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How to Erase a Memory – And Restore It

Researchers at the University of California, San Diego School of Medicine have erased and reactivated memories in rats, profoundly altering the animals' reaction to past events.

The study, published in the June 1 advanced online issue of the journal *Nature*, is the first to show the ability to selectively remove a memory and predictably reactivate it by stimulating nerves in the brain at frequencies that are known to weaken and strengthen the connections between nerve cells, called synapses.

"We can form a memory, erase that memory and we can reactivate it, at will, by applying a stimulus that selectively strengthens or weakens synaptic connections," said senior author Roberto Malinow, MD, PhD, professor in the Department of Neurosciences and neurobiology section of the Division of Biological Sciences.

Scientists optically stimulated a group of nerves in a rat's brain that had been genetically modified to make them sensitive to light, and simultaneously delivered an electrical shock to the animal's foot. The rats soon learned to associate the optical nerve stimulation with pain and displayed fear behaviors when these nerves were stimulated.

Analyses showed chemical changes within the optically stimulated nerve synapses, indicative of synaptic strengthening.

In the next stage of the experiment, the research team demonstrated the ability to weaken this circuitry by stimulating the same nerves with a memory-erasing, low-frequency train of optical pulses. These rats subsequently no longer responded to the original nerve stimulation with fear, suggesting the pain-association memory had been erased.

In what may be the study's most startlingly discovery, scientists found they could re-activate the lost memory by re-stimulating the same nerves with a memory-forming, high-frequency train of optical pulses. These re-conditioned rats once again responded to the original stimulation with fear, even though they had not had their feet re-shocked.

“We can cause an animal to have fear and then not have fear and then to have fear again by stimulating the nerves at frequencies that strengthen or weaken the synapses,” said Sadegh Nabavi, a postdoctoral researcher in the Malinow lab and the study’s lead author.

In terms of potential clinical applications, Malinow, who holds the Shiley Endowed Chair in Alzheimer’s Disease Research in Honor of Dr. Leon Thal, noted that the beta amyloid peptide that accumulates in the brains of people with Alzheimer’s disease weakens synaptic connections in much the same way that low-frequency stimulation erased memories in the rats. “Since our work shows we can reverse the processes that weaken synapses, we could potentially counteract some of the beta amyloid’s effects in Alzheimer’s patients,” he said.

Co-authors include Rocky Fox and Christophe Proulx, UCSD Department of Neurosciences; and John Lin and Roger Tsien, UCSD Department of Pharmacology.

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