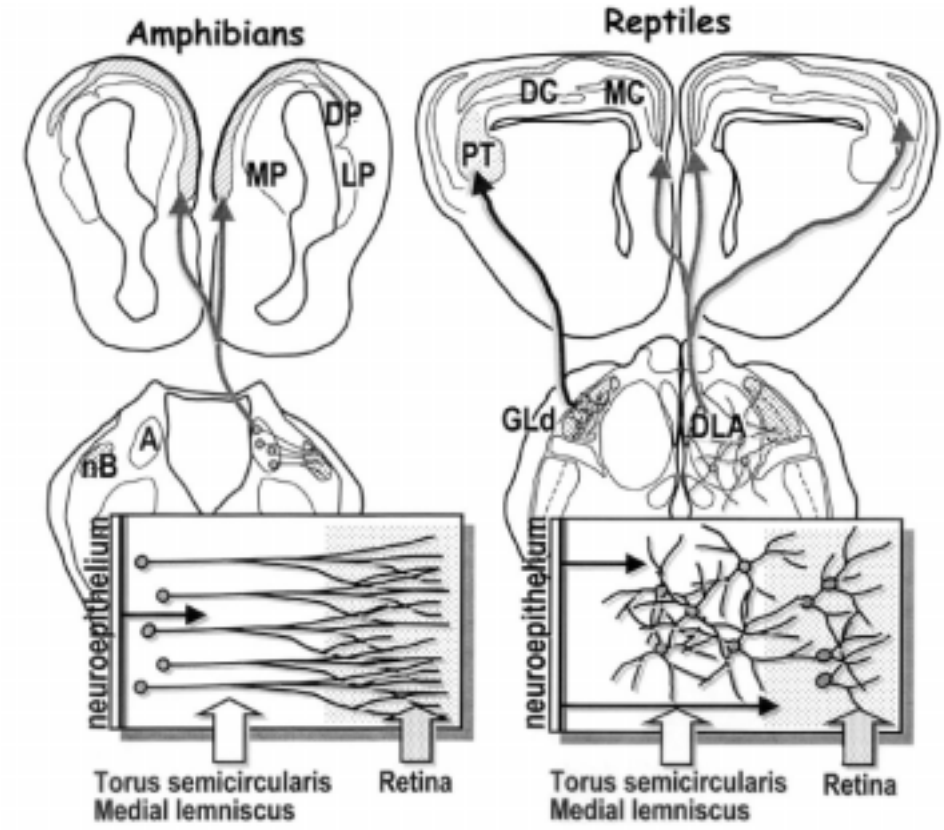


Figure 2 (Martinez-Garcia). Comparison of the thalamocortical pathways in amphibians (left; modified from Wicht & Himstedt 1988) and reptiles (right; based on Kenigfest et al. 1997; Martinez-Garcia & Lorente 1990) suggests a simple change in the histogenetic development of the dorsal thalamus that can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

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& 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.

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