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Upending Decades of Dogma, Brain Cells in Mice That Create Mental Maps Are More Connected Than Previously Thought

New techniques for monitoring small groups of brain cells in mice challenge a tenet of how neurons work together to form memories

NEW YORK, December 01, 2021

For the first time, scientists have looked at how the very smallest clusters of cells used to perform computations in the brains of mice record a memory of a place. Unexpectedly, the researchers discovered overlooked connections between cells important for forming new memories, adding a new twist to decades of dogma about how mental maps of the world are created.

Led by postdoctoral researcher Tristan Geiller, PhD, in the Losonczy lab at Columbia's Zuckerman Institute, the new study appeared Dec. 1 in *Nature*. The new connections revealed in the study could help to explain how a change in the activity of one cell percolates through the brain.

"Our new discovery about how cells in the brains of mice communicate to create memories is a step toward figuring out how our own brains form memories," said Attila Losonczy, MD, PhD, a principal investigator at Columbia's Zuckerman Institute. "With a better understanding of the fundamentals of how memories are formed, you can start wondering about treatments in conditions associated with memory problems."

Intimate Conversations Between Brain Cells

When scientists investigate how the brain works, they normally do so either on the level of single cells or on the scale of regions consisting of enormous amounts of cells communicating across the brain. Until recently, much remained unknown about the level in-between, circuits made of just a small group of brain cells linked together in intimate, small-scale conversations.

Technical challenges have made it difficult to study such small groups of cells. This new project brought together a team to overcome these challenges, including experts in cellular and molecular biology from the Polleux lab at Columbia's Zuckerman Institute; computational neuroscientists from the lab of Claudia Clopath, PhD, at the Imperial College London; Balázs Rózsa, PhD, an expert in optical imaging at the Institute of Experimental Medicine in Budapest; and Andrew Murray, PhD, who studies neural circuits at the Sainsbury Wellcome Centre at University College London.

"Studying these circuits is exciting because they are the smallest units with which computations are performed in the brain," Dr. Geiller said. “We still have so much to learn about them." Previous work examined such circuits in a relatively easily accessible surface portion of the brain, the visual cortex, which handles vision. In the new study, the researchers investigated these circuits in a more deeply buried region, the hippocampus, which is the brain's memory center.

Connecting to Place Cells

The researchers focused on place cells, which encode memories of locations.
"Scientists have known for decades that individual place cells respond to specific locations, helping the brain create maps of the environment,” said Dr. Geiller. “But little has been known about how the cells talk to other cells to perform the mental computations that encode these memories of a location in a place cell."

The scientists developed new techniques to not only record the activity of single place cells in mice, but that of all the neurons linked with those cells: including excitatory neurons that activate other brain cells and inhibitory cells, known as interneurons, that suppress other cells.

Interneurons often put the brakes on place cells. But Dr. Geiller and his colleagues noticed that when a place cell first started firing in response to a location, the interneurons linked to it stopped inhibiting it. This took the brakes off, allowing the place cell to become attuned to a location.

An Exciting Finding For Excitatory Cells

Dr. Geiller also generated an artificial place cell in the rodents’ brains by using light to stimulate a cell in the hippocampus when the animal visited a specific location. The act of creating this memory of a location caused excitatory cells connected to the place cells to perk up and communicate with each other.

This was completely unexpected. Decades of research had suggested that in the part of the hippocampus where memories of places are encoded, CA1, the excitatory cells don't talk to each other; they only talk to inhibitory cells.

"One of our most striking findings is that excitatory cells here are connected, overwriting what's been dogma," said Dr. Losonczy, who is also a professor of neuroscience at Columbia's Vagelos College of Physicians and Surgeons. "These interconnected excitatory cells talking to their siblings allow a single place cell to trigger a massive reconfiguration of the circuit."
The reconfiguration revealed in this research might help the brain strengthen its memory when it comes to important locations, from food sites for animals living in the wild to coffee shops for humans living in cities. When one cell becomes active, the brain may recruit other cells to keep it active. The Losonczy lab plans to explore how these newly discovered networks of connections are formed in future research.

"One possibility is these interconnected cells are born together during various times in brain development — say, on the same day — and stay wired together, to fire together," Dr. Losonczy said. "This could be a very intriguing model of how memory circuits are structured during development."

A better understanding of how memories are created in the brain could one day help lead to ways to overcome the degradation or loss of memories. "Surgical interventions aiming at restoring memories can be less invasive and more controlled," Dr. Geiller said. "If we can pinpoint which neurons encode a certain memory, activation of one of these said neurons with light or targeted stimulations can hopefully be sufficient to trigger the recall of a past experience."

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This paper, "Local circuit amplification of spatial selectivity in the hippocampus," appeared on Dec. 1 in *Nature*. The work was supported by the National Institutes of Health grants T32GN007367, 1S10OD023587-01; National Institute of Mental Health grants 1R01MH124047, 1R01MH124867, F30MH125628, F31MH117892; the National Institute of Neurological Disorders and Stroke grants 1U19NS104590, 1U01NS115530, R01NS067557, R21NS109753-442 01A1, K99NS115984-01; and the Kavli Foundation, the Gatsby Charitable Foundation and Wellcome Trust. The authors declare no competing interests.

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