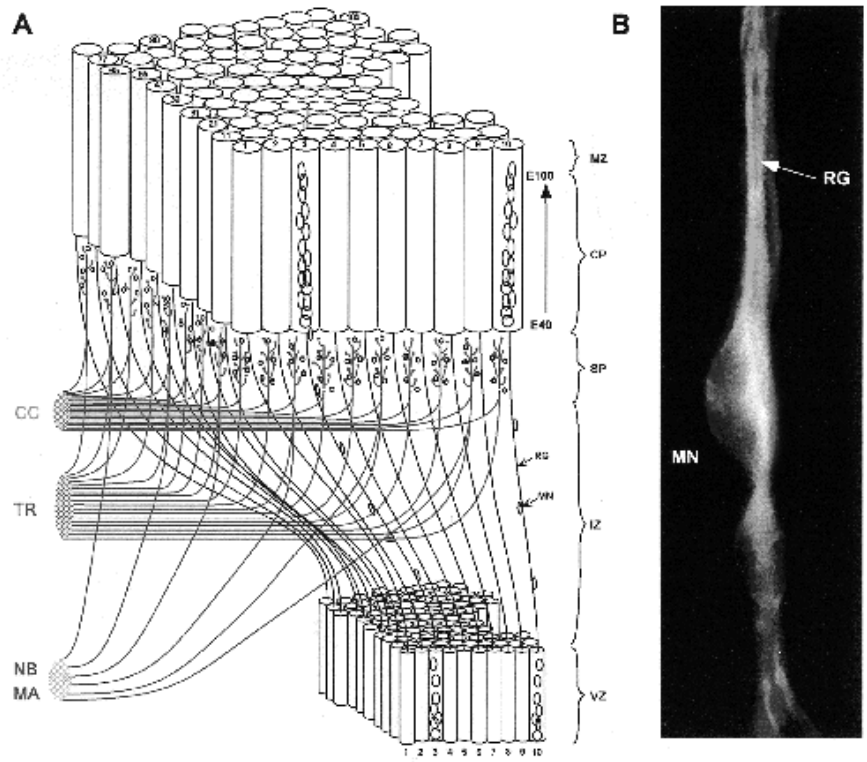
Images in Neuroscience

Carol A. Tamminga, M.D., Editor

Brain Development, VI



On the left is a three-dimensional reconstruction of the basic developmental events including migration of neurons (MN) to the cerebral cortex along surface of radial glial fibers (RG). The figure emphasizes the radial glial guided mode of neuronal migration that underlies its elaborate columnar organization in primates (e.g., see V.B. Mountcastle, *Brain* 1997; 120:701–722). The cohorts of neurons generated in the proliferative ventricular zone (VZ) traverse the intermediate zone (IZ) and subplate zone (SP) containing "waiting" afferents from several sources—corticocortical bundles (CC), thalamic radiation (TR), nucleus basalis (NB), and monoamine centers (MA)—and finally pass through the earlier generated deep layers before settling in at the interface between developing cortical place (CP) and marginal zone (MZ). The relation between a cell's position in a proliferative ventricular zone and its position within the subplate zone and cortical place is preserved during cortical expansion by transient radial glial scaffolding (for details, see P. Rakic, *Science* 1988; 241:170–171). On the right is a fluorescence image of migrating cortical neuron (green, labeled with neuron-specific antibody) that is attached to the process of embryonic radial glial cell (red, labeled with glia-specific antibody) by junctional molecules that provide bonds between two of them (purple, labeled with specific antibody; described in E.S. Anton et al., *Journal of Neuroscience* 1996; 16:2283–2293). The recognition and adhesion molecules are essential for guidance of neurons to the appropriate layers of the cerebral cortex.

Radial Migration and Cortical Evolution

Normal cortical development underlies normal human cognition and behavior. Thus, understanding the mechanisms of cortical development is essential for getting insight into the pathogenesis of inherited brain disorders. One remarkable feature is that neurons that constitute cerebral cortex are not generated in the cortex itself; rather, they migrate from the site of their origin to proper laminar and areal positions. In primates, including humans, cortical neurons are generated during the first half of gestation in the ventricular zone of the developing brain near the surface of the cerebral ventricle. In addition to cortical neuronal progenitors, this region contains a population of elongated radial glial cells whose projections span the entire cortical thickness. These cells are attached to the ventricular surface by their end feet and have radial processes that protrude toward the pial surface, spanning the cortical width. These radial processes form the scaffolding for neuronal movement into cortex

and exist only transiently, during this phase of cortical formation. The cerebral cortex is built below the cerebral surface by migration of neurons that are produced at the margin of the cerebral ventricle. Successively generated neurons migrate along the radial glia guides and settle in an inside-to-outside order within the developing cortex. Each successively generated neuron must bypass predecessors that migrated along the same glial fiber, before ultimately settling at the outermost level of the cortical plate. The neurons become arranged radially in stacks—named ontogenic columns. A column consists of cells that originate from several clones but share the same birthplace, migrate along the common pathway, and settle within the same ontogenic column. There are many complex and multifaceted processes necessary for initiation of this neuronal migration, for pathfinding along the way, for locomotion itself, and, finally, for the appointment of neuronal position within cortex. Within the ventricular zone, before neuronogenesis, two broad phases of cellular division can be distinguished: 1) a stage of symmetric cell division in which two daughter cells are generated from each progenitor cell, producing founder cells for the prospective cerebral cortex; and 2) a stage of asymmetric cell division in which one permanent postmitotic neuron is generated, producing neuronal precursors of ontogenic columns through continuous asymmetric divisions. The duration of phase 1 determines the number of radial units in the cortex of a given species and, indirectly, the size of the cortical surface. The duration of phase 2 determines the number of neurons in each ontogenic column and, hence, cortical thickness. The expansion in the surface of the neocortex in primates could be attributed to a change in the genetic mechanisms that control 1) the timing or mode of cell division, or both; and 2) the switch between the two phases during cerebral development. Thus, a small mutation in a regulatory gene (or genes) for these developmental functions might have played a significant role in the evolution of neocortical size.

PASKO RAKIC, M.D., SC.D.
New Haven, Conn.

Address reprint requests to Dr. Tamminga, Maryland Psychiatric Research Center, University of Maryland, P.O. Box 21247, Baltimore, MD 21228. *Figure adapted from P. Rakic: A Small Step for the Cell, a Giant Leap for Mankind. Trends in Neuroscience 1995; 18:383–388.*