

# The Molecular and Genetic Mechanisms of Neocortex Development

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## KEYWORDS

- Neocortex • Development • Neocortical proliferation
- Migration • Cerebral palsy

The mammalian neocortex is a remarkably complex organ. It contains many neuronal cell types, oligodendrocytes, and glia, together accounting for over 10 billion cells in the human brain that form perhaps  $10^{13}$  to  $10^{15}$  intricate connections (synapses) with other regions of the central nervous system. In its human form, the neocortex exists at its most complex and evolved state. It is the region of our brain responsible for sensation, action, cognition, and consciousness. Despite the seemingly overwhelming complexity of the neocortex, various groups have made significant progress toward unraveling the mystery of how it is formed. This article focuses on the three major processes that give rise to the mature neocortical structure: neurogenesis, neural migration, and maturation or the establishment of functional neocortical connectivity. Definitions of the terms used herein are listed in **Box 1**. In the process of this discussion, we highlight results and ideas that offer a glimpse into the future.

## OVERVIEW OF NEOCORTEX DEVELOPMENT

In humans, as in other vertebrates, the remarkably complex central nervous system begins by the process of neural induction as a relatively simple collection of cells on the dorsal side of the gastrula-stage embryo, the neural plate.<sup>1</sup> The plate eventually expands, its lateral ends fold upward and toward each other at the midline, and the ends fuse into the embryologic neural tube at around embryonic day (E) 30 in humans.<sup>2</sup>

In mammals, the developing neocortex forms in the dorsolateral wall at the rostral end of this neural tube. Here in the embryonic cerebral vesicles, or prosencephalon, the vast majority of neurons that are destined for the neocortex arise in

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**Box 1****Definition of terms relevant to neocortex development**

**Neural induction:** process by which the embryonic chordamesoderm at the three-layer embryo stage coaxes the overlying ectoderm into becoming the neural plate or neuroectoderm

**Neurogenesis:** embryologic process during which neural progenitor cells arise

**Neuronogenesis:** embryologic process during which neural progenitors fully differentiate into neurons as opposed to glia

**Neural progenitors:** pluripotent stem cells that can give rise to either neurons or glia

**Neural migration:** embryologic process by which a neural progenitor travels from its birthplace to a final destination within the nervous system

**Basic helix-loop-helix:** transcription factor protein family (members include MyoD, Beta2/NeuroD1) named for its structural motif which consists of two alpha helices connected by a short loop

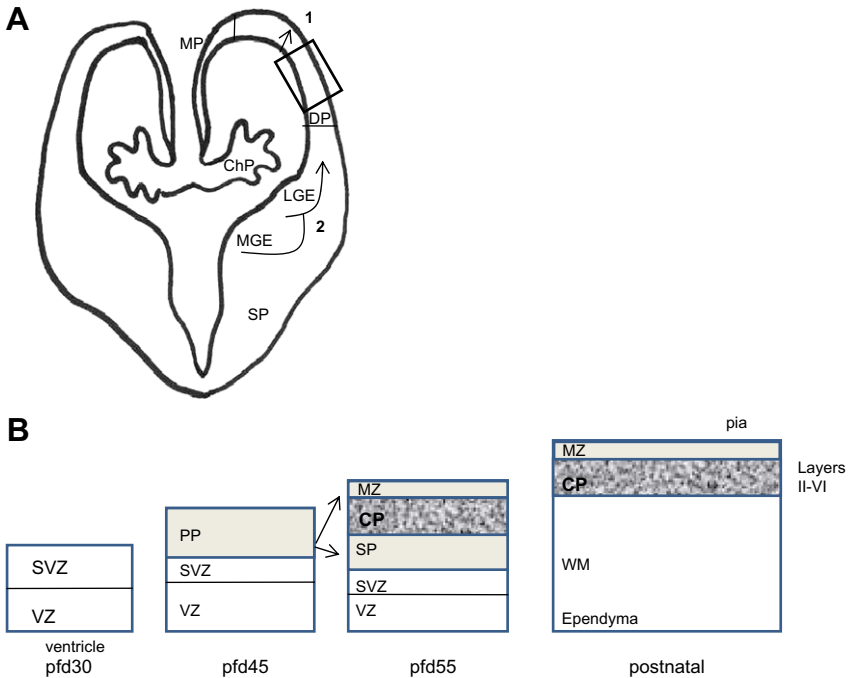
**Long-term depression:** neurophysiologic property characterized by weakened synaptic activity

a pseudostratified epithelial cell layer made up of two distinct germinal regions that surround the early ventricular lumen: the ventricular zone (VZ) located immediately adjacent to the ventricle and the subventricular zone (SVZ) which lies superficially on the VZ (**Fig. 1**).<sup>3</sup>

The early cycles of cellular proliferation in the VZ result primarily in the symmetric expansion of cells termed *radial glia*. These radial glia are direct descendants of the neural plate and, as such, have been shown to be pluripotent neural stem cells in nature retaining the capacity for producing multiple neural cell types and for self-renewal.<sup>4-6</sup> This process determines not only the total pool of neural stem cells, or so-called “proliferative units,” from which the nascent cortical structure is later derived but also markedly increases the surface area and thickness of the VZ. At around E33 a second phase of proliferation predominates, in which the stem cells begin to divide asymmetrically to produce a single clone and a more committed neural progenitor that temporarily withdraws itself from the cell cycle. This process marks the beginning of neurogenesis.<sup>7</sup>

The next key step in neocortical development following neural progenitor proliferation is migration, which occurs between weeks 10 and 20 in the human.<sup>3</sup> As mentioned earlier, the mature mammalian neocortex contains six layers of neurons. Development of these layers involves both radial and tangential migration routes that are taken by the various neuronal progenitors on their way to their final laminar destination (see **Fig. 1**). Congenital migration disorders may display derangements in either one or both directions.

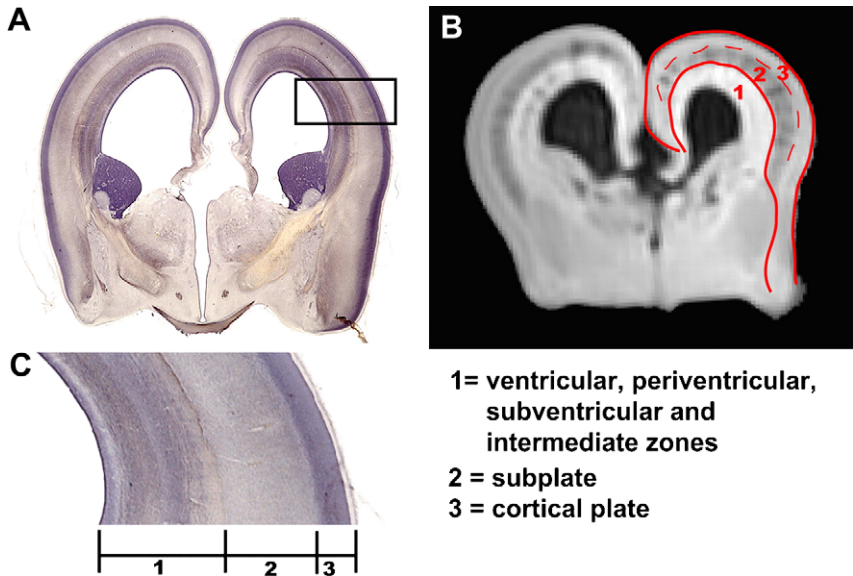
In the first stage of neural migration, the preplate forms (see **Fig. 1** and **Fig. 2**). It is composed of the first wave of neural progenitors migrating out of the VZ. Concurrently, Cajal-Retzius cells appear at the outermost aspect of the preplate. This specialized population of early neurons secretes reelin, a signaling molecule that helps to attract subsequent waves of migrating neural progenitors.<sup>8</sup> In the next migrational stage, a second wave of postmitotic neural progenitors enters the preplate and splits it into the more superficial marginal zone (MZ) and subplate (SP) below constituting the embryologic cortical plate. Subsequent waves of migrating neuronal progenitors migrate past the subplate, stopping just short of the MZ (or layer I of the mature cortex) and forming the various neocortical lamina in the process. Early birth-dating studies using tritiated thymidine in primates and rodents established that these progenitors



**Fig. 1.** Overview of cortical development. (A) Radial (1) and tangential (2) modes of migration. (B) Inset from above. Neocortical layering. During early stages (post fertilization day [pfd 30]) the cortex consists of the outer subventricular zone (SVZ) and ventricular zone (VZ). The emergence of the preplate (PP) occurs around pfd 45. Newly generated neurons from the VZ migrate into the cortical plate (CP) and split the PP into the marginal zone (MZ) and subpallium (SP) (arrows). The SP has a critical role in establishing the inside-out lamination of cells, as well as the efferent and afferent cortical axonal projections. In the adult, these developmental layers evolve into the white matter (WM). ChP, choroid plexus; DP, dorsal pallium; LGE, lateral ganglionic eminence; MGE, medial ganglionic eminence; MP, medial pallium.

accumulate in their respective layers using a radial, inside-out sequence pattern with the earliest born neurons populating the innermost lamina (or layer VI) and subsequent waves becoming the more superficial layers V, IV, III, and II, respectively.<sup>9,10</sup> Another key recent observation in this field involves cortical neurons that express the neurotransmitter gamma aminobutyric acid (GABA). These neurons appear to derive almost exclusively from the more distant germinal zones of the medial and lateral ganglionic eminences (MGE/LGE). From here they migrate tangentially to their respective laminar destination in the neocortex.<sup>11</sup> Recently, it has also been shown that neurons destined for a specific layer of neocortex are generated closely in time whether they originate in the nearby VZ or the more distant MGE/LGE.<sup>12</sup>

As the development of the brain proceeds, the final process in the formation of the fully mature mammalian neocortex is the establishment of functional connections between the various brain regions. One of the more fascinating stories to have developed in recent years involves the role of transient laminar zones within the developing neocortex known as the SP (see **Fig. 2**), which act as “waiting rooms” where axons



**Fig. 2.** Layers of the developing cerebral cortex from humans. (A–C) Coronal histologic slides of a 17-week fetal brain, similar to a coronal slice taken by diffusion tensor imaging of a 17-week fetal brain, and an enlarged region corresponding to the boxed area. The red contour establishes the boundary of the cortical plate and subplate (CP+SP). The dashed red curve separates the cortical plate and subplate. The annotation of each boundary is shown at bottom right. (From Huan H, Xue R, Zhang J, et al. Anatomical characterization of human fetal brain development with diffusion tensor magnetic resonance imaging. *J Neurosci* 2009;29:4263; with permission.)

making their way to the cortex temporarily arrest before continuing on toward their respective targets. The SP is easily visible as a major structure in the fetal brain on pathology or brain MRI but after development is largely replaced by white matter in the adult.

#### ADVANCES IN NEOCORTICAL NEUROGENESIS

Much of our understanding of the generation of cell type diversity found in the mature neocortex is based on studies primarily in chicks and mice. In particular, the results from work on spinal cord and retina development in these animals have revealed that, across the entire central nervous system, various compartments share common developmental strategies. One such strategy involves the specification (around the time of neural tube formation) or patterning of the early neocortical primordium in response to extracellular (often secreted) morphogen gradients, such as sonic hedgehog (Shh), bone morphogenetic protein (Bmp), and fibroblast growth factor (Fgf).<sup>13–15</sup> A number of transcription factor genes, most notably of the homeodomain and basic helix-loop-helix (bHLH) class, are resultantly expressed and inform their respective progenitor “pools” to commit to a particular cellular fate.<sup>16,17</sup> This process has been deemed the transcriptional factor “combinatorial code.” It allows an exponential number of cellular fates to be generated by a relatively modest amount of transcription factor gene products. In theory, a code based on only two homeodomain and three bHLH genes can result in as many as 25 different specific neocortical cell types.

Besides the laminar organization that the developing neocortex takes on, the mature neocortex also subdivides in a tangential fashion. Two main mechanisms appear to take hold of the development of the neocortex along this axis. The first holds that the tangential subdivisions of the early neocortex are prespecified into a sort of “protomap” by gradients and countergradients of molecules during neurogenesis.<sup>18–20</sup> The second mechanism or “protocortex hypothesis” holds that a particular neuron’s fate is determined by its attachment to thalamocortical afferents that made their way into the developing neocortex.<sup>21,22</sup> Recent molecular evidence strongly supports both of these mechanisms as fundamental in establishing the final elements of mature neocortical differentiation and functional connectivity.

Primary microcephaly (MCPH) is the clinical finding of a reduced fronto-occipital head circumference of greater than 3 standard deviations below age- and sex-matched controls, reflecting a reduced brain volume<sup>23</sup> in the absence of other causes or physical findings. It has been hypothesized that the reduced size of the brain in MCPH patients is due to premature asymmetric division of neural stem cells in proliferative zones such as the VZ, resulting in a reduced number of postmitotic neural progenitors. Microcephalic individuals generally have a small cerebral cortex; hence, the majority are mentally retarded. MCPH in particular is typically an autosomal recessive disorder resulting directly from hypoplasia of the cerebral cortex with a generalized reduction in the overall size of the brain. Occipital-frontal circumferences are typically 4 to 12 standard deviations below normal, and patients have mild-to-severe mental retardation as a result. Surprisingly these patients tend to lack any other predominant neurologic features such as spasticity or epilepsy.

MCPH is genetically heterogeneous, mapping thus far to six known loci, four of which have been identified.<sup>24</sup> Immunofluorescence studies reveal that these loci encode proteins that localize to the cellular centrosome, suggesting a mitotic yet brain-specific mechanism responsible for limiting the number of neural progenitors produced. Further insights into the role of MCPH gene products will no doubt be of therapeutic significance in the future, in particular toward identifying or establishing clinically beneficial neural stem cell lines for transplant.

## ADVANCES IN NEURAL MIGRATION

Despite its similarity with the spinal cord and retina, there exists an important added complexity with respect to the generation of the cell diversity found within the mature neocortex. There are two broad classes of neocortical neurons: (1) interneurons that express the neurotransmitter GABA and make relatively local connections, and (2) projection neurons that express glutamate and extend axons to both local intracortical and distant subcortical and subcerebral targets. During development, projection neurons are generated primarily in the dorsolateral (or pallial) wall of the telencephalon in the germinal VZ and SVZ zones previously mentioned.<sup>25</sup> From there they migrate relatively locally in a radial inside-out fashion to their respective lamina. This development is in contrast to that of GABA-containing interneurons which are generated in the ganglionic eminences of the ventral (or subpallial) telencephalon and migrate relatively long distances to their final neocortical destination.

Compelling evidence suggests that these cells find their final destination within the developing neocortex specifically through a rearrangement of cytoskeletal components in response to extracellular cues mediated by various intracellular signaling pathways.<sup>26</sup> Thought of in this way, three large classes of genes underlie the vast majority of neural migration disorders that are seen clinically: (1) those involving the formation of the extracellular environment encountered by migrating neurons and

axons, (2) those encoding for intracellular signaling mechanisms, and (3) those encoding the intracellular machinery that mediates cellular and axonal physical movement.<sup>27</sup> One such family of genes involved in the extracellular environment encodes for the enzymatic regulators of glycosylation, which, in turn, control the appearance of a specific extracellular cue that is encountered by migrating cells. Mutations in this group appear to delineate boundaries along a particular pathway where a cell may arrest during migration. An example in humans are the genes involved in the brain phenotype known as cobblestone lissencephaly, in which the surface of the brain has a disorganized bumpy exterior lacking both gyri and sulci. Microscopically, these bumps consist of collections of neurons that abnormally migrated past the pial layers and into the meninges. In some instances, the abnormally migrating neurons have been thought of as having crossed from one side of the cerebral hemisphere to the other, fusing the two together at the midline. Cobblestone lissencephaly is only one feature in a group of conditions known as the congenital muscular dystrophies. These disorders, which are characterized by the features of muscular dystrophy, developmental eye abnormalities, and cobblestone lissencephaly, include Fukuyama congenital myotonic dystrophy, muscle eye-brain disorder, and Walker-Warburg syndrome. Recent work involving the genetic background of these disorders reveals that the mutated genes in this group encode actual or putative glycosyltransferases that detrimentally affect the dystrophin-glycoprotein complex.<sup>28–31</sup> Cobblestone lissencephaly itself appears to be the result of loss of the integrity of the limiting glial membrane, loss of the “stop signal” found there, or the dissociation of migrating neurons from the otherwise intact migrational scaffold.

#### ADVANCES IN NEURAL CONNECTIVITY

When neurons near their final laminar destination, they send and receive axons and form dendrites and synapses with local and distant cerebral structures. This process begins in the second half of gestation and extends into the postnatal period. An interesting feature is the role of transient layers of cells from the earliest migrations that seem to behave as a “waiting room” for the axons of distant afferents making their way into the neocortex. One example of these layers is the SP that forms when the early preplate is split by a second wave of early neocortical progenitors.

When the SP was initially characterized, first in the human and then in the monkey in mid-1970s, few prominent neuroscientists recognized the significance of its existence.<sup>32–34</sup> This fact is not surprising given that the earliest reports essentially argued for a reinterpretation of neocortical laminar development. Another reason for missing the significance of the SP had to do with its seemingly underdeveloped state and relatively small size in experimental rodents in comparison with humans and monkeys where it had initially been characterized.<sup>35</sup> It was not until 1991 that Rakic first demonstrated in the rhesus monkey that thalamocortical axons destined for the visual cortex in fact wait in the SP just before migrating into and past the cortical plate.<sup>36</sup> Work by Shatz and colleagues provided conclusive evidence of the role of the SP in establishing not only functional thalamocortical connections but development of the neocortex’s functional columnar architecture.<sup>37,38</sup> Although several genes are known to be expressed in SP neurons, there is as yet no evidence for specific genetic derangements leading to absence or prolonged existence of the SP.

The SP is present in all mammals, but its morphologic characteristics and persistence in adulthood vary among species. In the human, the SP exists during the period from 13 weeks post fertilization through 6 to 9 months’ postnatal. In fact, SP neurons and the afferent synaptic connections that meet them essentially represent the most

significant reservoir of functional connectivity in the preterm infant. Thought of in this way, the SP exists at a time when neocortical synaptic architecture is still relatively immature or even absent, and more importantly coincides with the age of peak vulnerability to perinatal brain injury.<sup>39,40</sup> Blindness due to impairment of visual cortex formation (“cortical blindness”) is particularly common in infants with perinatal white matter injury. Much of this association may be directly attributed to the vulnerability of the SP and its relative importance to the development of normal visual cortex.<sup>41</sup> Some encouraging results in the field of neuroimaging demonstrate that thalamocortical fibers residing in the SP and designated for the somatosensory cortex may, in fact, detour around a particular lesion.<sup>42</sup>

### LOOKING INTO THE FUTURE

The study of human fragile X syndrome provides a hopeful glimpse into the possibility not only of better treatment but ultimately of prevention of the most common type of congenital mental retardation and autism. In humans, fragile X syndrome is caused by transcriptional silencing of the *Fmr1* gene that normally encodes the fragile X mental retardation protein (FMRP). This silencing is specifically caused by expansion of a CGG repeat sequence in the *Fmr1* promoter region that disrupts the formation of a functional RNA polymerase complex. FMRP normally regulates the translation of mRNA by inhibitory binding. One way FMRP accomplishes this binding is by inhibiting translation of certain proteins at the synapse.<sup>43</sup> The resultant effect is increased dendritic arborization leading to hyperconnectivity or the retainment of too many functional synapses.<sup>44</sup>

In addition, the protein metabotropic glutamate receptor 5 (mGluR5) appears to be involved in local protein synthesis at the synapse in response to glutaminergic activity. In particular, it appears to establish a “lasting effect” as seen in a model for long-term depression, which may have a role in the impaired brain activity seen in patients who have fragile X syndrome.<sup>45–47</sup> Taken together, these findings have led to the mGluR theory of fragile X syndrome. A particularly exciting prospect of this theory has been the development of potentially disease-modifying agents acting through mGluR5.<sup>48–50</sup> Human trials of mGluR5 antagonists have begun for fragile X syndrome and a broad range of other neuropsychiatric conditions.

A causal connection has also been established concerning neuronal migration during development and altered neocortical excitability. The brains of individuals presenting with pharmacologically intractable epilepsy frequently contain foci of abnormally migrated neurons. Until the development of more effective anti-epileptic medications, surgical resection may be the best alternative for reducing the number of seizures in refractory cases. For individuals whose defects are more widespread, the risks of surgery actually offer a worse prognosis. In subcortical band heterotopia, a strip of heterotopic gray matter largely composed of abnormally migrated neurons can be found between the ventricular wall and the cortical mantle separated by a band of white matter. Subcortical band heterotopia is most often caused in females by mutations in the X-linked gene for doublecortin (*Dcx*), a microtubule-binding protein found to be essential for normal migration. A rat model for subcortical band heterotopia showed that delayed expression of *Dcx* rescued the formation of this condition while also reducing seizure risk.<sup>51</sup>

### SUMMARY

Congenital brain malformations are a significant cause of morbidity and mortality. In recent years, significant advances in basic neuroscience research have improved

our understanding of the molecular and genetic underpinnings of neocortical development. Continued advances in genomics and proteomics research will no doubt move us toward an even better understanding of these and other developmental processes, with the hope of one day being able to provide parents and clinicians with the information they so desperately need to make informed decisions. To say that a leap from these basic laboratory studies into the clinical realm will occur in the next few years is probably naïve at best. Instead, we hope to convey that while the basic mechanisms of neocortical development continue to be worked out along with overcoming the proper technical hurdles, we will begin to enter a new age of research, diagnosis, and treatment of congenital brain malformations and their associated disorders.

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