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# "THE DEVELOPMENTAL AND FUNCTIONAL LOGIC OF NEURONAL CIRCUITS": COMMENTARY ON THE KAVLI PRIZE IN NEUROSCIENCE

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**Abstract—The first Kavli Prize in Neuroscience recognizes a confluence of career achievements that together provide a fundamental understanding of how brain and spinal cord circuits are assembled during development and function in the adult. The members of the Kavli Neuroscience Prize Committee have decided to reward three scientists (Sten Grillner, Thomas Jessell, and Pasko Rakic) jointly "for discoveries on the developmental and functional logic of neuronal circuits".**

**Pasko Rakic performed groundbreaking studies of the developing cerebral cortex, including the discovery of how radial glia guide the neuronal migration that establishes cortical layers and for the radial unit hypothesis and its implications for cortical connectivity and evolution.**

**Thomas Jessell discovered molecular principles governing the specification and patterning of different neuron types and the development of their synaptic interconnection into sensorimotor circuits.**

**Sten Grillner elucidated principles of network organization in the vertebrate locomotor central pattern generator, along with its command systems and sensory and higher order control.**

**The discoveries of Rakic, Jessell and Grillner provide a framework for how neurons obtain their identities and ultimate locations, establish appropriate connections with each other, and how the resultant neuronal networks operate. Their work has significantly advanced our understanding of brain development and function and created new opportunities for the treatment of neurological disorders. Each has pioneered an important area of neuroscience research and left a legacy of exceptional scientific achievement, insight, communication, mentoring and leadership.** 

Key words: Grillner S, Jessell TM, Rakic P, cerebral cortex, cortical layers, radial glia, radial unit hypothesis, neuronal migration, connectivity, evolution, spinal cord, sensorimotor circuits, molecular specification of neurons, locomotor, central pattern generator, network organization, brain anatomy, human, monkey, primate, histogenesis, tritiated thymidine, neurogenesis, spatiotemporal map, last mitotic division, neuronal identity, "migration disorders", ocular dominance columns, cytoarchitectonic, ependyma, proliferative unit, prot-map, neuronal progenitors, substance P, sensory transmitters, sensory neurons, pain, opiates, capsaicin, acetylcholine receptors, recognition molecules, embryonic development, hybridoma, monoclonal antibodies, epitopes, surface molecules, molecular markers, commissural interneurons, chemotropic, floor plate, axonal pathfinding, nerve fiber trajectories, notochord, signaling gradient, nuclear transcription factors, dorsoventral patterning, motoneuron pools, anteroposterior patterning, retionoic acid, hox genes, motoneuron diseases, amyotrophic lateral sclerosis, adhesion molecules, sensorimotor reflex circuits, sonic hedgehog, shh, motor control, muscle spindles, stretch reflex, reticulospinal, vestibulospinal, mammalian, cat, fish, lamprey, supraspinal centers, swimming, locomotion, anatomy, electrophysiology, fictive locomotion, bistable membrane, excitatory aminoacid, NMDA receptors, rhythmicity, computer simulation, laser scanning confocal microscopy, spinal cord injury, striatum, goal-directed behavior, informatics, neuroinformatics, neuromechanical model.

Pasko Rakic received his MD in 1960 and his PhD in 1969 from the University of Belgrade. During this period he held posts as Clinical and Research Fellow at Harvard Medical School and as Assistant Professor at the University of Belgrade. From the beginning of his research career he was drawn to human brain anatomy and development. Early work while at Harvard focused on the histogenesis of cortical structures in both humans and mice, using among other techniques the labeling of newly synthesized DNA with tritiated thymidine to determine the birthdates of neurons. Rakic continued to use this technique to study the timing of neuron production, particularly in the monkey, publishing a long list of papers that has provided a spatiotemporal map of neurogenesis throughout much of the primate brain. Many of these seminal studies remain to this day principle reference works for researchers studying the development of specific brain, and especially cortical, areas. Noting that neurons occupying different cortical layers are generated during sequential epochs of proliferation, Rakic proposed that a neuron's eventual physical destination and phenotype are specified at the time of its last mitotic division (Rakic, 1974), thereby launching efforts to understand the role of intrinsic determinants of neuronal identity which continue to this day.

In 1971, now an Assistant Professor at Harvard, Rakic published a seminal paper describing an intimate anatomical relationship between migrating neurons and radial glia in the macaque monkey (Rakic, 1971a,b). Prior to this, the radial glia were enigmatic, with no known function despite their peculiar morphology, stretching from the inner surface to the outer surface of the developing brain. Rakic's work clearly implicated the radial glia as substrates for the radial migration of newly generated neurons (Fig. 1). The mechanism and its functional implications would preoccupy Rakic for many years to come, and attract a substantial number of other researchers to the question of how neurons migrate to their ultimate destinations in the cortex and elsewhere in the brain. Rakic was the first to discover a specific gene whose mutation disrupts neuronal migration (Rakic and Sidman, 1973), and has continued to make seminal contributions in this area, extending to the role of

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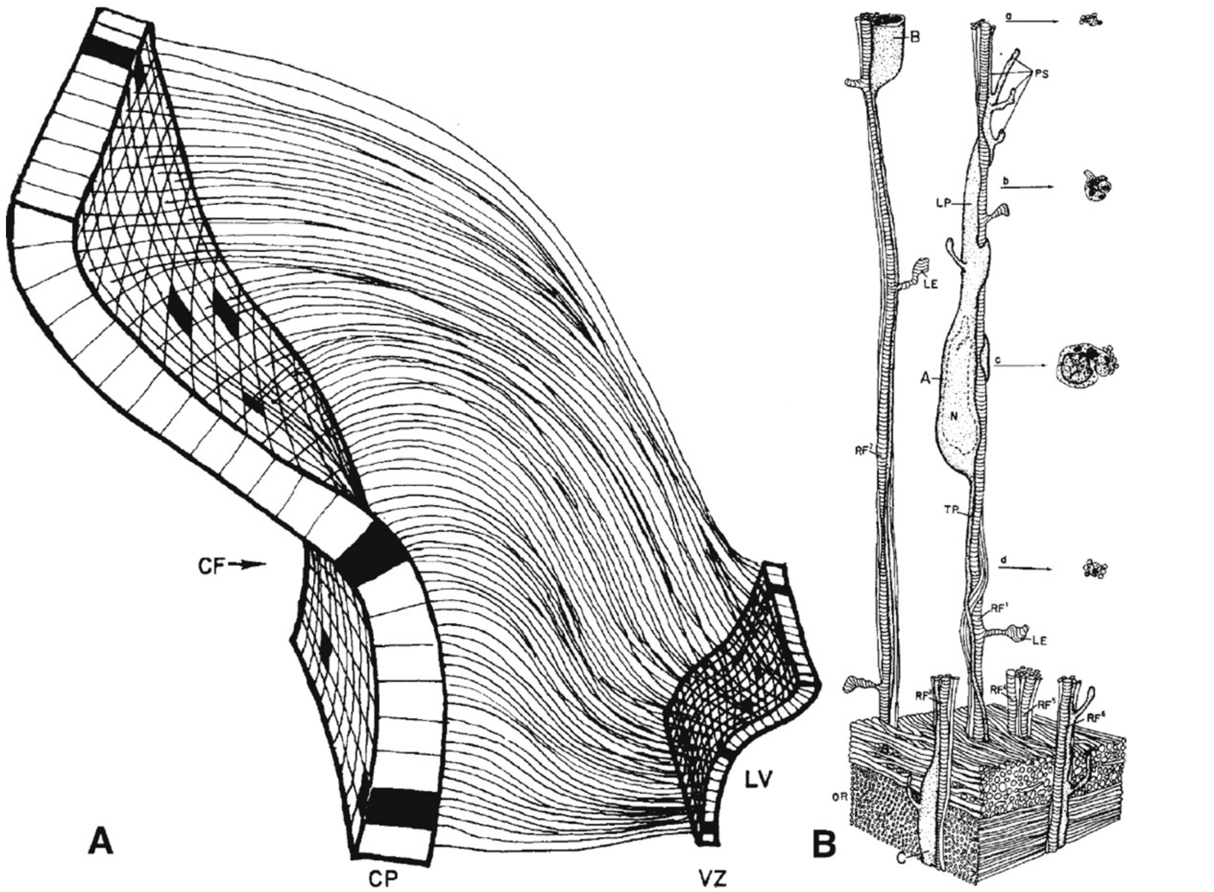


**Fig. 1.** The radial unit hypothesis as depicted by Rakic. Panel A shows the radial migratory pathways that map the inner array of neuronal progenitors (LV) to the mature cortical layers (CP). Panel B shows the intimate relationship between a migrating neuron (N) and a radial glial fiber (RF). From Rakic (2003) Developmental and evolutionary adaptations of cortical radial glia. Cerebral Cortex 13:541–549.

intrinsic and extrinsic molecular factors that influence, regulate, and disrupt the migratory process. His work has in large part established the foundation for current efforts at understanding the etiology of various human brain malformations and disorders that result from disturbances of neuronal migration, now known collectively as "migration disorders".

While working on neurogenesis in the monkey visual cortex, Rakic used his skill at intrauterine surgery to test whether connections in the visual system that subserve the formation of ocular dominance columns form prenatally in primates. Ocular dominance had been studied previously by eventual Nobel Prize winners David Hubel and Torstein Weisel, who had shown that the relevant connections form postnatally in kittens, when visual experience can exercise a pivotal activity-dependent influence. Rakic's finding that the ocular dominance columns in the primate visual cortex form prenatally (Rakic, 1981) argued for an innate contribution to the ocular dominance pattern, a proposal that has since been supported by experiment in other species including the cat, and also set the stage for later work addressing the fundamental role of spontaneous activity in shaping brain circuits, before sensory experience becomes a major factor.

In 1978, Rakic became Professor at Yale University, where he has continued to work since. There he continued to pioneer the study of cortical development, not only regarding neuronal migration per se, but also on how this contributes to the partitioning of cortex into functional areas (Rakic, 1988). His insight into the four-dimensional process of cortical development and its regulation by sensory input led eventually to the formulation of a conceptual framework for corticogenesis, the "radial unit hypothesis" (Fig. 1). In his own words: "According to this hypothesis, the ependymal layer of the embryonic cerebral ventricle consists of proliferative units that provide a proto-map of prospective cytoarchitectonic areas. The output of the proliferative units is translated via glial guides to the expanding cortex in the form of ontogenetic columns, whose final number for each area can be modified through interaction with afferent input". In his seminal review article in 1988 (Rakic, 1988) he integrated findings from numerous studies and methodological approaches to show how these supported the hypothesis. He expanded on this theme to propose that radial units could form the basis for cortical microcircuits, as well as the coinage of the evolutionary expansion in cortical area that has led to ever more complex and sophisticated vertebrate brains (Rakic, 1995;