Neurons' sugar coating is essential for long-term memories

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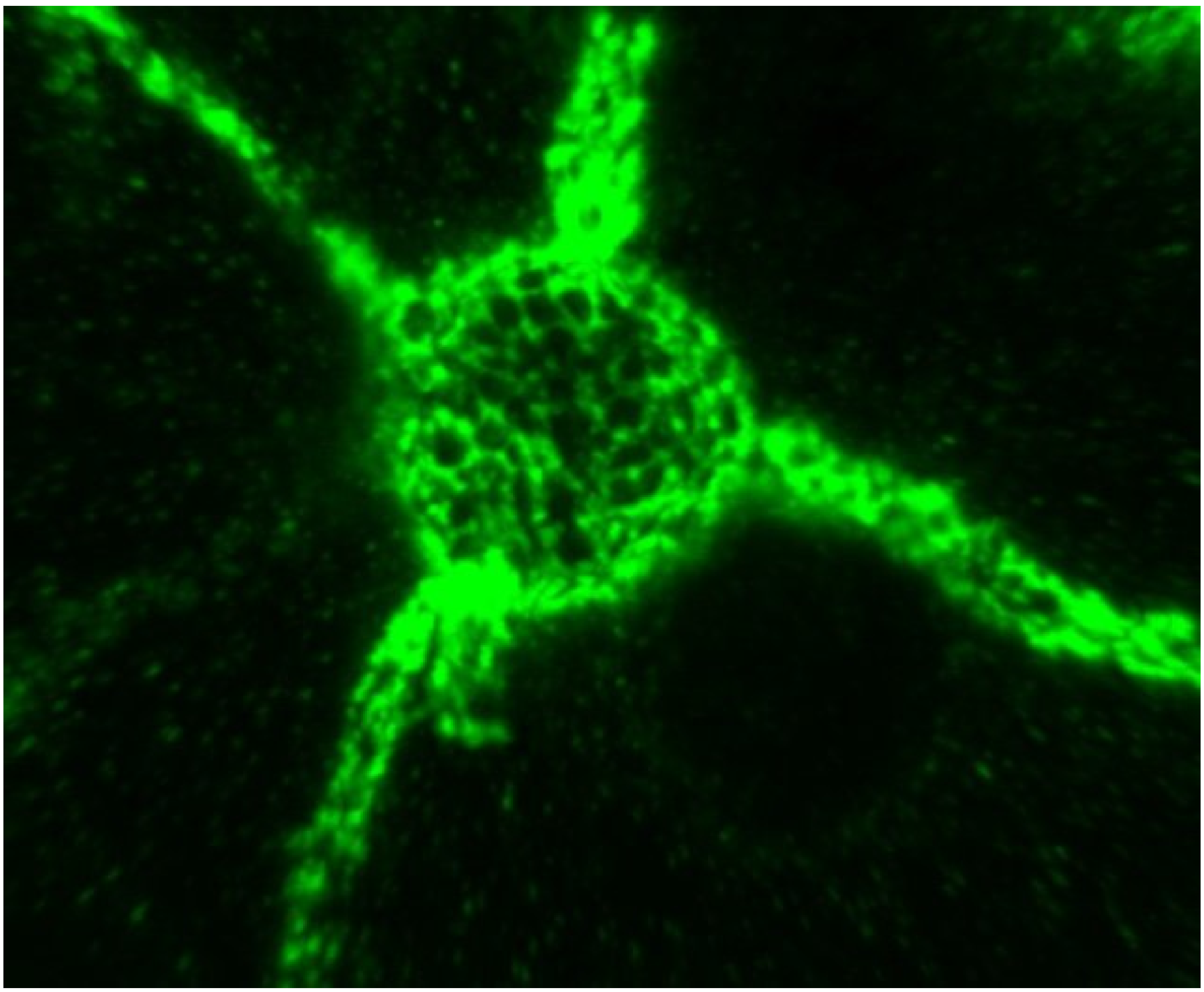

The image shows a perineuronal net (green) surrounding a neuron Credit: Kristian K. Lensjø

How the brain is able to store memories over long periods of time has been a persistent mystery to neuroscientists. In a new study, researchers from the Centre for Integrative Neuroplasticity (CINPLA) at the University of Oslo show that long-lived extracellular matrix molecules called perineuronal nets are essential for distant memories.

The new research published in *Proceedings of the National Academy of Sciences*, shows that removal of the nets disrupts distant but not recent memories.

Previously, researchers have mainly focused on molecules inside the nerve cells. The team of investigators, led by Drs. Marianne Fyhn and Torkel Hafting, studied perineuronal nets that tightly cover the outside of neurons. The nets are made up of sugar-coated proteins, forming a rigid structure that contains holes where connections to other neurons are kept in place.

When new memories are formed, the connections between neurons change. The authors hypothesized that perineuronal nets might stabilize the new, memory-related connections to support long-term memories. To test memory function, the team performed a classical conditioning experiment, where rats learn to associate a light blink with an unpleasant event. This type of learning creates a robust and long-lasting memory.

A surprisingly strong effect

After learning, the rats were divided into two groups, one where the perineuronal nets were left intact and one where they were removed in a small area of the cortex, termed secondary visual cortex, an area known to be involved in memory storage. When the rats were asked to recall the memory a month later, the results were astonishing—the group without the nets did not remember anything. The experiments show that perineuronal nets are essential for long-term memories, because without them, the memory is lost.

"We were quite surprised by how strong the effect was in those first experiments, since we only manipulated molecules outside the neurons and not inside" says Elise H. Thompson, one of the leading authors of the paper.

"While we expected to see some effect of the intervention, previous studies on the nets had focused on their role in development and learning, not memory storage. It was very exciting to see that the memory was in fact gone," Thompson adds.

In a follow-up experiment where the memory was tested only a few days after learning, the team found that the memory was intact, and that the disappearing effect was specific to old memories. "Because the net is a very stable structure it may stabilize memories as they age, but when a memory is new, it survives without extra stabilizing factors," says Dr. Kristian K. Lensjø, another leading author of the paper.

Potential for novel drug targets

While scientists understanding of the processes that govern the transition from short-term to long-term memory has expanded greatly in recent years, those needed for a memory to persist across years remain unresolved. This research is an important step toward understanding what components are needed to store memories for a lifetime.

"If we can increase our understanding of how memories are processed over months and years in the healthy brain, we can start to untangle what goes wrong when they are eventually lost in detrimental diseases like Alzheimer's and dementia. The surprising finding that extracellular molecules are involved in these processes also suggests potential novel drug targets," explains Marianne Fyhn, leader of the CINPLA project.

More information: Elise Holter Thompson et al. Removal of perineuronal nets disrupts recall of a remote fear memory, *Proceedings of the National Academy of Sciences* (2017). DOI: 10.1073/pnas.1713530115

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