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REVIEW ARTICLE
Comparative aspects of cerebral cortical development

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Abstract

This review aims to provide examples of how both comparative and genetic analyses contribute to our understanding of the rules for cortical development and evolution. Genetic studies have helped us to realize the evolutionary rules of telencephalic organization in vertebrates. The control of the establishment of conserved telencephalic subdivisions and the formation of boundaries between these subdivisions has been examined and the very specific alterations at the striatocortical junction have been revealed. Comparative studies and genetic analyses both demonstrate the differential origin and migratory pattern of the two basic neuron types of the cerebral cortex. GABAergic interneurons are mostly generated in the subpallium and a common mechanism governs their migration to the dorsal cortex in both mammals and sauropsids. The pyramidal neurons are generated within the cortical germinal zone and migrate radially, the earliest generated cell layers comprising preplate cells. Reelin-positive Cajal–Retzius cells are a general feature of all vertebrates studied so far; however, there is a considerable amplification of the Reelin signalling with cortical complexity, which might have contributed to the establishment of the basic mammalian pattern of cortical development. Based on numerous recent observations we shall present the argument that specialization of the mitotic compartments may constitute a major drive behind the evolution of the mammalian cortex. Comparative developmental studies have revealed distinct features in the early compartments of the developing macaque brain, drawing our attention to the limitations of some of the current model systems for understanding human developmental abnormalities of the cortex. Comparative and genetic aspects of cortical development both reveal the workings of evolution.

Introduction

Owing to the advances made in the development of mouse genetics, the mouse has become the favoured model system for the basic understanding of cortical development (Goffinet & Rakic, 2000). Gene functions implicated in human brain developmental abnormalities (including childhood epilepsy, schizophrenia, autism and attention deficit disorder; see Francis *et al*., 2006) are currently being analysed in various transgenic mouse models. These models have proved to be invaluable in the understanding of mammalian cortical development but there are also numerous limitations. For specific questions regarding cortical development, carnivores and primates are the preferred model organisms and for many aspects of human developmental disorders there are as yet no appropriate animal models. It is imperative that the differences between model organisms and humans are fully taken into account when conducting gene function analyses.

The last decade brought important progress in the understanding of various developmental steps in mammalian cerebral cortical development and has left us with an increased need for comparative analysis of these programs. The cellular and molecular mechanisms of radial migration of neurons within the cortex and tangential migration of GABAergic neurons from the subpallium have been established in both mammals (mouse, rat, carnivores and primates) and sauropsids, and some of the guidance mechanisms have been elucidated (Xu *et al.*, 2004; Métin *et al*., 2006). The formation of the first cortical layers and the distribution and origin of the first postmitotic cells is much better understood in both mammals and other vertebrates (e.g. Bielle *et al*., 2005). New distinct compartments of neurogenesis have been identified in the developing mammalian cerebral cortex, and it is hypothesized that these compartments contribute different cell popu-

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lations (Noctor *et al*., 2004; Wu *et al*., 2005; Guillemot *et al*., 2006). Finally, cell-cycle parameters have been documented in the mouse and primate germinal zones (Caviness *et al*., 1995; Polleux *et al*., 1997; Lukaszewicz, 2005). By comparing brain development in different species we can gain insight into the origin of the mammalian neocortex and into the evolutionary changes that might have occurred.

Comparative developmental analysis can provide insight into brain evolution

There are great variations from the basic pattern of forebrain organization in different vertebrates (Fig. 1). While many of these forebrain structures can be related to each other unambiguously, others have been cryptic (Northcutt & Kaas, 1995; Karten, 1997; Striedter, 1997; Reiner, 2000; Molnár & Butler, 2002a,b). We are still left with numerous unanswered questions. What aspects of development had to change to produce a multilayered cortex and subsequently to produce a larger cortex? What aspects of cell proliferation, polarity of construction of the cortical plate or cell migration and differentiation along the pallial–subpallial boundary had to be reconfigured during evolution to arrive at the developmental mechanisms used by primates today? Recent comparative gene expression studies together with detailed comparative analysis of forebrain development try to provide insight into the evolutionary changes that might have occurred.

In this review we shall first give an overview of the telencephalic organization in vertebrates: genetic control of the establishment of conserved forebrain subdivisions and the formation of boundaries between these developmental compartments, with particular attention to the striatocortical junction. This is the region where the major differences occur in mammals and sauropsids. First, we shall give examples of genetic studies on the vertebrate forebrain which have helped our understanding of evolutionary rules. Second, we shall review the differential origin of pyramidal and nonpyramidal cortical neurons. Comparative studies and genetic analyses show that the dual origin of these two basic neuron types is a very general feature of the cortical organization across all vertebrates studied so far. GABAergic interneurons have a common origin in the subpallium and a common mechanisms govern their migration. Third, we shall make comparisons among the early generated cell layers comprising preplate cells then, fourth, we shall make comparisons among the germinal zones. Based on numerous recent observations we shall present an argument that the elaboration of mitotic compartments might have been the drive behind mammalian cortical evolution. Fifth, we shall compare cell-cycle parameters in the dorsal cortex. Unfortunately we shall have to restrict this comparison to mammals because no such data are available on other vertebrates. We shall not discuss comparative aspects of early cell death, although we realize that this is a very interesting aspect of cortical development (Rakic, 2005a). The developmental (Mallamaci & Stoykova, 2006) and evolutionary (Krubitzer & Kahn, 2003) aspects of cortical regionalization are extremely exciting issues, but they could not be given justice here and we refer the reader to recent reviews of this issue (Grove & Fukuchi-Shimogori, 2003; Guillery, 2005; Krubitzer & Kaas, 2005). We shall finish with a review of relevant human cortical developmental disorders and point out the limitations of some of our model systems. Much of our recent understanding of cortical development comes from studies on the mouse, and work on primate cortical development has been carried out in only a handful of laboratories around the world. Despite the small quantity of work on the primate, a number of unique primate features have been revealed, features which are significant in terms of general evolutionary trends in cortical development and crucial for understanding development of the human cortex. We believe that by stressing the differences in nonmammalian vertebrates and the differences within mammals we can generate more thought and debate on these important issues.

Telencaphalic organization in vertebrates; differences at the striatocortical junction between mammals and reptiles

Gene expression and function studies in mouse and chick provide evidence for a common organization of the developing telencephalon in vertebrates (Smith-Fernandez *et al*., 1998; Puelles *et al*., 2000). Based on the conserved expression of homeobox-containing and other transription factors it has been proposed that the pallium consists of four subdivisions: the medial, the dorsal, the lateral (LP) and the ventral (VP) pallium; these contain the anlagen of, respectively, the hippocampus, isocortex, olfactory cortex with part of the amygdala and the claustrum–amygdalar complex (Puelles *et al*., 2000). The subpallium contains three major subdivisions: the lateral ganglionic eminence (LGE), subdivided into dorsal (dLGE) and ventral (vLGE) parts, the medial and caudal ganglionic eminences contributing mostly to the generation of striatum, pallidum and amygdala respectively, but also to the neocortex through tangentially migrating streams of cells (reviewed by Marín & Rubenstein, 2001).

Results from gene expression analyses have led to the recognition that the domain of the ventral pallium actually extends over the lateral-most territory of the LGE where it abuts upon the domain of the dLGE, outlining thereby the pallial–subpallial border (PSPB). As early as embryonic day (E)9.0 the PSPB is delineated by the homeodomain containing transcription factors Pax6 and Gsh2, which are expressed in the progenitors of the pallium and subpallium, respectively (Walther & Gruss, 1991; Corbin *et al*., 2000; Toresson *et al*., 2000; Yun *et al*., 2001). The VP progenitors express at a very high level both *Pax6* (Stoykova *et al*., 1996, 1997) and its direct target gene *Ngn1/2* (Scardigli *et al*., 2003). A recent study provides evidence that, at early developmental stages, nonoverlapping or only partially overlapping streams of cells with distinct molecular expression profiles emerge

FIG. 2. Overview of three current theories on the evolution of the dorsal pallium in amniotes. In each row, a drawing of a transverse hemisection through the telencephalon of a developing bird is shown to the left, and two drawings of transverse hemisections through the telencephalon of a developing mammal are shown to the right, with the far right drawing being the more caudal one and through the level of the amygdala. In the top row, the structures are identified (see abbreviations below). The second row illustrates the ADVR–lateral neocortex hypothesis of Reiner (1993) and Butler (1994), derived from the equivalent cell hypothesis of Karten (1969). The third row illustrates the ADVR–claustroamygdalar hypothesis, variations of which are supported by Bruce & Neary (1995), Striedter, 1997), Puelles and coworkers (Puelles *et al*., 2000, 2001; Medina *et al*., 2005), and Martínez-Garcia *et al*. (2002). The fourth row illustrates the ADVR–lateral neocortex plus claustroamygdalar field homology hypothesis of Butler & Molnár (2002). The colours and fill patterns are used to indicate comparative structures for each hypothesis. As the piriform cortex is not shown as a separate entitiy in the mammalian figures but rather is included in the LP-VP regions, it is not coloured in most cases. All of these hypotheses basically agree on a discrete homology of most or all of piriform cortex across amniotes. Abbreviations: ADVR, anterior dorsal ventricular ridge; CPi, piriform cortex; HA, hyperpallium apicale; LP, lateral pallium; LNC, lateral neocortex (i.e. collothalamic-recipient neocortex); LPCA, lateral pallial cortical area; M, mesopallium; MNC, medial neocortex (i.e. lemnothalamic-recipient neocortex); MP, medial pallium; N, nidopallium; P, pallidum; S, septal nuclei; St, striatum; V, lateral ventricle; VP, ventral pallium. Figure kindly modified and provided by A. B. Butler from Butler & Hodos (2005) and reproduced with permission from John Wiley and Sons, Hoboken, New Jersey.

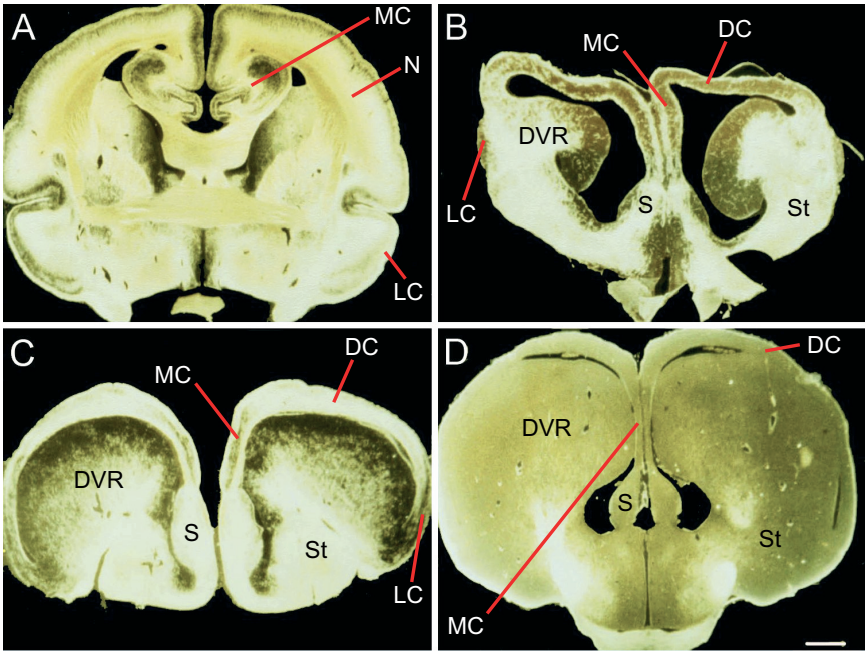
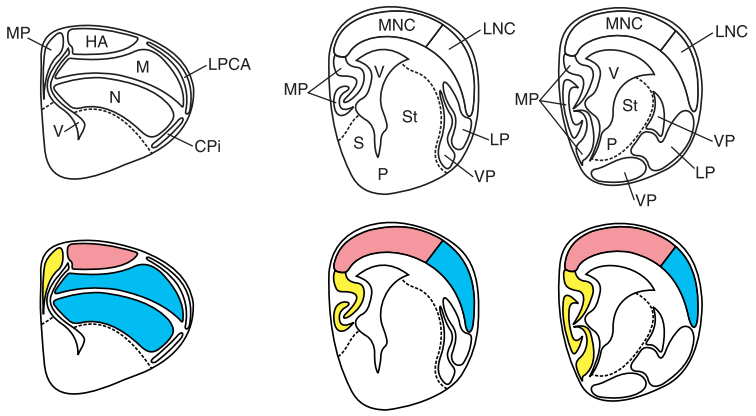


FIG. 1. Fibre-stained coronal sections of four different amniote brains viewed under dark-field illumination to demonstrate the spectacular differences between forebrain organization in (A) marsupial, Native Cat, *Dysaurus hallucatus*; (B) turtle, *Pseudemus scripta elegans*; (C) iguana, *Iguana iguana*; (D) crocodile (Australian). Note the thicker dorsal cortex in marsupial (A) and the huge ball-like structure in B–D protruding into the lateral ventricle. ST, striatum; MC, medial cortex; LC, lateral cortex; S, septum; DVR, dorsal ventricular ridge. (Modified from Molnár & Butler, 2002b; reproduced with the permission of Elsevier Science B.V.) Scale bar, 1 mm.



Karten (1969), Reiner (1993, 2000), Butler (1994)

Bruce & Neary (1995), Puelles et al. (2000)

Butler and Molnár (2002), Molnár and Butler (2002a,b)

from the VP and LP domains, migrate towards the basal telencephalon and contribute to the formation of different nuclei of the amygdalar complex (Tole *et al*., 2005). In the Small eye mutant where Pax6 is not functional (Hill *et al*., 1991), the expression of the VP markers Dbx2 and sFrp2 (Kim *et al*., 2001; Yun *et al*., 2001; Assimacopoulos *et al*., 2003) is abolished. Furthermore, the progenitors of the VP and LP do not express pallial markers but instead take on subpallial characteristics (Stoykova *et al*., 1996, 2000; Toresson *et al*., 2000; Yun *et al*., 2001) determined by the expression of subpallial marker genes (Kroll & O'Leary, 2005). The high expression level of Pax6 in the VP progenitors appears to be necessary for the specification of the nucleus of the lateral olfactory tract and the lateral, basolateral and basomedial nuclei of the amygdala that fail to form in the Small eye mutant (Tole *et al*., 2005), and ventral pallium has further severe abnormalities in the Pax6/lacZ-knockout mouse (Jones *et al*., 2002).

Judged by the absence of Emx1 expression in the progenitors of the ventral pallium and the abundant expression of Tbr1 in the mantle zone in mouse and chick, it has been proposed that the avian nidopallium (Reiner *et al*., 2004; previously called neostriatum) corresponds to the VP domain in the mouse (Puelles *et al*., 2000). Chicken genes homologous to *Pax6*, *Dlx2* and *Emx1* are expressed in a topologically similar pattern, suggesting that the avian 'palaeostriatum' corresponds to part of the mouse subpallium (Puelles *et al*., 2000). The developmental programme of the pallial–subpallial boundary might have undergone some important reorganizations during evolution (Butler & Molnár, 2002; Molnár & Butler, 2002a,b), resulting in the rearrangements of several structures and opening up the path for further cortical development. There are numerous hypotheses on the possible evolutionary changes that led to the transformation of ventral pallium in mammals (Striedter, 1997, 2005; Reiner, 2000; see Fig. 2). Further work on gene expression patterns with special attention to genes shared by critical structures (lateral cortex, claustrum, lateral amygdala and endopyriform cortex) could eventually resolve these challenging questions (Arimatsu, 1994; Wang & Molnár, 2005; Fig. 3). As our understanding of genetics and comparative aspects of development progresses new hypotheses emerge.

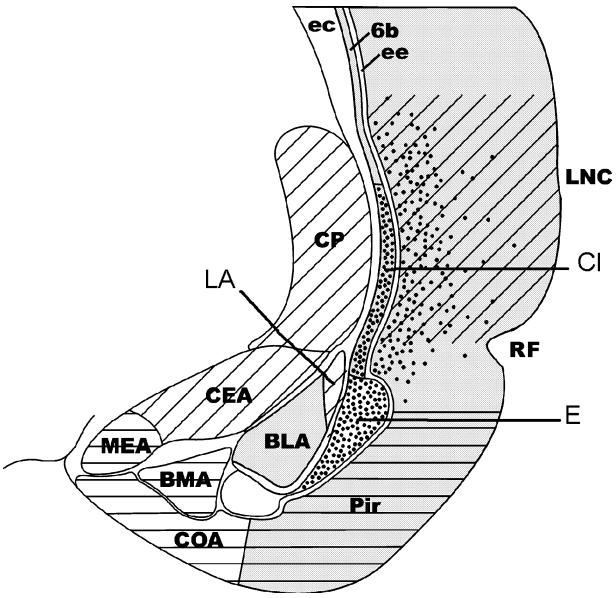


FIG. 3. The schematic diagram illustrates the special relationships among components of the lateral part of the telencephalon of mammals. Overlapping but noncongruent distribution of hodological and gene expression patterns are represented in the lateral part of a coronal section through the right hemisphere of a rat. Dots represent latexin-positive neurons; Emx-1-positive regions are shaded grey. Collothalamic inputs are indicated by diagonal lines and those of olfactory inputs by horizontal lines. The claustrum (Cl) is filled with latexin-positive cells and is Emx1-positive. The collothalamic-recipient lateral amygdala (LA) lies dorsolaterally adjacent to BLA. Abbreviations: BLA, BMA, CEA, COA, LA and MEA, basolateral, basomedial, central, cortical, lateral and medial nuclei of the amygdala, respectively; CP, caudate–putamen; ec, external capsule; ee, extreme capsule (as present in most mammals, but not in rat); LNC, lateral neocortex; Pir, piriform cortex; RF, rhinal sulcus; 6b, layer 6b of neocortex. Drawings adapted from Butler & Molnár (2002).

Differential origin of pyramidal and nonpyramidal cortical neurons

The principal neuronal types of the cerebral cortex are the excitatory pyramidal cells, which project to distant targets, and the inhibitory nonpyramidal cells, which are the cortical interneurons. These two functional classes are both present in the mammalian isocortex and in the dorsal cortex of sauropsids although this latter lacks several cell types found in mammals. Projection neurons and inhibitory interneurons may therefore represent the basic components required to build a functional cortex, making it plausible that the two functional types of cells were already present in the common ancestor (Blanton *et al*., 1987; Reiner, 1991). Pyramidal neurons are generated in the cortical neuroepithelium and migrate radially to reach the cortex following an inside–outside gradient in mammals (Rakic, 1995). In rodents, only a few nonpyramidal cells are generated in the cortical ventricular zone (Parnavelas, 2000). It was recently established that cells of the pallidum also contribute to the formation of the cerebral cortex with interneurons (de Carlos *et al*., 1996; Anderson *et al*., 1997; Tamamaki *et al*., 1997). These cells migrate tangentially through the striatocortical junction to reach the cortex. Great interest in further comparative studies has been generated by this discovery. Such migratory patterns had been predicted for developing mammals as part of a 'reptilian–mammalian transformation' (Karten, 1969, 1997); however, comparative studies have revealed the existence of similar tangential migration in sauropsids, restricted to GABAergic neurons (Cobos *et al*., 2001; Tuorto *et al*., 2003). It seems that the various transformations at the pallial–subpallial boundaries observed in mammals and sauropsids occur in addition to and largely independently of the tangential migratory streams of the GABAergic neurons (Molnár & Butler, 2002a,b).

The exact origin of the tangentially migrating GABAergic neurons in mammals has been the subject of controversy. It is now well established that the vast majority of these cells originate in the medial and caudal ganglionic eminences, the primordia of the globus pallidus (Lavdas *et al*., 1999; Sussel *et al*., 1999; Wichterle *et al*., 1999; Corbin *et al*., 2001; Nery *et al*., 2002; Yozu *et al*., 2005). Experiments in living whole forebrain slice cultures have shown that these neurons follow long tangential migratory routes to their positions in the developing cortex. The molecular and cellular mechanisms of both migratory pathways have been extensively studied and some links with human pathologies analysed (Francis *et al*., 2006).

The percentage of GABAergic neurons in avian pallial regions and their relatively uniform distribution closely resembles the pattern seen in other vertebrates, including mammals (Veenman & Reiner, 1994; Jarvis *et al*., 2005). In birds as in rodents, most GABAergic interneurons originate in the ventral telencephalon (Fig. 4). However, the relative contribution of the pallidum (or medial ganglionic eminence of the telencephalon) and of the palaeostriatum (or lateral ganglionic eminence of the telencephalon) to the GABAergic population is debated (Cobos *et al*., 2001; Tuorto *et al*., 2003). In rodents, the GABA phenotype of cortical interneurons differentiates

under the control of transcription factors of the Dlx family that are expressed in ventral forebrain territories (Stuhmer *et al*., 2002). The differentiation of GABAergic neurons is probably controlled by the same genetic pathway in distant species such as reptiles, birds and mammals. Indeed, orthologs of Dlx genes have been cloned that define ventral forebrain domains with homologous functions in these three classes (Fernandez *et al*., 1998; Puelles *et al*., 2000). In lamprey prolarvae also, GABA-immunoreative neuronal populations differentiate initially in the ventral forebrain in a region corresponding topologically to the ganglionic eminence of the mouse embryo (Melendez-Ferro *et al*., 2002). The predominantly ventral subpallial origin of GABAergic interneurons seems therefore to be a common feature of vertebrate forebrains. However, there are major differences in the proportion of the GABAergic neurons generated locally in the pallium and in the subpallium (lateral and medial ganglionic eminences) in mouse, rat and primates. In humans it has been estimated that 65% of GABAergic neurons are born locally in the cortical germinal zone (Letinic & Rakic, 2001; Fig. 4), whereas in mouse this estimate is only 5% (Letinic *et al*., 2002; Tan, 2002). Interestingly, in humans the dorsal thalamic association nuclei of the diencephalon receive their GABAergic neurons from the ganglionic eminence of the telencephalon (Letinic & Rakic, 2001). This interneuron migration from telencephalon to diencephalon is believed to be specific to humans, although we still lack information on these developmental steps in great apes.

During embryonic development, GABAergic neurons which originate in the ventral subpallium progressively colonize the dorsal pallium (see Métin *et al*., 2006). *Emx* genes are expressed in this dorsal domain which mostly generates excitatory glutamatergic neurons (Anderson *et al*., 2002; Gorski *et al*., 2002) and in birds and reptiles it comprises the dorsal ventricular ridge (Fernandez *et al*., 1998; Puelles *et al*., 2000; Jarvis *et al*., 2005). In rodents, GABAergic neurons follow well defined migratory routes as observed in organotypic slices (López-Bendito *et al*., 2004; Nadarajah & Parnavelas, 2002; Nadarajah *et al*., 2002; see Fig. 4). In birds, GABAergic cells follow tangential routes in both the subpallium and pallium and show branched leading processes (Tuorto *et al*., 2003). Their similarities in morphology to mammalian tangentially migrating interneurons are suggestive of common mechanisms of migration (Bellion *et al*., 2005). Whether these mechanisms are shared by the other vertebrate species remains to be determined. So far, the sequence of development of GABAergic interneurons in the turtle cortex is suggestive of tangential migration from ventral territories though this remains to be firmly established (Blanton & Kriegstein, 1991).

In mammals, the capacity to migrate tangentially over long distances is maintained for interneuron precursors into maturity. Indeed, interneurons produced in the adult subventricular zone (SVZ) migrate tangentially toward the olfactory bulb (Lois & Alvarez-Buylla, 1993, 1994). Neurogenesis has also been described in the wall of the lateral ventricle in adult birds, lizards and turtles. In these classes as in mammals, the GABAergic neurons produced mostly accumulate in the olfactory bulb, suggesting again conserved mechanisms of tangential migration in distant species in the vertebrate forebrain (Garcia-Verdugo *et al*., 1989; Perez-Canellas & Garcia-Verdugo, 1996; Perez-Canellas *et al*., 1997).

Comparisons among first-generated cell layers

The germinal zones lining the ventricle generate the pyramidal neurons of the cerebral cortex. It is well established that newly produced neurons migrate out of the germinal zone according to a strict timetable (Raedler & Raedler, 1978; Bayer & Altman, 1990). In both carnivores and rodents, the first wave of postmitotic cells generated in the so-called ventricular zone (VZ) form the preplate. The preplate contains early-appearing Cajal–Retzius (CR) cells, GABAergic neurons and pioneer neurons (Meyer *et al*., 2000). The cortical plate is formed by subsequently generated neurons that split the preplate into a marginal zone and a subplate (Marin-Padilla, 1978; Smart & McSherry, 1982; Smart & Smart, 1982; Luskin & Shatz, 1985). The marginal zone and the cortical plate are destined to become the six-layered structure of the mature cortex. The pioneer neurons give rise to the 'presubplate' beneath the initial cortical plate (Kostovic & Rakic, 1990), which is the forerunner of the subplate, a transient waiting compartment for thalamocortical and corticocortical fibres. The subplate exerts an important control over later stages of cortical development (Ghosh & Shatz, 1992; Allendoerfer & Shatz, 1994). The cortical plate layers are formed according to an inside-out neurogenetic gradient, with later-generated cohorts bypassing earlier-born neurons to settle at the top of the cortical plate (Angevine & Sidman, 1961). Once in position, they detach from the radial glial guide. In consequence, the oldest neurons of the cortex occupy the deep layers whereas the upper layers are composed of late-born neurons. The concept of preplate partition, proposed on the basis of nonprimate data, has led to the idea that the subplate is a derivative of the preplate (Marin-Padilla, 1978; Luskin & Shatz, 1985). This constitutes a major departure from early-formed embryonic compartments in both human and nonhuman primates where a complex succession of transient embryonic layers accompanies the transition from the preplate to the cortical plate (Meyer *et al*., 2000; Smart *et al*., 2002; Fig. 5 is taken from Fig. 8 of Smart *et al*., 2002).

Nonetheless, there is a prominent subplate in human and nonhuman primates (Kostovic & Rakic, 1990; Smart *et al*., 2002). In monkeys the majority of subplate cells are born after the onset of cortical plate formation and cells continue to accumulate in this compartment up to mid-corticogenesis at E78 (see Fig. 5). This indicates that, whereas subplate neuron production is almost terminated by the onset of cortical plate production in rodents, in the monkey the generation of the subplate and cortical plate is simultaneous (Smart *et al*., 2002).

Preplate development in mammals and reptiles

The most prominent preplate components are the CR cells, which secrete high levels of Reelin (D'Arcangelo *et al*., 1995; Ogawa *et al*., 1995), and the aforementioned subplate cells (Allendoerfer & Shatz, 1994). The histogenetic inside-out principle, which is valid for all mammalian cortices, is closely related to the Reelin–Disabled 1 (Dab1) signalling pathway. The response of cortical plate neurons to the Reelin secreted by CR cells requires the Reelin receptors VLDLR and ApoER2 and the intracellular adapter Dab1 (reviewed by Bar *et al*., 2000). In Reelin-deficient reeler mice, the preplate fails to split and layer formation proceeds from outside to inside, giving rise to a grossly inverted cortex (Lambert de Rouvroit & Goffinet, 1998).

The importance of the Reelin–Dab1 pathway in controlling cortical architecture led to the suggestion that it might have been a driving factor in cortical evolution (Bar *et al*., 2000). Reelin expression has been studied in a large variety of vertebrates, from lamprey (Perez-Costas *et al*., 2002) to human (Meyer & Goffinet, 1998; Meyer *et al*., 2000). Reelin is present in the telencephalon of all vertebrates examined, but the cellular expression patterns are quite diverse. For instance, CR cells have not been detected in *Danio rerio* (zebrafish), even though a large proportion of telencephalic neurons are Reelin-positive (Perez-García *et al*., 2001; Costagli *et al*., 2002). In

amphibians, there is almost no radial migration and the rudimentary pallium is arranged in a periventricular grey matter. In *Hyla meridionalis* (Mediterranean treefrog), pallial cells are Reelin-negative but a few Reelin-positive neurons lie scattered just external to the periventricular cell layer (Perez-García *et al*., 2001). Reelin mRNA expression has been exhaustively mapped in the lizard (Goffinet *et al*., 1999), turtle (Bernier *et al*., 1999), chick (Bernier *et al*., 2000) and crocodile (Tissir *et al*., 2003).

These studies indicate that CR-like cells are present in all amniotes, irrespective of architectonic patterns and migration gradients. However, a remarkable feature which supports a driving role for Reelin in cortical evolution is the increasing intensity of the Reelin signal in CR cells as cortical complexity evolves. The inside-out gradient is an evolutionary acquisition of the mammalian cortical plate; birthdating studies in reptiles show that in *Emys* (turtle) and *Lacerta* (lizard) the cortex develops from ouside to inside (Goffinet *et al*., 1986). The amplification of the Reelin signal in the marginal zone with cortical complexity might have been an important step which, along with other factors, led from a single-layered reptilian-like cortex in the common amniote ancestor to the multilayered mammalian cortex (Bar *et al*., 2000). Another important point is the even higher increase of the Reelin signal in the human marginal zone (Meyer & Goffinet, 1998), which is achieved through the structural differentiation of CR cells, most notably of their axonal plexus which forms a dense, compact fibre tract separating the cortical plate from the marginal zone (Meyer & González-Hernández, 1993; Marin-Padilla, 1998; Fig. 6). In mice this axonal plexus is much less prominent than in humans, but Derer *et al*. (2001) showed that it contains secretory reservoirs of Reelin that are probably important for delivering the protein into the extracellular matrix. Likewise, a secretory human CR axonal plexus may allow the Reelin signal to diffuse and thereby increase the efficiency of the Reelin–Dab1 pathway of the human cortex (see Fig. 6C). Whatever happened during evolution the key developments were the changes in preplate structure and function and the appearance of the inside-out gradient in cortical plate formation. These changes paved the way to a larger cortex. However, this could only be achieved if the mammalian neuroepithelium underwent the necessary changes to produce more cortical cells.

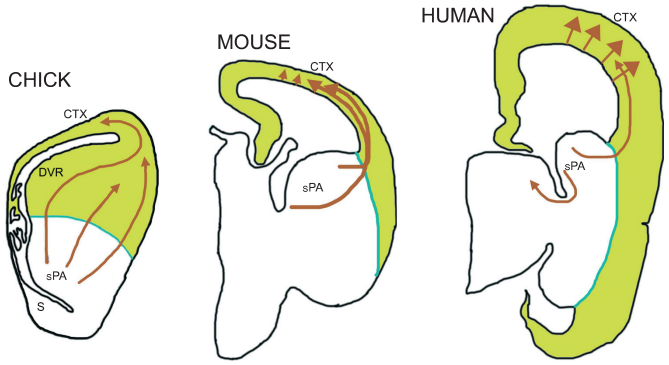
Comparisons of the germinal zones: the elaboration of mitotic compartments might have been the drive behind mammalian cortical evolution

The rodent–monkey differences in the postmitotic compartments are accompanied by major differences in the dimensions, configurations and developmental timing of the germinal zones. In rodents, the VZ is the major proliferative zone until well past mid-corticogenesis (Fig. 5). At E13 abventricular mitotic figures herald the onset of the secondary germinal zone, referred to as the subvenrticular zone or SVZ (Smart, 1973), and from E15 onwards the VZ starts to decline, signalling the end of the major period of neuron production (Smart, 1973; Smart & McSherry, 1982). In addition to these zones, cell proliferation has been reported in the marginal zone, cortical plate and intermediate zone (IZ) as well, both in rat and in human brains (Carney *et al*., 2004). Recently, gene expression and mouse mutant analyses have indicated that the SVZ in rodents is the major compartment contributing to generation of upper layers (Tarabykin *et al*., 2001; also see Guillemot *et al*., 2006). However, SVZ in rodents can account for no more than 35% of the cortical proliferative population at E15 (Takahashi *et al*., 1995). Accordingly, supragranular layers in rodents occupy not more than one-third of the thickness of the mature cortex. In the macaque monkey, SVZ cells are found at a relatively earlier stage in corticogenesis (E55; see Fig. 5 for equivalence of developmental stages in mouse and monkey) and show a much greater expansion than in the rodent, so that by mid-corticogenesis the SVZ has become the predominant germinal zone (Smart *et al*., 2002). This correlates with the predominance of supragranular layers in the mature primate cortex (Fig. 7B). The neurons of these layers do not project out of the cortex but instead connect different areas of the cortex or project locally (Peters & Jones, 1985). From E65 onwards, a specialized component of the SVZ, the outer (O) SVZ, emerges in primates (Fig. 5). Histologically the OSVZ has very different features from the randomly organized cells that are typical of the subventricular zone described in rodents and the early pre-E65 SVZ in the monkey. The dense, radially orientated precursors of the OSVZ constitute a unique primate feature and birthdating experiments show that it generates the supragranular layers of the cortex (Lukaszewicz *et al.*, 2005). The predominance of OSVZ in primates could be due to the increased importance of the cortico-cortical connections and therefore the supragranular layers in this order. It is possible that differences in microenvironmental cues of SVZ and VZ are responsible for creating neuronal subtype diversity. Similarly, further compartmentalization of SVZ in primates may be a correlate of the higher neuronal diversity of supragranular layers (Peters & Jones, 1985). It has recently been demonstrated that there are important differences between the OSVZ of areas 17 and 18 in the macaque cortex (Lukaszewicz *et al*., 2005). It will be interesting to further investigate these differences between simple cortices such as the retrosplenial areas compared to area 17 or compare hippocampal development and three-layered cortices of rodent and primate brains. The contribution of the neocortical SVZ to neuronal production seems to increase during evolution with the increasing complexity of the cortex (Fig. 7).

It has been noted that SVZ is rudimentary, if it exists at all, in lizards (Goffinet, 1983). Martínez-Cerdeno *et al*. (2005) recently measured the proportions of the proliferative zones on H&E-stained sections of turtle, mouse and ferret and showed that in turtle only a rudimentary SVZ was present and the proportions of SVZ were higher in ferret. Work on embryonic turtle and chicken dorsal cortex revealed very little abventricular proliferation with phospho-histone H3 immunolabelling or with bromodeoxyuridine in dorsal cortex (A. Cheung, A. Tavare and Z. Molnár, unpublished observations), but these dividing cells are more numerous in other areas including nidopallium. These observations question the existence of a rudimentary SVZ in dorsal cortex of turtle and chicken. Amphibians might be similar in this respect (Wullimann *et al*., 2005). If these results are confirmed in more mammalian vertebrates, they suggest that SVZ is characteristic of the mammalian neocortex. As SVZ is present in bird nidopallium and abventricular proliferation is present here during development (A. Tavare, A. Cheung and Z. Molnár, unpublished observations), it is conceivable that birds have evolved these developmental mechanisms for the supragranular cell types independently (Butler & Hodos, 2005). The issue of whether the large SVZ is correlated with gyrencephalic mammalian brains should be further investigated in large Amazonian rodents with gyrencephalic brains (such as the agoti and capybara) and in primates with lyssencephalic brains (mouse lemur and marmoset). The comparative results may inspire us to have a fresh look at human lissencephalies (smooth brain; see below).

Comparative aspects of cell-cycle parameters and cortical surface expansion

Cell-cycle duration of cortical precursors is considerably prolonged in macaque monkeys compared to mouse and rat. Whereas cell-cycle



duration is ~17 h in the mouse at the time of supragranular layer neurogenesis, it reaches 28 h in the VZ of macaque monkey visual cortex (Kornack & Rakic, 1998) and 36 h in the OSVZ (Lukaszewicz *et al*., 2005). Although these observations are limited to a handful of species, and New World monkeys or other rodent species may differ, it can be hypothesized that the prolonged duration of the cell cycle in

FIG. 4. Common mechanism of subpallial origin and tangential migration of GABAergic neurons in bird, rodent and human. Schematic outlines represent the cross-sections through chick, mouse and human forebrains. Orange arrows depict the migratory patterns of GABAergic neurons from subpallium (sPA). See text for details. The left panel was inspired by Cobos *et al*. (2001) and the right panels by Tan (2002).

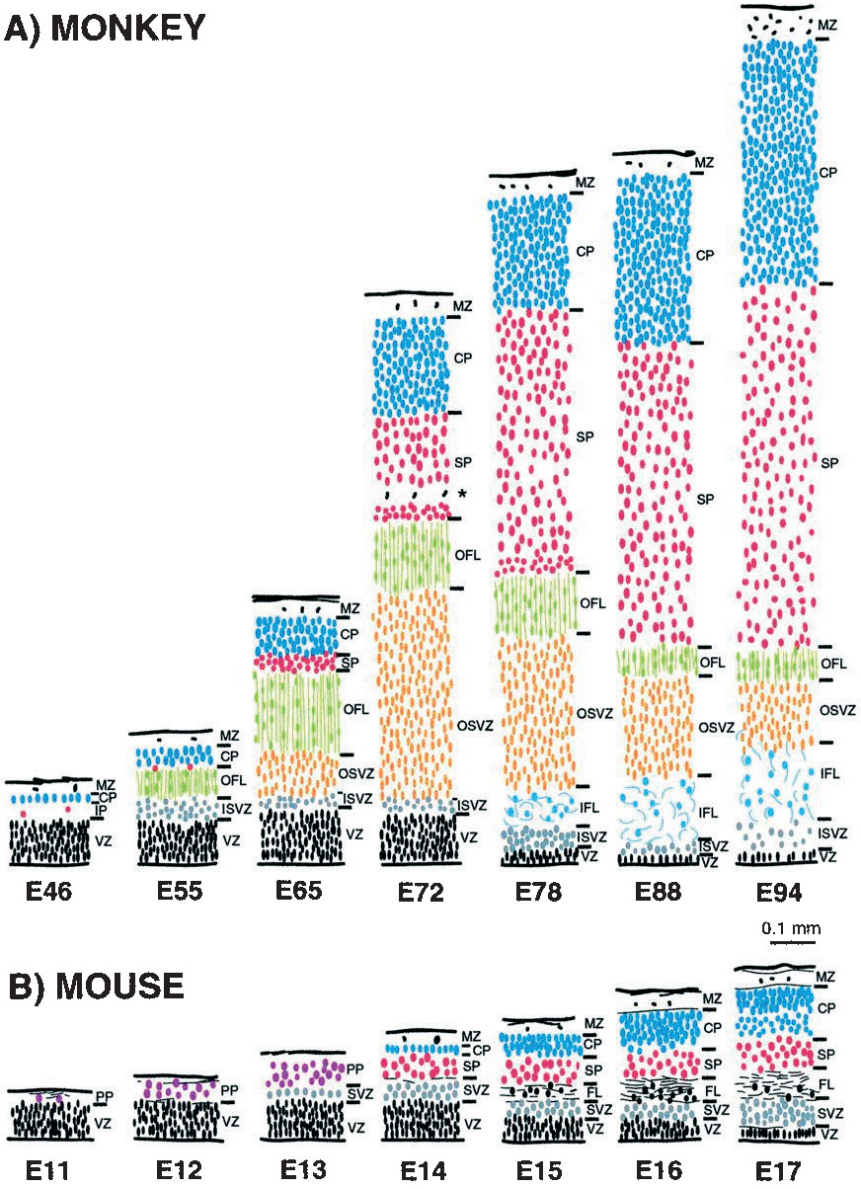


FIG. 5. Comparison of histological sequences in the developing mouse and monkey telencephalic wall. These drawings are of transects through putative area 17 in (A) monkey and (B) mouse at comparable developmental stages. The depth of each layer is drawn to a common scale. The internal detail of each layer is not to scale but depicts the orientation, shape and relative packing density of nuclei in each layer. The vertically aligned pairs have been chosen with reference to birthdating experiments so as to illustrate corticogenesis at equivalent developmental stages. Abbreviations: CP, cortical plate; IFL, inner fibre layer; ISVZ, inner subventricular zone; MZ, marginal zone; OFL, outer fibre layer; OSVZ, outer subventricular zone; SP, subplate proper; VZ, ventricular zone. Reproduced with permission from Smart *et al*. (2002). A curiously conspicuous 'clear-layer' marked by an asterisk (*), located in the deep subplate (SP), is transiently present at E72. At later stages it appears to merge into the SP.

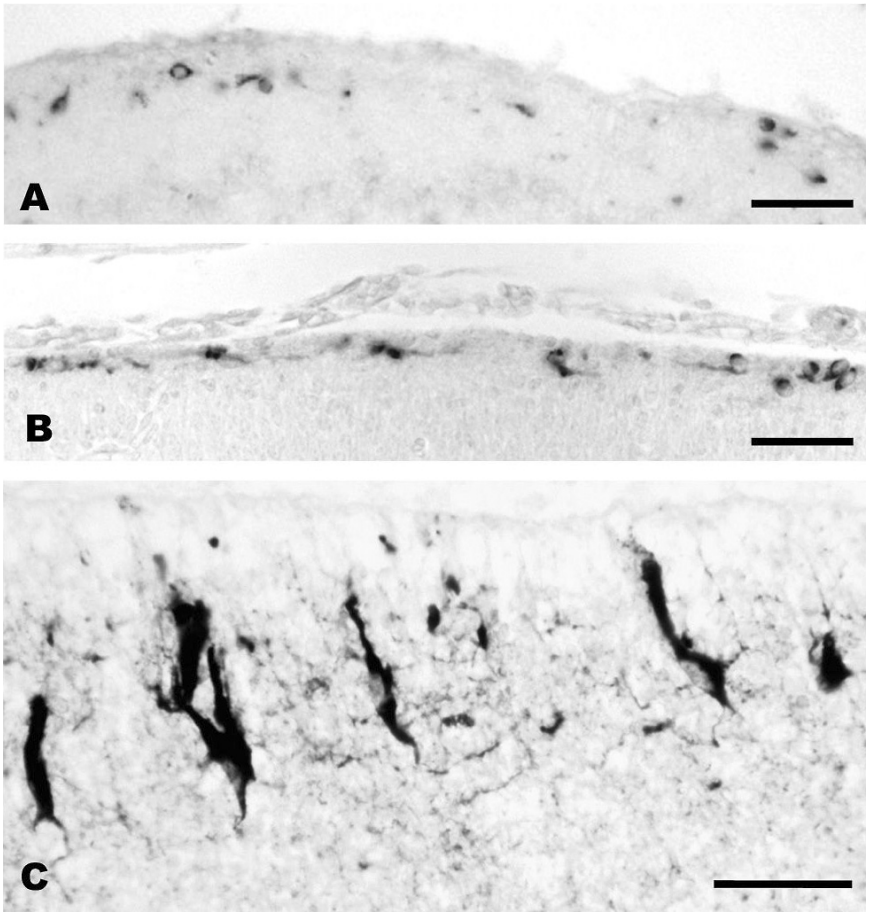


FIG. 6. Reelin-expressing Cajal–Retzius cells in (A) lizard, (B) mouse and (C) human cortex during development. Cajal–Retzius cells (A) in lizard embryo stage 38; (B) in mouse embryo at E14; (C) in human fetus at 21 gestational weeks. Cajal–Retzius cells increase in numbers and morphological complexity in mammals. Scale bars, 40 μm (A,B), 20 μm (C).

macaque monkey cortical precursors could be an adaptive feature underlying the evolutionary expansion of neocortex in primates (Rakic, 1995; Rakic, 2005b). The results of Lukaszewicz *et al*. (2005) indicate that this feature is most prominent in the OSVZ. Environmental signals which contribute to determining cortical precursor fate have been shown to act on cycling precursors (McConnell & Kaznowski, 1991; Polleux *et al*., 2001) so that the extended duration of the primate cell cycle may serve to ensure a fine adjustment of the rates of production of phenotypically defined neurons (Lukaszewicz *et al*., 2005). It is not known how evolutionary changes in developmental mechanisms have lengthened cortical progenitor cell-cycle times in primates as compared to rodents and whether this rule extends to all rodents including the species with gyrencephalic brains, and all primates including the species with lissencephalic brains. Lengthening of cell-cycle duration between rodent and primate stem cells could be a universal feature, as suggested by the recently published findings on cell-cycle characteristics of primate embryonic stem cells (Fluckiger *et al*., 2005), showing a significantly prolonged duration of cell-cycle time in the rhesus monkey compared to the mouse.

Partitioning of the germinal zone in cortical mitotic compartments enables different environmental influences (e.g. transcription factors and growth factors) to act in specific manners. There are numerous unanswered questions remaining that concern the embryonic compartments of the developing monkey cortex. For instance, the origin and role of the inner fibre layer that separates the inner (I)SVZ from the OSVZ is unknown. One possibility is that the outer fibre layer (OFL in Fig. 5) houses the fibres from the lateral geniculate nucleus as it labels with acetylcholinesterase, an early marker of geniculocortical projections (Smart *et al*., 2002). If this is the case it suggests that thalamic fibres are much more closely connected to the germinal zone in primates than in nonprimates and supports the possibility that the ascending pathways influence rates of proliferation in the cortex and ultimately contribute to setting up distinct proliferative programmes in the germinal zone and possibly determining cortical cytoarchitecture (Dehay *et al*., 2001; Carney *et al*., 2002, 2004; Carney, 2005; Lukaszewicz *et al*., 2005). It has been demonstrated *in vitro* that the thalamus can alter cell-cycle parameters in embryonic cerebral cortical progenitor cells (Dehay *et al*., 2001).

In addition, it is probable that changes in the genetic control of cell-cycle times are critical. One of the most potent regulators of the cell cycle in rodents is the Foxg1 winged helix transcription factor (formerly called BF1). Foxg1 belongs to a large family of Fox proteins, a family that has expanded greatly during evolution such that higher organisms have more Fox proteins (Lehmann *et al*., 2003; http://www.biology.pomona.edu/fox.html). In mice, the main site of expression of Foxg1 is in proliferating progenitor cells throughout most of the telencephalic neuroepithelium from the neural plate stage onwards (Hatini *et al*., 1994; Xuan *et al*., 1995; Dou *et al*., 1999; Warren *et al*., 1999). Xuan *et al*. (1995) and Hebert & McConnell (2000) examined transgenic mice in which *Foxg1* is disrupted by insertion of sequences encoding β-galactosidase ($Foxg1^{LacZ}$) or Cre recombinase ($Foxg1^{Cre}$). Defects have not been detected in heterozy-

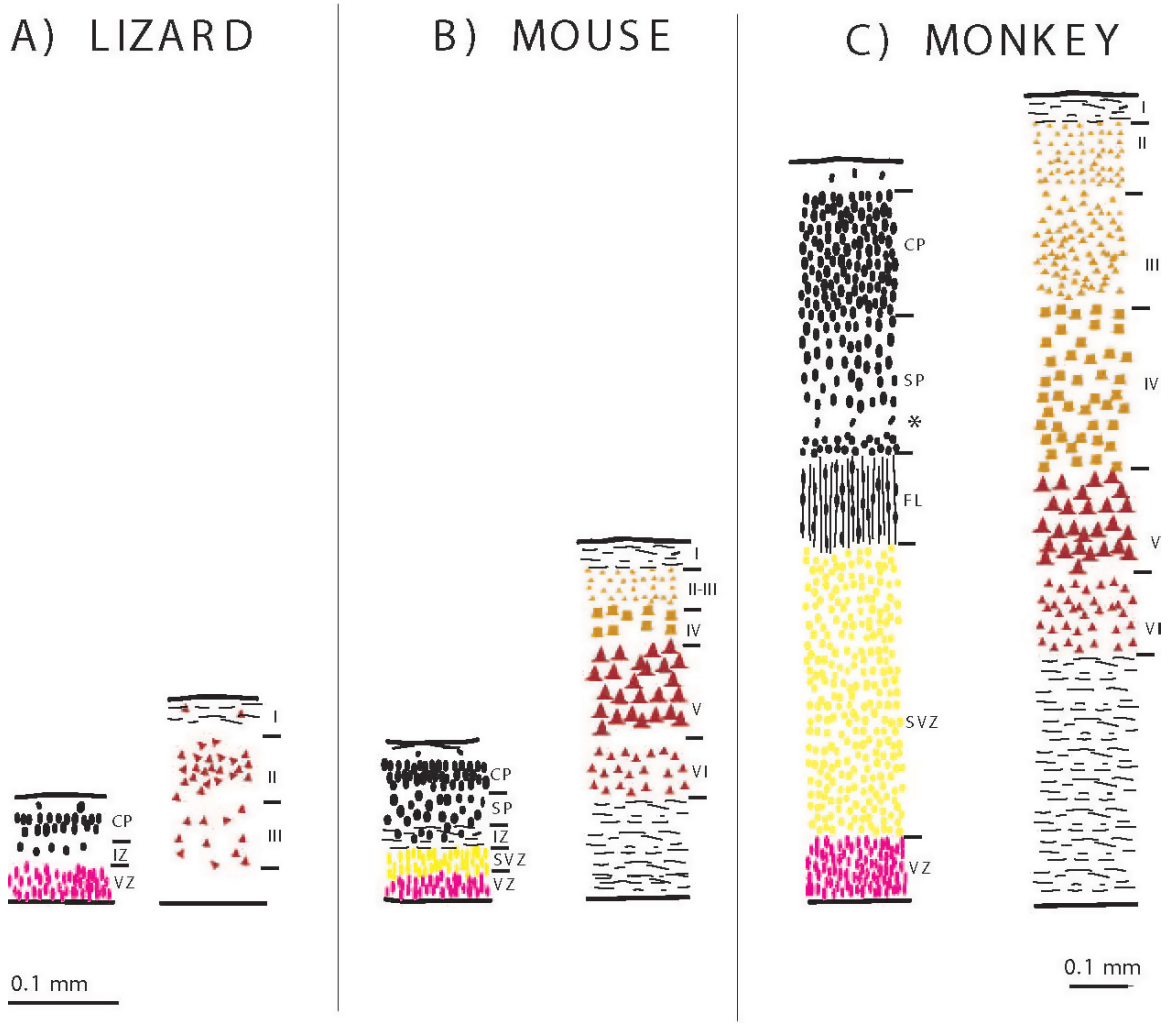


FIG. 7. There is a strong correlation between the increase in supragranular layer complexity and the increase in subventricular zone between (A) lizard, (B) mouse and (C) monkey. The left panels for mouse and monkey are from Fig. 5 from an E15 mouse and an E72 monkey. The right panels represent the layering in the adult. Ventricular zone and layers VI and V are labelled red, subventricular zone and supragranular layers are coloured yellow. Note that the increase in the complexity of supragranular layers is accompanied by an increase in the subventricular zone during development. For the sake of clarity SVZ includes ISVZ and OSVZ in the monkey panel.

gotes, but homozygotes die around birth and show hypoplasia of the entire telencephalon (Xuan *et al*., 1995; Dou *et al*., 1999; Hanashima *et al*., 2002; Pratt *et al*., 2002; Martynoga *et al*., 2005). The most detailed studies of the cell-cycle effects of Foxg1 knockout in forebrain progenitor cells were performed in dorsal telencephalon (Hanashima *et al*., 2002; Martynoga *et al*., 2005). Loss of Foxg1 causes an abnormally rapid increase in the length of the cortical cell cycle after E11.5 and an increased rate of withdrawal of cortical cells from the cell cycle, resulting in premature depletion of the progenitor cell pool. In humans there are two genes homologous to murine *Foxg1*, known as *FOXG1a* and *FOXG1b*, which are probably involved in cortical progenitor proliferation and are clustered together on the same chromosome, suggesting that they evolved as a result of gene duplication (Wiese *et al*., 1995). Perhaps this genetic difference is an important factor in accounting for cell-cycle differences between murine and human brains. Although speculative, the potential importance of FOX genes in human brain development is undeniable, with *FOXP2* having recently been shown to be important in speech and language development (Lai *et al*., 2001).

Evolution did not finish with the production of the six-layered mammalian isocortex evolved to be able to change its own development in response to the environment. While the basic structure of the neocortex is very similar across mammals (Rockel *et al*., 1980), there are huge variations in cortical organization (Krubitzer & Kaas, 2005). The cerebral cortex shows both an enlargement and an increase in the number of cortical areas during evolution, as is typefied by the comparison of the brains of the mouse lemur, *Microcebus*, and the brain of European rodents (Cooper, 1979; Krubitzer & Kahn, 2003). Numbers of functionally dedicated areas and size of cortex are not the only differences to be noted between mouse and macaque cortex. Another important difference is that mice are smooth-brained (lissencephalic) while macaques show pronounced cortical folding. These features of cortical organization have been approached in both genetic and comparative terms. For example, evolutionary expansion of the cortex suggests amplification of the founder pool of cortical precursors (Rakic, 1995; Rakic, 2005b). Increasing numbers of cortical areas could be due to afferent specification (Killackey, 1990; Guillery, 2005) while gyrification is a result of regional variations in proliferation (Smart & McSherry, 1986a,b). Although the functional significance of gyrification is still open to debate (Dehay *et al*., 1996; Van Essen, 1997) it remains a major macroscopic feature which has to be seriously considered in any evolutionary developmental investiga-

tion of cortex (Smart & McSherry, 1986a,b). It is important to point out that not all primates (over 200 species) show pronounced cortical folding. Several have only calcarine and lateral fissures (Butler & Hodos, 2005). There is an allometric relationship between brain size and folding. Thus small primates such as the mouse lemur and marmoset have smooth brains while large Amazonian rodents, such as the agoti and capybara, have relatively deep sulci in their brains. Understanding the formation of sulci and gyri is important for the comprehension of human mutations causing lissencephaly. Again, genetic and comparative approaches could contribute to the solution.

Necessity of comparative studies for understanding human cortical developmental disorders

Comparing rodents (including smooth- and folded-brained species) and primates (including species with small and large brains) is necessary to define species differences in the expression of those genes and gene products where mutations cause human lissencephaly. As the mouse is the principal model for experimental genetics, the question is whether the normally lissencephalic mouse brain can be compared directly to the highly convoluted human brain. In previous sections of this review the main differences between rodent and primate corticogenesis have been outlined (Figs 5 and 7). Monkey and human cortex are similar in the large size and protracted timetable of SVZ, IZ and subplate development, which greatly differ from their homologous compartments of the rodent.

The example of doublecortin (*DCX*) can best illustrate the difficulties in comparing mouse and human gene mutation defects (see also the review by Francis *et al*., 2006). The human *DCX* gene maps to chromosome Xq22.3-q23 (Gleeson *et al*., 1998; des Portes *et al*., 1998a) and encodes a protein that is associated with microtubules (Francis *et al*., 1999; Gleeson *et al*., 1999). Male patients have classical type I lissencephaly, a thickened, almost smooth cortex with abnormal layering, accompanied by severe mental retardation and epilepsy (Harding, 1996). Females who are heterozygous for *DCX* mutations have subcortical laminar heterotopia (des Portes *et al*., 1998b; Gleeson *et al*., 2000), a less severe malformation where an ectopic band of neurons lies in the white matter below an almost normal cortex, thus usually causing epilepsy. Surprisingly, inactivation of the *Dcx* gene in mice does not reproduce the severe brain defect known from human mutations but instead produces only a minor layering abnormality in the hippocampus (Corbo *et al*., 2002; also C. Kappeler, Y. Saillour, J.-P. Baudouin, F. Phan Dinh Tuy, C. Alvarez, C. Houbron, P. Gaspar, G. Hamard, J. Chelly, C. Métin, and F. Francis, unpublished observations).

A possible explanation for this discrepancy can be found in the normal expression pattern of *DCX* in the human brain (Meyer *et al*., 2002). *DCX* is first expressed at 5 gestational weeks (GW) in radial columns in the marginal layer. At 7GW, still a relatively early stage of human corticogenesis, it appears in tangentially orientated neurons in the SVZ, and from 8GW onward it is most prominent in horizontal neurons and fibres in SVZ and IZ, while the VZ is DCX-negative. A similar expression pattern is also observed in the monkey cortex (C. Dehay, unpublished observations). In the cortical plate, DCX expression is less intense and mostly localized to radial processes in the upper layers. On the whole, the pattern is consistent with DCX involvement in nonradial migration and in fact DCX expression has been found to often colocalize with calretinin, a marker of cortical interneurons (Meyer *et al*., 2002). The possibility that migration of interneurons is particularly affected in type I lissencephalies has been addressed recently (Pancoast *et al*., 2005; G. Meyer and F. Francis, unpublished observations). Dcx distribution in mouse brain appears less conspicuous, probably due to the smaller size of the SVZ and the heavy Dcx labelling of fibres in the compact IZ, masking migrating cells in this zone. Nevertheless, a clear expression of Dcx in horizontally orientated, apparently tangentially migrating, neurons was observed (Francis *et al*., 1999). Supporting a role for Dcx in migrating interneurons and the similarity of Lis1 mouse mutants (McManus *et al*., 2004), mild interneuron migration abnormalities have also been detected in Dcx-knockout mice (C. Kappeler, Y. Saillour, J.-P. Baudouin, F. Phan Dinh Tuy, C. Alvarez, C. Houbron, P. Gaspar, G. Hamard, J. Chelly, C. Métin, and F. Francis, unpublished observations). Nevertheless the human disorder remains markedly more severe.

With regard to the question of rodent–human comparisons, we thus learn from DCX that it is expressed precisely in those cortical compartments, SVZ and IZ, which are rudimentary in rodents but highly differentiated in primates (Figs 5 and 7). Thus it is perhaps not surprising that mouse knockouts poorly mimic the human disorder. Clearly, if the cellular and molecular mechanisms were the same in mouse and man, the mouse would have a large convoluted cortex. Comparative studies are therefore very important in recognizing the limitations of generalizations across species. Studies involving *DCX*, along with genes involved in human microcephaly (see the review by Francis *et al*., 2006), are clearly most important for a better understanding of primate brain evolution. Moreover, evolutionary theories can also be further tested by examining human developmental disorders (e.g. see Molnár & Butler, 2002a).

Concluding remarks

This review aimed to examine the comparative aspects of cortical development. Unfortunately there are only a handful of experimental model systems used in comparative developmental studies and the current comparisons are limited to a few mammals (rat, mouse, macaque monkey and human), chicken and turtle. Unfortunately little quantitative information is present even in these model systems. By examining neurogenesis, layer formation of the first postmitotic cells, radial migration of neurons within the cortex and tangential migration of GABAergic neurons from the subpallium we can speculate on the evolutionarily relevant changes in cortical development. The formation of the first-generated cell layers and the presence of the Reelin signalling pathway are similar in mammals, birds and reptiles. The subpallial origin and tangential migration of GABAergic neurons are also surprisingly conserved across most species studied. However, there are major transformations at the striatocortical junction, in the cortical germinal zones and in the amplification of the Reelin signalling pathway, which might all have contributed to the evolution of the mammalian neocortical development. Comparative developmental studies also reveal distinct primate features in the early compartments of the developing brain and suggest that the elaboration of the mitotic compartments could constitute a major drive behind mammalian cortical evolution. Comparative developmental biology draws our attention to the limitations of some of the model systems currently used to understand human cortical developmental abnormalities. Several gene functions implicated in human cortical developmental disorders have been studied in transgenic mouse models. While this approach has been extremely useful and has revolutionized the study of mammalian cortical developmental programs, recent comparative analyses reveal considerable differences. These distinctions will have to be taken into account when we study the range of gene function implicated in human brain developmental abnormalities (including childhood epilepsy, schizophrenia, autism and attention deficit disorder).

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Abbreviations

CR, Cajal–Retzius (cells); DCX, doublecortin; E, embryonic day; GW, gestational weeks; ISVZ, inner SVZ; IZ, intermediate zone; LP, lateral pallium; OSVZ, outer SVZ; SVZ, subventricular zone; VP, ventral pallium; VZ, ventricular zone.

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