Coupling progenitor and neuronal diversity in the developing neocortex

Govindan, Subashika; Jabaudon, Denis

How to cite

GOVINDAN, Subashika, JABAUDON, Denis. Coupling progenitor and neuronal diversity in the developing neocortex. In: FEBS Letters, 2017, vol. 591, n° 24, p. 3960–3977. doi: 10.1002/1873-3468.12846

This publication URL: https://archive-ouverte.unige.ch/unige:112470
Publication DOI: 10.1002/1873-3468.12846

FEBS Letters

FEBS PRESS science publishing by scientists

REVIEW ARTICLE

Coupling progenitor and neuronal diversity in the developing neocortex

Subashika Govindan and Denis Jabaudon

Department of Basic Neuroscience, University of Geneva, Switzerland

Correspondence
D. Jabaudon, Department of Basic Neuroscience, University of Geneva, 1 rue Michel Servet, 1211 Geneva, Switzerland
E-mail: denis.jabaudon@unige.ch

(Received 30 June 2017, revised 31 August 2017, accepted 6 September 2017, available online 16 October 2017)

doi:10.1002/1873-3468.12846

Edited by Wilhelm Just

The adult neocortex is composed of several types of glutamatergic neurons, which are sequentially born from progenitors during development. The extent and nature of progenitor diversity, and how it relates to neuronal diversity, is still poorly understood. In this review, we discuss key features of neocortical progenitors across several species, including their morphological properties, cell cycling behaviour and molecular signatures, and how these features relate to the competence of these cells to generate distinct types of progenies.

Keywords: neocortical development; neurogenesis; progenitor diversity

The adult neocortex is composed of several types of glutamatergic neurons, which assemble during development to form the circuits underlying many of our conscious perceptions and motor actions. These distinct neuronal subtypes are sequentially born from progenitors, but the extent and nature of progenitor diversity, and how it relates to neuronal diversity, is still poorly understood.

Neocortical neurons are generated by progenitors located in the ventricular zone (VZ), which is located below the cortical plate (i.e. developing cortex) and lines the walls of the ventricles [1]. In mice, neurogenesis starts on the tenth embryonic day (E10.5) and proceeds for about a week, until E18.5, after which astrogliogenesis occurs (see Ref. [2] for a recent review). Early born neurons migrate to form the deepest cortical layers (layers 6 and 5) while later born neurons migrate past them to reside more superficially and form upper layers (layer 2, 3 and 4). Deep layer neurons mostly send their axons to subcortical targets such as the thalamus, hindbrain or spinal cord, while superficial layer neurons mostly project intracortically, either locally (layer 4 neurons), or by forming long-range intracortical and interhemispheric projections. Numerous subtypes of neurons exist within each of the broad classes of subcortically projecting and intracortically projecting neurons, such that at least several dozens of different excitatory cell types ultimately compose neocortical circuits [2].

The origin of all neocortical neurons can be traced back to progenitors lining the inner surface of the neural tube. Initially, the neural tube consists of a single layer of progenitors, called neuroepithelial cells (NECs). NECs undergo self-replicating divisions from E8 to E9 in mice, creating a pseudostratified neuroepithelium, which will evolve to form the VZ, where all progenitors are initially located (Fig. 1A,D) [3]. From E9 on, NECs start to generate apical radial glia (aRG, also called ventricular radial glia or, simply, radial glia) and slowly disappear through self-consumption (Fig. 1C,D) [3]. aRGs, like NECs, have a bipolar morphology, and have radial extensions reaching the pial (i.e. basal) surface and the ventricular (i.e. apical) surface of the brain. They divide within the VZ to sequentially generate not only distinct neuronal cell types but also various types of intermediate progenitors (i.e. transit amplifying cells), which themselves will divide to give rise to neurons (Fig. 1A,C,D) [3].

Abbreviations

aIP, apical intermediate progenitor; aRG, apical radial glia; bIP, basal intermediate progenitor; bRG, basal radial glia; NEC, neuroepithelial cell; OSVZ, outer subventricular zone; SVZ, subventricular zone; VZ, ventricular zone.

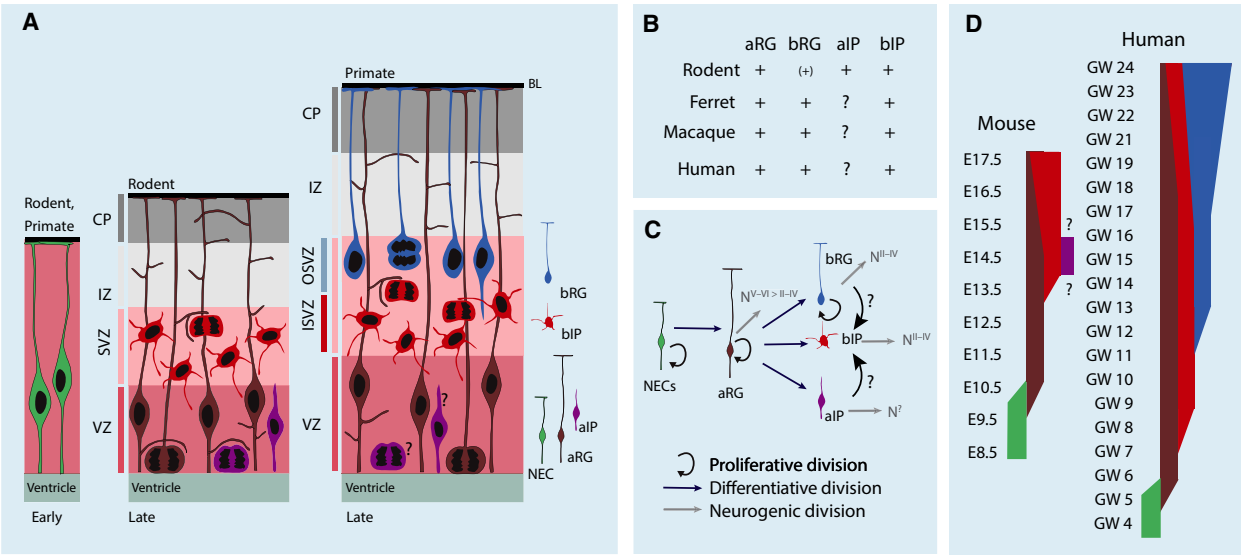

Fig. 1. Diversity of neocortical progenitors. (A) Anatomical distribution and morphological diversity of neocortical progenitors in rodents and primates. (B) Distribution of progenitors across species. (C) Progenitor-to-neuron relationships. (D) Developmental timeline of progenitor subtypes in mouse and humans. aIP, apical intermediate progenitor; aRG, apical radial glia; bIP, basal intermediate progenitor; bRG, basal radial glia; CP, cortical plate; E, embryonic day in mice; GW, gestational week in humans; ISVZ, inner subventricular zone; IZ, intermediate zone; NEC, neuroepithelial cell; OSVZ, outer subventricular zone; VZ, ventricular zone.

In the mouse, intermediate progenitors mostly consist of: (a) basal intermediate progenitors (bIPs), which lack apical and basal processes, and are located in the subventricular zone (SVZ), just above the VZ (Fig. 1A,C) [4,5] and (b) apical intermediate progenitors (aIPs, also called short neuronal precursors, or SNPs), which are unipolar with a short apical process and remain in the VZ [6,7].

A third type of progenitor, basal radial glia [(bRG), also called outer radial glia (oRG)], is mostly found in primates, including humans, and divides in the outer subventricular zone (OSVZ, located above the SVZ), yet these cells have an apical and basal process similar to aRGs [8,9]. NECs, aRGs and aIPs are all called 'apical' progenitors, because their soma remains within the VZ and they divide exclusively in contact with the ventricular wall. In contrast, mature bRGs and bIPs are classified as 'basal' progenitors as they reside and divide in the SVZ (Fig. 1A) [3].

As introduced above, and as will be further discussed in detail in this review, these distinct subtypes of progenitors are primarily distinguished by their location and morphology (Table 1). However, they also have distinct cycling behaviour, and, as is increasingly understood, distinguishing molecular properties (Tables 1, 3). Although our knowledge of these distinct cellular features has become more precise over the past few years, the functional implications of these features have remained difficult to assess. Critically, how individual properties are linked with the ability of progenitors to generate specific subtypes of neurons (i.e. with their competence) remains largely unknown. Also, whether distinct molecular subtypes of progenitors exist within these broad classes, and whether these have distinct competences (e.g. whether some progenitors might be fate restricted) is unclear.

In this review, we will sequentially highlight some of the key features of progenitor diversity, and attempt to link them with known cellular functions when possible. First, we will discuss the morphological diversity of these cells, next discuss their cell cycling behaviour, followed by their molecular diversity. Finally, we will conclude with more functional aspects relating to the molecular controls over the progenitor transitions from self-replicating cells to cells generating other subtypes of progenitors or neurons.

Morphological diversity

Morphology has historically been the first identifying feature of the distinct progenitor subtypes, along with the location of their cell soma. While NECs and aRGs have characteristic and somewhat overlapping features, basal progenitors appear more diverse, and are more difficult to characterize on morphological criteria alone, particularly in primates (Table 1). These features will be discussed sequentially below.

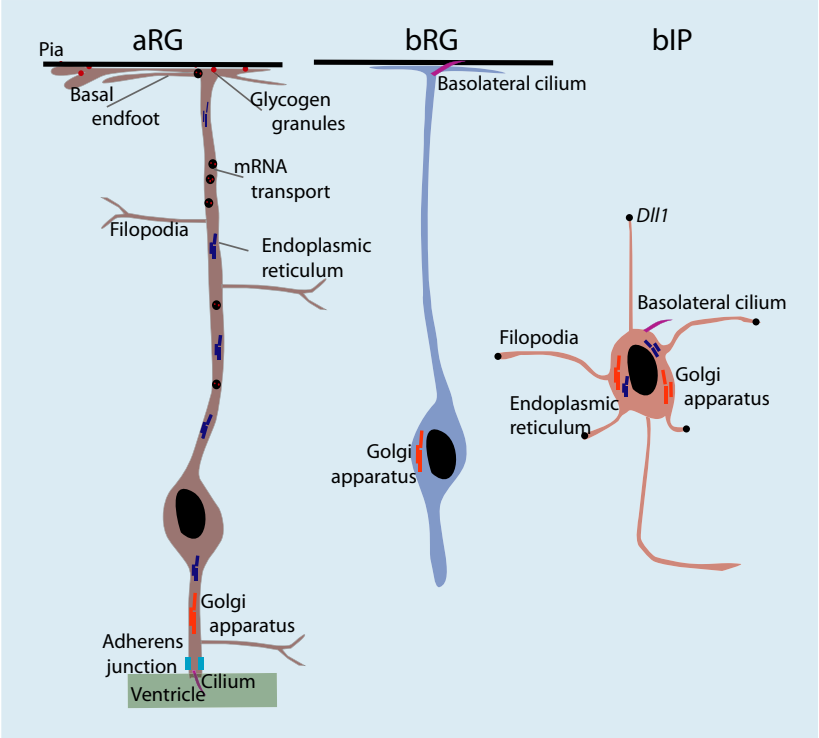

Fig. 2. Morphological and cellular features of select progenitors. aRG, apical radial glia; bRG, basal radial glia; bIP, basal intermediate progenitors; Dll1, delta-like ligand 1.

NECs and aRGs have a bipolar morphology

Neuroepithelial cells are initially cuboidal but during neurulation (i.e. formation of the neural tube) they start to elongate along their apicobasal axis. This results in an elongated morphology, with a long basal process contacting the pial surface and a short apical process contacting the ventricle [10]. A similar morphology is shared by aRGs (Fig. 2), and in both cell types, the basal process lengthens with the expansion of the neocortex during development [10]. The fact that the basal process extends all the way to the pial surface in aRGs (and in some bRGs, see below) has been used in several studies to label these cells by placing carbocyanide dyes such as DiI on the pial surface of the neocortex [11,12]. Being highly polarized, these cells also display asymmetric localization of cellular processes, cellular components and molecules. For example, the Golgi apparatus are preferentially localised at the apical process, while the endoplasmic reticulum is localised in both the apical and basal processes [13].

Apical components of NECs and aRGs consist in an apical process with endfeet. The apical endfeet of aRGs and NECs possess several subcellular structures that are critical to their function, including tight junctions in NECs and adherens junctions in NECs and aRGs, a centrosome, and a primary cilium [10]. As NECs differentiate into aRGs, tight junctions are downregulated at the apical plasma membrane, and an increase in adherens junction molecules is observed [14]. The anchoring of the apical process to the ventricular surface is mediated by molecules associated with adherens junction such as cadherins, nectins and beta-catenins [15,16]. Loss of aRG apical junctional proteins leads to loss of apical processes, disruption of apicobasal polarity, and conversion of aRGs to basal progenitors [17]. Both basal and apical processes are essential for interkinetic nuclear migration, that is, the loss of apical and basal end-feet leads to subapical crowding of mitotic cells and decreased proliferation [18,19].

The primary cilium is a slender extension contacting the ventricle at the apical endfoot of aRGs, and is thought to act as a sensor for extracellular cues in the cerebrospinal fluid (e.g. Shh signalling) [20]. The primary cilium is crucial for proliferation/neurogenic fate selection and cell cycle regulation [20], as illustrated by the effects of disrupting cilia-associated signalling, which reverses the apicobasal polarity of the aRGs, causing neurons to migrate towards the ventricle rather than the pia [21].

The basal components of aRGs and NECs are the basal process and endfeet. The basal process of aRGs contains microtubules and intermediate filaments, which is not the case for NECs [22] and attaches to the basal membrane at the pial surface, providing a scaffold for neurons to migrate radially into and within the cortical plate [23,24]. Accordingly, disruption of the basal processes of aRGs and its detachment to basement membrane leads to impaired neuronal migration [25–27].

A basal end-feet containing glycogen storage granules is present at the tip of the basal process [14] . Live imaging has revealed that this structure is active and can extend multiple filopodia-like structures to contact neighbouring aRGs and migrating neurons, although the functional significance of these interactions remains unclear [27,28]. Basal end-foot progress from a club-shaped structure to a highly branched one as corticogenesis proceeds, suggesting that aRG interactions could increase during development [27]. Interestingly, despite its remote location from the cell body, the basal end feet may also play a role in controlling cellular proliferation, through accumulation of CyclinD2 [29]. Indeed, during cell cycle, CyclinD2 mRNA accumulates at the basal endfeet of aRGs, where it is locally translated. During asymmetric divisions (see next chapter), the progeny that acquires the basal process with cyclin D2 becomes an aRG, while the other progeny acquires a distinct fate [29,30]. Finally, it is worth noting that mRNA can be transported along the basal processes preferentially for local translation at the basal end-feet, highlighting that this structure is a highly specialized cellular compartment [31].

Finally, centrosome and centrosome-associated proteins at the apical side play an important role in aRG fate and, as will be discussed in the next chapter, are critical for interkinetic migration [32,33]. Loss of centrioles leads to disruption of centrosomes and apical detachment from the ventricle, delocalization to SVZ and premature cell cycle exit [34].

Intermediate progenitors have diverse morphologies

In contrast to other progenitors, bIPs do not exhibit an apicobasal polarity. Instead, they extend multiple long-range projecting filopodia which contact other progenitors in the VZ and SVZ (Fig. 2). Notably, these filopodia form hook-like structures which engulf the soma of nearby mitotic cells [35]. Although bIPs lack a stabilized apical process, they can dynamically extend radial apical filopodia which reach into the VZ, within which it extends tangentially to interact with aRGs [5,35]. Interactions between bIPs and aRGs are thought to occur through the Notch signalling pathway, as bIPs express the Notch receptor ligand Dll1 and aRGs express Notch [35]. This pathway may thus provide a means through which bIPs can influence the proliferation and fate of aRGs. During mitosis, bIPs have a rounded soma within which intracellular organelles such as Golgi apparatus and endoplasmic reticulum are evenly distributed [13,36,37]. Newborn delaminating bIPs initially have a primary cilium at their basal endfeet, which may correspond to a relocated apical primary cilium following aRG division [13]. The localization of bIPs to the SVZ is thought to allow them to interact with blood vessels and incoming thalamocortical axons and undergo two-way interactions with these structures in cellular processes such as axonal guidance, angiogenesis and cell cycle [38–40].

The morphology of aIPs is less well characterized than that of other progenitor subtypes. They exhibit a short apical process contacting the ventricle and a short basal process extending within the VZ. During aIP mitosis at the ventricular surface, their soma is rounded, without any basal process distinguishing them from aRGs [6,7].

The bRGs may have a basal process, an apical process which does not reach the ventricular surface, or both an apical and basal process (Fig. 2) [41]. This morphological features distinguish them from bIPs. The basal process of bRGs is typically thicker and longer than their apical process [41,42]. In total, five morphological subtypes of bRGs have been reported, a fraction of which (about 25%) show dynamic morphologies changing from one subtype to another [41].

Cell cycle behaviour

Cell division is the key feature of progenitors, during which they either self-renew or give rise to a different type of daughter cell. Here, we will discuss the dynamic behaviour of progenitors during cytokinesis, progenitor division modes and differences in cell cycle properties.

NECs and aRGs undergo interkinetic nuclear migration; bRGs undergo mitotic somal translocation

Neuroepithelial cells and aRGS follow a cell cycle-coupled migration pattern, called interkinetic nuclear migration, which is explained below [5,43]. They undergo mitosis in contact with the ventricle, after which their soma move away from the ventricle while they enter the G1 phase. They then undergo S phase at the basal border of the VZ, making a U-turn to

move back towards the ventricle for the remainder of the S phase and G2 phase, finally undergoing mitosis again in contact with the ventricle [5,43]. Interkinetic nuclear migration is specific to NECs and aRGs, and intermediate progenitors do not undergo such a process [5,44]. Instead, within the SVZ, bIPs move both radially and tangentially, but do not display obvious cell cycle-related migratory features [5].

Upon cytokinesis, the soma of bRG cells moves basally along its basal process within the OSVZ; this movement is called mitotic somal translocation (MST) [8,9]. Unlike interkinetic nuclear migration, MST is centrosome independent and does not depend on microtubule organization [44], such that these two cellular processes are largely distinct.

Progenitor division modes

Progenitors can undergo three modes of cell division: (a) proliferative division, generating two progenitors, (b) differentiative division, giving rise to a proliferative progenitor and differentiative progenitor, and (c) neurogenic divisions, giving rise to neurons [3]. In morphological terms, this can be related to two broad types of cell division. So-called symmetric cell division results in progenies of similar fate, while asymmetric cell division results in progenies with two distinct fates [45]. While proliferative divisions are always symmetric, differentiative or neurogenic divisions can be symmetric or asymmetric, depending on whether the two daughter cells have the same fate.

Symmetric divisions are characterized by symmetric segregation of proteins or mRNA in the cytoplasm of the dividing cell, which is at least partly controlled by mitotic cleavage plane [46]. As discussed above, NECs predominantly undergo symmetric proliferative divisions [47,48]. In aRGs, during symmetric/proliferative divisions, the mitotic cleavage plane is perpendicular to the apical membrane, resulting in an even distribution of cellular components and apical membrane, and equivalent daughter cells. An oblique mitotic cleavage plane in contrast results in asymmetric distribution of the apical membrane: the progeny that inherits most of the apical membrane becomes an aRG, while the other progeny becomes a differentiating neuron or intermediate progenitor [45]. Horizontal cleavage planes in aRGs result in production of bRGs: typically, the cells inheriting the basal process become bRG while the cell inheriting the apical membrane becomes an aRG [37].

In bIPs, the mitotic cleavage planes have seemingly random orientations [47]. bIPs almost exclusively divide symmetrically to give rise to two neurons [4,47,48]. Interestingly however, asymmetric EGFR receptor activity is observed in bIP progeny during cytokinesis, such that the two daughter neurons may not be strictly equivalent [49].

Cell cycle length across progenitor subtypes

During neocortical development, cell cycle length increases as a greater fraction of cells undergo differentiative divisions [50,51]. Incidentally, duration of the cell cycle may have a direct impact on the type of neuron that is being produced [50]. G1 length is increased in neurogenic progenitors compared with proliferative progenitors [51], and selective increase in the length of G1 leads to differentiation division, while shortening G1 increases proliferative divisions [52,53]. Consistent with these findings, bIPs, which mostly generate neurons, have a longer G1 phase than aRGs (Table 1) [51,53]. This correlation between the length of the G1 phase and neurogenic fate suggests a tight link between the G1-regulating genes and proneural genes (i.e. genes which induce neuronal identity) [54]. In contrast, the S phase is shortened in neurogenic progenitors compared with proliferative progenitors (Table 1) [55]. This shortening in S phase is thought to reflect decreased DNA repair rather than a reduction in the duration of DNA replication [55]. Indeed, in proliferative divisions, erroneous DNA repair leads to apoptosis, whereas in differentiating divisions, DNA repair can be accommodated after cell cycle exit [55]. Supporting this possibility, transcriptional profiling of basal progenitors and apical progenitors in the S phase of cell cycle revealed that the late S phase genes and S phase inhibitors are enriched in basal progenitors, while DNA repair genes were downregulated in the basal progenitors compared with apical progenitors [55].

In the mouse, the duration of mitosis increases in aRGs as corticogenesis proceeds [55]. bIPs have a shorter mitosis duration than aRGs do (Table 1), probably reflecting the absence of spindle oscillatory behaviour necessary to decide the plane of cell division [47,55]. Interestingly, prolonging mitosis in apical progenitors increases neurogenic divisions in the mouse [56]; similarly, the prometaphase-metaphase transition is longer in neurogenic apical progenitors than in proliferative apical progenitors in humans and in chimpanzees [57].

Transcriptional diversity

Expression of distinct molecular markers, whether at the RNA or protein level, has been widely used to identify and distinguish progenitors (Table 2). More

recently, single-cell RNA sequencing has identified additional genes whose expression is distinct in different types of progenitors (Table 3). Here, we will briefly outline some of these markers and attempt to link them with specific progenitor behaviours when possible.

In line with their morphological similarities, NECs and aRGs have overlapping patterns of gene expression. They both express *Nestin, Pax6, Prom-1* and *Sox2* in mouse [22]. A few markers, however, are specifically enriched in aRGs vs. NECs, including *Vimentin, Glast, S100ß, Blbp* and *Tenasin C* [22]. Transcriptomic comparison of NECs and aRGs in the ferret has revealed that expression of WNT signalling genes such as LEF1, ZIC1 and AXIN2 were preferentially enriched in NECs while expression of NOTCH signalling genes were enriched in aRGs. Interestingly, cell adhesion molecules such as Fibronectins, integrins and cadherins were upregulated during the early NEC-to-aRG transition, suggesting that cell–cell interactions play a critical role in this process [58].

bIPs prominently express *Eomes, Svet1 and Insm1* [59,60]. Interestingly, while essentially all biPs express Eomes (also known as Tbr2), this gene is also expressed at lower levels in apical progenitors and newborn neurons (Telley *et al*. and see http://genebrowser.unige.ch/science2016) [61]. Eomes is thus a very sensitive marker of bIPs (i.e. essentially all bIPs express EOMES) but lacks specificity (i.e. cells other than bIPS also express EOMES). Several studies have used the EOMES promoter-driven reporter to identify bIP-born neurons and distinguish them from aRG-born neurons [62,63]. However, given the relative lack of specificity of this marker, it will be important to confirm this work with combinatorial genetic studies to unequivocally distinguish and characterize these two neuronal lineages.

With regard to bRGs vs. aRGs, single-cell RNA sequencing of human neocortical progenitors has recently identified *Tnc, Ptprz1, Fam107a, Hopx* and *Lifr* as bRG-specific markers in both humans and monkeys [64]. Finally, a number of transgenic mouse lines and plasmids now allow for the conditional labelling of specific progenitor subtypes. Typically, transgenic mice lines take advantage of the promoters of progenitor-specific molecular markers to drive the expression of reporter proteins, including fluorescent compounds or Cre/CreER^{T2} recombinases (Table 2). *In utero* electroporation is also widely used to transfect DNA in an apical progenitor in the S, G2 and M phase of their cell cycle [6,7]. Once incorporated into the cell, it takes about 5–10 h for plasmid-encoded protein to be expressed [7]. Of note, electroporated plasmids are not only confined to apical progenitors but are also directly integrated into basal progenitors (i.e. in the SVZ), such that this approach is not strictly specific for apical progenitors [7].

Several studies have taken advantage of the preferential enrichment of apical and basal progenitors in the VZ and SVZ, respectively, to identify type-specific transcriptional profiles [65,66]. Consistent with an enrichment of self-renewing progenitors in the VZ, VZ samples were enriched in cell cycle-related genes and proliferation-related genes such as Notch2 and Ctnnb1 [66]. Additionally, both mouse and human VZ were enriched in mRNA coding for extracellular membrane molecules. This included the FGFBP1 (FGF-binding protein) and EGF domain containing extracellular matrix protein EFEMP2 which may act as autocrine regulators of proliferation [66]. Similarly, transcriptional profiling of aRGs vs. bRGs revealed a large number of genes coding for ECM proteins, as well as for proteins involved in cell cycle regulation and metabolic process [67]. Extracellular molecules such as laminins, proteoglycans, integrins, growth factors and morphogen-associated molecules are also differentially expressed in the distinct germinal zones in humans [11,57,64,66]. Thus, the extracellular matrix and cell–cell interactions appear to be critically involved in determining progenitor behaviour and fate.

miRNAs are 18–22-nt-long noncoding RNAs that silence mRNAs by binding to the 3′UTR with target specificity. Suppression of miRNA activity in the developing neocortex does not appear to affect progenitor proliferation but rather daughter cell differentiation and survival, resulting in decreased cortical thickness [68]. Distinct miRNAs are differentially enriched in the different germinal zones of the developing neocortex in macaque, including between the external and internal portion of the OSVZ, suggesting that these transcripts have progenitor specific enrichments and may regulate distinct cellular properties [69]. A list of miRNAs with known involvement in corticogenesis is provided in Table 4.

Long noncoding RNAs (lncRNAs) are molecules with regulatory functions that shape the transcriptome of the cell through chromatin remodelling, transcriptional regulation, regulation of miRNA stability and mRNA splicing [70]. Single-cell lncRNA profiling across cell types in the human neocortex revealed that cell type-specific lncRNAs are rare [71]. Within progenitors, lncRNA DNA sequences can be found in close proximity to genes with known functions in neurogenesis [72,73]. For example, lncBrn1 is located close to the Brn1 gene, which is enriched in germinal zones at E15.5 in mice, a time at which layer 2 or 3 neurons

Table 1. Progenitor properties.

Properties	NECs	aRGs	aIPs	bRGs	bIPs
Apical process	Short	Short	Short	A subpopulation possess a short apical process not reaching the VZ	Short apical process without attachment to the ventricle
Basal process	Long with pial attachment, may split during cell division and retracted during cell division in humans	Long with pial attachment, unsplit during cell division	Short basal process reaching the border of VZ but none during mitosis	Long with pial attachment, unsplit during cell division	None
Filopodia interacting with other progenitors	Yes	Yes	Unknown	Yes	Yes
Migration kinetics	INM	INM	Unknown	MST	Basal movement to SVZ upon birth
Basal endfeet	Yes	Yes	No	Yes	No
Asymmetric Cell division	Yes	Yes	Unknown	Unknown	Unclear
Mitotic cleavage plane	Vertical to horizontal cleavage planes observed but does not dictate symmetric or asymmetric division	Vertical: symmetric division; Horizontal: asymmetric division generating bRG; Oblique: asymmetric cell division generating neurogenic progenitors and neurons	Unknown	Horizontal: symmetric cell division generating two bRGs	Random
Cell cycle length	G1 phase: basal progenitors > apical progenitors; S Phase: NgaRG < NgbIP > ProbIP < ProaRG; M Phase: bIPs < NgaRG < ProaRG, G2 is constant total cell cycle length: apical progenitors < basal progenitors, proliferative progenitors < neurogenic progenitor. (Data from mouse)				

aIP, apical intermediate progenitor; aRG, apical radial glia; bRG, basal radial glia; bIP, basal intermediate progenitors; INM, interkinetic nuclear migration; MST, mitotic somal translocation; NEC, neuroepithelial cells; Ng, neurogenic; Pro, proliferative; VZ, ventricular zone.

Table 2. Mouse lines and plasmids for labelling and manipulating progenitors.

Progenitor Specificity	Transgene/mouse line	Application	References
aRG	GLAST-EMTB-GFP	Visualization of microtubules in aRG, including for live imaging	Eom *et al.* (2011) [120]
	Emx2-Cre	Labels subset of aRGs. These aRGs are described as late neurogenic progenitors.	
	Nestin EGFP	GFP expression in aRGs, whole cell is visualized	Kawaguchi *et al.* (2001) [121]
	hGFAP-Cre	Cre expression in aRGs	Malatesta *et al.* (2003) [122]; Zhou *et al.* (2001) [123]
	GLAST-CreER^{T2}	Upon tamoxofen injection Cre is expressed specifically in aRGs	Mori *et al.* (2006) [124]
	DCX-RFP; Nestin-GFP	Dual-reporter strategy in which GFP^{+} RFP^{-} constitute pure aRG population eliminating nascent cells still expressing Nestin	Wang *et al.* (2011) [9]
	SOX1-GFP	Apical progenitors are labelled specifically	Aubert *et al.* (2003) [125]
	BLBP EGFP, dsRed, EYFP	GFP expression in aRGs. Whole cell is visualized	Schmid *et al.* (2006) [126]
bIPs	TBR2-GFP	GFP expression in Tbr2-expressing cells, including bIPs	Arnold *et al.* (2009) [127]
	TBR2-Cre	Cre expression in Tbr2-expressing cells, including bIPs	Vasistha *et al.* (2015) [63]
	TBR2-CreER^{T2}	Upon tamoxofen injection Cre is expressed specifically in Tbr2-expressing cells, including bIPs	Mihalas *et al.* (2016) [62]
Neurogenic progenitor	Tis21-CreER^{T2}	Upon tamoxifen injection Cre is expressed specifically in neurogenic progenitors	Wong *et al.* (2015) [128]
	Tis21-nucGFP	Labels neurogenic progenitors. GFP expression is nuclear	Haubensak *et al.* (2004) [4]
	Tubb3-mGFP; Tis21-nucGFP	Dual-reporter strategy in which GFP is localized to cell membrane in neurons and to nucleus in neurogenic progenitors	Attardo *et al.* (2008) [36]
	Insm1-GFPCre	This mouse expresses Cre and GFP in all developing brain, pancreas, PNS and gut endocrine cells	Osipovich *et al.* (2014) [129]
	Neurog2-CreER^{T2}	Upon tamoxifen injection, Cre is expressed specifically in neurogenic progenitors and neurons	Toma *et al.* (2014) [116]
	Tubb3-mGFP; Tis21-RFP	Dual-reporter strategy in which GFP is expressed in neurons and RFP is expressed in neurogenic progenitors	Aprea *et al.* (2013) [72]

Progenitor-type specificity	Plasmid	
aRGs	PBLBP-GFP, dsRed2	Schmid *et al.* (2006) [126], Gal *et al.* (2006) [6]
	PBLBP-Cre	Tyler and Haydar (2013) [130]
	PGLAST-Cre	Stancik *et al.* (2010) [7]
	PGLAST-EGFP pGLAST-dsred2	Gal *et al.* (2006) [6]
	pNestin-Cre	Stancik *et al.* (2010) [7]
aIPs (bIPs)	pTα1h-GFP	Gal *et al.* (2006) [6]
	pTα1-Cre	Stancik *et al.* (2010) [7]
	pTbr2-Cre	Tyler *et al.* (2015) [131]

Table 3. Transcriptomic studies across progenitor subtypes.

References	Profile of samples sequenced
D'Amour and Gage (2003) [132]	Mouse embryonic stem cells with SOX2 promoter-driven EGFP expression were injected in blastocysts and EGFP cells committed to neocortical fate were isolated at E14
Pinto *et al.* (2008) [91]	Isolation of neurogenic and non-neurogenic aRGs. High GFAP expressing Prominin+ aRGs (non-neurogenic) and low GFAP expressing Prominin+ aRGs (neurogenic) were sorted at E14.5 using flow cytometry. aRGs (GFAP+, Prominin+) were isolated at E18 without distinguishing between neurogenic or non-neurogenic aRGs
Kawaguchi *et al.* (2008) [133]	Single cells were manually isolated in the VZ/SVZ of mouse dorsal pallium at E14.5 and microarray was performed
Fietz *et al.* (2012) [66]	mRNA sequencing of VZ, SVZ, IZ and CP in mouse at E14.5 and VZ, ISVZ, OSVZ, IZ and CP from human neocortex at GW 13–16
Aprea *et al.* (2013) [72]	Proliferative progenitors, neurogenic progenitors and neurons were isolated based on Btg2 promoter-driven RFP expression and Tubb3 promoter-driven GFP expression
Lui *et al.* (2014) [134]	Gene coexpression analysis of serial sections of GW 14.5 human was compared with mouse aRGs and bIPs
Pollen *et al.* (2015) [64]	Single-cell RNA sequencing of VZ and SVZ of human neocortex at GW 16-18
Camp *et al.* (2015) [135]	Single-cell RNA sequencing in organoid models of brain development in humans
Mora-Bermudaz *et al.* (2016) [136]	Single-cell RNA sequencing was performed from organoid models of neocortical development in chimpanzee and human
Okamoto *et al.* (2016) [76]	Single cells were manually isolated in VZ/SVZ of mouse neocortex at E11, E14 and E16 microarray was performed. Single-cell apical progenitors were isolated at E10, E12 and E13
Telley *et al.* (2016) [61]	Single-cell RNA sequencing of neocortical cells 6, 12, 24 and 48 h after birth in E14.5 mouse neocortex

are being generated and lncBrn1 overexpression reduces layer 2 or 3 neuron numbers, which is similar to the effects of Brn1 knockdown [74]. Other examples of lncRNAs with known function in corticogenesis are provided in Table 4.

Controlling transitions between progenitor and neuronal types

The molecular programmes which drive progenitor behaviour have classically been divided into proliferative and neurogenic programmes [75]. Proliferative programmes are predominantly expressed by self-renewing progenitors, and are essential in maintaining the size of the progenitor pool necessary for subsequent neuron generation. Neurogenic programmes, on the other hand, are expressed upon commitment of proliferative progenitors to give rise to neurons and transit amplifying cells. Proliferative programmes decrease over time while neurogenic programmes increase. Interestingly, it has recently been shown that the developmental progression in the transcriptome of apical progenitors is independent of the number of cell cycles which these progenitors have undergone, suggesting that progression in progenitor competence is not driven by the incremental number of cell divisions, but rather by distinct, cell cycle-independent processes [76]. Here, we will briefly discuss some of the salient pathways and molecules involved in controlling the transition between NECs and aRGs, aRGs to bIPS, and aRGs to neurons.

NECs to aRG

The Notch signalling pathway and its downstream transcription factors, Hes1 and Hes5, have been shown to control the transition between NECs and aRGs [77,78]. Fgf10 also regulates the transition of NECs to aRGs, and maintains aRG fate (i.e. prevents aRGs from becoming bIPs) [79]. In the absence of Fgf10, there is prolonged generation of NECs and the NEC to aRG switch is hampered [80]. Another Fgf family member, Fgf2, acts to keep aRGs in a proliferative mode, through downregulation of p27kip1 and upregulation of cyclinD2 [81]. After initiation of neurogenesis, Fgf signalling is critical to maintain the proliferation of the progenitors.

Wnt signalling is another major pathway associated with aRG self-renewal, which acts by inducing the expression of Pax6 [75]. At later stages of corticogenesis, it promotes proliferation of bIPs through N-myc and Ngn1 [82] and differentiative division of bIPs [83].

Several transcription factors, including Sox2, Pax6 and Oct4, regulate the proliferation of aRGs. The absence of these transcription factors results in the downregulation of stem cell markers such as Nestin and GFAP in aRGs, and a reduction in proliferation [84,85]. Interestingly, loss of PAX6 leads to ectopic basal division of aRGs, probably because PAX6 stabilizes centrosome and cell anchoring in the apical side to maintain the epithelial features of aRGs [86]. The transcription factor Foxc1, when knocked down, leads to disrupted RA (retinoic acid) signalling, which

Table 4. miRNAs and lncRNAs implicated progenitor behaviour.

	Function	References
miR Name		
MiR-128	Repression of NPC proliferation; promotes neuron generation.	Zhang *et al.* (2016) [137]
Let7	Promotes neuronal progenitor differentiation and maintains neuronal lineage commitment.	Kawahara *et al.* (2012) [138]
MiR-137	Promotes cell cycle exit of aRGs and neuron generation by controlling levels of LSD1, a histone demethylase.	Sun *et al.* (2011) [139]
MiR 17-92	Controls levels of intermediate progenitor by modulating expression of Eomes and Pten.	Bian *et al.* (2013) [140]
MiR-124	Promotes neuron generation from progenitors.	Maiorno and Mallamaci (2009) [141]
miR-19a	Controls levels of intermediate progenitor by modulating Pten expression.	Knauss *et al.* (2013) [142]
MiR 9	Maintains neuronal lineage in aRGs, through regulation of Ngn1. Regulates notch signalling.	Zhao *et al.* (2015) [143]
miR 15b	Repression of NPC proliferation; promotes cell cycle exit.	Lv *et al.* (2014) [144]
miR 92b	Controls levels of intermediate progenitor by modulating gene expression of EOMES	Nowakowski *et al.* (2013) [145]
MiR-210	Promotes cell cycle exit in aRGs	Abdullah *et al.* (2016) [146]
MiR-17	Promotes neocortical progenitor proliferation by regulating P21 and Trp53inp1 expression	Chen *et al.* (2014) [147]
MiR-92	Controls levels of neurogenic progenitor by modulating gene expression of Tis21	Fei *et al.* (2014) [148]
MiR-134	Promotes neocortical progenitor proliferation	Gaughwin *et al.* (2011) [149]
lncRNA_Name		
RMST	Regulation of neural progenitor fate by binding to SOX2	Ng *et al.* (2013) [150]
MIAT	Enriched in mouse basal progenitors	Aprea *et al.* (2013) [72]
Fgf2-AS	Control of proliferation in neural progenitors	Aprea and Calegari (2015) [70]
Pnky	Differentiation of neural progenitors	Ramos *et al.* (2015) [151]
TUNA	Promotes neuron generation from progenitors	Lin *et al.* (2014) [152]
Linc-Brn1b	Regulates commitment of progenitors	Sauvageau *et al.* (2013) [74]
LOC646329	Enriched in human apical radial glia, promotes proliferation	Liu *et al.* (2016) [71]
utNgn1	Regulates neurogenic commitment of progenitors through expression of Ngn1.	Onoguchi *et al.* (2012) [153]
Gm17566	Regulates neurogenesis through regulation of Pax6	Aprea *et al.* (2013) [72]

causes aRG to undergo prolonged symmetric divisions, thereby perturbing neurogenesis [87].

aRG to bIP and neurons

Following progenitor expansion, transcription factors referred to as proneural genes act to induce differentiative divisions in aRGs. For example, loss of proneural genes, Mash1, Ngn1 or Ngn2, which are transcription factors, induces a reduction in neuron numbers and a shift in the fate of progenitors towards the glial lineage, that is, these cells maintain a proliferative potential. In contrast, Ngn2 overexpression induces premature cell cycle exit in progenitors and generation of neurons, and is thought to act by downregulating cyclins involved in G1-S transition during cell cycle [88]. Interestingly, neuronal genes, such as NeuroD1, NeuroD2 and Tubb3, have been reported within mitotic progenitors, suggesting that progenitors can be poised for a neuronal programme even during mitosis [61,72].

Tis21 mRNA is specifically expressed in VZ progenitors as they commit to produce neurons in the G1 phase of neurogenic divisions. TIS21 protein is also found in such cells, as well as in postmitotic daughter neurons [89]. Ngn2 mRNA is another transcript which identifies apical progenitors fated to produce neurons [90]. bIPs are solely neurogenic and express markers of neurogenic genes such as BTG2, NGN2, EOMES, Svet1 and INSM1. In contrast, bRGs, which can additionally self-renew, express proliferative aRG markers, such as SOX2, PAX6, FABP7, in addition to neuronal markers such as NRCAM, CTNND2 and SEZ6L [64]. Interestingly, Pax6 transcripts enriched in apical progenitors that will undergo proliferative cell divisions contain the exon 5a, while the isoform present in apical progenitor that will undergo differentiative divisions lack this exon [91]. Accordingly, overexpression of PAX6-5A in apical progenitors failed to affect neurogenesis [92]. This suggests that gene splicing mechanisms might play a major role in dictating progenitor fate and cell behaviour during neocortex development.

Eomes, another transcription factor, when overexpressed in aRGs increases the differentiative division of aRGs to bIPs and reduces self-renewal of aRGs [93]. Similarly Insm1, a zinc finger transcription factor, is crucial in maintaining the number of bIPs during neocorticogenesis and MDGA1, an extracellular protein, is required for the aggregation and proliferation of bIPs within the SVZ [94].

Cellular bases of cortical gyration

Although several reviews have been published on this topic [95,96], gyration (i.e. the formation of folds on the cortical surface) deserves to be briefly discussed here, because it is a macroscopic feature of the brain which is thought to be strongly associated with proliferation potential of progenitors. Gyration is observed in several mammalian species and most primates, and has been associated with an increased proliferation in SVZ: increased and decreased SVZ thickness is observed below prospective gyri and sulci, respectively, suggesting that expansion of basal progenitors in the SVZ underlie gyration [97]. Furthermore, the percentage of dividing cells in the OSVZ (presumably bRGs) across species is highly correlated with the gyration index, suggesting that bRGs are the major source of progenitors responsible for cortical gyration [97].

Increased proliferation of aRGs in the mouse (a lissencephalic mammal) through expression of the cell cycle regulators, Cyclin D1 and Cdk4, results in an increase in bIPs, but fails to generate gyri [98]. However, overexpressing the same regulators in the ferret neocortex, which has gyri, resulted in an increased number of gyri, suggesting that the precise subtypes of cells present and their cytokinetic properties critically determines radial cortical expansion [99]. Gyri can, however, be generated in mice; for example, embryonic intraventricular administration of FGF2 increases bIPs but not bRGs, and leads to the formation of lateral gyri [100]. Similarly, downregulation of TRNP1 and upregulation of ARGAP11B independently lead to an increase in bRGs and reported gyrus formation in the mouse neocortex [11,101]. Although the respective contribution of bIPs and bRGs to gyration is still debated, apical progenitor expansion does not appear to play a direct role. Indeed, overexpression of TRNP1 selectively increases aRG (and not bIPs), which results in tangential expansion of neocortex without gyrus formation [101]. In ferrets, proliferating bRGs have a longer cell cycle duration (including a longer G1 and S phase) compared with the proliferating aRGs, which may result in greater contribution of the former cells to neurogenesis at late developmental stages and account for gyration [102]. Altogether, these data support a critical contribution of intermediate progenitor proliferation to the formation of gyri.

Linking progenitor diversity with neuronal diversity

Whether fate-restricted apical progenitors giving rise only to specific classes of cell types exist is still a matter of debate. Genetic labelling approaches have suggested that $Cux2^+$ progenitors constitute a subpopulation of cells which only give rise to superficial layer neurons [103], but more recent work has questioned this result [104,105] such that more studies will be needed to settle this issue. Slowly diving progenitors fated to produce adult neuronal stem cells have recently been identified in the embryonic VZ, such that the existence of other fate-restricted progenitors in the dorsal pallium remains a genuine possibility [106].

In broader terms, neurogenesis can be characterized as direct or indirect, based on whether neurons are born directly from aRGs or through subsequent cell divisions of intermediate progenitors. The current consensus is that deep layer neurons are mostly born through direct neurogenesis, while superficial layer neurons are mostly born through indirect neurogenesis, *via* bIPs. This hypothesis is based on the fact that the appearance of the SVZ and bIPs coincides with the generation of upper layer neurons [60]. Also, expansion of the SVZ and intermediate progenitor repertoire is observed together with the expansion of superficial layer neurons during evolution [107,108]. Fate mapping studies using the Eomes promoter (which is active in bIPs and not aRGs) show, however, that both upper layer neurons and deep layer neurons may arise from indirect neurogenesis, but it is still not clear if Eomes expression is restricted only to bIPs or if it is also transiently expressed in neurons generated through direct neurogenesis [61,109]. Recent birthdating data using FlashTag to identify neurons born through direct neurogenesis has revealed that a significant proportion of the upper layer neurons is also derived directly from apical progenitors [61]. Finally, aIPs may be more likely than aRGs to give rise to layer 4 neurons [7]. Thus, whether aIPs with distinct neurogenic competences exist, and how this competence is dynamically controlled through corticogenesis remains a largely unsettled issue.

Plasticity in the competence of neocortical progenitors to generate distinct types of neurons during corticogenesis has been studied using heterochronic transplantation experiments. In ferrets, the only species in which this has systematically been studied, transplantation of progenitors that normally give rise to deeper layer neurons in brains of older embryos leads to the generation of more superficial layer neurons [110,111], while late-stage progenitors seemingly remained unaffected by transplantation into younger hosts [112]. Interestingly, the plasticity of early-stage progenitors to generate neurons based on their new environment is restricted to early cell cycle phase of the progenitors [111]. Together with the observation

that mouse progenitors preserve their competence to generate cell types in the same order as *in vivo* [113,114], these experiments suggest that the neurogenic competence of cortical progenitors appears to be mostly cell intrinsic, and characterized by a progressive restriction in competence: early progenitors are able to generate both deep and superficial layer neurons, while late progenitors appear to only generate superficial neurons. Foxg1 has been shown to be required for this collective progression in progenitor competence during corticogenesis: when Foxg1 is conditionally knocked down at E11.5, the cortex is overpopulated by early born Cajal–Retzius cells at the expense of next-born $Tbr1^+$ neurons, while when this is done at E12.5 it is overpopulated by $Tbr1^+$ neurons at the expense of next-born $Fezf2^+$ neurons (layer5) [115,116]. Environment, however, also plays a modulatory role in controlling these transcriptional programmes (since early progenitors are respecified in a more mature environment), but the nature (e.g. cell–cell interactions, diffusible ligands) and source (e.g. cerebrospinal fluid, vascular system) of the signals at play, and whether they are permissive or repressive, remain largely unknown.

Finally, as presented in the introduction, astroglial cells are generated at the end of corticogenesis, as neurogenesis subsides. Although a detailed characterization of this process is beyond the scope of this review, throughout neurogenesis, transcription factors referred to as proneural genes (e.g. Ascl1, Ngn1 and Ngn2) are active in progenitors to drive neuronal production [117,118]. Towards the end of corticogenesis, expression of these transcription factors decrease, leading to a decrease in neuronal production and induction of gliogenesis [118,119].

Conclusions and outlook

Progenitors are dynamic cells whose identities were initially defined based on their morphology and location. The recent advent of single-cell RNA sequencing now allows us to have access to the transcriptional signatures of these cells, and attempt to establish functional relationships between distinct molecular identities and specific cellular fates. Some interesting endeavours in the years to come will be to understand the relationship between cell cycle characteristics (and particularly cell cycle length) and daughter cell fate, to assess the molecular diversity of progenitors across developmental ages and investigate the issue of fate-restricted progenitors, and the extent to which neurons born from different types of progenitors at similar developmental time points differ in their circuit and functional properties. A fine-grained characterization of corticogenic events across species, including humans, should provide us with the framework to better understand developmentally rooted neurological and psychiatric disorders.

References

1 Caviness VS, Takahashi T and Nowakowski RS (1995) Numbers, time and neocortical neuronogenesis: a general developmental and evolutionary model. *Trends Neurosci* **18**, 379–383.

2 Jabaudon D (2017) Fate and freedom in developing neocortical circuits. *Nat Commun* **8**, 16042.

3 Taverna E, Götz M and Huttner WB (2014) The cell biology of neurogenesis: toward an understanding of the development and evolution of the neocortex. *Annu Rev Cell Dev Biol* **30**, 465–502.

4 Haubensak W, Attardo A, Denk W and Huttner WB (2004) Neurons arise in the basal neuroepithelium of the early mammalian telencephalon: a major site of neurogenesis. *Proc Natl Acad Sci U S A* **101**, 3196–3201.

5 Noctor SC, Martínez-Cerdeño V, Ivic L and Kriegstein AR (2004) Cortical neurons arise in symmetric and asymmetric division zones and migrate through specific phases. *Nat Neurosci* **7**, 136–144.

6 Gal JS, Morozov YM, Ayoub AE, Chatterjee M, Rakic P and Haydar TF (2006) Molecular and morphological heterogeneity of neural precursors in the mouse neocortical proliferative zones. *J Neurosci* **26**, 1045–1056.

7 Stancik EK, Navarro-Quiroga I, Sellke R and Haydar TF (2010) Heterogeneity in ventricular zone neural precursors contributes to neuronal fate diversity in the postnatal neocortex. *J Neurosci* **30**, 7028–7036.

8 Hansen DV, Lui JH, Parker PRL and Kriegstein AR (2010) Neurogenic radial glia in the outer subventricular zone of human neocortex. *Nature* **464**, 554–561.

9 Wang J, Zhang H, Young AG, Qiu R, Argalian S, Li X, Wu X, Lemke G and Lu Q (2011) Transcriptome analysis of neural progenitor cells by a genetic dual reporter strategy. *Stem Cells* **29**, 1589–1600.

10 Götz M and Huttner WB (2005) The cell biology of neurogenesis. *Nat Rev Mol Cell Biol* **6**, 777–788.

11 Florio M, Albert M, Taverna E, Namba T, Brandl H, Lewitus E, Haffner C, Sykes A, Wong FK, Peters J *et al.* (2015) Human-specific gene ARHGAP11B promotes basal progenitor amplification and neocortex expansion. *Science* **347**, 1465–1470.

12 Götz M, Stoykova A and Gruss P (1998) Pax6 controls radial glia differentiation in the cerebral cortex. *Neuron* **21**, 1031–1044.

13 Taverna E, Mora-Bermúdez F, Strzyz PJ, Florio M, Icha J, Haffner C, Norden C, Wilsch-Bräuninger M and Huttner WB (2016) Non-canonical features of the

Golgi apparatus in bipolar epithelial neural stem cells. *Sci Rep* **6**, 21206.
14 Kriegstein A and Alvarez-Buylla A (2009) The glial nature of embryonic and adult neural stem cells. *Annu Rev Neurosci* **32**, 149–184.
15 Kadowaki M, Nakamura S, Machon O, Krauss S, Radice GL and Takeichi M (2007) N-cadherin mediates cortical organization in the mouse brain. *Dev Biol* **304**, 22–33.
16 Singh S and Solecki DJ (2015) Polarity transitions during neurogenesis and germinal zone exit in the developing central nervous system. *Front Cell Neurosci* **9**, 62.
17 Hatakeyama J, Wakamatsu Y, Nagafuchi A, Kageyama R, Shigemoto R and Shimamura K (2014) Cadherin-based adhesions in the apical endfoot are required for active Notch signaling to control neurogenesis in vertebrates. *Development* **141**, 1671–1682.
18 Miyata T, Okamoto M, Shinoda T and Kawaguchi A (2015) Interkinetic nuclear migration generates and opposes ventricular-zone crowding: insight into tissue mechanics. *Front Cell Neurosci* **8**, 473.
19 Okamoto M, Namba T, Shinoda T, Kondo T, Watanabe T, Inoue Y, Takeuchi K, Enomoto Y, Ota K, Oda K *et al*. (2013) TAG-1-assisted progenitor elongation streamlines nuclear migration to optimize subapical crowding. *Nat Neurosci* **16**, 1556–1566.
20 Lepanto P, Badano JL and Zolessi FR (2016) Neuron's little helper: the role of primary cilia in neurogenesis. *Neurogenesis* **3**, e1253363.
21 Higginbotham H, Guo J, Yokota Y, Umberger NL, Su CY, Li J, Verma N, Hirt J, Ghukasyan V, Caspary T *et al*. (2013) Arl13b-regulated cilia activities are essential for polarized radial glial scaffold formation. *Nat Neurosci* **16**, 1000–1007.
22 Kriegstein AR and Götz M (2003) Radial glia diversity: a matter of cell fate. *Glia* **43**, 37–43.
23 Kosodo Y and Huttner WB (2009) Basal process and cell divisions of neural progenitors in the developing brain. *Dev Growth Differ* **51**, 251–261.
24 Nadarajah B and Parnavelas JG (2002) Modes of neuronal migration in the developing cerebral cortex. *Nat Rev Neurosci* **3**, 423–432.
25 Haubst N, Georges-Labouesse E, De Arcangelis A, Mayer U and Götz M (2006) Basement membrane attachment is dispensable for radial glial cell fate and for proliferation, but affects positioning of neuronal subtypes. *Development* **133**, 3245–3254.
26 Weimer JM, Yokota Y, Stanco A, Stumpo DJ, Blackshear PJ and Anton ES (2009) MARCKS modulates radial progenitor placement, proliferation and organization in the developing cerebral cortex. *Development* **136**, 2965–2975.
27 Yokota Y, Eom TY, Stanco A, Kim WY, Rao S, Snider WD and Anton ES (2010) Cdc42 and Gsk3 modulate the dynamics of radial glial growth, inter-radial glial interactions and polarity in the developing cerebral cortex. *Development* **137**, 4101–4110.
28 Yokota Y, Ring C, Cheung R, Pevny L and Anton ES (2007) Nap1-regulated neuronal cytoskeletal dynamics is essential for the final differentiation of neurons in cerebral cortex. *Neuron* **54**, 429–445.
29 Tsunekawa Y, Britto JM, Takahashi M, Polleux F, Tan SS and Osumi N (2012) Cyclin D2 in the basal process of neural progenitors is linked to non-equivalent cell fates. *EMBO J* **31**, 1879–1892.
30 Miyata T, Kawaguchi A, Okano H and Ogawa M (2001) Asymmetric inheritance of radial glial fibers by cortical neurons. *Neuron* **31**, 727–741.
31 Pilaz L-J, Lennox AL, Rouanet JP, Silver Correspondence DL and Silver DL (2016) Dynamic mRNA transport and local translation in radial glial progenitors of the developing brain. *Curr Biol* **26**, 3383–3392.
32 Taverna E and Huttner WB (2010) Neural progenitor nuclei IN motion. *Neuron* **67**, 906–914.
33 Wang X, Tsai JW, Imai JH, Lian WN, Vallee RB and Shi SH (2009) Asymmetric centrosome inheritance maintains neural progenitors in the neocortex. *Nature* **461**, 947–955.
34 Insolera R, Bazzi H, Shao W, Anderson KV and Shi S-H (2014) Cortical neurogenesis in the absence of centrioles. *Nat Neurosci* **17**, 1528–1535.
35 Nelson BR, Hodge RD, Bedogni F and Hevner RF (2013) Dynamic interactions between intermediate neurogenic progenitors and radial glia in embryonic mouse neocortex: potential role in Dll1-notch signaling. *J Neurosci* **33**, 9122–9139.
36 Attardo A, Calegari F, Haubensak W, Wilsch-Bräuninger M and Huttner WB (2008) Live imaging at the onset of cortical neurogenesis reveals differential appearance of the neuronal phenotype in apical versus basal progenitor progeny. *PLoS One* **3**, e2388.
37 LaMonica BE, Lui JH, Hansen DV and Kriegstein AR (2013) Mitotic spindle orientation predicts outer radial glial cell generation in human neocortex. *Nat Commun* **4**, 1665.
38 Javaherian A and Kriegstein A (2009) A stem cell niche for intermediate progenitor cells of the embryonic cortex. *Cereb Cortex* **19** (Suppl 1), i70–i77.
39 Gerstmann K, Pensold D, Symmank J, Khundadze M, Hübner CA, Bolz J and Zimmer G (2015) Thalamic afferents influence cortical progenitors via ephrin A5-EphA4 interactions. *Development* **142**, 140–150.
40 Dehay C, Savatier P, Cortay V and Kennedy H (2001) Cell-cycle kinetics of neocortical precursors are influenced by embryonic thalamic axons. *J Neurosci* **21**, 201–214.

41 Betizeau M, Cortay V, Patti D, Pfister S, Gautier E, Bellemin-Ménard A, Afanassieff M, Huissoud C, Douglas RJ, Kennedy H *et al*. (2013) Precursor diversity and complexity of lineage relationships in the outer subventricular zone of the primate. *Neuron* **80**, 442–457.
42 Gertz CC, Lui JH, LaMonica BE, Wang X and Kriegstein AR (2014) Diverse behaviors of outer radial glia in developing ferret and human cortex. *J Neurosci* **34**, 2559–2570.
43 Sakaue-Sawano A, Kurokawa H, Morimura T, Hanyu A, Hama H, Osawa H, Kashiwagi S, Fukami K, Miyata T, Miyoshi H *et al*. (2008) Visualizing spatiotemporal dynamics of multicellular cell-cycle progression. *Cell* **132**, 487–498.
44 Wang X, Tsai J-W, LaMonica B and Kriegstein AR (2011) A new subtype of progenitor cell in the mouse embryonic neocortex. *Nat Neurosci* **14**, 555–561.
45 Huttner WB and Kosodo Y (2005) Symmetric versus asymmetric cell division during neurogenesis in the developing vertebrate central nervous system. *Curr Opin Cell Biol* **17**, 648–657.
46 Chenn A and McConnell SK (1995) Cleavage orientation and the asymmetric inheritance of notchl immunoreactivity in mammalian neurogenesis. *Cell* **82**, 631–641.
47 Haydar TF, Ang E and Rakic P (2003) Mitotic spindle rotation and mode of cell division in the developing telencephalon. *Proc Natl Acad Sci U S A* **100**, 2890–2895.
48 Kosodo Y, Röper K, Haubensak W, Marzesco AM, Corbeil D and Huttner WB (2004) Asymmetric distribution of the apical plasma membrane during neurogenic divisions of mammalian neuroepithelial cells. *EMBO J* **23**, 2314–2324.
49 Sun Y, Goderie SK and Temple S (2005) Asymmetric distribution of EGFR receptor during mitosis generates diverse CNS progenitor cells. *Neuron* **45**, 873–886.
50 Caviness VS, Goto T, Tarui T, Takahashi T, Bhide PG and Nowakowski RS (2003) Cell output, cell cycle duration and neuronal specification: a model of integrated mechanisms of the neocortical proliferative process. *Cereb Cortex* **13**, 592–598.
51 Salomoni P and Calegari F (2010) Cell cycle control of mammalian neural stem cells: Putting a speed limit on G1. *Trends Cell Biol* **20**, 233–243.
52 Pilaz LJ, Patti D, Marcy G, Ollier E, Pfister S, Douglas RJ, Betizeau M, Gautier E, Cortay V, Doerflinger N *et al*. (2009) Forced G1-phase reduction alters mode of division, neuron number, and laminar phenotype in the cerebral cortex. *Proc Natl Acad Sci U S A* **106**, 21924–21929.
53 Calegari F (2005) Selective lengthening of the cell cycle in the neurogenic subpopulation of neural progenitor cells during mouse brain development. *J Neurosci* **25**, 6533–6538.
54 Nguyen L, Besson A, Roberts JM and Guillemot F (2006) Coupling cell cycle exit, neuronal differentiation and migration in cortical neurogenesis. *Cell Cycle* **5**, 2314–2318.
55 Arai Y, Pulvers JN, Haffner C, Schilling B, Nüsslein I, Calegari F and Huttner WB (2011) Neural stem and progenitor cells shorten S-phase on commitment to neuron production. *Nat Commun* **2**, 154.
56 Pilaz LJ, McMahon JJ, Miller EE, Lennox AL, Suzuki A, Salmon E and Silver DL (2016) Prolonged mitosis of neural progenitors alters cell fate in the developing brain article prolonged mitosis of neural progenitors alters cell fate in the developing brain. *Neuron* **89**, 83–99.
57 Mora-Bermúdez F, Badsha F, Kanton S, Camp JG, Vernot B, Köhler K, Voigt B, Okita K, Maricic T, He Z *et al*. (2016) Differences and similarities between human and chimpanzee neural progenitors during cerebral cortex development. *Elife* **5**, 371–375.
58 Zhu X, Li B, Ai Z, Xiang Z, Zhang K, Qiu X, Chen Y, Li Y, Rizak JD, Niu Y *et al*. (2016) A robust single primate neuroepithelial cell clonal expansion system for neural tube development and disease studies. *Stem Cell Reports* **6**, 228–242.
59 Englund C. (2005) Pax6, Tbr2, and Tbr1 are expressed sequentially by radial glia, intermediate progenitor cells, and postmitotic neurons in developing neocortex. *J Neurosci* **25**, 247–251.
60 Tarabykin V, Stoykova A, Usman N and Gruss P (2001) Cortical upper layer neurons derive from the subventricular zone as indicated by Svet1 gene expression. *Development* **128**, 1983–1993.
61 Telley L, Govindan S, Prados J, Stevant I, Nef S, Dermitzakis E, Dayer A and Jabaudon D (2016) Sequential transcriptional waves direct the differentiation of newborn neurons in the mouse neocortex. *Science* **351**, 1443–1446.
62 Mihalas AB, Elsen GE, Bedogni F, Daza RAM, Ramos-Laguna KA, Arnold SJ and Hevner RF (2016) Intermediate progenitor cohorts differentially generate cortical layers and require Tbr2 for timely acquisition of neuronal subtype identity. *Cell Rep* **16**, 92–105.
63 Vasistha NA, García-Moreno F, Arora S, Cheung AFP, Arnold SJ, Robertson EJ and Molnár Z (2015) Cortical and clonal contribution of Tbr2 expressing progenitors in the developing mouse brain. *Cereb Cortex* **25**, 3290–3302.
64 Pollen AA, Nowakowski TJ, Chen JR, Retallack H, Sandoval-Espinosa C, Nicholas CR, Shuga J, Liu SJ, Oldham MC, Diaz A *et al*. (2015) Molecular identity of human outer radial glia during cortical development. *Cell* **163**, 55–67.

65 Ayoub AE, Oh S, Xie Y, Leng J, Cotney J, Dominguez MH, Noonan JP and Rakic P (2011) Transcriptional programs in transient embryonic zones of the cerebral cortex defined by high-resolution mRNA sequencing. *Proc Natl Acad Sci U S A* **108**, 14950–14955.
66 Fietz SA, Lachmann R, Brandl H, Kircher M, Samusik N, der Schrö R, Lakshmanaperumal N, Henry I, Vogt J, Riehn A *et al*. (2012) Transcriptomes of germinal zones of human and mouse fetal neocortex suggest a role of extracellular matrix in progenitor self-renewal. *Proc Natl Acad Sci U S A* **109**, 11836–11841.
67 Florio M and Huttner WB (2014) Neural progenitors, neurogenesis and the evolution of the neocortex. *Development* **141**, 2182–2194.
68 De Pietri Tonelli D, Pulvers JN, Haffner C, Murchison EP, Hannon GJ and Huttner WB (2008) miRNAs are essential for survival and differentiation of newborn neurons but not for expansion of neural progenitors during early neurogenesis in the mouse embryonic neocortex. *Development* **135**, 3911–3921.
69 Arcila ML, Betizeau M, Cambronne XA, Guzman E, Doerflinger N, Bouhallier F, Zhou H, Wu B, Rani N, Bassett DS *et al*. (2014) Neuron neuroresource novel primate miRNAs coevolved with ancient target genes in germinal zone-specific expression patterns. *Neuron* **81**, 1255–1262.
70 Aprea J and Calegari F (2015) Long non-coding RNAs in corticogenesis: deciphering the non-coding code of the brain. *EMBO J* **34**, 2865–2884.
71 Liu SJ, Nowakowski TJ, Pollen AA, Lui JH, Horlbeck MA, Attenello FJ, He D, Weissman JS, Kriegstein AR, Diaz AA *et al*. (2016) Single-cell analysis of long non-coding RNAs in the developing human neocortex. *Genome Biol* **17**, 67.
72 Aprea J, Prenninger S, Dori M, Ghosh T, Monasor LS, Wessendorf E, Zocher S, Massalini S, Alexopoulou D, Lesche M *et al*. (2013) Transcriptome sequencing during mouse brain development identifies long non-coding RNAs functionally involved in neurogenic commitment. *EMBO J* **32**, 3145–3160.
73 Johnson MB, Wang PP, Atabay KD, Murphy EA, Doan RN, Hecht JL and Walsh CA (2015) Single-cell analysis reveals transcriptional heterogeneity of neural progenitors in human cortex. *Nat Neurosci* **18**, 637–646.
74 Sauvageau M, Goff LA, Lodato S, Bonev B, Groff AF, Gerhardinger C, Sanchez-Gomez DB, Hacisuleyman E, Li E, Spence M *et al*. (2013) Multiple knockout mouse models reveal lincRNAs are required for life and brain development. *Elife* **2**, e01749.
75 Martynoga B, Drechsel D and Guillemot F (2012) Molecular control of neurogenesis: a view from the mammalian cerebral cortex. *Cold Spring Harb Perspect Biol* **4**, a008359.
76 Okamoto M, Miyata T, Konno D, Ueda HR, Kasukawa T, Hashimoto M, Matsuzaki F and Kawaguchi A (2016) Cell-cycle-independent transitions in temporal identity of mammalian neural progenitor cells. *Nat Commun* **7**, 11349.
77 Gaiano N, Nye JS and Fishell G (2000) Radial glial identity is promoted by Notch1 signaling in the murine forebrain. *Neuron* **26**, 395–404.
78 Hatakeyama J, Bessho Y, Katoh K, Ookawara S, Fujioka M, Guillemot F and Kageyama R (2004) Hes genes regulate size, shape and histogenesis of the nervous system by control of the timing of neural stem cell differentiation. *Development* **131**, 5539–5550.
79 Kang W, Wong LC, Shi S-H and Hébert JM (2009) The transition from radial glial to intermediate progenitor cell is inhibited by FGF signaling during corticogenesis. *J Neurosci* **29**, 14571–14580.
80 Sahara S and O'Leary DDM (2009) Fgf10 regulates transition period of cortical stem cell differentiation to radial glia controlling generation of neurons and basal progenitors. *Neuron* **63**, 48–62.
81 Lukaszewicz A, Savatier P, Cortay V, Kennedy H and Dehay C (2002) Contrasting effects of basic fibroblast growth factor and neurotrophin 3 on cell cycle kinetics of mouse cortical stem cells. *J Neurosci* **22**, 6610–6622.
82 Viti J, Gulacsi A and Lillien L (2003) Wnt regulation of progenitor maturation in the cortex depends on Shh or fibroblast growth factor 2. *J Neurosci* **23**, 5919–5927.
83 Hirabayashi Y, Itoh Y, Tabata H, Nakajima K, Akiyama T, Masuyama N and Gotoh Y (2004) The Wnt/-catenin pathway directs neuronal differentiation of cortical neural precursor cells. *Development* **131**, 2791–2801.
84 Archer TC, Jin J and Casey ES (2011) Interaction of Sox1, Sox2, Sox3 and Oct4 during primary neurogenesis. *Dev Biol* **350**, 429–440.
85 Graham V, Khudyakov J, Ellis P and Pevny L (2003) SOX2 functions to maintain neural progenitor identity. *Neuron* **39**, 749–765.
86 Tamai H, Shinohara H, Miyata T, Saito K, Nishizawa Y, Nomura T and Osumi N (2007) Pax6 transcription factor is required for the interkinetic nuclear movement of neuroepithelial cells. *Genes Cells* **12**, 983–996.
87 Siegenthaler JA, Ashique AM, Zarbalis K, Patterson KP, Hecht JH, Kane MA, Folias AE, Choe Y, May SR, Kume T *et al*. (2009) Retinoic acid from the meninges regulates cortical neuron generation. *Cell* **139**, 597–609.
88 Lacomme M, Liaubet L, Pituello F and Bel-Vialar S (2012) NEUROG2 drives cell cycle exit of neuronal precursors by specifically repressing a subset of cyclins acting at the G1 and S phases of the cell cycle. *Mol Cell Biol* **32**, 2596–2607.

89 Iacopetti P, Michelini M, Stuckmann I, Oback B, Aaku-Saraste E and Huttner WB (1999) Expression of the antiproliferative gene TIS21 at the onset of neurogenesis identifies single neuroepithelial cells that switch from proliferative to neuron-generating division. *Proc Natl Acad Sci U S A* **96**, 4639–4644.
90 Ochiai W, Nakatani S, Takahara T, Kainuma M, Masaoka M, Minobe S, Namihira M, Nakashima K, Sakakibara A, Ogawa M *et al*. (2009) Periventricular notch activation and asymmetric Ngn2 and Tbr2 expression in pair-generated neocortical daughter cells. *Mol Cell Neurosci* **40**, 225–233.
91 Pinto L, Mader MT, Irmler M, Gentilini M, Santoni F, Drechsel D, Blum R, Stahl R, Bulfone A, Malatesta P *et al*. (2008) Prospective isolation of functionally distinct radial glial subtypes—lineage and transcriptome analysis. *Mol Cell Neurosci* **38**, 15–42.
92 Haubst N, Berger J, Radjendirane V, Graw J, Favor J, Saunders GF, Stoykova A and Götz M (2004) Molecular dissection of Pax6 function: the specific roles of the paired domain and homeodomain in brain development. *Development* **131**, 6131–6140.
93 Sessa A, Mao C, Hadjantonakis A-K, Klein WH and Broccoli V (2008) Tbr2 directs conversion of radial glia into basal precursors and guides neuronal amplification by indirect neurogenesis in the developing neocortex. *Neuron* **60**, 56–69.
94 Perez-Garcia C and O'Leary DM (2016) Formation of the cortical subventricular zone requires MDGA1-mediated aggregation of basal progenitors. *Cell Rep* **14**, 560–571.
95 Fernández V, Llinares-Benadero C and Borrell V (2016) Cerebral cortex expansion and folding: what have we learned? *EMBO J* **35**, 1021–1044.
96 Borrell V and Götz M (2014) Role of radial glial cells in cerebral cortex folding. *Curr Opin Neurobiol* **27**, 39–46.
97 Reillo I, de Juan Romero C, García-Cabezas MÁ and Borrell V (2011) A role for intermediate radial glia in the tangential expansion of the mammalian cerebral cortex. *Cereb Cortex* **21**, 1674–1694.
98 Lange C, Huttner WB and Calegari F (2009) Cdk4/CyclinD1 overexpression in neural stem cells shortens G1, delays neurogenesis, and promotes the generation and expansion of basal progenitors. *Cell Stem Cell* **5**, 320–331.
99 Nonaka-Kinoshita M, Reillo I, Artegiani B, Martínez-Martínez MÁ, Nelson M, Borrell V and Calegari F (2013) Regulation of cerebral cortex size and folding by expansion of basal progenitors. *EMBO J* **32**, 1817–1828.
100 Rash BG, Tomasi S, Lim HD, Suh CY and Vaccarino FM (2013) Cortical gyrification induced by fibroblast growth factor 2 in the mouse brain. *J Neurosci* **33**, 10802–10814.
101 Stahl R, Walcher T, De Juan Romero C, Pilz GA, Cappello S, Irmler M, Sanz-Aquela JM, Beckers J, Blum R, Borrell V and Götz M (2013) Trnp1 regulates expansion and folding of the mammalian cerebral cortex by control of radial glial fate. *Cell* **153**, 535–549.
102 Turrero García M, Chang Y, Arai Y and Huttner WB (2016) S-phase duration is the main target of cell cycle regulation in neural progenitors of developing ferret neocortex. *J Comp Neurol* **524**, 456–470.
103 Franco SJ, Gil-Sanz C, Martinez-Garay I, Espinosa A, Harkins-Perry SR, Ramos C and Müller U (2012) Fate-restricted neural progenitors in the mammalian cerebral cortex. *Science* **337**, 746–749.
104 Eckler MJ, Nguyen TD, McKenna WL, Fastow BL, Guo C, Rubenstein JLR and Chen B (2015) Cux2-positive radial glial cells generate diverse subtypes of neocortical projection neurons and macroglia. *Neuron* **86**, 1100–1108.
105 Guo C, Eckler MJ, McKenna WL, McKinsey GL, Rubenstein JLR and Chen B (2013) Fezf2 expression identifies a multipotent progenitor for neocortical projection neurons, astrocytes, and oligodendrocytes. *Neuron* **80**, 1167–1174.
106 Furutachi S, Miya H, Watanabe T, Kawai H, Yamasaki N, Harada Y, Imayoshi I, Nelson M, Nakayama KI, Hirabayashi Y *et al*. (2015) Slowly dividing neural progenitors are an embryonic origin of adult neural stem cells. *Nat Neurosci* **18**, 657–665.
107 Kriegstein A, Noctor S and Martínez-Cerdeño V (2006) Patterns of neural stem and progenitor cell division may underlie evolutionary cortical expansion. *Nat Rev Neurosci* **7**, 883–890.
108 Martıez-Cerden Võ, Noctor SC and Kriegstein AR (2006) The role of intermediate progenitor cells in the evolutionary expansion of the cerebral cortex. *Cereb Cortex* **16**, i152–i161.
109 Hevner RF, Hodge RD, Daza RAM and Englund C (2006) Transcription factors in glutamatergic neurogenesis: conserved programs in neocortex, cerebellum, and adult hippocampus. *Neurosci Res* **55**, 223–233.
110 Desai AR and McConnell SK (2000) Progressive restriction in fate potential by neural progenitors during cerebral cortical development. *Development* **127**, 2863–2872.
111 McConnell S and Kaznowski C (1991) Cell cycle dependence of laminar determination in developing neocortex. *Science* **254**, 282–285.
112 Frantz GD and McConnell SK (1996) Restriction of late cerebral cortical progenitors to an upper-layer fate. *Neuron* **17**, 55–61.
113 Shen Q, Wang Y, Dimos JT, Fasano CA, Phoenix TN, Lemischka IR, Ivanova NB, Stifani S, Morrisey

EE and Temple S (2006) The timing of cortical neurogenesis is encoded within lineages of individual progenitor cells. *Nat Neurosci* **9**, 743–751.
114 Qian X, Shen Q, Goderie SK, He W, Capela A, Davis AA and Temple S (2000) Timing of CNS cell generation. *Neuron* **28**, 69–80.
115 Kumamoto T, Toma K, Gunadi McKenna WL, Kasukawa T, Katzman S, Chen B and Hanashima C (2013) Foxg1 coordinates the switch from nonradially to radially migrating glutamatergic subtypes in the neocortex through spatiotemporal repression. *Cell Rep* **3**, 931–945.
116 Toma K, Kumamoto T and Hanashima C (2014) The timing of upper-layer neurogenesis is conferred by sequential derepression and negative feedback from deep-layer neurons. *J Neurosci* **34**, 13259–13276.
117 Kawaguchi A, Ogawa M, Saito K, Matsuzaki F, Okano H and Miyata T (2004) Differential expression of Pax6 and Ngn2 between pair-generated cortical neurons. *J Neurosci Res* **78**, 784–795.
118 Schuurmans C, Armant O, Nieto M, Stenman JM, Britz O, Klenin N, Brown C, Langevin LM, Seibt J, Tang H, Cunningham JM *et al.* (2004) Sequential phases of cortical specification involve Neurogenin-dependent and -independent pathways. *EMBO J* **23**, 2892–2902.
119 Nieto M, Schuurmans C, Britz O and Guillemot F (2001) Neural bHLH genes control the neuronal versus glial fate decision in cortical progenitors. *Neuron* **29**, 401–413.
120 Eom TY, Stanco A, Weimer J, Stabingas K, Sibrack E, Gukassyan V, Cheng J and Anton ES (2011) Direct Visualization of microtubules using a genetic tool to analyse radial progenitor-astrocyte continuum in brain. *Nat Commun* **2**, 446.
121 Kawaguchi A, Miyata T, Sawamoto K, Takashita N, Murayama A, Akamatsu W, Ogawa M, Okabe M, Tano Y, Goldman SA *et al.* (2001) Nestin-EGFP transgenic mice: visualization of the self-renewal and multipotency of CNS stem cells. *Mol Cell Neurosci* **17**, 259–273.
122 Malatesta P, Hack MA, Hartfuss E, Kettenmann H, Klinkert W, Kirchhoff F and Götz M (2003) Neuronal or glial progeny: regional differences in radial glia fate. *Neuron* **37**, 751–764.
123 Zhou C, Tsai SY and Tsai MJ (2001) COUP-TFI: an intrinsic factor for early regionalization of the neocortex. *Genes Dev* **15**, 2054–2059.
124 Mori T, Tanaka K, Buffo A, Wurst W, Kühn R and Götz M (2006) Inducible gene deletion in astroglia and radial glia-A valuable tool for functional and lineage analysis. *Glia* **54**, 21–34.
125 Aubert J, Stavridis MP, Tweedie S, O'Reilly M, Vierlinger K, Li M, Ghazal P, Pratt T, Mason JO, Roy D, et al. (2003) Screening for mammalian neural genes via fluorescence-activated cell sorter purification of neural precursors from Sox1-gfp knock-in mice. *Proc Natl Acad Sci* **100**, 11836–11841.
126 Schmid RS, Yokota Y and Anton ES (2006) Generation and characterization of brain lipid-binding protein promoter-based transgenic mouse models for the study of radial glia. *Glia* **53**, 345–351.
127 Arnold SJ, Sugnaseelan J, Groszer M, Srinivas S and Robertson EJ (2009) Generation and analysis of a mouse line harboring GFP in the Eomes/Tbr2 locus. *Genesis* **47**, 775–781.
128 Wong FK, Fei JF, Mora-Bermúdez F, Taverna E, Haffner C, Fu J, Anastassiadis K, Stewart AF and Huttner WB (2015) Sustained Pax6 expression generates primate-like basal radial glia in developing mouse neocortex. *PLoS Biol* **13**, e1002217.
129 Osipovich AB, Long Q, Manduchi E, Gangula R, Hipkens SB, Schneider J, Okubo T, Stoeckert CJ, Takada S and Magnuson MA (2014) Insm1 promotes endocrine cell differentiation by modulating the expression of a network of genes that includes Neurog3 and Ripply3. *Development* **141**, 2939–2949.
130 Tyler WA and Haydar TF (2013) Multiplex genetic fate mapping reveals a novel route of neocortical neurogenesis, which is altered in the Ts65Dn mouse model of Down syndrome. *J Neurosci* **33**, 5106–5119.
131 Tyler WA, Medalla M, Guillamon-Vivancos T, Luebke JI and Haydar TF (2015) Neural precursor lineages specify distinct neocortical pyramidal neuron types. *J Neurosci* **35**, 6142–6152.
132 D'Amour KA and Gage FH (2003) Genetic and functional differences between multipotent neural and pluripotent embryonic stem cells. *Proc Natl Acad Sci USA* **100**, 11866–11872.
133 Kawaguchi A, Ikawa T, Kasukawa T, Ueda HR, Kurimoto K, Saitou M and Matsuzaki F (2008) Single-cell gene profiling defines differential progenitor subclasses in mammalian neurogenesis. *Development* **135**, 3113–3124.
134 Lui JH, Nowakowski TJ, Pollen AA, Javaherian A, Kriegstein A and Oldham MC (2014) Radial glia require PDGFD-PDGFRβ signalling in human but not mouse neocortex. *Nature* **515**, 264–268.
135 Camp JG, Badsha F, Florio M, Kanton S, Gerber T, Wilsch-Bräuninger M, Lewitus E Sykes A, Hevers W, Lancaster M *et al.* (2015) Human cerebral organoids recapitulate gene expression programs of fetal neocortex development. *Proc Natl Acad Sci USA* **112**, 15672–15677.
136 Mora-Bermúdez F, Badsha F, Kanton S, Camp JG, Vernot B, Köhler K, Voigt B, Okita K, Maricic T, He Z *et al.* (2016) Differences and similarities between human and chimpanzee neural progenitors during cerebral cortex development. *Elife* **5**, 371–375.

137 Zhang W, Kim PJ, Chen Z, Lokman H, Qiu L, Zhang K, Rozen SG, Tan EK, Je HS and Zeng L (2016) MiRNA-128 regulates the proliferation and neurogenesis of neural precursors by targeting PCM1 in the developing cortex. *Elife* **5**, https://doi.org/10.7554/eLife. 11324.
138 Kawahara H, Imai T and Okano H (2012) MicroRNAs in neural stem cells and neurogenesis. *Front Neurosci* **6**, 30.
139 Sun G, Ye P, Murai K, Lang MF, Li S, Zhang H, Li W, Fu C, Yin J, Wang A *et al.* (2011) miR-137 forms a regulatory loop with nuclear receptor TLX and LSD1 in neural stem cells. *Nat Commun* **2**, 529.
140 Bian S, Hong J, Li Q, Schebelle L, Pollock A, Knauss JL, Garg V and Sun T (2013) MicroRNA cluster miR-17-92 regulates neural stem cell expansion and transition to intermediate progenitors in the developing mouse neocortex. *Cell Rep* **3**, 1398–1406.
141 Maiorano N and Mallamaci A (2009) Promotion of embryonic cortico-cerebral neuronogenesis by miR-124. *Neural Dev* **4**, 40.
142 Knauss JL, Bian S and Sun T (2013) Plasmid-based target protectors allow specific blockade of miRNA silencing activity in mammalian developmental systems. *Front Cell Neurosci* **7**, 163.
143 Zhao J, Lin Q, Kim KJ, Dardashti FD, Kim J, He F and Sun Y (2015) Ngn1 inhibits astrogliogenesis through induction of miR-9 during neuronal fate specification. *Elife* **4**, https://doi.org/10.7554/eLife. 06885.
144 Lv X, Jiang H, Liu Y, Lei X and Jiao J (2014) MicroRNA-15b promotes neurogenesis and inhibits neural progenitor proliferation by directly repressing TET3 during early neocortical development. *EMBO Rep* **15**, 1305–1314.
145 Nowakowski TJ, Fotaki V, Pollock A, Sun T, Pratt T and Price DJ (2013) MicroRNA-92b regulates the development of intermediate cortical progenitors in embryonic mouse brain. *Proc Natl Acad Sci* **110**, 7056–7061.
146 Abdullah AI, Zhang H, Nie Y, Tang W and Sun T (2016) CDK7 and miR-210 Co-regulate cell-cycle progression of neural progenitors in the developing neocortex. *Stem Cell Reports* **7**, 69–79.
147 Chen Y, Bian S, Zhang J, Zhang H, Tang B and Sun T (2014) The silencing effect of microRNA miR-17 on p21 maintains the neural progenitor pool in the developing cerebral cortex. *Front Neurol* **5**, 132.
148 Fei JF, Haffner C and Huttner WB (2014) 3′ UTR-dependent, miR-92-mediated restriction of Tis21 expression maintains asymmetric neural stem cell division to ensure proper neocortex size. *Cell Rep* **7**, 398–411.
149 Gaughwin P, Ciesla M, Yang H, Lim B and Brundin P (2011) Stage-specific modulation of cortical neuronal development by Mmu-miR-134. *Cereb Cortex* **21**, 1857–1869.
150 Ng SY, Bogu GK, Soh BS and Stanton LW (2013) The long noncoding RNA RMST interacts with SOX2 to regulate neurogenesis. *Mol Cell* **51**, 349–359.
151 Ramos AD, Andersen RE, Liu SJ, Nowakowski TJ, Hong SJ, Gertz CC, Salinas RD, Zarabi H, Kriegstein AR and Lim DA (2015) The long noncoding RNA Pnky regulates neuronal differentiation of embryonic and postnatal neural stem cells. *Cell Stem Cell* **16**, 439–447.
152 Lin N, Chang KY, Li Z, Gates K, Rana ZA, Dang J, Zhang D, Han T, Yang CS and Cunningham TJ (2014) An evolutionarily conserved long noncoding RNA TUNA controls pluripotency and neural lineage commitment. *Mol Cell* **53**, 1005–1019.
153 Onoguchi M, Hirabayashi Y, Koseki H and Gotoh Y (2012) A noncoding RNA regulates the neurogenin1 gene locus during mouse neocortical development. *Proc Natl Acad Sci USA* **109**, 16939–16944.