Researchers find 'lost' memories using light

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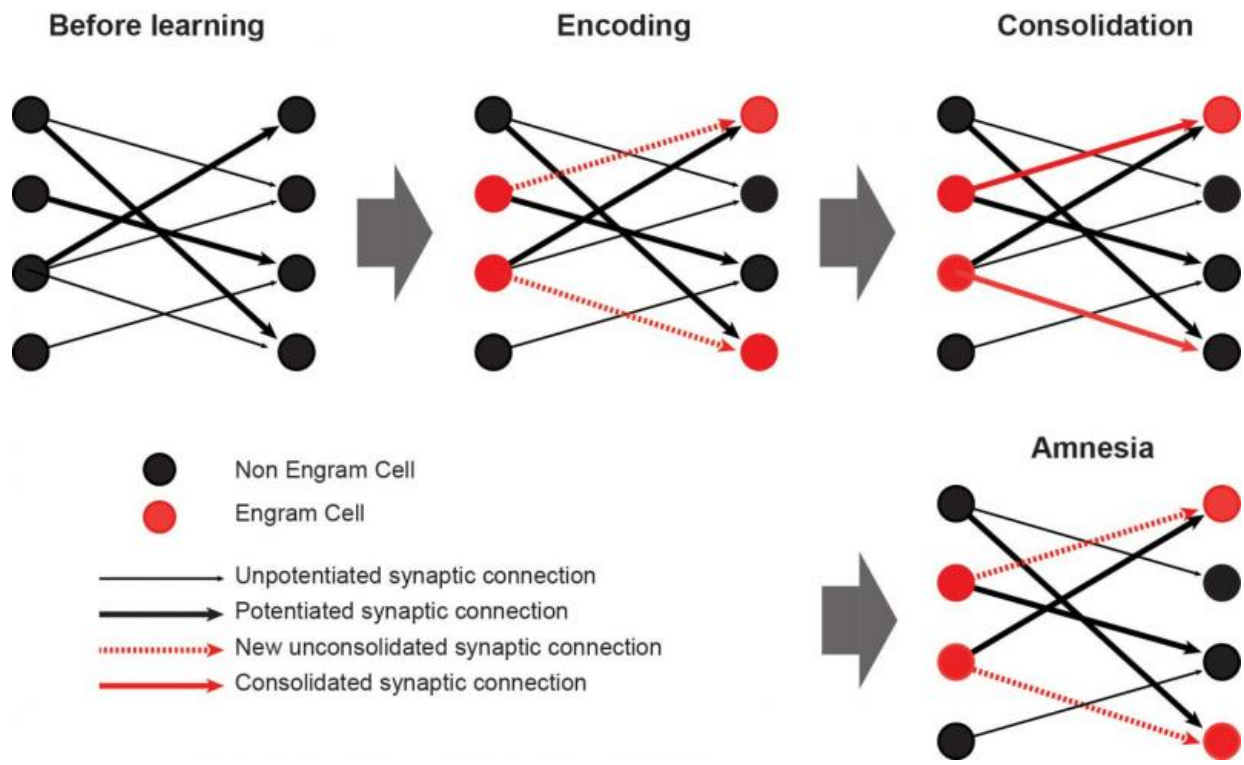


Schematic diagram illustrating the dynamic of the synaptic connectivity in a neural network recruited during the formation of a new memory. Before learning the neural network presents a connectivity arrangement characterized by a mix of potentiated (thick black lines) and unpotentiated (thin black lines) synapses. During memory encoding, a sparse number of cells (engram cells, red) are recruited giving rise to new connections or activating preexisting ones (dashed red line). Immediately after encoding the process of memory consolidation enables the stabilization of the new connections (thick red line). The stabilization is characterized by a permanent enhancement of the synaptic strength and is fundamental for memory retrieval. Disruption of the consolidation process by intervention such as protein synthesis inhibitors impairs the stabilization

potentiation of the new synaptic connections (thin red line) resulting in retrograde amnesia. The synaptic connectivity provides a substrate for memory storage whereas the potentiation of the synapses is required for memory retrieval. Credit: Michele Pignatelli

Memories that have been "lost" as a result of amnesia can be recalled by activating brain cells with light.

In a paper published today in the journal *Science*, researchers at MIT reveal that they were able to reactivate memories that could not otherwise be retrieved, using a technology known as optogenetics.

The finding answers a fiercely debated question in neuroscience as to the nature of amnesia, according to Susumu Tonegawa, the Picower Professor in MIT's Department of Biology and director of the RIKEN-MIT Center at the Picower Institute for Learning and Memory, who directed the research by lead authors Tomas Ryan, Dheeraj Roy, and Michelle Pignatelli.

Neuroscience researchers have for many years debated whether retrograde amnesia—which follows traumatic injury, stress, or diseases such as Alzheimer's—is caused by damage to specific brain cells, meaning a memory cannot be stored, or if access to that memory is somehow blocked, preventing its recall.

"The majority of researchers have favored the storage theory, but we have shown in this paper that this majority theory is probably wrong," Tonegawa says. "Amnesia is a problem of retrieval impairment."

Memory researchers have previously speculated that somewhere in the brain network is a population of neurons that are activated during the

process of acquiring a memory, causing enduring physical or chemical changes.

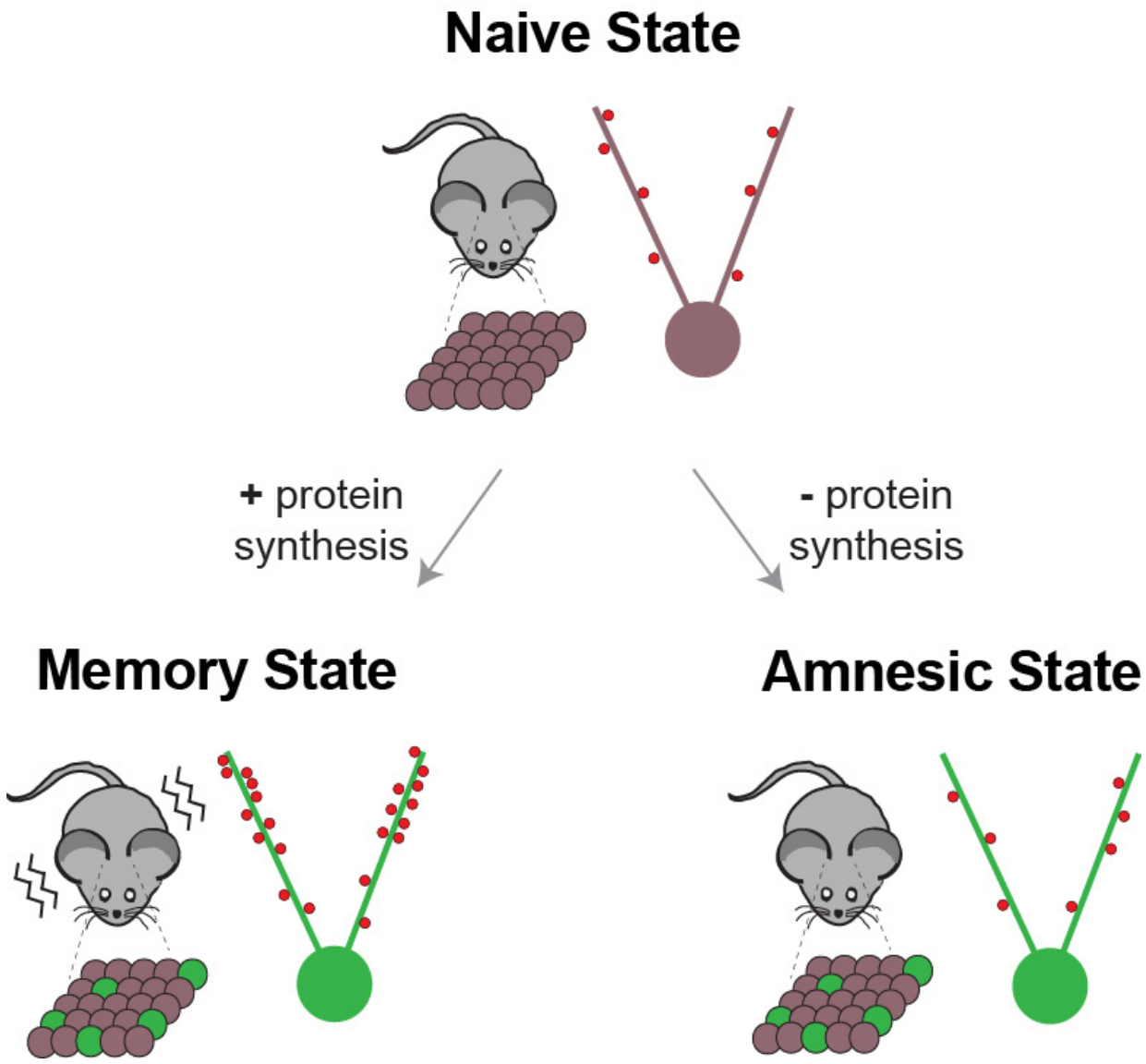
If these groups of neurons are subsequently reactivated by a trigger such as a particular sight or smell, for example, the entire memory is recalled. These neurons are known as "memory engram cells."

Shedding light

In 2012 Tonegawa's group used optogenetics—in which proteins are added to neurons to allow them to be activated with light—to demonstrate for the first time that such a population of neurons does indeed exist in an area of the brain called the hippocampus.

However, until now no one has been able to show that these groups of neurons do undergo enduring chemical changes, in a process known as memory consolidation. One such change, known as "long-term potentiation" (LTP), involves the strengthening of synapses, the structures that allow groups of neurons to send signals to each other, as a result of learning and experience.

To find out if these chemical changes do indeed take place, the researchers first identified a group of engram cells in the hippocampus that, when activated using optogenetic tools, were able to express a memory.



Behavioral expression of fear memory: In naïve (unlearned) state, mice have not gained a context-specific engram. In the learned memory state, mice have acquired a synapticaly potentiated fear engram, which causes them to express freezing behavior in the fearful context. In the amnesia state, protein synthesis inhibition has resulted in mice that have an interrupted and synaptically depotentiated fear engram, which does not cause freezing behavior in the fearful context, but can result in freezing behavior if directly activated. Credit: Dheeraj Roy

When they then recorded the activity of this particular group of cells, they found that the synapses connecting them had been strengthened. "We were able to demonstrate for the first time that these specific cells—a small group of cells in the hippocampus—had undergone this augmentation of synaptic strength," Tonegawa says.

The researchers then attempted to discover what happens to memories without this consolidation process. By administering a compound called anisomycin, which blocks protein synthesis within neurons, immediately after mice had formed a new memory, the researchers were able to prevent the synapses from strengthening.

When they returned one day later and attempted to reactivate the memory using an emotional trigger, they could find no trace of it. "So even though the engram cells are there, without protein synthesis those cell synapses are not strengthened, and the memory is lost," Tonegawa says.

But startlingly, when the researchers then reactivated the protein synthesis-blocked engram cells using optogenetic tools, they found that the mice exhibited all the signs of recalling the memory in full.

"If you test memory recall with natural recall triggers in an anisomycin-treated animal, it will be amnesiac, you cannot induce memory recall," Tonegawa says. "But if you go directly to the putative engram-bearing cells and activate them with light, you can restore the memory, despite the fact that there has been no LTP."

"Groundbreaking paper"

Further studies carried out by Tonegawa's group demonstrated that memories are stored not in synapses strengthened by protein synthesis in individual engram cells, but in a circuit, or "pathway" of multiple groups

of engram cells and the connections between them.

"We are proposing a new concept, in which there is an engram cell ensemble pathway, or circuit, for each memory," he says. "This circuit encompasses multiple brain areas and the engram cell ensembles in these areas are connected specifically for a particular memory."

The research dissociates the mechanisms used in memory storage from those of memory retrieval, according to Ryan. "The strengthening of engram synapses is crucial for the brain's ability to access or retrieve those specific memories, while the connectivity pathways between engram cells allows the encoding and storage of the memory information itself," he says.

More information: Engram cells retain memory under retrograde amnesia, *Science*, www.sciencemag.org/lookup/doi/ … 1126/science.aaa5542

Provided by Massachusetts Institute of Technology

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