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Neuronal migration and the evolution of the human brain

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Abstract

A new study demonstrating a pathway for neuronal migration in humans, but not in monkeys, suggests that migration has a key role in the evolution of the brain, as well as its development.

Neurons are natural migrants; most, if not all, of the neurons in the mammalian nervous system migrate from their places of birth to their locations of function. In the brain, neurons usually originate in the ventricular zone, where their precursor cells proliferate. They can then migrate radially to other layers in the brain, or tangentially (in a direction parallel to the surface of the brain) to other regions of the brain^{1–3}. Radial migration is dependent on radially aligned glial fibers, whereas tangential migration is independent of glial cells and perhaps relies on contacts with other neurons. Although radial migration was the focus of research in the 1970s and 1980s, tangential migration was suggested in the 1960s and, through work in the 1990s, has now been established as a major mode of neuronal migration. Neuronal migration is a crucial step in neural development, as defects in neuronal migration cause multiple human diseases.

Similar to other fields of experimental biology, our knowledge of neuronal migration is based primarily on experiments with brains of laboratory animals. Because developmental mechanisms are widely conserved across species ranging from flies and worms to humans, there has not been much effort devoted to experimental studies of neuronal migration in the human brain. However, a series of studies carried out by Pasko Rakic and colleagues, culminating in the paper published in this issue, show that certain important questions about the human brain can only be addressed by studying live tissue from the human brain (in this case, human brain slices from aborted fetuses)⁴. This study extends earlier suggestions, based on histological analysis of fixed human brains, that neuronal precursor cells migrate from a structure in the telencephalon, the ganglionic eminence (GE), to the thalamus in the diencephalon⁵. By comparing neuronal migration in humans with those in mice and monkeys, Rakic and colleagues demonstrate that the human brain may possess migratory pathways that do not exist in other mammals, or perhaps even in other primates.

Human thalamic nuclei connected to the frontal cortex are larger than those in other primates⁶. For example, the pulvinar nucleus in the dorsal thalamus (DT) is larger in primates than in other mammals and, among primates, is larger in humans than in chimpanzees and macaque monkeys. In previous work, Rakic and Sidman asked whether the larger pulvinar nucleus results from increased cell proliferation in the ventricular zone of the diencephalon. They found that there are two phases of pulvinar development in humans⁵. Whereas the early phase correlates with cell proliferation in the diencephalon, the late phase does not; cell proliferation in the diencephalon was not detected from the eighteenth to the thirty-fourth week of gestation, which is the major period of human pulvinar growth. This suggests that cells contributing to the late phase of pulvinar growth are not likely to be derived from the ventricular zone of the diencephalon⁵. During the late phase, the ganglionic eminence (GE), contains proliferative cells, and streams of cells extend from the GE to the thalamus. Cells in these

streams are bipolar in the tangential direction, which suggests that they are migrating. Rakic and Sidman thus proposed that cells from the GE migrate through these streams to the thalamus in the human brain⁵. The positioning of the streams, their transient nature, and the direction of the leading and trailing processes of cells in the streams are consistent with the possibility that these streams were migratory pathways. However, there was no direct evidence that cells actually migrate from the GE to the thalamus.

In similar studies, Ogren and Rakic found in macaque monkeys that only the early phase of pulvinar development occurs, and that the pulvinar nucleus does not receive contributions of neurons from the telencephalon⁷. These findings led to the suggestion that neuronal migration from the GE to the pulvinar nucleus might be unique to humans⁷.

In the work reported in this issue, Letinic and Rakic report the first direct evidence that neurons indeed migrate from the GE to the DT in human brain slices⁴. They placed the lipophilic dye DiI in the GE and found labeled cells in the DT, including the pulvinar and mediodorsal nuclei⁴. These neurons seem to be migrating in a fashion similar to other types of tangential migration described in the olfactory system⁸, as they seem to be independent of glial fibers, but instead rely on contacts with other neurons. Furthermore, the migrating neurons contain GABA, the major inhibitory neurotransmitter in the brain. Taken together with earlier studies of GABAergic neuronal migration from the GE to the neocortex^{9,10}, the new results in human tissue indicate that the GE contributes to GABAergic neurons in multiple regions of the brain.

Using similar techniques, Letinic and Rakic did not detect cell migration from the GE to the DT in the monkey or the mouse brains⁴. Because earlier work on human brains⁵ was done at times and under conditions different from the work on the mouse or the monkey brains⁷, the present study provides the strongest evidence that the GE to DT migratory pathway is apparent only in the human brain.

Previous studies in rodents showed that regions surrounding the migrating neurons in the GE can influence migration¹⁰. To address the question of what contributes to the difference in neuronal migration between human and mouse brains, Letinic and Rakic isolated explants of human and mouse GE and co-cultured them with either the DT or the subthalamus (ST), which is part of the path from the GE to the DT⁴. Human GE cells were attracted by human DT, whereas mouse GE cells were neither attracted nor repelled by the mouse DT (Fig. 1). ST was repulsive in the mouse explants, but neither repulsive nor attractive in the human explants. The repulsive and attractive activities are contact-independent, indicating that they are diffusible guidance cues. These results suggest that guidance cues in the DT and the ST could explain the presence of the GE to DT pathway in the human, and its absence in the mouse.

The Letinic and Rakic paper thus provides not only direct evidence for a new migratory pathway in the human brain, but also suggests possible cellular mechanisms that may underlie the differential migration of GE cells in humans and other species. It also raises a number of questions. For example, is the species difference in GE to DT migration due solely to changes in the positioning of the guidance cues, or to changes in cellular responsiveness in the GE cells? It will be interesting to see results from cross-species co-cultures of the GE with the DT and the ST, which may provide a more definite answer to the question of whether changes in GE responsiveness are involved in the species differences in GE to DT migration. It will also be interesting to characterize the molecular identities of the repulsive and attractive guidance cues in the ST and the DT. Two secreted proteins, Slit and netrin, can repel rodent GE neurons^{11, 12}. Their patterns of expression remain to be characterized in monkey and human brains, as well as in relevant regions of the mouse thalamus. Because a guidance cue can act as both a repellent and an attractant¹³, it is also possible that the same cues may function differently in the GE to DT pathway of different species.

One of the most interesting suggestions from the work of Rakic and colleagues is that new neuronal migration pathways may be involved in brain evolution. During the evolution of the mammalian brain, regions connected to each other anatomically and functionally are thought to co-evolve¹⁴, but mechanisms for co-evolution are not known. Results from Rakic and colleagues suggest a novel and specific mechanism for co-evolution of brain structures. Thus, the GE to DT pathway may enable the co-evolution of the frontal cortex and the thalamic nuclei that are connected to it. There are perhaps multiple migration pathways from the GE to thalamic regions¹⁵, and it will be interesting to know whether all of those pathways correlate with the evolution of the neocortex and the thalamus.

Evidence obtained so far indicates that the evolution of a new migratory pathway could, in principle, contribute to the presence of more neurons in the human thalamus. The significance of these pathways *in vivo* could be tested if these pathways could be experimentally manipulated in slices of mouse, monkey and human brains after the identification of distinct guidance cues. Perhaps studies of human patients with genetic defects disrupting a specific migratory pathway(s) may help answer the question of whether a migratory pathway leads to the evolution of a larger thalamus in humans.

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Fig 1.

Guidance activities involved in the GE–DT pathway. Schematic coronal sections of mouse and human brains at the level of the thalamus. +, attractive activity for cells from the GE; –, repulsive activity. GE, ganglionic eminence; DT, dorsal thalamus; ST, subthalamus; CP, choroid plexus.