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Reactivation in the hippocampus could support the consolidation of long-term cognitive maps

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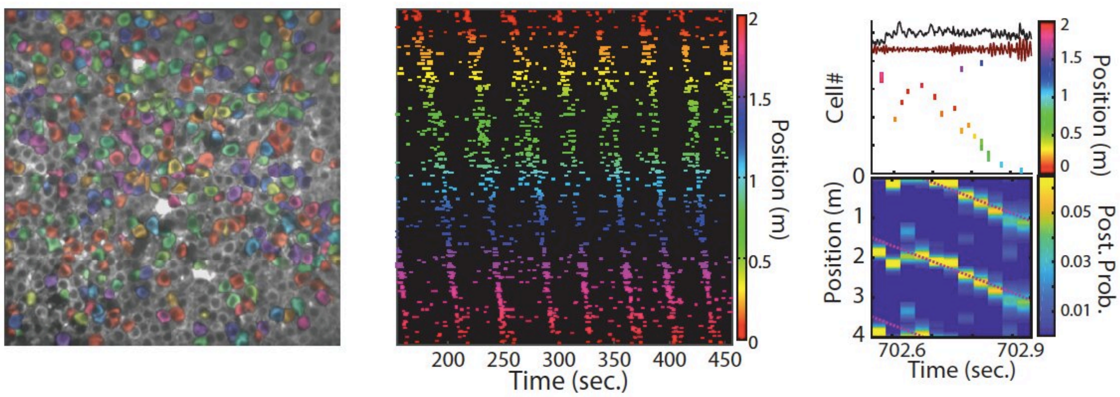

(Left) Hippocampal place cells imaged with two-photon imaging are (middle) sequentially active at particular locations as a mouse runs through the environment - each tick on the right graph corresponds to the activity of a particular cell on one of the 7 traversals shown. Cells and raster plots are color-coded by preferred place selectivity. (Right) afterwards when the animal is sitting quietly these neurons spontaneously replay their previously learned place sequence. Credit: Grosmark et al.

The hippocampus is an area of the brain known to play a key role in the encoding of long-term memories. In addition to contributing to the formation of event-related memories, this brain region supports the creation of so-called cognitive maps. These are mental maps of the world that guide humans as they navigate known environments; for instance, showing them how to get from one place to another.

Past neuroscience studies have found that hippocampal place cells, neurons that sequentially code information related to nearby spaces while humans and animals are exploring them, tend to 'replay' the same activity sequences after exploration. This fascinating process resembles the way in which humans might rewind and replay a song they recorded on an old-fashion cassette tape.

Researchers at Columbia University Medical Center have recently carried out a study investigating reactivation patterns in the hippocampus further, by examining hippocampal place cells in the mouse brain while mice completed spatial reward learning tasks and subsequently as they were resting. Their paper, published in *Nature Neuroscience*, suggests that reactivation patterns in the hippocampus play a crucial role in the consolidation of unbiased cognitive maps over time.

"Interestingly, unlike exploration-related place sequences, sequential reactivation events in the hippocampus occur during periods of inactivity and continue occurring even in a different environment than the one being replayed," Andres D. Grosmark, the lead researcher for the study, told Medical Xpress. "They also occur at a faster time scale than exploration-related sequences, so that, for instance, a sequence that took up 10 seconds during exploration may be replayed in just half a second."

The fact that hippocampal neurons appear to be engaging in a virtual mental travel suggests that they may in fact be "rehearsing" the spatial sequences that subjects learned while exploring their surrounding environment. Neuroscientists have thus hypothesized that reactivation patterns help to make new memories permanent, through a process known as memory consolidation.

"Importantly, not all hippocampal representations are permanent, in fact even on the exact same environment some neurons code stably for space while other neurons change their spatial selectivity from day to day," Grosmark said. "We hypothesized that the more replay that individual neurons participate in the longer-lasting and more stable their representations will become."

To test their hypothesis, Grosmark and his colleagues had to overcome a series of technical limitations. More specifically, so far, neuroscientists could either study memory replay (i.e., reactivation patterns in the hippocampus) in detail or monitor general changes in the hippocampus over the course of several days. To investigate whether the amount of replay that hippocampal neurons participate in impact the stability of the neural representations they created, the researchers had to study both these aspects simultaneously. They thus employed two methods for studying long-term memory in mice, namely calcium-imaging and electrophysiology.

"This allowed us to leverage the ability of electrophysiology to observe very fast time-scale dynamics, including replay, with the ability to follow populations of neurons over several weeks associated with calcium imaging techniques," Grosmark said. "In our study, we combined calcium imaging and electrophysiology to track the formation and consolidation of spatial memories in large populations of hippocampal neurons in mice over a period of two weeks."

The first method used by the researchers is calcium imaging, a microscopy technique that allows scientists to optically detect neural activity. Calcium imaging uses viral-techniques to cause neurons to express calcium-sensitive fluorophores, so that they briefly change color when they become active.

"Using some pretty fancy optics and lasers, this allows us to track the activity of large populations of neurons in awake, behaving mice," Grosmark said. "One of the key advantages of calcium imaging, is that since you are physically looking at the neurons, you can track them over a long period of time."

The second technique employed by Grosmark and his colleagues, called neuronal electrophysiology, entails the use of very small wires to record electrical activity inside the brain. Measuring this electrical activity allows neuroscientists to monitor changes happening in specific brain areas or in the brain as a whole.

"This technique has two key advantages," Grosmark explained. "Firstly, it records electrical signals very rapidly, allowing us to observe very fast, or very short, changes in activity within the brain. Secondly, the decades of experience using electrophysiology allow us to use the observed electrical activity to decode brain states, such as the online and offline states."

Brain activity can be divided into two main categories: online and offline activity. Online states occur when humans or animals are actively engaging with the world around them, for instance, while they are exploring their surroundings or completing a task. Offline states, on the other hand, are periods in which humans and animals disengage from the world.

"One example of an offline state is sleep; however, the offline states that we investigated in our study were spontaneously occurring 'quiet rest' periods, when the mice were awake but sitting quietly," Grosmark said. "Beyond the outward behavioral differences online and offline states can also be readily distinguished by the unique patterns of brain activity oscillations observed during these states. These different brain regimes are thought to support different functions."

As learning is typically associated with an active exploration of the environment, it is believed to take place during online states. On the other hand, offline states are thought to be important for consolidating memories and knowledge acquired during exploration (i.e., in online states).

"While we agree with this overall framework, our results suggest that rather than simply passively consolidating memories, offline states play an active role in selecting which memories become permanent and therefore play a complementary role in learning, compared to online states," Grosmark explained.

Over the past few decades, a rising number of neuroscience studies have explored how memories of rewarded actions are strengthened in the brain. In contrast with previous theories, Grosmark and his colleagues hypothesized that to support the learning of flexible behaviors, the brain should also incorporate information that does not have an obvious reward-value at the time it is acquired.

"For instance, when walking around in a new city, we may find ourselves repeatedly just getting from point A to point B—yet over the many times of taking this route, we slowly build a detailed map of all the points in between, even if we've never actually stopped long enough to appreciate them," Grosmark said. "In turn, when our schedule changes and we instead want to go from A to C, this 'latent' map we have quietly built up may well prove itself really useful. Moreover, learning doesn't occur in a vacuum; it happens within a constant cycle of engagement and disengagement from the world around us, corresponding to what we refer to as online and offline states."

In their experiments, the researchers observed that the recruitment of hippocampal neurons for post-learning reactivation events did in fact predict their long-term stability numerous days later. In addition, this consolidation effect was only observed for spatial representations of locations far from where the animals had been rewarded. This suggest that offline memory consolidation selectively strengthens neural representations that are less behaviorally important, and therefore susceptible being forgotten.

"We're really excited that our study leads to new insights into the roles that these different engaged and disengaged states play in learning; cooperatively resulting in the cognitively broad long-term memories that are useful both for finding our way back to important places and for flexibly arriving at new unexpected destinations," Grosmark said.

The findings could significantly enhance the present understanding of how animals and humans consolidate mental maps of their environment over time. In the future, they could pave the way for further studies examining reactivation patterns in the hippocampus, which could lead to new important discoveries.

"The fact that memory consolidation seems to be playing a unique and active role in learning opens up exciting avenues regarding how long-term memory content is sculpted," Grosmark added. "We now plan to uncover the neural circuit mechanisms underlying this offline selection process and examine how they become dysregulated in mental illnesses known to affect long-term memory."

More information: Andres D. Grosmark et al, Reactivation predicts the consolidation of unbiased long-term cognitive maps, *Nature Neuroscience* (2021). DOI: 10.1038/s41593-021-00920-7