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A Century of Progress in Corticoneurogenesis: From Silver Impregnation to Genetic Engineering

Pasko Rakic

Department of Neurobiology and Kavli Institute of Neuroscience, Yale University School of Medicine New Haven, CT, USA

Within the past 125 years, we have witnessed great strides in understanding development and evolution of the cerebral cortex, arguably the structure that makes us human. Among the distinguishing features of cortical development are discoveries that its constituent neurons are not generated locally and that after assuming their proper areal, radial, and laminar position, they serve the individual throughout the lifespan. Although the basic cellular events and all major developmental phenomena have been discovered by the use of classical methods, advents of new, evermore sophisticated experimental methods that range from neuroimaging to molecular genetics enable elucidation of the molecular and cellular mechanisms underlying evolutionary elaboration of the cortex and opens the possibility for the prevention and treatment of congenital disorders of the highest cognitive functions in humans.

Keywords: cerebral cortex, neurogenesis, neuronal migration, brain evolution, radial glia

Introduction

The pleasure of the challenge offered by writing an historical account of one's own research field is diminished only by the limit of its size, which necessitates leaving out important details, interesting anecdotes, and deserving credits. It is also intimidating to communicate such an account to the world's highest experts on the subject who rightfully believe that they could do better. So, from the start, I would like to emphasize that this communication is not a comprehensive historical treatise, which I may venture to write some day, but a personal reflection on the origin and progress in this field by an active researcher, avid reader, and collector of rare books in this field. I will first describe the discoveries of the basic concepts and principles of corticogenesis that have been made during the past century, followed by a short outline of the ongoing progress in deciphering molecular and cellular mechanisms. I will focus on the issues concerning where cortical neurons originate and how they attain their position, rather than on the equally important subjects of cell proliferation, formation of functional maps, and of subsequent formation of a synaptic connection. Neuronal migration is the major focus of the research in my laboratory, and I will rely heavily on our results in mice, human, and nonhuman primates to relate these advances to the compelling medical issues as well as to evolution of the human cerebral cortex, the only structure on the earth that will be involved in reading this article.

Discoveries of Major Principles and Basic Cellular Events

The development of the cerebral cortex has fascinated scientists and the general public alike because it addresses one of the most fundamental questions in all biology: how is the organ that mediates human conscience, intelligence, and creativity formed in each individual and how did it expand during evolution to culminate in the human? When I speak about the cerebral cortex and its function, I never underestimate its significance, as the cortex is what makes us human. So, to be bold, I believe that the understanding of cortical development will provide a long sought answer to the questions of who we are, where we come from, and where we might be going.

The research on corticogenesis, or more precisely, corticoneurogenesis, has become a sui generis side branch of the burgeoning field of contemporary developmental biology. The term corticoneurogenesis pertains to the process of production, allocation, migration, and settling of neurons into proper areal and laminar positions within the cortical sheet. Is building the cortex different from any other structure? Apart from the obvious biological similarities, are there also some differences between developmental strategies for building organs such as the gut, liver, or kidney and the cerebral cortex? It is generally accepted that the fundamental feature of cortical evolution and development is its parcellation into functionally distinct cytoarchitectonic areas composed of radial columns of neurons sharing common functional properties that receive specific input from the periphery and become interconnected via profuse association axons (reviewed in Goldman-Rakic 1987; Mountcastle 1997). In the cerebral cortex, more than in any other structure of our body, the function of a given neuron critically depends upon its laminar and areal position within the map. How is this unique and exquisitely complex cellular structure built?

Roots of Discoveries

The description of most cellular events involved in corticoneurogenesis can be traced back to the end of the 19th century. Considering the relatively crude, static methods available, it is both remarkable and instructive that old masters postulated all the basic concepts that have endured the test of time and are still, for the most part, valid. Even for contemporary readers outside of this specialized field, it may seem curious and counter intuitive that such a large structure is composed of the cellular elements that are generated outside of itself. The initial concept that cortical neurons migrate from the place of their origin near the cerebral ventricle to their final destinations in the overlying cortex was discovered only about a century ago, based on the exquisite observations and ingenious interpretation of human embryonic tissue sections stained with the classical histological methods. The critical finding was that mitotic figures (which signify cell division) are situated along the lumen

of the cerebral ventricles (at the time called germinal layer or matrix) and are virtually absent in the developing cortex forming below the pial surface (His 1874, Fig. 1*A,B*). In addition, there were also numerous radially oriented bipolar cells in the middle of the cerebral wall. Based on this circumstantial evidence, Wilhelm His concluded that neurons probably migrate to the cortex. This conclusion may look obvious and trivial today, but was revolutionary at the time, and would probably not be acceptable in contemporary journals without some additional experimental evidence.

Soon after the introduction of the Golgi silver impregnation method, the concept of the coexistence of glial and neuronal cells and phenomenon migration was confirmed remarkably quickly for an era without electronic communication and was reported almost simultaneously in Belgium, France, Germany, Italy, Spain, and Sweden (Koelliker 1879; Ramon y Cajal 1881; Magini 1888; Vignal 1888; Retzius 1893; Stefanowska **1898**). The silver deposits revealed silhouettes of glial (or primitive ependymal cells) that span the cerebral wall (Fig. 1*D*). In addition, they also observed transitional cell forms that range from round, situated near the cerebral ventricle, to the bipolar shape with the leading processes extending to the prospective cortex, confirming the idea that they migrate. The accumulation of bipolar cells in the superficial strata of the cortical plate (CP) and more complex pyramidal and multipolar forms in the deeper layers of the prospective cortex suggested to most of them that neurons may settle in an "inside out" sequence (Fig. 1*C*). However, to make things more interesting, Frederick Tilney, in his monumental and otherwise well written textbook on neuroanatomy (Tilney 1923), has stated that the cortex forms with the addition of newly born neurons that accumulate below

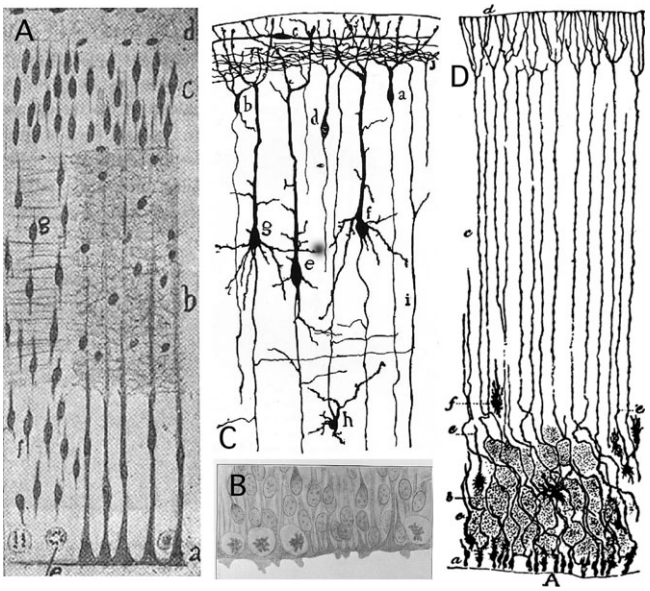

Figure 1. Examples of the type of observation of basic cellular events in the developing cerebrum by methods that were available at the turn of the 19th century. (*A*, *B*) Drawings of the mitotic figures at the ventricular surface of the embryonic human telencephalon by Wilhelm His. (*C*) Drawing of silver-impregnated cells in the developing mouse cerebral cortex by Ramon y Cajal showing stages of neuronal differentiation from the least mature, bipolar cells in the superficial layers and the more mature in the deep layers. (*D*) Whereas some epithelial (radial glial) cells are spanning the entire cerebral wall in the neonatal rabbit, there are numerous transitional cells forming into astrocytes (combined from His 1904, Hirtzl, Leipzig; Ramón y Cajal 1909, Maloine, Paris).

those previously generated, or in an "outside in" neurogenetic gradient, but this concept did not receive wide acceptance.

Renaissance with New Crafts

After the initial discoveries of the basic cellular events by the application of static morphological methods in the human embryo, very little significantly new was added in almost a century. The issue of the inside out gradient was settled by the application of a newly developed method of tagging replication DNA in dividing cells with radioactive (tritiated) thymidine (^{3}H-TdR) in the developing mouse cortex, which confirmed that, in general, newly generated neurons bypass those generated previously (e.g., Angevine and Sidman 1961). In 1968, the concept of differential distribution of dividing cells in the human cerebrum, suggested originally by His, was proven in the very same species by the application of ^{3}H-TdR in the experiment that involved one of the first applications of alive (in vitro) slice preparations in developmental biology (Rakic and Sidman 1968). The majority of the supravitally labeled cells in the wall of the human fetal cerebrum were situated close to the ventricular surface, although some could also be found in the intermediate zone (IZ, prospective white matter) and marginal zone (MZ, prospective layer I). Recent immunohistochemical analysis of the human telencephalon at early embryonic stages (30–37 postconceptual days) reveals that some abventricular mitosis occurs even before the onset of neurogenesis in the local ventricular zone (VZ) (Bystron and others 2006). However, the developing CP itself was found to be basically devoid of divisions until the beginning of gliogenesis (Rakic and Sidman 1968). Subsequent exposure of a series of macaque embryos to ^{3}H-TdR at different embryonic stages in vivo and sacrificed postnatally indicated that the inside to outside sequence is even more pronounced in the larger gyrencephalic and more slowly developing neocortex, which is similar in size, shape, and cellular composition to the human (Rakic 1974a, 1988a). The reason for this pattern is not clear, but one hypothesis is that earlier generated neurons provide some information to the later generations because genetic and/or environmental interference with sequential development has serious behavioral consequences (reviewed in Caviness and Rakic 1978; Rakic 1988b).

New findings obtained by methods such as electron microscopy and cell biology prompted the meeting of the Boulder Committee (1970). Based on observations from Golgi, electron microscopic serial sections, and ^{3}H-TdR autoradiographic analyses in human and mouse embryonic cerebrum, I drew a diagram of the dynamic cellular events in the embryonic cerebral wall and proposed the model that was used by this committee to suggest a new nomenclature (Fig. 2; Boulder Committee 1970). The terms included VZ for the layer of proliferative cells at the ventricular surface and subventricular zone (SVZ) to account for the layer of progenitors that were situated between the VZ and IZ. It was subsequently found that the SVZ in primates, including humans, produce mostly interneurons and glial cells (Rakic 1975, 2003; Letinic and others 2002) and eventually in the adult cerebrum transforms into the subependymal zone (SEZ), which produces mostly glial cells (e.g., Lewis 1968; McDemott and Lantos 1990; Sanai and others 2004). Similar transitions from the SVZ to SEZ occur in rodents, but they continue to produce neurons destined for the olfactory bulb (Lois and Alvarez-Buylla 1993). Although the drawing included the existence of both radially and tangentially

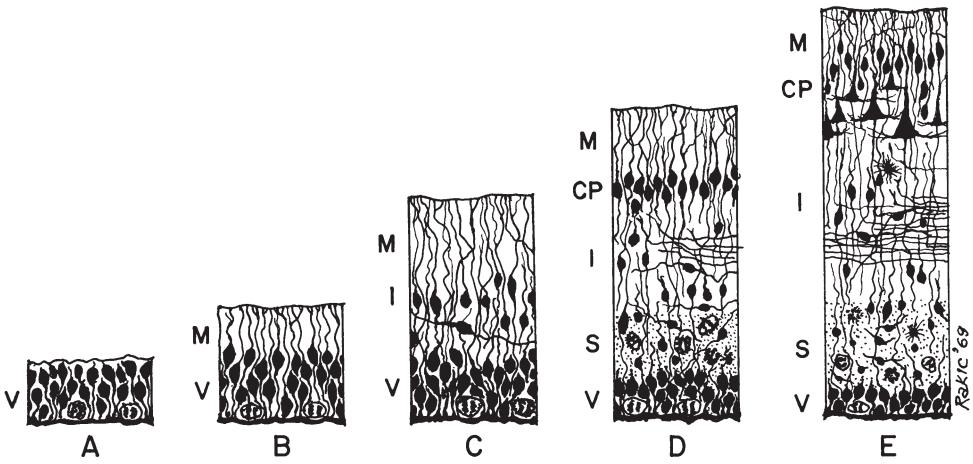

Figure 2. Schematic drawing of 5 stages (*A–E*) in the development of the vertebrate central nervous system, which delineates the transient embryonic cellular zones. Based on the drawing from the doctoral Thesis on "Studies on the proliferation, migration, and differentiation of neuroblasts during neurohistogenesis in mammals, particularly man" (Rakic 1969, Belgrade University). I, intermediate zone; M, marginal zone; S, subventricular zone; V, ventricular zone (Boulder Committee 1970).

migrating neurons, the emphasis in most studies during the past 3 decades was placed on radial migration, the most prominent mode of cell movement in the human cerebrum.

The combined use of ^{3}H-TdR autoradiography and serial section EM analysis indicated that proliferative cells in the VZ are organized as a pseudostratified epithelium in which precursor cells divide asynchronously; their nuclei move away from the ventricular surface to replicate their DNA and then move back to the surface to undergo another mitotic cycle (reviewed in Sidman and Rakic 1973). Initially, light and electron micrograph studies demonstrated completely rounded mitotic forebrain progenitors at the ventricular surface (Stensaas LJ and Stensaas SS 1968; Hinds and Ruffett 1971; Sidman and Rakic 1973) that were morphologically distinct from RGCs that span the full thickness of the neocortical wall, even during mitosis. In addition, immunocytochemical labeling with glial fibrillary acidic protein (GFAP) at light and EM levels revealed, that in primates, dissimilar to rodents, neuronal and glial cell lines coexist from the onset of corticogenesis (Fig. 3 *C–H* and Levitt and others 1981, 1983; Choi 1986; Zecevic 2004). However, the application of more sensitive methods indicates that glial and neuronal cell lines are also separated early in mice (McCarthy and others 2001).

Glial Scaffolding and Radial Unit Hypothesis

Elongated GFAP positive radial glial cells (RGCs) in humans dominate the scenery of the cerebral wall in the human fetus (Sidman and Rakic 1973; Gadisseux and Evrard 1985; Choi 1986; Kadhim and others 1988; deAzevedo and others 2003; Rakic 2003; Zecevic 2004). Among other well-known but often overlooked features of the RGC is that their basal end-feet compose the pial surface of the fetal cerebrum (glia limitans). In addition, a subset of RGCs in the primate fetal telencephalon does not divide for several months, whereas their elongated shafts serve as guides for migrating neurons (Schmechel and Rakic 1979b). Maintenance of the connection between the ventricular and pial surfaces in the large and convoluted cerebrum was considered important because immature neurons migrate to the overlying CP using the elaborate scaffolding of the RGCs as a substrate (Rakic 1972; Sidman and Rakic 1973; deAzevedo 2003; Zecevic 2004). Thus, in primates, RGCs may have evolved to provide a more permanent scaffolding for the formation of the convoluted cortex (Rakic 1976).

RGC scaffolding was considered to be essential for the preservation of positional information among cells within the protomap of the VZ after they migrate to the suprajacent CP that shifts as the hemispheric surface becomes more convoluted (Fig. 3, Rakic 1978). The predominant mode of migration in primates was radial, for example, perpendicular to the ventricular and pial surface, and, to compensate for the expansion of the cortex and development of its incipient convolutions, cohorts of neurons are generated in succession within the same site in the VZ (proliferating units) and migrate following the elongated and curvilinear shafts of the RGCs that span the entire fetal cerebral wall (Fig. 3*A,B*; Rakic 1972, 1978). The discovery of the glial-guided radial migration in primates that have up to a 1000 times larger cortical surface than in rodents, with little increase in thickness, led to the proposal of the "radial unit hypothesis" (Rakic 1988a). According to this hypothesis, the 2-dimensional positional information of the proliferative units in the VZ is transformed into 3-dimensional cortical architecture: the *x* and *y* axes of cells is provided by the site of cell origin in the VZ, whereas the *z* axis is provided by the time of their origin (Rakic 1988a). This concept has served as a useful working model for research on the cellular and molecular mechanisms involved in normal and abnormal cortical development (e.g., Tan and Breen 1993; Mountcastle 1997; Buxhoeveden and Casanova 2002; Chenn and Walsh 2003; Kriegstein and Noctor 2004; Zecevic 2004). According to this model, the cells of the CP and subplate (SP)—indeed even the VZ/SVZ where most cortical neurons originate—set up a primordial species-specific cortical map that preferentially attract appropriate thalamic afferents (Rakic 1988a). The protomap foreshadows the prospective cytoarchitectonic area and a set of limited possibilities and biological constraints. The final size of the individual cytoarchitectonic area and its specific molecular, cellular, and synaptic characteristics of the adult cerebral cortex are achieved through a cascade of reciprocal interactions between responsive cortical cells and afferents arriving from a variety of extracortical sources, particularly the dorsal thalamus (Rakic 1988a; Rakic and others 1991). Recent studies provide support for this model (e.g., Rubenstein and Rakic 1999; Grove and Fukuchi-Shimogori 2003; O'Leary and Borngasser 2006).

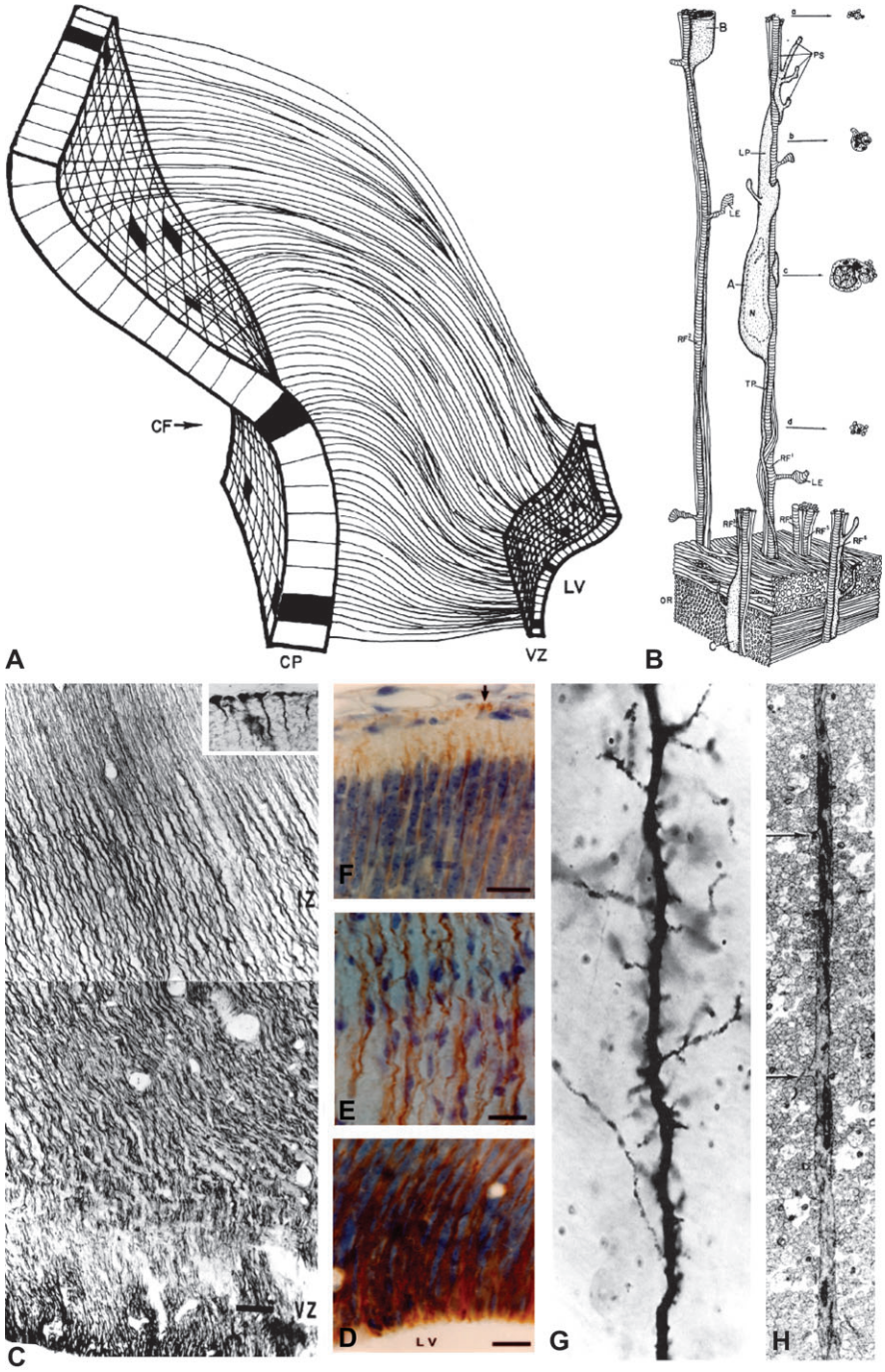

Figure 3. (*A*) The reconstruction of the portion of the medial cerebral wall at the level of the incipient calcarine fissure (CF) in the 80-day-old monkey fetus that illustrates connections of the corresponding points in the VZ with the increasingly distant CP by the elongated radial glial fibers that span the full thickness of the cerebrum. (*B*) Reconstruction of the bipolar neuron migrating along a RG fiber. (*C*) RGC cells in the E70 monkey fetal cerebrum immunostained with the antibodies to GFAP exposes the richness of the RG fiber scaffolding at the midpoint of cortical neurogenesis. The radial fibers continue to run from the VZ near the lateral cerebral ventricle (LV) across the IZ all the way to the CP (not shown), where many of them terminate with typical end-feet at the pial surface (inset). (*D–F*) GFAP-stained RG fibers taken from the 3 levels of the cerebral wall starting from the surface in (*D*) across the IZ (*E*) to the pial surface (*F*). The GFAP-negative migrating neurons (blue) are distinguishable from the GFAP-positive RG cells (brown). (*G*) RG fibers impregnated with the Golgi method (*E*) and viewed with the electron microscope; (*D*) elaborate numerous lamellate expansions that become more prominent at later stages of corticogenesis (assembled from Rakic 1972, 1978, 1984; Levitt and Rakic 1980).

RGC as Stem Cell

Because of a changing phenotype that defies classification and diversity of functions, RGCs acquire the reputation of a maverick among brain cells (Rakic 2003). However, the amazing diversity of their functions continues to evolve. Although it had been recognized for some time that the primary or conventional RGC phenotype could revert to the neuroepithelial form (now called neural stem cells) that generate neurons (e.g., Cameron and Rakic 1991), increasing in vivo and in vitro evidence demonstrates that RGCs can generate not only neuronal progenitors but also directly postmitotic neurons (Chanas-Sacre and others 2000; Hartfuss and others 2001; Noctor and others 2001,

2002; Tamamaki and others 2001; Gaiano and Fishell 2002; Heins and others 2002; Fishell and Kriegstein 2003; Malatesta and others 2003; Tramontin and others 2003; Weissman at al., 2003; Gal and others 2006; Rasin and others 2006). More recent observations have indicated the existence of a "transit-amplifying cell" that populates both the VZ and SVZ. These cells are considered dedicated neuronal progenitors derived from the parent RGCs that do not inherit the pial fiber (Fig. 4 and Rakic 2003; Noctor and others 2004; Gal and others 2006, reviewed in Martinez-Cerdeño and others 2006). Early divergence of basic cell types has been confirmed using the retroviral gene transfer method, which enables the study of cell lineages in the developing mammalian telencephalon, including primates (Luskin and Shatz 1985; Parnavelas and others 1991; Kornack and Rakic 1995).

The discovery that the RGC can produce neuronal progenitors as well as postmitotic neurons posed the question of the long held concept of homogeneity of the neuronal stem cell at the VZ/SVZ. The use of a variety of methods, including in utero electroporation with specific cellular markers, computer-assisted serial EM cell reconstruction, and time-lapse multiphoton imaging reveals the existence of RGCs that span the entire neocortical cerebral wall as well as short neural precursors (SNPs), with basal processes of variable length that are retracted during mitotic division (Fig. 4 and Gal and others 2006). The relative number of GFAP+ and GFAP– precursors changes systematically over the course of cortical neurogenesis (Levitt and others 1983). The neural stem cells can be isolated from both the rodent and human cerebrum VZ/SVZ and their properties analyzed in vitro (Kirschenbaum and others 1994; Laywell and others 2000; Carpenter and others 2001). Neural stem cells can also be tagged by the retroviral gene transfer method and their phenotype and migratory pattern followed in slices of postmortem human fetal tissue (Letinic and others 2002). The SNPs are marked by their preferential expression of the tubulin alpha-1 promoter, whereas RGCs instead express the glast and brain lipid–binding protein promoters (Gal and others 2006). Furthermore, the neuron-restricted class may be further specified to produce different classes of projections and local circuit neurons (Parnavelas and others 1991; Tan and others 1998). Heterochronous transplantation of VZ cells indicate that progenitors produce layer-specific neurons depending on the time when they are dissociated from the embryo (McConnell 1988) and deletion of isochronously generated neurons is not replaced (Algan and Rakic 1997). Thus, RGCs can give rise to both neuron and astrocytic progenitors that each can produce several generations of dedicated progenitors before their terminal differentiation (Fig. 4). This heterogeneity seems to be retained in the adult human cerebrum as demonstrated by molecular phenotyping of clonal neurospheres (Suslov and others 2002).

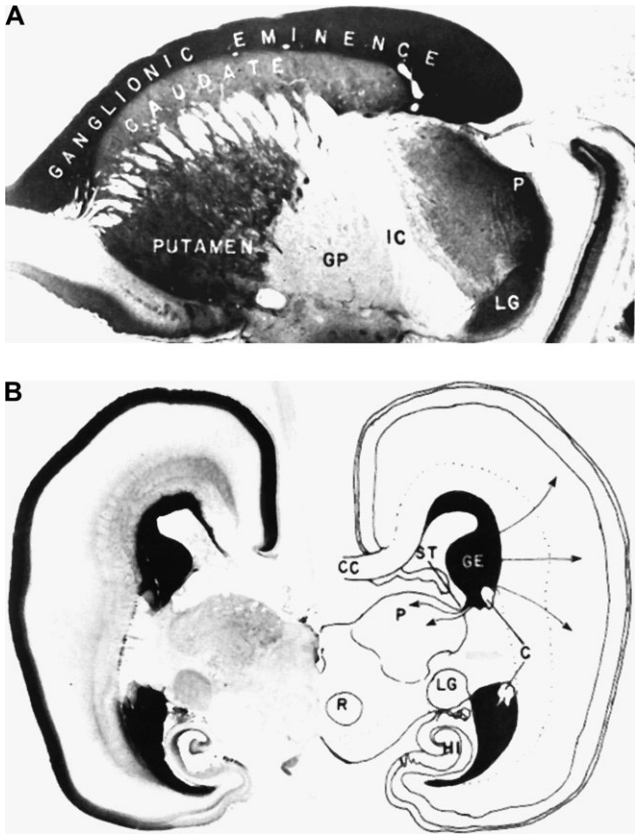

Figure 4. Migration of neurons from the GE in the embryonic human cerebrum. (*A*) As evident in sagittal sections of the human cerebrum at midgestation, the GE overlays the elongated caudate nucleus that is separated from the putamen by the emerging internal capsule. (*B*) As observed in the coronal sections, numerous cells migrate both radially and tangentially from the GE to the overlaying cerebral cortex, but the exact nature of the migrating cells in the human brain could not be discerned (assembled from Rakic 1974).

Transient Subplate Zone

The Boulder Committee schema (Fig. 2) did not include the transient subplate zone (SPZ), which was not described until the mid 1970s (Kostovic and Molliver 1974; Rakic 1977), and was fully elaborated only in the 1980s (Kostovic and Rakic 1980, 1990; Luskin and Shatz 1985; Ghosh and Shatz 1993). The SPZ consists of early generated neurons scattered among incoming axonal systems, glial cell and fibers, and trespassing migrating neurons. It was proposed that the SPZ serves as a "waiting compartment" and a cellular substrate for competition among the initial contingent of cortical afferents and direct their distribution to appropriate regions of the overlying CP (Rakic 1977; Kostovic and Rakic 1984; McConnell and others 1994; Kanold and others 2003). After these diverse inputs enter the CP, the SPZ disappears, and only a vestige of cells remain scattered within the subcortical white matter that are known as interstitial neurons (Kostovic and Rakic 1980; Chun and Shatz 1989). A comparison among various species indicates that the size of this SPZ increases during mammalian evolution and culminates in the areas subjacent to the association cortex in the human fetal cerebrum concomitantly with the enlargement of the corticocortical fiber systems and formation of convolutions (Kostovic and Rakic 1990; Kostovic and Goldman-Rakic 1983; Goldman-Rakic and Rakic 1984). There is also evidence that neuronal activity plays a role in the patterning of thalamic afferents in the transient SP zone prior to entering the overlaying CP (Catalano and Shatz 1998).

Ganglionic Eminence–Derived Cells

Although steady progress has been made in characterization of radial migration from the VZ/SVZ, research on migration from the large proliferative depot of the ganglionic eminence (GE) has been lagging. Initial morphological evidence indicated that a large population of neurons in the human telencephalon originate in the GE and migrate to the cerebral cortex (Fig. 5; Rakic 1974b). As evident in the sagittal sections of the human

fetal cerebrum at midgestation, basal ganglia in humans are organized very differently than in rodents, and the GE coats the full extent of the caudate nucleus which is separated from the rest of the neostriatum (putamen) by the internal capsule (Fig. 5*A*). Because of the large number of bipolar cells that migrate from the GE to the overlying neocortex, it was considered a "fountainhead" that provides both neuronal and glial cells to the cerebrum. In addition to the large number of glial cells that enter the prospective white matter (corpus semiovale), there is also a stream of bipolar neurons that migrate to the dorsal thalamus (Rakic and Sidman 1969; Letinic and Rakic 2001). However, the majority of the neurons from the GE migrate both radially and tangentially to the developing cerebral cortex, but at the time their nature could not be determined. It was the application of experimental methods in mice that have provided a plentitude of evidence that the cells, which originate from the GE to the dorsal telencephalon, differentiate into γ-aminobutyric acidergic (GABAergic) cortical interneurons (e.g., deCarlos and others 1996; de Carlos and O'Leary, 2002; Anderson and others 1997, 1999; Lavdas and others 1999; Tamamaki and others 2001; Wichterle and others 2001; Ang and others 2003; Letinic and others 2002; Polleux and others 2002; Tanaka and others 2003). However, this GABAergic system expands and becomes more elaborate during mammalian evolution. Thus, whereas in the mouse embryo, virtually all interneurons of the neocortex are imported from within the GE (reviewed in Marin and Rubenstein 2001), in the human, most of the cortical interneurons originate in the VZ/SVZ of the dorsal telencephalon subjacent to a given area (Letinic and others 2002). This is particularly evident in the primary visual cortex (area 17), which in old world primates, such as macaque and human, contains a significantly larger number of interneurons than the adjacent areas (Rakic 1976; Smart and others 2002). The formation of a sharp border between 2 areas involves differential rates of proliferation and production of interneurons in the subjacent VZ/SVZ (Lukaszewicz and others 2005). In addition, use of retroviral labeling in organotypic slices of the embryonic human forebrain revealed the existence of a distinct lineage of neocortical GABAergic neurons that expresses Dlx1/2 and Mash1 transcription factors that originate from the neocortical VZ/SVZ (Letinic and others 2002). This population in humans comprises about two-thirds of the neocortical GABAergic neurons; the remaining third originate from the GE, which is quite different proportion than in rodents. Such species-specific programs for the generation of distinct neuronal lineages that form increasingly diverse classes of interneurons may be differentially affected in disorders that are attributed to deficits and/or defects of local circuit neurons in humans (e.g., des Portes and others 1988; Rakic 1988b; Jones 1997; Lewis 2000; Gleeson and Walsh 2000).

Cessation of Corticoneurogenesis

At which time point in the lifespan of an individual does cortical genesis stop, or is there such a time point? It is well established that the duration of corticoneurogenesis in mammals is highly variable; as, in some species, it is completed at or before birth, whereas in the altricial animals, such as the ferret or rabbit, it continues long after birth. We have examined over 100 monkeys using ^{3}H-TdR or BrdU method for marking DNA replication in order to determine the time of origin of neurons in the 7 neocortical areas in the macaque monkey. Although we have observed that genesis of the granule cell class destined for the

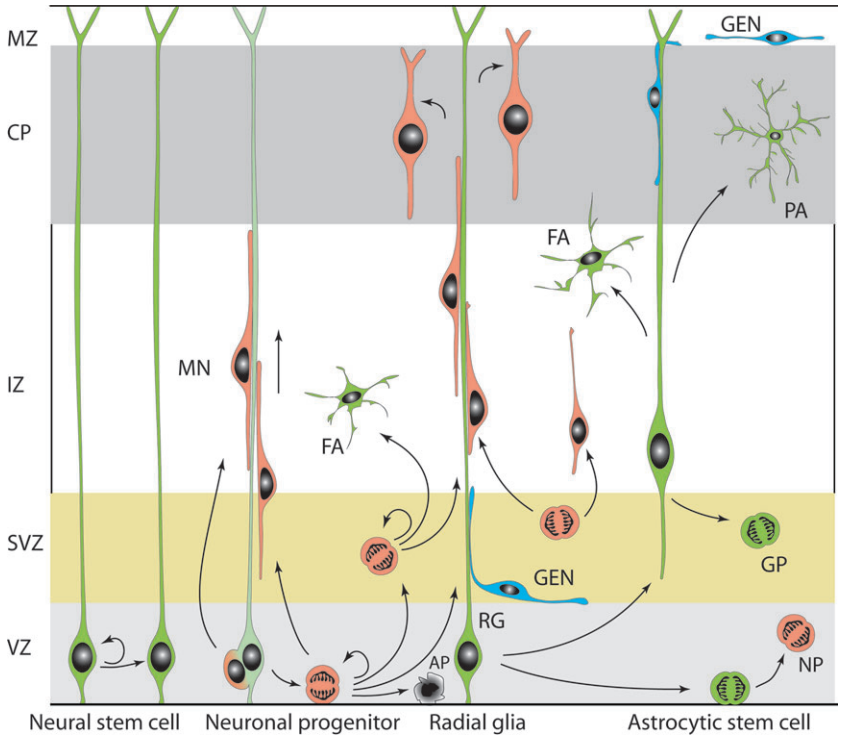

Figure 5. Schematic diagram of the evolving concepts of the relationship between radial glial cells (RG, green color) and radially migrating neurons (MN, red) from the VZ as well as tangentially migrating from the ganglionic eminence (GEN, blue) based on data from species ranging from the mouse to human and nonprimates. The RG initially divides symmetrically to produce additional RGs some of which eventually detaches from the VZ and undergoes apoptosis (AP) or transforms either directly or indirectly into fibrillary astrocytes (FA), protoplasmic astrocytes (PA), glial progenitors (GP), or astrocytic stem cells that retain a neurogenic potential (NP).

olfactory bulb and hippocampal dentate gyrus continues at a low rate even after sexual maturity (Kornack and Rakic 1999, 2001a), there is no convincing evidence of new neurons being added in any of the so far examined neocortical areas in the old world primate species (Rakic 1974a, 1976; Kornack and Rakic 2001b; Koketsu and others 2003; reviewed in Rakic 2002b). Based on a series of histological, qualitative, and quantitative data of the genesis of cortical neurons in humans, it is also considered to be completed before term (e.g., Poliakov 1965; Sidman and Rakic 1973, 1982; Korr and Schmitz 1999) and apparently remains stable throughout life as assessed by C^{14} labeling (Spalding and others 2005; Bhardwaj and others 2006). Thus, like many of the other classes of neurons of the mammalian brain, most cortical neurons appear to last the entire life span of an individual and are not renewable under normal conditions. This stands in contrast to continuous neurogenesis and renewal of neurons in many vertebrate species such as fishes, amphibians, and birds (reviewed in Rakic 2002a). Application of neuronal stem cells as substitution therapy for lost neurons is emerging as a new research frontier (e.g., Kokaia and others 2006) and would benefit from insight into why neurogenesis of cortical neurons normally ceases at a specific developmental period as well as why there are species specific and regional differences in the capacity for adult neurogenesis. I proposed that a stable population of cortical neurons that lasts throughout the life span has evolved to enable storage of long-term memory and retention of learned experience (Rakic 1985).

Deciphering Molecular Mechanism

Although the description of all major cellular events and formulations of basic concepts and principles of corticoneurogenesis has derived from studies by the static light and electronmicroscopic methods and DNA labeling as applied to the postmortem embryonic human brain, the contemporary experimental work on normal and genetically altered cortex in laboratory animals in vivo and in vitro enables analysis of the underlying molecular mechanisms. As evident from the exciting presentations conveyed through the articles in the present volume, this field is rapidly growing and cannot possibly be given justice in this short overview. For example, the regulation of cell division and programmed cell death that determines the number of cortical neurons became a separate subfield (e.g., Temple 2001; Caviness and others 2003; Lillien and Gulacsi 2006). Likewise, the formation of cortical maps also deserves separate review (e.g., Grove and Fukuchi-Shimogori 2003; reviewed in special issues of the Cerebral Cortex: Rubenstein and Rakic 1999; O'Leary and Borngasser 2006). Thus, I have to limit this short review to the advances made in understanding cellular events after completion of mitotic division, selection of the migratory pathway, and translocation of the nucleus followed by the cessation of movement at the final destination. I will try to emphasize the unprecedented possibilities offered by modern methods for getting new insights into this enormously complex biological process that involves sequential expression of genes, cascades of multiple molecular pathways, and continuous interactions among heterogeneous classes of cells.

Last Cell Division and Establishment of Polarity

As discussed in the preceding section, the neocortex consists of postmitotic terminally differentiated neurons. During and shortly after exit from the asymmetric cell division in the VZ at the ventricular surface, postmitotic daughter neurons become polarized with the leading process directed toward the CP aligned along the RGC shafts (Rakic 1972; Sidman and Rakic 1973: reviewed in Fishell and Kriegstein 2003). The molecular mechanism of this first step for cell departure has only begun to be unraveled. Thus, it was found that the apical processes are interconnected via Cadherin-based adherens junctions (Fishell and Kriegstein 2003; Gotz and Huttner 2005; Rasin and others 2006) so that the interkinetic (up and down) nuclear movement remains restricted to the VZ within the apical processes and their end-feet, which are incorporated into the ventricular surface. Mitosis, including anaphase, occurs regularly at the ventricular surface, as implied by classical in vivo and in vitro approaches (Misson and others 1991; Temple 2001) and confirmed with in vivo imaging (e.g., Haydar and others 2003; Noctor and others 2004; Gal and others 2006). The transformation of bipolar ventricular cells into either multipolar astrocytes or cuboid ependymal cells (Schmechel and Rakic 1979a; Levitt and Rakic 1980; Alvarez-Buylla and Lim 2004) coincides with the controlled downregulation of the apical–basolateral polarity of RGCs (Gotz and Huttner 2005). Futhermore, divergence into specific neuronal lines may occur prior to expression of GFAP in glial progenitors and astrocytes (Temple 2001). Neurons originated in the VZ/SVZ begin migration to the overlaying cortex only after completing the last cell division. As a first step, postmitotic neurons have to establish polarity. It was recently demonstrated that Numb (an inhibitor of Notch) segregates at the basolateral side of dividing cells and becomes enriched during interphase along the apical-most end at the adherens junctions associated with the E-cadherin (Rasin and others 2006). Thus, this molecular pathway appears to be important for determination of symmetric/asymmetric divisions as well as detachment of postmitotic cells from the ventricular lining and establishment of apical basal polarity of ventricular cells (Rasin and others 2006; reviewed in Hatakeyama and Kageyama 2006).

Neuronal Migration

How do postmitotic neurons, after detaching from the ventricular surface, move their bodies to the cortex particularly in the larger and convoluted human cerebrum where the leading process, at later stages, does not reach all the way to the increasingly distant CP? The initial EM observation of a close neuron–glial relationship in the fetal macaque cerebral wall (Rakic 1972) has indicated the presence of a differential binding affinity and suggested the existence of a "gliophilic" mode of migration that may be mediated by heterotypic adhesion molecules present on apposing neuronal and glial cell surfaces (Rakic 1981; 1990 Rakic and others 1994). The postmitotic cells, which did not obey glial constraints and move tangentially, often at a right angle to the radial glial palisades along the axonal tracts (e.g., bipolar cells in Figs 2 and 4) were considered "neurophilic" (Rakic 1991). In the past 3 decades, radial glial-guided migration has been observed in a variety of mammalian species that range from rodents to human (e.g., Sidman and Rakic 1973; Kadhim and others 1988; Hatten and Mason 1990; Misson and others 1991; O'Rourke and others 1992; Noctor and others 2001; deAzevedo 2003; Zecevic 2004). However, this is particularly evident in primates where the RGCs already differentiate both morphologically and biochemically within the first trimester (Rakic 1976; Schmechel and Rakic 1979a,

1979b; deAzevedo and others 2003; Zecevic 2004). The early expression of GFAP in the RGCs may be an evolutionary adaptation in primates, in which a subset of RGCs in primates stops dividing transiently during the peak of neuronal migration when their shafts not only provide a substrate for a long pathway but also their end-feet form the cerebral surface (Schmechel and Rakic 1979b). During this late period of corticoneurogenesis, as many as 30 migrating GFAP-negative neurons have been observed migrating along a single GFAP-positive radial glial fascicle in the human forebrain during mid gestation (Fig. 6, Rakic 2003).

What are the cellular mechanisms, and which molecules, are involved in the recognition of pathway and long distance guidance of migrating neurons which may be involved at the late stages of cortical development? The inference of differential adhesion between migrating neurons and radial glial fibers initially suggested the possibility that a single pair-binding, complementary molecules may account for this guidance (Rakic 1981). However, over time, it became evident that multiple classes of putative recognition and adhesion molecules are involved in a coordinated way in this complex phenomenon. It was postulated that a different set of surface molecules are involved in recognition, adhesion, and cessation of neuronal cell migration (Fig. 7, Rakic and others 1994). These molecules are selectively and transiently expressed in the leading process of postmitotic neurons at the surface adjacent to the radial glial fibers. Furthermore, they are involved in a cascade of multiple molecular interactions that eventually affect cytoskeletal remodeling that is essential for nuclear translocation (see below). As an example, from our laboratory, there is a glial membrane protein (NJPA1) that is localized in the plasmalemmal junction between migrating neurons and adjacent radial glial fibers (Cameron and Rakic 1994). Application of an antibody generated against this polypeptide causes withdrawal of the leading process, changes in micro tubular organization, and premature detachment of neurons from the radial glial shafts (Anton and others 1996). At present, multiple molecular species have been associated with neuronal migration that indicates the complexity of this process (e.g., Hatten and Mason 1990; Fishell and Hatten 1991; Cameron and Rakic 1994; Anton and others 1996, 1997, 1999; Schmid and Anton, 2003; Rio and others 1997; Gongidi and others 2004; Xie and others 2006). Most of the molecules so far tested are membrane bound, but there are also a number of secreted diffusible molecules serving as attracting and repulsing agents that influence direction of migration and allocation of neurons into a particular structure (Wu and others 1999). The genes and molecules are often classified with functionally laden names such as cyclins, inducers, proneural genes, transcription factors, recognition polypeptides, patterning genes, etc. The number of potential players, which exceed several hundred, is growing almost daily. Although most probably have specific tasks and are engaged in interactive cooperation, it is premature to assess their relative contribution and relationship to each other; however, we can expect big strides in this area of research within the next few years.

Nuclear and Somal Translocation

The tip of the leading process and axonal growth cones share many common properties and molecular mechanisms, but the major difference between them is that the leading process serves as a conduit for translocation of the nucleus and somatic cytoplasm. Neuronal migration to the cerebral cortex, similarly as in the other laminated structures of the central nervous system (CNS) such as the cerebellum, involves the initial extension of the leading process to a variable length, followed by the displacement of the nucleus within the cytoplasmic

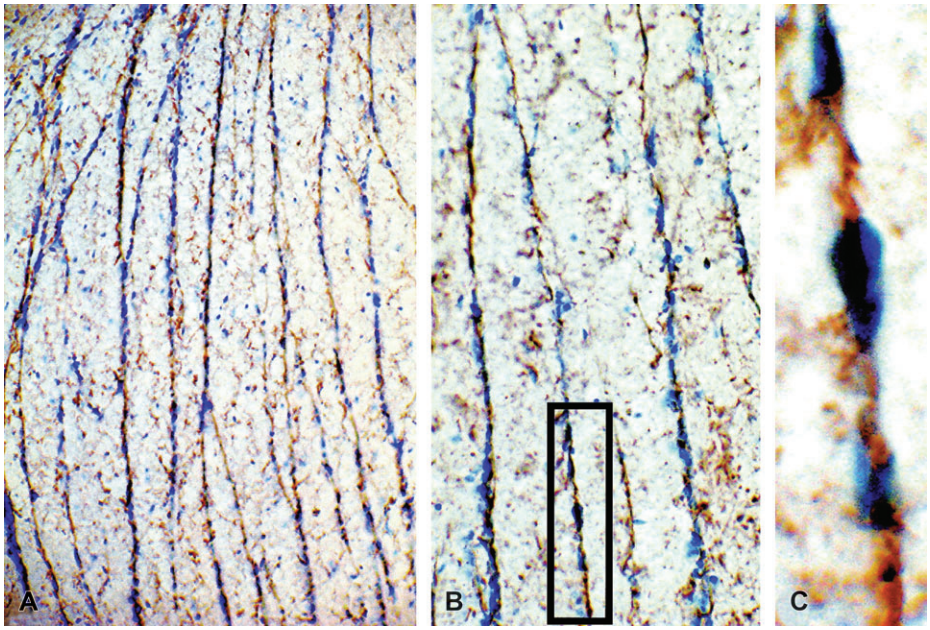

Figure 6. Neuronal migration at late stages of corticoneurogenesis in the human cerebrum. (*A*) Cohorts of migrating neurons visualized by toluidine blue stain (blue) are aligned along immunostained, GFAP-positive RG shafts (brown) crossing the portion of the IZ of the frontal lobe of the cerebral wall in the 18-week-old human fetus. (*B*) The adjacent section counter immunostained with vimentin (brown) showing rows of similarly aligned vimentin-negative neurons aligned along vimentin-positive RG shafts. (*C*) A higher magnification of the segment of the migratory pathway outlined with a rectangle in (*B*). The image illustrates that the nuclei of the migrating neurons are not enclosed within the cytoplasm of the RG shaft. The migrating cells cannot be reproduced in the same focal plane as they are situated at the opposite sides of the RG shaft (from Rakic 2003).

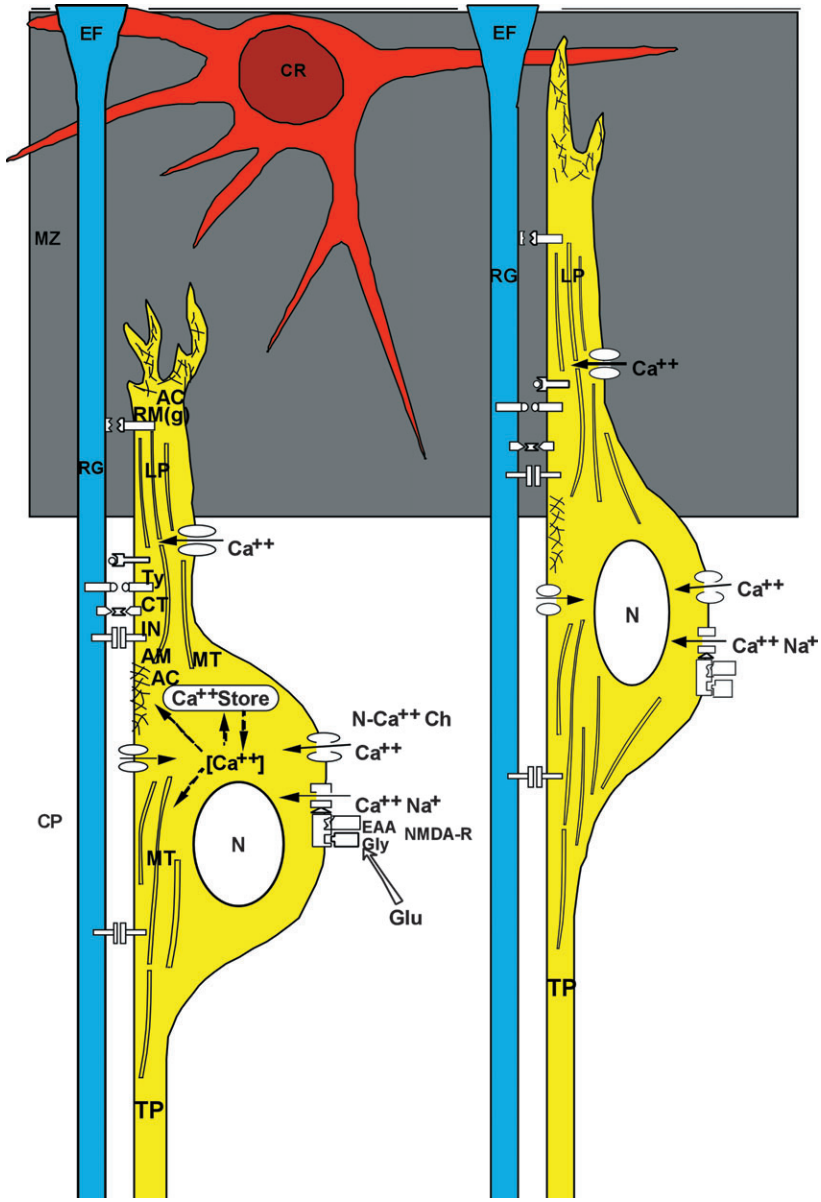

Figure 7. Model of a proposed cascade of molecular events that takes place during migration of postmitotic cells across the developing cerebral wall. Migrating cells extend a leading process (LP) that selectively follows the contours of the radial glial fiber (RF) as it spans the expanding cerebral wall. The cytoskeleton within the LP and trailing process (TP) contain prominent assemblies of microtubules (MT) and actin-like contractile proteins (AC) that are involved in elongation of the leading process (LP) and translocation of the nucleus (N) and the surrounding cytoplasm. The leading process enters the CP and MZ, but the nucleus stops at the CP/MZ interface (gray area). Various intracellular, membrane bound, and extracellular matrix molecules provide signals or are directly engaged in selection of the migratory pathway, rate of cell movement, and, finally, in the cessation of migration at the CP/MZ borderline. Further explanation is given in the text. AC, actin-like filaments; AM, homotypic adhesion molecule; CR, Cajal–Retzius cell; CT, catenin; EAA, excitatory amino acids; EF, end-foot of radial glial fiber; Glu, glutamate; Gly, glycine; I, integrine; LP, leading process; MT, microtubule; N, cell nucleus; RM(g), gliophilic recognition molecule; RM(n), neurophilic recognition molecule (modified from Rakic and others 1996).

cylinder of the leading process, which has been termed "nuclear translocation" (Rakic 1971, 1972; reviewed in Rakic 1981, 1990, Rakic and others, 1996). Although electron microscopic methods were not suitable for studying the dynamic molecular mechanisms underlying the movement, the finding indicated that the signaling proteins and cytoskeleton transformation may play a role in initiation and cessation of nuclear movement (e.g., Rakic and others 1996). The growth of the leading process is slow and temporarily independent of the saltatory movement of the nucleus (Komuro and Rakic 1993; Rakic and others 1996; Hatten 2002; Ang and others 2003; Schaar and McConnell 2005). Because the nucleus moves within the leading process in all migrating neurons, the classification of migration modes into the "somal translocation and locomotion types" may cause confusion because the distinction between early and late migration is in the length of the leading process rather than the mechanism of nuclear translocation within it. Initially, although the cerebral wall is relatively thin, the tip of the leading process can reach the CP, and the nucleus needs to move only a short distance in both the small rodent cerebrum as well as in the human at comparably early embryonic stages (Sidman and Rakic 1973; Nadarajah and others 2003). However, when the total length of the migratory pathway increases and the leading processes of many migrating neurons do not

span the entire width of the cerebral wall, the nucleus and surrounding cytoplasm are nevertheless being intermittently translocated to reach new distances (reviewed in Sidman and Rakic 1982; Rakic 1988a).

Migrating neurons whose leading processes do not span the entire width of the cerebral wall, particularly at the late stages, depend more on guidance mechanisms and may need an additional set of molecules to reach their proper areal and laminar destination (e.g., Hatanaka and others 2004). Reconstruction from serial EM sections showed that the leading process of neurons migrating to the superficial cortical layers has multiple extensions, which probe the environment (Rakic and others 1974). It was postulated that these extensions probe the environment until the leading process advances within the one that is attached to the preferred surface. Cell cultures, as well as in organotypic slices, where the conditions are similar to the environment in vivo, indicated that the nucleus stays mostly stationary, whereas the leading process extends slowly and that it then moves intermittently at a faster rate consistent with the rapid dissolution of microtubules, which allows space for the nucleus (e.g., Rakic and others 1996; Bellion and others 2005; Schaar and McConnell 2005).

Analysis of the polarity of microtubule assemblies (tubulin) polymers within the leading and trailing processes reveals that the positive ends of the newly assembled microtubules situated in the leading process are facing the growing tip, whereas their disintegrating negative ends face the nucleus (Rakic and others 1996). In the trailing process, by contrast, microtubule arrays are of mixed polarity. Thus, the extension of the leading process and translocation of the soma (nucleus and surrounding cytoplasm) within the membrane envelope may be orchestrated by a synchronized polymerization and disintegration of the microtubule that creates a rearrangement of the cytoskeletal scaffolding (Rivas and Hatten 1995; Rakic and others 1996; Schaar and McConnell 2005). Use of time-lapse imaging and pharmacological perturbation to manipulate the rate of cell migration in various structures including the telencephalon indicate that various receptor/channel complexes are involved in control of movement (Fig. 7; Komuro and Rakic 1993; Behar and others 1999; Hirai and others 1999). The composition of the receptor/channels on the surface of migrating neurons is different from the composition they have in the mature brain, but they are capable of regulating Ca^{2+} levels in the absence of any synaptic contacts (e.g., Farrant and others 1994). However, presently available data indicate that the combination of amplitude and frequency components of intracellular Ca^{2+} fluctuations may participate in controlling the rate and the dynamics of polymerization as well as the dynamic of depolymerization of the microtubule protein in the cytoplasm of the leading and trailing processes (Rakic and others 1996; Ang and others 2002). This is harmonious with the finding that disruption of the microtubule structure results in collapse of the migrating cell body and cessation of nuclear translocation (Rivas and Hatten 1995). Synergistic action of other molecular pathways may be involved in cytoskeletal rearrangement, such as Doublecortin and MEKK 4 that is important for mobilization of Filamin (Sarkisian and others 2006). Collectively, these findings are consistent with the suggestion that a variety of human disorders of neuronal migration may be caused by abnormality of the cytoskeletal machinery (des Portes and others 1988; Gleeson and Walsh 2000; Wynshaw-Boris and Gambello 2001; Feng and Walsh 2004).

Cessation of Migration

After passing between previously generated neurons, already settled in the deeper strata of the CP, the leading process enters the MZ, but the movement of the nucleus abruptly stops at the CP/MZ interface (Fig. 7). When migrating cells are prevented from detaching from the RGC's fibers at the CP/MZ interface, subsequently arriving neurons cannot bypass their predecessors and accumulate beneath the previously generated neurons, forming an outside-to-inside gradient of neurogenesis (Anton and others 1996; Gongidi and others 2004). A similar outside-to-inside sequence has been observed in the cortex of the neurological mutant *reeler* mouse (Caviness and Rakic 1978), which appears to be due to the deficit of reelin, the molecule secreted by Cajal–Retzius cells in the MZ and affects neuronal incorporation into appropriate layers (Ogawa and others 1995; Rakic and Caviness 1995; Tissir and Goffinet 2003). However, cessation of migration at the CP/MZ interface may be controlled by the contribution of an additional class of molecules that initiate disintegration of the neuron glia attachment. Under normal conditions, the leading process enters the MZ, but the nucleus and soma stop translocation at the CP/MZ interface. We identified a surface-based molecule (SC1) situated between the RGC and migrating neurons that is primarily localized in the segment of the radial shaft spanning the upper CP, where neurons terminate their migration. Inhibition of SC1 perturbs the appropriate laminar placement of cortical neurons, and its ectopic expression inhibits normal neuronal migration (Gongidi and others 2004). The temporal and spatial distribution of SC1 during cortical migration and its antiadhesive activity, both in vitro and in vivo, suggests that it may provide a cue for cessation of neuronal migration by enabling neuronal detachment from radial glial guides at the CP/MZ interface and may enable the next generations to take more superficial positions (Gongidi and others 2004).

Tangential Migration

The tangential mode of neuronal migration is considered to be 'neurophilic' as cells are usually aligned along tangentially oriented axonal fascicles or rows of postmitotic neurons (Rakic 1985, 1990). This type of migration was observed in many parts of the CNS, particularly the pons, but in the telencephalon involves mostly neurons originating from the GE (see above). More recent studies indicate that this category also includes diverse groups of neurons such as those originated in the telencephalic SVZ destined for the olfactory bulb (Lois and Alvarez-Buylla 1994; Menezes and Luskin 1994), from the GE to the dorsal neocortex (De Carlos and O'Leary 1992; Tamamaki and others 2001; Letinic and others 2002) or to the thalamus (Rakic and Sidman 1969; Letinic and Rakic 2001).

New advances in multiphoton laser scanning confocal microscopy now allows us to study tangential neuronal migration in real time and/or to manipulate neuronal migration in vivo by interfering with specific gene actions. In addition, imaging of the cerebral surface, both while keeping mouse embryos alive and in explants of human brain tissue, revealed that cortical interneurons originate from several sources and migrate via distinct and independent tangential streams to reach their final destination (Ang and others 2003; Haydar and others 2003; Marin and Rubenstein 2003). One group of cells migrate tangentially through the SVZ and IZ before taking a radial route to the CP; the other migrates via the MZ before moving inward

to the subjacent CP (Ang and others 2003). There is increasing evidence that direction of tangential migration depends on specific recognition of substrates composed of neurons capable of delivering them to the appropriate position within the radial columns (e.g., Denaxa and others 2001; Marin and Rubenstein 2003; Cobos and others 2006). However, the molecular cue involved in the coordination of this complex cell trafficking is only beginning to be unraveled. This system has evolved during primate evolution and would benefit from comparative studies at both the cellular and molecular level.

Evolutionary Considerations

Because the ultimate goal of studying corticogenesis is understanding development of the neocortex in humans, it is essential to consider both similarities as well as species-specific differences in the timing, sequence, and phenotypic differentiation that could provide insight into the pathogenesis of cortical abnormalities and cortical evolution. Numerous studies since the seminal work of His and Cajal have indicated that the basic principles of cortical development are similar in all mammalian species. As a result, most of the research, including my own, has been done on rodents, and I have argued elsewhere that the mouse is an "unexcelled model for studying development of the cerebral cortex" (Goffinet and Rakic 2000). However, it also became evident that the large primate cerebral cortex is built according to a more elaborate design compared with a smaller and nonconvoluted rodent cerebrum and has some distinct features not observed in commonly used laboratory animals. Although many species-specific differences that occurred over 250 million years of mammalian evolution are scientifically proven in the literature, they are often implicitly or even explicitly diminished. In our enthusiasm for the mouse model, we should not neglect to take advantage of the studying development of the primate neocortex with its functionally, highly significant phenotypic specializations. The type of work that can be done is obviously limited by logistic and other obstacles but will increase with the impending completion of the gene sequences in the macaque monkey. The advances in the field of human neuronal stem cell research will also help unravel secrets of cortical development in humans. The larger cerebral vesicle in primates, compared with rodents, at the stage before the first neurons are born, indicates that neuronal stem cells are already programmed to produce more cortical neurons (Rakic 1995; Bystron and others 2006). The other major difference of neurogenesis in the expanded SVZ and the formation of the mitotically active subpial granular layer in the MZ (Zecevic and Rakic 2001) is that the zone is particularly prominent in humans (Sidman and Rakic 1973, 1982). Such differences contribute to the introduction of species-specific cell types, new cytoarchitectonic fields, and the pattern of connectivity and transmitter/receptor composition that needs to be taken into account if we are to understand the etiology of congenital malformations in humans.

Our understanding of the cellular and molecular mechanisms of corticogenesis gives insight into the possible events that lead to the evolutionary expansion of the cerebral cortex. For example, a minor increase in the length of cell cycles or the number of cell divisions in the VZ can result in a large increase in the number of founder cells that form the proliferative units (Rakic 1988a). Because initial proliferation in the VZ proceeds exponentially by the prevalence of symmetrical divisions, an additional round of mitotic cycles during this phase doubles the number of proliferative units and, consequently, the number of radial columns (Rakic 1995). According to this model, fewer than 4 extra rounds of cell divisions can account for the 10-fold difference in size of the cortical surface between monkeys and humans (Fig. 4). In contrast, the 1000-fold difference between the size of the cerebral cortex in mouse and human can be achieved by less than 7 extra symmetrical divisions in the VZ before the onset of corticogenesis. This has been put to the test in mice in which production of proliferative units has been increased either by reduction in programmed cell death (Kuida and others 1996; Haydar and others 1999) or through an increase in production (Chenn and Walsh 2003). Thus, the field of corticoneurogenesis is not only important to the compelling problems of congenital disorders of higher cortical functions in humans but also gives us a hint about how we may have evolved to be masters of our destiny.

Notes

Excerpts from the Keynote lecture at the meeting on cortical development: neural stem cells to neural circuits, Santorini, 14 May 2005. *Conflict of Interest*: None declared.

Address correspondence to Pasko Rakic, Yale University, Neurobiology, New Haven, CT 06511. Email: pasko.rakic@yale.edu.

References

Algan O, Rakic P. 1997. Radiation-induced area- and lamina-specific deletion of neurons in the primate visual cortex. J Comp Neurol 381:335–352.

Alvarez-Buylla A, Lim DA. 2004. For the long run: maintaining germinal niches in the adult brain. Neuron 41:683–686.

Anderson S, Mione M, Yun K, Rubenstein JLR. 1999. Differential origins of neocortical projection and local circuit neurons: role of Dlx genes in neocortical interneurogenesis. Cereb Cortex 9:646–654.

Anderson SA, Eisenstat DD, Shi L, Rubenstein JL. 1997. Interneuron migration from basal forebrain to neocortex: dependence on Dlx genes. Science 278:474–476.

Ang ESBC, Haydar TF, Gluncic V, Rakic P. 2003. Four dimensional migratory coordinates of GABAergic neurons in the developing cerebral cortex. J Neurosci 23:5805–5815.

Angevine JB Jr, Sidman RL. 1961. Autoradiographic study of cell migration during histogenesis of cerebral cortex in the mouse. Nature 192:766–768.

Anton ES, Cameron RS, Rakic P. 1996. Role of neuron-glial junctional proteins in the maintenance and termination of neuronal migration across the embryonic cerebral wall. J Neurosci 16:2283–2293.

Anton ES, Kreidberg J, Rakic P. 1999. Distinct functions of α_3 and α_v integrin receptors in neuronal migration and laminar organization of the cerebral cortex. Neuron 22:227–289.

Anton ES, Marchionni MA, Lee K-F, Rakic P. 1997. Role of GGF/neuregulin signaling in interactions between migrating neurons and radial glia in the developing cerebral cortex. Development 124:3501–3510.

Behar TN, Scott CA, Greene CL, Wen X, Smith SV, Maric D, Liu QY, Colton CA, Baker JL. 1999. Glutamate acting at NMDA receptors stimulates embryonic cortical neuronal migration. J Neurosci 19:4449–4461.

Bellion A, Baudoin JP, Alvarez C, Bornens, M, Meten C. 2005. Nucleokinesis in tangentially migrating neurons comprises two alternating phases: forward migration of the Golgi/centrosome associated with centrosome splitting and myosin contraction at the rear. J Neurosci 254:173–181.

Bhardwaj RD, Curtis MA, Spalding KL, Buchholz BA, Fink D, Björk-Eriksson T, Nordborg C, Gage FH, Druid H, Eriksson PS, Frisén J. 2006. The age of human cerebral cortex neurons. Proc Natl Acad Sci USA. Forthcoming.

Boulder Committee. 1970. Embryonic vertebrate central nervous system. Revised terminology. Anat Rec 166:257–261.
Buxhoeveden DP, Casanova MF. 2002. The minicolumn hypothesis in neuroscience: a review. Brain 125:935–951.
Bystron I, Rakic P, Blakemore C. 2006. Neuronal stem cells and predecessor neurons in the primordium of the human forebrain. Nat Neurosci. Forthcoming.
Cameron RS, Rakic P. 1991. Glial cell lineage in the cerebral cortex: review and synthesis. Glia 4:124–137.
Cameron RS, Rakic P. 1994. Polypeptides that comprise the plasmalemal microdomain between migrating neuronal and glial cells. J Neurosci 14:3139–3155.
Carpenter MK, Inokuma MS, Denham J, Mujtaba T, Chiu CP, Rao MS. 2001. Enrichment of neurons and neural precursors from human embryonic stem cells. Exp Neurol 172:383–397.
Catalano SM, Shatz CJ. 1998. Activity-dependent cortical target selection by thalamic axons. Science 281:6556–6562.
Caviness VS Jr, Goto T, Tarui T, Takahashi T, Bhide PG, Nowakowski RS. 2003. Cell output, cell cycle duration and neuronal specification: a model of integrated mechanisms of the neocortical proliferative process. Cereb Cortex 13:592–598.
Caviness VS Jr, Rakic P. 1978. Mechanisms of cortical development: a view from mutations in mice. Ann Rev Neurosci l:297–326.
Chanas-Sacre G, Rogister B, Moonen G, Leprince P. 2000. Radial glia phenotype: origin, regulation, and transdifferentiation. J Neurosci Res 61:357–363.
Chenn A, Walsh CA. 2003. Increased neuronal production, enlarged forebrains and cytoarchitectural distortions in beta-catenin over-expressing transgenic mice. Cereb Cortex 13:599–606.
Chun JM, Shatz CJ. 1989. Interstitial cells of the adult neocortical white matter are the remnant of the early-generated subplate neuron population. J Comp Neurol 282:555–569.
Choi BH. 1986. Glial fibrillary acid protein in radial glia of early human fetal cerebrum: A light and electron microscopic immunocytochemical study. J Neuropath Exp Neurol 45:408–418.
Cobos I, Long JE, Thwin MT, John L Rubenstein JL. 2006. Cellular patterns of transcription factor expression in developing cortical interneurons. Cereb Cortex 16(Suppl 1):i82–i88.
deAzevedo LC, Fallet C, Moura-Neto V, Daumas-Duport C, Hedin-Pereira C, Lent R. 2003. Cortical radial glial cells in human fetuses: depth-correlated transformation into astrocytes. J Neurobiol 55: 288–298.
De Carlos JA, Lœpez-Mascaraque L, Valverde F. 1996 Dynamics of cell migration from the lateral ganglionic eminence in the rat. J Neurosci 16:6146–6156.
De Carlos JA, O'Leary DDM. 1992. Growth and targeting of subplate axons and establishment of major cortical pathways. J Neurosci 12:1194–1211.
Denaxa M, Chan CH, Schachner M, Parnavelas JG, Karagogeos D. 2001. The adhesion molecule TAG-1 mediates the migration of cortical interneurons from the ganglionic eminence along the corticofugal fiber system. Development 128:4635–4644.
des Portes V, Pinard JM, Billuart P, Vinet MC, Koulakoff A, Carrie A, Gelot A, Dupuis E, Motte J, Berwald-Netter Y, Catala M, Kahn A, Beldjord C, Chelly J. 1988. A novel CNS gene required for neuronal migration and involved in X-linked subcortical laminar heterotopia and lissencephaly syndrome. Cell 92:51–61.
Farrant M, Feldmeyer D, Takahashi T, Cull-Candy SG. 1994. NMDA-receptor channel diversity in the developing cerebellum. Nature 368:335–339.
Feng YY, Walsh CA. 2004. The many faces of filamin: a versatile molecular scaffold for cell motility and signaling. Nat Cell Biol 6:1034–1038.
Fishell G, Hatten ME. 1991. Astrotactin provides a receptor system for CNS neuronal migration. Development 113:755–765.
Fishell G, Kriegstein AR. 2003. Neurons from radial glia: the consequences of asymmetric inheritance. Curr Opin Neurobiol 13:34–41.
Gadisseux JF, Evrard P. 1985. Glial-neuronal relationship in the developing central nervous system. Dev Neurosci 7:12–32.
Gaiano N, Fishell G. 2002. The role of notch in promoting glial and neural stem cell fates. Annu Rev Neurosci 25:471–490.
Gal JS, Morozov YM, Ayoub AE, Chatterjee M, Rakic P, Haydar TF. 2006. Molecular and morphological heterogeneity of neural precursors in the mouse neocortical proliferative zones. J Neurosci 26:1045–1056.
Ghosh A, Shatz CJ. 1993. A role for subplate neurons in the patterning of connections from thalamus to neocortex. Development 117:1031–1047.
Gleeson JG, Walsh CA. 2000. Neuronal migration disorders: from genetic diseases to developmental mechanisms. Trends Neurosci 23:352–359.
Goffinet AM, Rakic P. 2000. Mouse brain development. Berlin, New York: Springer-Verlag. 339 p.
Goldman-Rakic PS. 1987. Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In: Plum F, Editor. Handbook of physiology, the nervous system, higher functions of the brain. Section I, Volume V, Part 1. Bethesda, MD: Am Physiol Soc. p 373–417.
Goldman-Rakic PS, Rakic P. 1984. Experimental modification of gyral patterns. In: Geschwind N, Galaburda AM, editors. Cerebral dominance: the biological foundation. Cambridge, MA: Harvard University Press. p 179–192.
Golgi C. 1874. Sulla fina anatomia del cervelleto umano. Opera Omnia. Milan, Italy: Hoepli.
Gongidi V, Ring C, Rakic P, Anton ES. 2004. Sparc-like 1 is a radial glia-associated terminator of neuronal migration in cerebral cortex. Neuron 41:57–69.
Gotz M, Huttner WB. 2005. The cell biology of neurogenesis. Nat Rev Mol Cell Biol 6:777–788.
Grove EA, Fukuchi-Shimogori T. 2003. Generating the cerebral cortical area map. Annu Rev Neurosci 26:355–380.
Hartfuss E, Galli R, Heins N, Gotz M. 2001. Characterization of CNS precursor subtypes and radial glia. Dev Biol 229:15–30.
Hatakeyama J, Kageyama R. 2006. Notch1 expression is spatiotemporally correlated with neurogenesis and negatively regulated by Notch1-independent Hes genes in the developing nervous system. Cereb Cortex 16(Suppl 1):i132–i137.
Hatanaka Y, Hisanaga SI, Heizmann CW, Murakami F. 2004. Distinct migratory behavior of early- and late-born neurons derived from the cortical ventricular zone. J Comp Neurol 479:1–14.
Hatten ME. 1985. Neuronal regulation of astroglial morphology and proliferation in vitro. J Cell Biol 100:384–396.
Hatten ME. 2002. New directions in neuronal migration. Science 297:1660–1663.
Hatten ME, Mason CA. 1990. Mechanism of glial-guided neuronal migration in vitro and in vivo. Experientia 46:907–916.
Haydar TF, Ang ESBC Jr, Rakic P. 2003. Mitotic spindle rotation and mode of cell division in the developing telencephalon. Proc Natl Acad Sci USA 100:2890–2895.
Haydar TF, Kuan C-Y, Flavell RA, Rakic P. 1999. The Role of cell death in regulating the size and shape of the mammalian forebrain. Cereb Cortex 9:621–626.
Heins N, Malatesta P, Cecconi F, Nakafuku M, Tucker KL, Hack MA, Chapouton P, Barde YA, Gotz M. 2002. Glial cells generate neurons: the role of the transcription factor Pax6. Nat Neurosci 5:308–315.
Hinds JW, Ruffett TL. 1971. Cell proliferation in the neural tube: an electron microscopic and Golgi analysis in the mouse cerebral vesicle. Z Zellforsch 115:226–264.
Hirai K, Yoshioka H, Kihara M, Hasegawa K, Sakamoto T, Sawada T, Fushiki S. 1999. Inhibition of neuronal migration by blocking NMDA receptors in the embryonic rat cerebral cortex: a tissue culture study. Dev Brain Res 114:63–67.
His W. 1874. Unserer Koperform und das Physiologishe Problem inrer Enstehung. Leipzig, Germany: Engelman. 176 p.
His W. 1904. Die Entwicklung des Monschlichen Gehirns Wahrend der Ersten Monate. Leipzigd: Hirzel.
Jimenez D, Lopez-Mascaraque L, de Carlos JA, Valverde F. 2002. Further studies on cortical tangential migration in wild type and Pax-6 mutant mice. J Neurocytol 31:719–728.
Jones EG. 1997. Cortical development and thalamic pathology in schizophrenia. Schizophr Bull 23:483–501.
Kadhim HJ, Gadisseux J-F, Evrard P. 1988. Topographical and cytological evolution of the glial phase during prenatal development of the

human brain: histochemical and electron microscopic study. J Neuropathol Exp Neurol 47:166–188.
Kanold PO, Kara P, Reid RC, Shatz JC. 2003. Role of subplate neurons in functional maturation of visual cortical columns. Science 301:521–525.
Kirschenbaum B, Nedergaard M, Preuss A, Barami K, Fraser RA, Goldman SA. 1994. In-vitro neuronal production and differentiation by precursor cells derived from the adult human forebrain. Cereb Cortex 4:576–589.
Koelliker AV. 1879. Entwicklungsgeschichte des Menschen und der höheren Tiere. Engelmann Leibzig, Germany. 418 p.
Kokaia Z, Thored P, Arvidsson A, Lindvall O. 2006. Regulation of stroke-induced neurogenesis in adult brain—recent scientific progress. Cereb Cortex 16(Suppl 1):i162–i167.
Koketsu D, Mikami A, Miyamoto Y, Hisatsune T. 2003. Nonrenewal of neurons in the cerebral neocortex of adult Macaque monkeys. J Neurosci 23:937–942.
Komuro H, Rakic P. 1993. Modulation of neuronal migration by NMDA receptors. Science 260:95–97.
Kornack DR, Rakic P. 1995. Radial and horizontal deployment of clonally related cells in the primate neocortex: relationship to distinct mitotic lineages. Neuron 15:311–321.
Kornack DR, Rakic P. 1999. Continuation of neurogenesis in the hippocampus of the adult macaque monkey. Proc Natl Acad Sci USA 96:5768–5773.
Kornack DR, Rakic P. 2001a. The generation, migration and differentiation of olfactory neurons in adult primate brain. Proc Natl Acad Sci USA 98:4752–4757.
Kornack DR, Rakic P. 2001b. Cell proliferation without neurogenesis in the adult primate neocortex. Science 294:2127–2130.
Korr H, Schmitz C. 1999. Facts and fictions regarding post-natal neurogenesis in the developing human cerebral cortex. J Theor Biol 200:291–297.
Kostovic I, Rakic P 1984. Development of prestriate visual projections in the monkey and human fetal cerebrum revealed by transient acetylcholinesterase staining. J Neurosci 4:25–42.
Kostovic I, Goldman-Rakic PS. 1983. Transient cholinesterase staining in the mediodorsal nucleus of the thalamus and its connections in the developing human and monkey brain. J Comp Neurol 219: 431–447.
Kostovic I, Molliver ME. 1974. New interpretation of laminar development of cerebral cortex. Synaptogenesis in different layers of neopallium in human fetus. Anat Rec 178:395.
Kostovic I, Rakic P. 1980. Cytology and time of origin of interstitial neurons in the white matter in infant and adult human and monkey telencephalon. J Neurocytol 9:219–242.
Kostovic I, Rakic P 1984. Development of prestriate visual projections in the monkey and human fetal cerebrum revealed by transient acetylcholinesterase staining. J Neurosci 4:25–42.
Kostovic I, Rakic P. 1990. Developmental history of the transient subplate zone in the visual and somatosensory cortex of the macaque monkey and human brain. J Comp Neurol 297:441–470.
Kriegstein AR, Noctor SC. 2004. Patterns of neuronal migration in the embryonic cortex. Trends Neurosci 27:392–399.
Kuida K, Zheng TS, Na S, Kuang C-Y, Yang D, Karasuyama H, Rakic P, Flavell RA. 1996. Decreased apoptosis in the brain and premature lethality in CPP32-deficient mice. Nature 384:368–372.
Lavdas AA, Grigoriou M, Pachnis V, Parnavelas JG. 1999. The medial ganglionic eminence gives rise to a population of early neurons in the developing cerebral cortex. J Neurosci 19:7881–7888.
Laywell ED, Rakic P, Kukekov VG, Holland EC, Steindler D. 2000. A identification of a multipotent astrocytic stem cell in the immature and adult mouse brain. Proc Natl Acad Sci USA 97:13883–13888.
Letinic K, Rakic P. 2001. Telencephalic origin of human thalamic GABAergic neurons. Nat Neurosci 4:931–936.
Letinic K, Zoncu R, Rakic P. 2002. Origin of GABAegic neurons in the human neocortex. Nature 417:645–649.
Levitt P, Cooper ML, Rakic P. 1981. Coexistence of neuronal and glial precursor cells in the cerebral ventricular zone of the fetal monkey: an ultrastructural immunoperoxidase analysis. J Neurosci l:27–39.
Levitt P, Cooper ML, Rakic P. 1983. Early divergence and changing proportions of neuronal and glial precursor cells in the primate cerebral ventricular zone. Dev Biol 96:472–484.
Levitt P, Rakic P. 1980. Immunoperoxidase localization of glial fibrillary acid protein in radial glial cells and astrocytes of the developing rhesus monkey brain. Comp Neurol l93:8l5–840.
Lewis DA. 2000. GABAergic local circuit neurons and prefrontal cortical dysfunction in schizophrenia. Brain Res Rev 31:270–276.
Lewis PD. 1968. Mitotic activity in the primate subependymal layer and the genesis of the gliomas. Nature 217:974–975.
Lillien L, Gulacsi A. 2006. Environmental signals elicit multiple responses in dorsal telencephalic progenitors by threshold-dependent mechanisms. Cereb Cortex 16(Suppl 1):i74–i81.
Lois C, Alvarez-Buylla A. 1993. Proliferating subventricular zone cells in the adult mammalian forebrain can differentiate into neurons and glia. Proc Natl Acad Sci USA 90:2074–2077.
Lois C, Alvarez-Buylla A. 1994. Long-distance neuronal migration in the adult mammalian brain. Science 264:1145–1148.
Lukaszewicz A, Savatier P, Cortay V, Giroud P, Huissoud C, Berland M, Kennedy H, Dehay C. 2005. G1 phase regulation, area-specific cell cycle control, and cytoarchitectonics in the primate cortex. Neuron 47:353–364.
Luskin MB, Shatz CJ. 1985. Neurogenesis of the cat's primary visual cortex. J Comp Neurol 242:611–631.
Magini G. 1888. Sur la nevroglie et les cellules nerveuses cerebrales chez les foetus. Arch Ital Biol 9:59–60.
Malatesta P, Hack MA, Hartfuss E, Kettenmann H, Klinkert W, Kirchhoff F, Gotz M. 2003. Neuronal or glial progeny: regional differences in radial glia fate. Neuron 37:751–764.
Marin O, Rubenstein JL. 2001. A long, remarkable journey: tangential migration in the telencephalon. Nat Rev Neurosci 2:780–790.
Marin O, Rubenstein JL. 2003. Cell migration in the forebrain. Annu Rev Neurosci 26:441–483.
Martinez-Cerdeño V, Noctor SC, Kriegstein AR. 2006. The role of intermediate progenitor cells in the evolutionary expansion of the cerebral cortex. Cereb Cortex 16(Suppl 1):i152–i161.
McCarthy M, Turnbull DH, Walsh CA, Fishell G. 2001. Telencephalic neural progenitors appear to be restricted to regional and glial fates before the onset of neurogenesis. J Neurosci 21:6772–6781.
McConnell SK. 1988. Fates of visual cortical neurons in the ferret after isochronic and heterochronic transplantation. J Neurosci 8:945–974.
McConnell SK, Ghosh A, Shatz CJ. 1994. Subplate pioneers and the formation of descending connections from cerebral cortex. J Neurosci 14:1892–1907.
McDemott KWG, Lantos PL. 1990. Cell proliferation in the subependymal layer of the postnatal marmoset, Callithrix jacchus. Dev Brain Res 57:269–277.
Menezes JRL, Luskin MB. 1994. Expression of neuron-specific tubulin defines a novel population in the proliferative layers of the developing telencephalon. J Neurosci 14:5399–5416.
Misson J-P, Austin CP, Takahashi T, Cepko CL, Caviness VS. 1991. The alignment of migrating neural cells in relation to the murine neopallial radial glial fiber system. Cereb Cortex 1:221–229.
Misson J-P, Edwards MA, Yamamoto M, Caviness VS. 1988. Mitotic cycling of radial glial cells of the fetal murine cerebral wall: a combined autoradiographic and immunohistochemical study. Dev Brain Res 38:183–190.
Mountcastle VB. 1997. The columnar organization of the neocortex. Brain 12:701–722.
Nadarajah B, Alifragis P, Wang ROL, Parnavelas JG. 2003. Neuronal migration in the developing cerebral cortex: observations based on real-time imaging. Cereb Cortex 13:607–611.
Nadarajah B, Brunstrom JE, Grutzendler J, Wong RO, Pearlman AL. 2001. Two modes of radial migration in early development of the cerebral cortex. Nat Neurosci 4:143–150.
Noctor SC, Martinez-Cerdeno V, Ivic L, Kriegstein AR. 2004. Cortical neurons arise in symmetric and asymmetric division zones and migrate through specific phases. Nat Neurosci 7:136–144.
Noctor SC, Flint AC, Weissman TA, Dammerman RS, Kriegstein AR. 2001. Neurons derived from radial glial cells establish radial units in neocortex. Nature 409:714–720.

Noctor SC, Flint AC, Weissman TA, Wong WS, Clinton BK, Kriegstein AR. 2002. Dividing precursor cells of the embryonic cortical ventricular zone have morphological and molecular characteristics of radial glia. J Neurosci 22:3161–3173.
Ogawa M, Miyata T, Nakajima K, Yagyu K, Seike M, Ikenaka K, Yamamoto H, Mikoshiba K. 1995. The reeler gene-associated antigen on cajal-retzius neurons is a crucial molecule for laminar organization of cortical-neurons. Neuron 14:899–912.
O'Leary DDM, Borngasser D. 2006. Cortical ventricular zone progenitors and their progeny maintain spatial relationships and radial patterning during preplate development indicating an early protomap. Cereb Cortex 16(Suppl 1):i46–i56.
O'Rourke NA, Dailey ME, Smith SJ, McConnell SK. 1992. Diverse migratory pathways in the developing cerebral cortex. Science 258:299–302.
Parnavelas JG, Barfield JA, Franke E, Luskin MB. 1991. Separate progenitor cells give rise to pyramidal and nonpyramidal neurons in the rat telencephalon. Cereb Cortex 1:463–491.
Poliakov GI. 1965. Development of the cerebral neocortex during first half of intrauterine life. In: Sarkisov SA, editor. Development of the child's brain. Leningrad, USSR: Medicina. p 22–52 [in Russian].
Polleux F, Whitford KL, Dijkhuizen PA, Vitalis T, Ghosh A. 2002. Control of cortical interneuron migration by neurotrophins and PI3-kinase signaling. Development 129:3147–3160.
Rakic P. 1971. Neuron-glia relationship during granule cell migration in developing cerebellar cortex. A Golgi and electronmicroscopic study in Macacus rhesus. J Comp Neurol 141:283–312.
Rakic P. 1972. Mode of cell migration to the superficial layers of fetal monkey neocortex. J Comp Neurol 145:61–84.
Rakic P. 1974a. Neurons in the monkey visual cortex: systematic relation between time of origin and eventual disposition. Science 183:425–427.
Rakic P. 1974b. Embryonic development of the LP-pulvinar complex in man. In: Cooper IS, Riklan M, Rakic P, editors. LP-pulvinar complex. Springfield, IL: Charles C. Thomas. p 3–25.
Rakic P. 1975. Timing of major ontogenetic events in the visual cortex of the rhesus monkey. In: Buchwald NA, Brazier M, editors. Brain mechanisms in mental retardation. New York: Academic Press. p 3–40.
Rakic P. 1976. Differences in the time of origin and in eventual distribution of neurons in areas 17 and 18 of the visual cortex in the rhesus monkey. Exp Brain Res 1(Suppl):244–248.
Rakic P. 1977. Prenatal development of the visual system in the rhesus monkey. Philos Trans R Soc Lond B 278:245–260.
Rakic P. 1978. Neuronal migration and contact guidance in primate telencephalon. Postgrad Med J 54:25–40.
Rakic P. 1981. Neuronal-glial interaction during brain development. Trends Neurosci 4:184–187.
Rakic P. 1985. Limits of neurogenesis in primates. Science 227:154–156.
Rakic P. 1988a. Specification of cerebral cortical areas. Science 241:170–176.
Rakic P. 1988b. Defects of neuronal migration and pathogenesis of cortical malformations. Prog Brain Res 73:15–37.
Rakic P. 1990. Principles of neuronal cell migration. Experientia 46:882–891.
Rakic P. 1995. A small step for the cell—a giant leap for mankind: a hypothesis of neocortical expansion during evolution. Trends Neurosci 18:383–388.
Rakic P. 2002a. Pre and post-developmental neurogenesis in primates. Clin Neurosci Res 2:29–39.
Rakic P. 2002b. Neurogenesis in adult primate neocortex: an evaluation of the evidence. Nat Rev Neurosci 3:650–671.
Rakic P. 2003. Elusive radial glial cells: historical and evolutionary perspective. Glia 43:19–32.
Rakic P, Cameron RS, Komuro H. 1994. Recognition, adhesion, transmembrane signaling, and cell motility in guided neuronal migration. Curr Opin Neurobiol 4:63–69.
Rakic P, Caviness VS, Jr. 1995. Cortical development: View from neurological mutants two decades later. Neuron, 14:1101–1104.
Rakic P, Knyihar-Csillik E, Csillik B. 1996. Polarity of microtubule assembly during neuronal migration. Proc Natl Acad Sci USA 93:9218–9222.
Rakic P, Sidman RL. 1968. Supravital DNA synthesis in the developing human and mouse brain. J Neuropathol Exp Neurol 27:246–276.
Rakic P, Sidman RL. 1969. Telencephalic origin of pulvinar neurons in the fetal human brain. Z Anat Entwicklungsgesch 129:53–82.
Rakic P, Stensaas LJ, Sayre EP. 1974. Computer-aided three-dimensional reconstruction and quantitative analysis of cells from serial electronmicroscopic montages of fetal monkey brain. Nature 250:31–34.
Rakic P, Suner I, Williams RW. 1991. A novel cytoarchitectonic area induced experimentally within the primate visual cortex. Proc Natl Acad Sci USA 88:2083–2087.
Ramon y Cajal S. 1881. Sur la structure de l'ecorce cerebrale de quelques mammiferes. La Cellule 7:125–176.
Ramón y Cajal S. 1909. Histologie du Système Nerveux de l'Homme et des Vertébrés. Vol. 1, Paris: A. Maloine (Reprinted in 1952 by Consejo Superior de Investigaciones Cientificas, Instituto Ramón y Cajal, Madrid).
Rasin M-R, Gazula V-R, Breunig JJ, Kwan KY, Li H-S, Liu-Chen S, Jan LY, Jan YN, Rakic P, Sestan N. 2006. Numb and numblike regulate the basolateral membrane localization of E-cadherin and neural stem cell polarity in the cerebral proliferative zones. Cell. Forthcoming.
Retzius G. 1893. Studien uber ependym und neuroglia. In: Biol Untersuch. Volume 5. Stockholm, NS. p 9–26.
Rio C, Rieff HI, Qi PM, Corfas G. 1997. Neuregulin and erbB receptors play a critical role in neuronal migration. Neuron 19:39–50.
Rivas RJ, Hatten MB. 1995. Motility and cytoskeletal organization of migrating cerebellar granule neurons. J Neurosci 15:981–989.
Rubenstein JLR, Rakic P. 1999. Genetic control of cortical development. Cereb Cortex 9:521–523.
Sanai N, Tramontin AD, Quinones-Hinojosa A, Barbaro NM, Gupta N, Kunwar S, Lawton MT, McDermott MW, Parsa AT, Manuel-Garcia Verdugo J, Berger MS, Alvarez-Buylla A. 2004. Unique astrocyte ribbon in adult human brain contains neural stem cells but lacks chain migration. Nature 427:740–744.
Sarkisian MR, Bartley CM, Chi H, Nakamura F, Flavell RA, Rakic P. 2006. MEKK4 deficiency results in dysregulated filamin expression and impaired neuronal migration. Forthcoming.
Schaar BT, McConnell SK. 2005. Cytoskeletal coordination during neuronal migration. Proc Natl Acad Sci USA 102:13652–13657.
Schmechel DE, Rakic P. 1979a. A Golgi study of radial glial cells in developing monkey telencephalon: morphogenesis and transformation into astrocytes. Anat Embryol 156:115–152.
Schmechel DE, Rakic P. 1979b. Arrested proliferation of radial glial cells during midgestation in rhesus monkey. Nature 227:303–305.
Schmid RS, Anton ES. 2003. Role of integrins in the development of the cerebral cortex. Cereb Cortex 13:219–224.
Sidman RL, Rakic P. 1973. Neuronal migration with special reference to developing human brain: a review. Brain Res 62:1–35.
Sidman RL, Rakic P. 1982. Development of the human central nervous system. In: Haymaker W, Adams RD, editors. Histology and histopathology of the nervous system. Springfield, IL: Charles C Thomas. p 3–145.
Smart IHM, Dehay C, Giroud P, Berland M, Kennedy H. 2002. Unique morphological features of the proliferative zones and postmitotic compartments of the neural epithelium giving rise to striate and extrastriate cortex in the monkey. Cereb Cortex 12:37–53.
Spalding KL, Bhardwaj RD, Buchholz BA, Druid H, Frisén J. 2005. Retrospective birth dating of cells in humans. Cell 122:133–143.
Stefanowska M. 1898. Evolutioin des cellules nerveuses corticales chez la souris apres la naissance. Trav Lab Physiol Invest Solvay 2:1–44.
Stensaas LJ, Stensaas SS. 1968. An electron microscope study of cells in the matrix and intermediate laminae of the cerebral hemisphere of the 45 mm rabbit embryo. Z Zellforsch 91:341–365.
Suslov ON, Kukekov VG, Ignatova TN, Steindler DA. 2002. Neural stem cell heterogeneity demonstrated by molecular phenotyping of clonal neurospheres. Proc Natl Acad Sci USA 99:14506–14511.
Tamamaki N, Nakamura K, Okamoto K, Kaneko T. 2001. Radial glia is a progenitor of neocortical neurons in the developing cerebral cortex. Neurosci Res 41:51–60.
Tan SS, Breen S. 1993. Radial mosaicism and tangential cell dispersion both contribute to mouse neocortical development. Nature 362:638–640.

Tan SS, Kalloniatis M, Sturm K, Tam PPL, Reese BE, Faulkner-Jones B. 1998. Separate progenitors for radial and tangential cell dispersion during development of the cerebral neocortex. Neuron 21:295–304.

Tanaka D, Nakaya Y, Yanagawa Y, Obata K, Murakami F. 2003. Multimodal tangential migration of neocortical GABAergic neurons independent of GPI-anchored proteins. Development 130:5803–5813.

Temple S. 2001. The development of neural stem cells. Nature 414:112–117.

Tilney F. 1923. The form and funtions of the central nervous system. New York: Hober. 1019 p.

Tissir F, Goffinet AM. 2003. Reelin and brain development. Nat Rev Neuroscience 4:496–505.

Tramontin AD, Garcia-Verdugo J, Lim DA, Alvarez-Buylla A. 2003. Postnatal development of radial glia and the ventricular zone (VZ): a continuum of the neural stem cell compartment. Cereb Cortex 13:580–587.

Vignal W. 1888. Recherches sur le developpement des elements des couches corticales du cerveau et du cervelet chez l'homme et les mammiferes. Arch Physiol Norm Pathol 2:228–254.

Weissman T, Noctor SC, Clinton BK, Honig LS, Kriegstein AR. 2003. Neurogenetic radial glial cells in reptile, rodent and human; from mitosis to migration. Cereb Cortex 13:550–559.

Wichterle H, Turnbull DH, Nery S, Fishell G, Alvarez-Buylla A. 2001. In utero fate mapping reveals distinct migratory pathways and fates of neurons born in the mammalian basal forebrain. Development 128:3759–3771.

Wu W, Wong K, Chen JH, Jiang ZH, Dupuls S, Wu JY, Rao Y. 1999. Directional guidance of neuronal migration in the olfactory system by the protein Slit. Nature 400:331–336.

Wynshaw-Boris A, Gambello MJ. 2001. LIS1 and dynein motor function in neuronal migration and development. Genes Dev 15:639–651.

Xie Z, Samuels BA, Tsai L-H. 2006. Cyclin-dependent kinase 5 permits efficient cytoskeletal remodeling—a hypothesis on neuronal migration. Cereb Cortex 16(Suppl 1):i64–i68.

Zecevic N. 2004. Specific characteristic of radial glia in the human fetal telencephalon. Glia 48:27–35.

Zecevic N, Rakic P. 2001. Development of layer I neurons in the primate cerebral cortex. J Neurosci 21:5607–5619.