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Birthday Matters for Wiring-Up the Brain's Vision Centers

Researchers at the University of California, San Diego School of Medicine have evidence suggesting that neurons in the developing brains of mice are guided by a simple but elegant birth order rule that allows them to find and form their proper connections.

The study is published online July 31 in *Cell Reports*.

"Nothing about brain wiring is haphazard," said senior author Andrew Huberman, PhD, assistant professor in the Department of Neurosciences, Division of Biological Sciences and Department of Ophthalmology, UC San Diego.

A mature, healthy brain has billions of precisely interconnected neurons. Yet the brain starts with just one neuron that divides and divides – up to 250,000 new neurons per minute at times during early development. The question for biologists has been how do these neurons decide which other neurons to connect to, a process neuroscientists call target selection.

The answer has both fundamental scientific value and clinical relevance. Some researchers believe that autism and other disorders linked to brain development may be caused, in part, by a failure of neurons to properly reposition their axons as needed when mistakes in target selection occur.

To better understand how a young brain gets wired, researchers focused on the development of retinal ganglion cells (RGCs) in mice. These cells connect the eyes and brain. Specifically, the main cell bodies of RGCs reside in the retina but their axons – slender projections along which electrical impulses travel – extend into the centers of the brain that process visual information and give rise to what we commonly think of as "sight," as well as other light-influenced physiological processes, such as the effect of light on mood.

For the study, scientists tagged RGCs and watched where they directed their axons during development. The experiments revealed that specific types of RGCs target specific areas of the brain, allowing mice to do things such as sense direction of motion, move their eyes and detect

changes in daily light cycles. It was also observed that some types of RGCs (such as those that detect brightness and control pupil constriction) are created early in development while others (such as those controlling eye movements) are created later.

The study's main finding is that early RGCs (those created early in the sequence of brain division) make a lot of connections to other neurons and a lot of mistakes, which they then correct by repositioning or removing their axons. By contrast, later RGCs were observed to be highly accurate in their target selection skills and made almost no errors.

"The neurons are paying attention to when they were born and reading out which choices they should make based on their birthdate," said Jessica Osterhout, a doctoral student in biology and the study's lead author. "It seems to all boil down to birthdate."

The idea that timing is important for cell differentiation is a classic principle of developmental biology, but this study is among the first to show that the timing of neuronal generation is linked to how neurons achieve specific brain wiring.

In addition to clarifying normal brain development, researchers plan to examine the role of time-dependent wiring mishaps in models of human disorders, such as autism and schizophrenia, as well as diseases specific to the visual system, such as congenital blindness.

"We want to know if in diseases such as autism neurons are made out of order and as a result get confused about which connections to make," Huberman said.

Co-authors include Rana El-Danaf and Phong Nguyen, both at UC San Diego.

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