Researchers demonstrate a new mechanism of neural plasticity underlying learning and memory processes

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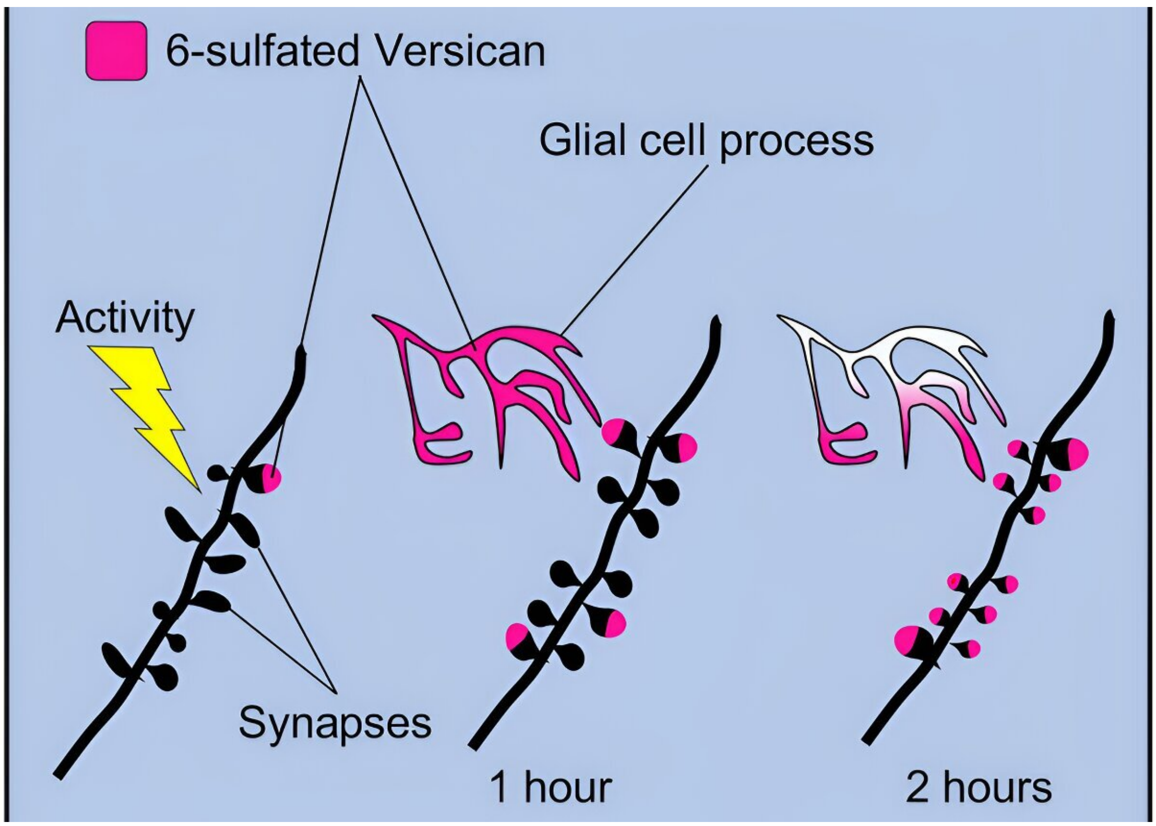

Graphical abstract. Credit: *Cell Reports* (2024). DOI: 10.1016/j.celrep.2024.114112

Neurons are important, but they are not everything. Indeed, it is "cartilage," in the form of clusters of extracellular matrix molecules called chondroitin sulfates, located in the outside nerve cells, that plays a crucial role in the brain's ability to acquire and store information.

A study published in *Cell Reports* describes a new mechanism of brain plasticity, or how nerve connections change in response to external stimuli. The paper is titled "Focal clusters of peri-synaptic matrix contribute to activity-dependent plasticity and memory in mice."

The work stems from a collaboration between the Harvard Medical School, the University of Trento, and the German Center for Neurodegenerative Diseases (DZNE) in Magdeburg.

"Sensory skills and the ability to understand our surroundings depend on the activity of the brain, which enables us to perceive and process stimuli that come from the outside world. Through our brains we are able to acquire and store new information, and to remember information we have already acquired," say Yuri Bozzi and Gabriele Chelini.

"This fascinating phenomenon is made possible by the brain's ability to continuously change the structure and effectiveness of neuronal connections (synapses) in response to external stimuli. An ability that goes by the name of synaptic plasticity. Understanding how synaptic modifications occur and how they contribute to learning and memory is one of the great challenges in neuroscience."

Yuri Bozzi is a professor at the University of Trento and co-senior author. Gabriele Chelini is the first author of the study. Chelini worked on this project starting in 2017, as a postdoctoral fellow in a lab directed by Sabina Berretta (McLean Hospital and Harvard Medical School, Boston), and completed the scientific publication during his years as a postdoctoral fellow in Bozzi's lab at the University of Trento.

At the center of the research are chondroitin sulfates, molecules well known for their role in joints, which also play a crucial function in brain plasticity, being an integral part of the brain's extracellular matrix, as was originally discovered in 2001 by Dr. Alexander Dityatev's group.

In 2007, a Japanese study described the presence of clusters of chondroitin sulfates, circular in shape, scattered seemingly randomly in the brain. This work had slipped into oblivion, however, until Sabina Berretta's translational neuroscience laboratory brought these structures back to the attention of the scientific community, renaming them CS-6 clusters (from chondroitin sulfate-6, which identifies their precise molecular composition) and demonstrating how these structures were associated with glial cells and were severely reduced in the brains of people with psychotic disorders.

Then in 2017, Gabriele Chelini, newly hired in Berretta's lab, was tasked with revealing the function of these clusters.

"First we went to explore these structures in detail, visualizing them at very high resolution. We found that they are essentially clusters of synapses coated with CS-6 and organized in a clearly recognizable geometric shape. We then highlighted a new type of synaptic organization," the scholars recount.

"At this point, we had to use some 'experimental creativity'; with a combination of behavioral, molecular and refined morphological approaches, we realized that these connections encapsulated in CS-6 clusters change in response to electrical activity in the brain."

"Finally, through collaboration with Alexander Dityatev at DZNE Magdeburg, and the efforts of Hadi Mirzapourdelavar from his group, we attenuated the expression of CS-6 in the hippocampus (the region of the brain responsible for spatial learning), and demonstrated that the presence of CS-6 is necessary for synaptic plasticity and spatial memory," Bozzi and Chelini point out.

"This work paves the way for a new way of thinking about brain functioning. It is possible that all synapses formed on different neurons within CS-6 clusters have the ability to respond chorally to specific environmental stimuli, and are involved in a common function aimed at learning and memory processes," they note.

"They seem to represent a new substrate of information integration and association formation at the multicellular level," add Dityatev and Berretta.

The work is the result of a collaboration between several laboratories, including the translational neuroscience laboratory (Sabina Berretta; McLean Hospital—Harvard Medical School, Boston), the neurodevelopmental disorders research laboratory (Yuri Bozzi; CIMeC—Centro Interdipartimentale Mente/Cervello, University of Trento) and the Molecular Neuroplasticity laboratory (Alexander Dityatev; DZNE Magdeburg).

More information: Gabriele Chelini et al, Focal clusters of peri-synaptic matrix contribute to activity-dependent plasticity and memory in mice, *Cell Reports* (2024). DOI: 10.1016/j.celrep.2024.114112

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