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Researchers 'reprogram' network of brain cells in mice with thin beam of light

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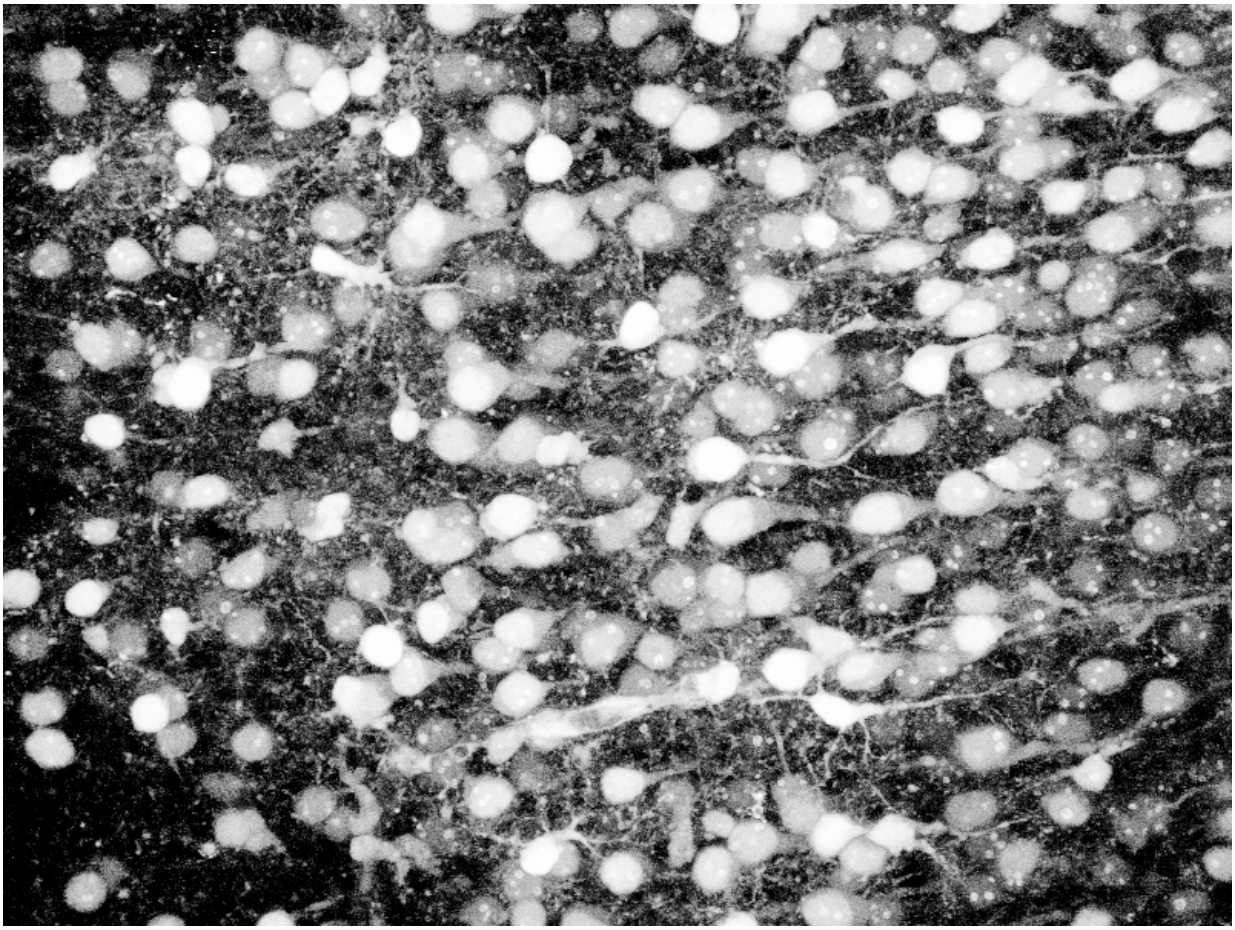

In this photo of living mouse neurons, calcium imaging techniques record the firing of individual neurons and their pulses of electricity. Credit: Yuste Laboratory/Columbia University

Neurons that fire together really do wire together, says a new study in *Science*, suggesting that the three-pound computer in our heads may be more malleable than we think.

In the latest issue of *Science*, neuroscientists at Columbia University demonstrate that a set of neurons trained to fire in unison could be reactivated as much as a day later if just one neuron in the network was stimulated. Though further research is needed, their findings suggest that groups of activated neurons may form the basic building blocks of learning and memory, as originally hypothesized by psychologist Donald Hebb in the 1940s.

"I always thought the brain was mostly hard-wired," said the study's senior author, Dr. Rafael Yuste, a neuroscience professor at Columbia University. "But then I saw the results and said 'Holy moly, this whole thing is plastic.' We're dealing with a plastic computer that's constantly learning and changing."

The researchers were able to control and observe the brain of a living mouse using the optogenetic tools that have revolutionized neuroscience in the last decade. They injected the mouse with a virus containing light-sensitive proteins engineered to reach specific brain cells. Once inside a cell, the proteins allowed researchers to remotely activate the neuron with light, as if switching on a TV.

The mouse was allowed to run freely on a treadmill while its head was held still under a microscope. With one laser, the researchers beamed light through its skull to stimulate a small group of cells in the visual cortex. With a second laser, they recorded rising levels of calcium in each neuron as it fired, thus imaging the activity of individual cells.

Before optogenetics, scientists had to open the skull and implant electrodes into living tissue to stimulate neurons with electricity and

measure their response. Even a mouse brain of 100 million neurons, nearly a thousandth the size of ours, was too dense to get a close look at groups of neurons.

Optogenetics allowed researchers to get inside the brain non-invasively and control it far more precisely. In the last decade, researchers have restored sight and hearing to blind and deaf mice, and turned normal mice aggressive, all by manipulating specific brain regions.

The breakthrough that allowed researchers to reprogram a cluster of cells in the brain is the culmination of more than a decade of work. With tissue samples from the mouse visual cortex, Yuste and his colleagues showed in a 2003 study in Nature that neurons coordinated their firing in small networks called neural ensembles. A year later, they demonstrated that the ensembles fired off in sequential patterns through time.

As techniques for controlling and observing cells in living animals improved, they learned that these neural ensembles are active even without stimulation. They used this information to develop mathematical algorithms for finding neural ensembles in the visual cortex. They were then able to show, as they had in the tissue samples earlier, that neural ensembles in living animals also fire one after the other in sequential patterns.

The current study in *Science* shows that these networks can be artificially implanted and replayed, says Yuste, much as the scent of a tea-soaked madeleine takes novelist Marcel Proust back to his memories of childhood.

Pairing two-photon stimulation technology with two-photon calcium imaging allowed the researchers to document how individual cells responded to light stimulation. Though previous studies have targeted and recorded individual cells none have demonstrated that a bundle of

neurons could be fired off together to imprint what they call a "neuronal microcircuit" in a live animal's brain.

"If you told me a year ago we could stimulate 20 neurons in a mouse brain of 100 million neurons and alter their behavior, I'd say no way," said Yuste, who is also a member of the Data Science Institute. "It's like reconfiguring three grains of sand at the beach."

The researchers think that the network of activated neurons they artificially created may have implanted an image completely unfamiliar to the mouse. They are now developing a behavioral study to try and prove this.

"We think that these methods to read and write activity into the living brain will have a major impact in neuroscience and medicine," said the study's lead author, Luis Carrillo-Reid, a postdoctoral researcher at Columbia.

Dr. Daniel Javitt, a psychiatry professor at Columbia University Medical Center who was not involved in the study, says the work could potentially be used to restore normal connection patterns in the brains of people with epilepsy and other brain disorders. Major technical hurdles, however, would need to be overcome before optogenetic techniques could be applied to humans.

The research is part of a $300 million brain-mapping effort called the U.S. BRAIN Initiative, which grew out of an earlier proposal by Yuste and his colleagues to develop tools for mapping the brain activity of fruit flies to more complex mammals, including humans.

More information: science.sciencemag.org/cgi/doi … 1126/science.aaf7560

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