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.