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pigeons, occupies more than 12% of the total telencephalon volume and is equivalent to the size of the basal ganglia (unpublished observation).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

Allocortical model
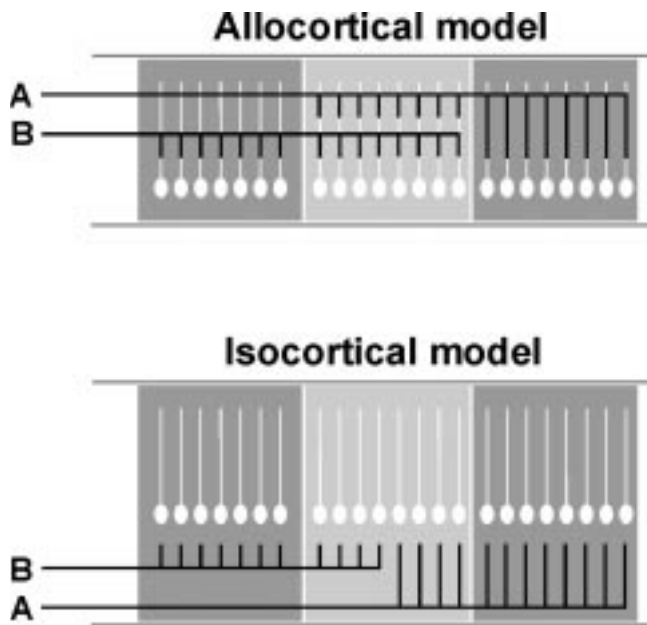

Isocortical model

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 ap-

propriate 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,