Recent advances in understanding neocortical development
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Abstract
The neocortex is the largest part of the mammalian brain and is the seat of our higher cognitive functions. This outstanding neural structure increased massively in size and complexity during evolution in a process recapitulated today during the development of extant mammals. Accordingly, defects in neocortical development commonly result in severe intellectual and social deficits. Thus, understanding the development of the neocortex benefits from understanding its evolution and disease and also informs about their underlying mechanisms. Here, I briefly summarize the most recent and outstanding advances in our understanding of neocortical development and focus particularly on dorsal progenitors and excitatory neurons. I place special emphasis on the specification of neural stem cells in distinct classes and their proliferation and production of neurons and then discuss recent findings on neuronal migration. Recent discoveries on the genetic evolution of neocortical development are presented with a particular focus on primates. Progress on all these fronts is being accelerated by high-throughput gene expression analyses and particularly single-cell transcriptomics. I end with novel insights into the involvement of microglia in embryonic brain development and how improvements in cultured cerebral organoids are gradually consolidating them as faithful models of neocortex development in humans.

Keywords
Radial Glia, cell lineage, OSVZ, cortex folding, basal progenitors, neurogenesis, human-specific neocortex, neocortical development, cerebral cortex evolution, progenitor proliferation

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Introduction
The cerebral cortex, or neocortex, is the part of our brains primarily responsible for abstract thinking and our unique cognitive abilities as human beings. It is by far the most complex biological structure, and it forms during embryonic development following a sequence of genetically predefined molecular and cellular events. This process of embryonic development recapitulates the emergence of the human cerebral cortex during evolution. Thus, understanding neocortical development in humans and other species tells us about the magnitude of its complexity, how it differs from neocortical development in non-humans, how it emerged during evolution from simpler brains, and what goes wrong in developmental brain disease.

Through the use of informative experimental animal species, much has been learned about the basic processes of neocortical development: neural stem and progenitor cell (NSPC) proliferation, generation, and migration of neurons from their place of birth to their final location in neocortical layers and the growth of neural processes and establishment of nerve connections. Recent advances in genome editing, tissue culture, and DNA sequencing have accelerated our understanding of neocortical development at many levels. Here, I briefly summarize some of the most significant advances in our understanding of neocortical development generated recently by the international community, and I give special attention to progenitor proliferation and neurogenesis of dorsal progenitors and projection neurons. Although much remains to be learned, the emerging picture shows that the evolutionary and developmental emergence of the human neocortex involved a plethora of genetic and epigenetic changes, including novel genes and variants, functional gene networks, and novel cell types and cellular specializations.

Neurogenesis
Development of the neocortex begins with the proliferation of NSPCs, which amplify their own pool prior to generating neurons. Recent work shows that the proliferation of NSPCs and their mode of neuron production vary across species, and previously unsuspected mechanisms of molecular regulation have been identified. Novel insights about the diversity of progenitor cells and how their neuronal output contributes to build the cerebral cortex are also emerging.

Progenitor cell diversity
Work in the last decade has identified a diversity of NSPC types and their lineage relationships. Following the seminal discovery of apical radial glial cells (aRGCs) as the primary type of cortical progenitor cell1–2, intermediate progenitor cells (IPCs) were identified3–4. IPCs are transit-amplifying progenitors expressing the transcription factor Tbr2 and producing the majority of excitatory neurons in the mouse and rat neocortex16,17,18. Most IPCs cluster and undergo mitosis in a layer basal from the ventricular zone (VZ), the subventricular zone (SVZ), although a subset reside in the VZ and undergo apical mitosis, named short neural precursors1,5. Further studies in primates led to the discovery of an expanded and specialized SVZ, subdivided in inner and outer domains (ISVZ and OSVZ, respectively)6. These layers were later identified in other species with an expanded neocortex, like ferret, cat, and sheep19 and even in New World monkeys and the Amazonian rodent agouti20,21. Progenitor cell lineage tracings in human, macaque, ferret, and mouse led to the discovery of additional types of basal progenitor cells in the developing neocortex, which are bound by complex lineage relationships. These include various types of basal radial glial cells (bRGCs)22,23–25 and subapical progenitor cells26. The relative abundance and proliferative capacity of these progenitor cell types are much greater in species with a neocortex that is large and folded (carnivores and primates) than in those where it is small and smooth (mouse and rat). This has been proposed to contribute to the evolutionary increase in complexity, or complexification, of the neocortex16–18.

Pioneer transcriptomic studies of the developing cerebral cortex using bulk tissue, identified differences in gene expression between germinal layers, cortical areas, developmental stages, and mammalian species15,16,26–28. This illustrated the profound diversity of transcriptional landscapes in cortical development at all levels, including folding and across phylogeny, and set the conceptual foundations for the next technological leap: transcriptomics of single cells. The advent of single-cell transcriptomic analyses has revolutionized our approach to studying cortical development by providing a global and unbiased picture of cell diversity with unprecedented resolution29–31. This technology has enabled identification of multiple sets of transcriptionally distinct progenitor cell classes in the cortical primordium, generating excitatory neurons22–29, and in the basal ganglia, generating inhibitory interneurons30,31.

Single-cell analyses are also beginning to shed light on long-standing hypotheses about the heterogeneity of cortical progenitor cells and the dynamics of their lineage and fate potential during development2–9,19–26. Early experimental studies of these fundamental questions indicated that the fate potential of cortical progenitors is temporally restricted, such that early progenitors can produce neurons for all cortical layers but late progenitors can produce neurons for superficial layers only34,35. Such late fate restriction would be cell-autonomous as late cortical progenitors continued producing superficial-layer neurons even when transplanted into the new cellular environment of a young host cortex36,37. The identification of a subset of RGCs that expressed Cux2 and that were fate-restricted to produce upper-layer neurons further supported this model35. However, such fate-restricted progenitors have not been identified in single-cell transcriptomic studies22,23,24,38. Rather, some of these studies support the existence of epigenetically regulated temporal molecular birthmarks in RGCs, which act in their daughter neurons as seeds for neuronal diversity. It is proposed that these conserved differentiation programs may then be integrated with environmental (non-cell-autonomous) cues to ultimately define the identity of the neuronal progeny39,40. Nevertheless, controversial points of view on these and related issues remain because of differences in single-cell data processing, analysis, and interpretation35,39,41.

Modes of neurogenesis and influence on cortex size
Cortical excitatory neurons may be generated directly from the primary progenitor cells (aRGCs) or indirectly via secondary basal progenitors such as IPCs and bRGCs. Indirect neurogenesis
is considered a milestone of mammalian cortical evolution, enabling a phenomenal increase in the numbers of neurons produced, particularly those destined to superficial layers, and leading to cortical expansion. Recent studies reveal that indirect neurogenesis is the major mode of producing deep as well as superficial cortical layers in mouse and that it also exists in non-mammals, albeit at lower levels and mostly in birds. At the molecular level, regulation of the balance between direct and indirect neurogenesis is phylogenetically conserved across amniotes, from snakes to birds and mammals, including humans, where high Robo1/2 signaling promotes expression of the Notch ligands Jag1/2 while repressing the canonical ligand Dll1. Blockade of this signaling system drives indirect neurogenesis, increasing neuron numbers and cortex size. Intriguingly, indirect neurogenesis also correlates with hyperpolarization of apical progenitor cells, which represses Wnt signaling. Changes in the mode of neurogenesis are responsible for the reduced cortex size in developmental brain disease, like microcephaly induced by Zika virus infection. In this case, activation of the unfolded protein response drives direct neurogenesis, leading to premature and limited neuron production and to a small cortex.

Regulation of progenitor cell proliferation
Cerebral cortex size depends on the mode of neurogenesis and also on the proliferative activity of cortical progenitor cells. Multiple mechanisms regulating progenitor cell proliferation have recently been uncovered. Regulation of gene transcription by epigenetic mechanisms has emerged as a key factor where histone deacetylases and methyltransferases regulate the generation and position of IPCs, neuron migration, and cortical lamination. Similarly, regulation of chromatin accessibility and other mechanisms related to non-coding genomic regions critically determines levels and patterns of gene expression in the developing cortex, defining neuron production, cortex size, and area identity.

One of the most exciting findings has been the identification of mRNA species transported within the long basal process of aRGCs and locally translated at their basal endfeet, next to the pial membranes. This includes proteins regulating the cell cycle, like Cen2, and lengthening of G1, S, and M phases of the cell cycle, which depletes progenitor cells causing premature neurogenesis or apoptosis.

IPC are usually depicted as round cells extending few short processes, and bRGCs are usually depicted as having a single smooth and unbranched basal process. Recent observations demonstrate that the degree of process branching and elaboration in both IPCs and bRGCs is greater in ferret and human (which have a large and folded cortex) than in mouse (which has a small and smooth cortex) and this is linked to a greater proliferation rate of these cortical progenitor cells. Basal progenitor process growth and proliferation are related to the membrane-bound protein PALMD, enabling these cells to receive pro-proliferative signals related to integrin function. Indeed, modulation of cortical progenitor cell proliferation by cell-extrinsic signals has now been demonstrated to occur from multiple sources, including growing axons and migrating neurons, extracellular neurotransmitters and ions, and Notch, Wnt, Fgf, and Shh signals.

Once IPCs and neurons are born from aRGCs, they must first delaminate and migrate away from the VZ toward the SVZ. This critical process is regulated by several signaling mechanisms, including Robo1, YAP, and Insml via the apical adherens protein Plekha7, and the centrosome-associated protein Akna.

Neuronal migration
Once neurons are born, they must migrate from their place of birth in the germinal layers to their final location in the neuronal layers. Neuronal migration is a multi-step process that begins with neuronal delamination from the VZ and movement to the SVZ. (See Silva et al. [2019] for an excellent review on neuron migration.)

Delamination
New advances in understanding cortical development have identified the microtubule-associated protein Lszt as a master regulator of cellular dynamics, promoting the delamination of neurons and bRGCs born from aRGCs by altering apical junction organization.

Multipolar phase transition
Once newborn neurons delamate from the VZ, they enter the SVZ and undergo a transition phase displaying multipolar morphology. During this process, NeuroD1 expressed by multipolar cells represses Prdm16, which regulates mitochondrial reactive oxygen species, and this signaling axis is crucial for the regulation of the multipolar phase migration. Dbnl, a protein interacting with F-actin, is another key regulator of neuronal multipolar morphology, polarity, and migration by regulating the levels of N-cadherin.

Bipolar locomotion
Cortical neurons resume radial migration by re-acquiring polarity and extending a single leading process as they exit the SVZ. This leading process establishes intimate adhesive interactions with the basal process of RGCs for guidance in their migratory displacement. The long-held concept that the leading process of these radially migrating neurons is single and unbranched has been challenged by new observations, demonstrating frequent branching and thus more complex migratory behaviors than previously reported. In fact, leading process branching is much more frequent in the developing cortex of ferret than mouse and is related to the tangential displacement of radially migrating neurons. Thus, this seems directly related to the maintenance of the radial organization of the cerebral cortex during the tangential expansion and folding of the neocortex. However, an excessive tangential displacement of cortical neurons is deleterious, and the horizontal tiling of the developing cerebral cortex, or regular distribution of its radial units, must be actively maintained. The microtubule stability regulator protein Memo1 plays key functions in the maintenance of RGC structure and cortical tiling by repressing the hyperbranching of the basal process of RGCs and the
Evolution of cerebral cortex development
A fundamental feature of the evolution of cerebral cortex in amniotes is the phenomenal increase in neuron number and expansion in size. This process is recapitulated during embryonic development, and recent work demonstrates the importance of the balance between direct and indirect neurogenesis. Mechanisms regulating this critical balance, including transcriptional programs regulated by progenitor cell membrane polarity and canonical signaling pathways like the unfolded protein response, some of which are highly conserved across amniotes like Robo and Dll, are beginning to be identified.

Beyond the emergence of indirect neurogenesis, cortical evolution involved additional key mechanisms. Cell lineage labeling and single-cell transcriptional analyses have revealed a remarkable evolutionary increase in diversity of cortical progenitor cells, particularly at the genetic level. This includes, for example, multiple subtypes of aRGCs and bRGCs identified in human, macaque, or ferret but not in mouse or rat. Likewise, innovations in progenitor cell lineages are critical for the emergence and expansion of the OSVZ, the basal germinal layer typical of big and folded brains, which is absent in mice and is perturbed in human diseases that affect brain size.

The search for genetic mechanisms evolved in primate and human phylogeny which are likely relevant in the evolution of their neocortex, has led to the identification of primate-specific and human-specific genetic programs expressed in the developing cerebral cortex. These include whole collections of primate-specific miRNAs targeting cell cycle genes and also miRNA-mRNA modules in the embryonic human brain that undergo dynamic transitions during development and that identify expression networks in specific cell types. As for protein-coding genes, recent studies have identified genes that emerged in the recent human lineage by means of total or partial duplication, and that promote cortical progenitor cell proliferation. Other studies have identified programs of gene expression in cortical progenitor cells that are human-specific.

Species with large brains have a tendency of being folded, and knowledge of specific mechanisms involved in cortex folding has also increased recently. This highlights the relevance of the sodium ion channel SCN3A function in progenitor cells, of gliogenesis, and of extracellular matrix proteins, in the mechanical aspect of tissue folding. Intriguingly, the organization of folds in the frontal cortex is widely conserved from Old World monkeys to hominoids, which offers a remarkable opportunity to study cortical evolution and the acquisition of higher brain functions in primates.

Discovering the developmental importance of microglia
Largely ignored previously in the field of neocortical development, microglia have become a new relevant component in our understanding of this process. Microglial cells are found in the developing neocortex at much earlier stages and at much greater abundance than previously considered; there, they interact intimately with progenitor cells and regulate their number, hence emerging as important players in the regulation of neurogenesis. Microglia may also contribute to progenitor cell delamination and expansion of ISVZ/OSVZ in primates. Moreover, microglia are critical regulators of brain wiring, contributing to the specification of neural circuits and relaying information from the periphery, including the microbiota.

Cerebral organoids as a model of human neocortical development
Although it is not possible to study the development of the human neocortex at the experimental level, major technological breakthroughs in the last few years on stem cell reprogramming and tissue culture offer possibilities that were previously unthinkable. Following the first protocol to generate cerebral organoids from human embryonic stem cells and induced pluripotent stem cells, these have become the Rosetta stone to study and manipulate human brain development. Not only can we now grow human cerebral organoids for many months, recapitulating many of the early features of cortical development, but they can be grown to form functional circuits and be responsive to sensory stimuli. Most importantly, the recent design of a culture protocol to generate highly reproducible cerebral organoids is a fundamental milestone for the consolidation of this as a faithful model of human brain development. Comparison between organoids grown from human and chimpanzee cells reveal human-specific features of cortical progenitor cells and the validity of these organoids to advance our understanding of human brain evolution.

Conclusions
Understanding neocortical development requires working at many different levels, from single-cell transcriptomics to tissue mechanics, and this must be applied to studying histogenesis at multiple levels, from neurogenesis to connectivity and cortex folding. Understanding neocortical evolution and disease requires understanding development across relevant informative species and in the context of genetic or contextual failure. Recent technological advances offer unprecedented opportunities for conducting this research; for example, single-cell genomic analyses help elucidate molecular changes in human brain disease at the resolution of cell types, and patient-derived iPSCs are used to model and hopefully rescue the disease. Only through our ability to use and combine these amazing tools in creative ways will we decipher what makes us human and what genetic changes occurred during evolution that led to the development and emergence of the human neocortex.
Abbreviations
aRGC, apical radial glial cell; bRGC, basal radial glial cell; IPC, intermediate progenitor cell; ISVZ, inner subventricular zone; NSPC, neural stem and progenitor cell; OSVZ, outer subventricular zone; RGC, radial glial cell; SVZ, subventricular zone; VZ, ventricular zone

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References
1. Malatesta P, Hartfuss E, Götz M: Isolation of radial glial cells by fluorescent-activated cell sorting reveals a neuronal lineage. Development. 2000; 127(24): 5253–60. PubMed Abstract
2. Noctor SC, Flint AC, Weissman TA, et al.: Neurons derived from radial glial cells establish radial units in neocortex. Nature. 2001; 409(6821): 714–20. PubMed Abstract | Publisher Full Text | F1000 Recommendation
3. Noctor SC, Martinez-Cerdeño V, Iavicoli S, et al.: Cortical neurons arise in symmetric and asymmetric division zones and migrate through specific phases. Nat Neurosci. 2004; 7(2): 136–44. PubMed Abstract | Publisher Full Text | F1000 Recommendation
4. Haubersak W, Attardo A, Denk W, et al.: Isolation of radial glial cells by fluorescent-activated cell sorting reveals a neuronal lineage. Development. 2000; 127(24): 5253–60. PubMed Abstract
5. Miyata T, Kawaguchi A, Saito K, et al.: Asymmetric production of surface-dividing and non-surface-dividing cortical progenitor cells. Development. 2004; 131(13): 3133–45. PubMed Abstract | Publisher Full Text | Full Text
6. Attardo A, Calegari F, Haubersak W, et al.: Live imaging at the onset of cortical neurogenesis reveals differential appearance of the neuronal phenotype in apical versus basal progenitor progeny. PLoS One. 2008; 3(6): e2888. PubMed Abstract | Publisher Full Text | Full Text
7. Kowalczyk T, Pontious A, Englund C, et al.: Intermediate neuronal progenitors (basal progenitors) produce pyramidial-projection neurons for all layers of the mammalian telencephalon. Nat Rev Neurosci. 2010; 11(3): 296–309. PubMed Abstract | Publisher Full Text | Full Text
8. Staniek EK, Navarro-Quirós I, Selke R, et al.: Heterogeneity in ventricular zone neural precursors contributes to neuronal fate diversity in the postnatal neocortex. J Neurosci. 2010; 30(20): 7028–36. PubMed Abstract | Publisher Full Text | Full Text | F1000 Recommendation
9. Smart IJM, Dehay C, Giroud P, et al.: Unique morphological features of the proliferative zones and postmitotic compartments of the neural epithelium giving rise to striate and extrastriate cortex in the monkey. Cerebral Cortex. 2002; 12(1): 37–53. PubMed Abstract | Publisher Full Text | Full Text | F1000 Recommendation
10. Reillo I, de Juan Romero C, García-Cabezas MA, et al.: A role for intermediate radial glia in the tangential expansion of the mammalian cerebral cortex. Cereb Cortex. 2011; 21(7): 1674–94. PubMed Abstract | Publisher Full Text | F1000 Recommendation
11. Kalava I, Reillo I, Murayama AY, et al.: Abundant occurrence of basal radial glia in the subventricular zone of embryonic neocortex of a lissencephalic primate, the common marmoset Callithrix jacchus. Cereb Cortex. 2012; 22(2): 469–81. PubMed Abstract | Publisher Full Text | Full Text
12. García-Moreno F, Vassilath NA, Trevisa N, et al.: Compartmentalization of cerebral cortical germinal zones in a lissencephalic primate and gyrencephalic rodent. Cerebral Cortex. 2012; 22(2): 482–92. PubMed Abstract | Publisher Full Text
13. Reillo I, Borrell V: Germinal zones in the developing cerebral cortex of ferret: ontology, cell cycle kinetics, and diversity of progenitors. Cereb Cortex. 2012; 22(9): 2039–54. PubMed Abstract | Publisher Full Text
14. Bélizneau M, Cortay V, Pattij D, et al.: Precursor diversity and complexity of lineage relationships in the outer subventricular zone of the primate. Neuron. 2013; 80(2): 442–57. PubMed Abstract | Publisher Full Text
15. Martinez-Martinez MA, De Juan Romero C, Fernández V, et al.: A restricted period for formation of outer subventricular zone defined by Cdh1 and Tmp1 levels. Nat Commun. 2016; 7: 11812. PubMed Abstract | Publisher Full Text | Full Text
16. Pérez-G-A, Shitamura A, Reillo I, et al.: Amplification of progenitors in the mammalian telencephalon includes a new radial glial cell type. Nat Commun. 2013; 4: 1215. PubMed Abstract | Publisher Full Text | Free Full Text
17. Linares-Benadero C, Borrell V: Deconstructing cortical folding: genetic, cellular and mechanical determinants. Nat Rev Neurosci. 2010; 11(3): 161–76. PubMed Abstract | Publisher Full Text
18. Dewey C, Kennedy H, Kosik KS: The outer subventricular zone and primate-specific cortical complexification. Neuron. 2015; 85(4): 683–94. PubMed Abstract | Publisher Full Text
19. Johnson MB, Kawassawa YI, Mason CE, et al.: Functional and evolutionary insights into human brain development through global transcriptome analysis. Neuron. 2009; 62(4): 494–509. PubMed Abstract | Publisher Full Text | Full Text | F1000 Recommendation
20. Miller JA, Ding SL, Sunkin SM, et al.: Translational landscape of the prenatal human brain. Nature. 2014; 508(7510): 199–206. PubMed Abstract | Publisher Full Text | Free Full Text
21. Aytala AE, Oh S, Xie Y, et al.: Transcriptional programs in transient embryonic zones of the cerebral cortex defined by high-resolution mRNA sequencing. Proc Natl Acad Sci U S A. 2011; 108(36): 14950–5. PubMed Abstract | Publisher Full Text | Free Full Text
22. Arola ML, Belayeu M, Cambonova EA, et al.: Novel primate miRNAs coevolved with ancient target genes in germinal zone-specific expression patterns. Neuron. 2014; 81(6): 1255–62. PubMed Abstract | Publisher Full Text | Free Full Text
23. de Juan Romero C, Bruder C, Tomassello U, et al.: Discrete domains of gene expression in germinal layers distinguish the development of gyrencephaly. EMBO J. 2015; 34(14): 1589–74. PubMed Abstract | Publisher Full Text | Free Full Text
24. Woodworth MB, Girskis KM, Walsh CA: Building a lineage from single cells: genetic techniques for cell lineage tracking. Nat Rev Genet. 2017; 18(4): 230–44. PubMed Abstract | Publisher Full Text | Full Text | F1000 Recommendation
25. Pollen AA, Nowakowski TJ, Shuga J, et al.: Low-coverage single-cell mRNA sequencing reveals cellular heterogeneity and activated signaling pathways in developing cerebral cortex. Nat Biotechnol. 2014; 32(10): 1053–8. PubMed Abstract | Publisher Full Text | Free Full Text
26. Miller DJ, Bhaduri A, Sestan N, et al.: Shared and derived features of cellular diversity in the human cerebral cortex. Curr Opin Neurobiol. 2019; 56: 117–24. PubMed Abstract | Publisher Full Text | F1000 Recommendation
27. Loo L, Simon JM, Xing L, et al.: Single-cell transcriptomic analysis of mouse neocortical development. Nat Commun. 2019; 10(1): 134. PubMed Abstract | Publisher Full Text | Free Full Text
28. Talley L, Agirmagan G, Prados J, et al.: Temporal patterning of apical progenitors and their daughter neurons in the developing neocortex. Science. 2019; 364(6403): 695. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
29. Nowakowski TJ, Bhaduri A, Pollen AA, et al.: Spatiotemporal gene expression trajectories reveal developmental hierarchies of the human cortex. Science. 2017; 358(6368): 1318–23. PubMed Abstract | Publisher Full Text | Full Text | F1000 Recommendation
30. Mi D, Li Z, Lim L, et al.: Early emergence of cortical interneuron diversity in the mouse embryo. Science. 2018; 360(6384): 81–6. PubMed Abstract | Publisher Full Text | Free Full Text
31. Mayer C, Hafemeister C, Bender RC, et al.: Developmental diversification of cortical inhibitory interneurons. Nature. 2018; 555(7679): 457–62. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
32. Talley L, Govindan S, Prados J, et al.: Sequential transcriptional waves direct the differentiation of newborn neurons in the mouse neocortex. Science. 2016; 351(6280): 1443–6. PubMed Abstract | Publisher Full Text | F1000 Recommendation
33. Obren P, Agirmagan G, Jabaudon D: Principles of progenitor temporal patterning in the developing invertebrate and vertebrate nervous system. Curr

Page 6 of 9
Tsunekawa Y, Britto JM, Takahashi M, Silver DL: Progenitor Positioning to Safeguard Neocortical Development. Neuron. 2018; 97(13): 2863–72. PubMed Abstract | Publisher Full Text | F1000 Recommendation

Desai AR, McConnell SK: Progressive restriction in fate potential by neural progenitors during cerebral cortical development. Development. 2000; 127(13): 2863–72. PubMed Abstract

Zahr SK, Yang G, Kazan H, et al.: A Translational Repression Complex in Developing Mammalian Neural Stem Cells that Regulates Neuronal Differentiation. Cell Stem Cell. 2018; 19(5): 590–606.e21. PubMed Abstract | Publisher Full Text | F1000 Recommendation

Kingstein A, Noctor S, Martinez-Cerdeño V: Patterns of neural stem and progenitor cell division may underlie evolutionary cortical expansion. Nat Rev Neurosci. 2006; 7(11): 883–90. PubMed Abstract | Publisher Full Text

Raics P: Evolution of the neocortex: a perspective from developmental biology. Nat Rev Neurosci. 2009; 10(10): 724–35. PubMed Abstract | Publisher Full Text | Free Full Text

Cárdenas A, Villaola A, de Juan Romero C, et al.: Evolution of Cortical Neurogenesis in Amniotes Controlled by Robo Signaling Levels. Cell. 2018; 174(3): 590–606.e21. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

Chung AF, Kondo S, Abdel-Mannan O, et al.: The subventricular zone is the developmental milestone of a 6-layered neocortex: comparisons in metatharian and eutherian mammals. Cereb Cortex. 2010; 20(5): 1071–81. PubMed Abstract | Publisher Full Text

Lagousse S, Crepe C, Nedekova DD, et al.: A Dynamic Unfolded Protein Response Contributes to the Control of Cortical Neurogenesis. Dev Cell. 2015; 35(5): 553–67. PubMed Abstract | Publisher Full Text

Alfaro C, Gladwyn-Ng I, Coudenc T, et al.: The unfolded protein response: a key player in Zika virus-Associated Congenital Microcephaly. Front Cell Neurosci. 2019; 13: 94. PubMed Abstract | Publisher Full Text | F1000 Recommendation

Gladwyn-Ng I, Cerdán-Barrón L, Alfaro C, et al.: Stress-induced unfolded protein response contributes to Zika virus-induced microcephaly. Nat Neurosci. 2018; 21(1): 63–71. PubMed Abstract | Publisher Full Text | F1000 Recommendation

Baizabal JM, Mistry M, Garcia MT, et al.: The Epigenetic State of PRDM16-Related Enhancers in Radial Glia Controls Cortical Neuron Position. Neuron. 2018; 98(5): 945–962.e8. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

Yang T, Zhang Y, Wang Y, et al.: HDAC1 and HDAC2 Regulate Intermediate Progenitor Positioning to Safeguard Neocortical Development. Neuron. 2019; 101(6): 1117–1133.e5. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

De la Torre-Ubieta L, Stein JL, Won H, et al.: The Dynamic Landscape of Open Chromatin during Human Cortical Neurogenesis. Cell. 2018; 172(1–2): 289–304.e18. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

Silver DL: Genomic divergence and brain evolution: How regulatory DNA influences development of the cerebral cortex. Bioessays. 2016; 38(2): 162–71. PubMed Abstract | Publisher Full Text | Free Full Text

Tsukawaka Y, Britto JM, Takashiki M, et al.: CycD2 in the basal process of neural progenitors is linked to non-equivalent cell fates. EMBO J. 2012; 31(8): 1879–92. PubMed Abstract | Publisher Full Text | Free Full Text

Pilaz LJ, Lennox AL, Roanet JP, et al.: Dynamic mRNA Transport and Local Translation in Radial Glial Progenitors of the Developing Brain. Curr Biol. 2016; 26(4): 3883–92. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

Pilaz LJ, Silver DL: Moving messages in the developing brain-emerging roles for mRNA transport and local translation in neural stem cells. FEBS Lett. 2017; 591(11): 1526–39. PubMed Abstract | Publisher Full Text | Free Full Text

Pilaz LJ, McMahon JJ, Miller EE, et al.: Prolonged Mitosis of Neural Progenitors Alters Cell Fate in the Developing Brain. Neuro. 2016; 89(1): 83–99. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

Lange C, Huttner WB, Calegari F: CdkkiCyclinD1 overexpression in neural stem cells shortens G1, delays neurogenesis, and promotes the generation and expansion of basal progenitors. Cell Stem Cell. 2009; 5(3): 320–31. PubMed Abstract | Publisher Full Text

Arad Y, Pulvers JN, Haffner C, et al.: Neural stem and progenitor cells shorten S-phase on commitment to neuron production. Nat Commun. 2011; 2: 154. PubMed Abstract | Publisher Full Text | Free Full Text

Fiete SA, Kelava I, Vogt J, et al.: OSVZ progenitors of human and ferret neocortex are epithelial-like and expand by integrin signaling. Nat Neurosci. 2010; 13(6): 690–9. PubMed Abstract | Publisher Full Text | F1000 Recommendation

Hansen DV, Liu J, Parker PR, et al.: Neurogenic radial glia in the outer subventricular zone of human neocortex. Nature. 2010; 464(7288): 554–61. PubMed Abstract | Publisher Full Text

Wang X, Tsai JW, LaMonica B, et al.: A new subtype of progenitor cell in the mouse embryonic neocortex. Nat Neurosci. 2011; 14(5): 555–61. PubMed Abstract | Publisher Full Text | Free Full Text

Rello I, de Juan Romero C, Cárdenas A, et al.: A Complex Code of Extrinsic Influences on Cortical Progenitor Cells of Higher Mammals. Cereb Cortex. 2017; 27(9): 4586–606. PubMed Abstract | Publisher Full Text | Free Full Text

Kalebić N, Ilarić G, Stepić B, et al.: Neocortical Expansion Due to Increased Proliferation of Basal Progenitors Is Linked to Changes in Their Morphology. Cell Stem Cell. 2019; 24(4): 536–550.e9. PubMed Abstract | Publisher Full Text | F1000 Recommendation

Silva CG, Peyre E, Adhikan MH, et al.: Cell-Intrinsic Control of Neuron Migration Drives Cortical Morphogenesis. Cell. 2018; 172(5): 1063–1078.e9. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

Silva CG, Peyre E, Nguyen L: Cell migration promotes dynamic cellular interactions to control cerebral cortex morphogenesis. Nat Rev Neurosci. 2019; 20(6): 318–29. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

Smith RS, Kenny CJ, Ganesv V, et al.: Sodium Channel SCN3A (Na1,3) Regulation of Human Cerebral Cortical Folding and Oral Motor Development. Neuro. 2018; 99(5): 905–913.e7. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

Mayer S, Chen J, Velmeshov D, et al.: Multimodal Single-Cell Analysis Reveals Physiological Maturation in the Developing Human Neocortex. Neuro. 2019; 102(1): 143–158.e7. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

Bonnefont J, Tiberi L, van den Ameele J, et al.: Cortical Neurogenesis Requires Bcl6-Mediated Transcriptional Repression of Multiple Self-Renewal-Promoting Extrinsic Pathways. Neuron. 2019; 103(6): 1096–1108.e4. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

Bonneton J, Tiberi L, van den Aemeele J, et al.: Cortical Neurogenesis Requires Bcl6-Mediated Transcriptional Repression of Multiple Self-Renewal-Promoting Extrinsic Pathways. Neuron. 2019; 103(6): 1096–1108.e4. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

Kostic M, Paradaen JTML, Long KR, et al.: YAP Activity is Necessary and Sufficient for Basal Progenitor Abundance and Proliferation in the Developing Neocortex. Cell Rep. 2019; 27(4): 1103–1118.e6. PubMed Abstract | Publisher Full Text | F1000 Recommendation

Tavano S, Tavema E, Kalebic N, et al.: Insir1 Induces Neural Progenitor Delamination in Developing Neocortex via Downregulation of the Adherens Junction Belt-Specific Protein Pleckat. Neuro. 2018; 97(6): 1239–1314.e8. PubMed Abstract | Publisher Full Text | F1000 Recommendation

Camargo Ortega G, Falk S, Johansson PA, et al.: The centrosome protein AKNA regulates neurogenesis via microtubule organization. Nature. 2019; 567(7746): 113–7. PubMed Abstract | Publisher Full Text | Free Full Text

Kawase T, Shitamukai A, Nagasaki A, et al.: Lats1 controls both neuronal delamination and outer radial glial-like cell generation during mammalian
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1. **Laurent Nguyen**  
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   **Competing Interests:** Laurent Nguyen has written with Victor Borrell on one consortium paper in the last three years.

2. **Simon Hippenmeyer**  
   Institute of Science and Technology Austria (IST Austria), Klosterneuburg, Austria  
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