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-