Medical Xpress

New study uncovers how brain cells form precise circuits before experience is able to shape wiring

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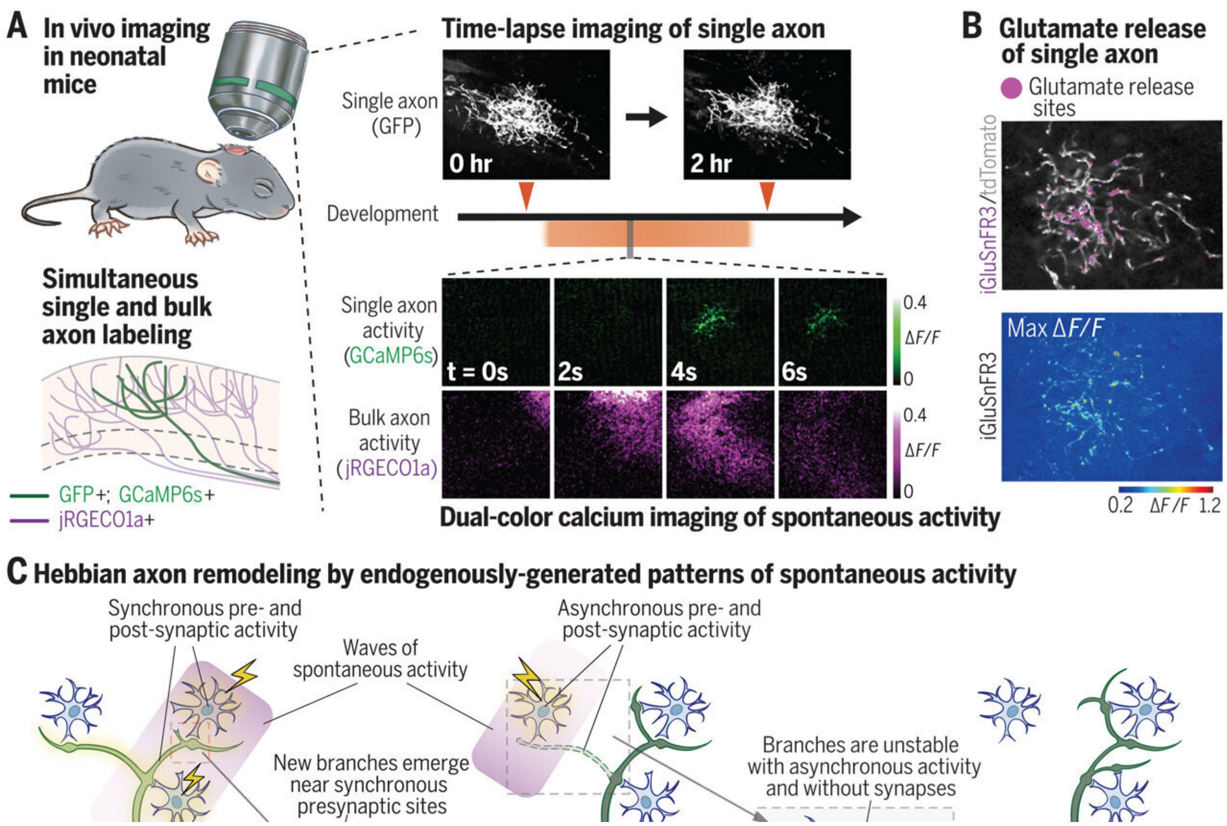

Hebbian axon remodeling. (**A**) Schematic of simultaneous in vivo time-lapse imaging of a single–RGC axon arbor and dual-color calcium imaging of spontaneous activity in the axon and neighboring axons in awake mice. (**B**) In vivo imaging of GRSs in a single axon. (**C**) Schematic of Hebbian axon remodeling mediated by spatiotemporal patterns of spontaneous activity. ΔF/F, fractional change in fluorescence; iGluSnFR3, fluorescent glutamate indicator;

tdTomato, red fluorescent protein. Credit: *Science* (2024). DOI: 10.1126/science.adh7814

In humans, the process of learning is driven by different groups of cells in the brain firing together. For instance, when the neurons associated with the process of recognizing a dog begin to fire in a coordinated manner in response to the cells that encode the features of a dog—four legs, fur, a tail, etc.—a young child will eventually be able to identify dogs going forward. But brain wiring begins before humans are born, before they have experiences or senses like sight to guide this cellular circuitry. How does that happen?

In a new study published in *Science*, Yale researchers have identified how brain cells begin to coalesce into this wired network in early development before experience has a chance to shape the brain. It turns out that very early development follows the same rules as later development—cells that fire together wire together. But rather than experience being the driving force, it's spontaneous cellular activity.

"One of the fundamental questions we are pursuing is how the brain gets wired during development," said Michael Crair, co-senior author of the study and the William Ziegler III Professor of Neuroscience at Yale School of Medicine. "What are the rules and mechanisms that govern brain wiring? These findings help answer that question."

For the study, researchers focused on mouse retinal ganglion cells, which project from the retina to a region of the brain called the superior colliculus where they connect to downstream target neurons.

The researchers simultaneously measured the activity of a single retinal ganglion cell, the anatomical changes that occurred in that cell during development, and the activity of surrounding cells in awake neonatal mice whose eyes had not yet opened. This technically complex experiment was made possible by advanced microscopy techniques and fluorescent proteins that indicate cell activity and anatomical changes.

Previous research has shown that before sensory experience can take place—for instance, when humans are in the womb, or in the days before young mice open their eyes—spontaneously generated neuronal activity correlates and forms waves.

In the new study, researchers found that when the activity of a single retinal ganglion cell was highly synchronized with waves of spontaneous activity in surrounding cells, the single cell's axon—the part of the cell that connects to other cells—grew new branches. When the activity was poorly synchronized, axon branches were instead eliminated.

"That tells us that when these cells fire together, associations are strengthened," said Liang Liang, co-senior author of the study and an assistant professor of neuroscience at Yale School of Medicine. "The branching of axons allows more connections to be made between the retinal ganglion cell and the neurons sharing the synchronized activity in the superior colliculus circuit."

This finding follows what's known as "Hebb's rule," an idea put forward by psychologist Donald Hebb in 1949. At that time, Hebb proposed that when one cell repeatedly causes another cell to fire, the connections between the two are strengthened.

"Hebb's rule is applied quite a lot in psychology to explain the brain basis of learning," said Crair, who is also the vice provost for research and a professor of ophthalmology and visual science. "Here we show that it also applies during early brain development with subcellular precision."

In the new study, the researchers were also able to determine where on the cell branch formation was most likely to occur, a pattern that was disrupted when the researchers disturbed synchronization between the cell and the spontaneous waves.

Spontaneous activity occurs during development in several other neural circuits, including in the spinal cord, hippocampus, and cochlea. While the specific pattern of cellular activity would be different in each of those areas, similar rules may govern how cellular wiring takes place in those circuits, said Crair.

Going forward, the researchers will explore whether these patterns of axon branching persist after a mouse's eyes open and what happens to the downstream connected neuron when a new axon branch forms.

"The Crair and Liang labs will continue to combine our expertise in brain development and single-cell imaging to examine how the assembly and refinement of brain circuits is guided by precise patterns of neural activity at different developmental stages," said Liang.

More information: Naoyuki Matsumoto et al, Hebbian instruction of axonal connectivity by endogenous correlated spontaneous activity, *Science* (2024). DOI: 10.1126/science.adh7814

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