

that it requires less and less dramatic developmental transformations. Furthermore, as mentioned, at this point there is no evidence indicative of the migratory process required by the recapitulation hypothesis.

Rejecting the recapitulation hypothesis and accepting the outgroup hypothesis implies the assumption that the reptilian and the mammalian brains diverged very early in their evolution, which would be consistent with the concept of therapsids diverging at the earliest points of the amniote radiation. An explanation of the expansion of the DVR in reptiles is still needed. However, we will preliminarily suggest that the reptilian solution was a more conservative outcome, in which emphasis in sensory processing was given by the mesencephalic projection systems (collothalamic), perhaps as it happens in other vertebrate classes. In mammals, the main innovation consisted of the early dominance of olfaction in sensory processing (possibly associated with nocturnal habits and with a new respiratory system; Carroll 1988; Kemp 1982), which triggered the development of olfactory-dorsal cortex-hippocampal associative networks, eventually facilitating the confluence of the lemnothalamic and collothalamic sensory streams in the dorsal pallium and hippocampus.

Finally, the present perspective raises questions that impinge directly on several lines of research. For example, the study of dorsoventral gradients in isocortical specification, the studies of tangential cell migration into the isocortex, and the role of Pax-6 in reptilian cortical lamination may have immediate relevance to the hypotheses proposed here. On the functional side, comparative studies on hippocampal and amygdalar functions in amphibians, reptiles, and mammals may be of special relevance in relation to the concept of isocortical expansion triggered by hippocampal-olfactory-cortical associative networks.

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APPENDIX

Glossary of Abbreviations

A	termination site of the auditory projection
ADVR	anterior dorsal ventricular ridge
AM	amygdala; basolateral amygdala
cdk5	cyclin-dependant protein kinase 5
CP	cortical plate
DCx	dorsal cortex
Dp	dorsal pallium
DVR	dorsal ventricular ridge
GEs	ganglionic eminences
GL	thalamic dorsal lateral geniculate nucleus
HIP	hippocampus
ICx	isocortex
IL	thalamic intralaminar nucleus
IT	intermediate territory
IT/VP	intermediate territory/ventral pallium
IZ	intermediate zone
LCx	lateral cortex
LEM/TAF	lemniscal/thalamofugal visual pathway
LGE	lateral ganglionic eminence

Lp	lateral pallium
MCx	medial cortex
MES/TEL	mesencephalic/tectofugal visual pathway
MGE	medial ganglionic eminence
Mp	medial pallium
MZ	marginal zone
NP	thalamic pulvinar nucleus
NR	thalamic nucleus rotundus
O	olfactory tuberculum
OCx	olfactory cortex
PDVR	posterior dorsal ventricular ridge
Se	septum
SP	subplate
STR	corpus striatum
vl	termination site of the lemniscal, thalamofugal projection
vc	termination site of the collicular, tectofugal projection
VP	ventral pallium
VZ	ventricular zone
W	Wulst

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From axis to triangle: The role of orbital cortex

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Abstract: This commentary focuses on the “olfactory cortices–hippocampal formation” axis, proposed by Aboitiz et al. to be that network which allowed the first mammals to create elaborate representations of space. I argue here that this neural axis can be extended to a triangle of structures which also includes the orbital cortex.

Aboitiz et al. present compelling evidence that the mammalian isocortex appeared on account of a dorsalizing effect during the early development of the pallium of the first mammals. The authors argue that the olfactory-hippocampal-dorsal cortex circuit was needed to create complex olfactory-based representations of space.

Though the data cited by the authors support the olfactory cortex–hippocampus theory (OHT), I propose that this network is extendable to the orbital cortices and that these form a necessary component of the network of brain regions responsible for complex representations of space.

The orbital cortex in the rat receives connections from the subiculum (Canteras & Swanson 1992; Jay & Witter 1991), and a light projection from the CA1 field of the hippocampus (Jay & Witter). Unilateral ablations of the ventral lateral orbital cortices in rats lead to spatial neglect (King et al. 1989), and bilateral lesions of the same area impair rats performing tasks that require spatial maps of the environment (Corwin et al. 1994). The orbital cortex of the rat also receives connections from such olfactory-related structures as the perirhinal cortex (Ramus & Eichenbaum 2000a) and the entorhinal cortex (Deacon et al. 1983; Swanson &

Kohler 1986). Damage to the orbital cortex impairs animals in the odor version of the delayed nonmatch to sample (DNMS) task when the memory delay is minimal, which suggests that this region is important in perceptual processing or learning of rules (Eichenbaum 2000a).

Neurons in the rat orbital cortex recorded during an eight-odor discrimination task correlate their activity with recent past information and anticipate future events (Schoenbaum & Eichenbaum 1995). Physiological studies of orbital neurons in the rat showed that these fire either for single events or associations of events such as initiation of trials, sampling of odors, and reward consumption of odor-guided DNMS tasks (Ramus & Eichenbaum 2000). Rodent, monkey, and human experimental data show that the orbital cortex is the place where inputs from sensory and emotional and motivational information converge and it may be involved in representation of goals (Rolls 2000; Schultz et al. 2000). The orbital cortices can be considered to be part of the partially overlapping networks that are involved in the visual and nonvisual representations of space where sensory information is associated with reward and motivational-related information for rules formation.

The survival of animals depends on the creation and storage of complex representations of space. These are not only collections of places associated with visual or nonvisual cues or associations of stimuli, but also sets of rules for navigation and associations between stimuli and rewards. The orbital cortex appears to be a place involved both in the creation of the rules needed to construct and use spatial representations in lower mammalian species such as rodents, and for encoding more abstract rules in monkeys and humans. Therefore, the successful survival of animals also depends on the orbital cortices. The existence of the orbital cortex and the connections with olfactory regions in insectivore species (Radke-Schuller & Kunzle 2000) may be an indication that this region was present in the earliest mammals, and it may have similar functions across mammalian species.

The experimental findings presented above suggest that the olfactory cortex–hippocampal formation axis can be extended to a triangle of structures involved in olfactory representations of the environment, the “olfactory cortex–hippocampal formation–orbital cortex,” and it may appear early in the mammalian speciation. Nonmammalian vertebrate species present homologous structures of the olfactory cortex and the hippocampal formation, but the orbital cortex appears to be characteristic only to mammals.

One can therefore hypothesize that the network of cortical regions made of the olfactory regions, hippocampal formation, and orbital cortices is that circuit which allowed early mammals to construct complex representations of space, first olfactory-based but which, following the hypothesis of Aboitiz et al., became more visual when diurnal mammalian species emerged.

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The third alternative: Duplication of collopallium in isocortical evolution

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Abstract: One hypothesis of isocortical evolution requires tangential migration of glutaminergic neurons. A second requires invasion of collothalamoic afferents into the dorsal pallium, a territory that in sauropsids is solely lemnopallial. A third alternative is noted here – duplication of the original collopallial territory. The duplicated region would be formed by radial migration of excitatory neurons and would maintain its collothalamoic innervation.

The central point of this target article – the “hippocampal-olfactory hypothesis” for isocortical evolution and its adaptive advantage – is sound and has precedent in the literature. For example, Butler (1994a) noted that

Selection pressures strongly favored those amniotes in which this pallial expansion . . . occurred. The relay of information from both divisions [collothalamoic and lemnothalamoic pallia] . . . to the medial pallium for memory-related functions . . . would have conferred a significant competitive advantage.

The idea of an adaptive advantage gained by increased sensory inputs to the limbic system is compatible with each of several current hypotheses for the gain and expansion of the isocortex.

Two possible scenarios for isocortical expansion are considered in the target article. Did the isocortex evolve as an expansion of the dorsal pallium, as defined by Puelles et al. (2000), and thus have a unitary origin? Alternatively, did the isocortex have a dual origin, such that its developmentally medial part evolved as an expanded dorsal pallium and its lateral part evolved due to tangential migration of glutaminergic neuronal elements from a more ventrolateral part of the pallial mantle? The latter idea can be discarded for lack of evidence. The former, single-origin scenario would have involved a substantial change in connectivity. Because the dorsal pallium is in receipt of only lemnothalamoic projections in sauropsids (Butler 1994a), its expansion and gain of collothalamoic afferents would require substantial changes in the molecular cues expressed in the subplate and perhaps elsewhere. As in all cases of proposed neural homology, both developmental and hodological data must be weighed and accounted for, particularly because connections are the result of molecular cues expressed and utilized during development.

A key issue regarding isocortical evolution is whether a ventral pallial division can be separately distinguished on gene-expression criteria. A ventral pallium was identified by lack of *Emx-1* expression (Puelles et al. 2000; Smith-Fernandez et al. 1998), and at least some of its derivatives are collothalamoic targets in both mammals and sauropsids. However, Gorski et al. (2002) have demonstrated that all pallial regions contain neurons that express *Emx-1* at some time during development. All parts of the pallium – medial, dorsal, lateral, and ventral – express *Pax-6*, *Tbr-1*, and *Emx-1*. Although the ventral pallial territory may be distinguished by some other markers, such as differences in the degree of expression of cadherins (Redies et al. 2001), it may vary only as a matter of degree from other pallial areas due to gene-expression gradients rather than as a sovereignly discrete entity.

A third alternative exists that involves dual evolutionary origin of the isocortex but does not require either changes in molecular guidance cues or tangential migration of glutaminergic neurons. Although differing to some extent in details and rationales, dual-origin hypotheses for the isocortex have been previously proposed (e.g., Abbie 1940; Butler 1994a; Karten 1969; Reiner 1993; 2000; Sanides 1970). The “dual expansion hypothesis” (Butler 1994a) was based to a large extent on the recognition that two separate divisions of the dorsal thalamus – the lemnothalamus and collothalamus – exist, have different patterns of telencephalic projections, and were differentially expanded in the mammalian and sauropsid lineages (Butler 1994b; 1995). Recently, the separate identities of these two dorsal thalamic divisions have received strong support from molecular data, including calcium-binding protein immunoreactivity, *Gbx2* expression, and *Math4a* expression (Dávila et al. 2000; González et al. 2002; Martínez-de-la-Torre et al. 2002). If there are two such separate divisions of the dorsal thalamus, two comparably separate divisions of the isocortex – lemnocortex and collocortex – might likewise exist in mammals and be under separate selective pressures.

The third alternative requires only a feature of collocortex that is already firmly established: the marked propensity of collocortical areas to duplicate themselves, as has occurred independently within several mammalian lineages (Allman 1977; Kaas 1982; 1995; Krubitzer 2000). The recently proposed field homology