Cerebral cortex expansion and folding: what have we learned?

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Abstract

One of the most prominent features of the human brain is the fabulous size of the cerebral cortex and its intricate folding. Cortical folding takes place during embryonic development and is important to optimize the functional organization and wiring of the brain, as well as to allow fitting a large cortex in a limited cranial volume. Pathological alterations in size or folding of the human cortex lead to severe intellectual disability and intractable epilepsy. Hence, cortical expansion and folding are viewed as key processes in mammalian brain development and evolution, ultimately leading to increased intellectual performance and, eventually, to the emergence of human cognition. Here, we provide an overview and discuss some of the most significant advances in our understanding of cortical expansion and folding over the last decades. These include discoveries in multiple and diverse disciplines, from cellular and molecular mechanisms regulating cortical development and neurogenesis, genetic mechanisms defining the patterns of cortical folds, the biomechanics of cortical growth and buckling, lessons from human disease, and how genetic evolution steered cortical size and folding during mammalian evolution.

Keywords evolution; ferret; gyrencephaly; humans; neocortex

DOI 10.15252/embj.201593701 | Received 15 December 2015 | Revised 23 February 2016 | Accepted 17 March 2016 | Published online 7 April 2016

The EMBO Journal (2016) 35: 1021–1044

Introduction

In 1990, Wally Welker published a landmark book chapter updating on all that was known about the physiological, experimental, and pathological causes of cortical folding and misfolding, including comparative and phylogenetic considerations (Welker, 1990). Twenty-five years later, we have been invited to present an update of current knowledge on this matter. Welker’s review was 134 pages long and cited 665 references, and much progress has been made since then. Clearly, if our review on cortical folding has to fit in this issue of The EMBO Journal, something has to be done. Our solution is to limit the size of this review by focusing and briefly touching on what we feel have been the most significant advances in this period leading to our current understanding of the biology of this problem.

Cellular mechanisms leading to cerebral cortex expansion and folding

In order to understand the developmental mechanisms involved in cortical expansion and folding, we will frame these within the basic principles of cerebral cortex development as found in the most common animal model, the mouse.

Telencephalic neuroepithelium

In the early embryo (in mouse c. 9 days postconception, E9), the expansion of the rostral-most domain of the neural tube gives rise to the two telencephalic vesicles. The dorsal half of these vesicles is then

One of the most prominent features of the human brain is the fabulous size of the cerebral cortex and its folding, visible as bulges and grooves on its external surface. Most animals with a large brain have a folded cortex, whereas most animals with a small brain have a smooth cortex, without folds. The cerebral cortex is a laminar tissue where neurons lie on the upper part, and the lower or inner part contains most of the wire connecting neurons between brain areas. In big brains, this sheet of neural tissue covering the outside of the brain is disproportionately larger than the deep brain structures it covers, and instead of adopting a balloon-like conformation it folds onto itself, minimizing total brain and cranial volume. In addition to minimizing brain volume, cortical folding is of key importance for the optimization of brain wiring and functional organization (Klyachko & Stevens, 2003), and alterations in cortical size or folding lead to severe intellectual disability and intractable epilepsy in humans (Walsh, 1999; Barkovich et al., 2012).

The process of cortical folding takes place during brain development, and thus, it is essentially a developmental problem. In this review, we will start describing exciting discoveries made over the last fifteen years on the central role of progenitor cell proliferation and survival in cortical size, the discovery of novel germinal zones and progenitor cell types, which are greatly overrepresented in gyrated brains, and their key function in cortical folding. This will be followed by our understanding of the genetic mechanisms regulating the patterns of cortical folding and the biomechanics of this process, what we have learned from human disease, and finally will close with a view of how genetic evolution may have steered cortical size and folding during mammalian evolution.
molecularly specified as the primordium of the cerebral cortex. At this stage, the cortical primordium is solely composed of a monolayer of neural stem neuroepithelial cells (NECs; Bayer & Altman, 1991). NECs are highly polarized and attached to each other by adherens and tight junctions at the level of the apical domain (inner surface of the telencephalic vesicle) and which move their cell nucleus between the apical and the basal sides of the neuroepithelium in coordination with the cell cycle: basal-directed movement during G1, basal position during S-phase, apical-directed movement during G2, and mitosis at the apical surface. This cyclic movement is known as interkinetic nuclear migration and is completely asynchronous between NECs, conferring the neuroepithelium a pseudostratified appearance (Sauer, 1935; Bayer & Altman, 1991; Taverna & Huttner, 2010). NECs only undergo symmetric self-amplificative divisions, whereby each division generates two daughter NECs, hence exponentially increasing their number (Miyata et al., 2010; Fig 1).

Because NECs are the founder progenitor cells of the cerebral cortex, their pool size determines the numbers of their derived neurogenic progenitor cells and the final number of cortical neurons, and hence, it has a fundamental impact on the size of the mature cerebral cortex. Accordingly, already at this early stage, the size of the telencephalic vesicles is much larger in the human than in mouse embryo, reflecting significant differences in size of the neuroepithelium as a consequence of different NEC abundance (Sidman & Rakic, 1973; Rakic, 1995). NEC abundance may be increased by extending the time period of their self-amplification and delaying the onset of neurogenesis, as observed in primates compared to rodents (Rakic, 1995, 2009; Kornack & Rakic, 1998). The importance of NEC amplification on cortical size has been experimentally demonstrated in mouse, where NEC abundance in the embryonic cortex may be increased by either promoting their re-entry into cell cycle or preventing programmed cell death (Chenn & Walsh, 2002; Kingsbury et al., 2003). In both cases, increased NEC abundance leads to expansion in surface area and folding of the neuroepithelium.

**Proliferation and neurogenesis**

Immediately prior to the onset of neurogenesis, NECs start losing tight junctions and begin acquiring features typical of glial cells,
including the expression of brain lipid-binding protein (BLBP), vimentin, and Pax6, thus becoming apical radial glial cells (aRGCs; see Taverna et al (2014) for a detailed review on the cell biology of this process). Like NECs, aRGCs undergo interkinetic nuclear migration, divide at the apical surface of the developing cortex and, at this early stage (c. E10 in mouse), also undergo self-amplifying divisions. However, aRGCs gradually start dividing asymmetrically to generate one aRGC plus a different cell. These new cells accumulate at the basal side of the cortical primordium, while the cell bodies of aRGCs remain in the apical side, forming the ventricular zone (VZ; Fig 1). With the accumulation of cells above the VZ, the basal process of aRGCs elongates while remaining attached to the basal lamina and is now termed radial glial fiber. Asymmetric aRGC divisions generate one aRGC plus either one neuron or one intermediate progenitor cell (IPC; Malatesta et al, 2000; Noctor et al, 2001, 2004; Haubensak et al, 2004; Miyata et al, 2004; Fig 1). IPCs are secondary progenitor cells without apical–basal polarity, do not undergo interkinetic nuclear migration, reside and divide in a location immediately basal to the VZ, the subventricular zone (SVZ), and contrary to aRGCs, they all express the transcription factor Tbr2 (Englund et al, 2005). In mouse, the vast majority of IPCs divide once to produce 2 neurons (neurogenic, self-consuming divisions), and hence, they are viewed as a strategy to amplify the production of cortical neurons. However, because each IPC self-consumes at mitosis, their relative abundance compared to aRGCs is quite low (Kowalczyk et al, 2009). IPCs in the cerebral cortex generate most cortical excitatory neurons (Attardo et al, 2008; Kowalczyk et al, 2009), whereas inhibitory interneurons are generated extra-cortically (Anderson et al, 1997). As neurogenesis progresses, there is a lower requirement for aRGC expansion/ renewal and a greater need for neuron production, so there is a gradual predominance of asymmetric aRGC divisions producing IPCs (Noctor et al, 2004; Kowalczyk et al, 2009).

In addition to aRGCs and IPCs, the embryonic mouse cortex includes other much less abundant types of progenitor cells. Populating the VZ, we find apical intermediate progenitors (aIPs), which divide at the apical surface to produce neurons (Stancik et al, 2010; Tyler et al, 2015), and subapical progenitors (SAPs), which divide within the VZ, but away from the apical surface to generate IPCs (Pilz et al, 2013). Populating the SVZ, we find basal radial glial cells (bRGCs), which share many similarities with aRGCs including a basal process extended radially and contacting the basal lamina of the telencephalon, and expression of the transcription factor Pax6, but whose cell body is located and divides at basal positions in the SVZ (Shitamukai et al, 2011; Wang et al, 2011; Fig 1). As opposed to aRGCs, bRGCs in mouse do not self-amplify or produce IPCs, but are highly neurogenic (Wang et al, 2011).

In gyrencephalic species like humans, monkey, or ferret, the abundance of aRGCs is much greater than in species with a smooth cortex like mouse, producing a more extended VZ. This is a direct consequence of the higher abundance of founder NECs at earlier stages (see above), further promoted by an increased self-amplification of aRGCs in these species. In addition to having an extended VZ, the most remarkable distinction of gyrencephalic species is having a thickened SVZ populated by an outstanding abundance of basal progenitors, especially at later stages of neurogenesis when these greatly outnumber apical progenitors (Smart et al, 2002; Lukaszewicz et al, 2005; Reillo et al, 2011; Reillo & Borrell, 2012). This abundance of basal progenitors is accompanied by the splitting of the SVZ in inner (ISVZ) and outer (OSVZ) subdivisions, not found in mouse (Smart et al, 2002; Fietz et al, 2010; Hansen et al, 2010; Reillo et al, 2011; Reillo & Borrell, 2012).

The OSVZ contains a wide diversity of progenitor cell types with high amplificative potential, and the combination of these two factors is considered key for cortical expansion and folding (Lui et al, 2011; Betizeau et al, 2013; Borrell & Gotz, 2014). Contrary to the lissencephalic mouse, in gyrencephalic species few basal progenitors are IPCs, but most are bRGCs (Hansen et al, 2010; Reillo et al, 2011; Reillo & Borrell, 2012; Betizeau et al, 2013). A seminal videomicroscopy study demonstrated that in macaque (a gyrated primate), bRGCs come in different modalities, which frequently transition between them and with IPCs, and all of these types of progenitors may self-amplify prior to generating neurons (Betizeau et al, 2013). Importantly, in gyrencephalic cortices like macaque and ferret, neurogenesis takes place during a period of time much longer than in rodents (up to tenfold; Takahashi et al, 1993; Kornack & Rakic, 1998; Lukaszewicz et al, 2005; Reillo & Borrell, 2012), allowing more rounds of cell division and increasing neuronal output (Dehay & Kennedy, 2007; Florio & Huttner, 2014). On these grounds, we and others have proposed that the OSVZ, with its wealth of neurogenic basal progenitors, plays central roles in the dramatically increased neurogenesis and folding in the cerebral cortex of higher mammals (Fig 2A; Fietz & Huttner, 2011; Lui et al, 2011; Borrell & Reillo, 2012; Borrell & Calegari, 2014; Borrell & Gotz, 2014; Florio & Huttner, 2014). This idea is well supported by experimental work in the gyrencephalic ferret, which demonstrates that forced overproliferation of OSVZ progenitors increases cortical surface area and folding, whereas blockade of their proliferation has the opposite effect (Reillo et al, 2011; Nonaka-Kinoshita et al, 2013). The central relevance of the OSVZ in cortical expansion and folding resides not only on its prominent contribution to increase neuron production, but also specifically on its high content of bRGCs, as explained in the next section.

**Radial migration**

Newborn cortical excitatory neurons must travel (migrate) from their layer of birth to the vicinity of the cortical surface, where they will coalesce into nascent neuronal layers. This process is named radial migration (Rakic, 1972). The scaffold of radial glial fibers, which span perpendicular between the ventricular and the pial surface of the cortex, provides the necessary substrate and guide for these neurons during their radial migration, much like the rail tracks for a train. This cell–cell interaction is under tight molecular regulation, and its disruption leads to severe defects of neuronal positioning and layer formation in the cortex (Sidman & Rakic, 1973; Rakic et al, 1974; Rakic, 1978; Anton et al, 1997, 1999; Elias et al, 2007). Due to this dependence of radially migrating neurons on radial glial fibers, the trajectory of these fibers largely defines the migratory route and final location along the cortical surface of new neurons (Rakic, 1995). Consequently, sibling neurons born from one progenitor normally occupy neighboring positions in the mature cerebral cortex (Fig 2B; Soriano et al, 1995; Gupta et al, 2003; O’Leary & Borngasser, 2006; Gao et al, 2014).

In contrast to the mouse cerebral cortex, a characteristic feature of folded cortices during development is their much greater surface area on the pial than on the ventricular side (Sidman & Rakic, 1973; Kriegstein et al, 2006; Rakic, 2009). This expansion of the pial
Figure 2.
surface relates to the increased numbers of cortical neurons, largely based on the expansion of basal progenitors. Several hypotheses have been proposed to explain how basal progenitors may promote this difference between pial and ventricular surface during development (Kriegstein et al., 2006; Fietz & Huttner, 2011). However, a critical issue overseen in early hypotheses is that whereas the addition of basal progenitors explains increased neurogenesis without expanding the ventricular surface area, the amount of radial fibers from aRGCs also does not expand, which is problematic. If the radial fiber scaffold does not increase as neurogenesis increases, then radial fibers (the rail tracks for migrating neurons) become a limiting factor to be shared by the augmented population of radially migrating neurons. As a result, neurons pile up in thickened cortical layers without a significant lateral separation, and thus, surface area does not increase and folds do not form. Intriguingly, this is reminiscent of human lissencephaly, where cortical layers are several-fold thicker than normal and folds fail to form (see section below). However, this is not the case in gyrencephalic brains, where the outer surface area of the cerebral cortex increases several orders of magnitude more than thickness (i.e., the human cortex has 1,000 times more surface area than in mouse, but is only 10 times thicker) and without a similar increase in VZ surface area.

Thus, the radial fiber scaffold must be modified so that the increased numbers of radially migrating neurons do not pile in thick layers, but are distributed along the cortex. An elegant solution to this problem is to create a divergence in the array of radial fibers with additional, intercalated fibers. Under this circumstance, neurons migrating radially and in intimate association with radial fibers find additional paths for migration, which has two advantages: (i) overcrowding of the migratory paths is released so radial migration is not delayed and (ii) radially migrating neurons are delivered to distant positions along the cortical surface (Fig 2B). The source of additional radial fibers to create this divergence is bRGCs (Reillo et al., 2011). Basal RGCs have a radial fiber extended to the pial surface, their cell soma is located in ISVZ or OSVZ, basal from aRGCs, and they are not anchored to the apical VZ surface. Hence, bRGCs are in the optimal position to provide additional radial fibers to create the divergence and fanning out of the radial fiber scaffold, without increasing VZ surface area, as reported in ferret (Fig 2B; Reillo et al., 2011). Importantly, in spite of the divergence of radial fibers, thanks to bRGCs their density remains high through the cortical thickness, and many are even intercrossed (Rakic et al., 1974; Reillo et al., 2011), so neurons can disperse laterally while maintaining radial glia-dependent migration, as recently demonstrated in ferret (Gertz & Kriegstein, 2015). In the developing ferret cortex, the fanning of the radial fiber scaffold is significant in prospective gyrus, but not in prospective sulcus regions, which further supports that this is a driving force in cortical surface area expansion and folding (Lui et al., 2011; Reillo et al., 2011; Borrell & Reillo, 2012). Importantly, this “radial divergence model” has been validated by several laboratories, where bRGC abundance and proliferation have been experimentally manipulated in ferret and mouse. Partial blockade of OSVZ progenitor proliferation in the developing ferret cortex without a significant neuronal loss leads to a reduction in size of cortical folds (Reillo et al., 2011) and even lissencephaly (Poluch & Juliano, 2015). Conversely, forced overproliferation of OSVZ progenitor cells in ferret significantly increases cortical surface area and folding (Nonaka-Kinoshita et al., 2013). Finally, even in the naturally smooth mouse cortex, genetic manipulations forcing an increased abundance of bRGCs during embryonic development lead to the formation of cortical folds (Stahl et al., 2013; Florio et al., 2015).

**Differentiation**

Once neurons finish radial migration and detach from the radial fiber, they begin terminal differentiation. This process has a fundamental impact in the final size of the cerebral cortex, essentially by increasing the size of cell somas and the volume of the neuropile: growth and branching of apical and basal dendrites; extension, navigation, and branching of the axon; formation of spines and boutons for synaptic connectivity. Packing density of cortical neurons, cell body size, and extent of their dendritic and axonal arbors are remarkably different between mammals, correlating with brain size (Purves, 1988) and also contributing to cortical expansion (Reillo et al., 2011).

**Molecular regulation of cellular mechanisms**

Over the last two decades, hundreds of studies have deciphered some of the key molecular mechanisms regulating cerebral cortex development in mouse. Although this invaluable knowledge is frequently extensible to humans and other species at the level of basic cellular mechanisms, much less is really known about the molecular regulation of events key for cortical expansion and folding. In this section, we provide an overview of some of this knowledge, and how it may be extensive to cortical folding.

**NEC amplification versus transition to RGC**

At early stages of cortical development, several signaling cascades regulate the maintenance of NEC self-amplification. One of the most potent promoters of NEC self-amplification is the β-catenin pathway, such that its constitutive activation in mouse embryos leads to the overexpansion and folding of the cortical neuroepithelium (Chenn & Walsh, 2002). Expansion and significant folding of the mouse cortical neuroepithelium is also achieved by limiting developmental apoptosis, by means of lysophosphatidic acid signaling (Kingsbury et al, 2003). Conversely, the fibroblast growth factor (FGF) pathway, by means of FGF10, drives NECs into expressing radial glial cell markers and thus promotes their transition toward aRGC fate, terminating the phase of NEC amplification (Sahara & O’Leary, 2009).
Intriguingly, FGF signaling promotes retention of the aRGC fate, as it also inhibits the subsequent transition of aRGCs toward basal progenitors (Kang et al., 2009). The transition from NECs to aRGCs is also strongly promoted by the activation of the Notch signaling pathway (Gaiano et al., 2000; Hatakeyama et al., 2004; Fig 1).

**Progenitor amplification**

In addition to their role in blocking the maturation of cortical progenitors, FGF ligands promote their proliferation and inhibit neurogenesis by regulating the duration of the cell cycle. This role of FGF signaling is critical for cortical growth, as its loss at early stages accelerates neuron production and loss of RGCs, resulting in reduced cortical surface area (Rash et al., 2011). Conversely, overactivation of FGF signaling by infusion of FGF2 or FGF8b causes the overproliferation of cortical progenitors and cortical expansion in surface area (Rash et al., 2013; Fig 1). FGFs influence cortical progenitors via regulation of cell cycle proteins. FGF2 and insulin-like growth factor (IGF) 1 upregulate the expression of cyclin D1 and downregulate the expression of p27(kip1), a cyclin-dependent kinase (CdK) inhibitor, thereby shortening the G1 phase of the cell cycle and promoting self-amplificative divisions (Rabalio et al., 2000; Lukaszewicz et al., 2002; Mairet-Coello et al., 2009). Activation of this FGF signaling cascade drives cortical expansion, which is accompanied by the incipient folding of the otherwise smooth mouse cortex (Rash et al., 2013), and in the already gyrencephalic ferret cortex, it causes extra folding (Masuda et al., 2015). Not surprisingly, cortical progenitor populations may be expanded directly by overexpressing Cdk4 and cyclin D1 (Lange et al., 2009).

However, in the mouse cortex, this promotes cortical growth and megalencephaly, but not folding (Nonaka-Kinoshiita et al., 2013), which highlights the molecular and cellular complexity of the process of cortical folding (Borrell & Calegari, 2014).

Other important signaling pathways regulating cortical progenitor proliferation and self-renewal include the Wnt, BMP, MAPK, and Notch pathways. Unfortunately, none of these pathways have been found able to induce bona fide cortical folding in mouse, and there are no experimental data in naturally gyrencephalic species. One of the best-known pathways regulating the balance between progenitor proliferation and neurogenesis is Notch. In addition to promoting the transition from NECs to aRGCs at early developmental stages (Gaiano et al., 2000; Hatakeyama et al., 2004; Martynoga et al., 2012), activation of the Notch pathway at later stages inhibits the generation of IPCs from aRGCs (Mizutani et al., 2006; Ohata et al., 2011; Martynoga et al., 2012). Conversely, the onset of Dll1 expression (the main ligand of Notch1) coincides with the expression of the pro-neural proteins Ngn2 and Ascl1, which are major transcriptional regulators of neurogenesis and also directly regulate Dll1 expression (Castro et al., 2006; Martynoga et al., 2012). The Notch pathway can be additionally activated by Slit/Robo signaling, with similar consequences: impairment of neurogenesis at early stages by favoring the self-renewal of aRGCs (Borrell et al., 2012). Importantly, Notch signaling seems to be required for the self-renewal of OSVZ progenitors in the human cerebral cortex (Hansen et al., 2010).

Regarding Wnt, activation of this pathway promotes proliferation and self-renewal of aRGCs at early developmental stages (Machon et al., 2003; Woodhead et al., 2006; Zhou et al., 2006), while at later stages it promotes the maturation of aRGCs into IPCs (Viti et al., 2003; Hirabayashi et al., 2004) and it may even promote neurogenesis (Munji et al., 2011). Thus, the effects of Wnt signaling in cortical development are complex and time-regulated during development. The BMP pathway has similarly elusive and complex inputs into the regulation of cortical neurogenesis. At early developmental stages, BMP signals induce neurogenesis (Li et al., 1998; Mabie et al., 1999), while at later stages, they block neurogenesis to promote astrocyte differentiation (Gross et al., 1996). The Ras-MAPK-ERK pathway controls the mitogen-stimulated proliferation of cortical progenitors and its negative regulators, thus ensuring progenitor self-renewal and preventing premature differentiation (Phoenix & Temple, 2010). Finally, IGF-2 secreted into the cerebrospinal fluid by the choroid plexus is another potent mitogen promoting proliferation of VZ cortical progenitors (Lehtinen & Walsh, 2011; Lehtinen et al., 2011).

Recently, retinoic acid (RA) signaling has also been identified as important in regulating the balance between cortical progenitor self-renewal and neurogenesis, where RA secreted by the meningeal membranes promotes neurogenesis while limiting aRGC amplification (Siegenthaler et al., 2009). Contrary to the classical signaling pathways mentioned above, the RA pathway holds promise as an important regulator of cortical expansion and folding, as its genetic blockade induces remarkable folding of the mouse cortex (Siegenthaler et al., 2009). The downstream transducers of RA signaling in this context are not known, but the orphan nuclear hormone receptor CoupTF1 and the pro-neural transcription factors Ngn1 and 2 may be involved (Ribes et al., 2008; Harrison-Uy et al., 2013).

**Progenitor cell lineage**

Whereas cortical folding is positively correlated with increased brain size and greater numbers of neurons, mounting evidence from comparative neuroanatomy and human pathology strongly supports that increased neuron numbers are not sufficient, but cortical folding requires additional mechanisms of developmental regulation (Welker, 1990; Borrell & Reillo, 2012). As explained in the previous section, the tangential dispersion of radially migrating neurons seems key in the expansion of cortical surface area that leads to folding, and this depends on the relative abundance of bRGCs (Reillo et al., 2011; Pilz et al., 2013). Hence, lineage regulation of the different types of cortical progenitors, particularly the production and maintenance of bRGCs, is critical in this process (Borrell & Gotz, 2014).

In the cerebral cortex of mouse, ferret, and humans, bRGCs are generated from aRGCs in the VZ (Reillo et al., 2011; Shitamukai et al., 2011; Wang et al., 2011). This process is seemingly associated with, and controlled by, the mitotic spindle orientation of aRGCs (Shitamukai et al., 2011; LaMonica et al., 2013), which is known to have a strong influence on the acquisition of asymmetric cell fates by cortical progenitors (Postiglione et al., 2011; Xie et al., 2013). Progenitors in the early neuroepithelium divide mostly in perpendicular orientations while oblique cleavage planes augment as neurogenesis becomes predominant, and disruption of these orientations at early stages leads to depletion of the progenitor pool (Mitchison & Kirschner, 1984; Chen & McConnell, 1995; Yingling et al., 2008). Orientation of the mitotic spindle in the mammalian cerebral cortex is regulated by a number of factors, including LGN, Insc, and Lis1 (Yingling et al., 2008; Postiglione et al., 2011; Shitamukai et al., 2011; Fig 1).

In addition to the cleavage plane orientation, there are other cellular mechanisms regulating cortical progenitor cell fate,
particularly symmetric versus asymmetric fates, which include the
maintenance of the apical–basal polarity by Notch signaling, Par3,
Par6, prominin-1 (CD133), and other proteins related to the apical
adherens junctions (Hatakeyama et al., 2004; Gotz & Huttner, 2005;
Costa et al., 2008; Bultje et al., 2009; Krieger & Alvarez-Buylla,
2009; Imayoshi et al., 2010). A decrease in apical junction proteins
like Par3 or Par6 switch the mode of aRGC division from self-
renewing to neurogenic, while their overexpression promotes aRGC
self-renewal (Costa et al., 2008).

A landmark finding on the molecular regulation of cortical fold-
ing via control of progenitor cell lineage was the identification of
Trnp1, a key player in this process (Stahl et al., 2013). Trnp1 is a
DNA-associated protein initially identified as being strongly
expressed in self-amplifying aRGCs (Pinto et al., 2008). Starting at
high levels in the early embryo, Trnp1 expression decreases as
aRGCs gradually stop self-amplifying to produce IPCs and neurons.
Overexpression of Trnp1 promotes aRGC self-renewal at the
expense of IPCs and neurogenesis. Conversely, knockdown of Trnp1
function increases IPCs and, in addition, it dramatically increases
the abundance of bRGCs, otherwise very scarce in the mouse
embryo. Most importantly, these changes are associated with a
significant expansion of the cortical surface area and the formation
of structures resembling bona fide cortical folds, including modifi-
cation of the radial fiber scaffold and the divergent distribution of
radially migrating neurons (Stahl et al., 2013). Analyses of Trnp1
expression in the developing cortex of ferret and human embryos
are consistent with these functional results, as Trnp1 levels are
specifically low in cortical regions prospectively undergoing tangen-
tial expansion and folding (Stahl et al., 2013; de Juan Romero et al.,
2015). Thus, Trnp1 was the first gene able to induce bona fide fold-
ing of the mouse cerebral cortex.

A second gene causing folding of the mouse cortex has been
recently found: ARHGAP11B (Florio et al., 2015). This is a truncated
paralog of ARHGAP11A that arose on the human evolutionary
lineage after the divergence from the chimpanzee (Antonacci et al.,
2014), and hence does not exist in mouse. Similar to the loss of
function of Trnp1, experimental expression of ARHGAP11B in
mouse embryos drives cortical aRGCs into massively producing
basal progenitors, many of which are bRGCs, and this ultimately
translates into folding of the mouse cerebral cortex. The seminal
relevance of this study is the discovery of a gene with a likely
central role in human brain evolution and uniqueness, contributing
to further promote cortical expansion and folding in the hominid
lineage. High levels of the transcription factor Pax6 have also been
reported to promote the generation of bRGCs in mouse, but intriguingly
this does not cause cortical folding (Wong et al., 2015).

Progenitor cell heterogeneity: single-cell transcriptomics

One of the classical limitations of studies searching for genes impor-
tant in cortical development, expansion and folding was to analyze
progenitor cell pools instead of individual cells. The advent of single-
cell transcriptomics has revolutionized this field by allowing uncov-
ering an extraordinary molecular heterogeneity of progenitor cell
types in the developing cerebral cortex (Pollen et al., 2014). Impor-
tantly, this technology has revealed that aRGCs and bRGCs are
molecularly more heterogeneous in the developing folded cortex of
humans and ferret (3 classes of aRGC, 2 classes of bRGC) than in the
smooth cortex of mouse (2 classes of aRGC, 1 class of bRGC; Camp
et al., 2015; Johnson et al., 2015; Pollen et al., 2015). Although we are
just beginning to profit from the power of this technology, single-cell
transcriptomics is already highlighting the potential relevance of
specific signaling cascades and molecular programs in the formation
and maintenance of bRGCs in general and the OSVZ in particular.
For example, in agreement with previous population-wide transcript-
ic analyses and functional manipulations, the extracellular
matrix and its components are being highlighted as central in stimu-
lating cortical progenitor proliferation and self-renewal (Fietz et al.,
2010, 2012; Stenzel et al., 2014; Pollen et al., 2015).

Genetic patterning of cortical folds

What defines the location and shape of cortical folds and fissures as
they form in the developing cortex? The traditional view has been
that cortical folds form randomly, essentially based on the idea that
cortical growth exceeds cranial volume, and thus, cortical folding
occurs purely as a mechanical consequence of cranial constraint
(Welker, 1990). However, as discussed in a later section, evidence
indicates that both notions are wrong. If any portion of the cere-
brum fails to develop or grow, due to either pathological or experi-
mental causes, the skull tends to conform to the size and shape of
the remaining neural tissue, which in fact still folds, thus demonstrat-
ing that limited cranial volume does not force cortical folding
(Welker, 1990). Further evidence demonstrating that cortical folds
do not form randomly includes that (i) the pattern of folds and fis-
sures is highly stereotyped and well conserved between individuals
of a species, particularly in those with small gyrated brains (i.e.,
ferret, cat); (ii) folding patterns of phylogenetically related species
follow remarkably similar trends (Welker, 1990; Borrell & Reillo,
2012); (iii) even in species with large cortices and very complex
folding patterns, like humans, the deepest and earliest fissures to
develop do so at strikingly conserved positions, particularly in
monozygotic twins where the overall folding pattern is significantly
well conserved (Lohmann et al., 1999, 2008). Taken together, corti-
cal folding patterns appear subject to strong genetic regulation.

In species with a simple pattern of folds, like ferret and cat, the
stereotyped location of cortical folds and fissures is preceded and
mirrored by regional variations in progenitor cell proliferation, in all
three germinal layers, but most prominently in the OSVZ (Reillo
et al., 2011). Local manipulations of OSVZ proliferation in ferret
have a significant impact on the size and shape of cortical folds,
without altering cortical area identity nor lamination (Reillo et al.,
2011; Ghosh & Jessberger, 2013; Nonaka-Kinoshita et al., 2013).
To identify genes whose expression covaries with the stereotypic
patterning of progenitor proliferation and cortical folds, microarray
technology was recently used to compare the transcriptome of
progenitors in prospective folds versus fissures of the developing
ferret cortex (de Juan Romero et al., 2015). This analysis demon-
strates the existence of thousands of genes differentially expressed
(DEGs) between these regions, mostly in OSVZ and VZ. Identified
DEGs include genes key in cortical development and folding like
Trnp1 or Ccnd1, as well as genes mutated in human malformations
of cortical development. Many DEGs are expressed in modules along
the OSVZ and other germinal layers of the gyrencephalic ferret
and also the human embryo cortex, but not in the lissencephalic
mouse cortex (Sansom & Livesey, 2009; Elsen et al., 2013; de Juan
et al., 2015; Johnson et al., 2015; Pollen et al., 2015).
Most remarkably, expression modules along the OSVZ map faithfully the eventual location of cortical folds and fissures (de Juan Romero et al., 2015). This strongly supports a role for the OSVZ and some of those DEGs on cortical patterning, particularly in its stereotyped folding (Kriegstein et al., 2006; Lui et al., 2011; Reillo et al., 2011; Albert & Huttner, 2015; Fig 3).

Multiple genetic maps seem to overlap across germinal layers, as modular expression patterns also exist for DEGs in VZ and ISVZ of ferret and humans (de Juan Romero et al., 2011; Reillo et al., 2011; Taverna et al., 2014; Dehay et al., 2015). Indeed, many DEGs between the prospective gyrus and sulcus are known to regulate progenitor proliferation, neurogenesis, or fate specification, including key signaling pathways such as Notch, Shh, MAPK, and Wnt, which directly regulate cortical growth (see above). In the case of cortical folds, modular patterns of expression for a combination of genes, possibly different depending on the specific gyrus or sulcus, may impose differential tissue growth between modules, eventually leading to the evagination of the cortex and formation of folds (Smart & McSherry, 1986; Fig 3).

Small enhancer elements have been recently identified to drive reporter gene expression in discrete modules, or protodomains, also in the embryonic mouse cerebral cortex (Visel et al., 2013; Pattabiraman et al., 2014). These enhancers have been proposed to integrate broad transcriptional information, including expression of several transcription factors regulating cortical patterning, to define gene expression in those protodomains (Nord et al., 2013; Pattabiraman et al., 2014). Variations in such small enhancer elements may be indeed at the core of cortical patterning (and folding) during development and evolution (Borrell & Gotz, 2014; see below). However, the definition of discrete cortical subdivisions requires the regional control over the expression of protein-coding genes or their interfering RNAs (i.e., cell cycle regulators, cell fate determinants, neuron terminal selectors) in protodomains along the embryonic germinal layers, as demonstrated in ferret and humans, but not in mouse (Dehay & Kennedy, 2007; Molyneaux et al., 2007; Hobert, 2011; de Juan Romero et al., 2015). Walsh and colleagues recently identified a key regulatory element for the expression of human GPR56 which varies significantly across mammals and, when introduced in transgenic mouse embryos, drives different patterns of expression (Bae et al., 2014). Most importantly, GPR56 expression levels regulate cortical progenitor proliferation, and mutation of this regulatory element disrupts human cortex folding around the Sylvian fissure, demonstrating the importance of the expression pattern of this gene in defining the pattern of folds. Similarly, mutations in the regulatory region of human EOMES lead to significant alterations of cortical size and folding (microcephaly with polymicrogyria; Baala et al., 2007). In agreement with the notion of a protomap of cortical folding, both GPR56 and EOMES are expressed in modular patterns in the developing ferret and human cortex (de Juan Romero et al., 2015).

**Biomechanics of cortical folding**

**Cranial pressure**

One of the first hypotheses on the biomechanics of cortical folding proposed that cranial volume limits cortical size, so that as the cortical tissue grows in surface area the skull offers resistance to its outward expansion, forcing the neural tissue to fold onto itself (Le Gros Clark, 1945). The concept that brain morphology adapts to fit in a limited volume has been recently supported by experiments in chick embryos, where an experimentally expanded optic tectum folds to maintain cranial size (McGowan et al., 2012). However, studies focused specifically on the mammalian cerebral cortex have shown that cortical folding takes place even in the absence of
compressive constrain from the skull (Welker, 1990). For example, the removal of non-cortical brain tissue in sheep embryos alleviated any possible cranial pressure onto the growing cortex, and yet this did not suppress or simplify the formation of cortical folds (Barron, 1950; Muckli et al., 2009). On the contrary, development of the skull appears to be strongly influenced by brain growth, as cranial volume is significantly enlarged in pathologies where brain and cortical size are abnormally large, such as hydrocephalus or mega-lencephaly (Barkovich et al., 2012).

Axonal tension
The first attempt to mathematically model the biomechanical basis of cortical folding dates back four decades (Richman et al., 1975). This model proposed that cortical folding occurs as a result of differential growth between upper and lower cortical layers, which generates stress that is sufficient to induce cortical surface buckling. Thirty years later, Kriegstein and colleagues (Kriegstein et al., 2006) proposed that basal progenitors increase significantly neurogenesis at later stages, precisely when upper layers form, and that this enables the differential growth between layers and ultimately drives cortical folding. Whereas the Richman model showed that this principle is sufficient to convert a flat surface into wavy, it relies on such a difference in stiffness between neuronal layers that it seems unrealistic (Bayly et al., 2014).

Two decades passed before an alternative model was proposed to explain the biomechanics of cortical folding: the tension-based theory (Van Essen, 1997). This theory by Van Essen was conceptually based on D’Arcy Thompson’s analysis on how tension and pressure can interact with structural asymmetries to determine the shape of biological structures (Thompson, 1917). Van Essen argued that cortico-cortical axons are under strong tension, exerting significant pulling forces capable of deforming the cortical mantle, and that these cortico-cortical connections are not symmetric or homogeneously distributed, but some areas are more strongly connected together than with others. Under this scenario, he proposed that those areas connected with a larger amount of axons withstand a greater pulling force, and thus come close together to form a fold, whereas areas poorly interconnected are relayed to the opposite banks of a sulcus. This hypothesis attracted the enthusiasm of many, not only for its simplicity but also for its coherence. Indeed, two simple but fundamental observations made this a very attractive model: (i) The cortical sheet is physically tethered in only one axis, initially by radial processes and followed by connections between cortex and subcortical nuclei (De Carlos & O’Leary, 1992). Tension along these processes may provide a cohesive force against intraventricular hydrostatic pressure, ensuring that the cortical mantle remains tightly wrapped around the subcortical interior. (ii) Specific and topographically organized cortico-cortical projections are established early in development while convolutions are forming (Coogan & Van Essen, 1996; Hilgetag & Barbas, 2006). Van Essen proposed that if developing CNS axons in vivo generate even a modest fraction of the specific tension measured in vitro (Dennerll et al., 1988), then populations of axons pulling together should have ample strength to cause folding of the highly pliable embryonic cortical sheet (Van Essen, 1997). Importantly, this hypothesis also provided a basis for individual variability in brain morphology.

Remarkably, the tension-based theory was widely accepted for more than a decade without rigorous experimental testing. But 14 years later, Taber, Bayly, and colleagues performed a series of very simple and elegant experiments that frontally challenged the foundations of this theory (Xu et al., 2010). Their idea was that if axonal tension between opposite sides of a gyrus pulls them together, then these should come apart if these axons are cut and tension is released. This was tested in living brain slices from developing ferrets of various ages throughout the period of gyrus formation. These experiments showed that axons are indeed under considerable tension in the developing brain, but most of this tension is found along axon bundles in deep white matter tracts, not within the core of individual gyri and thus too far to play a major role in initiating, sustaining, or maintaining cortical folding (Armstrong et al., 1991; Xu et al., 2010). In addition, other computational models show that cortical folding may occur in the complete absence of cortico-cortical fibers, only as an effect of buckling instability (see below; Toro & Burnod, 2005).

Tissue buckling
Folding of the cerebral cortex, like any other tissue, is limited by its physical–mechanical properties of rigidity and pliability, which define the relationship between cortical thickness and surface area. As a general principle, given a cortical surface area, the periodicity of folding is inversely correlated with gray matter thickness (Hofman, 1985; Toro & Burnod, 2005; Pillay & Manger, 2007). This applies to interspecies differences (i.e., ungulates have a thinner and more folded cortex than primates, whereas in the manatee, the cortex is thicker and rather smooth; Welker, 1990) and also to human pathology, where lissencephalic patients with reduced folding display an abnormally thick cortex, and polymicrogyric cortices are abnormally thin (Olson & Walsh, 2002; Barkovich et al., 2012).

A very recent study proposes a general law for this inverse correlation between thickness and folding, based on measurements from 62 different species and describing a mathematical relationship between total cortical surface area, thickness, and exposed area (Mota & Herculano-Houzel, 2015). The basic idea is that cortical folding is similar to crumpling a ball of paper, where the periodicity of individual folds will be high in a ball of thin smoking paper (small folds) and very low if using thick cardboard paper (large folds). According to this study, the combination of total cortical area and thickness grows with exposed cortical area to the power of 1.25, in a similar fashion as the area of a circle increases with its radius raised to the power of 2. This relationship is also proposed to represent the topological configuration involving the minimal energy, and therefore, cortical folding may settle into the configuration of least energy (Mota & Herculano-Houzel, 2015). But there are several fundamental problems with the paper ball analogy: (i) It describes the folding of a structure that no longer grows, whereas the cortex folds while it continues to develop and grow; (ii) it is based on physical models only valid for single-molecule thin materials; (iii) the theory considers that the whole brain folds, whereas cortex folds while it continues to develop and grow; (iv) it is not based on single-molecule thin materials; (v) the theory considers that the whole brain folds, whereas cortex folds while it continues to develop and grow. Finally, folding of the cerebral cortex does not occur randomly, as crumpling of a paper ball, but in a rather highly stereotyped process, defining patterns that are characteristic and distinct for each species. Prior to their appearance, folding patterns are delineated by regional variations of progenitor cell proliferation (Reillo et al., 2011), and by modules of differential gene expression along germinal layers, as recently demonstrated via

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The EMBO Journal  Vol 35 | No 10 | 2016  1029
transcriptomic expression analyses (de Juan Romero et al, 2015). These fundamental heterogeneities of the developing cortex immediately prior to folding are completely ignored by the Mota and Herculano-Houzel model. Additional problems with this model, at the mathematical level, have been recently highlighted (De Lussanet, 2016).

Using a finite element computational model, Taber and colleagues suggested that a critical factor leading to the formation of outward folds is differential cortical growth (Xu et al, 2010), which precisely matches our experimental data and histogenic model of regional cortical expansion and folding in ferret (Reillo et al, 2011). This hypothesis where the local difference in tissue growth, particularly lateral/tangential expansion, is a key factor driving cortical folding (Reillo et al, 2011; Borrell & Reillo, 2012; Borrell & Gotz, 2014) is progressively gaining acceptance in the field (Ronan et al, 2014; Ronan & Fletcher, 2015; Striedter et al, 2015). Although these new findings contradict Van Essen’s tension-based hypothesis of cortical folding, and axonal tension may not directly be the driving force of cortical folding, alternative computational models do propose that axonal tension may play an important role in tissue buckling (Chada et al, 1997). In this case, however, models propose that upon incipient folding, the mechanical stress created induces cell proliferation and differential growth, which further accentuates the folded appearance of the cortex and defines the shape of cortical folds (Toro & Burnod, 2005).

A major breakthrough in our understanding of the biomechanics underlying cortical folding came with a recent study by Tallinen and colleagues (Tallinen et al, 2014). Many of the ingredients of this model were already present in the mentioned models of Richman, Toro, and Taber (Richman et al, 1975; Toro & Burnod, 2005; Xu et al, 2010), but this new study is the first to propose a coherent framework with physical simulations, computational simulations, and a very compelling mathematical analysis of the problem. The key point of this model is that two different materials are sticking together while growing homogeneously, if one grows faster than the other, the system becomes unstable and will change shape by folding, which is an emergent property of any such mechanical system (Tallinen et al, 2014). Most interestingly, solely based on the slightly different physical properties of the two materials (i.e., upper versus lower cortical layers), homogeneous continuous growth is sufficient to lead the system to develop a dramatic change in shape, forming a heterogeneous pattern of stress that in turn can influence the biology of the tissue (i.e., cell proliferation, apoptosis, cell fate, and even axon guidance). Therefore, tissue buckling and cortical folding may ultimately result from the mutual influence between physical properties, biomechanics, and differential tissue growth.

**Defects of cortical folding: human disease**

The size and folding of the cerebral cortex have a fundamental impact on brain function. Significant changes (excess or defect) in these parameters are the most common cause of severe intellectual disability and intractable epilepsy (Guerrini et al, 2008; Andrade, 2009). Defects in human cortical development have been recognized as being originated by the disruption of some of the cellular and molecular mechanisms described above in this review (Barkovich et al, 2012), hence critically impacting on key developmental events. In this section, we briefly present these human malformations grouped according to the main affection: brain size, cortical folding, or the formation of ectopias (groups of cells in an abnormal location). It is important to note that cortical malformations usually appear as compound phenotypes, only very rarely as a single defect (Fig 4).

**Brain size**

As explained in the first section, the pool size of founder and neurogenic cortical progenitors plays a central role in defining cortical size. Consequently, alterations in proliferation and/or survival of neural progenitors lead to abnormal brain size, either excessive (megalecephaly), defective (microcephaly), or imbalanced (dysplasia; Barkovich et al, 2012; Fig 4).

**Microcephaly**

Microcephaly is a rare developmental disorder in which affected individuals display a significantly reduced brain size compared to controls (Bond et al, 2002; Gilmore & Walsh, 2013). This condition may be mild (only brain size is affected) or severe (small brain size and altered cortical folding; Bilguvar et al, 2010; Yu et al, 2010; Adachi et al, 2011). Microcephaly has been associated with mutations in genes important for a wide variety of cellular processes: DNA repair efficiency; cell cycle length; mitotic spindle positioning; and centrosome maturation, duplication, and position (Table 1). For example, the most common causes of primary microcephaly are mutations in microcephalin (MCPH1), which lengthens the cell cycle and alters chromosome alignment during mitosis (Jackson et al, 2002; Woods et al, 2005; Gruber et al, 2011), and ASPM, which is important to maintain the orientation of the mitotic cleavage plane (Kumar et al, 2004; Shen et al, 2005; Fish et al, 2006; Gul et al, 2006; Table 1). For an extensive review on the role of different genes identified in microcephalic patients on the emergence of this condition, please refer to Bizzotto and Francis (2015).

**Megalecephaly**

Megalecephaly is characterized by an abnormal enlargement of the brain, which has been related to an excessive production of progenitor cells and cortical neurons due to a decreased apoptosis, or a shortening of cell cycle and increased cell cycle re-entry (Dehay & Kennedy, 2007; Hansen et al, 2010; Wang et al, 2011; Barkovich et al, 2012). As in other malformations, severe forms of megalencephaly may occur together with altered patterns of cortical folding. Usually, the increased abundance of progenitor cells and neurons results in polymicrogyria or excessive cortical folding (Barkovich et al, 2005). In fact, megalencephaly normally occurs in syndromes, in combination with other alterations of development, such as MPPH (macrocephaly, polymicrogyria, polydactyly, hydrocephalus), M-CMTC (macrocephaly cutis marmorata telangiectasia congenita), and MCAP (macrocephaly capillary malformation; Mirzaa et al, 2004; Conway et al, 2007; Tore et al, 2009). The genetic causes of megalencephaly are only partially understood, but recent progress highlights the importance of phosphatidylinositol 3-kinase (PI3K)-Akt signaling, which seems to play a central role in controlling brain size (DiLiberti, 1998; Lee et al, 2012; Riviere et al, 2012; Mirzaa et al, 2013; Table 1).

**Dysplasia**

A very common group of malformations of cortical development related to epilepsy is focal cortical dysplasia (FCD), which classically has included patients showing a variety of histologic...
alterations such as cortical disorganization and architecture (abnormal layering, polymicrogyria) and cells with abnormal location or morphology (neuronal heterotopia, balloon cells, neuronal cytomegaly; Palmini et al., 2004; Barkovich et al., 2005). These alterations may appear in any part of the cortex and affect regions of different size, even multiple cortical lobes (Tassi et al., 2002), which determine the semiology of seizures. Genes in the mTOR pathway are emerging as important players on the origin of developmental cortical dysplasias (Crino et al., 2006; Barkovich et al., 2012). FCDs are distinguished in three different varieties (Blumcke et al., 2011; Barkovich et al., 2012): (i) type I (isolated), with disrupted cortical lamination that may be radial (Ia), tangential (Ib), or both (Ic); (ii) type II (isolated), presenting dysmorphic neurons with balloon cells (IIb) or without them (IIa); (iii) type III, associated with another main lesion, such as hippocampal sclerosis (IIia), glial or gli-neuronal tumor (IIib), vascular malformation (IIlc), and others (trauma, ischemic injury, encephalitis) (IIId) (Blumcke et al., 2011).

### Cortical folding

Alterations of cortical folding in the human brain have been classically attributed to defects of neuronal migration (Ross & Walsh, 2001). However, disruption of neuron migration and positioning also leads to other cortical defects with a mild alteration of cortical folding, such as lissencephaly type II and subcortical band heterotopia. The latter will be discussed in the next section focused on ectopias.

**Lissencephaly (smooth brain)** This includes several disorders collectively characterized by the simplification of the folding pattern: agryia (complete absence of folds), pachygyria (simplified pattern of folds), and subcortical band heterotopia (gyral pattern is either

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**Figure 4. Human cortical malformations and their phenotypic manifestations.**

Schematic of horizontal sections through the cerebral cortex of a normal human brain compared to those of patients with cortical malformation: microcephaly, lissencephaly type I, polymicrogyria, subcortical band heterotopia (double cortex), and periventricular nodular heterotopia. The table summarizes the phenotypic manifestations associated with each malformation regarding brain size, cortical folding, and the formation of ectopias. The most representative effects are highlighted and color-coded: Features negatively affected by the pathology are in red, features augmented in green, and particularities are in blue. Uncolored cells indicate additional alterations that may be associated with the primary defect.
normal or simplified with broad convolutions and a thickened cortex; Guerrini & Marini, 2006; Fig 4). Lissencephalies are classified into two main types: type I or classic, caused by mutations in genes related to the cytoskeleton and affecting cell migration; newborn neurons fail to migrate properly and, instead of forming the characteristic six layers, they accumulate below the preplate in only four distinguishable layers, resulting in a largely disorganized and thickened cortex (Golden & Harding, 2004). Type II, or

| Malformation | Molecular mechanism | Genes | References |
|--------------|---------------------|-------|------------|
| Size         | Microcephaly        | DNA repair efficiency | MCPH1, PNKP, PNCT | Woods et al (2005); Griffith et al (2008); Sheen et al (2010); Gruber et al (2011) |
|              | Cell cycle length   | ASPM, STIL, AKT3 | Boland et al (2007); Desir et al (2008); Kumar et al (2009); Passemard et al (2009) |
|              | Mitotic spindle positioning | ASPM, STIL, WDR62, NDE1, TCOF1, DYNC1H1, TUBG1, KIF5C, KIF2A | Feng & Walsh (2004); Bilguvar et al (2010); Nicholas et al (2010); Yu et al (2010); Sakai et al (2012); Poirier et al (2013) |
|              | Centrosome maturation, duplication, and position | NDE1, CDK5RAP2, CENPJ, ASPM, CENPH1, WDR62, STIL, CEP152, CEP63 | Abreu et al (2000); Aikuraya et al (2011); Bhat et al (2011); Bond et al (2005); Graser et al (2007); Bakircioglu et al (2011); Mathiessen et al (2013); Mirzaa et al (2014); Nicholas et al (2010); Sir et al (2011); Thornton & Woods (2009); Yao et al (2000) |
|              | Megalencephaly      | Cell growth | PI3K-AKT signaling AKT3, PIK3R2, PIK3CA | DiLiberti (1998); Lee et al (2012) #7409; Mirzaa et al (2013); Poduri et al (2013); Riviere et al (2012) |
| Dysplasia    | Cell cycle and growth, ribosome biogenesis, mRNA translation | mTOR pathway activation (tuberous sclerosis complex 1–tuberous sclerosis complex 2) | Cino et al (2006); Barkovich et al (2012) |
| Folding      | Lissencephaly type I | Radial migration | LIS1, Dcx, TUBB3, TUBA1A, RELN | D’Arcangelo et al (1995); Sapir et al (1997); Pilz et al (1998); Caspi et al (2000); Dulabon et al (2000); Hong et al (2000); Rice & Curran (2001); Fallet-Bianco et al (2008); Morris-Rosendahl et al (2008); Kumar et al (2010) |
|              | Cortical lamination | RELN | D’Arcangelo et al (1995); Dulabon et al (2000); Hong et al (2000); Rice & Curran (2001) |
| Polymicrogyria | Cell adhesion, regulation of phosphorylation, cell motility, synaptogenesis, angiogenesis | SPRX2 | Roll et al (2006) |
|              | Gene regulator      | GPR56 | Piao et al (2002, 2004, 2005); Bae et al (2014) |
|              | Cytoskeleton regulation | TUBB2B, TUBB3, TUBA1A, TUBA8, KBP | Abdollahi et al (2009); Jaglin & Chehly (2009); Jansen et al (2011); Tischfield et al (2011); Poirier et al (2013); Valence et al (2013); Squier & Jansen (2014) |
|              | Neurite outgrowth   | KBP | Valence et al (2013) |
|              | DNA repair efficiency | NHEJ1 | Cantagrel et al (2007) |
|              | Microdeletions in 22q11 | | Robin et al (2006) |
|              | Suggested: centrosomal role | WDR62 | Yu et al (2010) |
| Ectopia      | SBH/double cortex   | Cytoskeleton regulation/neuronal migration defects | DCX, LIS1, TUBA1A, TUBG1, EML1 | Gleeson et al (1998); Francis et al (1999); Sicca et al (2003); Keays (2007); Mineykio et al (2010); Kieler et al (2014) |
|              | Lissencephaly type II (cobblestone) | Pial surface stability | POMT1, POMT2, FKTN, FKRP, LARGE, POMC1NT1, LAMB1 | Brockington et al (2001); Yoshida et al (2001); Beltran-Valero de Bernabe et al (2002); Longman et al (2003); van Reeuwijk et al (2005b); Roscioli et al (2012); Willer et al (2012); Kariminejad et al (2013) |
| Periventricular heterotopia | Actin cytoskeleton | FLNA | Fox et al (1998); Sheen et al (2001); Parrini et al (2006); Ferland et al (2009) |
|              | Vesicle trafficking | ARFGEF2 | Sheen et al (2004); Ferland et al (2009) |
|              | Neuronal migration  | C6orf70 | Conti et al (2013) |
|              | Molecular adhesion  | FAT4 | Cappello et al (2013) |
|              | Molecular adhesion  | DCHS1 | Cappello et al (2013) |
|              | (unknown)           | Microdeletions in 22q11 | Kiehl et al (2009) |
cobbledstone, is caused by alterations in the interaction between radial glia and the pial surface, which result in the disruption of the cortical surface and the overflow of neurons above the meninges (Bizzotto & Francis, 2015).

Most cases of type I lissencephaly are due to mutations in LIS1 or DCX (Pilz et al., 1998). These are proteins that interact with the tubulin cytoskeleton allowing its polymerization and stability (Sapir et al., 1997; Caspi et al., 2000). This is also the case for TUBB3 and TUBA1A, mutated in 1–4% of type I lissencephalies (Morris-Rosendahl et al., 2008; Kumar et al., 2010) and 30% of lissencephalies with cerebellar hypoplasia (impaired growth). Interestingly, the loss and simplification of folds displayed by these patients are very similar to those associated with mutations in LIS1, suggesting a shared molecular pathway (Barkovich et al., 2012). A small number of patients with autosomal recessive type I lissencephaly with cerebellar hypoplasia have mutations in RELN, also a gene essential for radial migration and normal cortical lamination in mouse and humans (D’Arcangelo et al., 1995; Dulabon et al., 2000; Hong et al., 2000; Rice & Curran, 2001; Table 1).

Polymicrogyria (many small folds) This includes a group of cortical malformations characterized by the formation of abnormally abundant and small cortical folds. It usually also involves the interdigitation of white matter resulting in abnormal lamination (Barkovich et al., 1999; Walsh, 2001). The defects in cortical lamination may be either simplification, with four layers similar to type I lissencephaly, or complete disruption and disorganization. Most frequently polymicrogyria (PMG) phenotypes are very complex and combined with other alterations such as microcephaly (Bilguvar et al., 2010; Yu et al., 2010). Due to this phenotypic complexity, the causative genes for human PMG have been very elusive. Genetic mutations linked to PMG include alterations in SPRX2 (Roll et al., 2006), microsomal deletions in 22q11 (Bassett et al., 2005; Robin et al., 2006), and mutations in a number of cytoskeleton-associated genes (Table 1). Nongenetic causes of PMG have also been identified including insults during embryogenesis such as hypoxia, hypoperfusion, and congenital infections (Jacobs et al., 1999; Squier & Jansen, 2014).

Ectopia The proper position of cortical neurons depends on a complex cellular and molecular regulation of two variables: where and when. Neurons must migrate through the entire cortical thickness and stop precisely near the cortical surface, a process determined by the time and place of their generation. Altering these events leads to misplaced neurons, a malformation generically called ectopia (out of place; Fig 4).

Subcortical band heterotopia/double cortex This type of ectopia is characterized by the accumulation of neurons in the cortical white matter (Barkovich et al., 2001; Ross & Walsh, 2001). Typically, the cluster of ectopic neurons forms a thick band of cells below an otherwise normal cortical gray matter (Gleeson et al., 1998; Francis et al., 1999). Importantly, double cortex is accompanied by a reduction in the size of the cerebral cortex due to the loss of neurons from the normocortex. This frequently affects cortical surface area and thickness, and in some cases, it even results in microgyria (Barkovich et al., 2012). Genetic mutations causative of double cortex affect a variety of cytoskeleton-interacting proteins (Table 1).

Cobblestone Whereas most types of heterotopia are due to deficient neuronal migration, cobbledstone (type II lissencephaly) is caused by their excessive migration. In this case, the anchoring and attachment of the radial fiber of RGCs to the pial surface is disrupted, thus altering the basement membrane (Yamamoto et al., 2004; Luo et al., 2011). Given that the cortical basement membrane and the attachment of RGCs to it are the finish line for radially migrating neurons, this disruption leads to their overmigration, which continue moving up to the meningeal space, thus resembling cobbledstones on the cortical surface (van Reeuwijk et al., 2005a). Several complex syndromes cause cobbledstone lissencephaly: Fukuyama congenital muscular dystrophy (FCMD), muscle-eye-brain disease (MEB), and Walker–Warburg syndrome (WWS). In spite of this wide spectrum of phenotypes, mutations linked to cobbledstone are found in genes involved in the attachment of the radial glial fiber to the pial surface (Li et al., 2008; Luo et al., 2011), or associated with reduced glycosylation of alpha dystroglycan, which is fundamental to anchor the dystrophin complex to the extracellular matrix (van Reeuwijk et al., 2005a; Roscioli et al., 2012; Buyssse et al., 2013). Six major genes have been identified encoding putative or confirmed glycosyltransferases (Table 1).

Periventricular heterotopia Contrary to cobbledstone, in periventricular heterotopia (PH) cortical neurons are unable to undergo radial migration. Due to defective remodeling of the actin cytoskeleton, newborn neurons cannot perform the changes in cell shape and locomotion required for their migration and completely fail to leave the germinal zones, remaining in the vicinity of the ventricular surface clustered into nodules, which eventually act as epileptic foci (Sheen et al., 2001, 2005; Sheen & Walsh, 2005; Sarkisian et al., 2006, 2008; Andrade, 2009). These periventricular nodules may appear in a variety of locations and conformations: bilateral, unilateral, laminar, sub-ependymal, and subcortical white matter (Andrade, 2009; Ferland et al., 2009). Remarkably, most of the cortex appears completely normal and patients show no gross defects in intellectual development or performance. PH may appear alone or as part of complex syndromes, associated with other cortical malformations such as microcephaly (Parrini et al., 2006). The most frequent genetic alterations linked to periventricular nodular heterotopia affect FLNA and ARFGGEF2 (Table 1; Fox et al., 1998; Sheen et al., 2001, 2004; Parrini et al., 2006; Ferland et al., 2009). Although these two proteins have very different cellular functions (FLNA acts on the actin cytoskeleton; ARFGGEF2 has a role in intracellular membrane and vesicle trafficking), they may act in a common pathway and even interact directly (Sheen et al., 2004; Ferland et al., 2009). It has been proposed that the disruption of vesicle trafficking due to alterations of the cytoskeleton may impair cell adhesion and the integrity of the apical adherens junctions, thus leading to the formation of the periventricular nodules (Ferland et al., 2009).

Evolution of cortical folding Brain size varies in several orders of magnitude between mammalian species, which is mostly the result of a disproportionate difference in size of the cerebral cortex (Finlay & Darlington, 1995). Increased cortical size is largely due to increased surface area (Rakic, 1995), and this is accompanied by cortical folding and fissuring, which in part allow its effective packing within a minimal
cranial volume (Welker, 1990; Albert & Huttner, 2015). Based on our previous sections, evolution of cerebral cortex size and topology may be attributable to modifications in the abundance and behavior of cortical progenitor cells (Borrell & Reillo, 2012). Changing the duration of the cell cycle, generating IPCs, and increasing their abundance would augment exponentially the production of neurons and therefore brain size, whereas generating bRGCs would augment cortical surface area and folding (Borrell & Calegari, 2014; Lewitus et al., 2014).

Early gyrification and secondary loss
Classically, the remarkable expansion and folding of the mammalian cerebral cortex along evolution has been viewed as a unidirectional process, where the small and smooth cortex of a primitive ancestor (presumed similar to mouse) gradually evolved to be larger, more complex, and folded, and from there on, it further evolved to have an increasing number of folds, like the human cortex (Kriegstein et al., 2006; Rakic, 2009). However, this view was challenged recently with the hypothesis that gyrencephaly might be an evolutionarily ancient trait, expressed in a common ancestor to all mammals and retained during speciation (Borrell & Reillo, 2012). This hypothesis is based on two facts: a) gyrencephaly develops in species from across mammalian phylogeny, ranging from monotremes and marsupials to ungulates, carnivores, primates, and even rodents, and b) during embryonic development of the cerebral cortex, gyrencephaly differs from lissencephaly in two critical features: subdivision of SVZ into ISVZ and OSVZ and high abundance of basal progenitors (bRGCs and IPCs in ISVZ+OSVZ) that greatly outnumber apical progenitors (aRGCs in VZ; Reillo et al., 2011; Borrell & Reillo, 2012; Kelava et al., 2012; Reillo & Borrell, 2012). Based on these facts, it seems most parsimonious to propose that gyrencephaly emerged in the stem mammal ancestor upon the innovative generation of bRGCs and OSVZ, and these traits were retained along mammalian speciation. This hypothesis of early gyrification was subsequently supported by studies using a phenomic character matrix of living placental orders and fossil species, which conclude that the ancestor of placental mammals was a small gyrencephalic animal (O’Leary et al., 2013). In this scenario, the smooth cortex of lissencephalic mammals (namely rodents and lagomorphs) would have emerged by the simplification, or phenotypic reversal, of gyrencephaly. This reversal may have occurred by reducing the abundance and self-amplificative capacity of basal neurogenic progenitors and bRGCs, as supported by recent studies (Kelava et al., 2012, 2013; Martinez-Cerdeno et al., 2012; Borrell & Gotz, 2014; De Juan Romero & Borrell, 2015). There are various examples of phenotypic and genomic reversals documented (Teotonia & Rose, 2001), one of its attributes being the ability to acquire new evolutionary trajectories (Borowsky & Wilkens, 2002). The seeming ability of the mammalian brain to undergo significant phenotypic reversals and change in various directions during evolution may explain the remarkable adaptability of mammals along this process (Kelava et al., 2013).

Molecular evolution
As discussed previously, the biology of cortical progenitor cells is regulated by the coordinated action of multiple proteins, and the experimental manipulation of these proteins has a profound influence on cortical size and folding. However, it remains to be defined whether the development of folded versus smooth cortices is due to the differential regulation of these genes between species during their normal development, and if so how they became differently regulated during evolution. Only recently, we have begun to identify molecular changes occurred during evolution that provide answers to these questions.

Human accelerated regions (HARs) Our understanding of the genetic basis of cerebral cortex evolution was jump-started by the generalized interest in identifying the genetic determinants of human uniqueness (Dorus et al., 2004). Strategies to identify the genetic and molecular mechanisms underlying the distinction of humans focused on searching for variations between the genome of human and immediate relatives in phylogeny. In a seminal study, Lahn and colleagues compared the genomic sequence of humans, chimpanzee, rat, and mouse and found that the genome is moderately well conserved across these species, but the human genome showed sites of uniquely high divergence rate (Dorus et al., 2004). Subsequently, they also found evidence demonstrating that genetic evolution is still ongoing in humans, with hotspots in genes related to brain development and also relevant in pathology of human cortical development, such as ASPM and MCPH1 associated with microcephaly (Evans et al., 2004, 2005; Mekel-Bobrov et al., 2005).

Whereas sequence changes in protein-coding genes might seem the most straightforward mechanism to drive brain evolution (Hill & Walsh, 2005), further analyses have revealed an even more likely role for regions regulating gene expression (Prabhakar et al., 2008; Bae et al., 2014). Improved genomic comparisons between humans and chimpanzees identified hundreds of small DNA segments, the sequence of which diverged rapidly in humans (Pollard et al., 2006a,b). These segments were called “human accelerated regions” (HARs), in reference to their uniquely high rate of nucleotide substitution in the immediate human lineage. This accelerated evolution was proposed to have contributed to acquiring the unmatched size and complexity of the human brain in a relatively brief period (Pollard et al., 2006a). Importantly, instead of being part of protein-coding genes, HARs are mainly located in introns and intergenic regions, strongly suggesting their role in gene regulation (Bejerano et al., 2006; Pollard et al., 2006b). Significantly, relevant genes nearby HARs code for transcription factors and other DNA binding proteins involved in development and morphogenesis. In fact, HAP1, the HAR with the highest level of difference, contains an RNA gene (HAR1F) expressed in Cajal–Retzius cells during development, a peculiar type of cell essential for neuronal migration and lamination of the cerebral cortex (Pollard et al., 2006b).

Novel regulatory sequences Recent analyses of HARs focusing on their sequence, histone modification, chromatin state, and transcription factor binding sites conclude that at least 30% of HARs are developmentally enhancers (Capra et al., 2013). Indeed, the activity of 29 noncoding HARs was tested by generating transgenic mice, which demonstrated that the majority of them are active enhancers in humans and chimpanzee. This confirms that HARs are good candidates as human-specific regulatory regions and also that human-specific brain evolution might be particularly associated with changes in spatial–temporal gene expression, instead of changes in protein sequence (King & Wilson, 1975; Mouse Genome
Sequencing Consortium et al, 2002; Lunter et al, 2006; Pollard et al, 2006b; Ponting & Lunter, 2006; Prabhakar et al, 2008).

In order to investigate how the activity of enhancers influences the developing telencephalon, Visel and colleagues performed an in vivo digital atlas of transgenic mouse embryos using 145 selected enhancers to drive reporter gene expression (Visel et al, 2013). Using a similar strategy, Pattabiraman and colleagues generated stable transgenic mouse lines to characterize the gene-promoting activity of putative enhancers and demonstrated that these exhibit sharp boundaries of reporter gene expression in the E11.5 mouse pallium (Pattabiraman et al, 2014). These mouse lines were also used to determine the regional fate map of the mouse telencephalon, which demonstrated the existence of distinct progenitor protodomains defined by the activity of those enhancers at various developmental stages.

More recently, the evolution of active genomic enhancers was demonstrated with the analysis of the human GPR56 locus, mutated in malformations of cortical development including polymicrogyria (Baé et al, 2014). In this study, a collection of transgenic mice was generated driving GFP expression from a portion of the same GPR56 enhancer from various species (humans, mouse, marmoset, dolphin, and cat). The enhancer from these gyrencephalic species drove a similar GFP expression pattern, but this was different from the endogenous pattern in the lissencephalic mouse. Given that mouse and primates share a phylogenetic ancestor more recent than with carnivores and cetaceans (Bininda-Emonds et al, 2007), the similar regulation of GPR56 expression among these gyrencephalic species suggests convergent evolution.

**Novel non-protein-coding genes** In addition to variations in enhancer sequences, an extra level of control over the spatial–temporal patterns of gene expression is provided by non-protein-coding RNAs. Mounting evidence demonstrates the relevance of noncoding RNAs (miRNAs, IncRNAs, etc.) on cerebral cortex development (Aprea & Calegari, 2015; Liu & Sun, 2015), and their significance on evolution is supported by their increased number at evolutionary divergence points (Heimbeg et al, 2008). As for the regulation of cerebral cortex expansion and folding, hundreds of miRNAs have been found expressed in apical and basal progenitor cells of the developing cortex of macaque embryos, but not in mouse (Arcila et al, 2014). These primate miRNAs prominently target proteins regulating the cell cycle and neurogenesis, hence contributing to the differential growth, amplification, and complexification of germinal layers and cortical areas, including the OSVZ (Łukaszewicz et al, 2005; Dehay & Kennedy, 2007). Altogether, the coevolution of emergent miRNAs and their target genes suggests that novel miRNAs became integrated into ancient gene circuitry to exert additional control over cortical progenitors, ultimately leading to the acquisition of primate-specific cortical features and, potentially, higher brain performance (Dehay et al, 2015).

**Novel protein-coding genes** As shown by Lahn and colleagues (Dorus et al, 2004), biological evolution also comes from variations in the sequence of protein-coding genes (True & Carroll, 2002). Looking for gene innovations that might have been involved in cortical expansion and folding during evolution, the focus has recently turned specifically onto cortical progenitor cells. A transcriptomic search for genes differentially expressed in radial glial cells between species identified 56 genes expressed in human, but not mouse, RGCs (Florio et al, 2015). Among these, ARHGAP11B was uniquely intriguing because it had the highest degree of radial glia-specific expression, and there is no mouse ortholog. In fact, ARHGAP11B arose from partial duplication of the ARHGAP11A gene on the human lineage after separation from the chimpanzees, and thus, it is a hominid-specific gene (Antonacci et al, 2014). Most impressively, experimental expression of ARHGAP11B in ARGs of the embryonic mouse cortex promoted the generation of self-renewing basal progenitors (particularly bRGCs) and, in turn, increased cortical surface area and induced the formation of cortical folds in mouse (Florio et al, 2015). Therefore, the emergence of new protein-coding genes along mammalian phylogeny, such as ARHGAP11B in the hominid lineage, may have contributed significantly to the evolutionary expansion and folding of the mammalian cerebral cortex.

**Concluding remarks and open questions**

The expansion and folding of the mammalian cerebral cortex during embryonic development is a rather complex process regulated by multiple factors, where the abundance, type, and lineage of cortical progenitor cells play central roles. These cellular mechanisms are subject to molecular regulation by multiple proteins and signaling pathways, the expression of which is tightly controlled by a variety of enhancer elements and non-protein-coding genes. The specific spatial–temporal expression patterns of some of these proteins on the embryonic cortex faithfully map the prospective pattern of folds and fissures, and their mutation frequently leads to malformations of cortical size and folding in human patients. Yet, we are still far from identifying the specific role of these genes and their spatial–temporal regulation on the normal development of the human cerebral cortex.

Studying cortical development and folding across species helps us to understand the evolution of this complex process, and in return, we hope that this helps us to understand the aspects of cortical development critical to its expansion and folding during embryogenesis. Again, more and more refined molecular and genomic analyses are shedding some light on this problem, and emerging experimental animal models in this field like the ferret are of great help, but the truth is that we remain far from having a significant level of understanding.

Given the complexity of the developmental mechanisms involved in the expansion and folding of the cerebral cortex, and thus its tremendous cost in terms of genetic, cellular, and histogenic evolution, the ecological advantages must be more than remarkable. But what are the advantages of cortical folding? Clearly, a bigger cortex contains more neurons and more neuropile, and thus in principle, it provides greater computational power. Folding brings together highly interconnected cortical areas, thus minimizing cortical wiring and favoring high speed associational communication, ultimately optimizing brain circuitry (Klyachko & Stevens, 2003). However, the human cortex is neither the largest nor the most folded among mammals, as compared with elephants or dolphins, for example, and yet it is assumed that humans have a higher intelligence over any other earthly species. Are we really more intelligent than these other species? (Roth & Dicke, 2005) Or is it only that we have the
advantage of speech and manual ability to express our intellectual abilities? Is there a trade-off between cortical size, folding, and intellectual performance? Modern humans and Neandertals co-existed until 30,000 years ago, but we persisted and the latter perished. Was there some critical (albeit small) disadvantage in the organization or folding of the Neandertal brain? Was their extinction related to a less competitive intelligence? Were their cortical circuits or synapses less efficient? With the genomes of Neandertal and modern humans at hand, the specific differences in their DNA sequence identified (Green et al., 2010; Pruefer et al., 2014), in combination with novel in vitro models of human brain development like cerebral organoids (Lancaster et al., 2013), these fascinating questions may soon be approachable. Hopefully, our understanding of the mechanisms and consequences of cortical expansion and folding will be much deeper 25 years from now.

Acknowledgements
We thank people from our laboratory for discussions and R. Toro for critical comments on the manuscript. We apologize that, because of space limitations, many primary and historical publications could not be cited. V.F. was recipient of a Formación de Personal Investigador fellowship from the Spanish Ministry of Economy and Competitiveness (MINECO), and C.L. was supported by the European Union Seventh Framework Programme FP7/2007–2013 under the project DESIRE (Grant Agreement No. 602531). Work in our laboratory is also supported by grants from MINECO (BFU2012-33473) and European Research Council (ERC StG 612377) to V.B. The Instituto de Neurociencias is a “Centre of Excellence Severo Ochoa”.

Conflict of interest
The authors declare that they have no conflict of interest.

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