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Thoughts on the development, structure and evolution of the mammalian and avian telencephalic pallium

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Various lines of evidence suggest that the development and evolution of the mammalian isocortex cannot be easily explained without an understanding of correlative changes in surrounding areas of the telencephalic pallium and subpallium. These are close neighbours in a common morphogenetic field and are postulated as sources of some cortical neuron types (and even of whole cortical areas). There is equal need to explain relevant developmental evolutionary changes in the dorsal thalamus, the major source of afferent inputs to the telencephalon (to both the pallium and subpallium). The mammalian isocortex evolved within an initially small dorsal part of the pallium of vertebrates, surrounded by other pallial parts, including some with a non-cortical, nuclear structure. Nuclear pallial elements are markedly voluminous in reptiles and birds, where they build the dorsal ventricular ridge, or hypopallium, which has been recently divided molecularly and structurally into a lateral pallium and a ventral pallium. Afferent pallial connections are often simplified as consisting of thalamic fibres that project either to focal cell aggregates in the ventral pallium (predominant in reptiles and birds) or to corticoid areas in the dorsal pallium (predominant in mammals). Karten's hypothesis, put forward in 1969, on the formation of some isocortical areas postulates an embryonic translocation into the nascent isocortex of the ventropallial thalamorecipient foci and respective downstream ventropallial target populations, as specific layer IV, layers II–III, or layers V–VI neuron populations. This view is considered critically in the light of various recent data, contrasting with the alternative possibility of a parallel, separate evolution of the different pallial parts. The new scenario reveals as well a separately evolving tiered structure of the dorsal thalamus, some of whose parts receive input from midbrain sensory centres (collothalamic nuclei), whereas other parts receive oligosynaptic 'lemniscal' connections bypassing the midbrain (lemnothalamic nuclei). An ampler look into known hodological patterns from this viewpoint suggests that ancient collothalamic pathways, which target ventropallial foci, are largely conserved in mammals, while some emergent cortical connections can be established by means of new collaterals in some of these pathways. The lemnothalamic pathways, which typically target ancestrally the dorsopallial isocortex, show parallel increments of relative size and structural diversification of both the thalamic cell populations and the cortical recipient areas. The evolving lemnothalamic pathways may interact developmentally with collothalamic corticopetal collaterals in the modality-specific invasion of the emergent new areas of isocortex.

Keywords: pallium; subpallium; thalamus; ventral pallium; amygdala; claustrum

1. THE DORSAL PALLIUM (OR PROSPECTIVE ISOCORTEX) IS AN ISLAND INSIDE THE PALLIUM

The ample literature on the evolution of the mammalian cerebral cortex in many cases shows attempts to deal with this issue by considering the development and connectivity of the neocortex–isocortex (a six-layered cortex only present in mammals) in isolation from neighbouring parts of the telencephalon. In this review, I aim to second the alternative view that cortical evolution is best approached by keeping in mind that the isocortex is only one of the components of the telencephalic pallium (a developmental unit), and actually seems to be the last pallial part that emerges during evolution. The pallium is a primary embryonic telencephalic neighbourhood formed roughly at the top of the telencephalic vesicle, distinguished early on from the underlying subpallium by specific gene expression codes (Puelles *et al*. 2000). The subpallium is the embryonic site where the subpallial nuclei, or basal ganglia, are formed (figure 1*a*,*b*). The prospective subpallium is marked early on by the expression of *Dlx* genes in the subventricular and mantle zones (Liu *et al*. 1997; Eisenstat *et al*. 1999), whereas the pallium is defined by *Pax-6* in the ventricular zone and *Tbr-1* in the mantle zone, among other markers (Stoykova & Gruss 1994; Bulfone *et al*. 1995; Puelles *et al*. 2000). Both pallium and subpallium soon regionalize into subregions (and eventually there appear various nuclei, or cortical areas and layers), which nevertheless keep their primary molecular defining traits (leaving aside added migratory complexities; see figure 1*a–d* and below (§3).

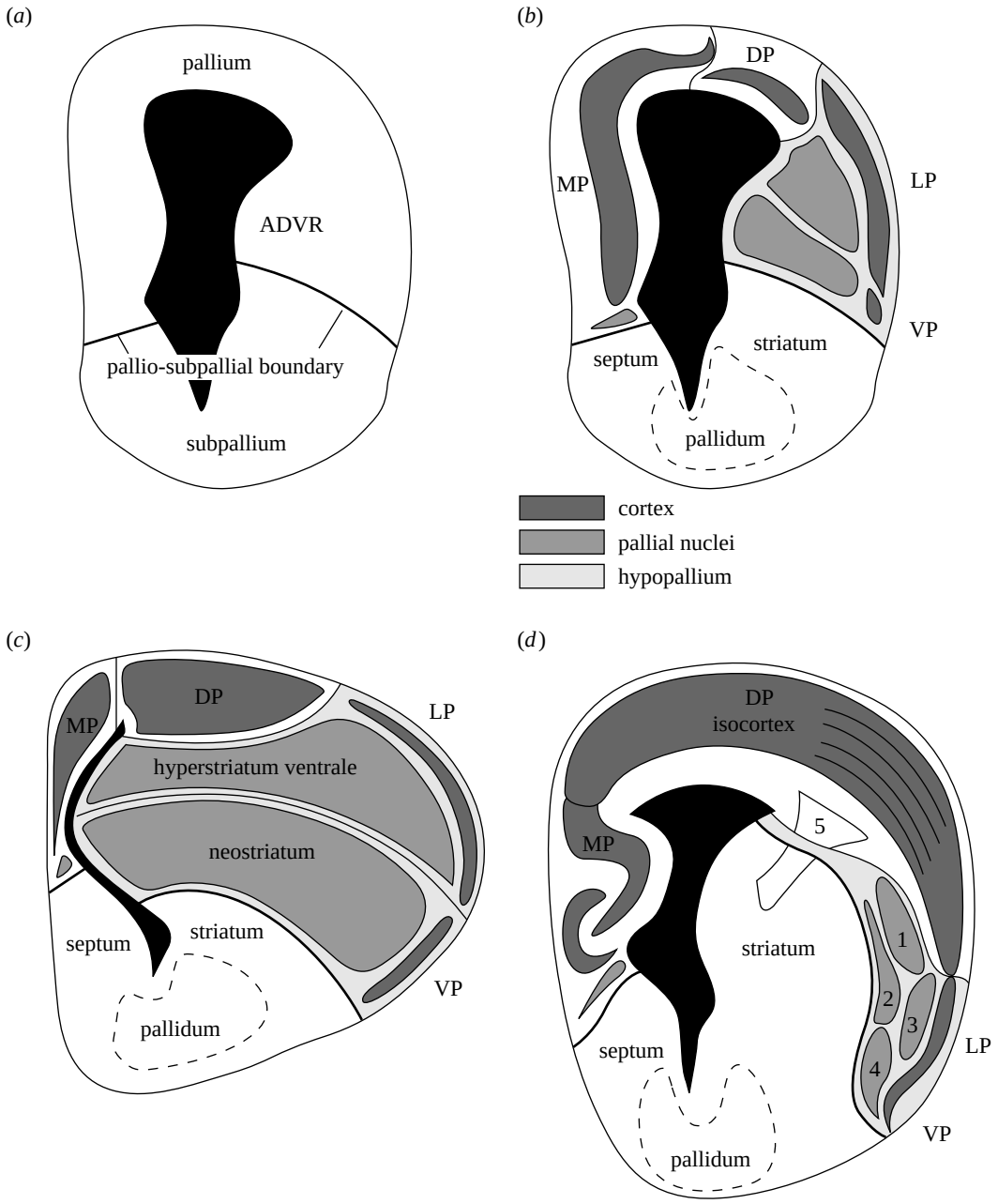

Figure 1. Schematics of topologically conserved pallial and subpallial structure of the telencephalon in reptiles, birds and mammals, leaving aside peculiarities found rostrally (olfactory bulb) and caudally (amygdala). (*a*) The pallium–subpallium boundary separates laterally and medially the pallium from the subpallium. The anterior dorsal ventricular ridge (ADVR) lies in the lateral part of the pallium, close to this boundary. (*b*) Hypothetical reptile ancestor. Main medial, dorsal and lateral regions of the pallium in reptilian brains, including the area we newly distinguish as a ventral region of the pallium. The cortically differentiated parts appear shaded in dark grey, whereas the pallial nuclei appear in light grey (note small pallial part of septum). The lateral and ventral pallium display both cortical and deep nuclear elements and build jointly the classic hypopallium (very light grey). Major parts of the subpallium are indicated as well. (*c*) Schema of the avian telencephalon, using the same symbolism used in (*b*) and adding some terms used in avian nomenclature. Note large size increment in the ADVR. (*d*) Schema of the mammalian telencephalon, using the same symbols used in (*b*, *c*). Note conversion of DP into isocortex, changes in MP (divided now into hippocampus and dentate gyrus) and changes in LP and VP, with superficial displacement of pallial nuclei relative to the internal capsule. 1, dorsolateral claustrum; 2, ventromedial claustrum; 3, dorsal endopiriform nucleus; 4, ventral endopiriform nucleus; 5, internal capsule. (For any abbreviations not already defined in the text, see legend to figure 6.)

Compared across vertebrates, the pallium does not always differentiate as a cortex (particularly in anamniotes), but seems to regionalize anyway into roughly comparable medial, dorsal and lateral pallial regions on the basis of histochemical, gene expression and hodological data. Therefore, these pallial parts are thought to be field-homologous across the taxa, and jointly are relevant for understanding 'cortical evolution'. So, the term 'pallium' is related to, but more comprehensive than, the term 'cortex', since it applies to homologous embryonic and adult pallial regions, independently of whether a cortical structure is differentiated or not. Observations of the pallium in extant reptiles clearly suggest that the reptilian ancestors of mammals had

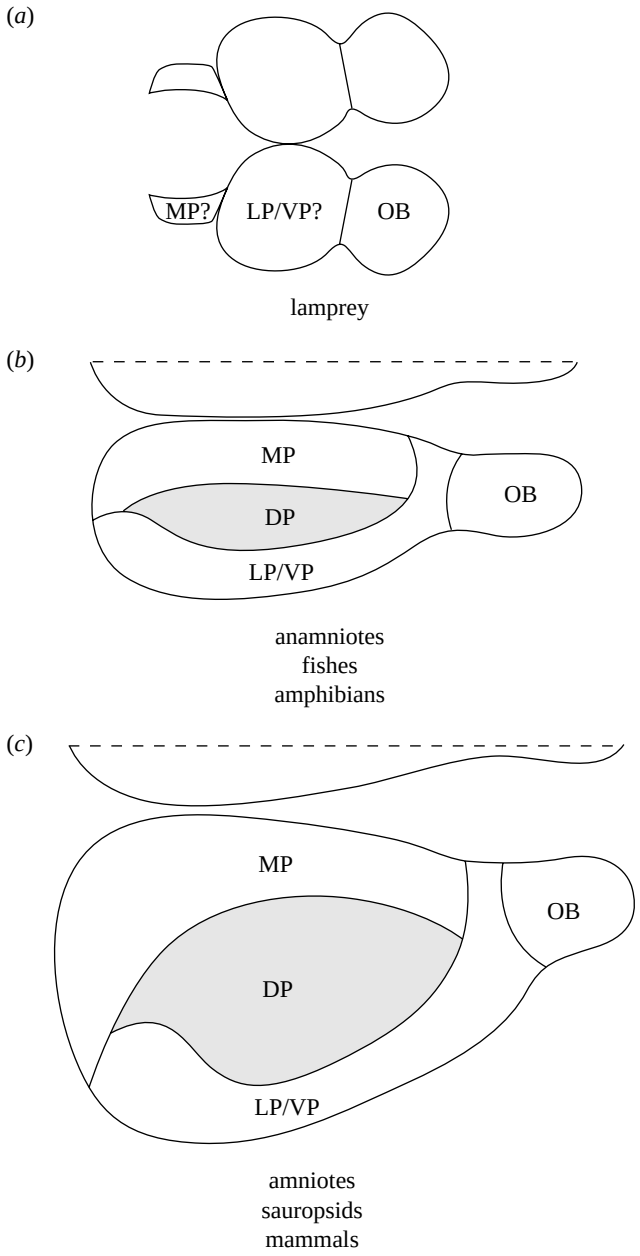

Figure 2. Drawings illustrating the telencephalon of lampreys, anamniotes and amniotes in dorsal view, showing the limits of the dorsal pallium island. The lamprey telencephalon is represented as incompletely evaginated and possibly lacking a dorsal pallium (see text (§ 1, paragraph 5)). (For any abbreviations not already defined in the text, see legend to figure 6.)

already evolved some sort of primitive cortical structure (neurons migrated away from the periventricular zone and partially stratified in a cortical plate) in each of the pallial subregions (medial, dorsal and lateral; figure 1*b*). These were later modified by increased cellularity, stratification and surface growth into the avian and mammalian pallial cortex (figure 1*c*,*d*). The mammalian dorsal pallium transforms into the more complex and extensive, six-layered isocortex (note these six layers may be partially indistinct in some 'basal mammals', as, for instance, the insectivore tenrec (Northcutt & Kaas 1995; Krubitzer *et al*. 1997)). The medial pallium forms the hippocampal allocortex, and the lateral pallium builds the olfactory allocortex (the proportionately less extensive allocortex displays maximally three or four layers; MP and LP in figure 1*d*). The lateral allocortex contacts rostrally and caudally the medial allocortex (figure 2).

Besides allo- and isocortex, the pallium contains nuclear pallial derivatives, placed near the subpallium (the sauropsidian dorsal ventricular ridge (DVR), figure 1*a*,*b*), which are represented in mammals by the claustrum, the endopiriform nuclei (figure 1*d*), and the lateral and basal parts of the amygdala (see figure 6*b*); in addition, a small portion of the septal nuclei may be considered pallial, dorsally to the major subpallial part of the septum (figure 1*d*) (Johnston 1913; Holmgren 1925; Puelles *et al*. 2000). The olfactory bulb, anterior olfactory areas, and the olfactory allocortex cover most of the nuclear parts of the pallium (part of the claustrum underlies instead the insular cortex). The cortical amygdaloid nuclei may be considered a caudal extension of olfactory allocortex, covering the pallial amygdaloid nuclei (figure 6*b*).

The mammalian isocortex therefore appears in topological representations as an isolated 'dorsal pallium' island, which lacks olfactory projections and is surrounded by lateral and medial allocortical pallium and some pallial nuclei (figure 2) (Holmgren 1922, 1925; Schepers 1948; Bayer & Altman 1991; Nieuwenhuys 1998). The surface of this island compared with total pallial surface is smaller in anamniotes and in non-mammalian amniotes (sauropsids) than in mammals (figure 2), and it acquires maximal relative size in gyrencephalic mammalian brains (as opposed to basal mammals having a lissencephalic telencephalon). The non-mammalian pallial regions show the same topological relationships, but lack the histogenetic differentiation characteristic of mammals. It has been much debated how the reptilian pallial cortical primordia transformed during evolution into the mammalian allo- and isocortex.

It is usually assumed that all vertebrates have some amount of dorsal pallium. In fact, it can be debated whether lampreys (agnathans) have a dorsal pallium area at all. Pombal & Puelles (1999) argued that at least the area usually postulated to represent dorsal pallium in lampreys is not convincing from a topological point of view, since it seems to fall within the subpallium. Practically all the evaginated pallium of lampreys receives olfactory projections, and the standard candidate for medial pallium remains non-evaginated (figure 2) (see Nieuwenhuys & Nicholson 1998). One wonders whether both lateral and medial pallial elements need to be inside a unified telencephalic primordium (be it everted, as in teleosts, or evaginated, as in other anamniotes and all amniotes) for the emergence of a dorsal pallial island. It is conceivable that interactive regulation of proliferative dynamics across a larger initial pallial surface may allow a novel dorsal pallial area to arise. All vertebrate lineages that evolved after the agnathans diverged show an integrated pallium subdivided into three parts, usually called lateral, dorsal and medial (figure 1*a*–*d*) (Holmgren 1922, 1925; Northcutt 1995). We have recently proposed the distinction of a fourth pallial part (this will be introduced in more detail below (§ 3)), calling it 'ventral pallium' (Puelles *et al*. 1999, 2000).

Given this preliminary analysis, the usual eschewing of olfactory, hippocampal, and claustroamygdaloid elements

when discussing isocortical development and evolution (i.e. Kaas 1995; Krubitzer 1995) would seem to be validated, although this is not the case if the interest really centres on all the cortex. Indeed, the developing olfactory cortex cannot be separated in causal explanation from the pallial nuclear elements radially underlying it, nor can perhaps the hippocampal cortex be causally separated from the associated septum and commissural plate. There is a distinct possibility that the island of dorsal pallium (prospective isocortex) is dependent on its lateral and medial neighbours for its emergence and maintenance. Recent studies of developmental genes expressed in the pallium frequently observe gene expression domains that do not distinguish initially the prospective boundaries between the major pallial subregions, and occasionally form opposed gradients of expression extending across the whole pallium (reviewed in Price & Willshaw 2000). There accordingly seems to exist a common initial developmental field, wherein any particular pallial domain becomes different on the basis of positional information relative to the edges and to the other individually emerging distinct parts. This process continues by steps into the areal regionalization and finer columnar subdivisions of both allo- and isocortex (Kaas 1995; Krubitzer 1995) and may involve a series of partially overlapping, but different, causal developmental mechanisms (i.e. proliferation, differentiation, cell migration, stratification, synaptogenesis).

The basic causal questions therefore resolve hierarchically into the following. What causes the existence of a unified everted or inverted (evaginated) telencephalic vesicle. What causes its primary division into pallial and subpallial regions. What causes allocortex and associated pallial nuclei to appear. What causes the dorsal pallium to appear. What causes the dorsal pallium to grow disproportionately and evolve its typical six-layered structure in mammals. Which fundamental processes lead to areal subdivision and functional differentiation within this cortex?, etc. Unfortunately, I am unable to answer properly any of these questions and shall therefore content myself with presenting some thoughts which seem to bear at least tangentially on some of these issues.

2. THE PALLIUM IN SAUROPSIDS

The pallial scenario becomes more complicated when we try to see how the pallium as a whole changed separately in evolution from reptilian forms into mammalian and avian forms (birds are evolutionary latecomers relative to mammals; they exemplify parallel evolutionary possibilities diverging from shared ancestral reptilian forms). Once it was established by studies of chemoarchitectony and connectivity which are the homologues of the mammalian subpallium in sauropsids (comprising, basically, the striatum and pallidum; figure 1*b–d*), it was obvious that the pallium of reptiles and birds contains massive nuclear areas within the ventricularly prominent formations called in reptiles the 'anterior dorsal ventricular ridge' (ADVR) and the 'basal dorsal ventricular ridge' (BDVR) (Ulinsky 1983; Kriegstein *et al*. 1986). This conclusion agreed with earlier embryological conclusions regarding these ridges as being pallial, on topological grounds (Holmgren 1925; Källén 1951*a*,*b*,*c*, 1953, 1962). In birds, we unfortunately still use an obsolete nomenclature that erroneously attributes the suffix 'striatum' to the pallial DVR components, so that the reptilian BDVR equals the avian 'archistriatum', and the ADVR homologue is subdivided into overlying parts called 'neostriatum' and 'hyperstriatum ventrale' (figure 1*c*). This division actually may exist as well in the reptilian ADVR and even extend into the BDVR, but usually is not taken into consideration (Ulinsky 1983; ten Donkelaar 1998; see discussion in Puelles *et al*. 2000). Apart from the massive DVR pallial elements, reptiles and birds also possess overtly or covertly layered cortical primordia, including distinct olfactory, limbic, hippocampal and 'dorsal pallial' cortices; all of these are less stratified than the mammalian homologues. It has been underlined that the reptilian cortical plate is typically built by outside-in stratification of neurons, whereas the mammalian one is largely formed inside out (Bar & Goffinet 2000).

In the comparison of the sauropsidian DVR and cortical formations with the mammalian schema of the pallium, two divergent interpretations have emerged and been variously supported over time. These favour, respectively, the idea of adjacent fields developing independently, or the possibility of massive tangential translocation of cell populations from one field into another.

Holmgren (1925) postulated that in the mouse there exist medial, dorsal and lateral parts of the pallium, plus a number of pallial nuclear masses of the claustroamygdaloid complex, which lie topologically deep with respect to the lateral, olfactory pallium, forming with it a radially complete complex called 'hypopallium'. The expression 'radially complete' means extending from the ventricle to the pial surface along radial glia lines; note these often become curved during morphogenesis (figure 1*b*). Accordingly, the complete hypopallium and the neighbouring dorsal pallium would represent two independent radially complete sectors of the telencephalic wall, and the same relationship applies for the medial pallium (and any areal subdivisions within them). The mammalian hypopallium was held by Holmgren (1925) to be field-homologous to the sauropsidian hypopallium, composed of the olfactory cortex (lateral pallium homologue) plus the DVR formations (held to be a claustroamygdaloid homologue). From the strictly topological point of view, this analysis seems sound, as corroborated by the respective patterns of radial glia and some hodological data (Kálmán *et al*. 1993; Bruce & Neary 1995; Striedter & Beydler 1997; Striedter 1997). It is schematically represented in figure 1*a–d*.

Experimental neuroanatomical study of pathways that transfer visual, somatosensory and auditory signals from the dorsal thalamus into the pallium indicated in a first analysis that mammalian pathways always target specific isocortical primary or secondary areas, synapsing mainly on layer IV cortical interneurons, whereas, in contrast, a number of sauropsidian sensory pathways target nuclear subregions of the reptilian ADVR, or homologous parts of the avian neostriatum (basal nucleus, ectostriatum, field L). Only a few avian thalamic projections (mainly a visual pathway) seemed to end in the dorsal pallium (only turtles among reptiles clearly imitated this) (figure 3*a*). However, later studies did find additional dorsal

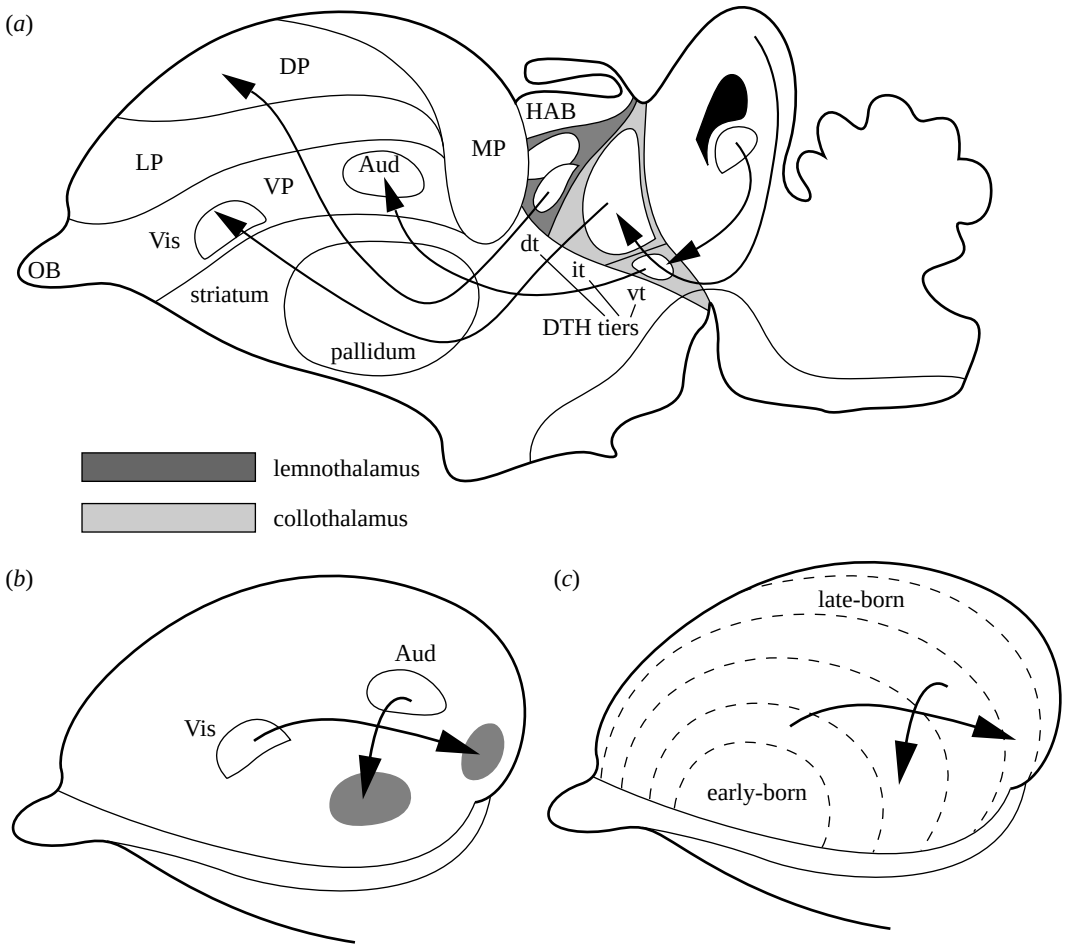

Figure 3. (*a*) Schema of thalamotelencephalic pathways in sauropsids in side-view. Examples are shown of collothalamic nuclei of the dorsal thalamus (light grey), which project to nuclei distributed in the ventral pallium, whereas nuclei in the lemnothalamus (dark grey, under the HAB) project to the dorsal pallium. Collothalamic nuclei receive projections from the midbrain (represented here only by visual and auditory inputs coming from the tectum and torus, respectively). (*b*, *c*) Assumptions implicit in Karten's (1969, 1991) hypothesis on the mass migration of discrete ventropallial cell populations into specific areas of isocortex. (*b*) Illustration of spatially specific and partially intercrossing theoretical migration paths from the relative loci in the sauropsidian ventral pallium to the respective cortical areas, in the case of auditory and visual pathways to temporal and extrastriate visual cortex. (*c*) Schema of gradientally ordered patterns of neurogenesis in the cortex superposed on the migration routes, suggesting the need for considerable coordination of these hypothetic cell movements in order to achieve properly ordered integration into the cortical target areas and laminae. (For any abbreviations not already defined in the text, see legend to figure 6.)

thalamic input into separate areas of the avian dorsal pallium, coming from nuclei conveying somatosensory and motor control signals (reviewed by Medina & Reiner 2000). Of course, one possible explanation of the apparent discrepancy in thalamotelencephalic connectivity between mammals and sauropsids was that emergence and elaboration of these connections may have occurred in a divergent, non-comparable way in the independent radial complexes of the hypopallium and the overlying dorsal pallium, leading to strictly non-comparable features (as suggested by Ulinsky (1983) and Jones (1985)). However, the transition from reptilian ancestors into mammals now seemed to require not only emergence of a complete set of thalamocortical connections, but also the disappearance of the ancestral connections targeting the hypopallium.

Karten (1969) introduced the alternative hypothesis that the hypopallial targets of sensory projections in sauropsids were in fact neuronal populations individually homologous to the mammalian layer IV interneurons found in some cortical areas subserving the respective sensory modalities (i.e. the auditory cortex). In order for this 'cell population' homology to be plausible, these layer IV cell populations would have to originate during embryonic stages in the mammalian hypopallium, outside the dorsal pallium, and migrate tangentially (across and under the lateral pallium) to reach their proper isocortical target areas, integrating there specifically into layer IV. The hypothesis was later extended to include other cell populations suggested to be individually homologous to layer II–III and layer V–VI pyramidal cortical neurons, according to observed circuities found within the DVR, and interpreted as analogous to the intracolumnar circuitry described in the mammalian isocortex (Karten & Shimizu 1989; Shimizu & Karten 1990; Karten 1991, 1997). Since all these neuronal populations do not show a layered distribution in the sauropsidian DVR, being arranged instead as independent nuclear

regions, it is clear that this extended hypothesis implies even higher sophistication of the molecular system that hypothetically would guide each population to its appropriate cortical area and layer (figure 3*b*). Given the neat overall gradiental relationship detected by autoradiographic studies between dates of neuronal birth and ulterior topographical and laminar position in the isocortex (Bayer & Altman 1991), this differential guidance would also have to be as precisely organized in time as in space (figure 3*c*). Note that Karten (1969) (and later work cited above) only postulated this mechanism for some cortical areas; this implies that a similar six-layered structure would be constructed by simple radial migration from the underlying neuroepithelium in some places and by selective differential tangential migrations from the hypopallium in other places, but still achieving a common stratification and neurogenetic gradient.

Karten (1969) speculated initially that the origin for these migrations might be the lateral ganglionic eminence, which is now known to represent largely the primordium of the striatum. Later he suggested as a potential cell source the overlying thick subventricular layer found close to the lateral angle of the lateral ventricle. Recently, we learned that the striatal primordium participates with the medial ganglionic eminence (pallidal primordium) in generating massive streams of inhibitory interneurons that migrate both subventricularly and subpially into the cortex (De Carlos *et al*. 1996; Anderson *et al*. 1997; Lavdas *et al*. 1999; Parnavelas 2000). Note that thalamorecipient layer IV interneurons are thought to be mainly excitatory (Valverde 1985; Freund *et al*. 1985; Carder & Hendry 1994; Lund *et al*. 1994). These migratory streams are not known to have any directional or target-layer specificity. More troubling, they are by their origin subpallial, whereas the sauropsidian hypopallium, which contains the thalamic target cell populations that hypothetically migrate in mammals, is clearly pallial.

Does this mean that the thalamorecipient target cell groups in the sauropsidian hypopallium actually originate from the underlying subpallium? At least two lines of evidence allow us to discount this possibility. First, experiments studying polyclones labelled by iontophoresis of biotinylated dextranamine into the early chicken telencephalic wall showed distinctly that neostriatum (ventral DVR) cell populations originate within the pallium, separately from subpallial populations (Striedter *et al*. 1998). Moreover, fate-map analysis with quail grafts at late neural plate stages in the chick forebrain (stages 7–8) showed that the prospective subpallium is neatly separated from the prospective ventral DVR in the pallium, independently of the existence of a migration of subpallial inhibitory interneurons into the pallium, entirely comparable with the mammalian one (Cobos *et al*. 2001; see preliminary data in Rubenstein *et al*. 1998).

Some sort of an impasse seemed to have been reached. Holmgren's (1925) field-homology hypothesis directly comparing the sauropsidian with the mammalian hypopallium, although topologically sound, did not seem able to explain the divergent sensory afferents from the dorsal thalamus, nor did it say anything about how the mammalian isocortex evolves. Karten's (1969, 1991, 1997) hypothesis, although uncomfortably complex in its assumptions, provided a particularly interesting explanation of the connectivity data, which has dominated the field since then. A tangential migration was first suggested to be important in cortical development, and it was postulated that somehow the sauropsidian hypopallium was involved in the emergence of the six-layered mammalian isocortex by reshuffling of homologous cell populations that conserve their connectivity properties. Whereas the embryonic locus postulated by Karten as a cell source for the tangential migrations has indeed been found to participate in massive tangential migrations into the cortex and the olfactory bulb, features like the inhibitory typology of the corresponding cells, their indiscriminate mode of migration into all cortical layers and their clear-cut subpallial nature, inconsistent with clonal and fate-mapping studies in the chick, jointly showed that this was not the predicted migration. That is, these cells are not homologous to the pallial ones receiving sensory projections in the sauropsidian hypopallium. Accordingly, there is to date no evidence whatsoever corroborating the specific migrations postulated within Karten's (1969, 1991, 1997) hypothesis, although the experiments of Anderson *et al*. (1997) did prove that massive tangential migrations of interneurons colonizing the cortex are possible. Glutamatergic cortical neurons (pyramidal cells and spiny stellate interneurons) meanwhile are thought to originate within the radially corresponding part of the cortical ventricular zone (Mione *et al*. 1994; Tan *et al*. 1998; Anderson *et al*. 1999). An alternative source for hypopallial cells that might move into the isocortex only came into the foreground as developmental genes began to be mapped and compared in the telencephalon of several vertebrates.

3. COMPARABLE GENE PATTERNS

Many developmental genes are strongly conserved in their nucleotide sequences, expression patterns and functions among vertebrates (often also across both invertebrates and vertebrates). Some genes are known to be essential for the development of given brain primordia, once their functions have been assessed in a number of ways (mainly loss-of-function or gain-of-function experiments by mutation, together with transgenic manipulation, and electroporation or transfection of DNA). Occasionally they are expressed continuously in the corresponding primordium from its early inception into postnatal conditions, and can be used therefore as molecular markers in different vertebrates. In this way, for instance, many neural developmental genes first discovered in *Drosophila* were later described in the mouse neural tube, and their expression patterns were entirely comparable topologically with those of the homologous genes in zebrafish, which, as a teleostean, is a rather distant vertebrate relative of mammals (Püschel *et al*. 1992; Macdonald *et al*. 1994; Akimenko *et al*. 1994; Hauptmann & Gerster 2000). This persistence of a diversity of gene expression patterns bespeaks their causal participation in generating and elaborating the Bauplan of the brain, its basic organization plan, which is now thought to be common to all vertebrates (Puelles 1995; Pombal & Puelles 1999). While a characteristic genetic profile signals homology of developmental brain divisions,

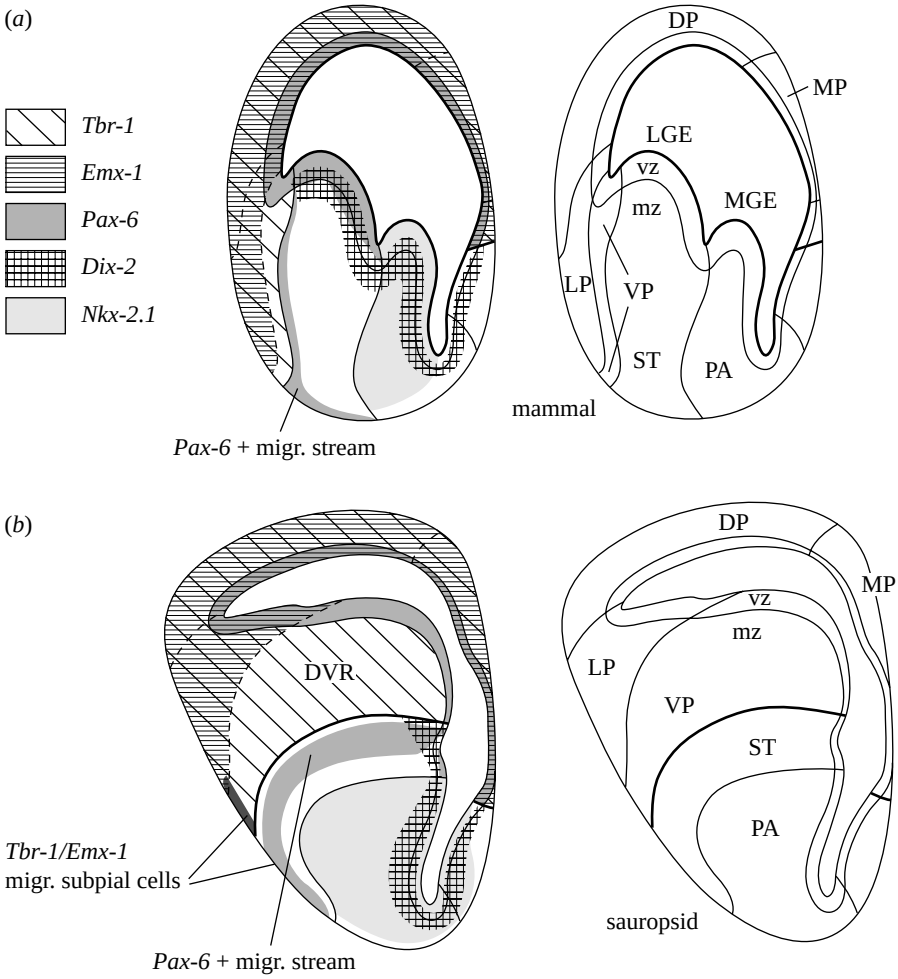

Figure 4. Schemata of gene markers used to define molecularly the diverse pallial and subpallial subdivisions in mammals and birds (the latter essentially comparable with reptilian patterns). Note clear-cut division of the hypopallium into superposed parts differing in *Emx-1* expression. This served to propose the existence of the ventral pallium (Puelles *et al*. 1999, 2000). Note also radially migrating *Pax-6*-positive neurons inside the striatum in both mouse and chick. (For any abbreviations not already defined in the text, see legend to figure 6.)

homology of specific cell populations or nuclei formed inside any division needs to be established separately by additional, more restricted markers in concert with traditional comparative methods.

Systematic comparison of telencephalic pallial and subpallial components in tetrapods was started independently by Smith-Fernández *et al*. (1998) and ourselves (Puelles *et al*. 1999, 2000). The paper by Smith-Fernández *et al*. (1998) importantly showed that, when compared with the subpallium, as identified in frog, turtle, chick and mouse embryos by the *Dlx-1* marker, the expression domain of the pallial marker gene *Emx-1* in all cases covered the medial, dorsal and lateral pallium parts, but only a dorsal part of the nuclear hypopallium. The unlabelled ventral portion of the hypopallium of the mouse was a thin stripe extending from the ventricular zone, just under the lateral angle of the lateral ventricle, to the pial surface, laterally to the olfactory tuberculum. The corresponding *Emx-1*-negative domain in turtle and chick embryos actually represented the large ventral part of the DVR (the neostriatum; see figure 4). The mouse negative stripe diminished in size in older embryos and was largely undetectable near term, although it persists caudally in the amygdaloid region. In contrast, the sauropsidian equivalent remains voluminous and is easily visible in the adult. The *Emx-1*-negative domain in all studied species was confirmed to be pallial by the common strong expression in the ventricular zone of the gene *Pax-6*, which is only weakly present in the subpallium. A nearby radially migrating stream of *Pax-6*-positive neurons was interpreted by Smith-Fernández *et al*. (1998) as defining positively their *Emx-1*-negative 'intermediate zone' mantle. We disputed this last point, but corroborated the rest (Puelles *et al*. 1999, 2000).

Our observations extended the relevant *Emx-1* data, but a more precise analysis in the chick and mouse disclosed that the stream of radially migrating *Pax-6* cells does not occur across the *Emx-1*-negative zone, but lies close by, within the striatal subpallium (figure 4). Mapping of another pallial marker gene, *Tbr-1*, showed that it is ubiquitous in the telencephalic pallial mantle (Bulfone *et al*. 1995), thus confirming that the *Emx-1*-negative domain in both mouse and chick embryos not only has a *Pax-6*-positive neuroepithelium, but also largely contains *Tbr-1*-positive pallial neurons (Puelles *et al*. 1999, 2000). We proposed that this molecularly distinct ventral part of the hypopallium should be distinguished as 'ventral pallium' from the overlying dorsal hypopallial part, or

'lateral pallium' proper, which uniformly expresses *Emx-1*. Note that both the mouse claustroamygdaloid complex and the ADVR–BDVR formations of sauropsids result thus divided longitudinally into an *Emx-1*-positive lateropallial part and an *Emx-1*-negative ventropallial part.

The molecular definition of the ventral pallium as a radially complete and evolutionarily conserved area in tetrapods, intercalated between the pallium–subpallium boundary and the other parts of the pallium apparently serves to see the old conflict between the Holmgren (1925) and Karten (1969) hypotheses under a new light. There exist generally in vertebrates two molecularly distinct parts of the classic hypopallium. If these fields are mutually homologous across tetrapods, as suggested by the conserved patterns for *Dlx*, *Pax-6*, *Emx-1* and *Tbr-1* found among representatives of these species (Smith-Fernández *et al*. 1998; Puelles *et al*. 1999, 2000; A. Brox, B. Ferreiro, L. Medina and L. Puelles, unpublished data in frog), then the migrations postulated by Karten (1969, 1991, 1997) should start in mice precisely from its thin ventral pallium domain. As far as I know, there is as yet no experimental testing of the possibility that such migrations exist. In view of the previous failure of both descriptive embryological methods and autoradiographic analysis of cell migrations to discover the massive palliopetal migrations originating in the subpallium (Anderson *et al*. 1997; Lavdas *et al*. 1999; Parnavelas *et al*. 2000), this possibility certainly should not be discounted until there is convincing experimental testing.

4. THE CLAUSTROAMYGDALOID COMPLEX AND ITS CONNECTIONS

Remarkbly, the ventral pallium of the mouse does not disappear altogether (as one would expect if all its cells move into the cortex). At least part of its component cell populations seem to migrate along radial glial guidelines, and they aggregate superficially to the internal capsule, close to the olfactory cortex, as a ventromedial component of the claustrum and the ventral endopiriform nucleus (figure 1*d*), or populate caudally the lateral and basomedial amygdala (figure 6*b*) (here and in the next sentence I correct in the light of additional unpublished data (G. González, L. Medina, J. L. R. Rubenstein and L. Puelles) the slightly different tentative interpretation of the amygdala offered in Puelles *et al*. (1999, 2000)). The *Emx-1*-positive lateral pallium forms the larger dorsolateral part of the claustrum and extends caudally across the dorsal endopiriform nucleus into the basolateral amygdala; see figures 1*d* and 6*b*). Central and medial parts of the amygdala express subpallial marker genes (Puelles *et al*. 2000), agreeing with the anatomical conclusions of Swanson & Petrovich (1998) and earlier authors (Holmgren 1925; Källén 1951*a*,*b*).

This means that, in any case, testing of Karten's migration hypothesis (see also a variant in Reiner (2000)) needs to be done with the anticipation that not all ventropallial cells can move into the cortex, since some must remain *in situ*, building these claustroamygdaloid derivatives. Incidentally, such experiments should also examine whether some elements of the lateral pallium nuclear components may also migrate tangentially into the dorsal pallial cortex. Alternatively, if tangential migrations from the ventral and lateral pallium into the cortex are absent in mammals, then the ventropallial and lateropallial parts of the claustroamygdaloid complex represent the respective complete derivatives, strictly in agreement with Holmgren's (1925) hypothesis (see also Striedter 1997; Aboitiz 1999).

While these claustral and amygdaloid distinctions may be seen as introducing excessive complication in our understanding of this already complex domain, they are actually helpful for illuminating the comparative problem of hypopallial sensory connections in sauropsids, or, at least, seem to offer a new scenario in which this problem may be solved. Following data show that the molecular difference highlighted by the differential expression of *Emx-1* correlates with differential hodological patterns.

First, we have a separate lateropallial part of the sauropsidian hypopallium (*Emx-1*-positive) which receives sparse, if any, thalamic input, according to available data. This part is molecularly comparable and possibly homologous to the dorsal hypopallial derivatives of the mammalian brain, largely the dorsolateral claustrum, dorsal endopiriform nucleus and basolateral amygdala (Bruce & Neary 1995; Swanson & Petrovich 1998). Neither the dorsal claustrum nor the dorsal endopiriform nucleus receives important afferents from the dorsal thalamus, being instead connected bidirectionally with the overlying isocortex. The basolateral amygdala is sparsely innervated by thalamic afferents (Turner & Herkenham 1991).

Second, there is the ventropallial part of the sauropsidian hypopallium (*Emx-1*-negative), which receives several dense focal inputs from a variety of dorsal thalamic nuclei, characterized by receiving their inputs from midbrain stations in the respective pathways (so-called 'collothalamic nuclei'; see Butler (1994*a*,*b*, 1995)). The hypothesis that the mammalian ventral pallium is field-homologous to this domain suggests that one should search for collothalamic projections into the corresponding mammalian nuclear derivatives, comprising mainly the ventromedial claustrum, ventral endopiriform nucleus and lateral–basomedial parts of the amygdala. Curiously enough, given that this topic has never been investigated from our present viewpoint, there is evidence that such connections exist. Dorsal thalamic neurons in the posterior thalamus, posterior intralaminar or paralaminar nuclei and medial geniculate complex of the rat have been shown to project to the ventromedial claustrum (Kaufman & Rosenquist 1985; Sloniewski *et al*. 1986; Carey & Neal 1986), and rather intensely to the lateral amygdala (figure 6*b*) (see Doron & LeDoux 1999, 2000). These thalamic areas receive sensory projections from the cerebellum, midbrain inferior colliculus and from deep layers of the superior colliculus (i.e. Holstege & Collewijn 1982; Künzle 1996, 1998).

Third, the diverse areas of the mammalian isocortex or the sauropsidian dorsal pallium that receive projections from specific dorsal thalamic nuclei are characterized by receiving their inputs from pathways sidestepping the midbrain (so-called lemnothalamic nuclei (Butler 1994*a*,*b*, 1995)). Such nuclei are not as well-developed in sauropsids as in mammals, but recent investigations have shown that they occupy a conserved topological position within the dorsal thalamic anlage.

5. THE DORSAL THALAMUS

It has been traditionally difficult to study the development of individual nuclei in the dorsal thalamus, due to its mode of regionalization. Initially, there appears a dense and apparently homogeneous immature neuronal mass in the mantle layer, which later slowly becomes subdivided into a set of nuclear complexes by glial cell packaging, or by differential typological maturation of neurons and neuropile growth. Some time later individual nuclei become visible, but fine details like the layers in the lateral geniculate nucleus only form perinatally under the influence of functional competition. The overall layering pattern in the dorsal thalamus is outside in, although some exceptions have been recorded.

The tendency has predominated to regard the whole dorsal thalamus in any vertebrate as a single homogeneous field and to compare individual nuclei across species mainly by their relative topography and the nature of the respective connections (i.e. Jones 1985; Pritz 1995). However, the initial assumption that there would be one visual nucleus, one somatosensory nucleus, and so on for all modalities, was soon proven wrong; several nuclei for each functional modality exist in species that have been studied thoroughly, making simple hodological comparisons very difficult.

The intuition that these thalamic nuclei can be grouped topographically into those whose afferents come from the midbrain (collothalamic nuclei) and those whose afferents are lemniscal (lemnothalamic nuclei) sparked considerable interest, particularly because these groups occupy constant topological positions across species and distinctly differ in their projection targets (Butler 1994*a*,*b*, 1995). Collothalamic nuclei are placed ventrocaudally in the dorsal thalamus and project into the subpallium and hypopallium (more precisely, into the ventral pallium), whereas the lemnothalamic nuclei are found dorsally and project into the dorsal pallium or medial pallium (figure 3*a*). The topographical terms 'dorsally' and 'ventrally' are used here within the dorsoventral coordinates of the prosomeric model (Puelles & Rubenstein 1993; Puelles 1995); as shown in figure 5, we also depart in other details from the collo- and lemnothalamic subdivision contemplated by Butler (1995). Connectivity studies clearly support a collo- and lemnothalamic schema in all tetrapods, although there is considerable variation in the cytoarchitectonic appearance of the dorsal thalamus in frogs, lizards, turtles, birds or mammals and a number of exceptions are known (Jones 1985). The latter (i.e. a collicular projection into the lemnothalamic pulvinar nucleus) may be due to evolutionary variation of the connectivity properties of thalamic cell populations, independently of their ancestral positional origin.

We have studied recently the developing chick dorsal thalamus while mapping a set of cell adhesion proteins of the cadherin family (Yoon *et al*. 2000; Redies *et al*. 2000). It was found that the earliest division of the primordial dorsal thalamic cell mass is into three dorsoventral tiers (figures 3*a* and 5). We called them dorsal, intermediate and ventral tiers (Redies *et al*. 2000). Each of these complexes is a complete radial unit and becomes separated from the others by glial scaffolding (I am simplifying for this account; see these papers for full details). Differential cadherin expression accompanies the progressive individuation of specific thalamic nuclei (Redies 1997, 2000), as it accompanies areal differentiation in the mouse cortex (Suzuki *et al*. 1997).

The lemnothalamic nuclei, as for example the lateral geniculate nucleus, clearly develop inside the dorsal tier (which limits dorsally with the habenula or epithalamus); the non-auditory collothalamic nuclei (i.e. the visual nucleus rotundus, etc.) develop in the intermediate tier, and the auditory nucleus ovoidalis complex arises in the ventral tier, being the ventral-most element in the dorsal thalamus (figure 5). Parallel studies on the adult lizard dorsal thalamus, mapping acetylcholinesterase (Martínez-de-la-Torre 1985) or calcium-binding proteins (Dávila *et al*. 2000) showed that the three-tiered structure exists as well in lacertid reptiles, with identical nuclear relationships. Previous studies in anamniotes suggested an incipient differentiation of dorsoventral tiers in these brains as well (frogs, Puelles *et al*. (1996), Milán & Puelles (1999); lamprey, Pombal & Puelles (1999)). The comparison of these diverse forms indicates a minute dorsal tier in anamniotes and a distinctly larger dorsal tier in sauropsids (such that in lizards the dorsal tier is barely larger than the intermediate tier, whereas in the chick this disproportion and the number of dorsal tier nuclei increase significantly; figure 5).

Projection of this morphogenetic trend speculatively into mammalian conditions, with the insight that collothalamic projections comparable with the reptilian and avian ones come from the posterior thalamic complex, posterior intra- or paralaminar nuclei and medial geniculate complex (Linke & Schwegler 2000), suggests that these last elements may represent the ventrocaudally compressed derivatives of the mammalian intermediate and ventral tiers, dwarfed by a massive growth of the mammalian dorsal tier, containing a large variety of lemnothalamic centres projecting to the well-differentiated isocortex (figure 5) (similar ideas were already advanced by Martínez-de-la-Torre (1985) and Guillén (1991)).

This does not imply that the sauropsidian thalamic dorsal tier already contains *in nuce* all the dorsal tier derivatives of mammals (other than as an evolutionary potency of neuroepithelial genetic determinants). It can well be that the so-called 'associative' thalamic nuclei of mammals, represented by the lateral dorsal, lateral posterior, pulvinar and medial nuclei, which on the whole lack specific lemniscal afferent pathways and mainly interconnect bidirectionally with late-appearing associative isocortex, may be new elements that only emerge in mammals (they are unequally developed among mammals and have maximal relative size in *Homo*, as occurs with the hodologically corresponding associative parieto-temporal and prefrontal cortices).

Accordingly, the dorsal tier accompanies in its relative size increase the preliminary elaboration of the dorsal pallium and eventual proto-cortex in non-mammals, and its mass explodes together with the emergence of the six-layered isocortex in mammals. Additional neurogenetic expansions seem related to the advent of the pulvinar and other 'associative' nuclei, and are linked to special elaboration of associative and limbic cortices in primates

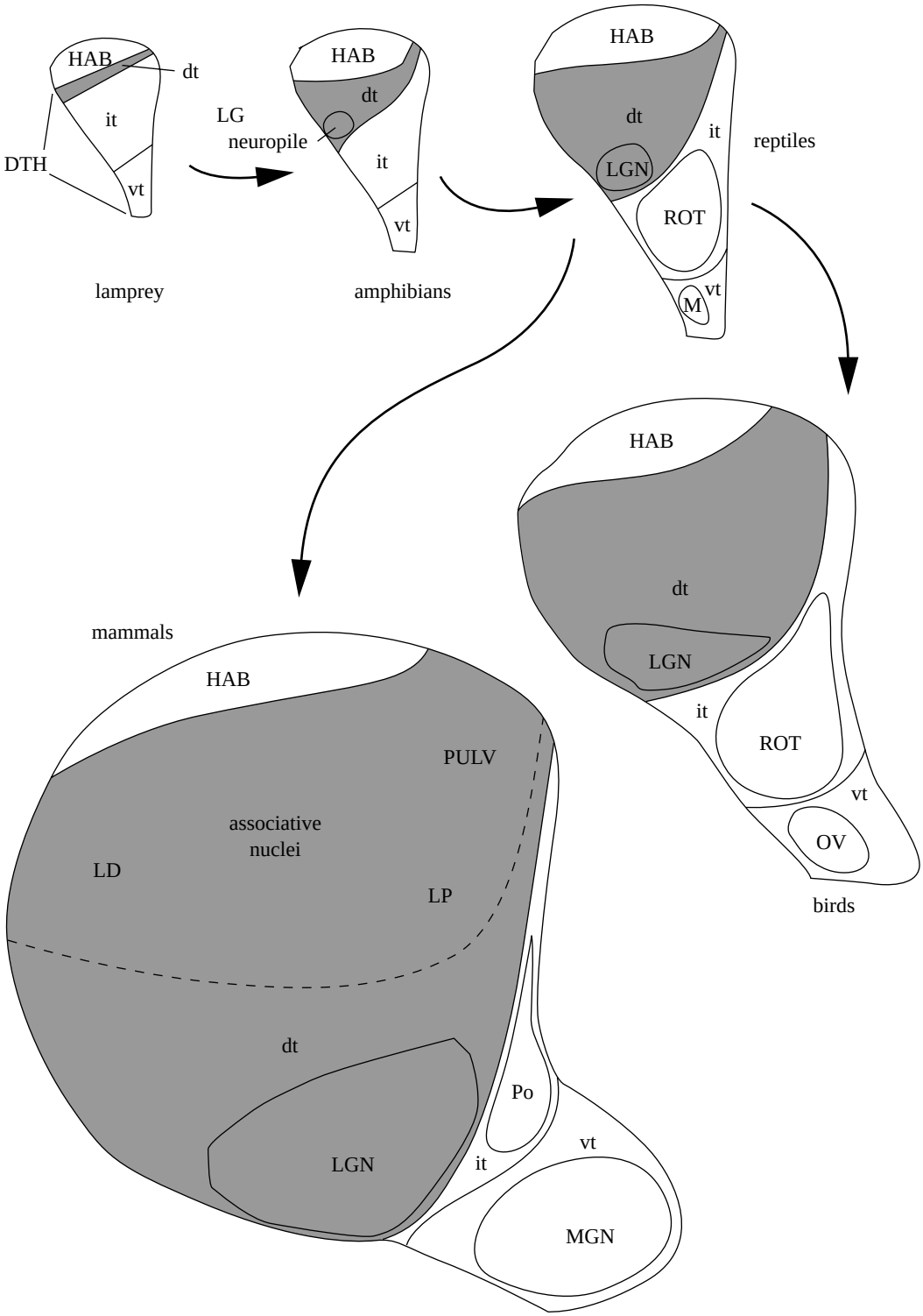

Figure 5. Schemata of the fundamental tiered constitution of the dorsal thalamus (alar field of prosomere 2) in lamprey, frog, lizard, chick and mouse, showing the respective evolutionary changes in relative size, and conserving the initial topology, irrespective of massive development of the dorsal tier in mammals. Rostral is orientated to the left and the dorsoventral dimension is implicit in the names of the tiers. Note that the LGN, MGN (or the respective sauropsidian homologues M or OV) and ROT, postulated to be field-homologous to the mammalian Po, jointly illustrate the topological invariance. The dashed line in the schema for mammals delimits the evolutionarily late-appearing and dorsally placed associative thalamic nuclei (including LD, LP and PULV nuclei). It is unclear whether this complex exists as such in sauropsids. (For any abbreviations not already defined in the text, see legend to figure 6.)

and perhaps other mammals as well. This hypothetical evolutionary trend correlates with global retarded and protracted neurogenesis in the mammalian thalamus and cortex alike. Although the published homogeneous cortical neurogenetic gradients of rodents (figure 3*c*) may not reflect the sites of late evolutionary increment in primate associative cortex, there is evidence that the matching of thalamocortical connections occurs irrespective of total size (Höhl-Abrahao & Creutzfeldt 1991; Hoffman *et al*. 1999). To my knowledge, this point has not

been properly investigated yet; it would be important to know whether presumably recently added cortical areas arise heterochronically relative to the conserved primary cortical areas. From this point of view it is remarkable that novel areas of primates, for example, tend to surround the primary areas shared with basal mammals (Krubitzer 1995). This poses a developmental problem that needs to be solved. As regards the dorsal thalamus, the ventral tier nuclei, i.e. the medial geniculate nucleus, always are the earliest-generated parts in the dorsal thalamus, whereas the dorsal tier nuclei, and particularly the pulvinar and medial nuclei, are the last to be generated (chick, Crossland & Uchwat (1983); rat, Bayer & Altman (1995); monkey, Rakic (1977) and Ogren & Rakic (1981)).

Interestingly, while the early-generated deep layers of the superior colliculus continue projecting visual and multimodal input to the primordial collothalamic target in the intermediate tier (posterior thalamus, intralaminar complex), later-born cells incorporated into more superficial layers of the superior colliculus evolve a second collothalamic pathway that projects into the pulvinar–lateral posterior complex (this runs as an exception against the rule for dorsal tier nuclei, which should receive only lemnothalamic projections, but brain evolution notoriously does not obey our rules). In his current theory, Karten (Karten 1991 1997; Karten & Shimizu 1989, 1991; Shimizu & Karten 1990; Karten *et al*. 1997; Luksch *et al*. 1998) insists that this late-appearing connection is homologous to the tectorotundic one (tectum-intermediate tier) found in sauropsids, without comparing it in neurogenetic details with the parallel, presumably more ancient connection coming from the deep collicular layers.

6. ANY INSIGHTS INTO CORTICAL EVOLUTION?

After the foregoing considerations, which certainly need considerable complementation with specific experimental data, some possible insights seem to wave hazily in front of us.

The complex hypothesis of Karten (1991, 1997) is not supported by suitable evidence at this moment and needs to pay attention to the problem posed by parallel collothalamic pathways. Holmgren's (1925) hypothesis agrees with modern gene-mapping data and is more parsimonious with *ad hoc* assumptions at all levels of analysis, independently of complexities introduced by the diverse palliopetal and palliofugal tangential cell migrations reported in recent years.

Both sauropsids and mammals have collo- and lemnothalamic projections to the ventral pallium and dorsal pallium, respectively (plus a third, trans-pulvinar route probably only present in mammals). However, the lemnothalamic projections are much better elaborated in birds than in reptiles, suggesting parallel or divergent evolution of these pathways in birds and mammals. The avian dorsal pallium, or Wulst, is in many aspects (i.e. cellularity and layering) not comparable with the reptilian dorsal cortex or the mammalian isocortex, although it clearly is their field-homologue, judged by topological position and lemnothalamic hodology (see Medina & Reiner 2000). A detailed genetic profile of the avian Wulst would help establish which elements of its structure may be considered truly comparable with the mammalian isocortex. Each molecularly defined embryonic neural primordium in the telencephalon and thalamus seems capable of independent elaboration and growth, although their respective topological positions in the neural tube may condition the range and limits of their differential histogenetic behaviour (Finlay *et al*. 1998), as well as the embryonic or postnatal circumstances in which novel genetic and histogenetic equilibria emerge in the form of new nuclei, new pallial lamination patterns, or new cortical areas.

The medial geniculate body is a case in point. It arises in the thalamic ventral tier in both sauropsids and mammals, and nobody seems to doubt nowadays that it is homologous across tetrapods. Nucleus medialis, the homologue structure in reptiles, lies close to the ventricle, divided into core and shell domains, and projects into the striatum (subpallium) and the ADVR (ventral pallium; figures 3*a*, 5 and 6*a*); it follows the rule for collothalamic nuclei, since its input comes from the caudal midbrain. The avian homologue, called nucleus ovoidalis, also shows core and shell portions and is also periventricular (figures 3*a* and 5). It projects likewise into the striatum and the ADVR (field L of the caudal neostriatum). There is only some degree of refinement of its core–shell structure and DVR terminal field (subfields L1–L3).

However, if we compare the mammalian medial geniculate body (figure 6*b*), we notice several new features that emerge jointly: the complex is now superficial in the dorsal thalamus (it has migrated radially, but keeps its fundamental ventral tier position; figures 5 and 6*b*), the core of the nucleus is now subdivided into ventral, intermediate and dorsal subnuclei, whereas the shell is built by diverse cell aggregates capping it superficially, ventrally and caudally and trailing all the way back to periventricular levels (peripeduncular nucleus, marginal shell, suprageniculate nucleus, magnocellular subnucleus, posterior intralaminar nucleus, lateral and medial subparafascicular nuclei). The latter all share a number of chemoarchitectonic markers, notably CGRP peptide and calbindin, and have comparable projection patterns (Yasui *et al*. 1991; Brauth & Reiner 1991; Puelles *et al*. 1992; Lanuza *et al*. 2000). Finally, this complex projects to the striatum, the lateral amygdala (ventral pallium) and the temporal isocortex (figure 6*b*). The last connection has recently been shown to be due at least in part to collaterals from the same axons that project to the amygdala (Doron & LeDoux 2000; Linke & Schwegler 2000).

It seems that something special happened in ancestral mammals in the ventral tier of the dorsal thalamus, leading to early superficial migration of a large part of the complex (but keeping the auditory midbrain input), as well as to internal regionalization (subnuclei) and development of a new collateral projection into the dorsal pallium (while keeping and perhaps refining the ancestral ones to the striatum and ventral pallium). We must assume that these thalamic changes were dependently or independently accompanied by the emergence of a minimal set of auditory cortical fields in the primordial isocortex (since each subnucleus has slightly different corticopetal properties) and even by parallel histogenetic changes in the auditory part of the midbrain (see discussion of the marked evolutionary changes of this structure

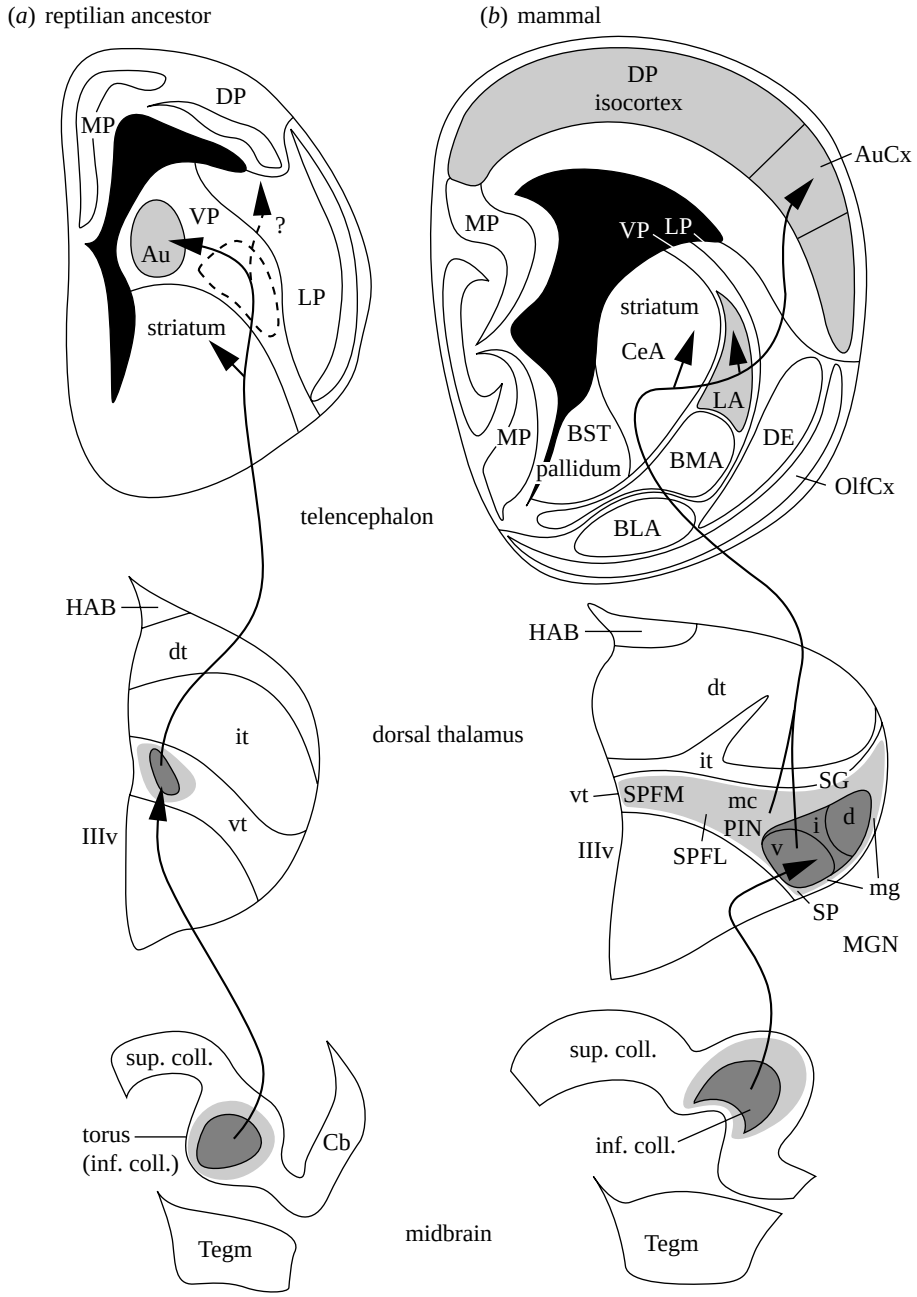

Figure 6. Schematics of the auditory pathway through the medial geniculate complex in a hypothetic ancestral reptile (supposed to be largely similar to present-day reptiles in these aspects), as compared with a hypothetical primitive mammal. Note the superficial massive migration of the MGN nucleus and the expansion of its shell domains. Concomitant changes appear in the inferior colliculus of the midbrain (shown in sagittal view) and in the telencephalic targets. The ventropallial and striatal targets are conserved, but now form part of the claustroamygdaloid domain (represented here as embedded in the amygdaloid lateral and central nuclei, respectively), while novel collaterals penetrate across the lateral pallium and connect with an emergent auditory cortical area of the nascent isocortex. Such collaterals may have been produced in embryonic ancestral reptiles, but might not be retained due to insufficiency of the adhesive or signalling properties of the immature cortex (dashes and question mark at left). This interpretation postulates modified conservation of ancestral striatal and ventropallial connections for collothalamic pathways and development of novel isocortical targets accessed via collaterals of the pre-existent connections. Lemnothalamic pathways completely bypass the subpallium and both parts of the hypopallium and penetrate directly into the available cortical areas. Guidance of numerically increased populations of axons into the evolving mammalian cortex may be due in part to the pioneering lemnothalamic connections that pre-exist in sauropsids, and/or to the new systems of collaterals of the collothalamic pathways. (Abbreviations used here and/or in other figures: Au or Aud, auditory nucleus of ventral pallium (field L in birds); AuCx, auditory isocortex; BLA, basolateral amygdaloid nucleus; BMA, basomedial amygdaloid nucleus; BST, bed nucleus of stria terminalis; Cb, cerebellum; CeA, central amygdaloid nucleus; d, dorsal MGN nucleus; DE, dorsal endopiriform nucleus; DP, dorsal pallium; dt, dorsal tiers of dorsal thalamus; DTH, dorsal thalamus; HAB or Hab, habenula; i, intermediate MGN nucleus; IIIv, third ventricle; inf. coll., inferior colliculus; it, intermediate tier of dorsal thalamus; LA, lateral amygdaloid nucleus; LD, laterodorsal thalamic nucleus; LG, lateral geniculate; LGE, lateral ganglionic eminence; LGN, lateral geniculate nucleus; LP, lateral pallium; M, medial nucleus (reptiles; auditory); mc, magnocellular MGN subnucleus; mg, marginal zone of MGN; MGE, medial ganglionic eminence; MGN, medial geniculate nucleus; MP, medial pallium; mz, mantle zone of

in Puelles *et al*. (1994)). For all we know, these widely separated and complex changes occurred simultaneously in larger or smaller degree, and did not imply any fundamental change of topology (no tangential migration), even if the medial geniculate moves to the surface and the auditory cortex participates as a recipient in the immigration of subpallial inhibitory interneurons. The changes apparently did involve development of new collaterals (and, incidentally, an evolutionary breaching of the ancient rule that collothalamic pathways only connect with ventral pallium). Changes in the expression or regulation of cell adhesion or signalling molecules might be sufficient to explain some of this novelty (Redies 2000), but cortical arealization is a complex problem in itself.

Dispersed projections from the caudal intralaminar nuclei (derived from the intermediate tier) to layer I of the whole isocortex may also represent newly evolved collaterals of earlier sauropsidian axons projecting only to the subpallium and the ventral pallium. Is it possible that such novel collaterals in some way might have helped the separately evolving dorsal tier elements to find their way into the separately growing cortex?

The evolution of the pallium thus seems to be tied up with the evolution of the dorsal thalamus and midbrain. As regards visual pathways, the midbrain progressively loses relative protagonism in the evolution of reptiles into mammals (in contrast with the auditory pathway). However, the visual midbrain retains some of this protagonism in the evolution of birds, judging by the relative sizes of the thalamic and pallial targets (the intermediate and ventral tiers and the visual part of the ventral pallium or ectostriatum, respectively, which are quite large and well differentiated in birds), independently of the parallel development of the dorsal tier and its dorsal pallial targets. We shall need to investigate whether there is any causal relationship between the increment in the thalamic dorsal tier and the emergence of the mammalian isocortex. Consider the lamprey, possibly lacking a dorsal pallium and having a minute thalamic dorsal tier, as mentioned above (§ 1). Perhaps both elements grew independently thereafter, but this occurred coordinately, due to general causes affecting both of them. Both lie at evolution-prone regions, where proliferation tends to be protracted and differentiation restrained for a long time (Finlay *et al*. 1998). However, new thalamic centres tend to appear dorsally, in agreement with the overall ventrodorsal gradient of the alar plate (the dorsal thalamus is part of the alar plate (Puelles 1995)), whereas new cortical areas arise surrounding earlier areas of the same functional modality (Kaas 1995; Krubitzer 1995). Moreover, it seems that thalamic afferents are not needed for initial isocortical regionalization, as shown by a mouse knockout for the gene *Gbx-2* (a marker of dorsal thalamic neurons, which fail to project to the cortex in this mutant (Miyashita-Lin *et al*. 1999)). Perhaps difussible signalling may affect jointly the dorsal aspect of the dorsal thalamus and the telencephalic pallium (transmitted across the medial pallium), as suggested, for instance, by the overlapping sources of bone morphogenetic proteins or fibroblast growth factor-17 at the respective choroidal taeniae (Furuta *et al*. 1997; Xu *et al*. 1999). A non-homogeneously distributed increase in isocortical surface would imply a repatterning of the proto-map (Rakic 2000) and of the matching of the thalamocortical projections. One imagines developmental parameters that normally may buffer the small variations in relative size, thus achieving conservation of the 'normal' pattern of areas and the respective internal topographical order of thalamic-responsive columns. However, variation beyond threshold limit values of the same unknown parameters may lead to local instability and emergence of novel cortical areas.

Last, but not least, evolution of the isocortex obviously has parallel effects on parahippocampal cortex and limbic cortex in general, where many information streams converge at the root of higher motivation, learning and recall functions, and, finally, surely also on the pallial amygdala, which apparently subserves conditioned reflexes (Doron & LeDoux 1999, 2000). Developmental molecular and experimental studies considering globally all components of the evolving pallium should help us to understand better the complications of telencephalic and, particularly, cortical evolution.

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Figure 6. (*Cont*.) neuroepithelium; OB, olfactory bulb; OlfCx, olfactory cortex; OV, ovoidal nucleus (auditory thalamic nucleus in birds); PA, pallidum; PIN, posterior intralaminar nucleus; Po, posterior nuclear complex; PULV, pulvinar; ROT, nucleus rotundus (visual collothalamic mass in sauropsids); SG, suprageniculate nucleus; SP, suprapeduncular nucleus; SPFL, lateral subparafascicular nucleus; SPFM, medial subparafascicular nucleus; ST, striatum; sup. coll., superior colliculus; Tegm, tegmentum; v, ventral MGN subnucleus; Vis, visual nucleus of the ventral pallium (ectostriatum in birds); VP, ventral pallium; vt, ventral tier division of the dorsal thalamus; vz, ventricular zone of neuroepithelium.)

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