

Don't Regret to Forget

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Although the brain is capable of learning and memorizing masses of complex information, we wouldn't be as intelligent or adaptive if our minds weren't constantly urging us to forget. Forgetting is defined as a lack of expression of memories that had once been expressed (Tello-Ramos et al., 2018). While memory loss from disease or trauma is typically caused by pathophysiological abnormalities, the natural process of forgetting reflects the brain's attempt to remove unneeded information to make room for more. Kluge and Gronau (2018) argue that adaptability is pertinent to individuals in unfamiliar environments, and previously learned information must be forgotten to focus on what is currently most relevant. Therefore, forgetting is arguably among the most important mental processes allowing humans to adapt to new environments, encode memories, and recall information in the blink of an eye.

Davis and Zhong (2017) argue that different forms of memory require different mechanisms for forgetting, although precise mechanisms for losing short-term and long-term memories are still largely unknown. Anderman et al. (2021) further proposed that the pathway for forgetting is directly related to how information was initially encoded. The researchers claim that differences exist between forgetting item-based and event-based memories. Evidently, the mechanisms underlying forgetting are complex and dependent on many factors, and while more is known about how humans learn and form memories, much less is known about how we forget.

Previously, long-term depression (LTD), a decrease in synaptic strength over time, was proposed as a potential mechanism for forgetting. Furthermore, it has been suggested that LTD is promoted by increased receptor endocytosis (Hirano 2018). Fewer receptors on the surface of the neuron mean less neurotransmitter is perceived, over time developing into the depression of synaptic strength. Miguez et al. (2016) reported that the endocytosis of AMPA receptors facilitates the development of LTD. Therefore, it can be inferred that endocytosis of AMPA receptors may contribute to forgetting.

Previous research has shown that receptor trafficking is dependent on calcium influx into neurons. However, the exact calcium sensors that mediate receptor endocytosis were unknown. Awasthi et al. (2018) devised a study focused on a specific synaptotagmin, a type of synaptic membrane protein that has a high calcium affinity and is known to undergo endocytosis in dendrites upon stimulation. Research has shown that Synaptotagmin-3 (Syt3) is one of two calcium-binding synaptotagmins found in hippocampal neurons, a brain region involved in learning and memory (Wu et al. 2017). Awasthi et al. hypothesize that Syt3 mediates postsynaptic receptor endocytosis, leading to forgetting through LTD.

To ascertain the location of Syt3 on the membrane, Awasthi et al. expressed a protein dye in hippocampal neuron cultures to distinguish whether Syt3 is embedded in axons or dendrites. Syt3 was visually observed to be primarily on cell bodies and dendrites, confirming its proximity to synapses.

Next, Syt3 was confirmed to internalize in response to stimulation using a similar method of injecting protein-dye to quantify internal versus external Syt3. However, the next goal was to determine whether the AMPA receptor is internalized alongside it. Wildtype neurons used Syt3 to internalize AMPA receptors along with its GluA2 subunit, whereas Syt3 knockouts showed no internalization of receptors.

The researchers next aimed to understand Syt3's effect on synaptic signal strength. They quantified the levels of excitatory signals reaching wildtype and knockout neurons to assess whether removing Syt3 affects the development of LTD. In wild-type neurons, a decrease in excitatory signals indicated AMPA receptor endocytosis, eventually leading to LTD. In knockout neurons, an abrupt and prolonged increase in ex-

citatory signals indicated a lack of AMPA receptor endocytosis. Awasthi et al. conclude that the removal of Syt3 precedes an impairment of LTD.

To assess the phenotypical implications of Syt3 removal, Awasthi et al. conducted behavioral testing on wildtype and Syt3 knockout mice. Mice were initially taught to navigate to a hidden platform in a water maze, during which both groups showed no differences in their ability to learn the platform's location. The platform was then shifted to an entirely new location in the maze. Syt3 knockout mice gravitated toward the platform's original location more frequently than wildtype, indicating their lack of forgetting of that position (Figure 1B).

However, this lack of forgetting comes with a price. Working memory was assessed using a water maze task in which the platform's location was moved daily. The mice were tasked with learning the new position and forgetting the position from the previous day. Because Syt3 knockout mice tended not to forget, they typically visited previous days' positions more frequently than the newest positions. In contrast, wild-type mice were more easily capable of forgetting previous platform positions to perform better in location the newest position. This test is evidence that forgetting is crucial to the optimal functioning of working memory.

Awasthi et al. concluded that Syt3 is a postsynaptic membrane protein that facilitates the endocytosis of AMPA receptors, decreasing the ability of the cell to receive incoming neurotransmitters and decreasing the strength with which the signal gets passed forward. The long-term depression of synaptic strength precedes the forgetting of memories encoded by signals traveling through it.

These results expand our understanding of the biological mechanisms underlying forgetting. This information is critical to pharmaceutical development, which can potentially prevent or slow the rate of memory loss in certain neurological conditions. However, it's important to remember the negative impact Syt3 removal had on working memory in the results of Awasthi et al. Syt3 should be further studied to better understand its function in the cell, as we may not be aware of all the effects manipulating Syt3 in the brain can have. For instance, one study found a link between increased Syt3 expression and obesity development (Zhang et al. 2020). Factors like these were not considered in the research of Awasthi et al. but should be investigated further to understand Syt3's importance in the body as a whole.

More recently, Noyes et al. (2021) discovered that a gene known as Caspase-2 may code for a protein involved in AMPA receptor internalization. Reduced expression of Caspase-2 in mice revealed spatial memory improvements by slowing the rates of forgetting and blocking the activity of an enzyme involved in receptor internalization.

Ultimately, while our understanding of how forgetting occurs in the brain is currently expanding, we still have a long way to go before we have a definitive answer for why we forget.

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