

Rakic P. 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, 1971.

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This study provided electron microscopic evidence that postmitotic granule neurons are guided by elongated Bergmann glial cells during their migration across the developing cerebellar cortex. This finding has established the role of nonneuronal cells in pathway recognition and has led to the concept of membrane-mediated differential adhesion for guidance of neuronal migration. [The *SCI*® indicates that this paper has been cited in over 315 publications.]

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This was my first electron microscopic study, and I conducted it soon after arriving from Yugoslavia to assume an assistant professorship at Harvard Medical School. At that time, interest in the cerebellar cortex was at a peak among neuroscientists at the quadrangle. Enrico Mugnaini, Sandy Palay, and Dick Sidman were working on the cytology and genetic regulation of this intriguing structure, and there was plenty of exciting discussion and useful advice. I read the book *The Cerebellum as a Neuronal Machine*¹ cover to cover as if it were a thriller.

The question that intrigued me the most was how is this geometrically perfect and yet highly complex neuronal lattice constructed? Since the pioneering work by Ramón y Cajal, the cerebellar cortex was recognized as unique in that its cells arise from two sources situated at opposite surfaces of the neural wall. For example, Purkinje and Golgi II neurons arrive by outward migration from the ventricular surface, whereas postmitotic granule cells turn out to be mavericks among neurons as they originate at the pial surface and then migrate inward. By labeling their DNA with ³H-thymidine, I found that in the rhesus monkey, granule cells have their last mitotic division during the late gestational and early neonatal period. How do postmitotic cells find their way through neural tissue that, at this age, is already densely packed with synapses?

Three-dimensional reconstruction from serial electron micrographs revealed the remarkable morphogenetic transformation and movement of granule cells in relation to the other cellular elements. Most significantly, their leading motile processes were invariably apposed to elongated Bergmann glial fibers. The affinity between these two cell types was implied by the fact that migrating neurons followed a glial fiber while passing by more numerous and often more regular processes of other cells. The selectivity of this attachment indicated the existence of recognition molecules and suggested a guiding role for glial fibers. Since then, this phenomenon has been observed in species ranging from amphibia to man (reviewed in reference 2).

I myself fancy that the key to success for this paper was the semischematic "four-dimensional" diagram of cellular events that I drew for the publication. In addition to space parameters, I introduced the time dimension to reveal the dynamic aspects of a granule cell's morphogenetic transformation during migration. Construction of this diagram from serial electron micrographs, systematically exposing cellular elements of different ages, was not unlike an archeological reconstruction of history by digging through layers of the earth's crust. It allowed my natural inclination towards visual expression. I revised this drawing two years later for another paper,³ and, to my delight, it has been reproduced in numerous textbooks.

I suspect that this paper has been quoted for several reasons: first, it was a clearly documented example of neuronal migration with a tangible cellular explanation. Second, the phenomenon appeared to be ubiquitous in the vertebrate cerebellum.² Third, it led to the discovery that neocortical neurons also use glial guides as a migratory substrate.⁴ Finally, this phenomenon proved to be a useful model for analysis of neuronal migration *in vivo* and *in vitro* at the molecular level.^{5,6} This paper has been quoted more frequently in the last few years, indicating that, with the advent of new techniques, neuronal migration is becoming a subject of more intensive research.

1. Eccles J C, Ito M & Szentágothai J. *The cerebellum as a neuronal machine*. Berlin: Springer-Verlag, 1967. 335 p.
2. Rakic P. Principles of neuronal migration. (Cowan W M. ed.) *Handbook of physiology*. New York: American Physiological Society. (In preparation.)
3. ———. Kinetics of proliferation and latency between final division and onset of differentiation of the cerebellar stellate and basket neurons. *J. Comp. Neurol.* 147:523-46, 1973. (Cited 90 times.)
4. ———. Mode of neuronal migration to the superficial layers of fetal monkey neocortex. *J. Comp. Neurol.* 145:61-84, 1972. (Cited 240 times.)
5. Hatten M E & Mason C A. Neuron-astroglia interaction *in vitro* and *in vivo*. *Trends Neurosci.* 9:168-74, 1986.
6. Lindner J, Zinsler G, Werz W, Goridis C, Bizzini B & Schachner M. Experimental modification of postnatal cerebellar granule cell migration *in vitro*. *Brain Res.* 377:298-304, 1986.