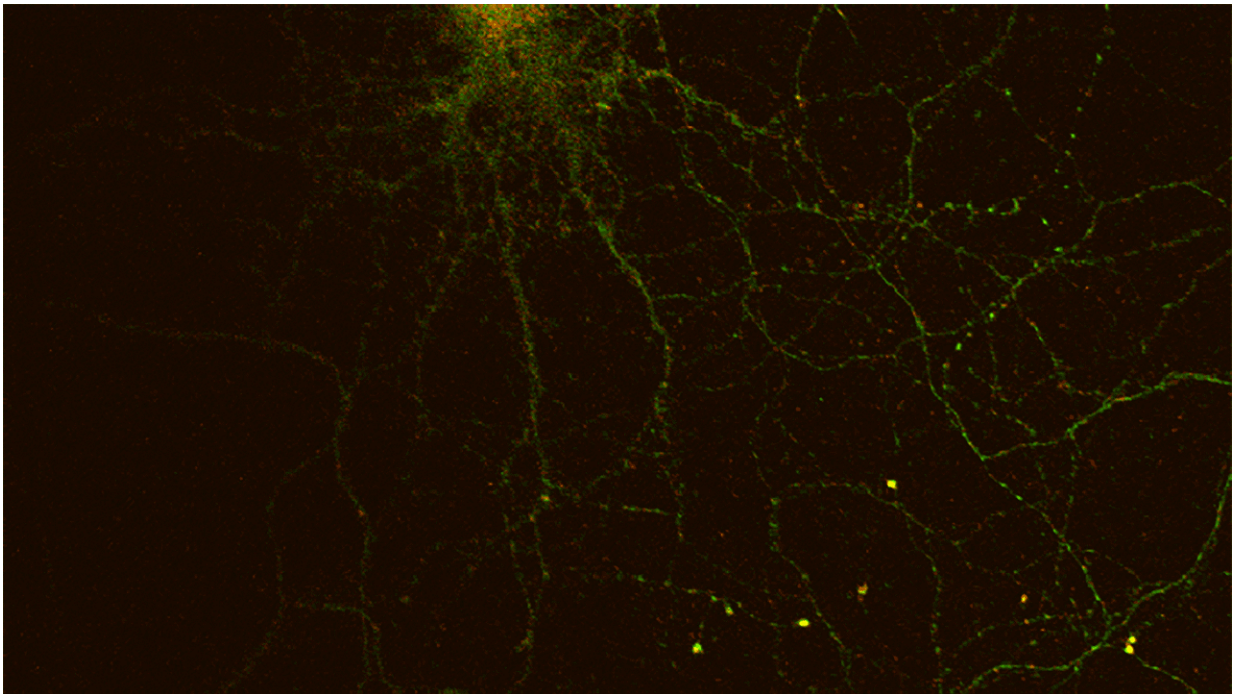


Pinpointing how cells regulate long-lasting memories

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CPEB3 (green) localizing to a neuron's dendrites after stimulation. Credit: Lenzie Ford and Luana Fioriti/Kandel lab/Columbia's Zuckerman Institute

The brain has a knack for safekeeping our most treasured memories, from a first kiss to a child's birth. In a new study in mouse cells, Columbia neuroscientists have mapped some of the molecular machinery that helps the brain maintain these kinds of long-term memories. By observing the activity of nerve cells of the brain, called

neurons, that were extracted from the brain's memory center, the researchers outlined how the protein CPEB3 primes neurons to store memories that stand the test of time.

These findings, published today in the *Proceedings of the National Academy of Sciences*, provide a never-before-seen view into one of the brain's most universal and basic cellular functions. They also suggest new targets against neurodegenerative diseases characterized by memory loss, most notably Alzheimer's disease.

"Memory is what makes us who we are. It permeates our lives and is fundamental to our very existence," said Eric Kandel, MD, the study's co-senior author who is codirector of Columbia's Mortimer B. Zuckerman Mind Brain Behavior Institute, a University Professor and a Kavli Professor of Brain Science at Columbia. "But at its core, memory is a biological process, not unlike a heartbeat. With today's study, we've shed new light on the molecular underpinnings behind our brain's ability to make, keep and recall memories over the course of our lives."

All memories, even fleeting ones, are made when tiny branches, called axons, which extend out from neurons, connect to each other. These connection points, called synapses, are like handshakes: They can be strong or weak. When they weaken, memories vanish. But when they strengthen, memories can stand the test of time. Strengthening a synapse, researchers recently reported, causes an observable change to neurons' anatomy.

In 2015, Dr. Kandel and his team identified a protein in mice, CPEB3, that plays a critical role in this anatomical change. They found that CPEB3 is present at the brain's synapses when memories are formed and recalled. When the researchers prevented mice from making CPEB3, the animals could form a new memory but could not keep it intact.

"Without CPEB3, the synaptic connections collapsed and the memory faded," said Luana Fioriti, Ph.D., Laboratory Head at Mario Negri Institute for Pharmacological Research, Assistant Telethon Scientist at Dulbecco Telethon Institute in Milan, Italy and adjunct associate research scientist on sabbatical in the Kandel lab. Dr. Fioriti is the paper's co-senior author. "Discovering CPEB3's precise function inside the neurons was the impetus for today's study."

Within the hippocampus, the brain's memory center, CPEB3 is produced at regular intervals inside the centers of neurons. In today's study, the Columbia team found that once CPEB3 is produced it is transferred to P bodies, isolation chambers that keep CPEB3 dormant and ready for use.

"P bodies do not have a physical barrier, like a membrane, to contain CPEB3," said Lenzie Ford, Ph.D., a postdoctoral research scientist in the Kandel lab and the paper's co-first author. "Instead, P bodies are denser than their surroundings. This difference in densities holds P bodies together, creating a kind of biophysical forcefield that keeps CPEB3 contained inside and away from the other parts of the cell."

Once laden with dormant CPEB3, the researchers found, P bodies leave a neuron's center and travel down its branches toward the synapses. When an animal has an experience and begins to form a memory, the P bodies dissolve. CPEB3 is released into synapses to help create that memory. Over time, as more CPEB3 is released, these synapses strengthen. This alters the neurons' anatomy and, as a result, stabilizes that memory.

"Our results underscore the central role that protein synthesis plays in the maintenance of memory," said Dr. Kandel, a Howard Hughes Medical Institute Investigator whose pioneering work on the molecular basis of memory earned him the 2000 Nobel Prize in Physiology or Medicine. "And while there are likely additional processes involved that we have

yet to discover, this study, which incorporated state-of-the-art biochemical, genetic and microscopy tools, reveals an elegant biological mechanism of memory in unmatched detail."

Beyond what this research reveals about memory, it also provides insight into [neurodegenerative diseases](#) characterized by memory loss. Because of CPEB3's demonstrated importance in memory storage, and because a version of CPEB3 is also present in the human brain, this protein represents a promising area of focus.

"The science of how synapses form and are strengthened over time is important for deciphering any disorder in which synapses—and the memories associated with them—degrade and die, such as Alzheimer's disease," said Dr. Fioriti. "By continuing to build this understanding, we could one day develop useful methods to boost CPEB3 in a way that prevents synaptic degradation, thus slowing [memory loss](#)."

Another area of focus, according to the Columbia team, relates to the protein SUMO, which the team also found played a central role in this process.

"One of our most intriguing findings is that CPEB3 does not move into P bodies on its own; another protein called SUMO guides it there," said Dr. Ford. "This process, called SUMOylation, represents another promising avenue for the further study of [memory](#)—both in health and disease."

More information: Lenzie Ford et al., "CPEB3 inhibits translation of mRNA targets by localizing them to P bodies," *PNAS* (2019).
www.pnas.org/cgi/doi/10.1073/pnas.1815275116

Provided by Columbia University

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