New study reveals role of hippocampus in two functions of memory

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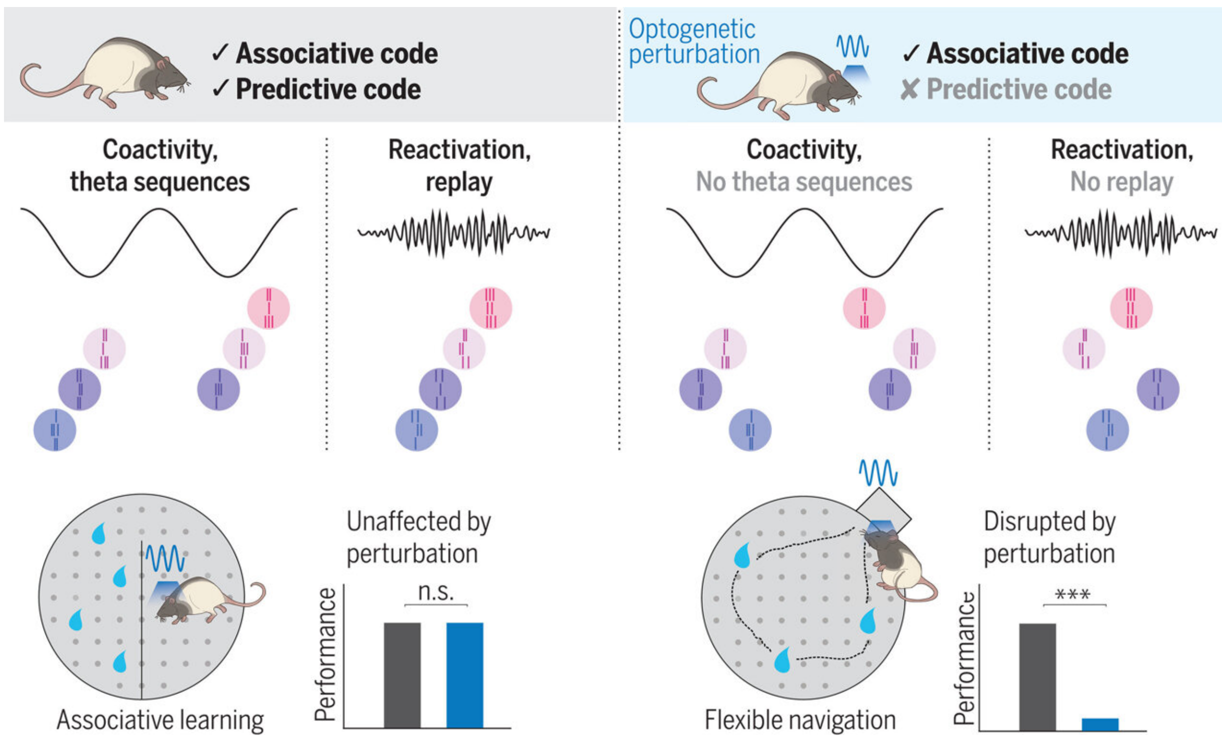

Associative and predictive codes in the hippocampus. Our optogenetic manipulation perturbed hippocampal sequences without affecting cell coactivity, thus selectively disrupting the predictive code. After learning, cell assemblies were reactivated, but their order was not preserved, abolishing sequential replay (right). Perturbing the predictive code had no effect on associative learning (bottom left) but did disrupt the flexible learning of novel optimal trajectories on a maze (bottom right). [Rat illustrations: Yu Kang]. Credit: *Science* (2023). DOI: 10.1126/science.adi8237

For the first time, a study in rats teases apart the role of the hippocampus in two functions of memory—one that remembers associations between time, place and what one did, and another that allows one to predict or plan future actions based on past experiences.

The breakthrough reveals that these two memory tasks, both coded in the hippocampus, can be separated. The finding has important implications for one day treating memory and learning issues found in dementia and Alzheimer's disease.

The study, "Associative and Predictive Hippocampal Codes Support Memory-Guided Behaviors," which is published in *Science*, used advanced optogenetic techniques to disable one type of memory while maintaining the other.

"We uncovered that two different neural codes support these very important aspects of memory and cognition, and can be dissociated, as we did experimentally," said Antonio Fernandez-Ruiz, assistant professor of neurobiology and behavior, and Nancy and Peter Meinig Family Investigator in the Life Sciences, in the College of Arts and Sciences (A&S). Azahara Oliva, assistant professor of neurobiology and behavior (A&S), is a main collaborator and co-author of the study.

One type of neural code controls the ability to make associations, such as remembering that apples are sold at the neighborhood grocery store. The other type is predictive, and involves the ability to flexibly use memory to plan a new behavior; for example, if you always travel the same route to the store, but one day the road is closed, you can use an internal memorized map of the neighborhood to make a prediction of a new route.

Until now, nobody has known how the hippocampus supports these functions and if there was any relationship between the two.

In the study, the researchers developed a system that used many electrodes placed in a rat's brain to track the activity of many neurons simultaneously while the rat engaged in a behavior. Then, the team used optogenetics to very precisely control the activity of neurons. To do so, the researchers inject a virus into the rat's brain, which infects neurons so they express an artificial protein that can activate or silence (depending on the type of protein) those neurons when a light is shined inside the brain.

The researchers tweaked this method to selectively perturb, but not completely silence, a set of neurons. In this way, they could affect certain neurons while not altering the general properties of the brain.

They used this method to perturb a region in the hippocampus involved in learning a new task, such as traveling from point A to point D. When a rat moves along a new environment, neurons encode milestones—such as the rat took a left at point B, and a right at point C, to arrive at D, where there was a reward.

"That sequence of steps is encoded in the brain as a sequence of cells firing," Fernandez-Ruiz said. "The way we will remember this in the future is that when we are sleeping, the same sequence of activity is replayed, so the same neurons that encode [the path] will fire in the same order."

By perturbing a region of the hippocampus, the researchers were able to scramble the sequence of neurons firing along that path. When asleep, the neurons failed to fire in sequence to solidify the memory. The rat could remember the locations of points A and D, but the pathway to get from one to the other was lost. In this way, the associative aspects of memory were maintained but the predictive part of it was lost.

In one experiment, rats with perturbed hippocampi had to explore a maze and find a new path every day to collect a reward. "That behavior required it to form a map, and required planning and prediction capabilities, and remember it to guide its movements," Fernandez-Ruiz said. With the manipulation to their hippocampi, the rats could not remember how to get the reward.

In a second experiment, the rats had to learn to associate a particular location in the environment with a reward. When the predictive capabilities were impaired, this associative memory remained intact. The researchers proved they could decouple these two types of memory.

The findings have implications for treating Alzheimer's disease and other forms of dementia, where patients experience neural degeneration in the hippocampus as well as memory and navigation problems.

"By looking at which type of memory deficits occur in a patient," Fernandez-Ruiz said, "we can try to infer what type of underlying neuronal mechanism has been compromised, which will help us develop more targeted interventions."

More information: Can Liu et al, Associative and predictive hippocampal codes support memory-guided behaviors, *Science* (2023). DOI: 10.1126/science.adi8237

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