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Evolutionary Expansion of the Neocortex - Cell Biological Features and Underlying Mechanisms

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Abstract. The neocortex is a major part of the mammalian brain and a key structure for human behavior, cognition and language. During the course of brain evolution, the neocortex in many mammalian species underwent an increase in its size and complexity, which is thought to provide a basis for the increased cognitive abilities of humans. The differences in neocortex size and complexity between various mammalian species stem from developmental processes that regulate the production of neocortical neurons. Neural stem and progenitor cells with their unique cell biological characteristic are instrumental for such developmental processes. In this review we will discuss key aspects of the evolutionary expansion of the neocortex, and specifically the features present during fetal/embryonic development. We will then discuss the cell biological characteristics of neural stem and progenitor cells and mechanisms underlying the evolutionary expansion of the neocortex.

Introduction

The neocortex is the largest part of the cerebral cortex, the outer layer of the cerebrum. The neocortex is formed from the dorsolateral telencephalon, the rostral-most region of the neural tube (Sidman and Rakic, 1973; Taverna et al., 2014). Studies of neocortex development started at the end of the 19th century when Wilhelm His proposed that the surface of the cerebral ventricles is lined with mitotic cells, whereas newborn neurons migrate from the site of their generation basally to the forming cortical plate (reviewed in (Bentivoglio and Mazzarello, 1999; Rakic, 2006)). Giuseppe Magini, who applied the Golgi impregnation method to the fetal cerebral cortex, observed that mitotic cells extended radial fibers towards the pial surface and that intercalated migrating neurons were present along those fibers (reviewed in (Bentivoglio and Mazzarello, 1999; Rakic, 2003b). Radioactive labeling of DNA replication showed that the migrating newborn neurons, on their way to their final position in the cortical plate, bypass the previously generated neurons, resulting in an inside-out manner of building the developing neocortex (Angevine and Sidman, 1961). A major advance in understanding neocortex development came with the introduction of immunohistochemistry and electron microscopy in the early 1970s. Pasko Rakic, who introduced the name "radial glia" (RG) for the mitotic cells extending long radial processes, showed that these processes are used as a scaffold for the newborn neurons to migrate basally (Rakic, 1972; Sidman and Rakic, 1973). The glial nature of RG was confirmed by expression of glial proteins, such as GFAP, and by observations that at later stages of neocortex development, RG transform into astrocytes (Levitt and Rakic, 1980; Schmechel and Rakic, 1979; Voigt, 1989).

Only in the early 2000s, it was shown by four independent groups that RG are progenitors of newborn neurons in the developing neocortex (Malatesta et al., 2000; Miyata et al., 2001; Noctor et al., 2001; Tamamaki et al., 2001). The next major advance occurred with the discovery of additional neuron-generating mitotic cells located away from the ventricular surface (Haubensak et al., 2004; Miyata et al., 2004; Noctor et al., 2004). These progenitor cells that undergo mitosis away from the ventricle are now known as basal progenitors (BPs). In contrast, the progenitor cells that undergo mitosis at the ventricle are known as apical progenitors (APs).

The six-layered neocortex is a unique feature of mammals, which emerged in evolution around 160-220 million years ago (Figure 1) (Bininda-Emonds et al., 2007; Meredith et al., 2011; O'Leary et al., 2013). It is thought that mammalian neuronal types that build the six-layered neocortex diversified from ancestral neuronal types that can today be found in the reptilian three-layered cortex (Briscoe and Ragsdale, 2018; Tosches et al., 2018). Recently, a reconstruction of the phenotype of the hypothetical most recent ancestor of all placental mammals has been reported (O'Leary et al., 2013). This animal, which lived 65 million years ago, had a folded neocortex (O'Leary et al., 2013), which is considered to be one of the hallmarks of an expanded neocortex (see also below and Lewitus et al., 2014). This ancestor of placental mammals also contained a corpus callosum (O'Leary et al., 2013), the nerve tract connecting the two hemispheres of the brain, which is another anatomical feature related to neocortex expansion (see below). It is worth noting that some of these features, such as folding, predate the emergence of placental mammals, as they are present in extant marsupials (Figure 1). A recent study analyzed neural progenitor cells in the wallaby and found similar types of BPs as in placental mammals, suggesting that similar mechanisms might underlie neocortex expansion also in the marsupial lineage (Sauerland et al., 2018).

Most of our knowledge regarding neocortex development in placental mammals comes from studies in rodents (mouse and rat), primates (macaque and human) and carnivores (ferrets) (Figure 1). Therefore, in this review, we will also focus primarily on these three mammalian orders. We will describe the key features of neocortex organization and discuss how these features changed during the evolutionary expansion of the neocortex. In the second part, we will discuss the role of neural progenitor cells in underlying the evolutionary expansion of the neocortex, as well as key cell biological mechanisms that drove such expansion.

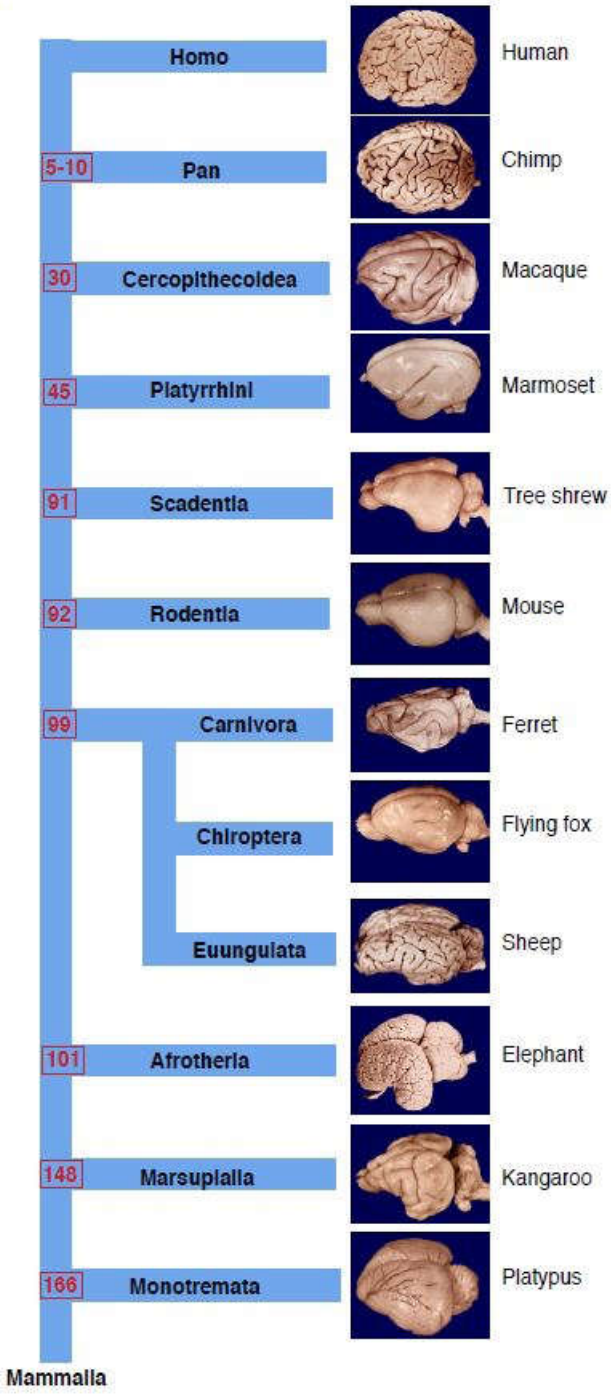

Fig 1. . Evolution of mammalian neocortex. *Simplified version of the mammalian phylogenetic tree, with the numbers indicating approximate time of divergence from the lineage leading to human, expressed in million years. The data are from (Bininda-Emonds et al., 2007; Meredith et al., 2011). Brain images (not in scale) of the representative species of each lineage are presented on the right and are from www.brainmuseum.org.*

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Neocortex organization

With regard to neurons, the mammalian neocortex contains projection neurons and interneurons and exhibits a columnar, laminar and areal organization that is common across all mammalian orders (Florio and Huttner, 2014; Kalebic et al., 2017; Mountcastle, 1997; Rakic, 2009). However, the number, size and complexity of neocortical columns, laminae and areas increased during mammalian evolution (Geschwind and Rakic, 2013) (though not in every species of a given order). We first briefly describe the general features of this neocortex organization and then discuss the principles of the evolutionary expansion of the neocortex.

Columnar organization

The adult neocortex is organized vertically into columns – groups of cells linked synaptically across the horizontal laminae (Mountcastle, 1997). These functional columns work modularly, and neurons in a given column exhibit stereotypical connections (Rakic, 2008). It is thought that functional columns of the adult neocortex consist of various ontogenetic columns (Rakic, 1988) that arise during neocortex development and comprise neurons which originate over time from a single apical neural progenitor.

Laminar organization

Horizontally, the adult neocortex is organized into six different cortical layers, with the layer I being the outermost and layer VI the innermost layer. During development, the earliest-born neurons form the first layered structure named preplate, which later splits into the superficial marginal zone (future layer I) and the more deeply located subplate (Bayer and Altman, 1991; Molyneaux et al., 2007). Projection neurons, which are born in the neocortical germinal zones (GZ), migrate through the intermediate zone (IZ) and finally reach their position in the developing cortical plate (CP), which emerges between the subplate and marginal zone (Molyneaux et al., 2007). The production of projection neurons follows an "inside-out" manner (with the exception of layer I neurons), with the layer VI neurons generated first and layer II neurons generated last (Angevine and Sidman, 1961; Bayer and Altman, 1991; Rakic, 1988). Neurons within each layer share similar identities and connections. Thus, deep-layer neurons (layers V and VI) preferentially exhibit corticofugal projections and upper-layer neurons (layers II-IV) mainly establish cortico-cortical connections (Molyneaux et al., 2007).

Areal organization

Neocortical areas are specialized regions defined by their specific cytoarchitecture and function. Development of cortical areas is primarily controlled by morphogens secreted from patterning centers of the dorsal telencephalon, which induce differential expression of transcription factors in the neocortical cells, finally determining area identity (Kaas, 2013; O'Leary et al., 2007; O'Leary and Sahara, 2008).

Evolutionary expansion of the neocortex

Characteristics of the evolutionary expansion of the neocortex

During mammalian evolution, the neocortex underwent enlargement in many species so that its size substantially varies between different mammals. This is best reflected when comparing adult human and mouse brains. The mass of the human brain is more than 3000-fold greater than that of the mouse brain and contains more than 1000 times more cells (Herculano-Houzel, 2009; Lewitus et al., 2014). Although the evolutionary expansion of the neocortex happened independently in most mammalian orders (Borrell and Reillo, 2012; Lewitus and Kalinka, 2013; Lewitus et al., 2014), it is thought to be guided by similar principles.

Three different parameters are considered to play a role in neocortex expansion – production of neurons per unit time, cell survival rate and length of the neurogenic period (Kuida et al., 1998; Lewitus et al., 2014; Wilsch-Bräuninger et al., 2016). The production of neurons is thought to be the key parameter underlying neocortex expansion. An increase in neuron production without affecting the length of the neurogenic period can be achieved either by increasing the pool size of neural stem and progenitor cells or by shortening the length of the cell cycle of these cells. The survival of newborn neurons also plays a role in neocortex expansion as it has been shown that inhibiting physiological apoptosis can lead to an increase in brain size (Kuida et al., 1998; Kuida et al., 1996; Rakic and Zecevic, 2000). The length of the neurogenic period has recently been proposed as a key parameter underlying the evolutionary expansion of the neocortex within a specific lineage, namely, when the neurogenic program is the same (Lewitus et al., 2014). It has thus been proposed that the three-fold increase in neocortex size between chimpanzee and human could be explained largely by taking into account only the length of the neurogenic period (Lewitus et al., 2014).

The enlargement of the neocortex concerns both its surface area and its thickness (Figure 2) (Geschwind and Rakic, 2013; Rakic, 2000, 2009). The former is more pronounced as the average neocortex thickness increased, for example, only two-fold from rodents to primates, whereas surface area increased several hundred times, notably 1000 times between mouse and human (Rakic, 2009). There are two possible scenarios how to accommodate additional neurons without strongly increasing neocortex thickness – (i) by increasing cortical surface area, or (ii) by increasing neuronal density.

Given the limited volume of the cranial cavity, it is generally accepted that neocortical folding is a major evolutionary solution to accommodate an increased neocortical surface area (Florio and Huttner, 2014; Kelava et al., 2013; Rakic, 2009; Zilles et al., 2013). Neocortical

folding is present in all mammalian orders, and the present data suggest that folding correlates with neocortex expansion (Borrell and Reillo, 2012; Fernandez et al., 2016; Lewitus et al., 2013). As it appears that the Jurassic-era mammalian ancestor already exhibited a folded cerebral cortex (Lewitus et al., 2014; O'Leary et al., 2013), it suggests that gyrencephaly was lost and its extent increased several times independently during mammalian evolution (Kelava et al., 2013).

Changes in neuronal density are also observed in conjunction with evolutionary increases in neuron numbers. Remarkably, all non-primate orders have been reported to scale with decreasing neuronal density as the number of neurons increases (Herculano-Houzel et al., 2015). It has been proposed that this implies that as cortices of non-primate species contain more neurons, the size of these neurons increases (Herculano-Houzel et al., 2015). This however does not apply to primates, which maintain high neuronal densities even with very high numbers of neurons. As a result primate cortices contain more neurons per unit mass than non-primate cortices, suggesting that regulating neuronal density is another mechanism for evolutionary expansion of the neocortex (Herculano-Houzel et al., 2015).

Another characteristic of neocortex expansion is the differential growth of existing neocortical areas as well as the acquisition of novel areas, in particular in the frontal cortex (Kaas, 2013; Krubitzer and Kaas, 2005; Rakic, 2009). The final size and pattern of neocortical areas is thought to be determined already during development, a notion that has been postulated by Pasko Rakic's protomap hypothesis (Rakic, 1988). According to this hypothesis, various gradients of certain molecules are expressed in the embryonic neocortex that specifically guide and attract afferent systems to appropriate positions where they can interact with specific cells (Geschwind and Rakic, 2013; Rakic, 1988). Differential gene expression and molecular gradients identified across the embryonic neocortex largely confirmed this hypothesis. One recent example is the differential gene expression in a prospective gyrus vs. a prospective sulcus of embryonic ferret neocortex (De Juan Romero et al., 2015). Interestingly, the genes found to be differentially expressed between the prospective gyrus and sulcus of ferret exhibited a similar expression pattern in fetal human, but showed no obvious pattern in embryonic mouse neocortex, suggesting the existence of a protomap also during the development of folding (De Juan Romero et al., 2015).

Models of neocortex expansion

The first proposed model for the evolutionary expansion of the neocortex was the radial unit hypothesis by Pasko Rakic (Geschwind and Rakic, 2013; Rakic, 1988, 1995, 2009). According to this hypothesis, cortical neurons occupy a tangential position determined by the relative position of their precursor cells and a radial position according to the time of their origin (Rakic, 1988). Thus, an increase in the number of radial units, i.e. ontogenetic columns, could explain an increase in neocortex surface area, without changing the thickness of the neocortex if the number of cells is not changed within each column (Geschwind and Rakic, 2013; Rakic, 1995). A longer initial phase of AP proliferation could hence expand the AP pool and increase the number of ontogenetic columns, finally resulting in expansion of the neocortex surface area. This model has been tested by forcing APs to re-enter the cell cycle by expressing a constitutively active ß-catenin (Chenn and Walsh, 2002) or by blocking AP apoptosis by ablating caspase 9 (Kuida et al., 1998). In both cases increasing the founder pool of neural stem cells resulted in neocortex expansion. However, this induced expansion resulted in greater surface area of both the pial surface and the ventricular surface. Although ventricular surface area also increased during mammalian neocortex evolution, the expansion was far greater at the pial side, with formation of characteristic folds only on that side (Fietz and Huttner, 2011; Florio and Huttner, 2014; Kriegstein et al., 2006; Lui et al., 2011).

An important conceptual addition regarding neocortex expansion was provided by Ian Smart, who first proposed that the ability to undergo mitosis away from the ventricle is a necessary prerequisite for this expansion (Smart, 1972a, 1972b). An increase in neural stem and progenitor cell proliferation away from the ventricle would then result in a transiently thicker abventricular germinal zone and a greater production of neurons per ontogenetic column. This in turn could explain the increase in surface area at the pial side without affecting the ventricular surface area. The subsequent description of histological zones and detailed characterization of BPs has supported this concept and resulted in identification of cellular and molecular mechanisms underlying the evolutionary expansion of neocortex (see below).

Expansion of neuronal layers

Although the major parameter of the evolutionary expansion of the neocortex pertains to neocortex surface area, the average two-fold increase in cortical thickness between rodents and primates (Rakic, 2009) deserves special discussion. This increase in cortical thickness comprises several zones, but it is most pronounced in the supragranular layers (layers II and III). Specifically, the thickness of these layers is doubled in primates compared to rodents and is the greatest in great apes, in particular humans (Hutsler et al., 2005). Furthermore, the thickness of infragranular layers (layers V and VI) decreased in primates compared to rodents, resulting in far greater proportional thickness of the supragranular layers in primates than in rodents (Hutsler et al., 2005). A comparison between several different primate species suggests that the thickness of supragranular layers increased together with neocortex expansion, with humans having 1.5-fold thicker supragranular layers than macaque (Hutsler et al., 2005). Interestingly, carnivores exhibit intermediate characteristics, with ferret exhibiting 2-fold thicker supragranular layers compared to mouse and having these layers 2-fold thinner compared to human (Hutsler et al., 2005). The supragranular layers harbour

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neurons involved in establishing ipsi- and contra-lateral connections (Lodato and Arlotta, 2015; Molnar et al., 2006). The latter, known also as callosal projection neurons, play a key role in high-level associative complexity (Fame et al., 2011). Callosal projection neurons, together with the corpus callosum itself which is made by their axons, evolved with the emergence of, and are specific to, placental mammals (Aboitiz and Montiel, 2003; O'Leary et al., 2013). Later during mammalian brain evolution, callosal projection neurons underwent a disproportionally large expansion from rodents to primates, in line with their major site of residence in the supragranular layers (Fame et al., 2011; Mihrshahi, 2006; Molnar et al., 2006).

In addition to the evolutionary expansion of the supragranular layers, it has been shown that the transient fetal subplate zone undergoes expansion as well. The subplate is populated by neurons that build connections between the thalamus and the cortex and is generated by both cortical and extracortical progenitors (Kostovic and Rakic, 1980, 1990; Molnar et al., 2014). A comparison between human and macaque indicated that both size and duration of the subplate zone increases during evolution and likely culminates in humans (Kostovic and Rakic, 1990). Furthermore, the phase of production of subplate neurons is longer in primates than in rodents. Whereas in rodents the generation of the cortical plate starts after the formation of the subplate, in primates both types of neurons are produced simultaneously (Smart et al., 2002).

Expansion of germinal zones

During neocortex development the major contribution to inter-species differences arises from the differences in the thickness of germinal zones (GZs). The embryonic mouse neocortex contains two distinct germinal zones (Boulder Committee: Angevine et al., 1970), the ventricular zone (VZ) and the subventricular zone (SVZ) (Figure 2). Whereas VZ thickness did not undergo significant changes during neocortex evolution, the SVZ underwent massive evolutionary expansion (Figure 2) (Reillo and Borrell, 2012; Reillo et al., 2011). The VZ is the first formed GZ and, as the name implies, directly lines the lateral ventricles of the developing brain. In mouse, the VZ is the major proliferative zone during early and mid-neurogenesis. At E15 the VZ starts to shrink, concomitant with the final neurogenic stages (Smart, 1973). The second GZ generated is the SVZ, which in mouse can be distinguished as a distinct zone at E13 (Smart, 1973), with the BPs destined to the SVZ starting to be generated at E10.5 (Haubensak et al., 2004). The SVZ is situated more basally than the VZ and is by far the predominant GZ with regard to neuron production (Attardo et al., 2008; Smart et al., 2002; Smart, 1973). Thus, the SVZ is the source of late-born neurons, which include neurons fated for the supragranular layers (Tarabykin et al., 2001). Considering the above-mentioned increase in supragranular layer thickness, it has been proposed that the evolutionary expansion of the SVZ likely underlies neocortex expansion (Fietz and Huttner, 2011; Lui et al., 2011; Molnar et al., 2006; Smart et al., 2002; Tarabykin et al., 2001).

In mammals with an expanded neocortex, such as carnivores and primates, the SVZ contains two cytoarchitectonically distinct subzones that cannot be identified in murines: the inner SVZ (ISVZ) and the outer SVZ (OSVZ) (Figure 2). The ISVZ exhibits features similar to the mouse SVZ, namely, densely packed and randomly arranged nuclei (Smart et al., 2002). In contrast, the OSVZ contains sparsely distributed radially arranged nuclei that resemble those in the VZ (Smart et al., 2002). The macaque OSVZ arises from E65 onwards and contains progenitors that give rise to supragranular layers, suggesting that specifically the OSVZ and its progenitors underlie the evolutionary expansion of these layers (Dehay et al., 2015; Lukaszewicz et al., 2005). The OSVZ has been readily identified in other mammalian species with an expanded neocortex. Thus, the ferret exhibits a marked OSVZ (Fietz et al., 2010; Kawasaki, 2014; Reillo and Borrell, 2012; Smart and McSherry, 1986) that arises from VZ progenitors between E34 and E36 (Martinez-Martinez et al., 2016). Anatomically, the primate and ferret OSVZ is separated from the ISVZ and from the intermediate zone (IZ) by axon-rich inner and outer fiber layers, respectively (Dehay and Kennedy, 2007; Kawasaki et al., 2013; Smart et al., 2002; Zecevic et al., 2005). Considering that mouse exhibits a single fiber layer between the SVZ and IZ, it has been proposed that the existence of the inner fiber layer is also a characteristic of an expanded neocortex (Kawasaki, 2014; Smart et al., 2002; Zecevic et al., 2005). Further evidence in support of this idea comes from studies in ferret which suggest that the inner fiber layer is at least partially derived from supragranular layer neurons (Kawasaki et al., 2013), in line with the observed increase in supragranular layer thickness (Kawasaki, 2014).

Whether the mere presence of an OSVZ is sufficient or not to explain the evolutionary expansion of neocortex has been addressed by studies in a near-lissencephalic primate, the marmoset (Garcia-Moreno et al., 2012; Kelava et al., 2012). This species exhibits a pronounced OSVZ, which is comparable to that of macaque or ferret, but shows no (or a very minor level of) neocortex folding, which is often used as a measure of neocortex expansion, notably with regard to the increase in neocortical surface area (Garcia-Moreno et al., 2012; Kelava et al., 2012). An evolutionary model of primate neocortex folding has suggested that the marmoset evolved from a gyrencephalic ancestor and during this process became near-lissencephalic, a concept known as secondary lissencephaly (Kelava et al., 2013; Kelava et al., 2012). Conversely, analysis of the GZs of a gyrencephalic rodent, the agouti, has revealed the presence of an OSVZ in this species (Garcia-Moreno et al., 2012). Taken together, these studies suggest that the presence of an OSVZ may be necessary, but not sufficient, for gyrencephaly to occur. Rather, an increased pool of proliferative neural progenitors in the OSVZ is considered to be the driving force of the evolutionary expansion of the neocortex (Dehay et al., 2015; Fernandez et al., 2016; Florio and Huttner, 2014; Kalebic et al., 2017; Lui et al., 2011).

Neural stem and progenitor cells in the evolutionary expansion of the neocortex

Neural stem and progenitor cell types

Neural stem and progenitor cells are typically classified based on their cell biological features, namely, the location of their mitosis. Apical progenitors (APs) undergo mitosis at, or very close to, the apical (ventricular) surface, whereas basal progenitors (BPs) undergo mitosis at a basal position, typically within the SVZ (Figure 2). Furthermore, the cell bodies of APs spend their entire cell cycle in the VZ, and these cells always maintain contact with the ventricular surface, whereas BPs exhibit no such contact (Kalebic et al., 2017). A third type of neural progenitor cells, called subapical progenitors (SAPs), has recently been identified (Pilz et al., 2013). SAPs exhibit mixed features. Like APs, SAPs maintain apical contact during mitosis. In contrast, SAPs undergo mitosis at a basal (subapical) position, similarly to BPs.

Three subtypes of APs can be distinguished: neuroepithelial cells (NECs), apical radial glia (aRG, also referred to as ventricular RG) and apical intermediate progenitors (aIPs). NECs are the only genuine stem cells of the developing neocortex. They are highly proliferative in all mammalian species and are the source of all other neural cells. NECs divide symmetrically, generating two NECs, until the onset of neurogenesis, when they start dividing asymmetrically and generate an aRG and a more differentiated daughter cell, such as a BP or (rarely) a neuron (Götz and Huttner, 2005; Kalebic et al., 2017; McKay, 1989; Miyata et al., 2010; Taverna et al., 2014). aRG are the major progeny of NECs and, indirectly, the major source of cortical neurons (Figure 2). They maintain some properties of NECs, but also exhibit new "glial" and "radial" features, notably the expression of the glial markers and the presence of a basal process that spans the entire thickness of the cortical wall at early stages of development. aRG are highly proliferative and, like NECs, undergo both symmetric proliferative divisions to increase their number and asymmetric divisions to generate other progenitor types or (rarely) neurons (Götz and Huttner, 2005; Kriegstein and Alvarez-Buylla, 2009; Pinto and Gotz, 2007; Rakic, 2003a, b; Taverna et al., 2014). aIPs are neurogenic progenitors that divide only once to generate two neurons (Figure 2) (Gal et al., 2006; Tyler and Haydar, 2013).

Two major subtypes of BPs can be distinguished: basal intermediate progenitors (bIPs) and basal radial glia (bRG, also referred to as outer RG) (Figure 2). Both BP subtypes are highly heterogeneous in their proliferative capacity and cell biological features within a given mammalian species. Furthermore, BP characteristics vary largely between different mammalian species. bIPs are nonepithelial BPs that can be classified further into proliferative and neurogenic bIPs, based on their proliferative capacity (Figure 2) (Florio and Huttner, 2014; Lui et al., 2011). Proliferative bIPs can undergo multiple proliferative divisions to generate further bIPs (Hansen et al., 2010; Noctor et al., 2004). Because of its amplifying nature, this cell type is sometimes referred to as transit amplifying progenitor (TAP) (Lui et al., 2011). Neurogenic bIPs typically divide only once to generate two neurons (Haubensak et al., 2004; Miyata et al., 2004; Noctor et al., 2004). The relative abundance of proliferative and neurogenic bIPs varies between different mammalian species, with the general trend that species with an expanded neocortex, such as human, contain a higher relative proportion of proliferative bIPs as opposed to species with a small neocortex, such as mouse.

bRG are the most recently characterized subtype of neural progenitor cells (Figure 2). The initial observations by Iain Smart and colleagues in 2002 (Smart et al., 2002) induced the characterization of bRG in fetal human and developing ferret neocortex independently by three groups (Fietz et al., 2010; Hansen et al., 2010; Reillo et al., 2011). bRG were originally described as monopolar cells contacting the basal lamina, but lacking contact with the ventricle. They exhibit epithelial characteristics and express a set of radial glial markers, hence their name. Soon upon their characterization, bRG were proposed to be the key cell type responsible for the evolutionary expansion of the neocortex (see below) (Fietz and Huttner, 2011; Lui et al., 2011).

APs and the evolutionary expansion of the neocortex

As stated above, APs have a high proliferative capacity across all mammals studied. Nonetheless, there are differences between the proliferative capacity of APs across mammals that are thought to contribute to the evolutionary expansion of the neocortex. These differences include (i) increasing the number of their symmetric cell divisions per unit time to generate more APs; (ii) prolonging the duration of their proliferation, which also results in an increase in AP number; and (iii) increasing the generation of BPs, notably bRG.

Maintaining a pool of proliferative APs for a sufficient amount of time is required for normal neocortex development. The duration of this AP proliferative phase is considered to be a major determinant of the number of radial units (Geschwind and Rakic, 2013; Rakic, 1988). The unique and most important cell biological feature of APs is the presence of an apical domain, containing the apical plasma membrane (Taverna et al., 2014; Wilsch-Bräuninger et al., 2016). This membrane, and in particular the primary cilium, is essential for the APs to sense, and respond to, various signals from the cerebrospinal fluid (Lehtinen and Walsh, 2011). Considering that the cerebrospinal fluid is a major source of pro-proliferative signals (Lehtinen et al., 2011), the primary cilium is likely to be a key organelle underlying normal neocortex development. A key feature of the primary cilium is the mother centriole (referred to as basal body), which mediates the nucleation of the ciliary microtubules. Upon an aRG mitosis, the mother centriole is preferentially inherited by the self-renewing aRG (Wang et al., 2009). Disruption of this inheritance leads to a premature depletion of aRG from the VZ, suggesting that centrosome inheritance is required for AP maintenance in the developing neocortex (Wang et

al., 2009). Moreover, during an aRG mitosis, the mother centriole remains associated with the ciliary membrane remnant, which directs the centrosome back to the apical plasma membrane of the self-renewing aRG, resulting in the formation of a primary cilium in that daughter cell before its sister cell (Paridaen et al., 2013). Disruptions of proteins that form the apical domain or are involved in cilium function are found in human cases of cortical malformations and ciliopathies, further reflecting the importance of the ventricular contact for normal neocortex development (Bizzotto and Francis, 2015; Romero et al., 2018).

Increasing the proliferation rate of aRG can mediate the lateral expansion of the neocortex, but as this expansion is more pronounced on the basal than apical side of the developing neocortex, the addition of radial units cannot alone explain the disproportional expansion on the basal versus apical side. Besides adding radial units, aRG can contribute to the expansion of the neocortex on the basal side by increasing the production of BPs. Upon an asymmetric aRG division, the cell fated to become a BP first establishes its cilium on the basolateral, rather than apical, side (Wilsch-Brauninger et al., 2012). This is followed by the loss of apical contact and the disintegration from the apical junction belt, a process referred to as delamination (Wilsch-Bräuninger et al., 2016). The apical junctional complexes are another feature of APs involved in signaling and exert a key role in establishing and maintaining AP apical-basal polarity (Taverna et al., 2014). They can be split between the two daughter cells or inherited exclusively by the daughter cell fated to become an AP (Shitamukai et al., 2011; Wilsch-Bräuninger et al., 2016).

The molecular mechanism of delamination is still poorly understood, but recent progress does suggest that delamination might have an important role in the evolutionary expansion of the neocortex. Forced delamination of mouse aRG was shown to lead to the generation of bRG (Tavano et al., 2018), the BP type considered to be instrumental for neocortex expansion. However, in mouse, the vast majority of delaminating BPs are bIPs, which exhibit very low proliferative capacity. Thus, the delamination process in the developing mouse neocortex is coupled with a decrease in the proliferative capacity of the resulting BPs compared to the mother APs. In contrast, the bRG in fetal human neocortex maintain as high a proliferative capacity as aRG, in line with the observation that they arise directly from aRG (Gertz et al., 2014). This suggests that the generation of highly proliferative BPs from APs might be an important mechanism contribution to neocortex expansion (Kriegstein et al., 2006; Namba and Huttner, 2017).

BPs and the evolutionary expansion of the neocortex

Current views on the evolutionary expansion of the neocortex state that the main progenitor cell type responsible for this expansion are BPs (Fietz and Huttner, 2011; Lui et al., 2011). As mentioned earlier, the advantage of undergoing mitosis away from the ventricle was proposed already in 1972 (Smart, 1972a, 1972b). However, only the identification of the OSVZ (Smart et al., 2002) and the characterization of neurogenic progenitors that undergo mitosis in the SVZ (Haubensak et al., 2004; Miyata et al., 2004; Noctor et al., 2004) opened the way to start identifying cellular and molecular features of BPs that are key for neocortex expansion (Fish et al., 2008; Kriegstein et al., 2006).

BPs, and in particular bRG, differ across the various mammalian species in their proliferative capacity (Figure 2). The general trend is that in species with an expanded neocortex, such as primates, BPs have a greater proliferative capacity than in species with a small neocortex, such as mouse. In this context, bRG are thought to be instrumental for the evolutionary expansion of the neocortex. bRG in mice were detected shortly after the initial observations in primates and carnivores, however, the abundance of these cells in rodents was significantly lower than in primates (Shitamukai et al., 2011; Wang et al., 2011). Similar to bIPs, also bRG in mouse appeared to be highly neurogenic and not to undergo self-amplifying cell divisions (Shitamukai et al., 2011; Wang et al., 2011; Wong et al., 2015). In contrast, the bRG population in fetal human and macaque neocortex is expanded, and these cells undergo several cycles of self-amplifying divisions before generating neurons (Betizeau et al., 2013; Hansen et al., 2010; LaMonica et al., 2013).

The mechanisms underlying the increase in BP proliferative capacity from rodents to carnivores and primates has been a major focus of many studies in the last years. It is now known that this increase depends on both cell biological features of BPs and an OSVZ-intrinsic mechanism of creating a proliferative niche away from the ventricular surface (Fietz and Huttner, 2011; Florio and Huttner, 2014; Kalebic et al., 2017; Lui et al., 2011).

Cell biological features of BPs underlying neocortex expansion

It has recently been shown that a key cell biological feature underlying BP proliferative capacity is their morphology (Figure 2) (Kalebic et al., 2019). BPs in human contain a greater number of cell processes than BPs in ferret and mouse (Figure 2) (Kalebic et al., 2019). The number of BP processes is particularly interesting in the context of bRG. In human, ferret and mouse neocortex, bRG were initially characterized as monopolar cells contacting the basal lamina with their long radial basal process (bRG-b) (Fietz et al., 2010; Hansen et al., 2010; Reillo et al., 2011; Shitamukai et al., 2011; Wang et al., 2011). The basal process of bRG can serve to receive pro-proliferative signals from the basal lamina (Fietz et al., 2010) and, like that of aRG, as a scaffold for neuronal migration (Borrell and Reillo, 2012; Fernandez et al., 2016; Fietz and Huttner, 2011; Gertz and Kriegstein, 2015; Lui et al., 2011). The latter function has recently been shown to be particularly important for migration of human neurons fated for supragranular layers (Nowakowski et al., 2016). Whereas for the migration of infragranular neurons, both aRG and bRG basal processes are used as scaffold, upon the transition from infragranular to supragranular

neuron production, the scaffold of radial basal fibers has been shown to transform into a discontinuous structure, resulting in human supragranular neurons arriving to their position in the cortical plate by only using bRG basal processes (Nowakowski et al., 2016).

A seminal study in macaque (Betizeau et al., 2013) revealed a greater variety of bRG morphotypes than the monopolar morphotype with a basal radial process. These include (i) bRG harboring only an apically-directed process that, however, does not reach the ventricle (bRG-a), (ii) a bipolar morphotype containing both an apically-directed and a basal process (bRG-ab), and (iii) transient bRG which harbor no dominant radial processes (Figure 2) (Betizeau et al., 2013). Some of these newly characterized morphotypes were also detected in ferret and mouse developing neocortex (Pilz et al., 2013; Reillo et al., 2017; Wong et al., 2015). Recently, further complexity of bRG in human and ferret developing neocortex was found (Kalebic et al., 2019). In these two species, but not in mouse, two additional bRG morphotypes have been identified: a bRG with a bifurcated basal process (bRG-bbf) and a bRG with an apically-directed and a bifurcated basal process (bRG-abbf) (Figure 2) (Kalebic et al., 2019). Containing two basal processes is particularly interesting in the context of the roles of this process for maintaining the proliferative capacity of bRG and for serving as a scaffold for migrating neurons, as discussed above.

The correlation of BP morphology, and specifically of the number of their processes, with the proliferative capacity of these cells suggests that extrinsic signals might be involved in promoting BP proliferation in species with an expanded neocortex (Kalebic et al., 2019). Various extrinsic signals coming from other progenitors, projection neurons and interneurons, blood vessels and extracellular matrix (ECM) have been identified and proposed to influence BP proliferation (Fietz et al., 2010; Masuda et al., 2015; Reillo et al., 2017; Stenzel et al., 2014; Tan et al., 2016). Many of these signals are thought to contribute to the generation of a proliferative niche in the OSVZ of species with an expanded neocortex.

A proliferative niche in the OSVZ as a basis underlying neocortex expansion

From various gene expression studies in human and mouse developing neocortex (Albert et al., 2017; Camp et al., 2015; Fietz et al., 2012; Florio et al., 2015; Pollen et al., 2015), a new concept emerged suggesting that ECM is a key component of an OSVZ niche in species with an expanded neocortex. Thus, ECM is the major GO term enriched in the proliferative germinal zones of fetal human (VZ, ISVZ and OSVZ) and embryonic mouse (VZ) neocortex (Fietz et al., 2012). ECM components have also been found to be enriched in human developing neocortex compared to mouse (Albert et al., 2017; Fietz et al., 2012; Florio et al., 2015). Cell type and single-cell analyses further revealed that BPs themselves likely generate the proliferative niche as they express various ECM components (Albert et al., 2017; Camp et al., 2015; Florio et al., 2015; Pollen et al., 2015). Specifically, proteoglycans and laminins have been shown to be involved in proliferation of BPs in the developing neocortex (Long and Huttner, 2019). It is thought that ECM promotes proliferation in two ways; by modulating signaling of growth factors, such as FGF (Kerever et al., 2007), and by directly signaling via ECM receptors (Fietz and Huttner, 2011; Long and Huttner, 2019). In addition, ECM has been shown to affect neocortex development by regulating progenitor cell shape, neuronal differentiation and migration and by altering the morphology of the tissue. A recent study identified a mixture of ECM components that was sufficient to induce precocious folding of fetal human neocortex tissue in explant culture (Long et al., 2018). Interestingly, this folding was not caused by an increase in neural progenitor proliferation, but rather through a direct effect of ECM components on tissue morphology, further expanding the spectrum of ECM contributions to neocortex development (Long and Huttner, 2019; Long et al., 2018).

ECM components are thought to exert their direct pro-proliferative role mostly via their main receptors, the integrins. Integrins are well-known regulators of aRG proliferation and morphology (Loulier et al., 2009; Radakovits et al., 2009). The characterization of an ECM-mediated OSVZ niche and of proliferative bRG in ferret and human developing neocortex prompted studies on the putative role of integrins for BP proliferation. Functional disruption of integrins in ferret led to a specific decrease in bRG, without affecting bIPs (Fietz et al., 2010), suggesting an important role of integrins for maintaining the proliferation of bRG. Whether integrins are required for receiving pro-proliferative signals from the basal lamina or from the local OSVZ niche remained unknown. Important insights came from subsequent studies in mice. Activation of integrins in embryonic mouse neocortex led to an increase in bIP proliferation, showing that local SVZ signals might have a key importance here (Stenzel et al., 2014). Recently, it has been shown that increasing the number of BP processes in mouse BPs leads to an increase in BP proliferation via integrin signaling (Kalebic et al., 2019). Blocking of integrins in the embryonic mouse neocortex was sufficient to annul the morphology-mediated increase in BP proliferation, suggesting that integrin-mediated signaling from the ECM components may well be a major mechanism underlying the pro-proliferative OSVZ niche in species with an expanded neocortex (Kalebic et al., 2019).

Human-specific genes affecting BP proliferation

Our current understanding suggests that cell biological features of BPs and an ECM-modulated OSVZ niche are key factors underlying the evolutionary expansion of the mammalian neocortex. Indeed, the available data suggest that these features are more enhanced in macaque and ferret compared to mouse, and in macaque more than in ferret. Fetal human neocortex, however, has been considered to contain additional factors that further enhance neocortex expansion. This led to a search for human-specific genomic and gene expression traits, particularly for those pertinent to the developing

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neocortex (Dennis and Eichler, 2016; Florio et al., 2015; Pollen et al., 2019; Pollen et al., 2015). A recent analysis of previously published transcriptome datasets (Fietz et al., 2012; Florio et al., 2015; Johnson et al., 2015; Miller et al., 2014; Pollen et al., 2015) identified 15 human-specific genes preferentially expressed in neural progenitors compared to neurons (Florio et al., 2018). Functional studies have so far been reported for two of these genes: ARHGAP11B and NOTCH2NL.

Both ARHGAP11B (Florio et al., 2015; Florio et al., 2016) and NOTCH2NL (Fiddes et al., 2018; Florio et al., 2018; Suzuki et al., 2018) have been ectopically expressed in embryonic mouse neocortex and shown to be able to increase BP proliferation. Interestingly, their effects on BP proliferation mostly involved bIPs and not bRG. Expression of ARHGAP11B in embryonic ferret neocortex, however, resulted in an increase in both bIP and bRG proliferation (Kalebic et al., 2018), suggesting that a favorable environment of a gyrencephalic neocortex may be required to support ARHGAP11B-mediated effects on bRG. NOTCH2NL was shown to increase human cortical progenitor maintenance in vitro (Suzuki et al., 2018), whereas disruption of NOTCH2NL in human cerebral organoids led to a reduction of progenitor proliferation and premature neuronal differentiation (Fiddes et al., 2018). These effects of NOTCH2NL were shown to be mediated by Notch signaling, one of the major signaling pathways regulating neocortex development (Fiddes et al., 2018; Suzuki et al., 2018).

The long-term consequences of the effects of ARHGAP11B on BPs have also been studied. The ARHGAP11B-promoted increase in BP proliferation in mouse led to an increase in SVZ thickness, followed (in half of the embryos) by an induction of neocortex folding, which normally is never observed in this species (Florio et al., 2015). In ferret, expression of ARHGAP11B led to an extension of the neurogenic period and increased the generation of late-born neurons, fated to the upper layers of the neocortex (Kalebic et al., 2018). This increased production of upper-layer neurons led to an increase in neuronal density, resulting in ARHGAP11B-expressing ferrets diverging from the non-primate scaling rules and adhering to the primate ones (Kalebic et al., 2018). In this context it is worth concluding that certain human-specific genes expressed in BPs within an OSVZ niche can recapitulate key features of the evolutionary expansion of the neocortex when ectopically expressed in species with a smaller neocortex.

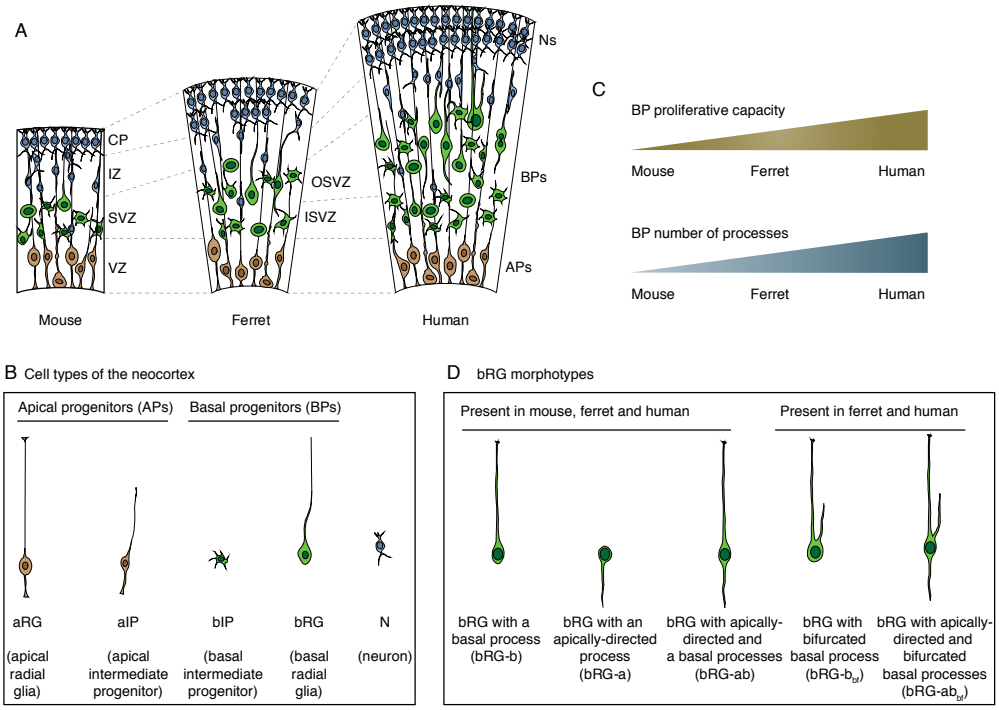

Fig 2. Cell biological features of the evolutionary expansion of the mammalian neocortex.(A) *Expansion of the germinal zones during the embryonic/fetal development. The ventricular zone (VZ) is the major proliferative zone in species with a small neocortex (mouse) and is populated with apical progenitors (APs). In species with an expanded neocortex (ferret, human), the subventricular zone (SVZ) became the major proliferative zone; it can be divided into two distinct zones: inner and outer SVZ (ISVZ and OSVZ, respectively). These zones are populated with basal progenitors (BPs). Both types pf progenitors produce neurons (Ns) that migrate through the intermediate zone (IZ) to find their final position in the cortical plate (CP). (B) Cell types of the developing neocortex. At mid-neurogenesis APs can be divided into two subtypes of cells: apical radial glia (aRG) and apical intermediate progenitors (aIPs). BPs can be divided into basal intermediate progenitors (bIPs) and basal radial glia (bRG).(C) BPs are the major cell type underlying the evolutionary expansion of the neocortex. These cells exhibit a greater proliferative capacity and a greater number of cell processes in species with an expanded neocortex (ferret, human) compared to species with a small neocortex (mouse). (D) Morphotypes of bRG. Left, three bRG morphotypes found in all mammalian species examined (bRG-b, bRG-a, bRG-ab). Right, two bRG morphotypes identified only in species with an expanded neocortex (bRG-bbf and bRG-abbf).*

Outlook

Despite exciting recent progress in understanding the mechanisms underlying the evolutionary expansion of neocortex, several important questions still remain unanswered. Over the past years many new molecular regulators of neurogenesis have been identified, as well as new types of neural progenitor cells. Collectively, this work is showing a complexity of neocortex development that is greater than previously thought. This opens new research avenues for better understanding how BPs in species with an expanded neocortex are generated, how they maintain their proliferative capacity in the SVZ, which extrinsic signals do they receive, which cell biological features do they gain during neocortex evolution, and how all these features interact to result in an expanded neocortex. Finally, primate-specific and human-specific features are likely to play additional roles in many of these processes.

To address these questions, novel technological advances are being very helpful. Addition of new model organisms and cell culture models accompanied by the ability of genome editing are major technological innovations enabling researchers to effectively study the complexity of neocortex development and evolution. In the last 5 years CRISPR/Cas9-mediated genome editing revolutionized biomedical research and allowed unprecedented possibilities for genetic manipulation in virtually any organism (Komor et al., 2017). In the field of neocortex development and evolution, in vivo genome editing has been applied to disrupt gene expression in mouse neural progenitors (Kalebic et al., 2016) and neurons (Shinmyo et al., 2016; Straub et al., 2014), to label endogenous mouse proteins (Mikuni et al., 2016), to knock-in fluorescent tags in embryonic mouse and ferret neocortex (Tsunekawa et al., 2016), and to perform epigenome editing in mouse neural progenitors (Albert et al., 2017).

The ability of acute genetic manipulation in ferret during embryonic development (Kawasaki et al., 2012; Kawasaki et al., 2013) opened up new possibilities to study BPs in vivo in a gyrencephalic context (Kalebic et al., 2018; Masuda et al., 2015; Matsumoto et al., 2017; Toda et al., 2016). Application of genome editing to generate transgenic ferrets has recently shown that this gyrencephalic species successfully recapitulates some of the key aspects of human neurodevelopmental abnormalities such as microcephaly (Johnson et al., 2018). In addition to the established model organisms, new species are being studied. Particularly interesting from an evolutionary aspect are the members of the order Scadentia, the closest relatives to primates (Figure 1). Recent analysis of neural progenitor cells in tree shrews, which belong to Scadentia, is very helpful in this context (Romer et al., 2018). Non-human primates are highly valuable model organisms to study some of the most complex features of human neocortex development. Genetic modification of the nearly-lissencephalic marmoset (Kishi et al., 2014; Sasaki et al., 2009) and the gyrencephalic macaque (Niu et al., 2014) is now opening new possibilities to assess the complexity of the evolutionary expansion of the neocortex.

In addition to in vivo models, cerebral organoids (Lancaster et al., 2013) have proven to be a valuable source of information for some aspects of human neocortex development. One of the most promising applications of cerebral organoids is in comparing human neocortex development with that of other primates and in particular great apes (Mora-Bermudez et al., 2016; Otani et al., 2016; Pollen et al., 2019). Together with differences in gene expression (Mora-Bermudez et al., 2016; Pollen et al., 2019), these studies revealed very fine cell biological differences between human and chimpanzee neural progenitor cells (Mora-Bermudez et al., 2016). Combining cerebral organoids and in vivo studies using gyrencephalic species with the power of genome editing gives unparalleled opportunities to further dissect the complexity of the evolutionary expansion of the neocortex and human brain development.

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