

## REVIEW

# The evolution of cortical development: the synapsid-diapsid divergence

Andre M. Goffinet

**ABSTRACT**

The cerebral cortex covers the rostral part of the brain and, in higher mammals and particularly humans, plays a key role in cognition and consciousness. It is populated with neuronal cell bodies distributed in radially organized layers. Understanding the common and lineage-specific molecular mechanisms that orchestrate cortical development and evolution are key issues in neurobiology. During evolution, the cortex appeared in stem amniotes and evolved divergently in two main branches of the phylogenetic tree: the synapsids (which led to present day mammals) and the diapsids (reptiles and birds). Comparative studies in organisms that belong to those two branches have identified some common principles of cortical development and organization that are possibly inherited from stem amniotes and regulated by similar molecular mechanisms. These comparisons have also highlighted certain essential features of mammalian cortices that are absent or different in diapsids and that probably evolved after the synapsid-diapsid divergence. Chief among these is the size and multi-laminar organization of the mammalian cortex, and the propensity to increase its area by folding. Here, I review recent data on cortical neurogenesis, neuronal migration and cortical layer formation and folding in this evolutionary perspective, and highlight important unanswered questions for future investigation.

**KEY WORDS:** Cajal-Retzius cells, Cortical folding, Neural progenitors, Neural stem cells, Reelin

**Introduction**

The human cerebral cortex is probably the most-complex structure elaborated during biological evolution (Rakic, 2009). Essential to our unique cognitive abilities, it is the driver of our civilization, and arguably the sole instrument that may allow us to elaborate solutions to the impending anthropogenic ‘sixth extinction’ (Barnosky and Hadly, 2016). It is, therefore, quite natural to enquire about how our cortex evolved.

With the exception of amphioxus (considered the most primitive chordate), the forebrain is present in all vertebrates (Butler and Hodos, 2005). It is divided into the diencephalon (the caudal part of the forebrain) and telencephalon (see Glossary, Box 1), the dorsal part of which contains the cerebral cortex. The basal telencephalic ‘Bauplan’ is present in evolutionarily more-ancient vertebrates, such as lampreys, sharks and fishes. The main parts of the telencephalon were defined in amphibians by Herrick in his pioneering studies (Herrick, 1948), and consist of a mediobasal septum, a medial pallium, a dorsal pallium and a lateral pallium, and laterobasal areas that include ventral pallial areas, striatum and

amygdala; the cortex develops in pallial areas (Laberge and Roth, 2007). However, the forebrain in amphibians does not contain a bona fide cortex, defined as a sheet of neurons that migrate radially from germinative periventricular zones and extend their axons inwards to form a hemispheric white matter. The cerebral cortex, as defined in this way, appears for the first time in amniotes (Butler and Hodos, 2005). In this review, I discuss the evolution of the cerebral cortex in amniotes. Given the interdisciplinary nature of this theme, this cannot be an exhaustive review and I refer the reader to other excellent sources for further information on cortical development (Florio and Huttner, 2014; Lein et al., 2017; Rakic, 2009), on comparative neuroanatomy (Aboitiz and Montiel, 2012; Butler and Hodos, 2005; Butler et al., 2011; Puelles et al., 2017) and on amniote evolution (Benton, 2015a; Carroll, 1988; Colbert et al., 2001; Rowe et al., 2011). Here, I focus primarily on the issue of how comparative studies of cortical development in present-day amniotes can help us understand better the molecular mechanisms that shape our cortex. First, I provide a brief overview of amniote evolution, before summarizing how the cortex is organized in synapsids and diapsids. I then discuss two key aspects of cortical development, neurogenesis and folding, and the similarities and differences in the two amniote groups. These discussions also highlight a number of key questions for future analysis.

**Overview of amniote evolution**

It is believed that the closed egg of amniotes (also known as the cleidoic egg), which allowed embryos to develop in a terrestrial rather than an aquatic environment, evolved only once (Benton, 2015a; Ferner and Mess, 2011). Amniotes are monophyletic: all lineages, extinct and present, derive from a single ‘stem amniote’, the ancestor of present mammals, reptiles and birds. Although no fossil stem amniote has been unequivocally identified, they likely appeared circa 314 million years ago (MYA), in the late Carboniferous (Pennsylvanian, see simplified tree in Fig. 1), and presumably derived from advanced amphibians of the labyrinthodont type (Benton, 2015a; Colbert et al., 2001).

Two main lineages, the synapsids and sauropsids, diverged very early from stem amniotes: specimens of both lineages appear in the fossil record around the same time that amniote fossils appear (Benton, 2015a). The phylogenetic relationships of amniotes are largely assessed based on a few simple morphological traits of the skull, namely the localization and number of temporoparietal bony arches – structures that derive from the neural crest of the first branchial arch (Box 2). As yet, we do not understand why these traits are so invariant and consistent. Presumably, they reflect the existence of highly conserved genetic components of evolution that govern key aspects of the body plan.

The synapsid lineage (one arch, see Box 2) gave rise to premammals and mammals. Early synapsids are often referred to as ‘mammal-like reptiles’, a term that I will not use further, for reasons explained in Box 2. Because extinct premammals and all

University of Louvain, Avenue Mounier, 73 Box B1.73.16, B1200 Brussels, Belgium.

\*Author for correspondence (angoffinet@uclouvain.be)

✉ A.M.G., 0000-0002-8003-2680

**Box 1. Glossary**

**Cajal-Retzius (C-R) cells.** Early-born mammalian neurons that are generated all around the dorsal telencephalon, migrate tangentially in the marginal zone and secrete the extracellular protein reelin. Most of them die during the early postnatal period.

**Cortical plate.** A dense layer at the outer aspect of the embryonic telencephalon that contains neurons destined to form the cerebral cortex.

**Dorsal ventricular ridge.** A forebrain structure in reptiles and birds, the homolog of which in mammals is not fully known. Its anterior part is considered to be part of the telencephalon but, contrary to dorsal telencephalon, is located ventral to the lateral ventricles.

**Endocast.** Internal cast of the hollow cranial cavity that more or less models the brain contained inside. Made by injection of polymers into the cavity or, more recently, by computer tomography reconstruction of the cavity.

**Gyrencephalic.** Refers to animals with a folded cortex in which clefts (sulci) separate folds (gyri). Most, but not all, primates are gyrencephalic, as are several non-primate mammals, such as carnivores.

**Heterotopia.** The presence of a particular tissue type at a non-physiological site. During brain development, heterotopia can form at various locations when neurons fail to migrate properly to their destination. Periventricular heterotopia are usually nodular and form when brain cells remain close to the ventricle. Subcortical band heterotopia (SBH) extend in the white matter under the cortex and form a sheet that resembles a second cortex. This is referred to as 'double cortex' malformation.

**Homoplastic.** A character shared by a set of species but not present in their common ancestor. This character has been acquired independently, by what is called evolutionary convergence.

**Lissencephalic.** Refers to animals with a smooth ('lisse' in French) cortex devoid of folds, such as all diapsids and some mammals, including most rodents.

**Marginal zone.** The most external superficial zone of the embryonic cortex. It contains few neurons, among which are preplate derivatives and Cajal-Retzius cells. In the adult, the marginal zone will become the cortical molecular layer 1.

**Meninges.** Mesenchymal structures located between bone and brain tissue. Meninges contain blood vessels that irrigate the brain and local cells such as fibroblasts. They are separated from brain tissue by a basal lamina that participates in the formation of the external limiting membrane.

**Micropolygyria.** A human brain malformation probably due to abnormal neuronal migration, characterized by the presence of zones where the cortex forms too many (poly) small (micro) gyri.

**Neocortex.** The part of the brain involved in higher-order brain functions, such as sensory perception, motor command and cognition. In the human brain, the neocortex is the largest part of the cerebral cortex that covers the brain hemispheres.

**Pachygryria.** A human brain malformation probably due to abnormal neuronal malformation, characterized by a reduced number of cortical sulci, and wide and thickened gyri.

**Pallium.** In the telencephalon, the pallium (mantle) refers to the layers of gray and white matter that cover the upper surface of the cerebrum in vertebrates; it is, thus, nearly synonymous with the 'cerebral cortex', and both terms are often used interchangeably.

**Pelycosaurs.** Early synapsids closely related to stem synapsids, which appeared during the Carboniferous period and were widespread during the Permian period, before they were superseded by the therapsids.

**Pioneer layer 1 neurons.** A poorly characterized set of early generated neurons that initially form the telencephalic preplate and settle in the depth of the marginal zone when the cortical plate cells displace them externally. They are different from, although sometimes confused with, C-R cells.

**Reelin.** A large glycoprotein secreted by C-R cells in the embryonic cortical marginal zone, and to a lesser extent by other cells. Reelin is required for the radial organization of the cortex. Reelin mutations in human lead to a specific form of lissencephaly that is less severe than Lissencephaly 1.

**Synapomorphy.** A characteristic present in an ancestral species and shared exclusively, sometimes in modified form, by its evolutionary descendants. The meaning is close to 'homology', a feature derived from a common ancestor, and contrasts with 'homoplasy', which is derived by convergent evolution.

**Telencephalon.** The rostral part of the forebrain. The cerebral cortex or pallium develops in the dorsal telencephalon, and the striatum from the ventral telencephalon.

**Therapsids.** Large group of early synapsids that appeared in the Carboniferous period and were the dominant terrestrial vertebrates in the Permian period. Some survived the Permian-Triassic extinction and stem mammals originated from them.

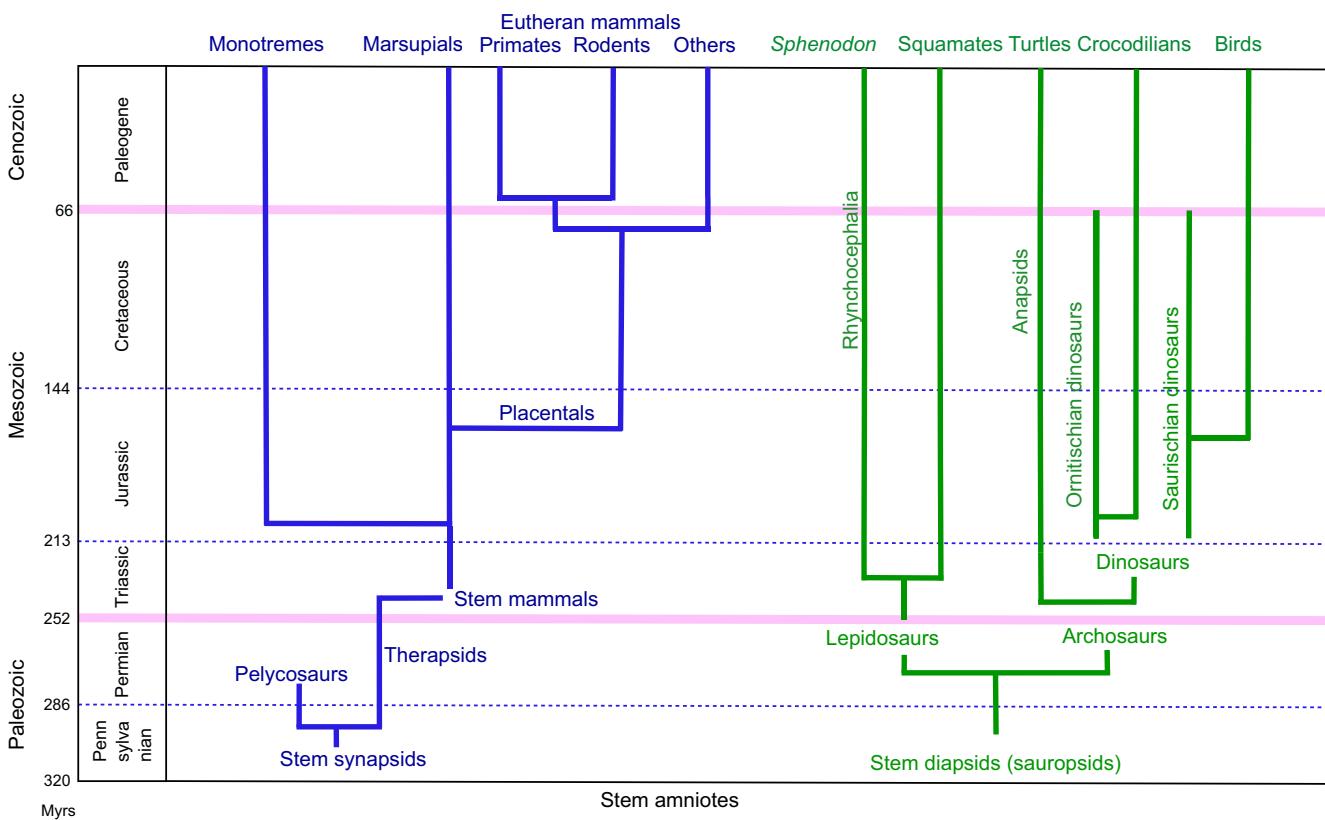
**Ventricular zone.** A zone situated all around forebrain ventricles where apical neural progenitor cells, initially neuro-epithelial and later apical radial glial cells, proliferate to generate neurons directly and through production of basal progenitors.

mammals, extinct and present, are synapsids, I refer to their common ancestor as the 'stem synapsid'. The other lineage is the sauropsid lineage, also referred to as Reptilia (Benton, 2015a). This lineage encompasses anapsids, which have no temporal arch/opening and are represented today by chelonians (turtles), and the diapsids, which have two arches/openings and are represented by other reptiles and birds (Benton, 2015a). Modern diapsids include lepidosaurs and archosaurs. Lepidosaurs comprise the large group of squamates (lizards and snakes), and rhynchocephalia, a group of lizard-like reptiles that includes only two living species of *Sphenodon* (New Zealand's tuatara). Archosaurs are represented by crocodilians (the modern remnants of ornithischian dinosaurs), chelonians (Benton, 2015a) and also birds – derived from saurischian dinosaurs (Brusatte et al., 2015). It is generally assumed that stem amniotes, like their amphibian ancestors, had anapsid skulls, and anapsid chelonians were for a long time considered to reflect the ancestors of all sauropsids, and even perhaps the elusive stem amniote. However, DNA sequence data and the discovery of new fossils led to the revised view that chelonians are derived from archosaurs and belong to the diapsid lineage (Hedges and Poling, 1999; Schoch and Sues,

2016; Zardoya and Meyer, 2001). All living non-mammalian amniotes are therefore diapsids (at least in evolutionary terms), and I propose to simplify terminology and refer to their common ancestor as 'stem diapsid' rather than by the more complex and somewhat equivocal terms of 'stem sauropsid' or 'stem reptile'.

An important, sometimes overlooked point is that early synapsids were evolutionarily highly successful during the Permian period (~299–252 MYA). They were represented by pelycosaurs and therapsids (see Glossary, Box 1), which are well documented in the fossil record, particularly thanks to the superb strata in North America and Russia that contain pelycosaur fossils, and to the Karoo basin in South Africa and Ural region in Russia, where most therapsid specimens are found (Benton, 2015b; Kemp, 2006). Some pelycosaurs and therapsids were large animals and dominated the Permian terrestrial environment (Chinsamy-Turan, 2012), whereas diapsids were relatively small and less successful (Benton, 2015a; Carroll, 1988).

This situation lasted until about 252 MYA, when the Permian-Triassic (PT) mass extinction, the largest of the major extinction events (Benton, 2015b; Shen et al., 2011), wiped out almost all



**Fig. 1. Simplified tree of amniote evolution from stem amniotes.** Blue, synapsid lineage; green, diapsid lineage; pink bars, Permian-Triassic (PT) and Cretaceous-Paleogene (CP) mass extinction events; Myrs, megayears.

synapsids and most other species. The PT extinction, during which at least 80% of terrestrial vertebrates disappeared, was more dramatic than the later Cretaceous-Paleogene (K-Pg) extinction that led to the demise of dinosaurs 66 MYA. A few therapsids survived the PT extinction, and stem mammals appeared among them. Early mammals were diminutive, shrew-like insectivores that mostly hid under ground, which led to decreased visual performance and the loss – relative to diapsids – of opsins, leading to dichromatism (with a later duplication leading to trichromatism in Old World monkeys) (Gerkema et al., 2013; Rowe et al., 2011). Throughout the remainder of the Mesozoic era, premammals and mammals were minor members of the Jurassic and Cretaceous faunas, which were dominated by diapsid archosaurs and then specifically by dinosaurs. Although they were ecologically quite insignificant, mammals diversified extensively during this long period, and it is in the Cretaceous period that the main divisions of mammals became established (Bininda-Emonds et al., 2007; dos Reis et al., 2012). After the K-Pg extinction that wiped out dinosaurs, mammals became evolutionarily more successful than diapsids and underwent a great expansion at the beginning of the Cenozoic period, ‘the age of mammals’ (Benton, 2015a; Colbert et al., 2001; O’Leary et al., 2013). They progressively came to dominate almost all habitats, with extreme forms ranging from the diminutive bumblebee bat (*Craseonycteris thonglongyai*) and etruscan shrew (which weighs just a few grams), to blue whales.

It is worth emphasizing that, far from being evolutionarily recent, the primate line is descended from early placental mammals, when the main early placental lineages formed during late Cretaceous times, about 70 MYA. Primates and rodents diverged about 60 MYA, after the K-Pg extinction, when the variety of mammals exploded

(Bininda-Emonds et al., 2007; dos Reis et al., 2012; O’Leary et al., 2013). This early divergence of lineages should be kept in mind when comparing cortical development among different mammals.

#### Cortical regionalization in amniotes

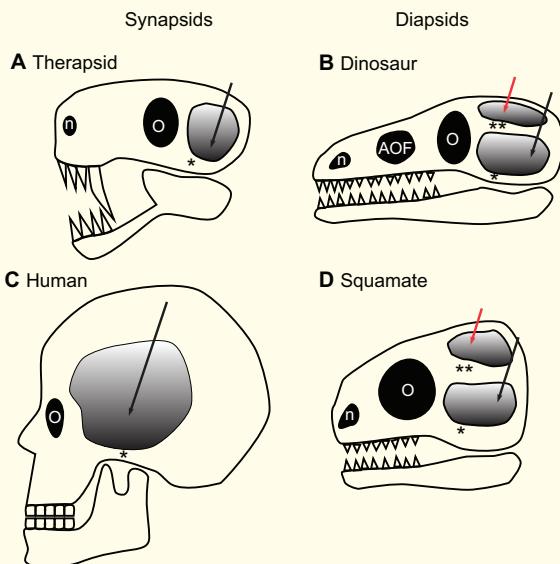
In all amniotes, the cerebral cortex develops in the telencephalon in an invariant manner. Therefore, a cerebral cortex was presumably present in stem amniotes and defines an evolutionary homology. There are different views about comparative telencephalic regionalization (Butler et al., 2011). Here, I use a simple version of the ‘tetrapartite pallium model’ (Puelles et al., 2016, 2017), in which the amniote cortex/pallium (see Glossary, Box 1) is divided into three dorsal fields and a ventral sector. The dorsal telencephalic fields include medial, dorsal and lateral components, all of which are present in modern mammals and diapsids (Fig. 2). There is general agreement that the medial cortex in diapsids corresponds to the mammalian hippocampal formation, the dorsal cortex to the neocortex (see Glossary, Box 1) and the lateral cortex to the piriform cortex (Puelles et al., 2017). Excitatory neurons in the medial and dorsal cortex are born in corresponding medial and dorsal ventricular zones (VZs; see Glossary, Box 1). The fate and lineage of neurons born in the ventral VZ is somewhat less clear, partly because they migrate along complex and highly convoluted pathways. In diapsids, neurons destined for the anterior dorsal ventricular ridge (ADVR, see Glossary, Box 1 and below) are generated in the ventral VZ; in mammals, this small ventral VZ may contribute to neurons in the insula, claustrum and amygdala.

Prominent among diapsid pallial/cortical areas is the large ventrolateral ADVR (Fig. 2B,C), which in birds corresponds to the nido- and mesopallium. As yet, the ADVR has not been identified in

## Box 2. Remarks about amniote classification and terminology

The phylogenetic tree of amniotes consists of two main branches: the synapsids, which comprise pre-mammals and mammals; and the diapsids, which are now represented by birds, squamates (lizards and snakes), Crocodylia, *Sphenodon* and turtles. The terms 'synapsid' and 'diapsid' refer to the presence of one (syn) or two (di) cranial bone arches [the root 'apsis' (ἀψίς) is Ancient Greek for 'arch'] and corresponding holes located behind the orbit (see Figure). Thus, synapsids (A,C) have one low temporal arch (asterisk) that surrounds the temporal fenestra/opening (black arrow). This single arch was present in pelycosaurs and therapsids (A), and corresponds to the mammalian zygomatic arch (asterisk in C). Diapsids (B,D) have two arches and fenestrae, a lower temporal arch that is analogous to the lower arch in synapsids (asterisk) with corresponding lower fenestra (black arrow), plus an additional arch (double asterisks) that borders an upper temporal fenestra/opening (red arrow). AOF, ante-orbital fenestra (a dinosaurian feature, absent in other diapsids); n, nostril; O, orbit.

Until recently, paleontological texts referred to the common amniote ancestors of mammals, reptiles and birds as 'stem reptiles' or the etymologically equivalent 'cotylosaur' (Benton, 2015a; Carroll, 1988; Colbert et al., 2001). They also used terms such as 'mammal-like reptile' for the synapsid ancestors of mammals. However, this position has now altered and, according to modern views, synapsid 'mammal-like reptiles' were different from sauropsids/Reptilia, and were therefore not bona fide reptiles. No diapsid was ancestral to any synapsid or vice versa (Butler et al., 2011).



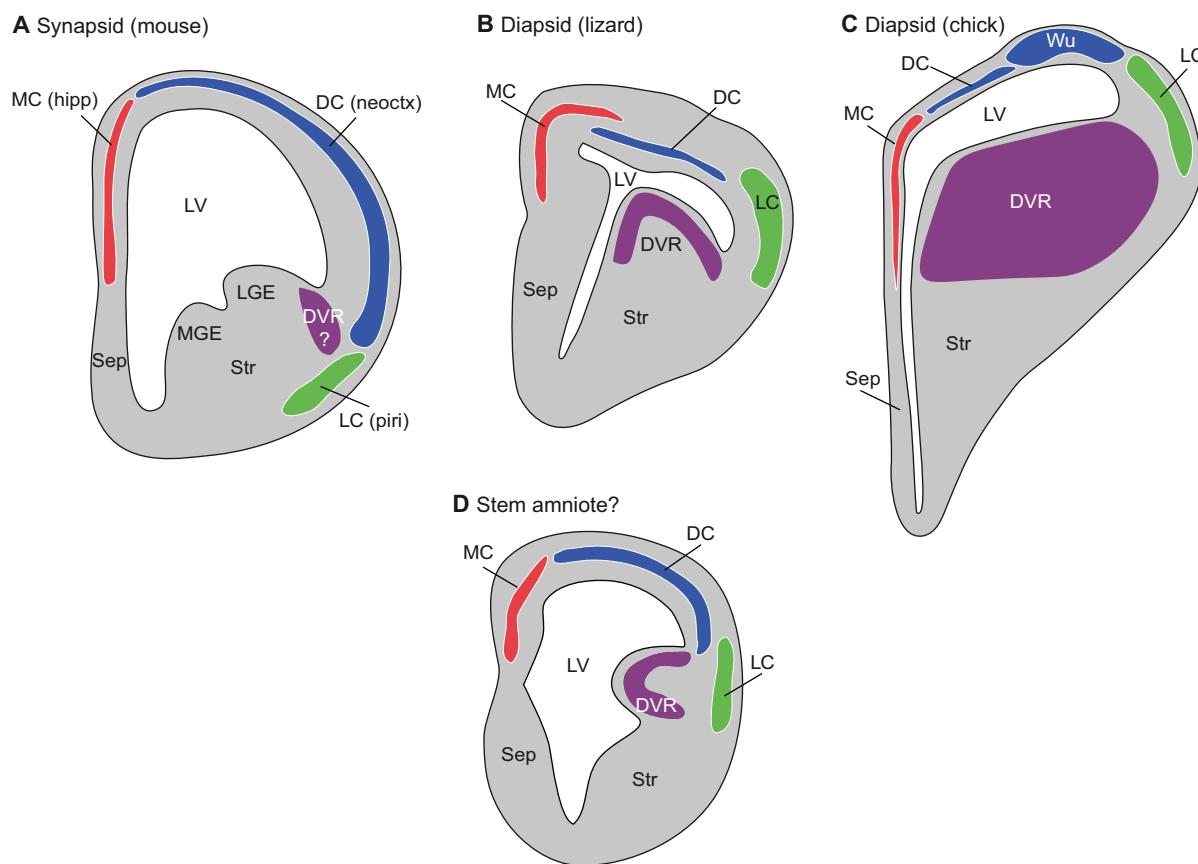
pre-amniotes. Because it is prominent in all modern diapsids, the ADVR is likely to have been present in stem diapsids. Whether a mammalian equivalent to the ADVR exists has been a matter of considerable debate and remains unresolved (Montiel et al., 2016; Puelles et al., 2017). The VZ of the diapsid ADVR expresses markers of the mammalian cortical VZ (Fernández et al., 1998), especially *Pax6*. In mammals, *Pax6* expression is high in the dorsal cortical ventricular zones, and extends to a narrow zone ventral to the angle of the lateral ventricle, also known as the 'anthem' (Subramanian et al., 2009). This narrow zone may be the origin of the mammalian remnant of the ADVR (Fernández et al., 1998; Montiel et al., 2016; Puelles et al., 2016, 2017). From these findings, it is reasonable to propose that the ADVR appeared in stem amniotes (Fig. 2D), then enlarged in diapsids and became less prominent in synapsids.

In line with paleontological views and with the early divergence of the synapsid and diapsid lineages, comparisons of the telencephalon among mammals, turtles, squamates, *Sphenodon*, crocodiles and birds show that, apart from the conserved features mentioned above, the telencephalon of all diapsids studied to date is very different to that in mammals. Despite important differences among diapsid cortices, they are clearly more similar to one another than they are to any mammalian cortex (Butler and Hodos, 2005). Comparative studies of embryonic brains have emphasized this even further (Goffinet, 1983; Goffinet et al., 1986). The mammalian piriform cortex is perhaps the only area that resembles its diapsid homolog, both in terms of relative size and connectivity with the olfactory bulb. In monotremes, marsupials and eutherian mammals, the hippocampus is much more developed than it is in any diapsid, in which it is reduced to a simple cortical layer with no definite morphological evidence of CA ('cornu ammonis') fields and no anatomically defined dentate gyrus. The diapsid dorsal cortex contains a single layer of pyramidal cells and interneurons, and the large pallium in birds is organized in nuclei rather than in layers (Dugas-Ford et al., 2012). By comparison, even lissencephalic mammals (see below and Glossary, Box 1) have a thick cortex with the classical neuronal layers overlaid by a marginal zone (see Glossary, Box 1). Mammalian cortical layers 6 to 2 develop in sequence, from inside to outside (Rakic, 2009). In contrast, cortical layering is rudimentary in diapsids and, with the possible exception of the turtle dorsal cortex (Xi et al., 2008), the cortical plate (see Glossary, Box 1) develops either from outside to inside or with no preferential gradient at all (Goffinet et al., 1986). The neocortex is also widely expanded tangentially in monotremes, marsupials and eutherian mammals, and is partitioned into many more areas than in diapsids. Conversely, as mentioned above, the large ADVR of diapsids – which also matures from outside to inside – is very diminutive in mammals (Fernández et al., 1998; Montiel et al., 2016; Puelles et al., 2016, 2017).

The comparative data on cortical regionalization summarized above are clearly in line with the fundamental division of amniotes into synapsid/diapsid lineages. In the next sections, I will consider the cellular events and processes that regulate cortical development irrespective of regionalization.

## Overview of cortical development in amniotes

Mammalian cortical development is best documented in mice and primates (Florio and Huttner, 2014; Lui et al., 2011; Molnár and Clowry, 2012; Rakic, 2009). It begins with neurogenesis (Fig. 3A), during which different neurons form from neural progenitor cells (NPCs) located around lateral ventricles, in the VZ (Fig. 3A), and later in the VZ and in subventricular zones (SVZs) (Fig. 3B,C). Early born neurons migrate through the intermediate zone (IZ); they initially form a loose horizontal plexus called the preplate (PP) (Fig. 3A) and later the denser cortical plate (CP). With the appearance of the CP, early PP neurons settle in the marginal zone to form pioneer layer 1 neurons (distinct from Cajal-Retzius cells; see Glossary, Box 1 for definitions of both) and under the CP, in the subplate (future layer 6b) (Hoerder-Suabedissen and Molnár, 2015) (Fig. 3B). Neurons are deposited in the CP from inside to outside, first forming layers 6 and 5 (populated by deep layer neurons), followed by layers 4, 3 and 2 (upper layer neurons) (Fig. 3C). Most (at least 80%) cortical neurons are excitatory glutamatergic cells generated from cortical NPCs and they migrate radially to the cortex. The others are GABAergic cortical interneurons generated in the ganglionic eminences in the ventral telencephalon that reach the cortex by tangential migration (Anderson et al., 1997; Lavdas



**Fig. 2. Forebrain cortical/pallial organization in amniotes.** (A–D) Schematics of coronal sections at mid-forebrain level in amniote embryos. By comparing cortical organization in A, a present day synapsid mammal (mouse) with that of two diapsids (B, lizard; C, chick), it is possible to propose in D the organization in a putative ancestral stem amniote. BF, basal forebrain; DC, dorsal cortex (blue); DVR, dorsal ventricular ridge (violet); LC, lateral cortex (green); LGE, lateral ganglionic eminence; LV, lateral ventricle; MC, medial cortex (red); MGE, medial ganglionic eminence; Sep, septum; Str, stratum; Wu, Wulst (visual cortical area in birds). hipp, hippocampal formation; neoctx, neocortex; piri, piriform cortex.

et al., 1999; Métin et al., 2007). CP neurons are radially ordered and this requires reelin signaling (see Glossary, Box 1) (Tissir and Goffinet, 2003). Near the end of migration, neurons extend dendrites and axons to initiate wiring; synaptogenesis occurs later, mostly after birth in most mammals.

Below, I will discuss briefly neurogenesis, neuronal migration, formation of PP, and CP and reelin signaling in mammals and diapsids. As will become apparent, some features are similar in all species examined, likely inherited from stem amniotes and regulated by conserved genetic networks, whereas others are absent or poorly defined in diapsids and probably specific to the mammalian brain.

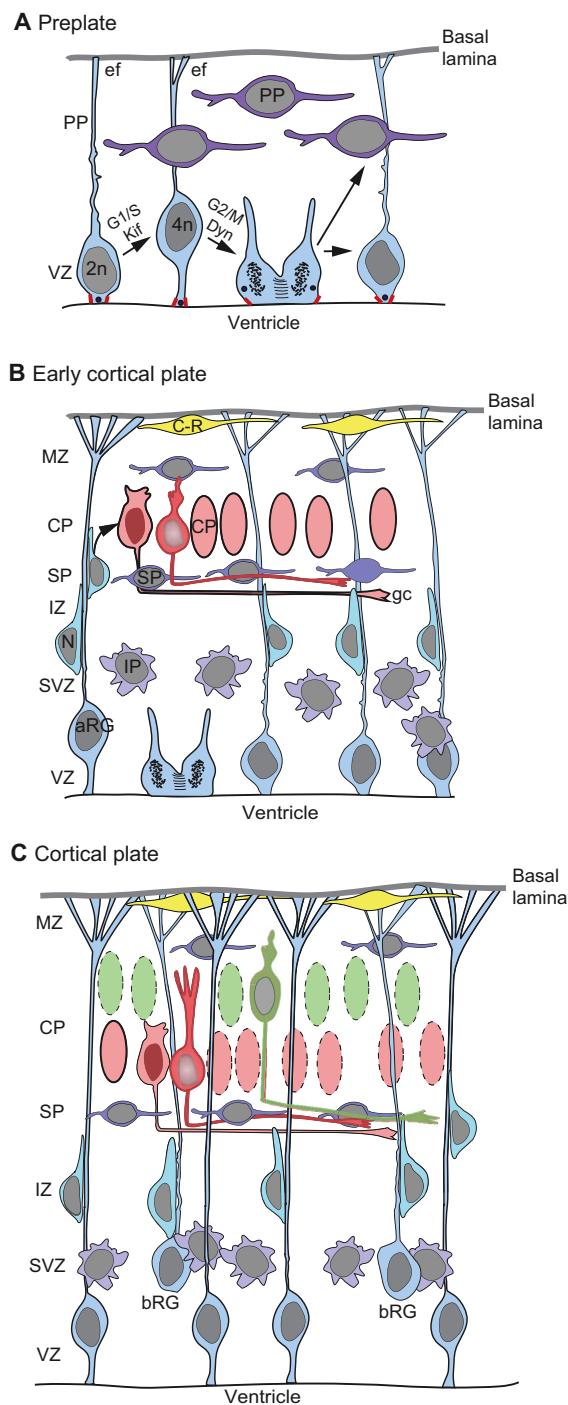
### Cortical neurogenesis

#### In mammals

In all mammals, neural progenitor cells (NPCs) are initially present as radial neuroepithelial (NE) cells that span the whole thickness of the neural tube (Fig. 3A). Interphase NE cells are attached together along the lateral ventricle by a junctional belt that surrounds their apical domain, and form end feet that contact the basal lamina at their pial pole. They divide symmetrically to amplify the progenitor pool (Fig. 3A). During the cell cycle, the nuclei of NPCs move such that S phase occurs at a distance from the ventricle, whereas M phase occurs along the ventricle where cells retain their junctional belt. The movement of the nucleus with the mitotic cycle, initially described as ‘to and fro’ (Sauer, 1935), is now referred to as

‘interkinetic nuclear migration’ (Miyata et al., 2014). At the onset of neurogenesis, NPCs modify their transcriptional profile and acquire markers of glia, such as brain lipid binding protein (BLBP). They are therefore labeled apical radial glia (RGs) or ventricular RGs. Like NE progenitors, aRGs are in contact with the ventricle as well as the pia. As they both have apical domains, NE cells and aRGs are often grouped together as apical progenitors (APs). aRGs can divide symmetrically, but also asymmetrically to give rise to an aRG and a neuron or an intermediate progenitor (IP) (Englund et al., 2005; Kowalczyk et al., 2009; Pontious et al., 2008). Early postmitotic neurons are identified morphologically and by their expression of *Tbr1* (T-box brain gene 1). IP cells lose all attachment to the ventricle and the pia, and settle in the SVZ (Fig. 4A). They express the transcription factor *Eomes1* (also known as *Tbr2*) and several neuronal genes, albeit at a lower level than do postmitotic neurons, and are committed to a neuronal fate. IP cells are thought to undergo a few (number not known) symmetric divisions, before undergoing terminal division into neurons (Kowalczyk et al., 2009; Pontious et al., 2008). The transition from radial glial NPC to IP is inhibited by FGF (Kang et al., 2009).

In addition to APs and IPs, some progenitors that resemble aRGs keep their attachment to the pia but lose their ventricular attachment and their apical domain. They are named basal (or outer) radial glia (bRGs) and are particularly abundant in the gyrencephalic cortices (see Glossary, Box 1) of ferret, macaque and human (Fietz et al., 2010; Hansen et al., 2010; Reillo et al., 2011). Cell bodies of bRGs



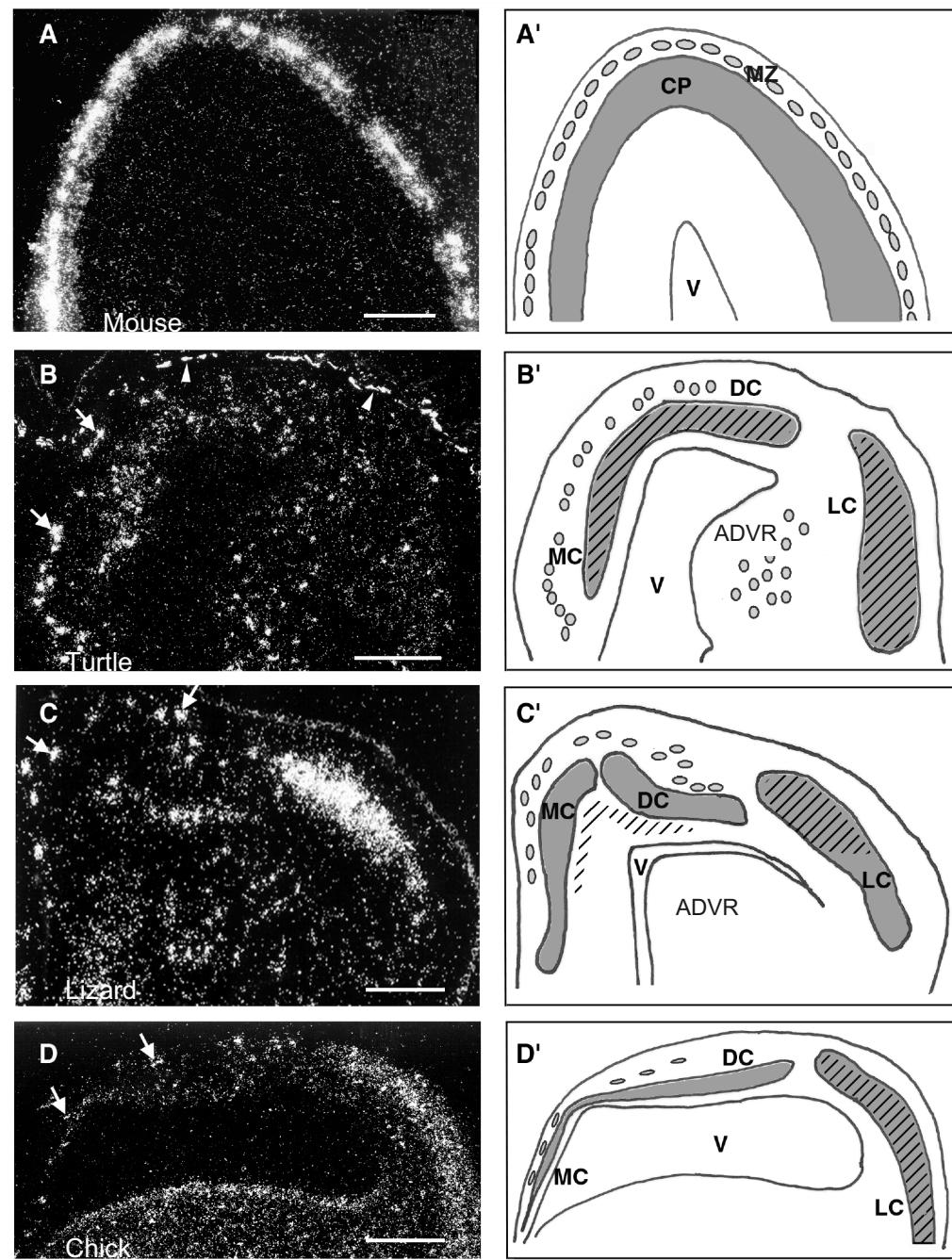
**Fig. 3. Neurogenesis, preplate and cortical plate formation in amniotes.** (A) Schematic of the cortical neuroepithelium and preplate (PP), showing neuroepithelial (NE) cells in interphase (diploid, 2n), in S-phase (4n) and mitosis, and early PP neurons generated from NE progenitors, which form a loose horizontal plexus. Dots indicate centrosomes and red bars indicate junctional belt complexes. ef, end feet; VZ, ventricular zone. (B) During cortical development, neurons (N) generated from apical/ventricular radial glia (aRGs), directly or via intermediate progenitors (IP), migrate along radial processes and settle radially to form the cortical plate (CP). CP neurons (red) send their axons capped with growth cones (gc) to the future white matter. Preplate cells (gray) are displaced inwards into the subplate (SP) or outwards the marginal zone (MZ). Cajal-Retzius (C-R) cells (yellow) migrate tangentially in subpial position. This is common to all amniotes, although C-R cells are much more numerous in mammals than in diapsids (see text). IZ, intermediate zone; SVZ, subventricular zone; VZ, ventricular zone. (C) In mammals, but not in diapsids, at later stages, younger upper CP neurons (green) migrate radially past previously deposited lower CP cells (red). Basal radial glial progenitors (bRGs) appear in the subventricular zone in addition to aRGs.

are located in the SVZ, and are especially abundant in its outer component (the OSVZ), a layer that is barely present in mice but prominent in macaque and humans (Fietz et al., 2010; Smart et al., 2002). It is worth noting that the SVZ, OSVZ and bRGs are also present but much less prominent in marmoset monkeys that almost lacks cortical folds (Kelava et al., 2012). Like aRGs, bRGs are able to self-renew, as well as to perform asymmetric neurogenic divisions (Betizeau et al., 2013; Martinez-Cerdeño et al., 2016; Pilz et al., 2013; Shitamukai et al., 2011; Wang et al., 2011), and to generate IP cells that then divide into neurons (LaMonica et al., 2012).

A lingering unresolved issue concerns the relative importance of the apical and basal domains of APs for the maintenance of NPC properties (Fig. 4). The apical domain of APs (and of adult NPCs)

(Han and Alvarez-Buylla, 2010) features a monocilium that is ideally positioned to sense signaling molecules in the cerebrospinal fluid (CSF) (Lehtinen and Walsh, 2011; Lehtinen et al., 2011). However, studies of aRGs upon loss of their centrioles show that the apical domain is dispensable for the preservation of stem cell properties (Insolera et al., 2014). It should also be noted that basal progenitors, which do not contact the CSF, also carry a monocilium – on their basolateral membrane (Paridaen et al., 2013; Wilsch-Braüniger et al., 2012).

Whereas the apical domain of NPCs may not be essential for their maintenance, all NPCs, including adult NPCs in the SVZ and in the subgranular layer (SGL) of the dentate gyrus (Goldberg and Hirsch, 2009; Mirzadeh et al., 2008) contact a basal lamina that is present at the pial surface and around brain endothelial cells; the latter contribute to the neural stem cell niche (Goldberg and Hirsch, 2009; Lange et al., 2016). Factors from the meninges (see Glossary, Box 1), such as retinoic acid and bone morphogenetic proteins (BMPs) (Choe et al., 2012; Siegenthaler et al., 2009), may regulate NPCs, whereas contact of NPC end-feet with the basal lamina that surrounds the meninges may favor the regulated exchange of signals with mesenchymal tissue (Boucherie et al., 2017). Conversely, the detachment of aRGs from the basal lamina does not suppress their stem cell potential, suggesting that this attachment is not necessary for maintaining stem cell properties (Haubst et al., 2006). This latter study showed that detachment of aRGs from basal lamina is accompanied by discontinuities in the external limiting membrane (composed of the basal lamina plus abutting end-feet of aRGs), a condition that increases communication between neural tissue and meningeal space. Interestingly, this is associated with the increased formation of deep-layer neurons from aRGs, and the decreased formation of upper layer neurons, accompanied with reduced formation of IP cells (Myshrrall et al., 2012; Zhou et al., 2006). If either contact to ventricle or attachment to basal lamina is required to maintain NPC properties, then the combined loss of the apical domain and of basal lamina contact – while the limiting membrane remains intact – should deprive NPCs from external signals (from the choroid epithelium via ventricles and from meninges) and thereby trigger their differentiation into IP cells and neurons. This would be reminiscent of the situation during neural induction, when neural tissue formation proceeds by default upon neutralization of ectoderm-promoting factors such as BMPs (Munoz-Sanjuan and Brivanlou, 2002). Perhaps the production of cortical neurons might likewise proceed by default, when NPCs are isolated from other tissues, as shown *in vitro* (Gaspard et al., 2008).



**Fig. 4. Reelin expressing cells in embryonic telencephalon.** Reelin mRNA expression was assessed using species-specific  $^{33}\text{P}$ -labeled riboprobes to provide a semi-quantitative comparison of its expression levels. Micrographs and schematics reproduced and adapted, with permission, from Bar et al. (2000) (A), Bernier et al. (1999) (B), Goffinet et al. (1999) (C) and Bernier et al. (2000) (D). Schematics adapted with permission from Bar et al. (2000). (A,A') In mouse embryonic dorsal telencephalon at E14.5, C-R cells strongly expressing reelin (arrows in A, ovals in A') cover the subpial cortical MZ (MZ in A'). Reelin expression is very high in mouse C-R cells relative to expression levels in B-D. A similar exposure time was used for (A-D) to allow reelin mRNA levels to be compared across species. (B,B') In turtle embryos (*Emys orbicularis*, Carnegie equivalent stage 21), reelin mRNA-expressing cells that might be homologous to C-R cells are seen in the MZ (arrows), and there is modest reelin expression in the cortical ribbon and in scattered cells in the anterior dorsal ventricular ridge (ADVR) (hatched areas in B'). Arrowheads indicate unrelated dark-field signal in pial melanophores. Arrows indicate Cajal-Retzius cells. (C,C') In lizard embryos (*Lacerta viridis*, Carnegie equivalent stage 21) a few C-R-like cells express reelin in the MZ in medial (MC) and dorsal cortex (DC) (arrows). There is also a zone of weaker expression in subcortical cells and in the dorsal part of lateral cortex (LC) (hatched in C'). (D,D') In chick embryos (Carnegie equivalent stage 21), a few C-R-like cells in the MZ express reelin (arrows), which is also expressed in a more-diffuse pattern in the lateral cortex (hatched area in LC in D'). CP, cortical plate; V, lateral ventricle. Scale bar: 200  $\mu\text{m}$ .

#### In diapsids

Compared with mammals, much less is known about cortical neurogenesis in diapsids (Goffinet, 1983; Goffinet et al., 1986; Medina and Abellán, 2009; Montiel and Molnár, 2013; Montiel et al., 2016; Rakic, 2009). As in mammals, NEs and, later, aRGs are the predominant neural progenitor cells, but their number is much lower. In birds, germinative layers in some telencephalic areas are thick and a SVZ is present (Cheung et al., 2007; Montiel and Aboitiz, 2015). A study of the distribution of T-box brain gene 1 (Tbr1)- and Tbr2-expressing cells in the chick shows that Tbr1 labels early neurons and that Tbr2-positive, possibly IP, cells are present in that species (Bulfone et al., 1999). Neurogenesis was recently studied in the gecko and results conform with predictions from data in mammals (Nomura et al., 2013). Specifically, NE cells

initially divide symmetrically, with a longer cell cycle than in mammalian NPCs (around 50 h versus 8–18 h in mammals), and then asymmetrically to give rise to neurons. No IP cells were detected directly outside of the VZ. A few Tbr2-positive cells could be detected outside the VZ, but were not labeled by a BrdU pulse; conversely, clonal analysis yielded a few clones with two neurons, indicating that some IP cells were present that had committed to the neuronal lineage (Nomura et al., 2013). Tbr2-positive cells that have delaminated from the VZ have been observed in the dorsal telencephalon in reptiles and birds (Cheung et al., 2007; Martínez-Cerdeño et al., 2016). It should be recognized, however, that Tbr2 might not specifically label IP cells in marsupials (Puzzolo and Mallamaci, 2010), and might be even less specific to IP cells in diapsids. Thus, although several key cellular features of neurogenesis are conserved between

synapsids and diapsids, both lineages differ quantitatively and massively in the numbers of NPC, and probably quantitatively by the presence of a mammalian specific IP amplification mechanism.

Contrary to embryonic cortical neurogenesis, adult neurogenesis is more active in diapsids than in mammals. With the exception of the olfactory bulb and dentate gyrus, few if any neurons are produced in telencephalic areas in adult mammals, at least under physiological conditions (reviewed by Ming and Song, 2011). In contrast, forebrain neurons are generated continuously in adult diapsids, such as crocodiles or lizards, the bodies of which grow during their whole life (Garcia-Verdugo et al., 2002), and also periodically in birds (Alvarez-Buylla and Kirn, 1997).

#### NPC proliferation and cortical folding

The importance of NPC proliferation for cortical development is underpinned by the identification of genes that are implicated in human hereditary primary microcephaly (MCPH) and related disorders (see Table 1 and references therein). MCPH is characterized by a small, yet reasonably well formed and folded, cortex, as if built to scale. Several causal genes for MCPH have been identified and the number is regularly increasing. Of particular relevance are the genes that code for the centromeric proteins that regulate chromosome attachment to the mitotic spindle, as well as those that encode centrosomal proteins important for the integrity and function of centrosomes and cilia, and proteins implicated in spindle formation and cell division. Presumably, mutations that impair NPC proliferation and that favor the premature formation of neurons, lead to a reduction in the NPC pool and thus to cortical atrophy. The relative preservation of cortical folding (discussed further below) in MCPH suggests that mutant apical progenitors are still able to produce basal progenitors (bRGs or IP cells, or both) in nearly normal proportion, so that the ratio between apical and basal progenitors remains unaffected, enabling cortical folding to proceed. Human samples of microcephaly are rarely examined pathologically, and studies of mature brains can only yield indirect information about development. If the model above is correct, the inactivation of microcephaly genes in a species with a foliated cortex, such as the ferret or macaque, should mimic the human condition and allow us to understand the contribution of the different NPC types to shaping the pattern and extent of cortical folding. Gene editing technologies such as TALEN and especially CRISPR/Cas have already been applied successfully in ferret (Kou et al., 2015) and monkey (Niu et al., 2014), and should make this possible.

Differential regulation of cortical neurogenesis in synapsids versus diapsids represents only one mechanism that can help to account for the changes in cortical structure across evolution. Next, I address the development of early postmitotic neurons, focusing on neuronal migration, especially radial migration, and on reelin signaling.

#### Neuronal migration and reelin

In all amniotes where it has been studied, glutamatergic excitatory neurons are generated in cortical ventricular and subventricular zones and migrate radially along the expansions of aRGs to form the cortical plate (Goffinet, 1983; Rakic, 2009). In contrast, GABAergic neurons formed in the ganglionic eminences (LGE and MGE; see Fig. 2A) in the basal telencephalon reach the cortex by tangential migration (Anderson et al., 1997; Cobos et al., 2001; Medina and Abellán, 2009; Métin et al., 2007; Tuorto et al., 2003). There is therefore a likely conservation of mechanisms that regulate migration in all amniotes. Neuronal migration is orchestrated by

intrinsic (cell-autonomous), as well as by extrinsic, cues provided by diffusible signals or extracellular matrix molecules (Lambert de Rouvroit and Goffinet, 2001; Manzini and Walsh, 2011; Métin et al., 2006). A detailed account of the cellular and molecular mechanisms of neuronal migration lies beyond the scope of this Review (I refer the reader instead to Tan and Shi, 2013), but I discuss below some key insights that would have been difficult to gain from *in vitro* cell biological investigations alone and have emerged from studies of human genetic disorders and mutant mouse models.

Like axonal growth cones, the leading process of migrating neurons progresses mainly by actin treadmilling. This is coupled to microtubule dynamics that regulate the progression of the nucleus in the leading process ('nucleokinesis'). Retraction of the trailing edge at the rear of migrating neurons requires actomyosin contractility, which implicates myosin 2 (reviewed by Vallee et al., 2009).

When actin microfilament dynamics are perturbed, neuronal migration is drastically impaired, sometimes barely initiated, as best exemplified by the presence of periventricular heterotopias (see Glossary, Box 1) in females heterozygous for mutations in the X-linked gene encoding filamin A (Fox et al., 1998) and by the presence of large subcortical band heterotopia (SBH) in mice with inactivation of the small GTPase Rho, an actin regulator (Cappello et al., 2012). Similarly, individuals with Baraitser-Winter syndromes, which are caused by heterozygous mutation in actin genes (Table 1), feature pachygryria (see Glossary, Box 1), lissencephaly or heterotopias. The scarcity of pathogenic mutations in humans of genes implicated in actin dynamics could be due to gene redundancy and/or to the aggressive resulting phenotypes, many of which might be lethal.

Most of the genes implicated in human and in mouse neuronal migration disorders are linked to microtubule organization and function, as shown by studies of congenital lissencephaly and pachygryria. Lissencephaly type 1 is characterized by a near complete absence of cortical folds, with thickened cortical ribbon and poorly defined lamination (Reiner et al., 1993). A breakthrough in the field came with the realization that some of the genes that cause lissencephaly are orthologous to nuclear distribution (NUD) genes that encode microtubule-interacting proteins required for the regular distribution of nuclei in the syncytium in filamentous fungi (Xiang et al., 1995). Inactivation of the mammalian orthologs of NUD genes in mice preferentially impacts nucleokinesis, the progression of the nucleus in the leading process (Morris et al., 1998; Walsh and Goffinet, 2000). Nucleokinesis is defective in children and/or mice with mutations in genes encoding tubulin  $\alpha 1$ , the adaptor Nde1, the kinase Cdk5, and its co-factors p25 and p35, the microtubule-associated proteins lissencephaly Lis1 and doublecortin, the microtubule-severing kinesin Kif2a, and the nuclear envelope proteins SYNE and others (see Table 1 for a more complete list and references). Given that the genes mutated in lissencephaly encode proteins that influence microtubule dynamics, it is not surprising that these proteins regulate NPC division and spindle organization as well as nucleokinesis. Perhaps the most surprising finding is that some genes implicated in microtubule dynamics, such as *Cdk5* (Gilmore et al., 1998), affect nucleokinesis and neuronal migration with little impact on NPC proliferation, whereas others, such as *Wdr62* and *Aspm* impact NPC proliferation to a greater extent (Jayaraman et al., 2016). For genes such as *Cdk5*, their expression in neurons and not in NPC explains this specificity, but this trivial explanation is not always valid. These different phenotypes likely reflect different roles for microtubule-associated proteins in NPC division and nucleokinesis, and could provide new

**Table 1.** Human and mouse gene mutations that produce abnormal cortical development

Disease	OMIM	Inheritance	Human protein and function (if known)	Reference to cortex-specific mouse mutant (if available)
<b>Autosomal recessive primary microcephaly (MCPH) and Seckel syndrome (SCKL)</b>				
MCPH1	607117	AR	Microcephalin (Jackson et al., 2002), G2/M checkpoint protein	(Gruber et al., 2011)
MCPH2	613583	AR	WDR62 (Nicholas et al., 2010), centrosome-associated protein	
MCPH3	608201	AR	CDK5RAP2 (Bond et al., 2005), Cdk5 regulation	
MCPH4	604321	AR	CASC5 (Genin et al., 2012), spindle assembly checkpoint protein	(Genin et al., 2012)
MCPH5	605481	AR	ASPM (Bond et al., 2002, 2003), spindle organization	
MCPH6	608393	AR	CENPJ (Bond et al., 2005), centromeric protein	(Fujimori et al., 2014)
SCKL4	613676			
MCPH7	612703	AR	STIL (Kumar et al., 2009)	
MCPH8	614673	AR	CEP135 (Hussain et al., 2012), centrosomal protein	
MCPH9	614852	AR	CEP152 (Guernsey et al., 2010), centrosomal protein	
SCKL5	613823			
MCPH10	615095	AR	ZNF335 (Yang et al., 2012), transcription factor	
MCPH11	615414	AR	PHC1 (Awad et al., 2013), polycomb group protein	
MCPH12	616080	AR	CDK6 (Hussain et al., 2013)	
MCPH13	616051	AR	CENPE (Mirzaa et al., 2014), centromeric protein	
MCPH14	616402	AR	SASS6 (Khan et al., 2014), centriolar assembly	
MCPH15	616486	AR	MFSD2A (Alakbarzade et al., 2015; Guemez-Gamboa et al., 2015)	
MCPH16	616681	AR	ANKLE2 (Yamamoto et al., 2014), nuclear membrane reassembly	
MCPH17	617090	AR	CIT (Harding et al., 2016; Li et al., 2016), citron kinase, cytokinesis	(Di Cunto et al., 2000)
MCPHxx			PIBF1 and CEP90 (Kodani et al., 2015), centrosomal protein	
MCPHA	607196	AR	SLC25A19 (Rosenberg et al., 2002)	
MSSP	614833	AR	RTTN rotatin (Shamseldin et al., 2015)	(Faisst et al., 2002)
Stromme syndrome	243605	AR	CENPF (Waters et al., 2015), centromeric protein	
SCKL1	210600	AR	ATR (O'Driscoll et al., 2003)	
SCKL2	606744	AR	RBBP8 (Qvist et al., 2011; Shaheen et al., 2014)	(Lee et al., 2012)
SCKL4 (see MCPH6)		AR		
SCKL5 (see MCPH9)		AR		
SCKL6	614728	AR	CEP63 (Sir et al., 2011), centrosomal protein	
SCKL7	614851	AR	Ninein (Dauber et al., 2012), centrosomal protein	
SCKL8	615807	AR	DNA2 (Shaheen et al., 2014), DNA replication	
SCKL9	616777	AR	ATRIP (Ogi et al., 2012), DNA damage checkpoint	
SCKL10	617253	AR	NSMCE2 (Payne et al., 2014), SUMO ligase, DNA repair	
Nijmegen breakage syndrome	251260		NBN (nibrin) (Varon et al., 1998), chromosome stability	
<b>Microcephaly with chorioretinopathy and/or other malformations</b>				
MCCRP1	251270	AR	TUBGCP6 (Puffenberger et al., 2012)	
MCCRP2	616171	AR	PLK4 (Martin et al., 2014), polo-like kinase	
MCCRP3	616335	AR	TUBGCP4 (Scheidecker et al., 2015)	
MCLMR	152950	AD	KIF11 (Ostergaard et al., 2012)	
FGLDS1	164280	AD	MYCN (van Bokhoven et al., 2005)	
FGLDS2	614326	AD	MIR17HG (de Pontual et al., 2011)	
MOPD1	210710	AR	RNU4ATAC (Edery et al., 2011; He et al., 2011), spliceosome component	
MOPD2	210720	AR	PCNT (Rauch et al., 2008), pericentrin/kendrin	
SCBMS	616632	AR	DIAPH1 (Al-Maawali et al., 2016; Ercan-Sencicek et al., 2015), formin	
<b>Cortical dysplasias, complex</b>				
CDCBM1	614039	AD	TUBB3 (Poirier et al., 2010)	NA
CDCBM2	615282	GM	KIF5C (Poirier et al., 2013)	(Kanai et al., 2000)
CDCBM3	615411	IC	KIF2A (Poirier et al., 2013)	(Homma et al., 2003)
CDCBM4	615412	AD	TUBG1 (Poirier et al., 2013)	NA
CDCBM5	615763	AD	TUBB2A (Cushion et al., 2014)	NA
CDCBM6	615771	AD	TUBB5 (Breuss et al., 2012)	NA
CDCBM8	613180	AR	TUBA8 (Abdollahi et al., 2009)	NA
Cortical dysplasia	614563	IC	DYNC1H1 (Poirier et al., 2013)	NA

Continued

**Table 1. Continued**

Disease	OMIM	Inheritance	Human protein and function (if known)	Reference to cortex-specific mouse mutant (if available)
<b>Lissencephaly type 1</b>				
LIS1	607432	IC, het	PAFAH1B1 (Reiner et al., 1993), dynein and microtubule regulation	(Hirotsume et al., 1998)
LIS3	611603	AD	TUBA1A (Keays et al., 2007; Poirier et al., 2007)	(Keays et al., 2007)
LIS4	614019	AR	NUDE (Alkuraya et al., 2011; Bakircioğlu et al., 2011), microtubule regulation	(Feng and Walsh, 2004)
LIS5	615191	AR	LAMB1 (Radmanesh et al., 2013), laminin	
LIS6	616212	AR	KATNB1 (Hu et al., 2014; Mishra-Gorur et al., 2014), katanin, microtubule severing	
LIS7	616342	AR	CDK5 (Magen et al., 2015), microtubule regulation	(Ohshima et al., 1996)
LISX1	300067	XLD	DCX (des Portes et al., 1998; Gleeson et al., 1998), microtubule regulation	(Corbo et al., 2002; Deuel et al., 2006)
LISX2	300215	XLD	ARX (Kitamura et al., 2002), transcription factor	(Kitamura et al., 2002)
<b>Lissencephaly type 2, cobblestone, muscle eye brain disease</b>				
Cobblestone/MDDGA1	236670	AR	POMT1 (Beltran-Valero de Bernabé et al., 2002)	
MDDGA2	613150	AR	POMT2 (van Reeuwijk et al., 2005)	
MDDGA3	253280	AR	POMGNT1 (Yoshida et al., 2001)	(Michele et al., 2002)
MDDGA4	253800	AR	FKTN/fukutin (Kobayashi et al., 1998)	
MDDGA5	613153	AR	FKRP (Beltran-Valero de Bernabé et al., 2004)	
MDDGA6	613154	AR	LARGE (van Reeuwijk et al., 2007)	
MDDGA7	614643	AR	ISPD (Willer et al., 2012)	
MDDGA8	614830	AR	POMGNT2 (Manzini et al., 2012)	
MDDGA9	616538	AR	DAG1 (Geis et al., 2013)	
MDDGA10	615041	AR	TMEM5 (Vuillaume-Barrot et al., 2012)	
MDDGA11	615181	AR	B3GALNT2 (Stevens et al., 2013)	
MDDGA12	615249	AR	POMK (Di Costanzo et al., 2014)	
MDDGA13	615287	AR	B3GNT1 (Buyssse et al., 2013)	
MDDGA14	615350	AR	GMPPB (Carswell et al., 2013)	
Perisylvian polymicrogyria, Cobblestone	604110	AR	GPR56 (Piao et al., 2004)	(Piao et al., 2004)
Cobblestone				Integrin α5 β1 (Marchetti et al., 2010)
Cobblestone				Presenilin 1 (Hartmann et al., 1999)
<b>Reelin-type lissencephaly</b>				
LIS2	257320	AR	RELN (Hong et al., 2000)	(D'Arcangelo et al., 1995)
<b>Periventricular (PVNH) and subcortical band heterotopia (SBH)</b>				
PVNH1	300049	XLD	FLNA (Fox et al., 1998)	
PVNH2	608097	AR	ARFGEF2 (Sheen et al., 2004)	
PVNH6	615544	AD	ERMARD (Conti et al., 2013)	(Conti et al., 2013)
SBH	600348	AR	EML1 (Kielar et al., 2014)	(Kielar et al., 2014)
SBH				MIlt4 (Gil-Sanz et al., 2014; Yamamoto et al., 2015)
SBH				Rap1a+b (Shah et al., 2016)
SBH				Cdh2 (Gil-Sanz et al., 2014)
SHB+other				RhoA (Cappello et al., 2012)
SHB+other				SUN1/2 (Zhang et al., 2009)
SHB+other				SYNE1/2 (Zhang et al., 2009)
Cortical dysplasia				Rapgef2 (Bilasy et al., 2009)
<b>Pachygryria (in association) (Baraister-Winter syndrome)</b>				
BRWS1	243310	AD	ACTB (Riviere et al., 2012)	
BRWS2	614583	AD	ACTG1 (Riviere et al., 2012)	

AD, autosomal dominant; AR, autosomal recessive; GM, germline mosaic; IC, isolated cases; XL, X-linked; XLD, X-linked dominant. For a more complete classification of human malformations of cortical development, see Barkovich et al. (2012). Empty cells mean data not available at date of publication.

avenues of investigation into the underlying mechanisms which, to my knowledge, are not fully understood.

'Doublecortex' is a human malformation caused by mutations in the X-linked gene doublecortin, which encodes a microtubule-associated protein (des Portes et al., 1998; Gleeson et al., 1998). In males, mutations generate lissencephaly type I, whereas heterozygous females have a complex phenotype of SBH overlaid with a thin but normally organized cortex. These phenotypes are interpreted in terms of defective neuronal migration. The defect would affect all cortical neurons in males, and of about half of them in females (due to random X inactivation) (des Portes et al., 1998;

Gleeson et al., 1998). SBH can also result from inactivation of autosomal genes, in which case the phenotype is attributed to defective migration of late-generated neurons due to a disorganized glial radial scaffold and aRG delamination. As noted above, large SBH were first induced upon inactivation of small GTPase Rho in the mouse cortex, and were shown to result from gene inactivation in RGs, rather than in migrating neurons (Cappello et al., 2012). SBH were observed in humans and mice with mutations of *Eml1* that encodes echinoderm microtubule-associated protein like 1 (*Eml1*). In mouse NPCs that lack *Eml1*, spindle orientation is abnormal and mutant NPCs loose attachment and delaminate from the VZ (Kielar

et al., 2014). Intriguingly, although *Eml1* is not X-linked like doublecortin, the phenotype is very reminiscent of the doublecortex malformation, and the thin cortical plate that overlays the heterotopic band is normally organized. The *Eml1* mutant SBH contains more late than early generated neurons, and mutant aRG extensions are disorganized. Presumably, *Eml1* inactivation affects primarily external processes of aRGs, which are more important for long-distance migration of late-generated cells than for short-distance migration of early-born neurons (Kielar et al., 2014). Rather similar phenotypes have been described in mice mutant for *Mllt4* (*Afdn*) which encodes afadin, a protein that connects nectin to the actin cytoskeleton at adherens junctions (Gil-Sanz et al., 2014; Yamamoto et al., 2015), for *Rap1*, a regulator of the actin network (Shah et al., 2016), and for *Lgl1* (lethal giant larvae homolog 1), which encodes a polarity protein expressed in NPCs (Jossin et al., 2017). In all those cases, a likely primary mechanism is the delamination of aRGs, leading to neuronal ectopia (Cappello et al., 2012; Gil-Sanz et al., 2014; Shah et al., 2016; Yamamoto et al., 2015). These recent findings hint at new features of neuronal migration that remain to be investigated further.

The mechanisms of neuronal migration in the diapsid cortex have yet to be studied in detail. Nevertheless, available morphological data show that, in turtle, lizard and crocodile embryos, cortical neurons move radially or tangentially, as in mammals (Garcia-Verdugo et al., 2002; Goffinet, 1983; Goffinet et al., 1986; Nomura et al., 2013), suggesting a conservation of mechanisms. However, the diapsid cortex is much thinner and less complex than its mammalian counterpart (Butler and Hodos, 2005; Butler et al., 2011; Puelles et al., 2017). As actin and microtubule dynamics, and radial glial guidance, are particularly important for long-distance migration and for the formation of mammalian upper cortical layers, these cellular mechanisms are likely to prove less crucial to cortical development in diapsids than in mammals.

A key difference between mammalian and diapsid cortices is the number and properties of Cajal-Retzius (C-R) cells (Fig. 4). In mammals, C-R cells are early-born transient neurons that originate from VZ at the frontier between ventral and dorsal telencephalic regions, and then in larger numbers from the dorsal cortical hem (Meyer et al., 2000). From their multiple sites of origin, C-R cells migrate tangentially in the subpial tier of the marginal zone (MZ), over all cortical sectors (Bielle et al., 2005; Meyer and Goffinet, 1998). They disappear progressively by apoptosis during late cortical maturation and only a few remain in the adult marginal zone (Meyer et al., 1999). They are characterized by the secretion of reelin (D'Arcangelo et al., 1995), a large extracellular protein that binds to lipoprotein receptors on the surface of end-migration neurons and activates a signal that orchestrates the radial organization of the cortical plate and cortical folding (Hong et al., 2000; Tissir and Goffinet, 2003). Turtles, lizards, crocodiles and birds have a few reelin-positive cells in the embryonic telencephalic marginal zone. However, those cells are scarce and the reelin signal individually associated with them is very weak compared with that in mammalian C-R cells (Fig. 4) (Bar et al., 2000; Bernier et al., 2000, 1999; Goffinet et al., 1999; Tissir et al., 2003). Lineage-tracing studies in quail indicate that avian reelin-positive cells originate from medial cortical fields, as in mice, but do not migrate from the anti-hem (Nomura et al., 2008). Therefore, the prominence of C-R cells in the embryonic MZ, and the resulting secretion of high amounts of reelin, is a defining feature of the mammalian cortex. It is impossible to know whether C-R cells were present in the early synapsid lineages (pelycosaurs and therapsids), but it should be possible to assess whether they are present in the

embryonic cortex of monotremes (echidna and platypus), which are evolutionarily related to early mammals.

Altogether, available evidence suggests that similar cellular mechanisms orchestrate neuronal migration in mammals and diapsids, and that differences are more quantitative than qualitative. On the other hand, the high number of reelin-producing C-R cells and their production of Reelin in the cortical marginal zone are key mammalian specific features and reflect qualitative differences between synapsids and diapsids. Next, I will consider how evolutionary and developmental similarities and differences between mammals and non mammals relate to the complex issue of cortical folding.

### Cortical folding

The most remarkable difference between the cortex of mammals and diapsids is the propensity of the mammalian cortex to fold. This has been emphasized by others (De Juan Romero and Borrell, 2015; Lewitus et al., 2014; Molnár and Clowry, 2012; Nonaka-Kinoshita et al., 2013; Striedter et al., 2015) and can be appreciated by consulting the superb database ‘Comparative Mammalian Brain Collection’ ([www.brainmuseum.org/](http://www.brainmuseum.org/)), on which most of statements below are based. Cortical folding is extreme in humans, apes, cetaceans and elephants, intermediate in many mammals, and absent in lissencephalic mammals, most of which have small body sizes. What is striking is that some cortical folding is present in species from all mammalian branches (Borrell and Reillo, 2012; Fernández et al., 2016; Lewitus et al., 2014; Reillo et al., 2011). For example, although most rodents are lissencephalic, porcupines have some cortical gyri and the cortex of the largest rodent, the capybara, is quite folded. Conversely, even in the primate lineage, where most species have a folded cortex, a small species such as the marmoset has a nearly smooth cortex, with only a shallow sylvian sulcus (Garcia-Moreno et al., 2012). Most marsupials, such as the opossum or koala, have a smooth cortex, but in the kangaroo, it is folded, although not extensively. Even in monotremes, platypus is lissencephalic, whereas echidnas have a highly gyrated cortex (Ashwell and Hardman, 2012). A correlation exists between folding and body size in a given mammalian phylum but not across phyla. In contrast, the brains of all diapsids, including the largest ones, such as crocodiles, monitor lizards and ostriches, are completely smooth.

Thus, the development of a folded cortex occurred repeatedly in all mammalian lineages. Is this a homologous (synapomorphic; see Glossary, Box 1) or a homoplastic (see Glossary, Box 1) feature generated by evolutionary convergence? Did premammals have a smooth or a folded cortex? Some therapsids were large animals with a significant cranial cavity. However, the rare endocasts (see Glossary, Box 1) that have been obtained from therapsid skulls indicate that their telencephalon was sagittally elongated and mostly invested with olfactory projections, most likely lissencephalic (Kemp, 2006). As mentioned above, premammals were diminutive, mouse-sized animals or smaller. Computerized tomography (CT) scan reconstruction of their cranial cavity provides strong evidence that their cortex was smooth, as predicted from their very small size (Rowe et al., 2011). Conversely, some studies using cladistics methods conclude that mammalian ancestors were gyrencephalic (Fernández et al., 2016; Lewitus et al., 2014; O'Leary et al., 2013). Whether stem mammals were lissencephalic or gyrencephalic remains a matter of debate and definitive evidence may never be provided. As cortical folding can occur in all mammalian but none of the diapsid lineages, a reasonable assumption is that the conditions required for cortical gyrus formation were acquired early in the synapsid branch. If cortical folding in several

mammalian lineage were homoplastic, due to evolutionary convergence, then I see no reason why some folding could not occur in some diapsids, particularly in birds, which generate large, primate-like numbers of neurons in their forebrain (Olkowicz et al., 2016), yet never develop well defined layers and folds.

I propose that cortical folding is best considered in terms of necessary conditions, bearing in mind that none of them is sufficient. Elegant models have been proposed to simulate cortical folding (Mota and Herculano-Houzel, 2015; Richman et al., 1975; Tallinen et al., 2014). Although they fall short of pointing to cellular mechanisms and experimental tests, they all underscore the importance of physical constraints. A first, quite obvious, condition for cortical folding is the generation of a sufficient number of neurons through the regulated proliferation of NPCs. To a first approximation, proliferation of NE and aRG progenitors is a key feature of tangential cortical spreading, whereas IP cells and bRGs contribute more to radial cortical thickness by forming preferentially upper layer neurons.

A second likely factor of folding is the relative rate of tangential expansion of deep and upper cortical layers. As mentioned above, several primary microcephalies in human with defective progenitor proliferation are associated with an elaborate cortical folding pattern (Friede, 1989), indicating that folding is possible with reduced numbers of neurons and hinting that the ratio of deep and upper cortical layers is relatively preserved in those malformations. Cortical size and folding is increased in mice by the expansion of basal NPCs (Florio et al., 2015; Nonaka-Kinoshita et al., 2013; Stahl et al., 2013) and gyration can be induced by FGF2 (Rash et al., 2013). Folding of the mouse cortex can also be induced by the double inactivation of the genes *Flrt1* and *Fltr3*, which encode adhesion proteins, indicating that finely tuned adhesion among young neurons is crucial to gyrus formation (Del Toro et al., 2017). Importantly, in these mouse models, gyration is restricted to the cortical ribbon and thereby differs from the folding induced by the overexpression of  $\beta$ -catenin (Chenn and Walsh, 2002), the inactivation of GSK3 (Kim et al., 2009) or by the downregulation of apoptosis upon inactivation of caspases (Kuida et al., 1998). In the latter models, the whole telencephalic wall undergoes folding, including the VZ and SVZ, in addition to the CP. A note of caution about mouse models with increased gyrus formation concerns the possibility that it could be caused by death of deep layer neurons rather than expansion of NPCs. As in humans with micropolygyria (see Glossary, Box 1) (Friede, 1989), the death of deep layer neurons could result in an imbalance between the upper and lower layers, resulting in folding.

A third condition required for cortical folding is the migration of neurons to the cortical plate. As mentioned above, mutations in several genes that regulate cytoskeletal dynamics lead to defective folding and to lissencephaly (Table 1). A fourth condition for gyrus formation is the concept of intercalation (Reillo et al., 2011; Striedter et al., 2015); upper layer neurons need to migrate across deep cortical layers and to intercalate, and this is necessary for folding. Intercalation at the end of migration is controlled by the reelin pathway and by C-R cells, which are therefore a key feature of cortical folding, as demonstrated by the specific lissencephalic phenotype observed in individuals with defective reelin signaling (Hong et al., 2000).

A fundamental question is which of the variety of mechanisms mentioned above prevent gyration in the diapsid brain? The lower numbers of cortical neurons in diapsids relative to mammals is certainly a key factor, although the forebrains of some birds contain neuron numbers comparable with those of primates, and this could be enough to trigger some folding (Olkowicz et al., 2016). As mentioned above, although basic features of NPC proliferation

appear quite similar in mammals and diapsids, there are obvious quantitative differences in NPC numbers as well as probable qualitative differences in NPC variety, such as bRGs and the IP cell amplification mechanism. What could be the genetic basis for premammals being able to invest a large energy budget during development to foster a vast expansion of cortical NPCs, whereas highly successful diapsids, such as dinosaurs and birds, could not? Could there be a way experimentally to increase cortical neurogenesis in birds or reptiles and assess the consequences? Another key factor is reelin. Compared with mammals, reelin-expressing cells are very few and reelin production very low in the diapsid cortex (Bar et al., 2000; Meyer et al., 2000; Nomura et al., 2008). This might result in the defective intercalation of end-migration neurons into the cortical plate, and thus contribute to an inability to fold, even if high numbers of neurons are generated (Striedter et al., 2015). To increase reelin in the bird marginal zone, reelin-expressing COS7 cells were grafted into the marginal zone of the quail embryonic cortex. Contrary to predictions, this did not modify cortical architecture, but it increased the extensions of aRGs and their attachment to the pia (Nomura et al., 2008). To try and induce the formation of C-R cells in birds, *Dbx1* – a gene expressed in mouse C-R cells from the antihem – was ectopically expressed by electroporation in the quail pallium, and this resulted in an increase in the number of reelin positive-cells reminiscent of an induction of C-R cells, and modifications of the morphology of aRGs and neuronal bipolar migration behavior, but not in fold formation (Nomura et al., 2008). These are encouraging results and the hypothesis that increasing C-R cell number and reelin secretion in the embryonic diapsid cortical marginal zone may promote cortical folding should be pursued further.

## Conclusions

Over the past 25 years, many genes and proteins that regulate neurogenesis, neuronal migration and architectonic development have been identified in human and mouse, and we are beginning to understand their mechanisms of action. As a result, the time is probably ripe to broaden our scope and to compare in depth the molecular mechanisms of cortical development among mammals and diapsids. Such issues are fascinating and reach into the heart of biology and evolution. They are not new, as most of them were formulated decades ago. Thus far, however, they could be addressed only using descriptive morphological methods. Now, new technologies are emerging to allow studies of cortical development in diapsid embryos, including development of species-specific antibody reagents, single-cell RNA sequencing, gene editing, high-speed and high-resolution video-microscopy, and embryo and stem cell culture and induction. The application of these techniques should help us to address several key unresolved issues, such as the genetic origin of the basic differences in the synapsid and diapsid brain Bauplan, the evolutionary origin of the machinery for cortical folding, and the mechanisms that orchestrated the fast evolution of the human cortex.

## Acknowledgements

I thank colleagues, especially Zoltan Molnar and Fadel Tissir, as well as anonymous reviewers and journal editors whose comments helped me focus some ideas.

## Competing interests

The author declares no competing or financial interests.

## Funding

The author's research is supported by the Fonds de la Recherche Scientifique (FNRS PDR T0002.13 and FNRS PDR T00075.15), Interuniversity Poles of Attraction (SSTC, PAI p6/20 and PAI7/20) and WELBIO (WELBIO-CR-2012A-07).

## References

- Abdollahi, M. R., Morrison, E., Sirey, T., Molnár, Z., Hayward, B. E., Carr, I. M., Springell, K., Woods, C. G., Ahmed, M., Hattingh, L. et al. (2009). Mutation of the variant alpha-tubulin TUBA8 results in polymicrogyria with optic nerve hypoplasia. *Am. J. Hum. Genet.* **85**, 737–744.
- Aboitiz, F. and Montiel, J. F. (2012). From tetrapods to primates: conserved developmental mechanisms in diverging ecological adaptations. *Prog. Brain Res.* **195**, 3–24.
- Alakbarzade, V., Hameed, A., Quek, D. Q. Y., Chioza, B. A., Baple, E. L., Cazenave-Gassiot, A., Nguyen, L. N., Wenk, M. R., Ahmad, A. Q., Sreekantan-Nair, A. et al. (2015). A partially inactivating mutation in the sodium-dependent lysophosphatidylcholine transporter MFSD2A causes a non-lethal microcephaly syndrome. *Nat. Genet.* **47**, 814–817.
- Alkuraya, F. S., Cai, X., Emery, C., Mochida, G. H., Al-Dosari, M. S., Felie, J. M., Hill, R. S., Barry, B. J., Partlow, J. N., Gascon, G. G. et al. (2011). Human mutations in NDE1 cause extreme microcephaly with lissencephaly [corrected]. *Am. J. Hum. Genet.* **88**, 536–547.
- Al-Maawali, A., Barry, B. J., Rajab, A., El-Qessny, M., Seman, A., Coury, S. N., Barkovich, A. J., Yang, E., Walsh, C. A., Mochida, G. H. et al. (2016). Novel loss-of-function variants in DIAPH1 associated with syndromic microcephaly, blindness, and early onset seizures. *Am. J. Med. Genet. A* **170**, 435–440.
- Alvarez-Buylla, A. and Kirn, J. R. (1997). Birth, migration, incorporation, and death of vocal control neurons in adult songbirds. *J. Neurobiol.* **33**, 585–601.
- Anderson, S. A., Eisenstat, D. D., Shi, L. and Rubenstein, J. L. (1997). Interneuron migration from basal forebrain to neocortex: dependence on Dlx genes. *Science* **278**, 474–476.
- Ashwell, K. W. S. and Hardman, C. D. (2012). Distinct development of the cerebral cortex in platypus and echidna. *Brain Behav. Evol.* **79**, 57–72.
- Awad, S., Al-Dosari, M. S., Al-Yacoub, N., Colak, D., Salih, M. A., Alkuraya, F. S. and Poizat, C. (2013). Mutation in PHC1 implicates chromatin remodeling in primary microcephaly pathogenesis. *Hum. Mol. Genet.* **22**, 2200–2213.
- Bakircioglu, M., Carvalho, O. P., Khurshid, M., Cox, J. J., Tuysuz, B., Barak, T., Yilmaz, S., Caglayan, O., Dincer, A., Nicholas, A. K. et al. (2011). The essential role of centrosomal NDE1 in human cerebral cortex neurogenesis. *Am. J. Hum. Genet.* **88**, 523–535.
- Bar, I., Lambert de Rouvroit, C. and Goffinet, A. M. (2000). The evolution of cortical development. An hypothesis based on the role of the Reelin signaling pathway. *Trends Neurosci.* **23**, 633–638.
- Barkovich, A. J., Guerrini, R., Kuzniecky, R. I., Jackson, G. D. and Dobyns, W. B. (2012). A developmental and genetic classification for malformations of cortical development: update 2012. *Brain* **135**, 1348–1369.
- Barnosky, A. D. and Hadly, E. A. (2016). *Tipping Point for Planet Earth: how Close are we to the Edge?* New York, NY: Thomas Dunne.
- Beltran-Valero de Bernabé, D., Currier, S., Steinbrecher, A., Celli, J., van Beusekom, E., van der Zwaag, B., Kayserili, H., Merlini, L., Chitayat, D., Dobyns, W. B. et al. (2002). Mutations in the O-mannosyltransferase gene POMT1 give rise to the severe neuronal migration disorder Walker-Warburg syndrome. *Am. J. Hum. Genet.* **71**, 1033–1043.
- Beltran-Valero de Bernabé, D., Voit, T., Longman, C., Steinbrecher, A., Straub, V., Yuva, Y., Herrmann, R., Sperner, J., Korenke, C., Diesen, C. et al. (2004). Mutations in the FKRP gene can cause muscle-eye-brain disease and Walker-Warburg syndrome. *J. Med. Genet.* **41**, e61.
- Benton, M. J. (2015a). *Vertebrate Paleontology*, 4th edn. Oxford: Wiley Blackwell.
- Benton, M. J. (2015b). *When Life Nearly Died: the Greatest Mass Extinction of All Time*, Rev. edn. New York: Thames & Hudson.
- Bernier, B., Bar, I., Pieau, C., Lambert de Rouvroit, C. and Goffinet, A. M. (1999). Reelin mRNA expression during embryonic brain development in the turtle *Emys orbicularis*. *J. Comp. Neurol.* **413**, 463–479.
- Bernier, B., Bar, I., D'Arcangelo, G., Curran, T. and Goffinet, A. M. (2000). Reelin mRNA expression during embryonic brain development in the chick. *J. Comp. Neurol.* **422**, 448–463.
- Betizeau, M., Cortay, V., Patti, D., Pfister, S., Gautier, E., Bellemain-Ménard, A., Afanassieff, M., Huissoud, C., Douglas, R. J., Kennedy, H. et al. (2013). Precursor diversity and complexity of lineage relationships in the outer subventricular zone of the primate. *Neuron* **80**, 442–457.
- Bielle, F., Griveau, A., Narboux-Néme, N., Vigneau, S., Sigrist, M., Arber, S., Wasif, M. and Pierani, A. (2005). Multiple origins of Cajal-Retzius cells at the borders of the developing pallium. *Nat. Neurosci.* **8**, 1002–1012.
- Bilsky, S. E., Satoh, T., Ueda, S., Wei, P., Kanemura, H., Aiba, A., Terashima, T. and Kataoka, T. (2009). Dorsal telencephalon-specific RA-GEF-1 knockout mice develop heterotopic cortical mass and commissural fiber defect. *Eur. J. Neurosci.* **29**, 1994–2008.
- Bininda-Emonds, O. R. P., Cardillo, M., Jones, K. E., MacPhee, R. D. E., Beck, R. M. D., Grenyer, R., Price, S. A., Vos, R. A., Gittleman, J. L. and Purvis, A. (2007). The delayed rise of present-day mammals. *Nature* **446**, 507–512.
- Bond, J., Roberts, E., Mochida, G. H., Hampshire, D. J., Scott, S., Askham, J. M., Springell, K., Mahadevan, M., Crow, Y. J., Markham, A. F. et al. (2002). ASPM is a major determinant of cerebral cortical size. *Nat. Genet.* **32**, 316–320.
- Bond, J., Scott, S., Hampshire, D. J., Springell, K., Corry, P., Abramowicz, M. J., Mochida, G. H., Hennekam, R. C. M., Maher, E. R., Fryns, J.-P. et al. (2003). Protein-truncating mutations in ASPM cause variable reduction in brain size. *Am. J. Hum. Genet.* **73**, 1170–1177.
- Bond, J., Roberts, E., Springell, K., Lizarraga, S. B., Scott, S., Higgins, J., Hampshire, D. J., Morrison, E. E., Leal, G. F., Silva, E. O. et al. (2005). A centrosomal mechanism involving CDK5RAP2 and CENPJ controls brain size. *Nat. Genet.* **37**, 353–355.
- Borrell, V. and Reillo, I. (2012). Emerging roles of neural stem cells in cerebral cortex development and evolution. *Dev. Neurobiol.* **72**, 955–971.
- Boucherie, C., Boutin, C., Jossin, Y., Schakman, O., Goffinet, A. M., Ris, L., Gaill, P. and Tissir, F. (2017). Neural progenitor fate decision defects, cortical hypoplasia, and behavioral impairment in Celsr1-deficient mice. *Mol. Psychiatry* (in press).
- Breuss, M., Heng, J. I.-T., Poirier, K., Tian, G., Jaglin, X. H., Qu, Z., Braun, A., Gstrein, T., Ngo, L., Haas, M. et al. (2012). Mutations in the beta-tubulin gene TUBB5 cause microcephaly with structural brain abnormalities. *Cell Rep.* **2**, 1554–1562.
- Brusatte, S. L., O'Connor, J. K. and Jarvis, E. D. (2015). The origin and diversification of birds. *Curr. Biol.* **25**, R888–R898.
- Bulfone, A., Martinez, S., Marigo, V., Campanella, M., Basile, A., Quaderi, N., Gattuso, C., Rubenstein, J. L. R. and Ballabio, A. (1999). Expression pattern of the Tbr2 (Eomesodermin) gene during mouse and chick brain development. *Mech. Dev.* **84**, 133–138.
- Butler, A. B. and Hodos, W. (2005). *Comparative Vertebrate Neuroanatomy: Evolution and Adaptation*, 2nd edn. Hoboken, NJ: Wiley-Interscience.
- Butler, A. B., Reiner, A. and Karten, H. J. (2011). Evolution of the amniote pallium and the origins of mammalian neocortex. *Ann. N. Y. Acad. Sci.* **1225**, 14–27.
- Buisse, K., Riemersma, M., Powell, G., van Reeuwijk, J., Chitayat, D., Roscioli, T., Kamsteeg, E.-J., van den Elzen, C., van Beusekom, E., Blaser, S. et al. (2013). Missense mutations in beta-1,3-N-acetylgalactosaminyltransferase 1 (B3GNT1) cause Walker-Warburg syndrome. *Hum. Mol. Genet.* **22**, 1746–1754.
- Cappello, S., Böhringer, C. R. J., Bergami, M., Conzelmann, K.-K., Ghanem, A., Tomassy, G. S., Arlotta, P., Mainardi, M., Allegro, M., Caleo, M. et al. (2012). A radial glia-specific role of RhoA in double cortex formation. *Neuron* **73**, 911–924.
- Carroll, R. L. (1988). *Vertebrate Paleontology and Evolution*. New York, N.Y.: Freeman.
- Cars, K. J., Stevens, E., Foley, A. R., Cirak, S., Riemersma, M., Torelli, S., Hoischen, A., Willer, T., van Scherpenzeel, M., Moore, S. A. et al. (2013). Mutations in GDP-mannose pyrophosphorylase B cause congenital and limb-girdle muscular dystrophies associated with hypoglycosylation of alpha-dystroglycan. *Am. J. Hum. Genet.* **93**, 29–41.
- Chenn, A. and Walsh, C. A. (2002). Regulation of cerebral cortical size by control of cell cycle exit in neural precursors. *Science* **297**, 365–369.
- Cheung, A. F. P., Pollen, A. A., Tavare, A., DeProto, J. and Molnár, Z. (2007). Comparative aspects of cortical neurogenesis in vertebrates. *J. Anat.* **211**, 164–176.
- Chinsamy-Turan, A. (2012). *Forerunners of Mammals: Radiation, Histology, Biology*. Bloomington: Indiana University Press.
- Choe, Y., Siegenthaler, J. A. and Pleasure, S. J. (2012). A cascade of morphogenic signaling initiated by the meninges controls corpus callosum formation. *Neuron* **73**, 698–712.
- Cobos, I., Puelles, L. and Martínez, S. (2001). The avian telencephalic subpallium originates inhibitory neurons that invade tangentially the pallium (dorsal ventricular ridge and cortical areas). *Dev. Biol.* **239**, 30–45.
- Colbert, E. H., Minkoff, E. C., Morales, M. and Colbert, E. H. (2001). *Colbert's Evolution of the Vertebrates: a History of the Backboned Animals Through Time*, 5th edn. New York: Wiley.
- Conti, V., Carabalona, A., Pallesi-Pocachard, E., Parrini, E., Leventer, R. J., Buhler, E., McGillivray, G., Michel, F. J., Striano, P., Mei, D. et al. (2013). Periventricular heterotopia in 6q terminal deletion syndrome: role of the C6orf70 gene. *Brain* **136**, 3378–3394.
- Corbo, J. C., Duewel, T. A., Long, J. M., LaPorte, P., Tsai, E., Wynshaw-Boris, A. and Walsh, C. A. (2002). Doublecortin is required in mice for lamination of the hippocampus but not the neocortex. *J. Neurosci.* **22**, 7548–7557.
- Cushion, T. D., Paciorkowski, A. R., Pilz, D. T., Mullins, J. G. L., Seltzer, L. E., Marion, R. W., Tuttle, E., Ghoneim, D., Christian, S. L., Chung, S.-K. et al. (2014). De novo mutations in the beta-tubulin gene TUBB2A cause simplified gyral patterning and infantile-onset epilepsy. *Am. J. Hum. Genet.* **94**, 634–641.
- D'Arcangelo, G., Miao, G. G., Chen, S.-C., Soares, H. D., Morgan, J. I. and Curran, T. (1995). A protein related to extracellular matrix proteins deleted in the mouse mutant reeler. *Nature* **374**, 719–723.
- Dauber, A., LaFranchi, S. H., Maliga, Z., Lui, J. C., Moon, J. E., McDeed, C., Henke, K., Zonana, J., Kingman, G. A., Pers, T. H. et al. (2012). Novel microcephalic primordial dwarfism disorder associated with variants in the centrosomal protein ninein. *J. Clin. Endocrinol. Metab.* **97**, E2140–E2151.
- De Juan Romero, C. and Borrell, V. (2015). Coevolution of radial glial cells and the cerebral cortex. *Glia* **63**, 1303–1319.
- Del Toro, D., Ruff, T., Cederfjall, E., Villalba, A., Seyit-Bremer, G., Borrell, V. and Klein, R. (2017). Regulation of cerebral cortex folding by controlling neuronal migration via FLRT adhesion molecules. *Cell* **169**, 621–635.e16.

- de Pontual, L., Yao, E., Callier, P., Faivre, L., Drouin, V., Cariou, S., Van Haeringen, A., Geneviève, D., Goldenberg, A., Oufadem, M. et al. (2011). Germline deletion of the miR-17 approximately 92 cluster causes skeletal and growth defects in humans. *Nat. Genet.* **43**, 1026-1030.
- des Portes, V., Pinard, J. M., Billuart, P., Vinet, M. C., Koulakoff, A., Carrié, A., Gelot, A., Dupuis, E., Motte, J., Berwald-Netter, Y. et al. (1998). A novel CNS gene required for neuronal migration and involved in X-linked subcortical laminar heterotopia and lissencephaly syndrome. *Cell* **92**, 51-61.
- Deuel, T. A. S., Liu, J. S., Corbo, J. C., Yoo, S.-Y., Rorke-Adams, L. B. and Walsh, C. A. (2006). Genetic interactions between doublecortin and doublecortin-like kinase in neuronal migration and axon outgrowth. *Neuron* **49**, 41-53.
- Di Costanzo, S., Balasubramanian, A., Pond, H. L., Rozkalne, A., Pantaleoni, C., Saredi, S., Gupta, V. A., Sunu, C. M., Yu, T. W., Kang, P. B. et al. (2014). POMK mutations disrupt muscle development leading to a spectrum of neuromuscular presentations. *Hum. Mol. Genet.* **23**, 5781-5792.
- Di Cunto, F., Imarisio, S., Hirsch, E., Broccoli, V., Bulfone, A., Migheli, A., Atzori, C., Turco, E., Triolo, R., Dotto, G. P. et al. (2000). Defective neurogenesis in citron kinase knockout mice by altered cytokinesis and massive apoptosis. *Neuron* **28**, 115-127.
- dos Reis, M., Inoue, J., Hasegawa, M., Asher, R. J., Donoghue, P. C. J. and Yang, Z. (2012). Phylogenomic datasets provide both precision and accuracy in estimating the timescale of placental mammal phylogeny. *Proc. Biol. Sci.* **279**, 3491-3500.
- Dugas-Ford, J., Rowell, J. J. and Ragsdale, C. W. (2012). Cell-type homologies and the origins of the neocortex. *Proc. Natl. Acad. Sci. USA* **109**, 16974-16979.
- Edery, P., Marcaillou, C., Sahbatou, M., Labalme, A., Chastang, J., Touraine, R., Tubacher, E., Senni, F., Bober, M. B., Nampoothiri, S. et al. (2011). Association of TALS developmental disorder with defect in minor splicing component U4atac snRNA. *Science* **332**, 240-243.
- Englund, C., Fink, A., Lau, C., Pham, D., Daza, R. A., Bulfone, A., Kowalczyk, T. and Hevner, R. F. (2005). Pax6, Tbr2, and Tbr1 are expressed sequentially by radial glia, intermediate progenitor cells, and postmitotic neurons in developing neocortex. *J. Neurosci.* **25**, 247-251.
- Ercan-Sencicek, A. G., Jambi, S., Franjic, D., Nishimura, S., Li, M., El-Fishawy, P., Morgan, T. M., Sanders, S. J., Bilguvar, K., Suri, M. et al. (2015). Homozygous loss of DIAPH1 is a novel cause of microcephaly in humans. *Eur. J. Hum. Genet.* **23**, 165-172.
- Faisst, A. M., Alvarez-Bolado, G., Treichel, D. and Gruss, P. (2002). Rotatin is a novel gene required for axial rotation and left-right specification in mouse embryos. *Mech. Dev.* **113**, 15-28.
- Feng, Y. and Walsh, C. A. (2004). Mitotic spindle regulation by Nde1 controls cerebral cortical size. *Neuron* **44**, 279-293.
- Fernandez, A. S., Pieau, C., Repérant, J., Boncinelli, E. and Wasif, M. (1998). Expression of the Emx-1 and Dlx-1 homeobox genes define three molecularly distinct domains in the telencephalon of mouse, chick, turtle and frog embryos: implications for the evolution of telencephalic subdivisions in amniotes. *Development* **125**, 2099-2111.
- Fernández, V., Llinás-Benadero, C. and Borrell, V. (2016). Cerebral cortex expansion and folding: what have we learned? *EMBO J.* **35**, 1021-1044.
- Ferner, K. and Mess, A. (2011). Evolution and development of fetal membranes and placentation in amniote vertebrates. *Respir. Physiol. Neurobiol.* **178**, 39-50.
- Fietz, S. A., Kelava, I., Vogt, J., Wilsch-Bräuninger, M., Stenzel, D., Fish, J. L., Corbeil, D., Riehn, A., Distler, W., Nitsch, R. et al. (2010). OSVZ progenitors of human and ferret neocortex are epithelial-like and expand by integrin signaling. *Nat. Neurosci.* **13**, 690-699.
- Florio, M. and Huttner, W. B. (2014). Neural progenitors, neurogenesis and the evolution of the neocortex. *Development* **141**, 2182-2194.
- Florio, M., Albert, M., Taverna, E., Namba, T., Brandl, H., Lewitus, E., Haffner, C., Sykes, A., Wong, F. K., Peters, J. et al. (2015). Human-specific gene ARHGAP11B promotes basal progenitor amplification and neocortex expansion. *Science* **347**, 1465-1470.
- Fox, J. W., Lamperti, E. D., Ekşioğlu, Y. Z., Hong, S. E., Feng, Y., Graham, D. A., Scheffer, I. E., Dobyns, W. B., Hirsch, B. A., Radtke, R. A. et al. (1998). Mutations in filamin 1 prevent migration of cerebral cortical neurons in human periventricular heterotopia. *Neuron* **21**, 1315-1325.
- Friede, R. L. (1989). *Developmental Neuropathology* (2nd rev. and expanded edn). Berlin; New York: Springer-Verlag.
- Fujimori, A., Itoh, K., Goto, S., Hirakawa, H., Wang, B., Kokubo, T., Kito, S., Tsukamoto, S. and Fushiki, S. (2014). Disruption of Aspm causes microcephaly with abnormal neuronal differentiation. *Brain Dev.* **36**, 661-669.
- Garcia-Moreno, F., Vasistha, N. A., Trevia, N., Bourne, J. A. and Molnár, Z. (2012). Compartmentalization of cerebral cortical germinal zones in a lissencephalic primate and gyrencephalic rodent. *Cereb. Cortex* **22**, 482-492.
- Garcia-Verdugo, J. M., Ferrón, S., Flames, N., Collado, L., Desfilis, E. and Font, E. (2002). The proliferative ventricular zone in adult vertebrates: a comparative study using reptiles, birds, and mammals. *Brain Res. Bull.* **57**, 765-775.
- Gaspard, N., Bouschet, T., Hourez, R., Dimidschstein, J., Naeije, G., van den Aemele, J., Espuny-Camacho, I., Herpoel, A., Passante, L., Schiffmann, S. N. et al. (2008). An intrinsic mechanism of corticogenesis from embryonic stem cells. *Nature* **455**, 351-357.
- Geis, T., Marquard, K., Rödl, T., Reihle, C., Schirmer, S., von Kalle, T., Bornemann, A., Hehr, U. and Blankenburg, M. (2013). Homozygous dystroglycan mutation associated with a novel muscle-eye-brain disease-like phenotype with multicystic leucodystrophy. *Neurogenetics* **14**, 205-213.
- Genin, A., Desir, J., Lambert, N., Biervliet, M., Van Der Aa, N., Pierquin, G., Killian, A., Tosi, M., Urbina, M., Lefort, A. et al. (2012). Kinetochore KMN network gene CASC5 mutated in primary microcephaly. *Hum. Mol. Genet.* **21**, 5306-5317.
- Gerkema, M. P., Davies, W. I. L., Foster, R. G., Menaker, M. and Hut, R. A. (2013). The nocturnal bottleneck and the evolution of activity patterns in mammals. *Proc. Biol. Sci.* **280**, 20130508.
- Gilmore, E. C., Ohshima, T., Goffinet, A. M., Kulkarni, A. B. and Herrup, K. (1998). Cyclin-dependent kinase 5-deficient mice demonstrate novel developmental arrest in cerebral cortex. *J. Neurosci.* **18**, 6370-6377.
- Gil-Sanz, C., Landeira, B., Ramos, C., Costa, M. R. and Müller, U. (2014). Proliferative defects and formation of a double cortex in mice lacking Mlt4 and Cdh2 in the dorsal telencephalon. *J. Neurosci.* **34**, 10475-10487.
- Gleeson, J. G., Allen, K. M., Fox, J. W., Lamperti, E. D., Berkovic, S., Scheffer, I., Cooper, E. C., Dobyns, W. B., Minnerath, S. R., Ross, M. E. et al. (1998). Doublecortin, a brain-specific gene mutated in human X-linked lissencephaly and double cortex syndrome, encodes a putative signaling protein. *Cell* **92**, 63-72.
- Goffinet, A. M. (1983). The embryonic development of the cortical plate in reptiles: a comparative study in *Emys orbicularis* and *Lacerta agilis*. *J. Comp. Neurol.* **215**, 437-452.
- Goffinet, A. M., Daumerie, C., Langerwerf, B. and Pieau, C. (1986). Neurogenesis in reptilian cortical structures: 3H-thymidine autoradiographic analysis. *J. Comp. Neurol.* **243**, 106-116.
- Goffinet, A. M., Bar, I., Bernier, B., Trujillo, C., Raynaud, A. and Meyer, G. (1999). Reelin expression during embryonic brain development in lacertilian lizards. *J. Comp. Neurol.* **414**, 533-550.
- Goldberg, J. S. and Hirschi, K. K. (2009). Diverse roles of the vasculature within the neural stem cell niche. *Regen. Med.* **4**, 879-897.
- Gruber, R., Zhou, Z., Sukchev, M., Joerss, T., Frappart, P.-O. and Wang, Z.-Q. (2011). MCPH1 regulates the neuroprogenitor division mode by coupling the centrosomal cycle with mitotic entry through the Chk1-Cdc25 pathway. *Nat. Cell Biol.* **13**, 1325-1334.
- Guemez-Gamboa, A., Nguyen, L. N., Yang, H., Zaki, M. S., Kara, M., Ben-Omran, T., Akizu, N., Rosti, R. O., Rosti, B., Scott, E. et al. (2015). Inactivating mutations in MFS2D2A, required for omega-3 fatty acid transport in brain, cause a lethal microcephaly syndrome. *Nat. Genet.* **47**, 809-813.
- Guernsey, D. L., Jiang, H., Hussin, J., Arnold, M., Bouyakdan, K., Perry, S., Babineau-Sturk, T., Beis, J., Dumas, N., Evans, S. C. et al. (2010). Mutations in centrosomal protein CEP152 in primary microcephaly families linked to MCPH4. *Am. J. Hum. Genet.* **87**, 40-51.
- Han, Y.-G. and Alvarez-Buylla, A. (2010). Role of primary cilia in brain development and cancer. *Curr. Opin. Neurobiol.* **20**, 58-67.
- Hansen, D. V., Lui, J. H., Parker, P. R. L. and Kriegstein, A. R. (2010). Neurogenic radial glia in the outer subventricular zone of human neocortex. *Nature* **464**, 554-561.
- Harding, B. N., Moccia, A., Drunat, S., Soukarieh, O., Tubeuf, H., Chitty, L. S., Verloes, A., Gressens, P., El Ghouzzi, V., Joriot, S. et al. (2016). Mutations in citron kinase cause recessive microlissencephaly with multinucleated neurons. *Am. J. Hum. Genet.* **99**, 511-520.
- Hartmann, D., De Strooper, B. and Saftig, P. (1999). Presenilin-1 deficiency leads to loss of Cajal-Retzius neurons and cortical dysplasia similar to human type 2 lissencephaly. *Curr. Biol.* **9**, 719-727.
- Haubst, N., Georges-Labouesse, E., De Arcangelis, A., Mayer, U. and Gotz, M. (2006). Basement membrane attachment is dispensable for radial glial cell fate and for proliferation, but affects positioning of neuronal subtypes. *Development* **133**, 3245-3254.
- He, H., Liyanarachchi, S., Akagi, K., Nagy, R., Li, J., Dietrich, R. C., Li, W., Sebastian, N., Wen, B., Xin, B. et al. (2011). Mutations in U4atac snRNA, a component of the minor spliceosome, in the developmental disorder MOPD I. *Science* **332**, 238-240.
- Hedges, S. B. and Poling, L. L. (1999). A molecular phylogeny of reptiles. *Science* **283**, 998-1001.
- Herrick, C. J. (1948). *The Brain of the Tiger Salamander, Ambystoma Tigrinum*. Chicago, USA: University of Chicago Press.
- Higginbotham, H., Guo, J., Yokota, Y., Umberger, N. L., Su, C.-Y., Li, J., Verma, N., Hirt, J., Ghukasyan, V., Caspary, T. et al. (2013). Arl13b-regulated cilia activities are essential for polarized radial glial scaffold formation. *Nat. Neurosci.* **16**, 1000-1007.
- Hirotsume, S., Fleck, M. W., Gambello, M. J., Bix, G. J., Chen, A., Clark, G. D., Ledbetter, D. H., McBain, C. J. and Wynshaw-Boris, A. (1998). Graded reduction of Pafah1b1 (Lis1) activity results in neuronal migration defects and early embryonic lethality. *Nat. Genet.* **19**, 333-339.
- Hoerder-Suabedissen, A. and Molnár, Z. (2015). Development, evolution and pathology of neocortical subplate neurons. *Nat. Rev. Neurosci.* **16**, 133-146.

- Homma, N., Takei, Y., Tanaka, Y., Nakata, T., Terada, S., Kikkawa, M., Noda, Y. and Hirokawa, N.** (2003). Kinesin superfamily protein 2A (KIF2A) functions in suppression of collateral branch extension. *Cell* **114**, 229–239.
- Hong, S. E., Shugart, Y. Y., Huang, D. T., Shahwan, S. A., Grant, P. E., Hourihane, J. O. B., Martin, N. D. T. and Walsh, C. A.** (2000). Autosomal recessive lissencephaly with cerebellar hypoplasia is associated with human RELN mutations. *Nat. Genet.* **26**, 93–96.
- Hu, W. F., Pomp, O., Ben-Omran, T., Kodani, A., Henke, K., Mochida, G. H., Yu, T. W., Woodworth, M. B., Bonnard, C., Raj, G. S. et al.** (2014). Katanin p80 regulates human cortical development by limiting centriole and cilia number. *Neuron* **84**, 1240–1257.
- Hussain, M. S., Baig, S. M., Neumann, S., Nürnberg, G., Farooq, M., Ahmad, I., Alef, T., Hennies, H. C., Technau, M., Altmüller, J. et al.** (2012). A truncating mutation of CEP135 causes primary microcephaly and disturbed centrosomal function. *Am. J. Hum. Genet.* **90**, 871–878.
- Hussain, M. S., Baig, S. M., Neumann, S., Peche, V. S., Szczepanski, S., Nürnberg, G., Tariq, M., Jameel, M., Khan, T. N., Fatima, A. et al.** (2013). CDK6 associates with the centrosome during mitosis and is mutated in a large Pakistani family with primary microcephaly. *Hum. Mol. Genet.* **22**, 5199–5214.
- Insolera, R., Bazzi, H., Shao, W., Anderson, K. V. and Shi, S.-H.** (2014). Cortical neurogenesis in the absence of centrioles. *Nat. Neurosci.* **17**, 1528–1535.
- Jackson, A. P., Eastwood, H., Bell, S. M., Adu, J., Toomes, C., Carr, I. M., Roberts, E., Hampshire, D. J., Crow, Y. J., Mighell, A. J. et al.** (2002). Identification of microcephalin, a protein implicated in determining the size of the human brain. *Am. J. Hum. Genet.* **71**, 136–142.
- Jayaraman, D., Kodani, A., Gonzalez, D. M., Mancias, J. D., Mochida, G. H., Vagnoni, C., Johnson, J., Krogan, N., Harper, J. W., Reiter, J. F. et al.** (2016). Microcephaly proteins Wdr62 and Aspm define a mother centriole complex regulating centriole biogenesis, apical complex, and cell fate. *Neuron* **92**, 813–828.
- Jossin, Y., Lee, M., Klezovitch, O., Kon, E., Cossard, A., Lien, W. H., Fernandez, T. E., Cooper, J. A. and Vasioukhin, V.** (2017). Lgl1 connects cell polarity with cell-cell adhesion in embryonic neural stem cells. *Dev. Cell* **41**, 481–495 e485.
- Kanai, Y., Okada, Y., Tanaka, Y., Harada, A., Terada, S. and Hirokawa, N.** (2000). KIF5C, a novel neuronal kinesin enriched in motor neurons. *J. Neurosci.* **20**, 6374–6384.
- Kang, W., Wong, L. C., Shi, S.-H. and Hebert, J. M.** (2009). The transition from radial glial to intermediate progenitor cell is inhibited by FGF signaling during corticogenesis. *J. Neurosci.* **29**, 14571–14580.
- Keays, D. A., Tian, G., Poirier, K., Huang, G.-J., Siebold, C., Cleak, J., Oliver, P. L., Fray, M., Harvey, R. J., Molnár, Z. et al.** (2007). Mutations in alpha-tubulin cause abnormal neuronal migration in mice and lissencephaly in humans. *Cell* **128**, 45–57.
- Kelava, I., Reillo, I., Murayama, A. Y., Kalinka, A. T., Stenzel, D., Tomancak, P., Matsuzaki, F., Lebrand, C., Sasaki, E., Schwamborn, J. C. et al.** (2012). Abundant occurrence of basal radial glia in the subventricular zone of embryonic neocortex of a lissencephalic primate, the common marmoset Callithrix jacchus. *Cereb. Cortex* **22**, 469–481.
- Kemp, T. S.** (2006). The origin and early radiation of the therapsid mammal-like reptiles: a palaeobiological hypothesis. *J. Evol. Biol.* **19**, 1231–1247.
- Khan, M. A., Rupp, V. M., Orpinell, M., Hussain, M. S., Altmüller, J., Steinmetz, M. O., Enzinger, C., Thiele, H., Höhne, W., Nürnberg, G. et al.** (2014). A missense mutation in the PISA domain of HsSAS-6 causes autosomal recessive primary microcephaly in a large consanguineous Pakistani family. *Hum. Mol. Genet.* **23**, 5940–5949.
- Kielar, M., Tuy, F. P. D., Bizzotto, S., Lebrand, C., de Juan Romero, C., Poirier, K., Oegema, R., Mancini, G. M., Bahi-Buisson, N., Olaso, R. et al.** (2014). Mutations in Emr1 lead to ectopic progenitors and neuronal heterotopia in mouse and human. *Nat. Neurosci.* **17**, 923–933.
- Kim, W.-Y., Wang, X., Wu, Y., Doble, B. W., Patel, S., Woodgett, J. R. and Snider, W. D.** (2009). GSK-3 is a master regulator of neural progenitor homeostasis. *Nat. Neurosci.* **12**, 1390–1397.
- Kitamura, K., Yanazawa, M., Sugiyama, N., Miura, H., Iizuka-Kogo, A., Kusaka, M., Omichi, K., Suzuki, R., Kato-Fukui, Y., Kamiyama, K. et al.** (2002). Mutation of ARX causes abnormal development of forebrain and testes in mice and X-linked lissencephaly with abnormal genitalia in humans. *Nat. Genet.* **32**, 359–369.
- Kobayashi, S.-i., Nakahori, Y., Miyake, M., Matsumura, K., Kondo-Iida, E., Nomura, Y., Segawa, M., Yoshioka, M., Saito, K., Osawa, M. et al.** (1998). An ancient retrotransposon insertion causes Fukuyama-type congenital muscular dystrophy. *Nature* **394**, 388–392.
- Kodani, A., Yu, T. W., Johnson, J. R., Jayaraman, D., Johnson, T. L., Al-Gazali, L., Sztriha, L., Partlow, J. N., Kim, H., Krup, A. L. et al.** (2015). Centriolar satellites assemble centrosomal microcephaly proteins to recruit CDK2 and promote centriole duplication. *Elife* **4**, e07519.
- Kou, Z., Wu, Q., Kou, X., Yin, C., Wang, H., Zuo, Z., Zhuo, Y., Chen, A., Gao, S. and Wang, X.** (2015). CRISPR/Cas9-mediated genome engineering of the ferret. *Cell Res.* **25**, 1372–1375.
- Kowalczyk, T., Pontious, A., Englund, C., Daza, R. A. M., Bedogni, F., Hodge, R., Attardo, A., Bell, C., Huttner, W. B. and Hevner, R. F.** (2009). Intermediate neuronal progenitors (basal progenitors) produce pyramidal-projection neurons for all layers of cerebral cortex. *Cereb. Cortex* **19**, 2439–2450.
- Kuida, K., Haydar, T. F., Kuan, C.-Y., Gu, Y., Taya, C., Karasuyama, H., Su, M. S.-S., Rakic, P. and Flavell, R. A.** (1998). Reduced apoptosis and cytochrome c-mediated caspase activation in mice lacking caspase 9. *Cell* **94**, 325–337.
- Kumar, A., Girimaji, S. C., Duvvari, M. R. and Blanton, S. H.** (2009). Mutations in STIL, encoding a pericentriolar and centrosomal protein, cause primary microcephaly. *Am. J. Hum. Genet.* **84**, 286–290.
- Laberge, F. and Roth, G.** (2007). Organization of the sensory input to the telencephalon in the fire-bellied toad, Bombina orientalis. *J. Comp. Neurol.* **502**, 55–74.
- Lambert de Rouvroit, C. and Goffinet, A. M.** (2001). Neuronal migration. *Mech. Dev.* **105**, 47–56.
- LaMonica, B. E., Lui, J. H., Wang, X. and Kriegstein, A. R.** (2012). OSVZ progenitors in the human cortex: an updated perspective on neurodevelopmental disease. *Curr. Opin. Neurobiol.* **22**, 747–753.
- Lange, C., Turrero Garcia, M., Decimo, I., Bifari, F., Eelen, G., Quaegebeur, A., Boon, R., Zhao, H., Boeckx, B., Chang, J. et al.** (2016). Relief of hypoxia by angiogenesis promotes neural stem cell differentiation by targeting glycolysis. *EMBO J.* **35**, 924–941.
- Lavdas, A. A., Grigoriou, M., Pachnis, V. and Parnavelas, J. G.** (1999). The medial ganglionic eminence gives rise to a population of early neurons in the developing cerebral cortex. *J. Neurosci.* **19**, 7881–7888.
- Lee, Y., Shull, E. R. P., Frappart, P.-O., Katyal, S., Enriquez-Rios, V., Zhao, J., Russell, H. R., Brown, E. J. and McKinnon, P. J.** (2012). ATR maintains select progenitors during nervous system development. *EMBO J.* **31**, 1177–1189.
- Lehtinen, M. K. and Walsh, C. A.** (2011). Neurogenesis at the brain-cerebrospinal fluid interface. *Annu. Rev. Cell Dev. Biol.* **27**, 653–679.
- Lehtinen, M. K., Zappaterra, M. W., Chen, X., Yang, Y. J., Hill, A. D., Lun, M., Maynard, T., Gonzalez, D., Kim, S., Ye, P. et al.** (2011). The cerebrospinal fluid provides a proliferative niche for neural progenitor cells. *Neuron* **69**, 893–905.
- Lein, E. S., Belgard, T. G., Hawrylycz, M. and Molnár, Z.** (2017). Transcriptomic perspectives on neocortical structure, development, evolution, and disease. *Annu. Rev. Neurosci.* **40**, 629–652.
- Lewitus, E., Kelava, I., Kalinka, A. T., Tomancak, P. and Huttner, W. B.** (2014). An adaptive threshold in mammalian neocortical evolution. *PLoS Biol.* **12**, e1002000.
- Li, H., Bielas, S. L., Zaki, M. S., Ismail, S., Farfara, D., Um, K., Rosti, R. O., Scott, E. C., Tu, S., Chi, N. C. et al.** (2016). Biallelic mutations in citron kinase link mitotic cytokinesis to human primary microcephaly. *Am. J. Hum. Genet.* **99**, 501–510.
- Lui, J. H., Hansen, D. V. and Kriegstein, A. R.** (2011). Development and evolution of the human neocortex. *Cell* **146**, 18–36.
- Magen, D., Ofir, A., Berger, L., Goldsher, D., Eran, A., Katib, N., Nijem, Y., Vladavsky, E., Tzur, S., Behar, D. M. et al.** (2015). Autosomal recessive lissencephaly with cerebellar hypoplasia is associated with a loss-of-function mutation in CDK5. *Hum. Genet.* **134**, 305–314.
- Manzini, M. C. and Walsh, C. A.** (2011). What disorders of cortical development tell us about the cortex: one plus one does not always make two. *Curr. Opin. Genet. Dev.* **21**, 333–339.
- Manzini, M. C., Tambunan, D. E., Hill, R. S., Yu, T. W., Maynard, T. M., Heinzen, E. L., Shianna, K. V., Stevens, C. R., Partlow, J. N., Barry, B. J. et al.** (2012). Exome sequencing and functional validation in zebrafish identify GTDC2 mutations as a cause of Walker-Warburg syndrome. *Am. J. Hum. Genet.* **91**, 541–547.
- Marchetti, G., Escuin, S., van der Flier, A., De Arcangelis, A., Hynes, R. O. and Georges-Labouesse, E.** (2010). Integrin alpha5beta1 is necessary for regulation of radial migration of cortical neurons during mouse brain development. *Eur. J. Neurosci.* **31**, 399–409.
- Martin, C.-A., Ahmad, I., Klingseisen, A., Hussain, M. S., Bicknell, L. S., Leitch, A., Nürnberg, G., Toliat, M. R., Murray, J. E., Hunt, D. et al.** (2014). Mutations in PLK4, encoding a master regulator of centriole biogenesis, cause microcephaly, growth failure and retinopathy. *Nat. Genet.* **46**, 1283–1292.
- Martínez-Cerdeñá, V., Cunningham, C. L., Camacho, J., Keiter, J. A., Ariza, J., Lovern, M. and Noctor, S. C.** (2016). Evolutionary origin of Tbr2-expressing precursor cells and the subventricular zone in the developing cortex. *J. Comp. Neurol.* **524**, 433–447.
- Medina, L. and Abellán, A.** (2009). Development and evolution of the pallium. *Semin. Cell Dev. Biol.* **20**, 698–711.
- Métin, C., Baudois, J. P., Rakic, S. and Parnavelas, J. G.** (2006). Cell and molecular mechanisms involved in the migration of cortical interneurons. *Eur. J. Neurosci.* **23**, 894–900.
- Métin, C., Alvarez, C., Moudoux, D., Vitalis, T., Pieau, C. and Molnár, Z.** (2007). Conserved pattern of tangential neuronal migration during forebrain development. *Development* **134**, 2815–2827.
- Meyer, G. and Goffinet, A. M.** (1998). Prenatal development of reelin-immunoreactive neurons in the human neocortex. *J. Comp. Neurol.* **397**, 29–40.
- Meyer, G., Goffinet, A. M. and Fairén, A.** (1999). What is a Cajal-Retzius cell? A reassessment of a classical cell type based on recent observations in the developing neocortex. *Cereb. Cortex* **9**, 765–775.
- Meyer, G., Schaaps, J. P., Moreau, L. and Goffinet, A. M.** (2000). Embryonic and early fetal development of the human neocortex. *J. Neurosci.* **20**, 1858–1868.

- Michele, D. E., Barresi, R., Kanagawa, M., Saito, F., Cohn, R. D., Satz, J. S., Dollar, J., Nishino, I., Kelley, R. I., Somer, H. et al.** (2002). Post-translational disruption of dystroglycan-ligand interactions in congenital muscular dystrophies. *Nature* **418**, 417–422.
- Ming, G.-L. and Song, H.** (2011). Adult neurogenesis in the mammalian brain: significant answers and significant questions. *Neuron* **70**, 687–702.
- Mirzaa, G. M., Vitre, B., Carpenter, G., Abramowicz, I., Gleeson, J. G., Paciorkowski, A. R., Cleveland, D. W., Dobyns, W. B. and O'Driscoll, M.** (2014). Mutations in CENPE define a novel kinetochore-centromeric mechanism for microcephalic primordial dwarfism. *Hum. Genet.* **133**, 1023–1039.
- Mirzadeh, Z., Merkle, F. T., Soriano-Navarro, M., Garcia-Verdugo, J. M. and Alvarez-Buylla, A.** (2008). Neural stem cells confer unique pinwheel architecture to the ventricular surface in neurogenic regions of the adult brain. *Cell Stem Cell* **3**, 265–278.
- Mishra-Gorur, K., Çağlayan, A. O., Schaffer, A. E., Chabu, C., Henegariu, O., Vonhoff, F., Akgümüş, G. T., Nishimura, S., Han, W., Tu, S. et al.** (2014). Mutations in KATNB1 cause complex cerebral malformations by disrupting asymmetrically dividing neural progenitors. *Neuron* **84**, 1226–1239.
- Miyata, T., Okamoto, M., Shinoda, T. and Kawaguchi, A.** (2014). Interkinetic nuclear migration generates and opposes ventricular-zone crowding: insight into tissue mechanics. *Front. Cell Neurosci.* **8**, 473.
- Molnár, Z. and Clowry, G.** (2012). Cerebral cortical development in rodents and primates. *Prog. Brain Res.* **195**, 45–70.
- Montiel, J. F. and Aboitiz, F.** (2015). Pallial patterning and the origin of the isocortex. *Front. Neurosci.* **9**, 377.
- Montiel, J. F. and Molnár, Z.** (2013). The impact of gene expression analysis on evolving views of avian brain organization. *J. Comp. Neurol.* **521**, 3604–3613.
- Montiel, J. F., Vasistha, N. A., Garcia-Moreno, F. and Molnár, Z.** (2016). From sauropsids to mammals and back: New approaches to comparative cortical development. *J. Comp. Neurol.* **524**, 630–645.
- Morris, N. R., Efimov, V. P. and Xiang, X.** (1998). Nuclear migration, nucleokinesis and lissencephaly. *Trends Cell Biol.* **8**, 467–470.
- Mota, B. and Herculano-Houzel, S.** (2015). BRAIN STRUCTURE. Cortical folding scales universally with surface area and thickness, not number of neurons. *Science* **349**, 74–77.
- Muñoz-Sanjuán, I. and Brivanlou, A. H.** (2002). Neural induction, the default model and embryonic stem cells. *Nat. Rev. Neurosci.* **3**, 271–280.
- Myshrrall, T. D., Moore, S. A., Ostendorf, A. P., Satz, J. S., Kowalczyk, T., Nguyen, H., Daza, R. A. M., Lau, C., Campbell, K. P. and Hevner, R. F.** (2012). Dystroglycan on radial glia end feet is required for pial basement membrane integrity and columnar organization of the developing cerebral cortex. *J. Neuropathol. Exp. Neurol.* **71**, 1047–1063.
- Nicholas, A. K., Khurshid, M., Désir, J., Carvalho, O. P., Cox, J. J., Thornton, G., Kausar, R., Ansar, M., Ahmad, W., Verloes, A. et al.** (2010). WDR62 is associated with the spindle pole and is mutated in human microcephaly. *Nat. Genet.* **42**, 1010–1014.
- Niu, Y., Shen, B., Cui, Y., Chen, Y., Wang, J., Wang, L., Kang, Y., Zhao, X., Si, W., Li, W. et al.** (2014). Generation of gene-modified cynomolgus monkey via Cas9/RNA-mediated gene targeting in one-cell embryos. *Cell* **156**, 836–843.
- Nomura, T., Takahashi, M., Hara, Y. and Osumi, N.** (2008). Patterns of neurogenesis and amplitude of Reelin expression are essential for making a mammalian-type cortex. *PLoS ONE* **3**, e1454.
- Nomura, T., Gotoh, H. and Ono, K.** (2013). Changes in the regulation of cortical neurogenesis contribute to encephalization during amniote brain evolution. *Nat. Commun.* **4**, 2206.
- Nonaka-Kinoshita, M., Reillo, I., Artegiani, B., Martínez-Martínez, M. Á., Nelson, M., Borrell, V. and Calegari, F.** (2013). Regulation of cerebral cortex size and folding by expansion of basal progenitors. *EMBO J.* **32**, 1817–1828.
- O'Driscoll, M., Ruiz-Perez, V. L., Woods, C. G., Jeggo, P. A. and Goodship, J. A.** (2003). A splicing mutation affecting expression of ataxia-telangiectasia and Rad3-related protein (ATR) results in Seckel syndrome. *Nat. Genet.* **33**, 497–501.
- Ogi, T., Walker, S., Stiff, T., Hobson, E., Limsirichaikul, S., Carpenter, G., Prescott, K., Suri, M., Byrd, P. J., Matsuse, M. et al.** (2012). Identification of the first ATRIP-deficient patient and novel mutations in ATR define a clinical spectrum for ATR-ATRIP Seckel Syndrome. *PLoS Genet.* **8**, e1002945.
- Ohshima, T., Ward, J. M., Huh, C. G., Longenecker, G., Veeranna, G., Pant, H. C., Brady, R. O., Martin, L. J. and Kulkarni, A. B.** (1996). Targeted disruption of the cyclin-dependent kinase 5 gene results in abnormal corticogenesis, neuronal pathology and perinatal death. *Proc. Natl. Acad. Sci. USA* **93**, 11173–11178.
- O'Leary, M. A., Bloch, J. I., Flynn, J. J., Gaudin, T. J., Giallombardo, A., Giannini, N. P., Goldberg, S. L., Kraatz, B. P., Luo, Z.-X., Meng, J. et al.** (2013). The placental mammal ancestor and the post-K-Pg radiation of placentals. *Science* **339**, 662–667.
- Olkowicz, S., Kocourek, M., Lucan, R. K., Portes, M., Fitch, W. T., Herculano-Houzel, S. and Nemec, P.** (2016). Birds have primate-like numbers of neurons in the forebrain. *Proc. Natl. Acad. Sci. USA* **113**, 7255–7260.
- Ostergaard, P., Simpson, M. A., Mendola, A., Vasudevan, P., Connell, F. C., van Impel, A., Moore, A. T., Loey, B. L., Ghalamkarpoor, A., Onoufriadiis, A. et al.** (2012). Mutations in KIF11 cause autosomal-dominant microcephaly variably associated with congenital lymphedema and choriorhinopathy. *Am. J. Hum. Genet.* **90**, 356–362.
- Paridaen, J. T. M. L., Wilsch-Bräuninger, M. and Huttner, W. B.** (2013). Asymmetric inheritance of centrosome-associated primary cilium membrane directs ciliogenesis after cell division. *Cell* **155**, 333–344.
- Payne, F., Colnaghi, R., Rocha, N., Seth, A., Harris, J., Carpenter, G., Bottomley, W. E., Wheeler, E., Wong, S., Saudek, V. et al.** (2014). Hypomorphism in human NSMCE2 linked to primordial dwarfism and insulin resistance. *J. Clin. Invest.* **124**, 4028–4038.
- Piao, X., Hill, R. S., Bodell, A., Chang, B. S., Basel-Vanagaite, L., Straussberg, R., Dobyns, W. B., Qasrawi, B., Winter, R. M., Innes, A. M. et al.** (2004). G protein-coupled receptor-dependent development of human frontal cortex. *Science* **303**, 2033–2036.
- Pilz, G. A., Shitamukai, A., Reillo, I., Pacary, E., Schwausch, J., Stahl, R., Ninkovic, J., Snippert, H. J., Clevers, H., Godinho, L. et al.** (2013). Amplification of progenitors in the mammalian telencephalon includes a new radial glial cell type. *Nat. Commun.* **4**, 2125.
- Poirier, K., Keays, D. A., Francis, F., Saillour, Y., Bahi, N., Manouvrier, S., Fallet-Bianco, C., Pasquier, L., Toutain, A., Tuy, F. P. et al.** (2007). Large spectrum of lissencephaly and pachygyria phenotypes resulting from de novo missense mutations in tubulin alpha 1A (TUBA1A). *Hum. Mutat.* **28**, 1055–1064.
- Poirier, K., Saillour, Y., Bahi-Buisson, N., Jaglin, X. H., Fallet-Bianco, C., Nababout, R., Castelnau-Ptakhine, L., Roubertie, A., Attie-Bitach, T., Desguerre, I. et al.** (2010). Mutations in the neuronal ss-tubulin subunit TUBB3 result in malformation of cortical development and neuronal migration defects. *Hum. Mol. Genet.* **19**, 4462–4473.
- Poirier, K., Lebrun, N., Broix, L., Tian, G., Saillour, Y., Boscheron, C., Parrini, E., Valence, S., Pierre, B. S., Oger, M. et al.** (2013). Mutations in TUBG1, DYNC1H1, KIF5C and KIF2A cause malformations of cortical development and microcephaly. *Nat. Genet.* **45**, 639–647.
- Pontious, A., Kowalczyk, T., Englund, C. and Hevner, R. F.** (2008). Role of intermediate progenitor cells in cerebral cortex development. *Dev. Neurosci.* **30**, 24–32.
- Puelles, L., Ayad, A., Alonso, A., Sandoval, J. E., Martínez-de-la-Torre, M., Medina, L. and Ferran, J. L.** (2016). Selective early expression of the orphan nuclear receptor Nr4a2 identifies the claustrum homologue in the avian mesopallium: Impact on sauropsidian/mammalian pallium comparisons. *J. Comp. Neurol.* **524**, 665–703.
- Puelles, L., Sandoval, J. E., Ayad, A., del Corral, R., Alonso, A., Ferran, J. L. and Martínez-de-la-Torre, M.** (2017). The pallium in reptiles and birds in the light of hte updated tetrapartite pallium model. In *Evolution of Nervous Systems* (ed. J. Kaas), pp. 519–555. Amsterdam, The Netherlands: Elsevier.
- Puffenberger, E. G., Jinks, R. N., Sougnez, C., Cibulskis, K., Willert, R. A., Achilly, N. P., Cassidy, R. P., Fiorentini, C. J., Heiken, K. F., Lawrence, J. J. et al.** (2012). Genetic mapping and exome sequencing identify variants associated with five novel diseases. *PLoS ONE* **7**, e28936.
- Puzzolo, E. and Mallamaci, A.** (2010). Cortico-cerebral histogenesis in the opossum *Monodelphis domestica*: generation of a hexalaminar neocortex in the absence of a basal proliferative compartment. *Neural. Dev.* **5**, 8.
- Qvist, P., Huertas, P., Jimeno, S., Nyegaard, M., Hassan, M. J., Jackson, S. P. and Børglum, A. D.** (2011). CtIP mutations cause seckel and jawad syndromes. *PLoS Genet.* **7**, e1002310.
- Radmanesh, F., Caglayan, A. O., Silhavy, J. L., Yilmaz, C., Cantagrel, V., Omar, T., Rostì, B., Kaymakcalan, H., Gabriel, S., Li, M. et al.** (2013). Mutations in LAMB1 cause cobblestone brain malformation without muscular or ocular abnormalities. *Am. J. Hum. Genet.* **92**, 468–474.
- Rakic, P.** (2009). Evolution of the neocortex: a perspective from developmental biology. *Nat. Rev. Neurosci.* **10**, 724–735.
- Rash, B. G., Tomasi, S., Lim, H. D., Suh, C. Y. and Vaccarino, F. M.** (2013). Cortical gyration induced by fibroblast growth factor 2 in the mouse brain. *J. Neurosci.* **33**, 10802–10814.
- Rauch, A., Thiel, C. T., Schindler, D., Wick, U., Crow, Y. J., Ekici, A. B., van Essen, A. J., Goedeke, T. O., Al-Gazali, L., Chrzanowska, K. H. et al.** (2008). Mutations in the pericentrin (PCNT) gene cause primordial dwarfism. *Science* **319**, 816–819.
- Reillo, I., de Juan Romero, C., García-Cabezas, M. A. and Borrell, V.** (2011). A role for intermediate radial glia in the tangential expansion of the mammalian cerebral cortex. *Cereb. Cortex* **21**, 1674–1694.
- Reiner, O., Carrozzo, R., Shen, Y., Wehnert, M., Faustiniella, F., Dobyns, W. B., Caskey, C. T. and Ledbetter, D. H.** (1993). Isolation of a Miller-Dieker lissencephaly gene containing G protein beta-subunit-like repeats. *Nature* **364**, 717–721.
- Richman, D. P., Stewart, M., Hutchinson, J. W. and Caviness, V. S. Jr** (1975). Mechanical model of brain convolutional development. *Science* **189**, 18–21.
- Riviere, J. B., van Bon, B. W., Hoischen, A., Kholmanskikh, S. S., O'Roak, B. J., Gilissen, C., Gijssen, S., Sullivan, C. T., Christian, S. L., Abdul-Rahman, O. A. et al.** (2012). De novo mutations in the actin genes ACTB and ACTG1 cause Baraitser-Winter syndrome. *Nat. Genet.* **44**, 440–444.
- Rosenberg, M. J., Agarwala, R., Bouffard, G., Davis, J., Fiermonte, G., Hilliard, M. S., Koch, T., Kalikin, L. M., Makalowska, I., Morton, D. H. et al.** (2002).

- Mutant deoxynucleotide carrier is associated with congenital microcephaly. *Nat. Genet.* **32**, 175-179.
- Rowe, T. B., Macrini, T. E. and Luo, Z.-X.** (2011). Fossil evidence on origin of the mammalian brain. *Science* **332**, 955-957.
- Sauer, F. C.** (1935). Mitosis in the neural tube. *J. Comp. Neurol.* **62**, 377-405.
- Scheidecker, S., Etard, C., Haren, L., Stoetzel, C., Hull, S., Arno, G., Plagnol, V., Drunat, S., Passemard, S., Toutain, A. et al.** (2015). Mutations in TUBGCP4 alter microtubule organization via the gamma-tubulin ring complex in autosomal-recessive microcephaly with chorioretinopathy. *Am. J. Hum. Genet.* **96**, 666-674.
- Schoch, R. R. and Sues, H.-D.** (2016). The diapsid origin of turtles. *Zoology (Jena)* **119**, 159-161.
- Shah, B., Lutter, D., Tsitsyura, Y., Glyvuk, N., Sakakibara, A., Klingauf, J. and Püschel, A. W.** (2016). Rap1 GTPases are master regulators of neural cell polarity in the developing neocortex. *Cereb. Cortex* **11**, e0154174.
- Shaheen, R., Faqeih, E., Ansari, S., Abdel-Salam, G., Al-Hassan, Z. N., Al-Shidi, T., Alomar, R., Sogaty, S. and Alkuraya, F. S.** (2014). Genomic analysis of primordial dwarfism reveals novel disease genes. *Genome Res.* **24**, 291-299.
- Shamseldin, H., Alazami, A. M., Manning, M., Hashem, A., Caluseiu, O., Tabarki, B., Esplin, E., Schelley, S., Innes, A. M., Parboos Singh, J. S. et al.** (2015). RTTN mutations cause primary microcephaly and primordial dwarfism in humans. *Am. J. Hum. Genet.* **97**, 862-868.
- Sheen, V. L., Ganesh, V. S., Topcu, M., Sebire, G., Bodell, A., Hill, R. S., Grant, P. E., Shugart, Y. Y., Imitola, J., Khouri, S. J. et al.** (2004). Mutations in ARFGEF2 implicate vesicle trafficking in neural progenitor proliferation and migration in the human cerebral cortex. *Nat. Genet.* **36**, 69-76.
- Shen, S.-Z., Crowley, J. L., Wang, Y., Bowring, S. A., Erwin, D. H., Sadler, P. M., Cao, C.-Q., Rothman, D. H., Henderson, C. M., Ramezani, J. et al.** (2011). Calibrating the end-Permian mass extinction. *Science* **334**, 1367-1372.
- Shitamukai, A., Konno, D. and Matsuzaki, F.** (2011). Oblique radial glial divisions in the developing mouse neocortex induce self-renewing progenitors outside the germinal zone that resemble primate outer subventricular zone progenitors. *J. Neurosci.* **31**, 3683-3695.
- Siegenthaler, J. A., Ashique, A. M., Zarbalis, K., Patterson, K. P., Hecht, J. H., Kane, M. A., Folias, A. E., Choe, Y., May, S. R., Kume, T. et al.** (2009). Retinoic acid from the meninges regulates cortical neuron generation. *Cell* **139**, 597-609.
- Sir, J.-H., Barr, A. R., Nicholas, A. K., Carvalho, O. P., Khurshid, M., Sossick, A., Reichelt, S., D'Santos, C., Woods, C. G. and Gergely, F.** (2011). A primary microcephaly protein complex forms a ring around parental centrioles. *Nat. Genet.* **43**, 1147-1153.
- Smart, I. H. M., Dehay, C., Giroud, P., Berland, M. and Kennedy, H.** (2002). Unique morphological features of the proliferative zones and postmitotic compartments of the neural epithelium giving rise to striate and extrastriate cortex in the monkey. *Cereb. Cortex* **12**, 37-53.
- Stahl, R., Walcher, T., De Juan Romero, C., Pilz, G. A., Cappello, S., Irmler, M., Sanz-Aquela, J. M., Beckers, J., Blum, R., Borrell, V. et al.** (2013). Trnp1 regulates expansion and folding of the mammalian cerebral cortex by control of radial glial fate. *Cell* **153**, 535-549.
- Stevens, E., Carsi, K. J., Cirak, S., Foley, A. R., Torelli, S., Willer, T., Tambunan, D. E., Yau, S., Brodd, L., Sewry, C. A. et al.** (2013). Mutations in B3GALNT2 cause congenital muscular dystrophy and hypoglycosylation of alpha-dystroglycan. *Am. J. Hum. Genet.* **92**, 354-365.
- Striedter, G. F., Srinivasan, S. and Monuki, E. S.** (2015). Cortical folding: when, where, how, and why? *Annu. Rev. Neurosci.* **38**, 291-307.
- Subramanian, L., Remedios, R., Shetty, A. and Tole, S.** (2009). Signals from the edges: the cortical hem and antihem in telencephalic development. *Semin. Cell Dev. Biol.* **20**, 712-718.
- Tallinen, T., Chung, J. Y., Biggins, J. S. and Mahadevan, L.** (2014). Gyration from constrained cortical expansion. *Proc. Natl. Acad. Sci. USA* **111**, 12667-12672.
- Tan, X. and Shi, S. H.** (2013). Neocortical neurogenesis and neuronal migration. *Wiley Interdiscip. Rev. Dev. Biol.* **2**, 443-459.
- Tissir, F. and Goffinet, A. M.** (2003). Reelin and brain development. *Nat. Rev. Neurosci.* **4**, 496-505.
- Tissir, F., Lambert De Rouvroit, C., Sire, J.-Y., Meyer, G. and Goffinet, A. M.** (2003). Reelin expression during embryonic brain development in *Crocodylus niloticus*. *J. Comp. Neurol.* **457**, 250-262.
- Tuorto, F., Alifragis, P., Failla, V., Parnavelas, J. G. and Gulisano, M.** (2003). Tangential migration of cells from the basal to the dorsal telencephalic regions in the chick. *Eur. J. Neurosci.* **18**, 3388-3393.
- Vallee, R. B., Seale, G. E. and Tsai, J.-W.** (2009). Emerging roles for myosin II and cytoplasmic dynein in migrating neurons and growth cones. *Trends Cell Biol.* **19**, 347-355.
- van Bokhoven, H., Celli, J., van Reeuwijk, J., Rinne, T., Glaudemans, B., van Beusekom, E., Rieu, P., Newbury-Ecob, R. A., Chiang, C. and Brunner, H. G.** (2005). MYCN haploinsufficiency is associated with reduced brain size and intestinal atresias in Feingold syndrome. *Nat. Genet.* **37**, 465-467.
- van Reeuwijk, J., Janssen, M., van den Elzen, C., Beltrán-Valero de Bernabé, D., Sabatelli, P., Merlini, L., Boon, M., Scheffer, H., Brockington, M., Muntoni, F. et al.** (2005). POMT2 mutations cause alpha-dystroglycan hypoglycosylation and Walker-Warburg syndrome. *J. Med. Genet.* **42**, 907-912.
- van Reeuwijk, J., Grewal, P. K., Salih, M. A., Beltrán-Valero de Bernabé, D., McLaughlan, J. M., Michielse, C. B., Herrmann, R., Hewitt, J. E., Steinbrecher, A., Seidahmed, M. Z. et al.** (2007). Intragenic deletion in the LARGE gene causes Walker-Warburg syndrome. *Hum. Genet.* **121**, 685-690.
- Varon, R., Vissinga, C., Platzer, M., Cerosaletti, K. M., Chrzanowska, K. H., Saar, K., Beckmann, G., Seemanová, E., Cooper, P. R., Nowak, N. J. et al.** (1998). Nibrin, a novel DNA double-strand break repair protein, is mutated in Nijmegen breakage syndrome. *Cell* **93**, 467-476.
- Vuillaume-Barrot, S., Bouchet-Séraphin, C., Chelbi, M., Devisme, L., Quentin, S., Gazal, S., Laquerrière, A., Fallet-Bianco, C., Loget, P., Odent, S. et al.** (2012). Identification of mutations in TMEM5 and ISPD as a cause of severe cobblestone lissencephaly. *Am. J. Hum. Genet.* **91**, 1135-1143.
- Walsh, C. A. and Goffinet, A. M.** (2000). Potential mechanisms of mutations that affect neuronal migration in man and mouse. *Curr. Opin. Genet. Dev.* **10**, 270-274.
- Wang, X., Tsai, J.-W., LaMonica, B. and Kriegstein, A. R.** (2011). A new subtype of progenitor cell in the mouse embryonic neocortex. *Nat. Neurosci.* **14**, 555-561.
- Waters, A. M., Asfahani, R., Carroll, P., Bicknell, L., Lescal, F., Bright, A., Chanudet, E., Brooks, A., Christou-Savina, S., Osman, G. et al.** (2015). The kinetochore protein, CENPF, is mutated in human ciliopathy and microcephaly phenotypes. *J. Med. Genet.* **52**, 147-156.
- Willer, T., Lee, H., Lommel, M., Yoshida-Moriguchi, T., de Bernabe, D. B. V., Venzke, D., Cirak, S., Schachter, H., Vajsar, J., Voit, T. et al.** (2012). ISPD loss-of-function mutations disrupt dystroglycan O-mannosylation and cause Walker-Warburg syndrome. *Nat. Genet.* **44**, 575-580.
- Wilsch-Bräunner, M., Peters, J., Paridaen, J. T. M. L. and Huttner, W. B.** (2012). Basolateral rather than apical primary cilia on neuroepithelial cells committed to delamination. *Development* **139**, 95-105.
- Xi, C., Zeng, S. J., Zhang, X. W. and Zuo, M. X.** (2008). Neurogenic development of the visual areas in the Chinese softshell turtle (*Pelodiscus sinensis*) and evolutionary implications. *J. Anat.* **212**, 578-589.
- Xiang, X., Osman, A. H., Osman, S. A., Xin, M. and Morris, N. R.** (1995). NudF, a nuclear migration gene in *Aspergillus nidulans*, is similar to the human LIS-1 gene required for neuronal migration. *Mol. Biol. Cell* **6**, 297-310.
- Yamamoto, S., Jaiswal, M., Charnig, W.-L., Gambin, T., Karaca, E., Mirzaa, G., Wiszniewski, W., Sandoval, H., Haelterman, N. A., Xiong, B. et al.** (2014). A *Drosophila* genetic resource of mutants to study mechanisms underlying human genetic diseases. *Cell* **159**, 200-214.
- Yamamoto, H., Mandai, K., Konno, D., Maruo, T., Matsuzaki, F. and Takai, Y.** (2015). Impairment of radial glial scaffold-dependent neuronal migration and formation of double cortex by genetic ablation of afadin. *Brain Res.* **1620**, 139-152.
- Yang, Y. J., Baltus, A. E., Mathew, R. S., Murphy, E. A., Evrony, G. D., Gonzalez, D. M., Wang, E. P., Marshall-Walker, C. A., Barry, B. J., Murn, J. et al.** (2012). Microcephaly gene links trithorax and REST/NRSF to control neural stem cell proliferation and differentiation. *Cell* **151**, 1097-1112.
- Yoshida, A., Kobayashi, K., Manya, H., Taniguchi, K., Kano, H., Mizuno, M., Inazu, T., Mitsuhashi, H., Takahashi, S., Takeuchi, M. et al.** (2001). Muscular dystrophy and neuronal migration disorder caused by mutations in a glycosyltransferase, POMGnT1. *Dev. Cell* **1**, 717-724.
- Zardoya, R. and Meyer, A.** (2001). The evolutionary position of turtles revised. *Naturwissenschaften* **88**, 193-200.
- Zhang, X., Lei, K., Yuan, X., Wu, X., Zhuang, Y., Xu, T., Xu, R. and Han, M.** (2009). SUN1/2 and Syne/Nesprin-1/2 complexes connect centrosome to the nucleus during neurogenesis and neuronal migration in mice. *Neuron* **64**, 173-187.
- Zhou, C.-J., Borello, U., Rubenstein, J. L. R. and Pleasure, S. J.** (2006). Neuronal production and precursor proliferation defects in the neocortex of mice with loss of function in the canonical Wnt signaling pathway. *Neuroscience* **142**, 1119-1131.