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Manipulating memory with light

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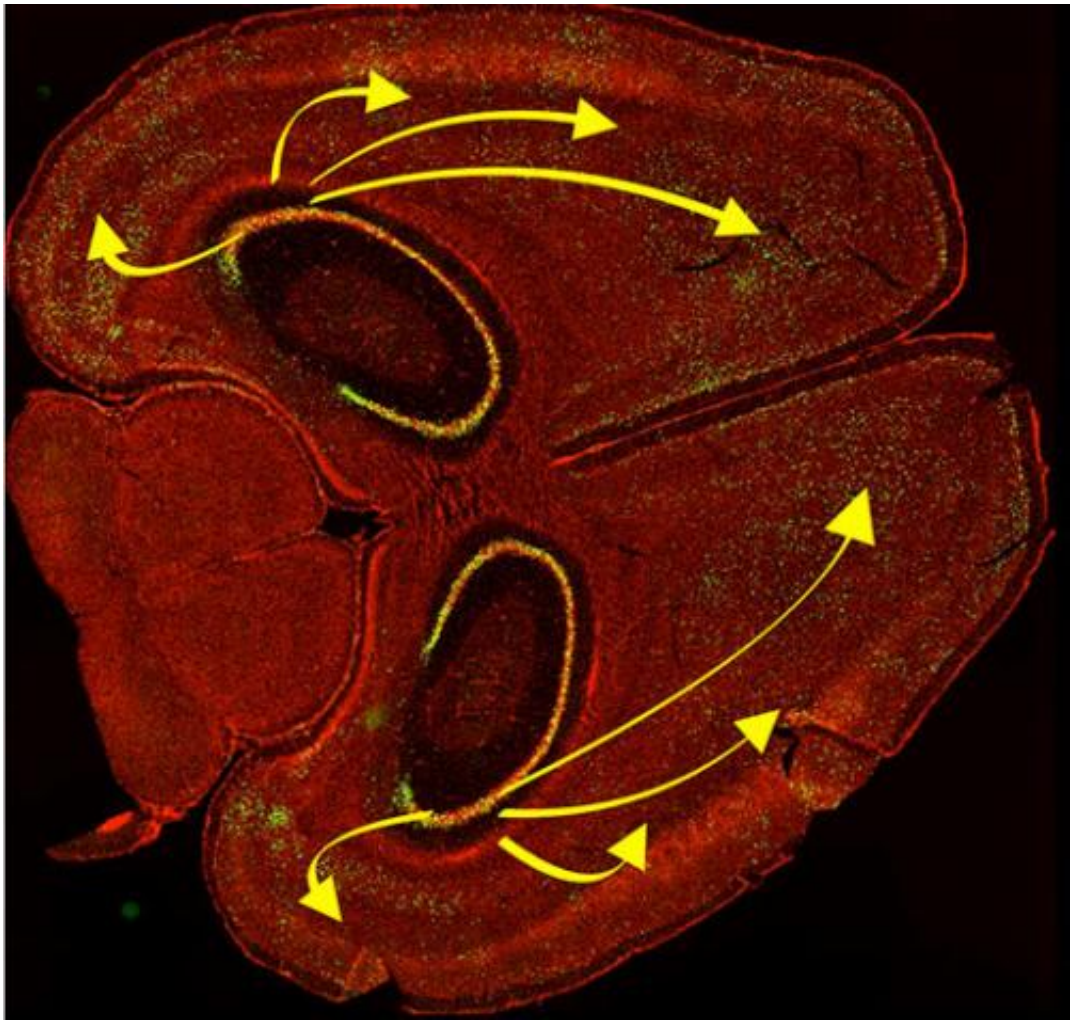

During memory retrieval, cells in the hippocampus (C-shape structures) connect to cells in the brain cortex. Activated cells in this mouse brain fluoresce green. The hippocampus helps the cells in the cortex recreate the pattern of activation from when the memory was formed, so the memory is retrieved. Credit: Kazumasa Tanaka/Brian Wiltgen, UC Davis

Just look into the light: not quite, but researchers at the UC Davis Center for Neuroscience and Department of Psychology have used light to erase specific memories in mice, and proved a basic theory of how different parts of the brain work together to retrieve episodic memories.

Optogenetics, pioneered by Karl Diesseroth at Stanford University, is a new technique for manipulating and studying nerve cells using light. The techniques of optogenetics are rapidly becoming the standard method for investigating brain function.

Kazumasa Tanaka, Brian Wiltgen and colleagues at UC Davis applied the technique to test a long-standing idea about memory retrieval. For about 40 years, Wiltgen said, neuroscientists have theorized that retrieving episodic memories—memories about specific places and events—involves coordinated activity between the cerebral cortex and the hippocampus, a small structure deep in the brain.

"The theory is that learning involves processing in the cortex, and the hippocampus reproduces this pattern of activity during retrieval, allowing you to re-experience the event," Wiltgen said. If the hippocampus is damaged, patients can lose decades of memories.

But this model has been difficult to test directly, until the arrival of optogenetics.

Wiltgen and Tanaka used mice genetically modified so that when nerve cells are activated, they both fluoresce green and express a protein that allows the cells to be switched off by light. They were therefore able both to follow exactly which nerve cells in the cortex and hippocampus were activated in learning and memory retrieval, and switch them off with light directed through a fiber-optic cable.

They trained the mice by placing them in a cage where they got a mild

electric shock. Normally, mice placed in a new environment will nose around and explore. But when placed in a cage where they have previously received a shock, they freeze in place in a "fear response."

Tanaka and Wiltgen first showed that they could label the cells involved in learning and demonstrate that they were reactivated during memory recall. Then they were able to switch off the specific nerve cells in the hippocampus, and show that the mice lost their memories of the unpleasant event. They were also able to show that turning off other cells in the hippocampus did not affect retrieval of that memory, and to follow fibers from the hippocampus to specific cells in the cortex.

"The cortex can't do it alone, it needs input from the hippocampus," Wiltgen said. "This has been a fundamental assumption in our field for a long time and Kazu's data provides the first direct evidence that it is true."

They could also see how the specific cells in the cortex were connected to the amygdala, a structure in the brain that is involved in emotion and in generating the freezing response.

Co-authors are Aleksandr Pevzner, Anahita B. Hamidi, Yuki Nakazawa and Jalina Graham, all at the Center for Neuroscience.

Provided by UC Davis