Brain cells activated, reactivated in learning and memory

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(Medical Xpress)—Memories are made of this, the song says. Now neuroscientists have for the first time shown individual mouse brain cells being switched on during learning and later reactivated during memory recall. The results are published Dec. 13 in the journal *Current Biology*.

We store episodic memories about events in our lives in a part of a brain called the hippocampus, said Brian Wiltgen, now an assistant professor at the Center for Neuroscience and Department of Psychology at the University of California, Davis. (Most of the work was conducted while Wiltgen was working at the University of Virginia.) In animals, the hippocampus is important for navigation and storing memories about places.

"The exciting part is that we are now in a position to answer a fundamental question about memory," Wiltgen said. "It's been assumed for a long time that the hippocampus is essential for memory because it drives reactivation of neurons (nerve cells) in the cortex. The reason you can remember an event from your life is because the hippocampus is able to recreate the pattern of cortical activity that was there at the time."

According to this model, patients with damage to the hippocampus lose their memories because they can't recreate the activity in the cortex from when the memory was made. Wiltgen's mouse experiment makes it possible to test this model for the first time.

"We can now do a nice test of hippocampal function," Wiltgen said.

Current thinking is that learning activates a group of neurons that undergo changes, making new connections with each other to store the memory. Retrieving the memory reactivates the network.

Researchers working with human subjects, at UC Davis and elsewhere, use imaging techniques such as functional magnetic resonance imaging to see which areas of the brain are switched on and off in learning and retrieval. But fMRI cannot pick out an object as small as a single cell.

Wiltgen and University of Virginia graduate student Kaycie Tayler used a genetically modified mouse that carries a gene for a modified green fluorescent protein. When nerve cells in the mouse are activated, they produce a long-lived green fluorescence that persists for weeks, as well as a short-lived red fluorescence that decays in a few hours.

However, the whole system can be suppressed by dosing the mouse with the antibiotic doxycycline, so Tayler and Wiltgen could manipulate the point at which they started tagging activated cells.

The mice were put into a new cage with an unfamiliar odor and given a few minutes to explore. Then they were given a mild electrical shock through the cage floor. When returned to the cage a couple of days later, the mice would remember the shock and stay frozen in one place.

When they examined the brains of the mice, the researchers could see which cells had been activated initially to form the memory and which were reactivated later to recall it.

About 40 percent of the cells in the hippocampus that were tagged during initial memory formation were reactivated, Wiltgen said. There was also reactivation of cells in parts of the brain cortex associated with place learning and in the amygdala, which is important for emotional memory.

There was no evidence of reactivation when the mice were tested in a new environment that they did not remember, Wiltgen said.

The researchers also looked at whether reactivation changed as memories got older. Over several weeks, reactivation in the cortex and parts of the hippocampus remained stable, but it decreased in other brain regions like the amygdala.

In future work, Wiltgen's team plans to examine the role of the hippocampus and other brain regions in forming memories and explore new ways to activate or block memories.

Other authors of the paper are Kazumasa Tanaka at the University of Virginia and Leon Reijmers at Tufts University School of Medicine. The work was supported by the McKnight Foundation, the National Science Foundation and the Nakajima Foundation.

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