

New technique sheds light on memory and learning

April 8 2024, by Katherine Fenz



Activity taking place within the dendrites that branch off of neuron cell bodies is key to memory formation. Credit: Rockefeller University

Less than twenty minutes after finishing this article, your brain will begin to store the information that you've just read in a coordinated burst

of neuronal activity. Underpinning this process is a phenomenon known as dendritic translation, which involves an uptick in localized protein production within dendrites, the spiny branches that project off the neuron cell body and receive signals from other neurons at synapses. It's a process key to memory—and its dysfunction is linked to intellectual disorders.

That makes the inner workings of dendritic translation a "holy grail for understanding memory formation," says Rockefeller's Robert B. Darnell, whose team just published [a study in *Nature Neuroscience*](#) describing a new platform capable of identifying the specific regulatory mechanisms that drive dendritic translation.

The team leveraged a method, dubbed TurboID, to discover an entire suite of previously unknown factors in memory formation, revealing now mechanisms that underlie how [protein synthesis](#) in dendrites contributes to learning and memory. The findings may also have implications for intellectual disabilities, such as Fragile X syndrome.

"Technological limitations have long prevented a comprehensive inventory of the activity at the synapse involved in memory formation," says lead author Ezgi Hacisuleyman, who conducted the research as a postdoctoral researcher in Darnell's laboratory. She is now an assistant professor at The UF Scripps Institute. "Our new techniques can accomplish this with extremely high resolution to look at neurons in vitro that are closely mimicking what we see in the brain."

"Hacisuleyman's work defines a whole new biochemical pathway which fits with, complements, and vastly expands what we already knew about memory and learning," adds Darnell, the Robert and Harriet Heilbrunn professor.

A unique way to metabolize RNA

Memory formation centers around the hippocampus, a brain region so central to learning that, when surgeons removed it from people with epilepsy in the 1940s, the patients remembered their childhoods but lost the ability to form new memories. It has since become clear that memories form, in part, because of new protein synthesis made locally in the dendrites of the hippocampus.

Darnell, a physician-scientist, observed the importance of dendritic translation firsthand while working with patients whose immune systems had attacked the hippocampus. "I would talk to a patient for 30 minutes, leave the room, walk back in, and it was like they had never seen me before," he says. "That's when I began focusing on why neurons of the hippocampus have their own system for regulating RNA metabolism—a system that no other cell in the body uses."

That system, it turns out, lies at the heart of how our brains form memories and learn new information, and became a focus for the Darnell lab, culminating in his team's 2003 development of CLIP, a method that allowed researchers to study the proteins that bind and influence RNA. But limitations remained.

"Many details about how neurons respond to stimuli at the dendrites were still missing," Hacısuleyman says. "We needed that information, because that plays a role in determining how neurons function—and where things often go awry in neurologic disease."

1,000 micropeptides

To get a better idea of the role that changes in dendrites play in learning, Hacısuleyman extended the TurboID platform to work in concert with RNA-sequencing, CLIP, translation and protein analysis. The platform allowed the team to track activity in dendrites before, during, and several

minutes after the neuron activates, capturing the moments critical to protein synthesis in the cell and, more importantly, the stage considered key to memory formation.

An analysis of these crucial moments revealed a microscopic upheaval in the dendrite. Upon activation, local ribosomes jump onto mRNAs, an action that has all the biochemical hallmarks of memory formation, and which models predicted will cause the dendrite to produce not only new proteins, but 1,000 small proteins known as micropeptides, with as-yet unknown function.

The team also identified an RNA-binding protein that helps seal the connection between these ribosomes and mRNA, and demonstrated that if that protein is disabled, the proposed micropeptides will not form.

"We never knew these micropeptides might even exist," Darnell says. "It opens a new field of study, where we can ask what these peptides might be doing and how they could play into [memory formation](#). It's such a vast discovery that there are dozens if not hundreds of avenues in which to pursue this."

Among the many observations that researchers will unpack in future studies, one stood out: the team noted that a certain protein stood out for its prolific binding of mRNA in the [dendrite](#). The protein, called FMRP, is key to brain development and function, and [genetic mutations](#) that adversely impact FMRP contribute to Fragile X syndrome, one of the most common genetic causes of intellectual disability.

"Our findings fit nicely with the molecular biology of FMRP, and also open the door to future insights into what is going wrong in Fragile X," Darnell says.

Beyond the paper's immediate findings, dendritic-TurboID could also

allow researchers to examine protein synthesis in other [brain regions](#) and apply the findings to different diseases. "We can now begin to look at many other sites with a fine-toothed comb," Hacısuleyman says.

"When you develop a new technique as Hacısuleyman did, you enter a room that nobody has ever been in before," Darnell adds. "The light turns on, and the findings just take your breath away."

More information: Ezgi Hacısuleyman et al, Neuronal activity rapidly reprograms dendritic translation via eIF4G2:uORF binding, *Nature Neuroscience* (2024). [DOI: 10.1038/s41593-024-01615-5](https://doi.org/10.1038/s41593-024-01615-5)

Provided by Rockefeller University

Citation: New technique sheds light on memory and learning (2024, April 8) retrieved 2 May 2024 from <https://medicalxpress.com/news/2024-04-technique-memory.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.