamic afferents into the dorsal pallium, a territory that in sauropsids is solely lemnopallial. A third alternative is noted here – duplication of the original collopallial territory. The duplicated region would be formed by radial migration of excitatory neurons and would maintain its collothalamic innervation.

The central point of this target article – the "hippocampal-olfactory hypothesis" for isocortical evolution and its adaptive advantage – is sound and has precedent in the literature. For example, Butler (1994a) noted that

> Selection pressures strongly favored those amniotes in which this pallial expansion . . . occurred. The relay of information from both divisions [collothalamic and lemnothalamic pallia] . . . to the medial pallium for memory-related functions . . . would have conferred a significant competitive advantage.

The idea of an adaptive advantage gained by increased sensory inputs to the limbic system is compatible with each of several current hypotheses for the gain and expansion of the isocortex.

Two possible scenarios for isocortical expansion are considered in the target article. Did the isocortex evolve as an expansion of the dorsal pallium, as defined by Puelles et al. (2000), and thus have a unitary origin? Alternatively, did the isocortex have a dual origin, such that its developmentally medial part evolved as an expanded dorsal pallium and its lateral part evolved due to tangential migration of glutaminergic neuronal elements from a more ventrolateral part of the pallial mantle? The latter idea can be discarded for lack of evidence. The former, single-origin scenario would have involved a substantial change in connectivity. Because the dorsal pallium is in receipt of only lemnothalamic projections in sauropsids (Butler 1994a), its expansion and gain of collothalamic afferents would require substantial changes in the molecular cues expressed in the subplate and perhaps elsewhere. As in all cases of proposed neural homology, both developmental and hodological data must be weighed and accounted for, particularly because connections are the result of molecular cues expressed and utilized during development.

A key issue regarding isocortical evolution is whether a ventral pallial division can be separately distinguished on gene-expression criteria. A ventral pallium was identified by lack of Emx-1 expression (Puelles et al. 2000; Smith-Fernandez et al. 1998), and at least some of its derivatives are collothalamic targets in both mammals and sauropsids. However, Gorski et al. (2002) have demonstrated that all pallial regions contain neurons that express Emx-1 at some time during development. All parts of the pallium – medial, dorsal, lateral, and ventral – express Pax-6, Tbr-1, and Emx-1. Although the ventral pallial territory may be distinguished by some other markers, such as differences in the degree of expression of cadherins (Redies et al. 2001), it may vary only as a matter of degree from other pallial areas due to gene-expression gradients rather than as a sovereignly discrete entity.

A third alternative exists that involves dual evolutionary origin of the isocortex but does not require either changes in molecular guidance cues or tangential migration of glutaminergic neurons. Although differing to some extent in details and rationales, dual-origin hypotheses for the isocortex have been previously proposed (e.g., Abbie 1940; Butler 1994a; Karten 1969; Reiner 1993; 2000; Sanides 1970). The "dual expansion hypothesis" (Butler 1994a) was based to a large extent on the recognition that two separate divisions of the dorsal thalamus – the lemnothalamus and collothalamus – exist, have different patterns of telencephalic projections, and were differentially expanded in the mammalian and sauropsid lineages (Butler 1994b; 1995). Recently, the separate identities of these two dorsal thalamic divisions have received strong support from molecular data, including calcium-binding protein immunoreactivity, Gbx2 expression, and Math4a expression (Dávila et al. 2000; González et al. 2002; Martínez-de-la-Torre et al. 2002). If there are two such separate divisions of the dorsal thalamus, two comparably separate divisions of the isocortex – lemnocortex and collocortex – might likewise exist in mammals and be under separate selective pressures.

The third alternative requires only a feature of collocortex that is already firmly established: the marked propensity of collocortical areas to duplicate themselves, as has occurred independently within several mammalian lineages (Allman 1977; Kaas 1982; 1995; Krubitzer 2000). The recently proposed field homology

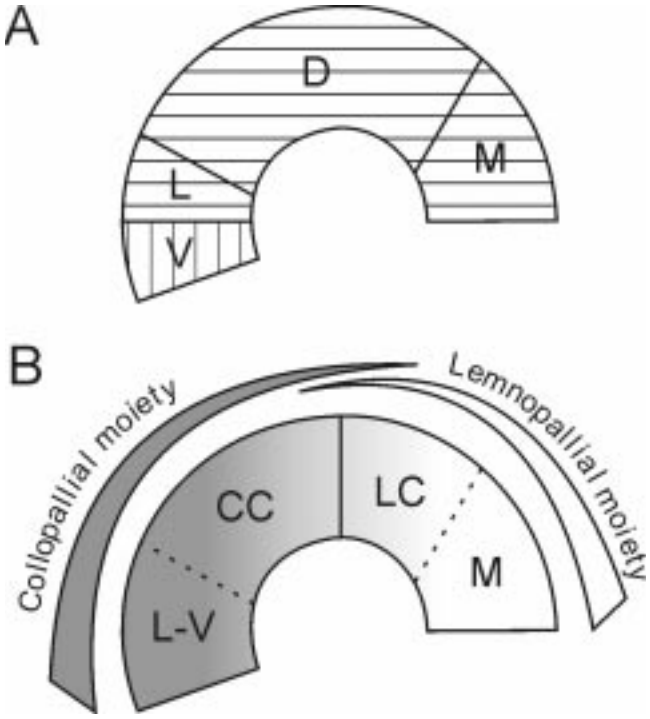

Figure 1 (Butler). **A:** Pallial divisions as originally proposed by Puelles et al. (2000) with Emx-1-positive medial (M), dorsal (D), and lateral (L) pallia and an Emx-1-negative ventral (V) pallium. Subsequent work (Gorsky et al. 2002) has demonstrated Emx-1-positivity in the ventral pallium as well. This model requires an invasion of collothalamic projections into the lateral part of the dorsal pallium. **B:** Collopallial and lemnopallial moieties proposed on the basis of lateromedial and mediolateral gradients (represented by curved narrowing slivers above the pallial hemisphere) of gene expression patterns. (The lateral and medial pallia are included here in this broader, developmental concept of the collo- and lemnopallial territories, even though in most cases they are not in direct receipt of the ascending thalamic projections.) This model retains collothalamic projections to collopallial territory. The collocortex (CC) arose by duplication of the original lateroventral (L-V) part of the pallium; only the lemnocortex (LC) is the derivative of the original dorsal pallium and is homologous to the Wulst of birds and the dorsal cortex of reptiles.

(Butler & Molnár 2002; Molnár & Butler 2002a; 2002b) of the sauropsid anterior dorsal ventricular ridge to the claustrum (where present; see Butler et al. 2002), pallial amygdala, and collocortex of mammals incorporates the idea that duplication of the ventrolateral pallium could account for the origin of the collocortex. With duplication, tangential migration of excitatory neurons is not required; within the more dorsally lying "copy" of the original collopallial field, radial migration of excitatory neurons would produce the cortex.

The specification of the collothalamic moiety (including lateral pallium, claustroamygdalar formation, and collocortex) and the lemnothalamic moiety (including medial pallium and lemnocortex) may be accomplished during development by a combination of gradients of gene expression patterns (Fig. 1). For example, Pax6, Tbr2, and Tlx are all expressed in a high-lateral to low-medial gradient across the pallium in mice (Muzio et al. 2002a; Stenman et al. 2003). This model allows for maintenance of developmental guidance cues for separate collothalamic and lemnothalamic projections and requires only radial migration of excitatory neurons in the collocortical region.

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Avian and mammalian hippocampus: No degrees of freedom in evolution of function

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Abstract: Aboitiz et al. suggest that the mammalian isocortex is derived from the dorsal cortex of reptiles and birds, and that there has been a major divergence in the connectivity patterns (and hence function) of the mammalian and reptilian/avian hippocampus. There is considerable evidence to suggest, however, that the avian hippocampus serves the exact same function as the mammalian hippocampus.

Aboitiz, Morales, and Montiel (Aboitiz et al.) are to be complemented for their fine thesis on the evolution of the mammalian isocortex. The issue I would like to raise is not with the developmental or connectional transformations that may have occurred, but rather with the purported functional transformations that accompanied the evolution of the mammalian isocortex from the dorsal pallium of reptiles and birds. (For ease of exposition, I will restrict my discussion to birds.)

In section 6.1, the authors argue that in mammals, thalamofugal and tectofugal sensory information blend together and ultimately project to the hippocampus and the amygdala. In birds, on the other hand, the majority of the thalamofugal sensory information is sent to the hippocampus but the majority of the tectofugal information is transmitted to the ADVR and the PDVR, the latter of which is comparable to the mammalian amygdala (see target article, sect. 3.2). According to the authors, these differences in connectional patterns suggest that the hippocampus of mammals receives a much heavier sensory projection than the hippocampus of birds, and that birds "may rely more on amygdalar components (PDVR/archistriatum) than on the hippocampus to process certain types of sensory and mnemonic information" (sect. 6.1, para. 1). The implication is that the avian hippocampus may process different, or perhaps a more restricted range of, information than the mammalian hippocampus.

Over the past six years we have conducted a number of studies looking at the function of the hippocampus in birds (Colombo & Broadbent 2000). Our data indicate that damage to the avian hippocampus causes the same constellation of impairments as does damage to the mammalian hippocampus. Part of the problem with the mammalian hippocampal lesion literature is that in most early studies the damage often extended well beyond the hippocampus into structures whose exact function was not known. So although early studies did show impairments on visual memory tasks after damage to the "hippocampus" (Zola-Morgan & Squire 1986), later studies in which the lesions were restricted to the hippocampus failed to find any impairments on the three standard tasks used to assay visual memory in mammals: visual delayed nonmatching-to-sample, visual concurrent discrimination, or, retention of a visual discrimination (Alvarez et al. 1995). (The small visual impairments seen at the longest delay on the visual delayed nonmatching-to-sample task in the Alvarez et al. [1995] study is likely the result of a design flaw that may have inadvertently introduced a spatial component into the task.) Just as in mammals, birds with damage to the hippocampus also show no impairments on these three visual memory tasks (Colombo et al. 1997b). In short, there is no convincing evidence to date that damage to the hippocampus in either mammals or birds impairs performance on a purely visual memory task.

In contrast to the lack of effects of hippocampal lesions on visual tasks, both mammals and birds with damage to the hippocampus show profound impairments on tasks that require the processing and retention of spatial information. Mammals with hippocampal damage, for example, are impaired on both the radial-arm maze task (Olton et al. 1979) as well as the water maze task (Morris et al. 1982). Likewise, birds with hippocampal damage are also impaired on an analogue of the radial-arm maze task

(Colombo et al. 1997a) and a dry-land version of the water maze task (Fremouw et al. 1997). The authors also argue in section 6.1 that "not all forms of spatial memory depend on the hippocampus in birds, as they do in mammals." In support of this statement, the authors point to the fact that navigation using the sun for directional information is impaired by hippocampal lesions in birds whereas navigation on the basis of landmark beacons is not. In fact, a similar finding can be seen in mammals (Pearce et al. 1998), further supporting the view that the avian hippocampus performs the same functions as the mammalian hippocampus.

The similarities between the mammalian and avian hippocampus are not restricted to standard tests of visual and spatial memory either. Both birds and mammals, for example, are also impaired on autoshaping. In the autoshaping procedure, animals are presented with a stimulus that, after a few seconds, is followed by the delivery of food. Following a number of such pairings, cortically intact animals will begin to peck at the stimulus in a reliable fashion, whereas both mammals (Good & Honey 1991) and birds (Reilly & Good 1989) with hippocampal damage are very slow to acquire the autoshaping response. Furthermore, in a recent study we have shown that the autoshaping problem is caused by the failure on the part of the hippocampal birds to actually make contact with the key; that is, they peck in the direction of the key but fail to hit it (Richmond & Colombo 2002). This impairment is reminiscent of the behavior of hippocampal rats in a water maze who, according to Whishaw et al. (1995), are not impaired in "knowing where" but in "getting there."

We have mentioned just a few of the similarities that can be seen following damage to the hippocampus in mammals and birds. More important, we have yet to come across a single instance in which hippocampal lesions in birds cause an impairment different from that caused by hippocampal lesions in mammals. This led us (Colombo & Broadbent 2000) to conclude, rather tongue-in-cheek, that despite 300 million years of independent evolution, there appear to be no degrees of freedom in the evolution of hippocampal function. It becomes important then to understand how this consistency in function has been maintained despite the developmental and connectional transformations that have occurred.

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Paleoecology and the overlap of homeotic genes for isocortex evolution

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Abstract: Two issues in synapsid brain evolution are discussed: the presumed structure and function of the brain of the Synapsida/Diapsida common ancestral, and the enlargement of dorsal telencephalon. Ecological niches possibly occupied by some Carboniferous tetrapods are considered in order to speculate about evolution of major telencephalic sectors. An alternative interpretation of isocortical origins, based on differences in Pax-6 expression, is suggested for discussion.

The target article by Aboitiz et al. raises some thought-provoking ideas about what, where, how, and why peculiar characteristics of the amniote brain originated. One evolutionary issue discussed by the authors is the brain organization of the Synapsida/Diapsida ancestral, summarized by the confrontation between outgroup and recapitulation hypotheses (Butler 1994a; 1994b; Karten 1991; Northcutt & Kaas 1995).

In order to decide between these hypotheses or to propose another, it would be fruitful to examine the ecology of ancient anamniote and amniote vertebrates based on fossil records. In this context, different ecological scenarios might be considered. The first one is the land conquest by *Ichthyostegidae* anamniote tetrapods, followed by the anamniote adaptive radiation during the Early Carboniferous period (Carroll 1988). A second scenario is the appearance of amniote tetrapods in the Late Carboniferous period, and the subsequent Anapsida/Diapsida/Synapsida divergence (Carroll 1988). The expansion of dorsal telencephalic areas in surface and thickness is a more recent evolutionary event, occurring in the Early Jurassic period together with the rise of ancestral mammals, as exemplified by *Hadrocodium* (Luo et al. 2001).

It is compelling to suppose that the conquest of land by vertebrates modified the selective pressures on the ostheomuscular system used for body support and locomotion, as well as on the morphophysiological systems employed for feeding, breathing, and reproduction (Carroll 1988). The nervous system necessarily had to be a central target for mutation selection in the new ecological niche. The amphibian lifestyle presumably forced sensory systems adapted to an aquatic environment (e.g., lateral line and olfactory systems) to become less useful on land, than others such as the visual system. Rhipidistian fishes and early amphibians probably were some of the most important freshwater predators (Carroll 1988). Once on land, the adaptive radiation of anamniotes occupied other feeding guilds, such as insectivory. In the insectivore anamniote clades, strong selective pressures were concentrated on the visual system to detect object size and movement.

The Anthracosaurs, among anamniote tetrapods, were probably the best adapted to live on land. In fact, many of them occupied the terrestrial invertebrates feeding guild. Captorhinomorphs were Anapsida early amniotes, considered as the stem reptile stock. These animals were closely related to the Anthracosaurs, and were probably also terrestrial insectivores (Carroll 1988). The adaptive radiation of the Late Carboniferous terrestrial arthropods (Carvalho 2000) created an abundant food source for amniotes. However, they had to be captured on the ground, forcing the animals to actively explore the environment to feed. The strategy of active feeding probably selected individuals with more developed and integrated audiovisual-somatosensory (collothalamic system/ADVR) and olfactory systems (piriform cortex), as well as good spatial memory (hippocampus), and highly coordinated movements (basal ganglia).

The collothalamic system of extant amphibian anamniotes projects only to the striatum (Wilczynski & Northcutt 1983). However, it also establishes connection with the DVR in reptiles (Bruce & Butler 1984b; Guirado et al. 2000) and with the isocortex of mammals (Butler 1994a; 1994b). It is possible that the undifferentiated anterior lateral pallium of terrestrial anamniotes became divided into a ventral, audiovisual-related structure (ADVR), and a more dorsal, olfactory-related structure (lateral cortex), as in amniotes. Developmental changes may have occurred that transformed the five neurogenetic sectors found in the telencephalon of amphibians into the six telencephalic sectors of reptiles and mammals. It could have become possible, given the transformation of the olfactory intermediate sector of Anthracosaurs into the more elaborated and adaptive structure (the lateral pallium and the ventral pallium) of Captorhinomorphs anapsids, that they became more capable of actively exploring the environment using both visual and olfactory systems. The projection into the lateral pallium of audiovisual-somatosensory information from the mesencephalon to ADVR, with information from the olfactory bulbs to piriform cortex, the concomitant development of olfactory and audiovisual spatial memory in the medial and dorsal pallium, and the convergence of these inputs to basal ganglia, all could have allowed active foraging behaviour.

The first Synapsids (pelycosaurs) were terrestrial vertebrate predators (Carroll 1988). It is conceivable that the capacity to hunt vertebrate preys requires cerebral configurations that integrate somatosensory, auditory, and visual inputs with complex olfactory information. This integration may possibly be performed by the polymodal connections of ADVR with highly developed olfactory

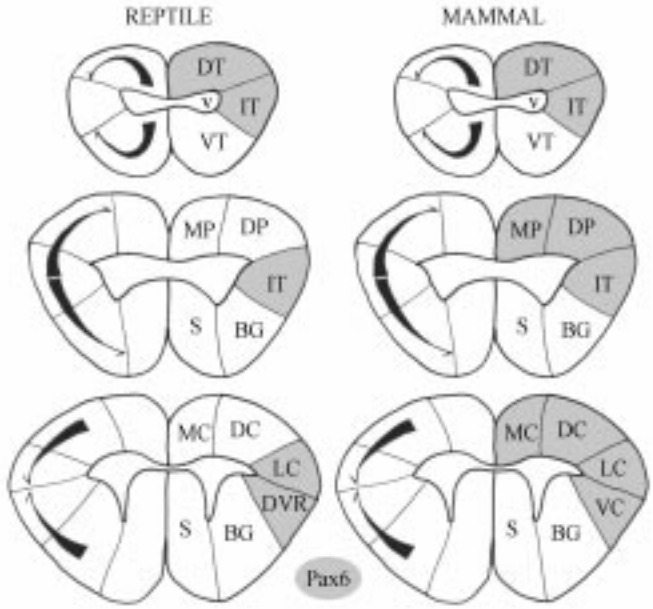

Figure 1 (Furtado). Schematic sequence of developmental events resulting in the specification of the main anterior telencephalic regions in reptiles and mammals, viewed in the coronal plane. Pax6 gene expression is shown in gray. Some gradients of inductors of pattern formation (segregation of isogenetic cell populations) are denoted by black arrows. The persistent expression of particular homeotic genes in dorsal areas of mammals could allow the specification of intermediate cell phenotypes within the dorsal cortex territory. BG, basal ganglia; DC, dorsal cortex; DP, dorsal pallium; DT, dorsal territory; DVR, dorsal ventricular ridge; IT, intermediate territory; LC, lateral cortex; MC, medial cortex; MP, medial pallium; S, septum; v, ventricle; VC, ventral cortex; VT, ventral territory.

connections in lateral, medial, and dorsal cortex. This suggests that the reptile/mammal common ancestral had a reptilian-like brain rather than an amphibian-like brain structure.

Brain changes in surface (area) and thickness (layers) that occurred in the synapsid lineage were not necessarily simultaneous. Fossil records suggest that the area enlargement did not occur until the Early Jurassic, exemplified by the brain of *Hadrocodium* (Luo et al. 2001). Nevertheless, the moment for the acquisition of new layers in the emerging isocortex is not very clear. The ecological scenario has to take into account the colonization of nocturnal ecological niches allowed by endothermy and the consequent exploratory behaviour driven by olfactory/auditory inputs. It is also necessary to include the nature of parental care, and maybe the coevolution of large-brained coelurosaurs.

Here we would like to suggest an alternative hypothesis that could conciliate the recapitulation hypothesis with the incompatibilities of the developmental criteria for homology, necessary to establish the origins of the isocortex. The hypothesis is based on the overlap (mixture) of two neurogenetic territories during the early stages of anterior telencephalon development. This overlap is possible if the border between the dorsal pallium territory and the intermediate territory (that will give rise to the lateral and ventral pallium) fails to be established (Fig. 1). The overlap led to the approximation of the audiovisual associative ADVR with the primary somatic-motor/visual/olfactory dorsal cortex, and allows the mixture and expansion of lemnothalamic/collothalamic systems within the dorsal pallium.

Pax-6 expression in pallial territory of avian embryo is interrupted early, but this does not occur in mammals (Puelles et al. 2000; Smith Fernandez et al. 1998; Stoykova 2000). Some mutation in the developmental genetic regulatory systems (Davidson 2001) could have led to a failure in the blockage of expression of Pax-6 (or another similar homeotic gene) within the pallial territory in the mammalian ancestral brain. This mutation could have gathered, in the same neurogenetic territory, cells that express pallial or intermediate territory-related homeotic genes. The maintained expression of Pax-6 in the mammalian dorsal pallium could have contributed to the specification of intermediate-like precursor cell, possibly radial glia (Götz et al. 1998; Malatesta et al. 2003), at the subventricular zone (Tarabykin et al. 2001) within dorsal pallium neurogenetic territory. These views suggest a homology between preplate/infragranular cells of mammalian isocortex with the dorsal cortex cells of reptiles and a homology between granular/supragranular cells with the ADVR cells. Inhibitory neurons came from subpallium in both taxa by tangential migration, following ancient and new routes to reach the isocortex (Anderson et al. 2001).

Mesozoic mammals and early mammalian brain diversity

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Abstract: Fossil remains witness the relationship between the appearance of the middle ear and the expansion of the brain in early mammals. Nevertheless, the lack of detachment of ear ossicles in the mammaliaform *Morganucodon,* despite brain enlargement, points to other factors that triggered brain expansion in early mammals. Moreover, brain expansion in some early mammalian groups seems to have favored brain regions other than the cortex.

The issue of the origin of the mammalian isocortex raises the question of the various evolutionary factors that produced a uniquely mammalian structure. The suggestion of the authors is that the mammalian isocortex originated in large part as a consequence of a dorsalizing influence in pallial development. The authors also assess how fossil evidence could shed light on isocortical origin. This is very welcome because, even in paleontological studies on early mammalian relationships, brain structure inferred from investigation of endocranial casts has been almost completely neglected (Kielan-Jaworowska 1997).

Besides functional demands involving the olfactory cortex, the dorsal cortex, and the hippocampus, an important functional correlate of the isocortical expansion is the detachment of the postdentary bones from the dentary, and the possible incorporation of these elements into the middle ear in early mammals (Luo et al. 2002; Rowe 1996b). The detachment of the auditory bones from the mandible and its coincidence with the enlargement of the brain is observed in several early mammalian fossil specimens.

There are some notable exceptions to this general pattern, such as the true mammalian form *Repenomamus* (Wang et al. 2001). As summarized by Luo et al. (2002), the brain vault is wider in the parietal region of *Hadrocodium,* and of the mammalian crown-group representative taxa, than in cynodonts and *Morganucodon. Hadrocodium* and the mammalian crown-group constitute a clade characterized by various diagnostic apomorphies. The mammalian crown-group is defined as the common ancestor of all living mammals and also includes the triconodonts (*Triconodon, Gobiconodon, Repenomamus*) and the multituberculates. The narrow braincase of some early true mammals such as *Repenomamus* and *Gobiconondon* is in concordance with the various evolutionary rates of the triconodont subgroups and with the paraphyletic nature of the triconodont group.

The consensus could be that mammals with enlarged isocortex have a fully evolved middle ear. The reverse is, however, not true.

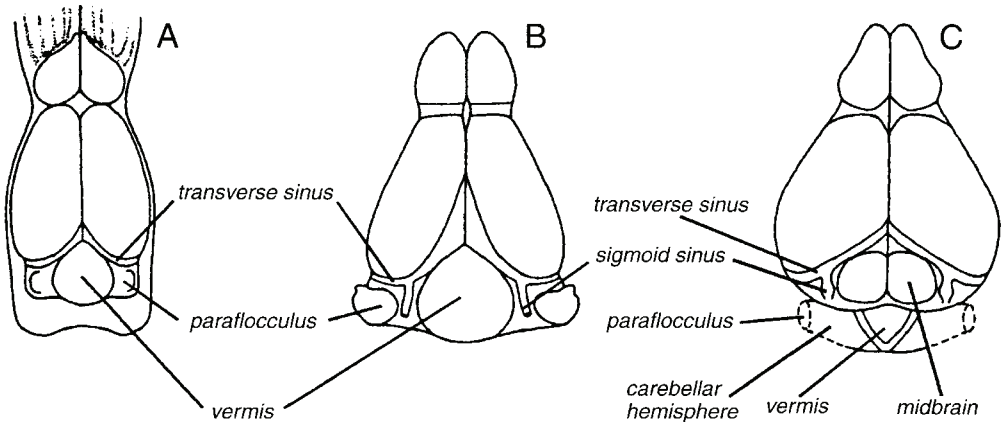

Figure 1 (Gilissen & Smith). Dorsal view of brain reconstructions in three Mesozoic mammals, based on endocranial casts. **A.** Triconodont *Triconodon.* **B.** Multituberculate *Chulsanbaatar.* **C.** Eutherian *Barunlestes.* A and B represent the cryptomesencephalic type, C represents the eumesencephalic type. Reprinted from Z. Kielan-Jaworowska, "Characters of multituberculates neglected in phylogenetic analyses of early mammals," *Lethaia,* 1997, vol. 29, pp. 249–66, by permission of Taylor and Francis AS.

In this context, the reference to *Morganucodon* is particularly interesting because it is the most completely known Late Triassic–Early Jurassic mammaliaform. *Morganucodon* and living mammals represent a clade characterized by a large suite of derived dental characters and basicranial features, but the ear ossicles are still attached to the lower jaw in *Morganucodon,* despite a clear brain enlargement when compared to mammal-like reptiles (Luo et al. 2002). This could be explained by contributions of hippocampal and multimodal association circuits to the enlargement of the isocortex more than to enhanced hearing, as suggested elsewhere by the authors. In any case, the importance of the transcallosal interhemispheric connections of the binaural cells makes the telencephalic auditory spatial processing a largely isocortical and, therefore, mammalian feature.

We acknowledge that mesozoic mammals are characterized by cerebral hemispheres diverging posteriorly. Nevertheless, according to Kielan-Jaworowska (1986), two distinct types of brain morphology can be defined within this pattern (Fig. 1). In some primitive mammals such as triconodonts, and especially multituberculates, the vermis and the paraflocculi are very large with no apparent cerebellar hemispheres and no dorsal midbrain exposure. In this type, the so-called "cryptomesencephalic type," the large vermis seems to push the cerebral hemispheres laterally, and the breadth of the posterior part of the brain is increased by the presence of the large paraflocculi. Therefore, the cerebral hemispheres appear to be larger posteriorly but this does not reflect expansion of the posterior part of the isocortex.

In the other type of brain morphology, the so-called "eumesencephalic type," the cerebral hemispheres are actually well developed, the presence of cerebellar hemispheres is apparent, and there is a large dorsal midbrain exposure. All extant mammals are derived from this second type. It must be emphasized that variability in dorsal midbrain exposure shows a huge variability even within orders of extant mammals (Kaas & Collins 2001). The eumesencephalic type is represented by the Cretaceous theria *Barunlestes* (Kielan-Jaworowska 1986) and possibly by the primitive mammaliaform *Morganucodon* (Kielan-Jaworowska 1986; 1997). It is not clear, however, if the partial expansion of the posterior part of the brain in *Morganucodon* is due to an enlargement of the posterior part of the cerebral hemispheres, because the posterior part of the endocranial cast is not well identified at the anatomic level in *Morganucodon.* Interestingly, the posterior part of the brain of cynodonts such as *Therioherpeton* also appears to be enlarged when compared to other cynodonts (cf. target article, Fig. 7; Kielan-Jaworowska 1986).

In view of the studies of Kielan-Jaworowska (1986; 1997), it is well possible that the posterior enlargement of the endocranial cast can in some cases be due to enlargement of the vermis and paraflocculi rather than to enlargement of the posterior part of the isocortex. This could be the case for the Mesozoic true mammalian group multituberculates. Such differences in mesozoic mammalian brain patterns obscure the scenario of a single trend leading to enlarged posterior parts of the isocortex from mammal-like reptiles to more advanced mammalian taxa.

The authors mention the observation that gross morphology of Mesozoic mammals resembles that of some present-day insectivores. It would be of high interest to better understand what kind of ecological micro-niches Mesozoic mammals occupied and, hence, if early mammalian brain evolution was already characterized by various trends comparable to or exceeding the situation that can be observed in extant Insectivora (Catania 2000).

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The dorsal thalamic connection in the origin of the isocortex

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Abstract: The origin of the isocortex may be seen as a series of gradual changes (each one with an adaptive value) from a reptilian-like cerebral cortex, as proposed by Aboitiz et al., or as a new dorsal pallium derivative in mammals which undergoes a surface expansion concomitant with the expansion of the dorsal tier of the dorsal thalamus.

The vision of the evolutionary origin of the isocortex offered by Aboitiz et al. must be applauded as an effort directed to integrate diverse connectional, developmental, and functional data, as well as to reconcile two completely different scenarios of the evolution of the isocortex. Overall, I agree with the main point of the target article – that the isocortex and the dorsal cortex of reptiles are field homologous because both are derivatives of the dorsal pallium. Aboitiz et al. present a very interesting review of the literature and analyze just up to the molecular levels, the events they consider

necessary to give rise to an isocortex. However, some refinement should be made to their review of the thalamo-telencephalic connections and, even more important, to their conception of the evolutionary processes originating the isocortex.

A recurrent problem in analyzing thalamo-telencephalic connections from a comparative view is to describe only one target (usually the more conspicuous) for the thalamic projections. This approach does not analyze the entire set of connections and tends to underestimate other thalamic projections. It implies that thalamic projections found in mammals and not in other vertebrates must be interpreted as redirected to one specific telencephalic target, when in fact new thalamic projections can be considered as further acquisitions (and likely appeared as collateral axons) within a basic common pattern of connections shared by different vertebrates, but with their own evolutionary history.

In reptiles, dorsal thalamic nuclei localized to the middle and ventral tiers receive strong mesencephalic (collicular) inputs and project to the basal ganglia (Gonzalez et al. 1990) and then to ventral (and likely lateral) pallium derivatives (Guirado et al. 2000). Thus, basal ganglia receive a major input from the dorsal thalamus, as in amphibians. On the other hand, dorsal thalamic efferent projections from dorsal tier nuclei end mainly in the medial, dorsal, and lateral cortices of reptiles. These connections convey lemnothalamic as well as collothalamic information (the latter through the dorsolateral anterior nucleus, a multimodal nucleus in the dorsal tier receiving afferent fibers from a variety of sources including the optic tectum). Therefore, the confluence of lemnothalamic and collothalamic pathways in the dorsal pallium is not an innovation of mammalian brains, as postulated in the target article. Aboitiz et al. propose that the development of collothalamic sensory projections into the isocortex was an important factor in the expansion of the isocortex. Why not consider the possibility that the development of the isocortex was *concomitant* with the development and increasing complexity (i.e., more mantle derivatives and more superficially located nuclei) of dorsal tier nuclei in the dorsal thalamus? These nuclei convey both lemniscal and collicular information to the isocortex.

On the other hand, the visual thalamofugal projection to the cerebral cortex has been usually considered as a major shared feature between the isocortex and the reptilian dorsal cortex. It should be noted that only turtles among reptiles seem to have a visual thalamic projection to the dorsal cortex. There is not any description of such a projection in other reptilian groups. Thus, depending on what phylogenetic analysis of the relations between turtles and mammals is considered, the more parsimonious explanation for this feature is either that the thalamo-cortical visual projection is secondarily lost in nonchelonian reptiles (the case of a close relation between turtles and mammals), or the result of a convergent (nonhomologous) evolution (the case of considering turtles as a group of reptiles with no direct relation to the ancestral anapsids).

Regarding the conceptual concern I cited above, Aboitiz et al. propose a scenario where changes necessary to construct a six-layered isocortex are sequentially explained. In other words, they intend to explain how to transform gradually a reptilian dorsal cortex into a mammalian isocortex. Aboitiz et al. assume that each gradual transformation has an adaptive value, and that selective pressures drive each transformation. These transformations (which are well delineated in the target article) actually correspond to changes in embryonic development that are able to modify the final state of the organ (in this case the brain). However, conceptually there is no need for each transformation to be adaptive. For example, the inside-out neurogenetic gradient itself does not necessarily need to have an adaptive value. It is the entire postnatal/adult structure that is presented to nature, then adaptation to environment allows for the fine-tuning (brain plasticity) of the structure. Thus, in my opinion, selective pressures can account for the adaptive, small changes in the adult brain morphology, but they are neither the driving forces for major changes (especially those features characterizing a whole class of vertebrates) nor the motor of evolution.

There is a tendency throughout the target article to compare the isocortex with the entire reptilian cortex; however, the isocortex would be better compared with those parts of the reptilian cortex derived from the dorsal pallium. I agree with Aboitiz et al. that two structures being homologous does not imply that homology must be found among each of their components: The reptilian pallium is homologous as a field to the mammalian pallium, but that does not imply that every component (subdivision) of the mammalian pallium must have a reptilian homologue. The isocortex may be seen as an innovation in mammals (i.e., a new derivative of the dorsal pallium) that undergoes a surface expansion concomitant with the expansion of the dorsal tier of the dorsal thalamus. In any case, to find the homologue of the isocortex in sauropsids implies first identifying a series of developmental processes characteristic and exclusive of the isocortex (e.g., the expression pattern of some regulatory genes; in this sense it is important to find molecular markers defining exclusively the dorsal pallium), and then finding a region in the pallium of sauropsids that displays differentially the same developmental processes.

Finally, an important proposal of Aboitiz et al. is that the progressive involvement of visual information in associative networks triggered the expansion of dorsal pallium derivatives. However, this phenomenon may also be the opposite: It may be that the expansion of the dorsal pallium allowed the progressive formation of associative networks (more complex structures allow the performance of more complex tasks).

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Occam's razor and the collothalamic projection

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Abstract: Aboitiz and colleagues propose that the tectorotundal pathway of birds and reptiles is homologous not to the mammalian colliculopulvinar system but to the posterior complex/intralaminar nuclei. However, as outlined below, a large amount of strong evidence points to a homology of the tectorotundal and the colliculopulvinar system. This makes it likely that DVR and isocortex might be in part homologous.

Aboitiz and colleagues present a brave attempt to integrate literature from diverse areas into a coherent theoretical frame. However, as often in grand approaches, obstacles are discussed away to preserve coherency. But the beauty of obstacles is their ability to uncover serious inconsistencies. This is exemplified in the issue of collothalamic projections.

The thalamic lateral posterior-pulvinar nucleus of mammals (LP-pulvinar) receives afferents from the superior colliculus and projects to the extrastriate cortex. If this structure is homologous to the reptilian and avian nucleus rotundus, the mammalian isocortex would probably be constituted by reptilian dorsal cortex plus parts of the DVR. Based on a review by Bruce and Neary (1995) and anatomical evidences (Dávila et al. 2000; 2002; Guirado et al. 2000; Redies et al. 2000), Aboitiz and colleagues argue that the rotundus is homologous to parts of the posterior complex/intralaminar nuclei. However, evidence to the contrary is huge.

The tectorotundal projection in birds and mammals. In birds, the rotundus receives bilateral afferents from the tectal stratum griseum centrale. At least five cell types constitute this tectorotundal pathway and four of them receive monosynaptic retinal in-

put (Hellmann & Güntürkün 2001). These cells are only driven by visual stimuli (Schmidt & Bischof 2001) and some have wide dendritic trees with "bottlebrush" endings on which retinal fibers synapse (Luksch et al. 1998). Their receptive fields are 20–40° in diameter with suppressive surrounds, they are best driven by small (<1°) moving stimuli, and they are inhibited by wholefield motion (Frost et al. 1990; Jassik-Gerschenfeld et al. 1970).

In mammals the bilateral collicular projection to the LP-pulvinar is composed of at least two cell types in the lower stratum griseum superficiale/stratum opticum (Major et al. 2000) that receive monosynaptic retinal input (Michael 1972), are only driven by visual stimuli (Mooney et al. 1985), and are characterized by wide dendritic trees with bottlebrush endings on which retinal fibers synapse (Major et al. 2000). The receptive fields of these cells are 10–30° in diameter with suppressive surrounds. The neurons are best driven by small moving stimuli (<1°) and are inhibited by wholefield motion (Graham et al. 1981; Hoffmann 1973).

In birds, the different tectorotundal celltypes project into distinct rotundal domains (Hellmann & Güntürkün 2001) that can be discerned functionally (Wang et al. 1993). In mammals, different colliculofugal celltypes also project to LP-pulvinar subdivisions (Abramson & Chalupa 1988) where they probably establish distinct functional domains (Soares et al. 2001). Additionally, a side path of tectorotundal axons synapses on GABAergic pretectal nuclei that project back both onto rotundus and LP-pulvinar (Major et al. 2000; Theiss et al. 2003).

In birds (Wang et al. 1993) and mammals (Merabet et al. 1998), rotundus and LP-pulvinar process image motion, velocity, and relative motion between object and background (Casanova et al. 2001). Both in birds and in mammals, these properties arise in part from local computations (Dumbrava et al. 2001; Sun & Frost 1998). In birds (Laverghetta & Shimizu 2003) and mammals (Adams et al. 2000) the thalamotelencephalic projections target specific areas without bifurcations to the basal ganglia and are then disseminated to further forebrain regions where they partly intermingle with the thalamofugal/geniculocortical system (Husband & Shimizu 1999; Weller et al. 1984).

Thus, the similarities between avian tectofugal and mammalian extrageniculocortical pathways are impressive. Therefore, Major et al. (2000) coined the term "cellular homology" to describe the notion that for bottlebrush neurons homology can be traced back to cellular subtypes.

Is the nucleus rotundus a part of the posterior complex/intralaminar nuclei? Based on Bruce and Neary (1995), several authors (Dávila et al. 2000; 2002; Guirado et al. 2000; Redies et al. 2000) have argued that the rotundus is part of the posterior/intralaminar complex and might be equivalent to the suprageniculate nucleus. Aboitiz and colleagues support this position. So what is the evidence?

One argument is based on the position of the tectal projection neurons: In birds (and reptiles) they are located in the deep stratum griseum centrale, whereas in mammals their position is more superficial in the stratum griseum superficiale/stratum opticum. However, this argument is based on a simplified transposition of the collicular condition onto the avian/reptilian tectum. In mammals, the distinction between superficial and deep is determined by the position of the stratum opticum. In birds and reptiles, with the stratum opticum being most superficial, a similar clear-cut division is not possible. If however, monosynaptic retinal input is used to group cells into superficial (retinorecipient) and deep (nonretinorecipient), then tectorotundal cells are clearly as superficial as mammalian colliculopulvinar cells.

The second argument focuses on cellular birth dates. Based on Dávila et al. (2000), Aboitiz et al. argue that the LP-pulvinar receives axons from late-born cells in superficial colliculus, whereas rotundus receives afferents from early-born deep tectal neurons. If this were the case, early-born deep collicular cells projecting to the posterior complex would be comparable to the early-born avian tectorotundal projection. This argument is easy to contradict. Dávila et al. (2000) cited Altman and Bayer (1981) to argue that LP-pulvinar projecting neurons are born at E15–16 and the earliest rat collicular neurons are born at E13 and belong to those that project to posterior/intralaminar nuclei. In fact, Altman and Bayer reported nothing like that. They observed that E13 is only the birth date of neurons in the intermediate magnocellular zone of the stratum album intermediale. They specifically reported no difference for birth times of cells in stratum griseum superficiale (superficial) and stratum griseum intermediale (deep), with both peaking at E16. Thus, the two laminae projecting to LP-pulvinar and to posterior/intralaminar (Katoh & Benedek 1995) have indistinguishable birth times! This argument is supported by Wu et al. (2000) who showed that the birth date of the chick tectorotundal pathway is similar to that of the colliculopulvinar system in monkeys, if the relatively longer developmental times in primates are taken into account.

The third argument is that the position of the avian rotundus is in the intermediate tier, whereas the mammalian pulvinar is a dorsal tier nucleus. This is based on Redies et al. (2000) who mapped cadherin expressions and radial glial topology in chicks to show prosomeric divisions. Unfortunately, it is not clear how the tier divisions of this study emerged from the presented data. All cadherins used can be found in all major divisions, and especially the rotundus expresses all cadherins mapped. At present, then, the prosomeric division of the avian thalamus is more theory-based than data-based. It does not provide a major challenge to the assumption that tectorotundal and colliculopulvinar systems are homologous.

However, let us assume for a moment that the rotundus is homologous to the suprageniculatus. Then we would have to explain why the rotundus has no afferents from the spinal cord (Berkley et al. 1986), vestibular nuclei (Mickle & Ades 1954), dorsal column nuclei (Feldman & Kruger 1980), reticular formation (Hicks et al. 1986), auditory structures (Berkley 1973), and the cerebellar fastigial nucleus (Katoh et al. 2000), but receives afferents from tectal cells with retinal input. Additionally, we would have to explain why rotundal and posterior/intralaminar units differ so radically (Korzeniewska et al. 1986).

Occam's razor. The tectorotundal pathway is homologous to the colliculopulvinar system. To defend the contrary requires the incorporation of a fantastic number of assumptions. These would have to explain the rearrangement of major projection streams, neurochemically defined systems, and cellular properties at the biophysical and morphological level. Such a pursuit would run contrary to the principle formulated by William of Occam: "You should not assume plurality without necessity." There is no necessity. Several theories have beautifully outlined the ways in which the temporal cortex could be related to the DVR (Butler & Molnar 2002; Reiner 2000). I see possibilities to incorporate these ideas to develop a true grand theory on isocortical evolution that is not plagued by unsolvable contradictions. The great effort of Aboitiz and colleagues is definitely worth this extra mile.

The evolution of neural dynamics permitting isocortical-limbic-motor communication

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Abstract: The first cortically based associative circuits integrated olfactory, motivational, and motor information. Many of the neural dynamics present in these evolutionarily ancient, olfactory-motor circuits, such as the broadband frequency, phase, and amplitude modulations seen during recognition of a rewarded olfactory stimulus, are also found in isocortical circuits. These results suggest that mechanisms permitting olfactory associative processing formed the basis for evolutionarily more recent large-scale couplings involving isocortical areas.

Aboitiz et al.'s argument that the mammalian isocortex evolved from the reptilian dorsal cortex is a tour de force that elegantly integrates comparative anatomical, developmental, genetic, paleontological, and behavioral evidence. We are neurophysiologists who study associative learning and predict impending motor action in mammals by recording simultaneously from olfactory and motor areas as they execute voluntary, skilled tasks. As such, we would like to address how the neural dynamics used by circuits including the isocortex, hippocampus, olfactory cortex, and motor areas may have concurrently evolved.

At the behavioral level, animals' actions stem from an integration of sensory cues, motivational states, and motor planning. Underpinning this integration is an intricate interplay among signal transduction, gene expression, and electrical activity within and across neurons that evolved over the course of billions of years. These biochemical and biophysical mechanisms in turn permit neurons to communicate with one another such that, at times, vast neural networks transmit information to and from one another using common rhythmic states. Our research has shown that in rodents, olfactory and motor circuits interact in a distinctive, time-locked manner just prior to the execution of a learned, olfactorily guided motor task (Hermer-Vazquez et al., in press). We believe that the dynamics allowing this integration date back to the earliest chordates such as amphioxus, which acted predominantly using olfactory cues (Holland & Holland 2001; Lacalli 2001; Satoh et al. 2002). The olfactory-motor linkage was refined in the agnathans and other early vertebrates, whose entire pallium received olfactory inputs subserving the behavioral goal of predation (cf. the target article; Lacalli 2001).

Further anatomical and physiological evidence suggests that the earliest cortically based sensory-motivational-motor linkages recruited olfactomotor dynamics. The lateral pallium of reptiles is thought to be homologous to the piriform cortex of mammals (Martinez-Garcia et al. 1986), which is considered to be an evolutionarily ancient multimodal associative area facilitating simultaneous linkages among olfactory, somatosensory, autonomic, motivational, and motor information (Johnson et al. 2000). Furthermore, the piriform cortex projects heavily to the entorhinal cortex (Johnson et al. 2000), just as the lateral cortex in reptiles (along with lemnothalamic inputs) projects heavily to the hippocampus (cf. the target article). With the evolution of cellular mechanisms permitting graded, *persistent* neural activity in the entorhinal-hippocampal complex, percepts could be *maintained* in memory (Egorov et al. 2002), facilitating the formation of associations among stimuli occurring at different points in time. Later in evolution (e.g., in primates), previously olfactory memory circuits such as those involving the perirhinal cortex came to be used for nonolfactory memory such as visual object recognition (Bussey et al. 2003; Murray & Richmond 2001).

These facts and arguments suggest that the emerging neural dynamics underlying olfactory-motor associations could have formed the basis for multimodal associations involving isocortical areas when collothalamic inputs were routed to the hippocampus. What are the hallmarks of the interlocking biochemical, biophysical, and large-scale network processes found in olfactory-motor circuits? One example that illustrates this multiscale coordination involves the frequency-dependent modulation of piriform and motor cortical activity by projections from a third brain system, the basal forebrain. Basal forebrain glutamatergic, GABAergic, and cholinergic neurons project topographically to both the piriform and motor cortices (Donoghue & Parham 1983; Manns et al. 2003; Rosin et al. 1999; Wenk et al. 1980; Woolf et al. 1984). The coordinated release of these neurotransmitters, among others, during attentive perception and recall, sculpts the patterns of activity in task-related neural circuits in part by modifying the dynamics between inhibitory and excitatory network elements (Hagevik & McClellan 1994; Poschel et al. 2002; Steriade 1997; Whittington et al. 1995). These modifications – again, among other effects – alter the coupled, transient oscillatory states seen across large networks such as the olfactomotor circuitry. There is debate over the precise role played by subthreshold oscillations and suprathreshold oscillations, as manifested in regular interspike intervals, in neural coding. However, most researchers now agree that both rate coding and temporal coding, including modifications of the phase, amplitude, and frequency of oscillations, are involved in neural computations (Ahissar 1998; Mehta et al. 2002). It is also widely agreed that oscillatory states and precise spike timing are required for many forms of learning, as instantiated in changes in synaptic efficacy via long-term potentiation or depression (Bach et al. 1995; Tsien 2000; Tsodyks 2002).

Our recordings of local field potentials and spikes in the posterior piriform cortex, primary motor cortex, and subcortical motor areas of awake, behaving rats exemplify the importance of oscillatory states during learned behaviors. During olfactory recognition preceding the execution of a learned motor skill to attain an olfactory target, we have found a characteristic, transient, low-frequency oscillation occurring across the olfactory and motor areas (Hermer-Vazquez et al., in press). Concurrently, the amplitude and coherence across beta to gamma frequency bands in these task-related areas increase (Hermer-Vazquez et al., in press). A growing body of evidence indicates that the release of acetylcholine, glutamate, and GABA by the basal forebrain, in concert with dopamine release by the nigrostriatal and VTA systems, norepinephrine release by the locus coeruleus, and the release of other neuromodulators, causes this suite of changes in frequency, phase, and amplitude (Cassim et al. 2002; Lestienne et al. 1997; Manns et al. 2003; Taschenberger et al. 2002). In contrast, when the animal is not engaged in olfactory-related behaviors, the low-frequency rhythms are not synchronized across olfactory cortices and other brain areas and activity in other frequency bands, on average, is at background levels (Manns et al. 2003; Vanderwolf 1992).

This evolutionarily ancient, momentary broadband coherence on olfactory stimulus recognition appears to have been conserved in isocortical-motor circuits. For example, during a visual GO–NO GO paradigm run with monkeys, coherence among multiple high frequency bands increased at specific moments during each trial in task-related visual and motor areas (Bressler et al. 1993), similar to what we have found in olfactory and motor circuits in rodents. Transient coherence across multiple high-frequency bands has also been reported across task-related isocortical visual and somatosensory areas in humans during an associative learning task in which a color cue predicted a mild electric shock (Miltner et al. 1999). Also as in the piriform cortex, hippocampus, and M1 (Barkai & Hasselmo 1997; Hasselmo 1999; Hasselmo et al. 2002; Linster & Hasselmo 2001), acetylcholine (Hohmann & Berger-Sweeney 1998; Kilgard & Merzenich 1998; Schultz et al. 2000) plays a prominent role in attention, synaptic plasticity, and recall in all tested isocortical areas (e.g., Hohmann & Berger-Sweeney 1998; Kilgard & Merzenich 1998; Schultz et al. 2000). These observations support the hypothesis that the spatial and frequency modulations seen in ancient vertebrate olfactomotor circuits formed the biophysical basis for communication across isocortical, limbic, and motor circuits.

Reptilian cortex and mammalian neocortex early developmental homologies

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Abstract: I agree with the view expressed in the target article that the early structural organization of the mammalian neocortex (the primordial neocortical organization) is different from its final one and resembles the more primitive organization of reptilian cortex. During the early development of the neocortex, a distinctly mammalian multilayered pyramidal-cell plate is introduced within a more primitive reptilian-like cortex, establishing simultaneously layer I (marginal zone) above it and layer VII (subplate zone)

below it. This multilayered pyramidal-cell plate represents a recent mammalian innovation in the evolution of the cerebral cortex of vertebrates. Hence, the term *neocortex* is preferable to *isocortex.*

This is an excellent and well-documented article. I will comment on one aspect of it – that concerning the early developmental homologies between the reptilian cortex and the mammalian neocortex. Based on a variety of embryological, functional connectivity, neurochemical, and genetic data, the authors of the target article propose the existence of developmental homologies between some components of the reptilian cerebral cortex and those of the deeper layers of the mammalian isocortex (neocortex) and suggest a common ancestral origin for them. Their observations imply a dual organization for the mammalian neocortex with primitive reptilian-like elements in lower cortical strata and more distinctly mammalian elements throughout the upper strata. The idea of a dual developmental origin for the mammalian neocortex was first introduced in a rapid Golgi study of the early embryonic development of the cat neocortex (Marín-Padilla 1971). From a morphological perspective, the cat neocortex starts to develop, after a transient subpial (marginal) organization with horizontal neurons, with the establishment of a primordial neocortical organization (PNO), recognized today as the preplate. This PNO is characterized by superficial horizontal neurons (precursors of Cajal-Retzius cells) and by deep pyramidal-like neurons with axons that reach the subcortical white matter and Martinotti-like neurons with ascending intracortical axons. The neuronal and fiber organization of the original PNO resembles the more primitive cortical organization of reptiles. Subsequently, a cortical o, more appropriately, a pyramidal-cell plate (PP), starts to form *within* this PNO by the progressive incorporation of migrating neurons from the paraventricular germinal matrix. The appearance of the PP results in the establishment of three distinct strata in the mammalian neocortex. They include, layer I (marginal zone) with Cajal-Retzius neurons, layer VII (subplate zone) with pyramidal-like (long circuit) and Martinotti (local circuit) neurons, and an expanding pyramidal-cell plate between them, from which layers VI, V, IV, III, and II will eventually evolve (Marín-Padilla 1971; 1978; Marín-Padilla & Marín-Padilla 1982). The PP is considered to represent a recent mammalian innovation that becomes progressively incorporated into a more primitive reptilian-like cortical organization represented by layer I (external plexiform lamina) and layer VII (deep plexiform lamina) composed of and characterized by specific neuronal types and fibers systems (Marín-Padilla & Marín-Padilla 1982). Moreover, the original PNO, now represented by layers I and VII, is considered to be functionally competent during the formation of the PP, roughly, from the 25th to the 43rd day of gestation in the cat (Marín-Padilla 1971; 1972).

According to Aboitiz et al., only the deepest elements of the neocortex original preplate retain the more primitive reptilian features. The developmental history of the deep pyramidal-like neurons of the cat neocortex suggests that, prior to the functional maturation of the pyramidal neurons of the PP, they are the only source of cortical-subcortical connections (Marín-Padilla 1971; 1972). Moreover, as the pyramidal neurons of the PP begin to mature functionally (around the 45th day of gestation, in the cat), the deep neurons of the subplate undergo significant developmental transformations, losing their original functional contacts with layer I and assuming the morphological feature of polymorphous neurons (Marín-Padilla 1972). On the other hand, the Cajal-Retzius cells of the original PNO (preplate) assume new and important roles in the development of the mammalian neocortex (Marín-Padilla 1990; 1992). By attracting migratory neurons toward layer I and establishing early functional contacts with their terminal dendritic bouquets, the Cajal-Retzius neuron plays a significant role in the formation of the mammalian neocortex, particularly of its pyramidal-cell plate (Marín-Padilla 1992). Both the unique morphology of the mammalian pyramidal neuron and its stratified inside-outside cortical placement are also developmental processes that depend on these neurons (Marín-Padilla 1992; 1989). The recent discovery of REELIN has corroborated most of the developmental roles attributed to the Cajal-Retzius neurons by these original morphological Golgi studies.

These early morphological Golgi studies support the ideas proposed in this target article. The distinctly mammalian multilayered pyramidal-cell plate represents a recent innovation which is introduced and progressively expands within a more primitive cortical organization that has features resembling those of the reptilian cortex. This primitive cortical organization may be functionally competent during the early embryonic life of mammals. Moreover, the basic body musculature of a mammalian young embryo is more reptilian-like than mammalian and should require a more primitive cortical control. The competence of the Golgi method in demonstrating the structural and, at times, the functional organization of the nervous system is acknowledged and its use is encouraged.

The origin of the amniote sensory and motor cortices

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Abstract: A rigorous cladistic analysis of the dorsal pallium of amniotes indicates that the stem amniote lacked sensorimotor areas. Reptiles apparently acquired a visual cortex by parcellation from the multimodal, hippocampal-like mediodorsal pallium of stem amniotes. The high number of sensory areas of the mammalian isocortex might derive from the specific properties it shows, such as growth-promoting influence on thalamic axons.

In their insightful target article, Aboitiz and collaborators assume the viewpoint that the sensorimotor cortices of all extant amniotes are homologous (Medina & Reiner 2000). If so, the mammalian isocortex would have been generated in two steps. First, the dorsal pallium of stem amniotes acquired sensory inputs from the dorsal thalamus (and descending motor projections). Second, in synapsids this pre-isocortex acquired new developmental mechanisms resulting in a six-layered architecture. In this commentary, I reconsider the evolution of the sensori(motor) cortex of amniotes and discuss its implications in the origin of the isocortex.

Whereas the Wulst of birds includes a somatomotor area (Wild 1992; Wild & Williams 2000), neither lizards (Bruce & Butler 1984a; Lohman & Van Woerden-Verkley 1978; Neary & Wilczynski 1977) nor turtles (Hall & Ebner 1970) show somatosensory thalamic projections to the cortex. Using the rudimentary methodology available at that time, Johnston (1916) reported movements elicited by electric stimulation of the rostral dorsal cortex in reptiles, but his results were never replicated. Indeed, lizards possess neither corticorubral pathways (Martinez-Marcos et al. 1999) nor cortical projections to other premotor centres (Hoogland & Vermeulen-Vanderzee 1989). Hence, the available evidence does not support the presence of a somatomotor cortex in extant reptiles.

Like the avian Wulst (Karten et al. 1973), the dorsal cortex (DC) of turtles displays a visual area that includes the pallial thickening (PT), which receives a projection from the dorsal lateral geniculate nucleus of the thalamus (GLd; Hall & Ebner 1970). In lizards this projection reaches just the pallial thickening (Kenigfest et al. 1997; Lohman & Van Woerden-Verkley 1978). Despite the lack of data in crocodiles, it is generally accepted that all sauropsids have a dorsal visual cortex. However, the avian and reptilian visual cortex is located in the rostral dorsal pallium, whereas in all mammals it is found in the caudal (iso)cortex (Kaas 1980; Krubitzer 1995). Just as the mediolateral topography of the pallium is fundamental to establish phylogenetic relationships among cortical structures, so too is the rostrocaudal topography, as the expression of ho-

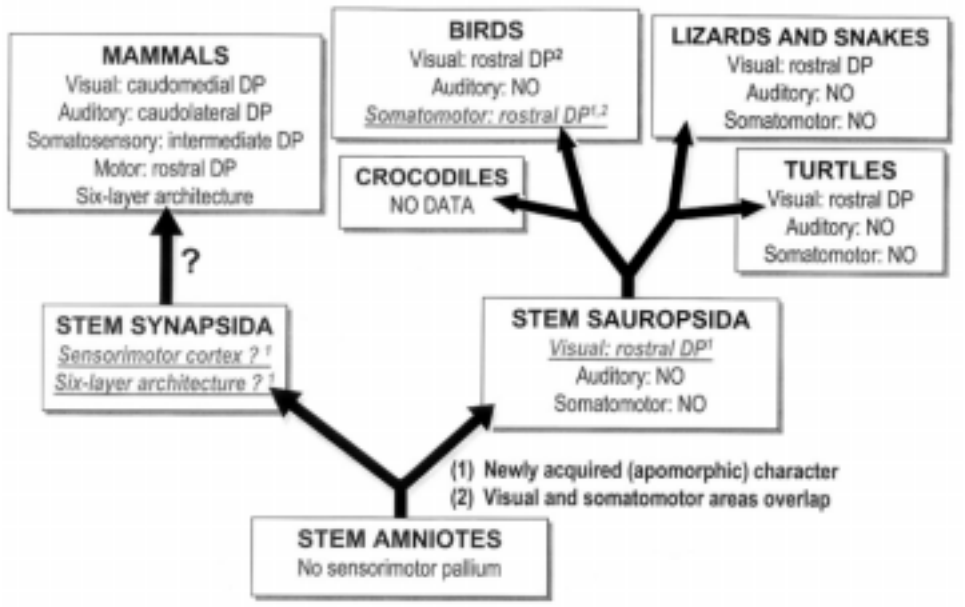

Figure 1 (Martinez-Garcia). Cladogram of the sensorimotor cortices of amniotes.

moeotic genes reveals (Bishop et al. 2000; Nothias et al. 1998; Okhubo et al. 2002). Because the visual cortices of synapsids and sauropsids derive from different portions of the dorsal pallium, they cannot be homologous *as visual cortices.*

In short, the sensorimotor cortices of synapsids (birds and reptiles) and dyapsids (mammals) arose from different pallial structures of stem amniotes (Fig. 1). Therefore, they are not homologous but were acquired independently in mammals and nonmammals. If so, identifying sensory areas in the dorsal cortex of reptiles and birds is not a useful strategy in the search for isocortex homologues in nonmammalian brains.

Therefore, understanding the origin of the sensory cortices requires analyzing how thalamo-pallial projections evolved during early amniote evolutionary history. On the one hand, the thalamostriatal projections (Wicht & Himstedt 1988; Wilczynski & Northcutt 1983) invaded the ventral pallium and a concomitant growth of this pallial region occurred. On the other hand, the thalamic projection to the mediodorsal pallium expanded in parallel to the development of the dorsal pallium (Fig. 2). The amphibian mediodorsal cortex receives a multimodal afferent from the anterior thalamic nucleus (A) (Vesselkin et al. 1971). This nucleus receives retinal (Scalia & Gregory 1970), toral (auditory; Wilczynski 1978, cited by Northcutt & Ronan 1992), and (indirect) spinal cord afferents (Neary & Wilczynski 1977), but multimodal convergence on anterior thalamic cells seems also mediated by inputs on their long dendrites that invade neighbouring areas, such as the retinorecipient neuropile of Bellonci (nB) (Rubaschkin 1903, cited by Wilczynski & Capranica 1984; Wicht & Himstedt 1988). Reptiles show a similar thalamocortical projection system since the medial and dorsal cortices receive a multimodal input (Belekhova & Ivazov 1983; Ivazov & Belekhova 1982) from the dorsolateral anterior thalamic nucleus (DLA; Bruce & Butler 1984a; Desan 1988; Lohman & Van Woerden-Verkley 1978). Both convergent afferents from the retina (Cruce & Cruce 1975; Kenigfest et al. 1997), torus semicircularis and spinal cord (Hoogland 1981) onto this thalamic nucleus DLA and the special dendritic architecture of its cells (Martinez-Garcia & Lorente 1990), whose dendrites develop spiny tufts in retinorecipient and tororecipient adjacent areas, account for the multimodal nature of DLA cells.

Therefore, the dorsal thalamus of reptiles displays an additional thalamic cell group lateral to the DLA (the GLd) that projects to the lateral aspect of the DC (and/or PT). Parcellation (Ebbesson 1980) might explain how reptiles acquired this new thalamo-cortical projection. A change in the development of the thalamus during the anamniote-amniote transition allowed further migration of neurons in the dorsal tier of the dorsal thalamus (Fig. 2, bottom). Distal cells became immersed in the retinorecipient neuropile but lost other afferents, thus forming the GLd, and their cortical target became a visual cortex.

A similar process might have occurred in the phylogeny of mammals, once the dorsal cortex had acquired those developmental mechanisms leading to the six-layered architecture. This change also resulted in new properties of the isocortex, such as growth-promoting influence on thalamic axons (Molnar & Blakemore 1995). Thus, the isocortex attracted axons from cell groups of the intermediate and ventral tiers of the dorsal thalamus (Davila et al. 2000), which resulted in the appearance of additional thalamocortical pathways.

The (medio)dorsal multimodal pallium of amphibians and reptiles displays a set of connections suggestive of a field homology with the mammalian hippocampo-subicular cortex (Hoogland & Vermeulen-Vanderzee 1989; Northcutt & Ronan 1992), which includes scarce projections to the periaqueductal midbrain and prerubral tegmentum (Guirado & Davila 2002). The expansion of these projections to premotor structures (such as the red nucleus) would have allowed a cortical control of motor function, a phenomenon that occurred independently in birds and mammals (Martinez-Marcos et al. 1999).

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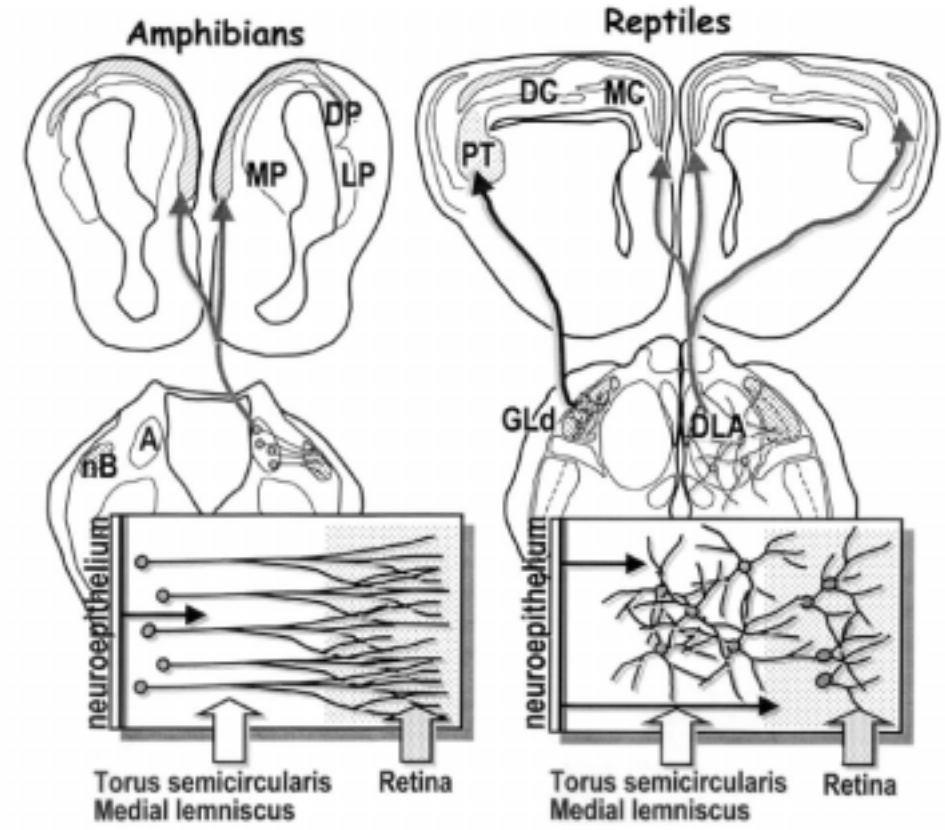

Figure 2 (Martinez-Garcia). Comparison of the thalamocortical pathways in amphibians (left; modified from Wicht & Himstedt 1988) and reptiles (right; based on Kenigfest et al. 1997; Martinez-Garcia & Lorente 1990) suggests a simple change in the histogenetic development of the dorsal thalamus that can explain the origin of the GLd and visual cortex in reptiles (bottom).

Histogenetic divisions, developmental mechanisms, and cortical evolution

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Abstract: An alteration in the developmental mechanisms that regulate telencephalic patterning or pallial growth may have led to an enlargement of the dorsal pallium during evolution, and to the origin of isocortex. Developmental mechanisms that may have produced a pallial enlargement, and the parallelism of this event with the enlargement of the dorsal thalamus during evolution are discussed.

The origin of the isocortex is one of most challenging questions in brain evolution. In the target article, Aboitiz and colleagues analyze this question using a combined approach that considers both developmental and functional data, as well as fossil record evidence. The use of developmental data is indeed extremely valuable in the effort to understand evolutionary processes.

Developmental regulatory genes (codifying either transcription factors or signaling proteins) are expressed in unique patterns in the neural tube, specifying its major rostrocaudal and dorsoventral divisions. These genes show highly conserved sequences and expression patterns and, in combination with topological and other data, have become very useful tools for identifying homologous brain divisions in different vertebrates (Puelles & Medina 2002). This approach led to a challenging proposal that considers four major pallial divisions comparable across vertebrates, and includes that the dorsal ventricular ridge of reptiles and birds is homologous to the claustrum and pallial amygdala of mammals as derivatives of the lateral and ventral pallial divisions, but not to the isocortex which derives from the dorsal pallium (Puelles 2001a; Puelles et al. 2000). To further test this homology, it will be useful to find and analyze in different vertebrates developmental regulatory genes specifically expressed in cells of ventricular zone and mantle of lateral or ventral pallial domains until late embryonic stages, and to analyze the role of such genes in the development of these pallial divisions.

Some developmental regulatory genes affect rostrocaudal or dorsoventral brain patterning, and blocking their action results in animals having a caudalized, rostralized, dorsalized, or ventralized brain, depending on the gene affected (Wilson & Rubenstein 2000). Aboitiz and colleagues propose that an alteration in the developmental mechanisms that regulate telencephalic patterning may have led to an enlargement of the isocortex during evolution. This may indeed represent one of the events that triggered the great development of the dorsal pallium and associated structures in the mammalian radiation. For example, a pallial enlargement is observed in mutant mice lacking expression of the subpallial gene *Gsh2,* and this is apparently due to a transformation of part of the striatum into a ventral pallium (Yun et al. 2001). On the other hand, an overexpression in genes controlling pallial patterning and/or growth, such as *Pax6, Emx1,* or *Emx2,* may have produced an enlarged pallium in evolution. High-level expression of either *Emx2* or *Pax6* is enough to stably activate corticogenesis and repress formation of striatum (Muzio et al. 2002a). *Emx2* and *Pax6* are expressed in opposite gradients in the cortex and have differential effects in the growth of caudomedial or rostrolateral cortical areas (Bishop et al. 2000). *Emx2* gradient is regulated by Wnt and Bmp signaling produced in the "cortical hem," a patterning center present in mammals and birds (Garda et al. 2002; Ragsdale

& Grove 2001; Theil et al. 2002). *Emx2* primarily modulates growth of the hippocampal formation and caudomedial isocortex (Bishop et al. 2000; 2003; Tole et al. 2000), whereas *Pax6* primarily modulates growth of rostrolateral isocortex and derivatives of lateral and ventral pallium (Bishop et al. 2000; Muzio et al. 2002b; Stoykova et al. 1996; Yun et al. 2001).

Thus, alterations in different genes have distinct effects on the pallium, which may help to explain the different models found in vertebrates. Aboitiz and colleagues propose that ancestral mammals, having nocturnal habits, likely had a large olfactory cortex, which made them more competitive in darkness, and this may have triggered an increase in the size/complexity of the hippocampal formation and isocortex through the development of associative networks. In this respect, it is interesting to note that a single mutation leading to an enlarged ventral pallium may produce animals with both a larger olfactory cortex (part of which derives from the ventral pallium) and a larger lateral amygdaloid nucleus (a derivative of the ventral pallium receiving collothalamic auditory input; Puelles 2001a; Puelles et al. 2000). Thus, a single mutation leading to an enlarged ventral pallium may have produced animals with a larger representation of both olfaction and audition in the pallium, and therefore better prepared to survive in darkness.

Another interesting aspect in isocortical evolution is the correlation between an enlargement in the dorsal pallium and a parallel enlargement in the dorsal thalamus. How to explain this parallelism? Again, developmental studies help to analyze this problem and indicate that early maturation of the isocortex or the dorsal thalamus is primarily governed by intrinsic factors. In the absence of *Gbx2* (a gene expressed in the dorsal thalamus but not in the cortex during normal development), thalamocortical fibers fail to grow but cortical arealization still occurs (Miyashita-Lin et al. 1999; Rubenstein 2000). On the other hand, mutant mice lacking pallial genes such as *Tbr1* or *Emx1/2* (expressed in the cortex but not in the dorsal thalamus during normal development) lack corticothalamic axons, but still thalamic neurons initially grow their axons (although these fail to reach the cortex), indicating that early dorsal thalamic maturation occurs (Bishop et al. 2003; Hevner et al. 2002). Nevertheless, the ingrowing axons are needed for final target maturation (Rubenstein 2000), and it appears that ingrowing thalamocortical axons release a diffusible mitogen that increases proliferation of cortical precursors (Dehay et al. 2001).

These findings are relevant to understanding cortical and thalamic development, as well as for trying to understand their parallel evolution. A pallial enlargement in evolution may be due to either alteration in genes regulating patterning or growth, or to an increase in the mitogenic activity or number of ingrowing axons. If the mitogenic activity is a constant feature of ingrowing thalamopallial and perhaps palliothalamic axons in vertebrates, it is also possible that any enlargement in either structure automatically leads to a parallel enlargement in the other. Finally, it is also possible that an alteration in a developmental regulatory gene related to general forebrain patterning (affecting both telencephalic and diencephalic patterning) may have led to a concomitant enlargement of both pallium and thalamus. It will be interesting to look for such types of effects when analyzing forebrain gene mutants in the future.

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Reshuffling or inventing prosomeres: Expensive radiation or expensive neural tissue?

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Abstract: The target article is an elegant synthesis of the developmental and functional data and views on the evolutionary origin of the mammalian isocortex, integrating results from cell and molecular biology, experimental neuroanatomy, and chemoarchitectonic studies. Complementarily, we give here an account of two modes of isocortical evolution (prosomere reshuffling and invention) in terms of costs of radiation and neural tissue.

The recent advent of cell and molecular biology to the study of the development and evolution of prosencephalon has not merely filled in some missing details, but has insightfully challenged our thinking about the evolutionary process. After a period when the issue of the development and origin of the isocortex seemed to have reached a safe point with the postulate that the sensory systems in the forebrain are similar in all amniotes, although differently organized in discrete nuclei of the dorsal ventricular ridge (DVR), and distributed in lamina, in sauropsidian and mammalian brains, respectively, we have come now to a new and plausible challenge of this view. The target article is an original integrative approach of both traditional arguments and modern challenges on the evolution of the isocortex.

The recapitulation hypothesis considers that the ancestor of mammals and reptiles had a brain with a DVR-like structure which dramatically transformed into parts of the isocortex (we shall call this evolutionary mode: *reshuffling of prosomeres*). The outgroup hypothesis implies that therapsids and mammals diverged very early in the amniote radiation, and that the DVR and isocortex have evolved in a functional, independent manner from an amphibian-like dorsal pallium of a common ancestor (*inventing prosomeres*).

If we evaluate the plausibility of these theories in terms of costs of radiation and neurogenesis, respectively, an interesting, although speculative, perspective can be revealed. Radiation can be generally attributed to rare duplication events and more frequent recombination events of active sequence domains. To date, there are no estimates of the ratio between these two genetic mechanisms in phylogenetic variation. On the other hand, the number and duration of cell cycles and the prolonged neurogenesis in primate brains are acknowledged as key determinants of isocortical development and expansion. Going back to theories on the origin and development of the isocortex, one may easily observe that the recapitulation hypothesis is more conservative when radiation is concerned, the functional remodeling of the DVR into an isocortex being more at the expense of neural tissue ("radiation is more expensive"). The outgroup hypothesis implies not radical remodeling, but derivation of the DVR and isocortex from an original dorsal pallium. This could be interpreted as more degrees of freedom for radiation, and more constraints on neurogenesis ("neural tissue is more expensive").

On this rationale, one cannot discern which theory of isocortical origin is more plausible in terms of evolutionary costs. If we judge these costs on the basis of evolutionary frequency of genetic duplication and recombination, and significant modification of cell cycle, respectively, we do not yet have enough data to give a definite evaluation. Lessons from adult neurogenesis seem to favor the view that the mitotic behavior of cells in the subventricular zone can be functionally modulated, resulting in modifications of the neurogenetic pattern. Therefore, neural tissue is not always expensive because it seems to be at the disposal of highly dynamic functional requirements. On the other hand, although genetic duplication is rare, the modulation of gene expression is, at least in some cases, activity-dependent.

We must realize that we have just learned to observe and influence at cell and molecular level, the development and evolution of the nervous system, in general, and prosencephalon and isocortex, in particular. The parsimony of such theories of isocortical origin will be marvelously evaluated when the costs and benefits of (experimental?) genotypic variation and modified neurogenesis can be controlled and quantified, but this scientific stage is not yet foreseeable. In the meantime, the integrative developmental and functional approach proposed by Aboitiz et al. offers an excellent account of the evolutionary origin of the mammalian isocortex.

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The use and abuse of developmental data

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Abstract: Structural similarity is helpful in recognizing homologous structures, but it does not define them. Such structures must also have phylogenetic continuity, a criterion that is ignored by Aboitiz et al. and by proponents of "field homology." "Similar" structures, as well as "field homologues" from "the same" embryonic field, are not necessarily homologous, and an outgroup analysis of developmental stages should be performed to establish homologies.

Aboitiz and colleagues have tackled one of the thorniest problems in comparative neurobiology, the evolutionary origin of mammalian isocortex, and they have reached a number of novel and insightful conclusions. They approach this problem, as have many researchers before them, by first attempting to identify which pallial structures in living reptiles might be ancestral (homologous) to the isocortex in mammals. Their analysis differs from most previous ones, however, by their further attempt to generate a scenario of how and why isocortex was elaborated in mammals. As in the previous studies, this approach hinges on how the authors define homology and what criteria they use to recognize homologous structures. Although they do not propose a formal definition of homology, it is clear that Aboitiz et al. believe homologous characters are characters that have a degree of similarity greater than chance, and they do not state or imply any further criteria. This is both insufficient and misleading. Although degree of similarity can be an important *indication* of homology, it cannot be a *definition* of homology because it does not distinguish between characters that are homologous and those that are homoplastic – that is, similar due to convergent or parallel evolution (Lauder 1994; Northcutt 1984; Wiley 1981). Homologous characters will likely be similar, but – equally important – they must have a continuous phylogenetic history, involving transformations (primitive to derived states) along only one lineage. If this criterion is not applied, any analysis of homology will be fundamentally flawed. The authors' concern about whether topographical, connectional, histochemical, or developmental similarities are more useful is therefore misplaced.

The authors are correct, however, in concluding that analyses of topographical, connectional, and histochemical similarities have not produced a consensus regarding the origin of mammalian isocortex (witness, for example, the number of different hypotheses regarding the reptilian homologue of mammalian isocortex generated in a recent Karger Workshop: Braford 1995). This failure explains the authors' impetus and the fact that their analysis differs from those of other recent authors (except Striedter 1997) in that it emphasizes the importance of developmental similarities. Drawing on recent comparative studies of the telencephalic expression of various developmental genes, they reject the predominant hypothesis that the DVR of reptiles is the homologue of isocortex in mammals. They do so on the assumption that the DVR originates developmentally from the intermediate pallial territory (ventral pallium), whereas isocortex appears to arise primarily from more dorsal pallial territories. As attractive as their conclusion is, it should come with a caveat: There have been no experimental lineage studies on pallial development in reptiles to establish that the intermediate pallial territory is the sole or primary origin of the DVR. Although the continuity of the DVR cell plate with the ventral border of the lateral cortex in tuataras (Cairney 1926) and turtles (Northcutt 1970) supports the conclusion that the DVR does arise from a territory ventral to the one that gives rise to the lateral cortex, a number of older descriptive studies (Hetzel 1974; Källén 1951; Kirsche 1972; Yanes et al. 1987) suggested that the lateral cortex and DVR of reptiles are generated by successive waves of neurogenesis from much of the dorsolateral pallial germinal zone. Therefore, until labeling studies have determined whether or not the cells of the DVR do arise from the intermediate pallial territory, the conclusion that they do so should remain tentative.

Even if lineage tracing studies do reveal that both the DVR of reptiles and the isocortex of mammals arise from the same embryonic germinal zone, other developmental data could still indicate that they are not homologous. Since phylogenetic changes in brains (or any structure) occur only through changes in an ancestral ontogeny (Garstang 1922), it is possible to do an outgroup analysis of the development of any two structures (Northcutt 1990; 2002). Even though two or more adult structures in different taxa arise from the same compartment of the germinal zone, they are not necessarily homologous; they must also possess homologous stages in their development. If two or more independent transformations occur among their developmental stages, the structures are indeed not homologous (Northcutt 1990; 1999; 2002). Thus, it is possible for homoplastic (i.e., nonhomologous) structures to develop from homologous developmental compartments. For example, the primary electroreceptive medullary target in those few teleosts that have electroreception (the electroreceptive lateral line lobe, EEL) and the primary electroreceptive medullary target in nonteleosts (the dorsal octavolateral nucleus, DON), almost certainly arise from the same rhombomeres. Because of the phylogenetic distribution of these electroreceptors and their medullary centers, however, comparative neurobiologists who have studied the evolution of electroreception in fishes do not believe that the EEL and DON are homologous (Bullock & Heiligenberg 1986). In this case, the rhombomeres would be homologous, but not all their adult derivatives would be so. In the same way, if development of the DVR in reptiles and development of the isocortex in mammals represent independent differentiations of homologous developmental germinal compartments, the adult structures should not be considered to be homologous.

Recently, some authors have proposed a very different interpretation of the relationships of independently differentiated structures from homologous germinal compartments under the rubric of "field homology" (Butler & Molnár 2002; Cookson 2001; Puelles & Medina 2002). They believe that field homologs exist when the development of multiple adult structures can be traced back to the "same" embryonic compartment (field), regardless of the transformations that have occurred. I believe that this type of comparison is an abuse of developmental data in order to make a one-to-one, but essentially meaningless, comparison among homoplastic adult structures and to recognize rigid developmental compartments that form an immutable Bauplan. This type of comparison de-emphasizes the staggering structural diversity that has evolved among vertebrates, diversity that must ultimately depend on the evolution of large numbers of genes and developmental processes.

Although the analysis of Aboitiz and colleagues suffers from many of the same problems that have plagued other studies that depended on establishing homologies, it is quite possible that they have, indeed, correctly recognized the reptilian homologue of mammalian isocortex. In any case, their analysis differs from all previous ones in providing an explanation that is not only highly innovative but also testable by examining the correlations that should exist if their scenario is correct.

Cranial factors in neocortical evolution

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Abstract: Our understanding of paleoneurology can benefit through considerations of how ontogenetic patterns of skull suture ossification can limit the phylogenetic expansion of underlying brain tissue to specific regions. Additionally, the influence of biochemical, rather than biomechanical, mechanisms on skull suture morphogenesis enable a reconceptualization of the skull as an independent evolutionary system from the brain.

The field of paleoneurology is constrained by the lack of fossilized remains of the cerebral cortex. As a result, our verifiable knowledge of neocortical evolution is limited to what we can deduce from endocranial casts of fossilized skulls, or through phylogenetic comparisons of the brain structures of modern species. As Aboitiz, Morales, and Montiel (Aboitiz et al.) have demonstrated in the target article, modern paleoneurology relies on a theoretical system that attempts to integrate our verifiable knowledge of neocortical evolution with inferences from paleontological, biological, molecular, and genetic lines of inquiry. However, our present theoretical system is constrained by a lack of attention to how mammalian neocortical evolution is intertwined with and limited by cranial factors. In contrast to the constraints on our knowledge of paleoneurology, we have a more detailed fossil record of the evolution of the skull than of the brain. As a result, it might be beneficial to integrate into our present theoretical system a line of paleoneurological inquiry based on our knowledge of the evolution of the skull.

Ontogenetically, the mammalian skull is not a unitary structure, but represents an integration of four skeletal components of independent origin: the cartilaginous neurocranium, the cartilaginous viscerocranium, the dermal skull roof, and the sclerotomal occipital region (Morriss-Kay 2001). Together, these four skeletal elements suture or fuse together to form the intact skull or skull vault. However, because these skeletal elements are comprised of different types of embryonic tissue, the suturing process is affected by the rate at which these skeletal elements ossify or fuse into bone. For example, the most rostral part of the dermal skull roof, overlaying the frontal poles of the brain, ossifies at the age of 6 years, whereas the more caudal part of the dermal skull roof, overlaying the fronto-parietal and temporal brain regions ossifies late in development, if at all. These different ontological patterns of suture ossification have implications in terms of limiting the phylogenetic growth of the brain to specific regions such as the posterior cortex.

Historically, views of cranial evolution have considered skull growth to be driven by the biomechanical tension exerted by the underlying expansion of the brain on skull sutures (Wagermans et al. 1988; Weidenreich 1941). Specifically, proponents of the biomechanical model have suggested that the tension exerted by the growth of the brain regulates skull suture morphogenesis by specifying the location of sutures as well as inhibiting the early ossification of sutures (Moss 1960; Smith & Tondury 1978). More recently, the biomechanical model has been challenged by research demonstrating that biochemical interactions between the tissue comprising cranial sutures and the underlying dura mater, rather than the expanding brain, inhibit suture ossification (Opperman et al. 1993; 1995). Interestingly, research using endocranial casts has demonstrated that over the course of evolution, a more complex dura mater venous sinus system has developed for regulating the drainage of cerebral blood (Saban 1995). It, therefore, remains to be determined how the increasing complexity of the dura mater venous sinus system has interacted with the cranial suturing process over evolutionary history. The work of Opperman and her colleagues is, therefore, important in that it has provided some evidence for the theoretical dissociation of the evolutionary systems of the skull and the brain through a biochemical rather than a biomechanical model. Moreover, Opperman's work implies that the phylogenetic growth of the skull may be independent from the phylogenetic growth of the brain.

To more fully understand how cranial factors may have influenced mammalian neocortical evolution, it might also be important to examine one of the evolutionary paradoxes of human neuroanatomy. In the human brain, the anterior tip of the hippocampus lies in close proximity to the hypothalamus. However, despite being only a few centimeters away, the efferent fibers of the hippocampus project to the hypothalamus via the fornix, curving up and, initially, away from the hypothalamus in a 270º arc that proceeds under the parietal lobes, around the anterior portion of the thalamus, and, finally, down into the hypothalamus (Carpenter 1991). Although this route of communication between the hippocampus and the hypothalamus might seem extremely roundabout, its existence can be explained by the way in which cranial factors limited the expansion of the dorsal cortex during evolution. Specifically, the early ontogenetic ossification of the cranial sutures overlaying the frontal lobe would not have been able to accommodate the anterior expansion of the dorsal cortex. As a result, it may be possible that the direction of growth of the dorsal cortex in the anterior direction was shifted to the opposite direction toward the late ossifying fronto-parietal and temporal sutures that could accommodate the expansion of the dorsal cortex. Accordingly, such a transfer in the direction of growth of the dorsal cortex would have pushed the posterior cortex down and underneath the rest of the brain so that it would begin migrating forward in the skull.

This pattern of cortical expansion, based on growth beneath nonossified cranial sutures, would enable the folding forward of the posterior portion of the cortex that would eventually lead to the formation of the temporal lobes. Furthermore, this forward migration, of what was previously the posterior cortex, served to carry the hippocampus into the temporal lobe. Thus, although prior to expansion of the neocortex the fornix originally took the shortest, most direct route to the hypothalamus, it now changed position relative to the hypothalamus, due to the forward migration of the hippocampus during neocortical evolution, so that its current route is quite circuitous. Additionally, this forward migration, which produced the temporal lobe, may also be responsible for the characteristic C-shaped curve formed by the striatum and the lateral ventricles.

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Relevance of medial and dorsal cortex function to the dorsalization hypothesis

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Abstract: The overall dorsalizing effect proposed by the authors may be consistent with behavioral evidence showing that the dorsal cortex of reptiles functions like the hippocampal formation of mammals. It is suggested that the dorsal cortex of reptiles expanded in this dorsalizing process to become both entorhinal/subicular cortex and sensory neocortex.

Aboitiz, Morales, and Montiel (Aboitiz et al.) present an interesting review that attempts to integrate anatomical, developmental, and behavioral data to describe the evolution of the neocortex. Some data on the behavioral effects of lesions of the telencephalon in turtles may bear on the authors' hypotheses. These data suggest that the dorsal cortex of reptiles, rather than being an area that provides visual input to the medial cortex or hippocampus, actually functions more like the entorhinal/subicular cortex of mammals. Lesions of the dorsal cortex have no effect on visual processing but produce learning and memory deficits similar to those found after lesions of the hippocampal formation in mammals. Thus, the dorsal cortex may have been the progenitor of two parts of the cortex of mammals: the entorhinal and subicular cortices, on the one hand, and the primary sensory visual and somatosensory cortices, on the other (Butler 1994a; Day et al. 2001). The suggestion by Aboitiz et al. that dorsalization occurred in the evolution of the mammalian brain may be consistent with this idea. Perhaps the dorsal cortex of reptiles enlarged and subdivided to form both subicular/entorhinal and neocortical subdivisions in mammals. Evidence for this idea is reviewed below.

First, although it receives a projection from the dorsal part of the lateral geniculate nucleus in turtles (Hall & Ebner 1970; Hall et al. 1977; Ulinski 1988), the dorsal cortex does not function in vision. Dorsal cortex lesions do not produce deficits on retention of visual pattern or intensity discriminations (Reiner & Powers 1983, reviewed in Powers 1990). This finding, in comparison with the profound deficits seen after lesions of nucleus rotundus in the thalamus or the core nucleus of the dorsal ventricular ridge (Reiner & Powers 1978; 1983), suggests that the function of the dorsal cortex is not visual.

Rather, the dorsal cortex seems to be involved in learning and memory. Lesions of the dorsal cortex in reptiles produce deficits in acquisition and reversal of pattern discriminations (Blau & Powers 1989; Cranney & Powers 1983), acquisition and reversal of spatial discrimination in an operant chamber (Grisham & Powers 1990), acquisition and reversal of go/no go discriminations (Grisham & Powers 1989), acquisition of a simple operant (Grisham & Powers 1989), and acquisition and retention of maze learning (Avigan & Powers 1995; Day et al. 2001; Peterson 1980; Petrillo et al. 1994). Dorsal cortex lesions also disrupt long-term habituation of head withdrawal to a looming stimulus (Moran et al. 1998), a finding that is especially striking because no deficit was found on short-term (within-day) habituation. Thus, the deficit was not sensory but associative: Turtles with lesions of the dorsal cortex seemed not to remember the habituation from day to day.

The medial cortex of reptiles is involved in spatial learning. Lesions of the medial cortex of lizards disrupt the learning of a maze (Day et al. 2001), and lesions of the medial cortex of turtles disrupt the ability of the turtles to use cognitive mapping strategies to locate the goal (Rodriguez et al. 2002a; 2002b). In the case of lizards, it was not possible to determine the learning strategy that was disrupted (Day et al. 2001).

The medial cortex of reptiles does not appear to be involved in other tasks that are mediated by the hippocampus of mammals. In an operant chamber for turtles, no effects of lesions of the medial cortex were found. The tasks investigated were acquisition and reversal of spatial discriminations (Grisham & Powers 1990), acquisition and reversal of visual intensity discriminations (Grisham & Powers 1990), acquisition, retention, and reversal of go/no go discriminations (Grisham & Powers 1989), and acquisition, extinction, and reacquisition of a simple operant (Grisham & Powers 1989). Many of these tasks are impaired by lesions of the hippocampal complex in mammals (O'Keefe & Nadel 1978). In addition, turtles with lesions of the medial cortex are not impaired in a cued version of maze learning (Rodriguez et al. 2002a; 2002b).

In mammals, lesions of the hippocampus and of the subicular/entorhinal cortex may have different effects (e.g., Bannerman et al. 2001; Hunt et al. 1994). Although the findings in mammals do not seem to map directly on to the findings in reptiles, the fact that function differs is reminiscent of findings in reptiles, where lesions of the medial cortex, equivalent to the hippocampus (Butler & Hodos 1996), produce maze learning deficits (that can be shown to be spatial) but not cue learning deficits, and lesions of the dorsal cortex, similar to the entorhinal/subicular cortex (Butler & Hodos 1996), produce cue learning and reversal learning deficits in addition to deficits in maze learning.

The dorsal cortex of some reptiles (e.g., turtles) is also the recipient of both visual and somatosensory projections from the thalamus. In lizards, the visual projection from the thalamus terminates in a lateral region termed the "pallial thickening" (Bruce & Butler 1984a). It is noteworthy that, in spite of this difference, the function of the dorsal cortex in lizards appears to be similar to that in turtles, in that lesions in both orders disrupt learning and memory (Day et al. 2001; Peterson 1980; Petrillo et al. 1994). Our data on the behavioral effects of lesions in the dorsal and medial cortex suggest that the dorsal cortex is not, as postulated by Aboitiz et al., a sensory area that provides sensory input to the medial cortex/hippocampus. Rather, these effects are consistent with the dorsal cortex being similar to entorhinal/subicular cortex.

Nonetheless, the dorsalization hypothesis proposed by Aboitiz et al. suggests a solution to the dilemma posed by the clear demonstration that the dorsal cortex is involved in learning and memory like the hippocampus of mammals but also contains sensory areas that seem to be the forerunners of primary sensory neocortex in mammals. The dorsalization hypothesis is consistent with the idea that, in the transition to mammals, the dorsal cortex may have expanded medially to become the entorhinal/subicular cortex and laterally to become the primary sensory cortices for vision and touch. The function of the dorsal cortex seems to correspond more to that of the entorhinal/subicular cortex, but the structural increase in area implied by the dorsalization hypothesis may have allowed an increased functional role for visual information in the thalamofugal system.

The data do not support the hypothesis

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Abstract: The position that Aboitiz et al. have taken on the regions of the stem amniote brain from which neocortex arose, and on homologies among telencephalic pallial regions in mammals and sauropsids, is premature. Nonetheless, if their intent is to promote thought, discussion, and experimentation on this important topic, then their paper is valuable.

Aboitiz et al. conclude that (1) stem amniotes possessed a dorsal cortex that was the antecedent of mammalian cerebral cortex medial to temporal sulcus (i.e., superior neocortex); (2) temporal neocortex (lateral to temporal sulcus) arose as an expansion of superior neocortex; and (3) the DVR of birds and living reptiles, which has many of the connections and functions of temporal neocortex, evolved from the same antecedent structures as parts of mammalian amygdala and claustrum, and any similarities between DVR and temporal neocortex are coincidental. I believe a major premise by which Aboitiz et al. reach their conclusions is flawed, and that recent findings render the latter two of the above conclusions problematic.

First, Aboitiz et al. use as their point of departure the Northcutt and Kaas (1995) dichotomy of opinions on evolution of cerebral cortex and DVR into an "outgroup" camp and a "recapitulation" camp. The former proposes that temporal neocortex has no homologue in living sauropsids, and the latter posits that stem amniotes possessed a DVR that was transformed into temporal neocortex in the mammalian lineage, and that this process is recapitulated during mammalian development. Aboitiz et al. reject the recapitulationist view for the valid reason that there is no evidence from brain endocasts of stem amniotes or from the brains

of living amphibians that stem amniotes possessed a DVR, or that the evolution of DVR into temporal neocortex is recapitulated during development. They thus embrace the seemingly default "outgroup" position. These two positions, however, do not exhaust all possible evolutionary scenarios for the relationship of DVR and cerebral cortex (Reiner 1996). Both Butler and I have suggested that the dorsal pallial sector of stem amniotes may have possessed a more lateral zone that was the forerunner of both DVR in sauropsids and temporal neocortex in mammals (Butler 1994a; Reiner 1993). Thus, a rejection of the recapitulationist view does not exclude the possibility that DVR and temporal neocortex both arose from a structure in stem amniotes that was not yet either a DVR or neocortex (Reiner 2000).

The evidence typically offered for homology of temporal neocortex and DVR is the high similarity in their structural organization. For example, both DVR and temporal neocortex contain a secondary visual area and a primary auditory area, and it has been suggested that the thalamic and midbrain cell groups giving rise to these telencephalopetal pathways are so highly similar between mammals and sauropsids that it is unlikely that they evolved separately (Karten 1991; Luksh et al. 1998; Major et al. 2000; Reiner 1993; 1994; 2000). Moreover, the topological arrangement of the primary visual, tectothalamic visual, primary auditory, and primary somatosensory areas in living reptiles (spanning dorsal cortex and DVR) is nearly identical to that in neocortex of primitive mammals (Reiner 2000). This pattern could not have been inherited from the amphibian ancestors of stem amniotes because there is no evidence that modern amphibians possess them (Northcutt & Kicliter 1980). Therefore, the similarity between modern reptiles and mammals in the topology of these "cortical" sensory areas may be due to common inheritance from stem amniotes.

Aboitiz et al. present two main reasons for rejecting the connectional evidence favoring DVR and temporal neocortex homology. First, they allude to recent efforts to use region-specific markers to divide the thalamus into sectors. For example, Puelles and colleagues have proposed that the thalamus consists of three stacked sectors, and that the nucleus (lateral posterior/caudal pulvinar, LP/cPUL) conveying tectofugal visual input to mammalian temporal neocortex resides in a different sector from the nucleus (rotundus) conveying tectofugal visual input to sauropsid DVR (Davila et al. 2000; Redies et al. 2000). The evidence for such thalamic compartmentalization, however, is as yet sketchy, and the claim that hodologically comparable nuclei reside in different sectors in mammals from birds is currently conjecture. By contrast, Bruce et al. (2002) used the developmentally regulated marker ErbB4 to show that the primary auditory and tectofugal visual nuclei of thalamus in birds are highly similar to those in mammals.

Aboitiz et al., secondly, reject the hodological evidence for DVR and temporal neocortex homology based on the claims of Puelles and colleagues (Davila et al. 2000) that the layer of the superior colliculus projecting to the LP/cPUL develops at a different time in relation to the other collicular layers from the tectal layer projecting to nucleus rotundus. This claim is, however, based on an undue simplification of published data on the laminar histogenesis of mammalian superior colliculus. In brief, Davila et al. claimed that the published data of Altman and Bayer (1981) show that the neurons of the collicular layer projecting to LP/cPUL (in the deep superficial gray) are generated later in development than are neurons in deep colliculus, and that the tectal layer projecting to avian rotundus arises earlier than other tectal layers. The claim for deep colliculus in mammals is based, however, on only one early-born minority large neuron type in one collicular sublayer. In fact, neurons of the superficial gray layer in mammals otherwise have birthdates notably overlapping those of neurons in other layers. A proper developmental analysis of this issue requires that the birthdates of those specific neurons projecting to LP/cPUL and to rotundus be determined, and this has not yet been done. Even then it is uncertain to what extent relative birthdate information can be used to make inferences about neuronal or laminar homology.

Aboitiz et al. also suggest that recent homeobox gene mapping studies (Puelles et al. 2000; Smith-Fernandez et al. 1998) favor the independent evolution of mammalian temporal neocortex and sauropsid DVR. In particular, Aboitiz et al. note the claim of Puelles et al. (2000) that expression of *Emx1* in mammalian telencephalon is restricted to developing hippocampal cortex, neocortex, olfactory cortex, and dorsal claustrum, but is absent from ventral claustrum and much of basolateral/basomedial amygdala. Puelles et al. (2000) termed the *Emx1*-negative region the "ventral pallium," and suggested that it was a phyologenetically conserved pallial sector. The ventral DVR in turtles and birds also does not appear to express *Emx1* during development, and Puelles et al. (2000) suggested that this territory was the ventral pallial sector of sauropsid telencephalon, and that it was homologous to ventral claustrum and parts of basolateral/basomedial amygdala.

Two recent lines of evidence have somewhat unraveled these claims. First, Butler et al. (2002) have shown that monotremes lack a claustrum. This raises the possibility that the claustrum may have arisen with the common ancestor of placental and marsupial mammals. Under these circumstances, no part of the DVR of birds and reptiles could be homologous to claustrum. Second, the claim that the *Emx1*-negative territory in mammals gave rise to ventral claustrum and much of the pallial amygdala was not based on thorough fate-mapping studies. Recent sensitive fate-mapping studies have revealed that among the putative ventral pallial nuclei, only the ventralmost part of the ventral claustrum is entirely *Emx1*-negative (Gorski et al., 2002; Guo et al. 2000). In contrast, nearly all pallial amygdaloid nuclei are rich in *Emx1*-expressing neurons. Although quantitative studies are needed to ascertain the abundance of any *Emx1*-negative neurons in the various pallial amygdaloid nuclei, there clearly are no pallial amygdaloid nuclei that are entirely *Emx1*-negative. Thus, the evidence does not favor that a ventral pallial territory persists during development and gives rise to specific ventral pallial nuclei in mammals, rendering problematic the claims of homology for ventral DVR of birds and specific claustro-amygdaloid nuclei in mammals.

On that ground, I believe it is premature to take the positions that Aboitiz et al. have taken on the origins of neocortex.

Conserved functional organization of the amniote telencephalic pallium

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Abstract: The dorsal and medial pallial formations of mammals, birds, and reptiles show overall functional striking similarities. Most of these similarities have been frequently considered examples of convergent evolution. However, a considerable amount of neurobiological comparative evidence suggests the presence of a common basic pattern of vertebrate forebrain organization. This common pattern can support functional conservation.

Aboitiz et al. draw an integrated developmental and functional hypothesis to account for the evolutionary origin of the mammalian isocortex. This effort is valuable because interrelating artificially separated fields – such as evolutionary biology, neuroanatomy, and developmental and functional neuroscience – will stimulate a productive discussion on the most fundamental organizing principles of brain and function. To contribute to this discussion, we will point out some disagreements with Aboitiz et al.'s proposal and also offer alternative scenarios.

First, Aboitiz et al. found their hypothesis of isocortex emergence in a presumptive difference in the function of the hippocampus of sauropsids relative to mammals. But this claim is not backed by the available experimental comparative data, which suggest, instead, that the function of the hippocampal pallium re-

mains notably well conserved in amniotes. For example, the hippocampal pallium of birds and reptiles share with the mammalian hippocampus the pattern of connectivity, histochemistry, topology, significant electrophysiological properties, and synaptic plasticity mechanisms. Thus, the profile of electrophysiological activity of the neurons in the avian hippocampus is notably similar to the unit types described in the mammalian hippocampus (Siegel et al. 2002). An electrophysiological theta rhythm can be recorded in the avian hippocampus that parallels the hippocampal theta of mammals (Siegel et al. 2000). Both NMDA-receptor dependent and non-NMDA dependent long-term potentiation have been found in the hippocampus of birds and in the medial cortex of turtles (Muñoz et al. 1998; Shapiro & Wieraszko 1996). In addition, presynaptic, CaMKII dependent, long-term depression and a variety of neurotransmission regulatory mechanisms have been recently described in the avian hippocampus which closely parallel those described in mammals (Margrie et al. 2000). All these impressive similarities suggest that mammals, birds, and reptiles share the basic mechanisms for information processing and learning and memory.

Strong evidence indicates also that the hippocampal pallium of reptiles and birds, like the mammalian hippocampus, play an essential and selective role in spatial cognition. The hippocampal pallium of pigeons and turtles is involved in the generation and use of maplike spatial allocentric or relational representations of the environment, but is not necessary for nonrelational, egocentric-based representations (Gagliardo et al. 1999; Rodríguez et al. 2002b). Furthermore, recent evidence indicates that the pallial homologue of the hippocampus in ray-finned fishes, one outgroup of amniotes, is similarly involved in allocentric spatial cognition (Rodríguez et al. 2002a; 2002b; Salas et al. 2003; Vargas et al. 2000), suggesting that these traits were present in the ancestral stock of amniotes that gave rise to mammals, birds, and reptiles. In this context, the shift in hippocampal function from olfactory to visual-spatial processing proposed by Aboitiz et al. is not likely. Moreover, considerable evidence indicates that the basic organization of the olfactory system is well conserved in vertebrates and no major innovation is present in mammals (Eisthen 1997).

In the dorsal pallium of amniotes, the degree of similarities at multiple functional levels is also notable. For example, at single cell level, the neurons of the avian visual Wulst closely parallel those of the mammalian striate cortex with respect to electrophysiological profiles and response properties, and organization of the receptive fields or binocularity (Pettigrew 1979). As in mammals, visual motion induces synchronous transient oscillations in the turtle visual cortex, based in cortico-cortical connections and cortico-thalamic loops (Prechtl 1994). Also mismatch negativity and oddball evoked potentials can be obtained in the turtle's visual cortex that closely resemble those observed in humans, cats, or rats, reflecting fundamental cognitive processes (Prechtl & Bullock 1994). The dorsal pallium of amniotes appears organized in multiple, separate sensorial and motor areas that parallel in relative topology, topographical organization, and connectivity (Medina & Reiner 2000), and display closely similar activity-dependent plasticity and reorganization characteristics (Manger et al. 2002). In addition, the dorsal pallium of reptiles, birds, and mammals is similarly involved in learning and remembering sensory discriminations (Macphail 2001; Powers 1990).

Besides the impressive multilevel, connectional, and functional similarities in the hippocampal and dorsal pallium of amniotes, some conspicuous divergences appear in the cytoarchitectural organization (e.g., the six-layered lamination, or an inside-out neurogenetic gradient of the mammalian isocortex). These differences have impelled the recurrent suggestion that the functional similarities of the hippocampal and dorsal pallium in amniotes are examples of convergent evolution. One possible way to reconcile this apparent contradiction comes from Karten's (1991) proposal that cortical circuits and lamination evolved independently in the phylogenetic history of the mammalian lineage. The basic constituent forebrain neuron populations and their interconnections could have evolved early in vertebrate phylogenesis and, being present in every amniote group, could support the observed common functional characteristics. In fact, despite an enormous range of morphological variation, equivalent telencephalic cell populations and their interconnections and highly conserved developmental patterns have been recognized not only in amniotes, but also in nonamniote vertebrates such as amphibians, ray-finned fishes, or cartilaginous fishes (Butler 1994a; Northcutt 1995; Puelles & Medina 2002).

Interestingly, in the mutant mice reeler, the hippocampal and isocortical neurons fail to align into appropriate cell layers. Nonetheless, these neurons make appropriate synaptic connections and also the electrophysiological response properties of the reeler isocortex seem remarkably normal (Rice & Curran 1999). The hypothesis of convergent evolution concerning several functional traits in amniotes might be the most parsimonious alternative if the feature essential for isocortical processing is lamination. But if the equivalent, conserved circuits are the most relevant feature, then in accordance with a principle of parsimony these functional characters are homologous. It should also be noted that not every morphological change can be considered to be an adaptive trait or to have an exact correspondence with a functional benefit. Some of the observed morphological traits could be incidental byproducts without a functional significance or could be neutral covariations linked to other (relevant) factor not taken in consideration.

Of course, the hexa-laminated structure of the mammalian isocortex may provide additional organizational and computational advantages, as well as some disadvantages and constraints. A rigorous cladistic methodology at multiple biological levels, including the functional analysis, can contribute to identify the fundamental features of the telencephalic pallium organization and the relevant adaptive and evolutionary mechanisms among a constellation of possible biological events.

Toward the answer, but still far to go

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Abstract: The target article about the origin and evolution of the isocortex triggers questions about unresolved issues that still need to be dealt with, including: (1) the evolutionary scenario of the origin of the lateral isocortex, (2) the expansion of the dorsal pallium in nonmammals, and (3) the heterogeneity of the anterior dorsal ventricular ridge.

Many hypotheses have been proposed about the origin of the mammalian isocortex; however, not one can fully account for all of the currently available hodological and developmental information. Therefore, the controversy continues. In the target article, Aboitiz et al. extensively review previous proposals and related issues. Their review has resulted in an interesting idea about the origin and evolution of the isocortex and provides directions for future comparative studies. I will comment on three unresolved issues provoked by their article.

First, I would like to comment on the general organization. The authors have categorized previous proposals about possible evolutionary scenarios of the isocortex into two main groups: those aligned with the recapitulation hypothesis and those aligned with the outgroup hypothesis. However, this dichotomy is not as up-to-date as it could be. Although the dichotomy at first lends readability, it also brings an inevitable lack of clear distinctions to the subtle but important differences among various new proposals. This is particularly the case when one tries to digest the different scenarios of the outgroup hypothesis, many of which have been presented and revised based on the recent findings of develop-

mental studies. In this sense, the target article would be more immediately useful as a framework for future studies if the categorization were based on interpretations of the origin of the lateral isocortex. Based on this criterion, the differences could be more manifest between the authors' proposal and other interpretations, including Karten (1969; 1991), Bruce and Neary (1995), Butler (1994a; 1994b), Butler and Molnár (2002), Fernández et al. (1998), Puelles et al. (2000), Reiner (1993), and Striedter (1997). In particular, the authors suggest that "the confluence of the lemnothalamic and the collothalamic pathways" occurred in the dorsal pallium in the origin of the mammalian brain. More details of this intriguing scenario will be needed to understand the authors' unique viewpoint on the origin of the lateral isocortex.

Second, I want to comment on the subject of the expansion of the dorsal pallium of nonmammals – birds in particular. As in mammals, birds experienced a massive expansion of the dorsal pallium Wulst, which today coexists with a developed anterior dorsal ventricular ridge. Unlike the dorsal cortex of many reptiles, the avian Wulst is a large longitudinal structure, which, in the case of pigeons, occupies more than 12% of the total telencephalon volume and is equivalent to the size of the basal ganglia (unpublished observation). Within the Wulst, the focus of investigation tends to be on only the small sensory-recipient areas (e.g., visual and somatosensory Wulst), whereas exact functions of the remaining large regions have not yet been clarified. Based on such a scarce amount of information, it has been difficult to identify the exact selective pressures that caused the expansion of the avian Wulst. In this context, it may be important and useful to compare the possible mechanisms involved in the expansion of the dorsal pallia in birds and mammals. For example, it is interesting to note that both birds and mammals are endothermic and share similarities in their lifestyles, such as the extensive care of offspring by parents (Shimizu 2001). As the authors suggest in the target article, networks involving the hippocampus and dorsal pallium might be important for developing and maintaining the lifestyles of mammals. This may be the case for birds as well. I completely agree with the authors, who suggest that further comparative studies about the hippocampus and amygdala functions are important for understanding the expansion of the dorsal pallium.

Finally, I would like to point out an issue related to the heterogeneous nature of the anterior dorsal ventricular ridge (ADVR) of sauropsids. As other researchers (including myself) have done previously, Aboitiz and colleagues developed their argument by focusing on only a portion of the ADVR (or "IT/VT") as "an important part of the ADVR." This simplification is understandable because, in contrast to extensive data regarding this portion of the ADVR – in particular, the sensory-recipient areas – only limited information is available on the rest of the ADVR. However, in order to study its origin and evolution we cannot ignore its heterogeneous nature. For example, the avian ADVR includes not only the neostriatum (N), but also the hyperstriatum ventrale (HV) located dorsal to the N. Often, only limited areas in the N that receive tectofugal thalamic input are the subject of hodological and developmental studies, although the rest of the N and HV are as large as the sensory-recipient areas in terms of size. Figure 5 of the target article presents a good example of the heterogeneous nature of the ADVR. The figure shows that the expression of some marker genes in the HV is more similar to the Wulst (i.e., Emx1+ / Tbr1+ / Pax6+) than to the rest of the ADVR (i.e., Tbr1+ / Pax6+). Although the origin of the HV needs to be clarified (i.e., whether cells in the avian HV are apomorphic or plesomorphic), these data caution us that the ADVR cannot be interpreted simply as a sensory-specific, homogeneous entity receiving input from the tectofugal pathways.

Cortical evolution: No expansion without organization

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Abstract: Aboitiz et al. describe a hypothesis on the origin of the isocortex. They propose the reptilian dorsal cortex to be the ancestral brain structure to the mammalian isocortex. But why did the dorsal cortex expand in mammals and not in reptiles? A change in development may have provided the mammalian cortex with the ability to organize and therefore the potential to expand.

The exclusive presence of a six-layered cortex in the dorsal pallium of mammals and its enormous expansion during evolution has long intrigued many scientists. In the target article, Aboitiz et al. describe a hypothesis on the origin of the isocortex in mammals that is based on the molecular and connectivity similarities between reptilian and mammalian brain structures. According to the authors, the dorsal cortex in reptiles is the main ancestral structure to the isocortex in mammals. The authors propose that a dorsalizing effect during early pallial development in mammalian-like reptiles was the trigger for the expansion of the dorsal cortex in mammals. The dorsalizing effect comprises an increase in the expression of genes in the dorsal pallium, an increase in the number of cells migrating from adjacent brain compartments into the isocortex, and an increased pool of progenitor cells in the dorsal ventricular zone. The expansion of the mammalian dorsal pallium is associated with the development of interconnected networks between the olfactory system and the hippocampus, where the dorsal cortex became progressively incorporated in order to develop complex behavior. The paper concludes that the addition of more neurons and the entrance of more projections in the dorsal cortex produced an enormous lateral expansion of the cortical plate.

Although these factors are important in cortical evolution, it does not explain why a simple pallium, like the dorsal cortex in reptiles, could transform into a highly complex pallium – the mammalian isocortex. For example, in the hippocampus, which according to my view resembles the cortical organization of the reptilian dorsal pallium (Supèr et al. 1998b), the number of projections into the marginal zone increased during mammalian evolution (Stephan & Manolescu 1980). These extra projections toward the hippocampus did not result, however, in a lateral expansion of the hippocampal cortical plate (Frahm & Zilles 1994). Similarly, more neurons are required but are not sufficient to produce lateral expansion of the cortical plate. In the primary visual cortex of primates, about twice the number of neurons are produced than are produced in any other cortical area (Rockel et al. 1980). The increase in neural production in this area does not produce a lateral expansion of the cortical plate but results in a higher density of neurons. Therefore, the existence of more connections or more neurons is not a sufficient explanation for the lateral expansion of the cortical plate and therefore of cortical evolution. It might be necessary to know the mechanism that allowed the dorsal cortex in mammals to expand in order to understand cortical evolution. The question is: What are the possible mechanisms for the transformation of the dorsal pallium into an isocortex?

Evolutionary expansion of the dorsal cortex is paralleled by an increase in the differentiation of the cortical plate (Northcutt & Kaas 1995). In the reptilian dorsal cortex, the cortical plate remained as one cell-dense layer that is subdivided into few, poorly segregated cortical areas. The evolution of the cortical plate in the mammalian dorsal cortex, in contrast, shows a progressive differentiation into numerous cortical (sub)layers and a segregation into many functional discrete regions (areas, columns). Unlike the reptilian cortex, the cortical plate in mammals evolved into a highly

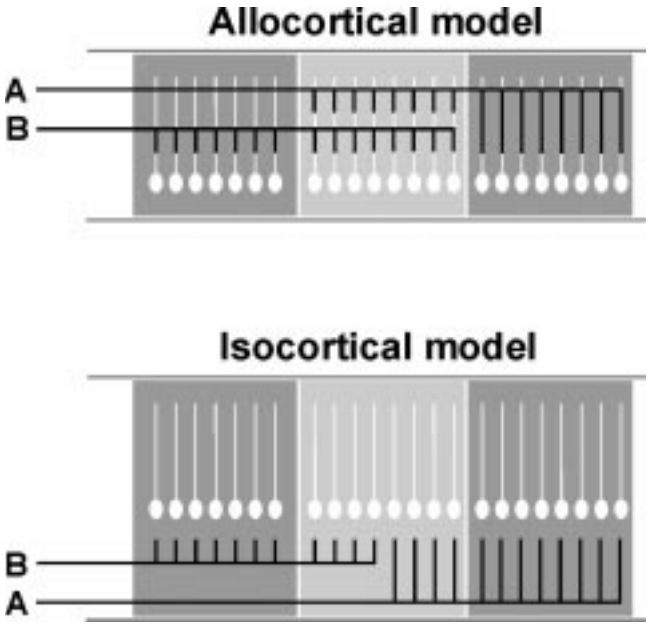

Figure 1 (Supèr). A schematic model showing the axonal ingrowth of the main afferents systems in reptilian dorsal cortex and hippocampus (Allocortical model) and in the mammalian dorsal cortex (Isocortex model). In the allocortical model the fibers enter, run, and terminate above the cortical plate. The fibers are thus in the same zone as the main receptive fields of the neurons – that is, the zone where the apical dendrites branch. In such a framework, segregation into functional discrete regions is difficult to achieve because distinct fibers can contact the same neurons. In the isocortical model the fibers enter and run below the cortical plate, and are therefore not in close contact with the receptive fields of the neurons. The fibers can be guided toward their appropriate cortical region by the subplate cells and they terminate specifically by ascending vertically into the cortical plate. In this framework, the creation of new cortical regions/areas by axonal segregation and by the addition of new fiber systems would enable the cortical plate to expand.

organized structure. The evolutionary enlargement of the mammalian dorsal cortex is somehow related to this increase in cortical differentiation. The mechanisms by which these differentiations develop are still not clear, but the segregation of the termination patterns of the axonal fibers, the enlargement of existing cortical areas, and the creation of new functional segregated cortical fields appear to be essential (Ebbesson 1984; Krubitzer 1995; Rakic 1995).

Based on developmental studies, it appears that the initial ontogenetic organization of the dorsal pallium in reptiles is similar to that in mammals where an early-generated preplate (marginal zone and subplate) precedes the formation of the cortical plate (Supèr et al. 1998b). These early cells are crucial in guiding the entrance of growing fibers (Allendoerfer & Shatz 1994; Supèr et al. 1998a). I propose that a rerouting of the entrance of the cortical afferents into the cortex from the marginal zone to the subplate enabled the differentiation and therefore the expansion of the dorsal cortex (Supèr et al. 1998b; Supèr & Uylings 2001). In the reptilian cortex, most ingrowing fibers run above the cortical plate in the zone where the receptive tufts of the apical dendrite branch extensively. This may have hampered axonal segregation and prevented the formation of numerous distinct cortical areas. In the mammalian isocortex, the fibers enter and run below the cortical plate and do not encounter the receptive fields of the cortical neurons. Here, fibers are guided by subplate cells towards their appropriate zone, and they terminate after vertically ascending into the cortical plate (Catalano et al. 1996; Catalano & Shatz 1998). In such a way, specific axonal-dendritic relationships can be formed. As illustrated in Figure 1, the entrance of (new) fibers below the cortical plate can develop functional segregated regions, create new areas, and allow the cortical plate to expand. In addition, ascending axons may terminate at a specific cortical depth to facilitate the formation of cortical layers.

The hypothesis by Aboitiz et al. mentions a dorsalizing effect to cause the expansion of the dorsal cortex in mammals, which allowed the entrance of more projections to accommodate complex behavior. This, however, does not explain the differentiation of the dorsal cortex that is essential for complex behavior. A better view on cortical evolution would therefore be to combine the dorsalizing effect with the organization of the cerebral cortex.

More dorsal cortex, yes, but what flavor?

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Abstract: Where the isocortex comes from is an important question, but even more important is understanding what it leads to – that is, what advantage is afforded by its peculiar organization in layers of distinct neuronal types. A computational hypothesis accounts for granulation and for the differentiation between supra- and infragranular pyramidal layers, as quantitatively advantageous to support fine topography in sensory maps.

Offering an extra spoonful of ice cream would be enough to elicit increased collaboration in many families; in some, though – including mine – forgetting to ask the kids which flavor they want might lead to the opposite outcome. Similarly, adding extra pieces of neural tissue can be reasonably assumed to have enhanced the information-processing capabilities of the species that were thus brain-augmented; but in order to say we understand the evolution of the mammalian cortex, we must account for why the additional piece had to have the distinctive and newly conceived microcircuitry of the isocortex.

The target article nicely reviews two hypotheses about the evolutionary trajectory that led to the mammalian isocortex, and presents compelling arguments in favor of one of them. It then sets this purely anatomical trajectory in the context of evolutionary pressures that, at the functional level, were demanding more resources for the associative networks linking olfaction to memory structures in the medial cortex. The authors' thoughtful consideration of these pressures provides us with a most useful starting point to tackle the next, and most important, issue: Why should evolution have "designed" the new resources with the characteristic layered structure of the isocortex, and not used any of the other several forms of neural tissue organization that were already available, presumably, to ancient reptiles?

It is clear to any naive external observer that a functional theory of the evolution of isocortical structures requires an analysis of the information-processing capabilities of cortical layers compared to those of alternative forms of neural organization. After all, processing information is what cortical layers do for a living, and their existence must be accounted for in terms of their raison d'être. Several authors have emphasized the developmental mechanisms at the basis of the ontogeny of neocortical circuits (see, e.g., Supèr & Uylings 2001). Understanding these mechanisms is clearly very important, but the question of *how* (to set up the system) should not be confused with the question of *why*. A consideration of developmental processes might perhaps lead one to rule out certain hypothetical forms of cortical organization, which it would be useful to have evolved, but which are ontogenetically impossible or impractical to wire up. Other than that,

neocortical circuits should probably be understood in terms of their function in the fully developed organism.

As the target article points out, the new isocortical network evolves between the olfactory cortex, which remains paleocortical in mammals, and the medial cortex, which evolves into the mammalian hippocampus, but without acquiring isocortical layers. The isocortical network promotes the expansion of the three main topographic sensory systems, visual, auditory, and somatosensory, into forebrain territory that had earlier been dominated by the nontopographic olfactory system. This suggests that the evolutionary advantage afforded by isocortical layers should be common to sensory processing that is topographic in nature (i.e., implemented through cortical maps isomorphic to the array of sensory receptors) and it should not pertain to nontopographic processing. Accounts that rely exclusively on an analysis of visual processing, on the other hand, may offer helpful indications about the role of individual layers (see Grossberg 1999; Kayser & Miller 2002), but are unlikely to offer a satisfactory explanation until they are generalized to other sensory modalities.

An evolutionary advantage that is common to vision, audition, and somatic sensation is also likely to be *quantitative* rather than *qualitative* in nature. It seems improbable that at the abstract and rarefied level at which the three modalities may be described within a common conceptual network, it would be possible to identify a qualitatively new function that the isocortex can carry out but the paleocortex cannot. It seems more reasonable to think of a quantitative improvement in carrying out functions that remain qualitatively the same.

In recent years I have explored the hypothesis that there are two key functions to consider, both of which can be expressed mathematically using a suitably defined formal model (Treves 2003). One is the cortical relay of positional information about a stimulus – that is, the transmission (with minimal information loss) of where a stimulus activates the array of sensory receptors. The second is the memory-based retrieval of identity information – the cortical analysis of all the perceptual aspects of a stimulus (some of which may be occluded or missing, and have to be reconstructed from memory) that are not mapped explicitly in terms of position on the array of receptors. Topographic maps in fact imply a generic distinction between "where" information, explicitly mapped on the cortical sheet, and "what" information, represented in a distributed fashion as a distinct firing pattern across neurons. These patterns can be stored on recurrent collaterals in the cortex, and such memory can help substantially in the analysis of current sensory input.

In analyzing how a neural network can carry out these two functions, quantitatively, it is important to control for the trivial effect of an increase in the number of network components, which is expected to be beneficial in itself. I have therefore simulated two simplified network models with the same number of components, one of which corresponds to an undifferentiated "paleocortical" patch of cortex, and the second to an "isocortical" patch, in which the main layers are differentiated. A quantitative, information theoretical analysis of these simulations demonstrates that a nonlaminated patch of cortex must compromise between transmitting "where" information and retrieving "what" information. Parameters can be chosen to optimize one or the other function, but not both at the same time. The differentiation of a granular layer affords a quantitative advantage, that is a (limited) improvement in the joint transmission of both information types, over the nongranular model. The further connectivity differentiation between infragranular and supragranular pyramidal layers is shown to match the mix of "what" and "where" information optimal for their respective target structures. The computational analysis therefore indicates that the isocortical patch may serve as an optimized component for combined topographic and memory-based information processing. One computational issue to address next is why it was so useful to use more of such components in the evolutionary process of multiplication of distinct cortical maps, known as arealization (Montagnini & Treves 2003).

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Authors' Response

An interdisciplinary approach to brain evolution: A long due debate

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Abstract: A dorsalization mechanism is a good candidate for the evolutionary origin of the isocortex, producing a radial and tangential expansion of the dorsal pallium (and perhaps other structures that acquired a cortical phenotype). Evidence suggests that a large part of the dorsal ventricular ridge (DVR) of reptiles and birds derives from the embryonic ventral pallium, whereas the isocortex possibly derives mostly from the dorsal pallium. In early mammals, the development of olfactory-hippocampal associative networks may have been pivotal in facilitating the selection of a larger and more complex dorsal pallium which received both collothalamic and lemnothalamic sensory information. Finally, although it is not clear exactly when mammalian brain expansion began, fossil evidence indicates that this was a late event in mammaliaform evolution.

After all the process of open peer commentary, we feel quite satisfied with the heated – but in our view, healthy – debate our target article provoked. Overall, we consider that the main points raised in the target article remain valid. There are, however, many interesting suggestions made by the commentators that can be significant additions to our theory. We will divide our response into different sections relating to the different topics addressed by the commentators. As in the target article, we would like to emphasize that each section of this discussion should be considered largely separate from the others, because alternatives in each section may be compatible with more than one alternative in other sections. We have dedicated more space to those points that in our view required clarification. Therefore, if some commentators appear to receive less attention than others, it is basically because we agree with their points of view rather than because we have neglected them.

R1. Homology issues and the dorsalization process

Perhaps the most basic conceptual issues were addressed by **Northcutt**, who questioned the concept of similarity as the sole criterion for homology, and underlined the concept of phylogenetic continuity. At the end of the target article (sect. 8) we mentioned that the DVR and the isocortex likely had separate evolutionary origins, and that embryonic

homology does not imply adult homology (see also Aboitiz 1988; 1995). In agreement with Northcutt, we would now like to emphasize these issues more.

Northcutt argues that the most important point regarding homology between DVR and the lateral isocortex (LICx) is not so much whether or not they have a common embryological origin, but whether or not in evolution they were separately acquired via independent developmental transformations. Thus, a common embryonic origin of the DVR and the LICx could be consistent with the outgroup hypothesis (OGH), if the two structures differentiated independently after the point of phylogenetic divergence, and with the recapitulation hypothesis (RECH), if a differentiated DVR was present in a common ancestor. Conversely, a situation of different embryonic origins of DVR and LICx fits the OGH well, but some exponents of the RECH might consider that this could be explained by a change of embryonic identity of an originally common anlage (see **Butler** and **Reiner**, however, this alternative may be very difficult to prove). As Northcutt says, perhaps what matters most to the latter researchers is not the historical process of divergence between mammals and sauropsids, but whether the isocortex has a single evolutionary origin (the dorsal pallium) or a dual origin (the dorsal and the ventral pallium). In our view this is a valid question. Even if there may not be adult homology, it should be determined whether or not there is *embryonic* homology between the precursors of the DVR and the LICx. If so, there would be phyletic continuity of the embryonic primordia of the two structures, although each has followed a separate developmental course.

Northcutt is also right in that a fine-grained cladistic developmental analysis of telencephalic development is required to shed light on the origins of these structures. Unfortunately, we feel that at this time there are not enough data to perform such a study. In the target article, we placed emphasis on embryological aspects mainly because at this point they may provide the best criterion to reconstruct the phylogenetic history. In this case, development seems to be more reliable than connectional similarity in reconstructing the historical process (see Aboitiz 1995; target article), and at this point suggests different developmental histories for the DVR and the LICx.

According to the comments received, we may distinguish two versions of the RECH. One is the original version, as proposed by Karten (1968; 1969) and restated here by **Salas, Broglio, & Rodriguez** (**Salas et al.**), which implies equivalency of sensory circuits between mammals and birds, and hence, an adult ancestral circuit whose gross morphology evolved in two different directions. This version is based mostly on similarity in connectivity patterns (see **Northcutt**). The original RECH faces some problems (some of these outlined by **Butler**, **Reiner**, and in the target article), not the least of which is that it is difficult to imagine a mechanism transforming the different components of the sauropsidian DVR into specific laminae in the isocortex. Furthermore, a likely possibility at this point is that the DVR and the LICx derive from different pallial sectors. If this were so, a massive tangential migration of excitatory elements from the ventral pallium to the dorsal pallium would be required for these circuits to be considered homologues. As discussed in the T.A., there is good evidence for tangential, ventro-dorsal migration of inhibitory cells from the subpallial ganglionic eminences, but not yet from the ventral pallium. Nevertheless, to be fair, perhaps not all the tangentially migrating cells in the telencephalon are GABAergic (Bellion et al. 2003; Polleux et al. 2002), leaving open the possibility of a contribution of ventral pallial excitatory cells to the LICx. In this context, the origin of the excitatory spiny granule cells of layer IV should be addressed in future studies. Cell tracing experiments are urgently needed to determine if, and to what extent, the LICx derives from the ventral pallium, or if part of the DVR derives from the dorsal pallium. As discussed in the target article such a tangential migration, if it exists, might be a consequence of a dorsalizing influence over the ventral pallium.

Considering this evidence, a new version of the RECH (**Butler**, **Furtado**, **Reiner**, and **Shimizu**) states that there is a common region that may have been independently transformed into the reptilian DVR and into the mammalian LICx. This version does not imply phyletic continuity between LICx and the DVR and therefore there may be no homology in **Northcutt**'s terms. Proponents of the new RECH may agree with a situation of separate embryonic origins: a ventricular zone originally destined to the ventral pallium might have been transformed into a cortical ventricular zone during mammalian evolution. The dorsalization process that we propose could provide the embryological mechanism required for this transformation. For example, a scenario of de-repression of Pax-6 expression as proposed by Furtado (among other changes) would be quite consistent with our proposal (see Stenman et al. 2003). As we mentioned in the target article, one difficulty with the new version of the RECH is the different topographic position of the DVR and the LICx with respect to the lateral cortex (see also Northcutt), which would imply a rearrangement of topographic boundaries in the adult. In addition, if separate embryonic origins were demonstrated for the DVR and the LICx in all reptiles and mammals, it would be practically impossible to prove that, phylogenetically, the LICx originally arose from an ancestral ventral pallial region.

Another point raised by **Butler** and **Reiner** is that the intermediate territory does express some Emx-1 in mammals, which is not fundamental for our proposal (in fact, this finding was made by defendants of the OGH; Gorski et al. 2002). The main point, for us, is that much of the DVR probably derives from a ventral pallial sector and that there is yet no evidence that the LICx derives from that sector. Reiner concludes that since "only the ventralmost part of the ventral claustrum is entirely Emx-1 negative," this renders "problematic the claims of homology for ventral DVR of birds and specific claustro-amygdaloid nuclei in mammals," which is exactly what we argued in the target article: we discussed the possibility that there may not be specific mammalian counterparts of the ADVR (see sect. 4.3). The fact that there may not be a structure homologous to the DVR in the ventral pallium does not imply that it should be sought in the dorsal pallium. Reiner also raises the issue that monotremes seem to lack a claustrum, which in our view is not indicative of any alternative of homology for DVR, even less for the RECH. Monotremes may have secondarily lost a claustrum; or if the claustrum is a late acquisition of mammals, there may be other structures, or simply no structures that correspond to the DVR.

Shimizu makes some interesting points in relation to the expansion of the dorsal pallium in birds, and a possible parallelism between mammals and birds in the development of

hippocampal-dorsal pallial networks. He also points out that the ADVR of birds is a highly complex structure and only a few components have been sufficiently studied. We completely agree on this, but the claims for homology between ADVR and LICx have been based on these few, well-studied regions. In this context, there are two intriguing components in the reptilian/avian DVR: (1) the hyperstriatum ventrale of birds (Emx-1 positive), which has been proposed to correspond to the reptilian dorsolateral ADVR and to the mammalian dorsolateral claustrum, dorsal endopiriform nucleus, and the basomedial amygdala, all Emx-1 positive (Guirado et al. 2000; Puelles et al. 2000); and (2) the avian archistriatum or posterior DVR of reptiles, whose homologies have been proposed to be many mammalian structures, including the (pallial) laterobasal amygdala (Lanuza et al. 1999), the (subpallial) centromedial amygdala (Smith-Fernández et al. 1998), and others (see Aboitiz et al. 2002). Certainly, further studies are needed to correctly determine the possible mammalian homologies to these structures, if they exist.

The OGH implies that there has been a re-routing of thalamic axons from the ventral pallium to the dorsal pallium (see target article, sects. 6.3, 6.4, and 8). **Butler** contends that the invasion of new territory by axons may be a too complex phenomenon, but in mammalian brain evolution this has occurred more than once (e.g., interhemispheric fibers and the corticospinal tract). In this context, transient embryonic structures like the subplate or cells in the pallial-subpallial or the telencephalic-diencephalic boundaries (Molnár et al. 2003) may have played key roles attracting both lemnothalamic and collothalamic axons into the developing cortical plate. Favoring the OGH, **Medina** and **Guirado** propose an enlargement of the dorsal pallium concomitant with expansion of the dorsal thalamus, which could be consistent with our dorsalization hypothesis. However, we are not sure yet whether this was an automatic consequence of increased thalamic axon growth. In mammals, thalamic expansion has been much more limited than cortical expansion, suggesting that thalamic influence may not account for all cortical growth. Furthermore, the concept of an expansion of dorsal tier thalamic nuclei as proposed by these authors largely relies on the presumed absence of homology between the mammalian pulvinar nucleus and the avian nucleus rotundus: the pulvinar would be a new nucleus which expanded greatly in the dorsal tier of the mammalian dorsal thalamus. On the other hand, **Güntürkün**, **Reiner**, and **Salas et al.** make an argument for homology between the rotundus and the pulvinar, and Güntürkün and Reiner, especially, strongly criticize the proposal of homology between the rotundus and the mammalian intralaminar nuclei. Although in a previous article (Aboitiz et al. 2002) we somehow favored the intralaminar-rotundus homology interpretation, at this point our intention was mainly to expose the two different viewpoints. We admit that this issue is not settled yet and further evidence may be needed to accept the intralaminar/rotundus homology hypothesis. As we stated in the target article, this issue is not germane to the OGH/RECH debate. In fact, the OGH appeared long before the pulvinar/rotundus homology was under question.

In addition, **Guirado** seems not to be convinced of adaptive explanations for macroevolutionary phenomena. Briefly, we consider that if an adaptive explanation is sound and consistent with the evidence, it should be taken as seriously as any other scientific proposal, and not be a priori rejected (Aboitiz 1990). Of course it is the entire postnatal structure that is presented to nature, but development makes up this structure, and changes in function imply structural changes mediated by development. Furthermore, purely developmental explanations are usually not sufficient to explain the origin of a structure: an obvious requisite for any evolutionary novelty is to work well (consider the evolution of the eye; see also comment by **Treves**). Guirado also thinks we are trying to compare the isocortex with all of the reptilian cortex, and that we claim that every component of the mammalian pallium must have a homologue in reptiles, which is not exactly what we argued in the target article.

Medina proposes several candidate genes for the dorsalization process, which need to be evaluated by future studies. In this context, it will be interesting to investigate the possible participation of the *sonic hedgehog/Gli* signaling pathway, which may promote cortical expansion (Ruiz i Atalba et al. 2002). We are not so sure that a single or a few mutations may have produced a fully working mammalian brain. It is perhaps more likely that changes in gene expression patterns involved several genes and occurred gradually, rather than all of a sudden. For example, there may be many genes that cooperate in the establishment of the pallial-subpallial boundary and in regulating cortical expansion (Bishop et al. 2003; Stenman et al. 2003). Probably many or all of these genes were involved in the origin of the isocortex. In this context, **Miu & Olteanu** propose a research program in which the costs and benefits of distinct developmental transformations should be weighed to evaluate the different alternatives. This could be a promising endeavor that may lead future research.

Martínez-García and **Guirado** claim that the argument for homology between the reptilian dorsal cortex and mammalian somatosensory and primary visual cortices is not correct; a cladistic analysis implies that the stem amniote had a multimodal pallium that underwent independent parcellation in the sauropsidian and in the synapsid lineages. **Powers** makes a similar argument when comparing the reptilian dorsal cortex with the mammalian entorhinal/subicular cortices. We believe that this is a very interesting possibility that deserves further study. In a way, this can be conceived of as a more radical form of the OGH that in our view would be consistent with the main hypotheses presented in the target article, especially with the claim that the mammalian and reptilian brains diverged very early in evolution. **Powers**'s suggestion for the role of dorsalization in the expansion of the dorsal cortex is also welcome. In this way, the dorsal pallium would have accommodated the lemnothalamic and collothalamic sensory input that began participating in associative networks.

R2. Evolution of cortical lamination

We would like to acknowledge **Marín-Padilla**'s earlier theory of a dual origin of cortical laminae, with an ancestral, early-produced component and a phylogenetically new, late-produced component. We think our hypothesis of cortical lamination (which is also partly based on Reiner 1993) has several points in common with Marín-Padilla's original proposals, especially the concept that the developmental sequence in this case seems to correspond with the phylogenetic sequence. The evidence that mutations in the gene Tbr-1 cause specific defects in the early cortical compo-

nents, and that mutations in other genes like Pax-6 cause deficits in late-produced components, supports this view. The early cortical components (especially cells in the subplate and layer VI) are reminiscent of an ancestral structure, which in mammals differentiated into a subplate and infragranular cortical layers. Note that in mammals, the ability to migrate past layers of preexisting cells developed among these early components. As said, cells in layer V may represent an intermediate stage in which cells acquired the migrating properties of the phylogenetically newer cortical neurons (cdk5/p35 dependant, glial-guided locomotion), but retain some phenotypic characteristics of ancestral cells (Aboitiz 1999a; Aboitiz et al. 2001b). As we mention in the target article, one point that deserves further study is to which extent the mammalian subplate can be considered comparable to early produced cells in the developing reptilian cortex or to cells in the adult reptilian cortex (Bernier et al. 1999; Cordery & Molnár 1999; Goffinet et al. 1999; Nacher et al. 1996; Supér et al. 1998b; Tissir et al. 2003). Another point that should be borne in mind is that the preplate has continued evolving in mammals by virtue of its role in cortical plate development. In addition, Marín-Padilla's suggestion about using the term "neocortex" rather than "isocortex," considering that it contains so many new elements, is reasonable to us. Our initial intention when using the term isocortex was to avoid implying a progressionist view of evolution, but if it were understood that this is not what is meant, we would see no problem in using the term neocortex.

Supèr contends that we do not explain "why" the dorsal cortex expands in mammals in conditions under which other structures like the hippocampus do not change their organization. He considers that the main cause for cortical expansion may have been the re-routing of thalamic axons from the superficial marginal zone to the deep subplate. As mentioned by other commentators (**Colombo**, **Martínez-García**, **Powers**, **Salas et al.**), hippocampal function and processing strategy may be somewhat more conservative than that of the isocortex, and its tangential organization is perhaps well suited for its functions (**Treves**). In addition, Supèr does not explain "why" axons were re-routed in the first place. We agree with Supèr in that the re-routing of corticothalamic axons may have released an important constraint on cortical expansion, but we are not so sure that this was the cause for all the rearrangements that occurred in isocortical origins. Rather, we prefer to think of this process as a gradual, reciprocal situation, in which small cortical expansions facilitated re-routing of some axons, which may have permitted some further expansion, then more re-routing, and so on. Still another possibility is that the true homolog of the reptilian cortex is the subplate (see comment by **Marín-Padilla**). If this was so, axonal rerouting might not have had to be so dramatic, since the cortical plate could have developed partly over the axons synapsing in the subplate/reptilian cortex (this would also be consistent with the notion of the inverted neurogenetic gradient as a strategy to maximize synaptic contacts with superficial afferents). An argument for a reciprocal relation may also be made about **Guirado**'s concern that cortical expansion drove the development of associative networks and not vice versa. These processes may have developed hand-in-hand, instead of occurring first one and then the other. Finally, Supèr argues that changes in cell number are not sufficient to increase cortical size, and gives as an example the visual cortex with a cell density double that of other cortical areas. Across species, there is a good correlation between neuronal number and cortical size (see, e.g., Haug 1987; Jerison 1973). In addition, the cortical cell numbers in mammals are probably orders of magnitude higher than in reptiles, not just double.

We welcome **Treves**'s analysis of processing capabilities of the isocortex; his "why" questions are more related to functional considerations that are interesting to investigate further. However, we think that the isocortical design may not be the only one that works; birds seem to do quite well with a different, non-laminated design (see **Shimizu**). In our view, isocortical architecture evolved as a consequence of a mixture of functional and developmental factors resulting in a design that worked well under specific circumstances – the world of early mammals. Subsequently, this design proved successful in colonizing other behavioral and ecological niches. The point we are trying to make is that some evolutionary innovations may originate as adaptive/developmental transformations that take place under very specific circumstances, and then turn out to be successful in a variety of conditions. This does not mean that this design is necessarily the optimal one that could be conceived for every situation.

R3. The "olfactory-hippocampal" hypothesis

We apologize for not having referred adequately to **Butler**'s early "olfactory-hippocampal" proposal and her considerations regarding the confluence of the lemnothalamic and collothalamic pathways in mammals. Our proposal also has a long date (cf. Aboitiz 1992). **Guirado** seems to disagree with the concept of confluence of collo- and lemnothalamic pathways in mammals as an evolutionary novelty. We claim that such a degree of confluence as is observed in mammals is not observed in reptiles. The fact remains that in sauropsids the bulk of the collothalamic input (which goes to the DVR) is largely independent from the lemnothalamic input (see also comments by Butler and **Shimizu**). In mammals, the pulvinar receives quite an important part of the visual collicular projection and sends a massive projection to the extrastriate cortex, in which both processing streams converge.

Bota and **Hermer-Vásquez & Hermer-Vásquez** propose to expand the olfactory-hippocampal axis to the orbitofrontal and the motor cortices, respectively. Hermer-Vásquez & Hermer-Vásquez also suggest a role for synchronized oscillatory activity as a linking mechanism in these networks. We are certainly in agreement with these proposals, especially considering that these associative networks may have been widespread in the early mammalian dorsal pallium. The point is to define an evolutionary starting point for these networks, which we believe may have been the hippocampal-olfactory axis. The proposals by **Martínez-García**, **Guirado**, and **Powers** about an ancestral multimodal dorsal pallium, perhaps comparable to the entorhinal/subicular cortex are especially relevant in this context.

Colombo and **Salas et al.** mention good evidence for conservatism of hippocampal involvement in spatial learning across vertebrates, which, as claimed by Colombo, raises the question of how function was maintained despite the important changes in overall connectivity in the differ-

ent lineages. Anatomical evidence suggests that there are more heavy sensory (collothalamic) inputs to the hippocampus of mammals than to that of reptiles (see comments by **Butler**, **Shimizu**, **Supèr**, and Butler 1994a; 1994b). In the target article, we mention that this is an intriguing question and is clearly matter for future comparative research. For example, an interesting lesion experiment would be to evaluate the role of collothalamic and lemnothalamic projections in spatial memory in mammals and reptiles. In addition, perhaps more subtle analyses will unveil processing differences in the hippocampi of mammals and reptiles, and many of the differences may be quantitative rather than qualitative. As we argue in the target article, a more detailed sensory input might not be necessary for the elaboration of crude maps of space but rather for complex forms of episodic memory and other memory functions (Eichenbaum 2000b).

Just to clarify issues, our main claim is that olfactory-hippocampal-dorsal cortex networks, present in ancestral reptiles and involved in spatial learning, were especially important in early mammals. The development of visual-olfactory associative networks involving the hippocampus may have a favored selection of an expanded dorsal pallium. In this way, despite an overall conservatism in function, perhaps more subtle forms of spatial or episodic memory and other functions may have developed in the hippocampus of the early mammalian brain.

R4. Fossil brains

Gilissen & Smith make an important contribution to our work by describing the multiple trends in brain expansion in early mammals, and the lack of detachment of ear ossicles in *Morganucodon,* implying that non-mechanical factors may have been important in early mammalian brain growth. In the target article, we admit that the interpretation of posterior brain expansion in *Morganucodon* may be questionable. Nevertheless, Gilissen & Smith point out that *Therioherpeton* (a Cynodont, see Figure 7 in the target article) might show signs of dorsal cortex expansion even earlier than *Morganucodon,* which would put the beginning of cortical expansion before what we originally proposed. However, the alternative that true brain expansion began much later, with the eumesencephalic type of brain (such as the eutherian *Barunlestes;* see Figure in Gilissen & Smith), is also possible. **O'Shea** proposes that there must have been interplay between patterns of braincase ossification, controlled by inhibitory signals from the dura mater, and evolutionary brain expansion in mammals. We believe that it could not be otherwise. Skull volume puts an obvious limit to brain expansion, and there must have been a coordinated evolution between these two parameters. This is a very interesting area for further research. Finally, we commend **Furtado** for his proposal of a scenario for early tetrapod evolution.

R5. Final comments

In the end, we feel that our main hypotheses are still in good standing after the commentary process. This has demonstrated that our proposal is a good basis for interdisciplinary research and discussion on the embryologic and evolutionary aspects of isocortical origins. Our intention at this point has been basically to outline a developmental and adaptive evolutionary scenario for isocortical origins, which needs to be evaluated by future research. The main idea is that a dorsalizing influence in telencephalic development triggered the origin of the isocortex, expanding the dorsal pallium both tangentially and radially. Generally speaking, a dorsalization process based on increased activity of dorsal-inducing factors may not help discriminate between the different hypotheses of homology of the isocortex. However, different homology hypotheses may imply specific mechanisms of dorsalization (tangential migration, change of identity of ventral pallial cells, or expansion of the dorsal pallium). We prefer the interpretation that the isocortex evolved its own circuitry and therefore its sensory circuits may not be homologous to those in the DVR of reptiles and birds. Furthermore, current developmental evidence suggests that the isocortex originated mostly from an ancestral dorsal pallium. Whether, in addition, some components of the ventral pallium became transformed into cortical phenotypes remains to be investigated, but, as stated, they would not be inconsistent with a dorsalization process. In this context, the controversy between the concepts of *field homology* and *embryonic homology* will probably remain for some time (Butler & Saidel 2000; Northcutt 1999; Puelles 2001b; Puelles & Medina 2002).

Except for some details, our views on the evolution of cortical lamination do not strictly contradict those of **Marín-Padilla** and **Supèr**, and we believe that they have both contributed importantly to this issue. Functional comparative studies may also be quite helpful in understanding the early evolution of cortical processing.

As an adaptive complement to this developmental process, we have proposed the "olfactory-hippocampal" hypothesis, which, even if it is not strictly new (Jerison 1973; Lynch 1986; Sagan 1977; see also commentary by **Butler**), contains new elements like the collothalamic/lemnothalamic confluence and the role of the olfactory-hippocampal axis in episodic memory (Eichenbaum 2000b). There is strong evidence of a conserved role of the hippocampus in spatial memory, but in mammalian evolution it may have incorporated additional or more complex forms of memory, partly because of the increased confluence of sensory inputs to this structure. In addition, we agree that in mammals these hippocampal-olfactory networks may correspond to widespread ensembles of activity in the lateral, dorsal, and ventral pallium, including elements like the orbitofrontal and motor cortices. The point is whether one can speak of an orbitofrontal and a motor cortex in the early evolution of the isocortex.

Finally, it has become clear that endocast information and the study of cranial anatomy may provide important clues to the origin of the mammalian brain. Open questions like when brain expansion began, and whether it was in Cynodonts or in crown mammals, will probably need to wait for further evidence.

We want to acknowledge all the reviewers and commentators for taking their time to participate in this exciting project. We feel that an open, interdisciplinary debate of this topic was long due, and expect that from this discussion new experiments will be made, oriented to address many of the questions that were raised.

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Letters "a" and "r" appearing before authors' initials refer to target article and response respectively.

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