Mice play virtual reality games to reveal how memories are selected for long-term storage

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Credit: Julia Kuhl

Neuroscientists watched the brains of mice as they played virtual reality games to elucidate how memory goes from its initial formation in the hippocampus to longer-term storage in the cortex. Reporting in the journal *Cell* on March 30, they found that the anterior thalamus—a brain region not classically involved in models of memory consolidation—is one essential stopover site where memories are processed and stabilized. By stimulating the anterior thalamus of mice while they were learning a virtual reality maze, the team was able to help mice retain memories that they would usually forget after a few weeks.

"We've identified a circuit in the brain that is important for identifying which memories are important and how they are filtered into longer-term storage," says Andrew Toader, who co-led the study alongside Josue Regalado, both graduate students at Rockefeller University. "As soon as the mice begin learning a task, the thalamus is performing this selection process and choosing which memories will go on to be stabilized in the cortex long-term."

The team identified the anterior thalamus as a region of interest by recording the brain activity of mice while they were forming and stabilizing memories over weeks in a virtual reality maze. The researchers noticed that neural activity in the anterior thalamus was elevated by the end of training and persisted for several weeks—the same amount of time that it usually takes for memories to be reorganized and stored in the cortex.

In the virtual reality sessions, the mice traveled along a corridor that was projected on a screen in front of them while they ran on a rotating Styrofoam ball. The corridor led to a final room in which the mice encountered one of three possible outcomes in the real world: unlimited sugar water that they could lick from a spout in front of them; a few drops of sugar water from the same spout; or a puff of air to the face. The mice received different types of cues—sounds, smells, and visual

stimuli—along the way to the final room that helped them learn the different scenarios and anticipate the reward (or brace themselves for an air puff) when they played the games again.

"We structured the virtual reality tasks so that they required a lot of engagement from the mouse in order to start the trial, run through the mazes, and get the rewards," says Regalado. "The more explicit and cognitive the task, the more we're able to look at how the different brain regions are engaged."

After the mice learned the three different scenarios, the researchers tested their ability to remember and differentiate between them over the next few weeks. They assessed the strength of the mice's memory based on how quickly the mice ran toward the final room—if they remembered correctly, the mice ran faster toward the sugar water and slower toward the air puff—and how much they licked the sugar-water spout in anticipation of reward. At the same time, the researchers tested whether stimulating or inhibiting the hippocampus or anterior thalamus during training would impact a mouse's ability to form memories and store them long term.

When the team inhibited the mice's hippocampus during training, the mice failed to learn the different virtual reality routes and their associated outcomes, even in the short term. Inhibiting the anterior thalamus during training, however, did not impact the mice's ability to learn or remember the task in the short term, but it did prevent them from committing it to long-term memory.

Furthermore, stimulating the anterior thalamus during training enhanced the mice's ability to commit memories into long-term storage. This was especially true of the scenario in which the mice only received a few drops of sugar water, which is a nice, but not particularly memorable, experience. Without any stimulation, most mice forgot the route that led

to this outcome, but stimulating the anterior thalamus helped them remember the way.

To further investigate the role of the thalamus memory storage, the team paired their virtual reality training program with new technology that allowed simultaneous imaging of single neurons in the hippocampus, thalamus, and cortex. "We could follow these same neurons over time and trace the memory of a mouse from when they first form a memory to weeks and months later," says Regalado.

The researchers found that, while the hippocampus was equally activated during training for both the unlimited sugar water and few drops of sugar water scenarios, the thalamus preferentially stored information about the more memorable unlimited sugar water scenario. "The thalamus sets up gradually increasing long-range interactions with cortex to stabilize these memories for long-term storage," says senior author Priya Rajasethupathy, a neuroscientist at Rockefeller.

"Some memories are more important to us than others," says Rajasethupathy. "We found that, not only do mice need the anterior thalamus to consolidate memories, but that by activating it, we could enhance consolidation of a memory that mice would usually forget."

"The analogy would be your birthday dinner versus the dinner you had three Tuesdays ago," says Toader. "You're more likely to remember what you had on your birthday because it's more rewarding for you—all your friends are there, it's exciting—versus just a typical dinner, which you might remember the next day but probably not a month later."

"There's a lot more to understand about how this selection and stabilization occur," says Rajasethupathy. "We think something like adrenaline or dopamine might be helping the thalamus to say, 'okay, this memory is important to me, that's not as important." And we still don't

understand how punctuated or continuous the memory stabilization process is, whether it occurs in one or a few steps or evolves continuously over a lifetime."

More information: Priya Rajasethupathy, Anteromedial Thalamus Gates the Selection and Stabilization of Long-Term Memories, *Cell* (2023). DOI: 10.1016/j.cell.2023.02.024. www.cell.com/cell/fulltext/S0092-8674(23)00167-8

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