& 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.