Published in final edited form as:
Clin Perinatol. 2009 September ; 36(3): 503–512. doi:10.1016/j.clp.2009.06.008.

The molecular and genetic mechanisms of neocortex development

Alejandro L. Diaz and **Joseph G. Gleeson**
Departments of Neurosciences and Pediatrics, University of California San Diego

Abstract

We review some of the key recent findings in the field of human cortical development. This development is divided into three major time-dependent phases: neural proliferation, migration, and maturation. The cells that constitute the cerebral cortex, including both inhibitory and excitatory neurons, proliferate in spatially distinct regions. These cells then migrate through multiple cellular boundaries, one of which is known as the subplate, before achieving final positioning within the 6-layered cerebral cortex. Following this migration, neurons undergo morphological changes that result in elaboration of dendrites and axons, and establish the multitude of cellular contacts that underlie neuronal processing. Many of the neurocognitive disorders that we treat in the clinic can trace their origin to a disorder in one or more of these key steps. Along with this update, we also highlight work that offers a glimpse at the future of therapy for developmental brain disorders that can result from disorders of these cellular events.

Keywords

neocortex; development

Introduction

The mammalian neocortex is a remarkably complex organ. It contains many neuronal cell types, oligodendrocytes, and glia, together accounting for over 10 billion in the human brain, that form perhaps 10^13-10^15 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 towards unraveling the mystery of how it is formed. This paper will focus 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. In the process we will highlight results and ideas that we think offer a glimpse into the future.

Corresponding author for proof and reprints (Also the co-author's current address): Joseph G. Gleeson, MD, Neurogenetics Laboratory, Howard Hughes Medical Institute, Leichtag Biomedical Research Building, Room 482, 9500 Gilman Drive, La Jolla, CA 92093-0665, USA, (858) 822-3535 (tel), (858) 246-0436 (fax), jogleeson@ucsd.edu.

I. Overview of Neocortex Development

In humans, as in other vertebrates, the remarkably complex central nervous system (CNS) 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* 1. The plate eventually expands, its lateral ends fold upwards and towards each other at the midline and fuse into the embryologic *neural tube* at around embryonic day (E) 30 in humans [2].

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 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 [3] (Fig. 1).

The early cycles of cellular proliferation in the VZ result primarily in the symmetrical expansion of cells termed *radial glia (RG)*. These RG 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 both producing multiple neural cell types and for self-renewal [4–6]. 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 both 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. [they did not respond to your note about simplifying this sentence] This process marks the beginning of *neurogenesis* 7.

The next key step in neocortical development following neural progenitor proliferation is migration which occurs between weeks 10–20 in the human [3]. 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 (Fig. 1). Congenital migration disorders may display derangements in either one or both directions.

In the first stage of neural migration, the *preplate* forms (Fig. 1–2). 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 will secrete reelin, a signaling molecule that will help attract subsequent waves of migrating neural progenitors [8]. In the next migrational stage, a second wave of post-mitotic neural progenitors enters the preplate and splits it into the more superficial *marginal zone (MZ)* and the *subplate (SP)* below constituting the embryologic *cortical plate*. Subsequent waves of migrating neuronal progenitors will migrate past the subplate stopping just short of the MZ (or layer I of the mature cortex) forming the various neocortical lamina in the process. Early birth-dating studies using tritiated thymidine in both primates and rodents established that these progenitors 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 [9,10]. Another key recent observation in this field involves cortical neurons that express the neurotransmitter gamma-amino-butyric 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 [they did not respond to your question, which laminae do they migrate into?] [11]. 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* 12.

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 subplate (Fig. 2), which act as "waiting rooms" where axons making their way to the cortex temporarily arrest before continuing on towards their respective targets [they did not respond to your request for references here]. The subplate is easily visible as a major structure in the fetal brain on pathology or brain MRI, but after development it is largely replaced by white matter in the adult.

II. 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 done in both chicks and mice. In particular, the results from work done on spinal cord and retina development in these animals reveal that across the entire CNS, 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 primoridia in response to extracellular (often secreted) morphogen gradients, such as *sonic hedgehog (Shh), bone morphogenetic protein (Bmp)* and *fibroblast growth factor (Fgf)* [13–15]. A number of transcription factors 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 [16,17]. 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. For example, 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 follows, as just mentioned, that the tangential subdivisions of the early neocortex are prespecified into a sort of "protomap" by gradients and counter-gradients of molecules during neurogenesis [18–20]. 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 [21,22]. 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 frontal-occipital head circumference (FOC) of greater than 3 standard deviations below age and sex-matched controls, reflecting a reduced brain volume [23], in the absence of other causes or physical finding. 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 post-mitotic neural progenitors. Microcephalic individuals generally have a small cerebral cortex and 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, OFCs [do you know what this stands for?] 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 [24]. Immunofluorescence studies reveal that they 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 towards identifying and/or establishing clinically beneficial neural stem cell lines for transplant.

III. Advances in Neural Migration

Despite the similarity with 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 exists two broad classes of neocortical neurons: interneurons that express the neurotransmitter GABA and make relatively local connections, and 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 we previously mentioned [25]. From there they will 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 is accumulating that demonstrates 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 [26]. Thought of in this way, three large classes of genes underlie the vast majority of neural migration disorders that are seen clinically: those involving the formation of the extracellular environment encountered by migrating neurons and axons, those encoding for intracellular signaling mechanisms, and finally those encoding the intracellular machinery that mediates cellular and axonal physical movement [27]. One such family of genes involved in 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 is the genes involved in the brain phenotype known as *cobblestone lissencephaly (CL)*, in which the surface of the brain has a disorganized bumpy exterior lacking both gyri and sulci. Microscopically, however, these bumps consist of collections of neurons that abnormally migrated past the pial layers and on 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 [they did not respond to your note that this was not clear]. CL, however, is only one feature in a group of conditions known as the congenital muscular dystrophies (CMD). These disorders, which are characterized by the features of muscular dystrophy, developmental eye abnormalities and CL, include Fukuyama congenital myotonic dystrophy (FCMD), muscle eye-brain disorder (MEB) and Walker-Warburg syndrome (WWS). 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 [28–31]. CL itself appears to be the result of either loss of the integrity of the limiting glial membrane, the “stop signal” found there, or the dissociation of migrating neurons from the otherwise intact migrational scaffold.

IV. Advances in Neural Connectivity

When neurons near their final laminar destination, they will both send and receive axons and form dendrites and synapses with both 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 subplate (SP) that forms when the early preplate is split by a second wave of early neocortical progenitors.

When the SP was initially characterized, first described in the human and then in the monkey in mid-1970s, very few prominent neuroscientists recognized the significance of its very existence [32–34]. This fact is not surprising, however, given that the earliest reports essentially argued for a re-interpretation 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 [35]. It was not until 1991 that Rakic first demonstrated in 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 [36]. Work by Shatz and her colleagues provided conclusive evidence of the SP's role in establishing not only functional thalamocortical connections but development of the neocortex's functional columnar architecture [37,38]. While a number of genes are known to be expressed in SP neurons, there has as yet been no evidence for specific genetic derangements leading to either absence or prolonged existence of SP.

The SP is present in all mammals but its morphological characteristics and persistence in adulthood varies among species. In the human the SP exists during the period from 13 weeks post-fertilization through 6–9 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 [39,40]. Blindness due to the 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 subplate and its relative importance to the development of normal visual cortex [41]. Some encouraging results in the field of neuroimaging demonstrate that thalamocortical fibers residing in the SP and designated for somatosensory cortex may in fact detour around a particular lesion [42].

V. Looking into the future

The study of human Fragile X Syndrome (FXS) 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, FXS is caused by *transcriptional silencing* of the Fmr1 gene that normally encodes the FX mental retardation protein (FMRP). This silencing is specifically caused by an 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 mRNAs by inhibitory binding. One way FMRP accomplishes this binding is by inhibiting translation of certain proteins at the synapse [43]. The resultant effect is increased dendritic arborization leading to hyperconnectivity or the retainment of too many functional synapses [44].

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 in part play into its role in the impaired brain activity seen in FXS patients [45–47]. Taken together, these findings have led to the 'mGluR theory' of FXS. A particularly exciting prospect of this theory has been the development of potentially disease-modifying agents acting through mGluR5 [48–50]. Human trials of mGluR5 antagonists have begun for both FXS 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 those individuals whose defects are more widespread, the risks of surgery actually offer a worse prognosis. In *subcortical band heterotopia (SBH)* 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. SBH is most often caused in females by mutations in the X-linked gene *doublecortin (DCX)*, a microtubule-binding protein found to be essential for normal migration. A rat model for SBH showed that delayed expression of Dcx rescued [they did not respond to your note “this is confusing”] the formation of SBH while also reducing seizure risk [51].

VI. Discussion/Conclusion

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 neocortical development, both its molecular and genetic underpinnings. Continued advances in genomics and proteomics research will no doubt move us towards an even better understanding of these and other developmental processes, with the hope of one day being able to provide both parents and clinicians with the information they so desperately need to make informed decisions. Of course, 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 the proper technical hurdles being overcome, we will no doubt begin to enter a new age of research, diagnosis, and treatment of congenital brain malformations and their associated disorders.

Definitions

Neural induction
: process by which the embryonic chordamesoderm at the 3-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 neuron 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 (LTD)

neurophysiologic property characterized by weakened synaptic activity

References

1. Chitnis AB. Control of neurogenesis--lessons from frogs, fish and flies. Curr Opin Neurobiol 1999;9:18–25. [PubMed: 10072374]
2. O'Rahilly, R.; Müller, F. The embryonic human brain: an atlas of developmental stages. Vol. 3. Hoboken, NJ: Wiley-Liss; 2006.
3. Bystron I, Blakemore C, Rakic P. Development of the human cerebral cortex: Boulder Committee revisited. Nat Rev Neurosci 2008;9:110–22. [PubMed: 18209730]
4. Haubensak W, Attardo A, Denk W, et al. Neurons arise in the basal neuroepithelium of the early mammalian telencephalon: a major site of neurogenesis. Proc Natl Acad Sci U S A 2004;101:3196–201. [PubMed: 14963232]
5. Anthony TE, Klein C, Fishell G, et al. Radial glia serve as neuronal progenitors in all regions of the central nervous system. Neuron 2004;41:881–90. [PubMed: 15046721]
6. Noctor SC, Martinez-Cerdeno V, Kriegstein AR. Neural stem and progenitor cells in cortical development. Novartis Found Symp 2007;288:59–73. [PubMed: 18494252]discussion 73–8, 96–8
7. Bystron I, Rakic P, Molnar Z, et al. The first neurons of the human cerebral cortex. Nat Neurosci 2006;9:880–6. [PubMed: 16783367]
8. Ogawa M, Miyata T, Nakajima K, et al. The reeler gene-associated antigen on Cajal-Retzius neurons is a crucial molecule for laminar organization of cortical neurons. Neuron 1995;14:899–912. [PubMed: 7748558]
9. Rakic P. Neurons in rhesus monkey visual cortex: systematic relation between time of origin and eventual disposition. Science 1974;183:425–7. [PubMed: 4203022]
10. Angevine JB Jr, Sidman RL. Autoradiographic study of cell migration during histogenesis of cerebral cortex in the mouse. Nature 1961;192:766–8. [PubMed: 17533671]
11. Anderson SA, Marin O, Horn C, et al. Distinct cortical migrations from the medial and lateral ganglionic eminences. Development 2001;128:353–63. [PubMed: 11152634]
12. Valcanis H, Tan SS. Layer specification of transplanted interneurons in developing mouse neocortex. J Neurosci 2003;23:5113–22. [PubMed: 12832535]
13. Placzek M, Briscoe J. The floor plate: multiple cells, multiple signals. Nat Rev Neurosci 2005;6:230–40. [PubMed: 15738958]
14. Aboitiz F, Montiel J. Origin and evolution of the vertebrate telencephalon, with special reference to the mammalian neocortex. Adv Anat Embryol Cell Biol 2007;193:1–112. [PubMed: 17595827]
15. Fuccillo M, Joyner AL, Fishell G. Morphogen to mitogen: the multiple roles of hedgehog signalling in vertebrate neural development. Nat Rev Neurosci 2006;7:772–83. [PubMed: 16988653]
16. Molyneaux BJ, Arlotta P, Menezes JR, et al. Neuronal subtype specification in the cerebral cortex. Nat Rev Neurosci 2007;8:427–37. [PubMed: 17514196]
17. Rallu M, Corbin JG, Fishell G. Parsing the prosencephalon. Nat Rev Neurosci 2002;3:943–51. [PubMed: 12461551]
18. O'Leary DD. Do cortical areas emerge from a protocortex? Trends Neurosci 1989;12:400–6. [PubMed: 2479138]
19. Mallamaci A, Stoykova A. Gene networks controlling early cerebral cortex arealization. Eur J Neurosci 2006;23:847–56. [PubMed: 16519650]
20. Rakic P. Specification of cerebral cortical areas. Science 1988;241:170–6. [PubMed: 3291116]
21. Sur M, Rubenstein JL. Patterning and plasticity of the cerebral cortex. Science 2005;310:805–10. [PubMed: 16272112]
22. Price DJ, Kennedy H, Dehay C, et al. The development of cortical connections. Eur J Neurosci 2006;23:910–20. [PubMed: 16519656]
23. Woods CG. Human microcephaly. Curr Opin Neurobiol 2004;14:112–7. [PubMed: 15018946]
24. Cox J, Jackson AP, Bond J, et al. What primary microcephaly can tell us about brain growth. Trends Mol Med 2006;12:358–66. [PubMed: 16829198]

25. Anderson SA, Kaznowski CE, Horn C, et al. Distinct origins of neocortical projection neurons and interneurons in vivo. Cereb Cortex 2002;12:702–9. [PubMed: 12050082]
26. Ayala R, Shu T, Tsai LH. Trekking across the brain: the journey of neuronal migration. Cell 2007;128:29–43. [PubMed: 17218253]
27. Bielas S, Higginbotham H, Koizumi H, et al. Cortical neuronal migration mutants suggest separate but intersecting pathways. Annu Rev Cell Dev Biol 2004;20:593–618. [PubMed: 15473853]
28. Winder SJ. The complexities of dystroglycan. Trends Biochem Sci 2001;26:118–24. [PubMed: 11166570]
29. Beltran-Valero de Bernabe D, Currier S, Steinbrecher A, et al. Mutations in the O-mannosyltransferase gene POMT1 give rise to the severe neuronal migration disorder Walker-Warburg syndrome. Am J Hum Genet 2002;71:1033–43. [PubMed: 12369018]
30. Yoshida A, Kobayashi K, Manya H, et al. Muscular dystrophy and neuronal migration disorder caused by mutations in a glycosyltransferase, POMGnT1. Dev Cell 2001;1:717–24. [PubMed: 11709191]
31. Kobayashi K, Nakahori Y, Miyake M, et al. An ancient retrotransposal insertion causes Fukuyama-type congenital muscular dystrophy. Nature 1998;394:388–92. [PubMed: 9690476]
32. Kostovic I, Molliver ME. A new interpretation of the laminar development of cerebral cortex: synaptogenesis in different layers of neopallium in the human fetus. Anat Rec 1974;178:395.
33. Kostovic I, Rakic P. Developmental history of the transient subplate zone in the visual and somatosensory cortex of the macaque monkey and human brain. J Comp Neurol 1990;297:441–70. [PubMed: 2398142]
34. Rakic P. Prenatal development of the visual system in rhesus monkey. Philos Trans R Soc Lond B Biol Sci 1977;278:245–60. [PubMed: 19781]
35. Kostovic I, Jovanov-Milosevic N. Subplate zone of the human brain: historical perspective and new concepts. Coll Antropol 2008;32 (Suppl 1):3–8. [PubMed: 18405051]
36. Rakic P. Experimental manipulation of cerebral cortical areas in primates. Philos Trans R Soc Lond B Biol Sci 1991;331:291–4. [PubMed: 1677473]
37. Ghosh A, Shatz CJ. A role for subplate neurons in the patterning of connections from thalamus to neocortex. Development 1993;117:1031–47. [PubMed: 8325233]
38. Kanold PO, Kara P, Reid RC, et al. Role of subplate neurons in functional maturation of visual cortical columns. Science 2003;301:521–5. [PubMed: 12881571]
39. Volpe JJ. Encephalopathy of prematurity includes neuronal abnormalities. Pediatrics 2005;116:221–5. [PubMed: 15995055]
40. McQuillen PS, Sheldon RA, Shatz CJ, et al. Selective vulnerability of subplate neurons after early neonatal hypoxia-ischemia. J Neurosci 2003;23:3308–15. [PubMed: 12716938]
41. McQuillen PS, Ferriero DM. Perinatal subplate neuron injury: implications for cortical development and plasticity. Brain Pathol 2005;15:250–60. [PubMed: 16196392]
42. Staudt M, Grodd W, Gerloff C, et al. Two types of ipsilateral reorganization in congenital hemiparesis: a TMS and fMRI study. Brain 2002;125:2222–37. [PubMed: 12244080]
43. Vanderklish PW, Edelman GM. Differential translation and fragile X syndrome. Genes Brain Behav 2005;4:360–84. [PubMed: 16098135]
44. McKinney BC, Grossman AW, Elisseou NM, et al. Dendritic spine abnormalities in the occipital cortex of C57BL/6 Fmr1 knockout mice. Am J Med Genet B Neuropsychiatr Genet 2005;136B:98–102. [PubMed: 15892134]
45. Huber KM, Kayser MS, Bear MF. Role for rapid dendritic protein synthesis in hippocampal mGluR-dependent long-term depression. Science 2000;288:1254–7. [PubMed: 10818003]
46. Grossman AW, Aldridge GM, Weiler IJ, et al. Local protein synthesis and spine morphogenesis: Fragile X syndrome and beyond. J Neurosci 2006;26:7151–5. [PubMed: 16822971]
47. Huber KM, Gallagher SM, Warren ST, et al. Altered synaptic plasticity in a mouse model of fragile X mental retardation. Proc Natl Acad Sci U S A 2002;99:7746–50. [PubMed: 12032354]
48. Bear MF. Therapeutic implications of the mGluR theory of fragile X mental retardation. Genes Brain Behav 2005;4:393–8. [PubMed: 16098137]

49. Aschrafi A, Cunningham BA, Edelman GM, et al. The fragile X mental retardation protein and group I metabotropic glutamate receptors regulate levels of mRNA granules in brain. Proc Natl Acad Sci U S A 2005;102:2180–5. [PubMed: 15684045]

50. Yan QJ, Rammal M, Tranfaglia M, et al. Suppression of two major Fragile X Syndrome mouse model phenotypes by the mGluR5 antagonist MPEP. Neuropharmacology 2005;49:1053–66. [PubMed: 16054174]

51. Manent JB, Wang Y, Chang Y, et al. Dcx reexpression reduces subcortical band heterotopia and seizure threshold in an animal model of neuronal migration disorder. Nat Med 2009;15:84–90. [PubMed: 19098909]

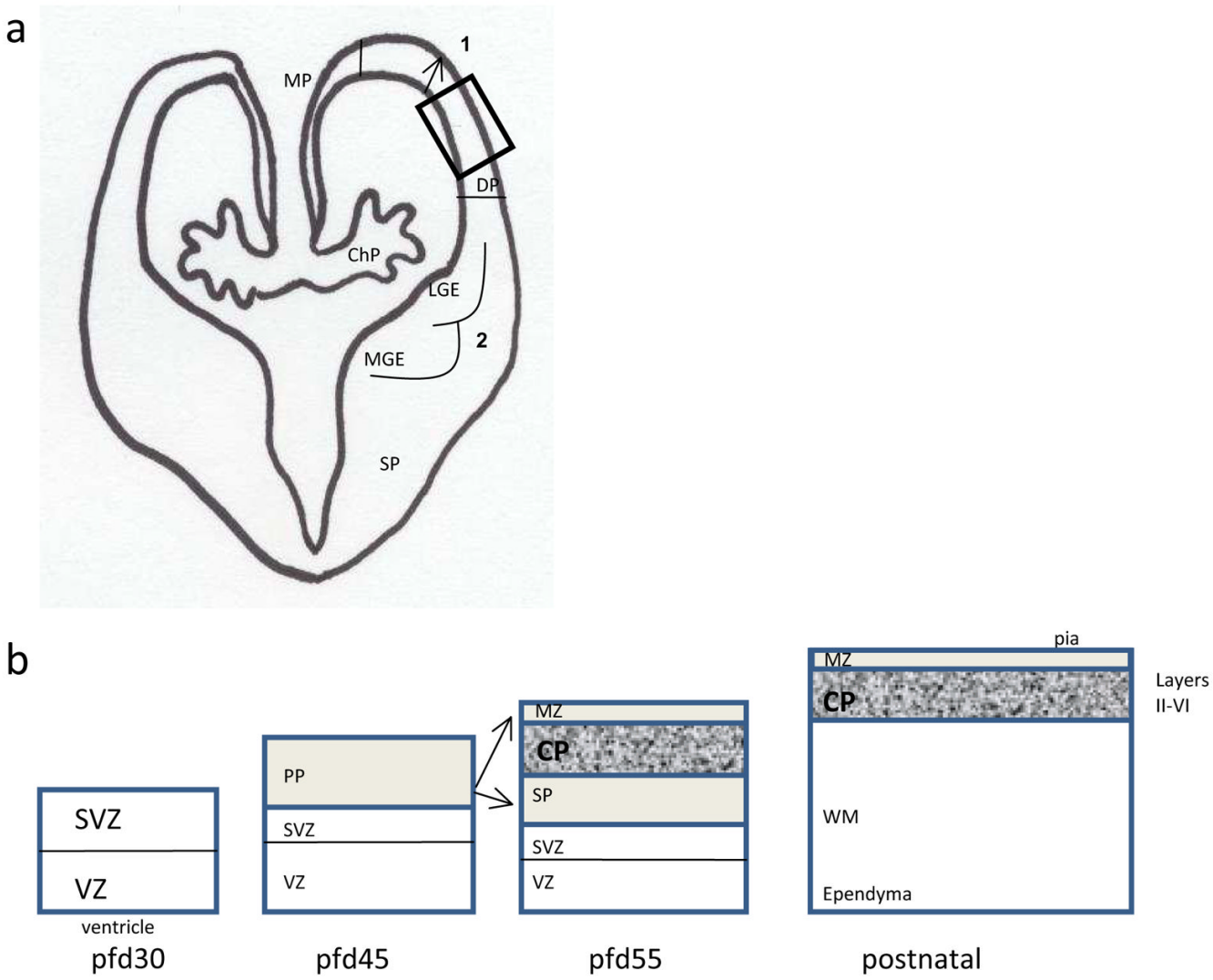

Figure 1.

Overview of cortical development. (a) Radial (1) and Tangential (2) modes of migration. MGE - medial ganglionic eminence, LGE - lateral ganglionic eminence, DP – dorsal pallium, SP – subpallium, MP – medial pallium, ChP – choroids plexus. (b) Inset from above. Neocortical layering. VZ – ventricular zone, SVZ – subventricular zone, PP – preplate, MZ – marginal zone, CP – cortical plate, WM – white matter. During early stages (post-fertilization day, pfd 30) the cortex consists of the outer SVZ and VZ. The emergence of the PP occurs around pfd 45. Newly generated neurons from the VS migrate into the CP, and split the PP into the MZ and SP (arrows). The SP plays 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.

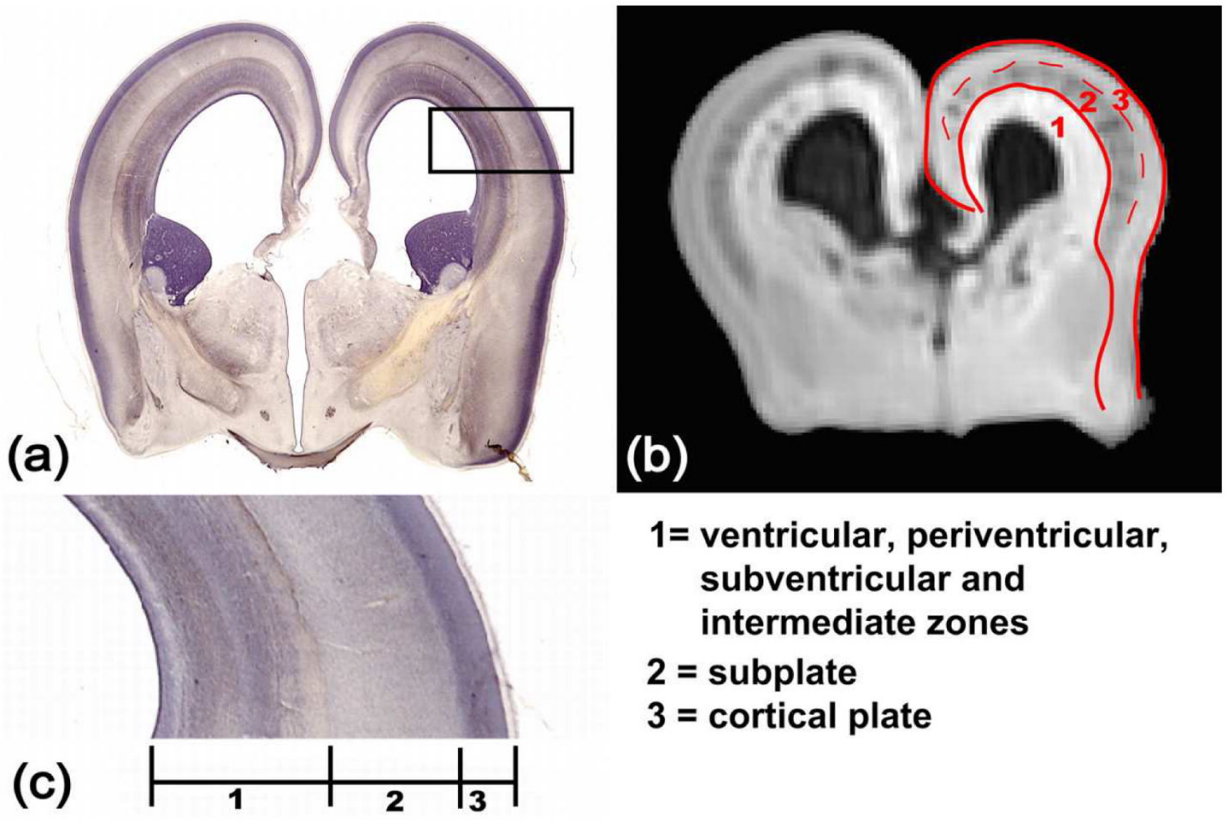

Figure 2.
Layers of the developing cerebral cortex from humans. (a-c) show a coronal histological slide of a 17-week fetal brain, similar to a coronal slice taken by diffusion tensor imaging of a 17-week fetal brain, and an enlarged region corresponding to the boxed area. The red contour establishes the boundary of the cortical plate and subplate (CP+SP). The dashed red curve separates the corticalplate and subplate. The annotation of each boundary is shown at bottom right (From Huan H. et al. J Neurosci. 29(13):4263 with permission).