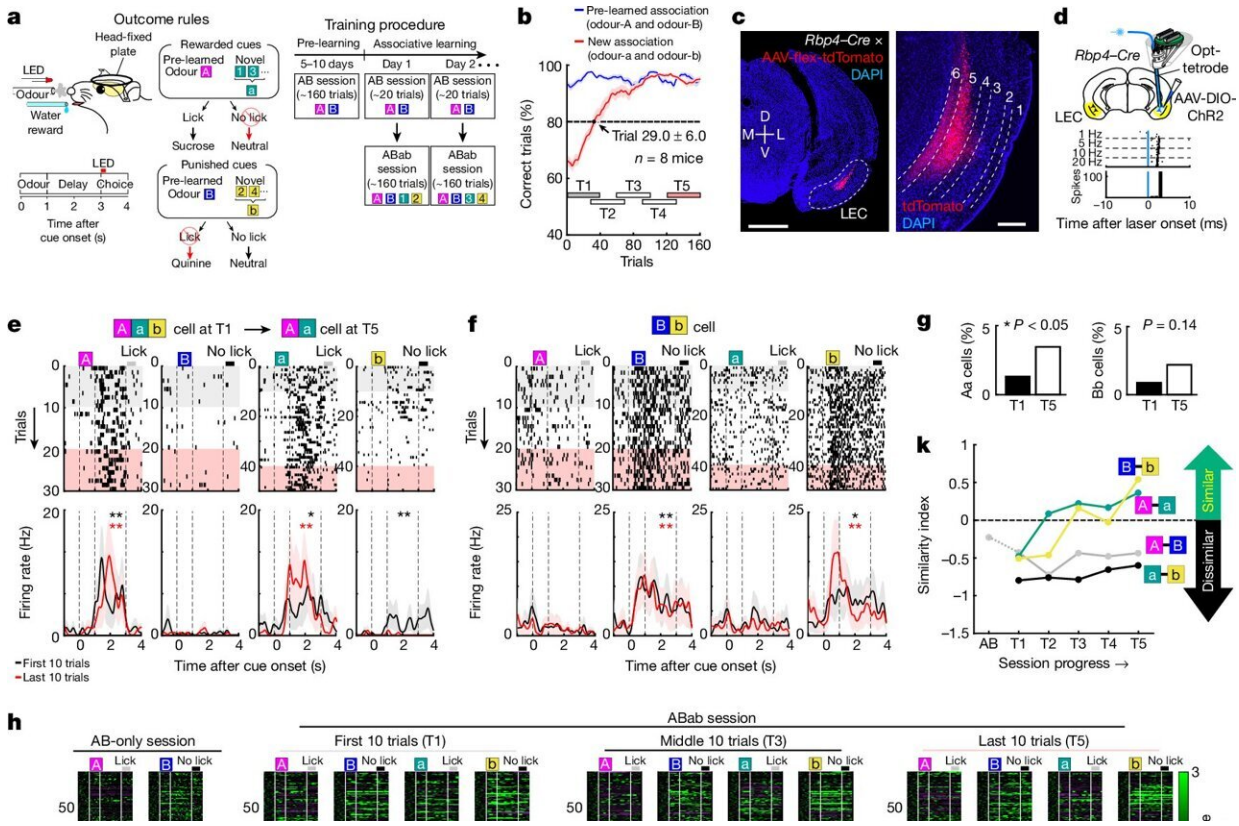
Discovery of 'item memory' brain cells offers new Alzheimer's treatment target

August 21 2024



$LEC_{L5/6}$ cells encode outcome rules during associative learning. Credit: *Nature* (2024). DOI: 10.1038/s41586-024-07868-1

Researchers from the University of California, Irvine have discovered the neurons responsible for "item memory," deepening our

understanding of how the brain stores and retrieves the details of "what" happened and offering a new target for treating Alzheimer's disease.

Memories include three types of details: spatial, temporal and item, the "where, when and what" of an event. Their creation is a complex process that involves storing information based on the meanings and outcomes of different experiences and forms the foundation of our ability to recall and recount them.

The study, published online today in the journal *Nature*, is the first to reveal the role of specific cells in how the brain classifies and remembers new information, particularly when linked to rewards or punishments.

"Understanding this process is crucial because it deepens our insight into the fundamental way our brains function, especially in learning and memory," said corresponding author Kei Igarashi, Chancellor's Fellow and associate professor of anatomy and neurobiology. "Our findings shed light on the intricate neural circuits that enable us to learn from our experiences and store these memories in a structured way."

Researchers studied mice brains, focusing on the deeper layers of the lateral entorhinal cortex, where they discovered specialized, item-outcome neurons essential for learning. Odors are critical sensory cues for item memory in mice.

Some neurons became active when exposed to the scent of banana, associated with a sucrose water reward. Other neurons responded to the smell of pine, associated with a bitter water negative outcome. A mental map divided into those two categories was formed in the LEC.

Anatomically, neurons in the deep-layer LEC are tightly connected with neurons in another brain region, the medial prefrontal cortex. Team

members observed that neurons in the mPFC developed a similar mental map during the learning process.

They also found that when the activity of the LEC neurons was inhibited, those in the mPFC failed to properly distinguish between positive and negative items, leading to impaired learning. Conversely, when the mPFC neurons were inhibited, the ability of the LEC to keep item memories separate was totally disrupted, impairing learning and item memory recall. This data indicated that the LEC and mPFC are co-dependent, working together to encode item memory.

"This study is a significant advancement in our understanding of how item memory is generated in the brain," Igarashi said. "This knowledge now opens up new avenues for investigating memory disorders, such as Alzheimer's disease. Our data suggests that item memory neurons in the LEC lose their activity in Alzheimer's. If we can find a way to reactivate these neurons, it could lead to targeted therapeutic interventions."

The two leading authors of this work were graduate students Heechul Jun of the Medical Scientist Training Program and Jason Y. Lee of the Interdepartmental Neuroscience Program. Other team members included research technicians Nicholas R. Bleza and Ayana Ichii, as well as postdoctoral researcher Jordan Donohue from the Kei Igarashi lab.

More information: Kei Igarashi, Prefrontal and lateral entorhinal neurons co-dependently learn item–outcome rules, *Nature* (2024). DOI: 10.1038/s41586-024-07868-1.
www.nature.com/articles/s41586-024-07868-1

Provided by University of California, Irvine