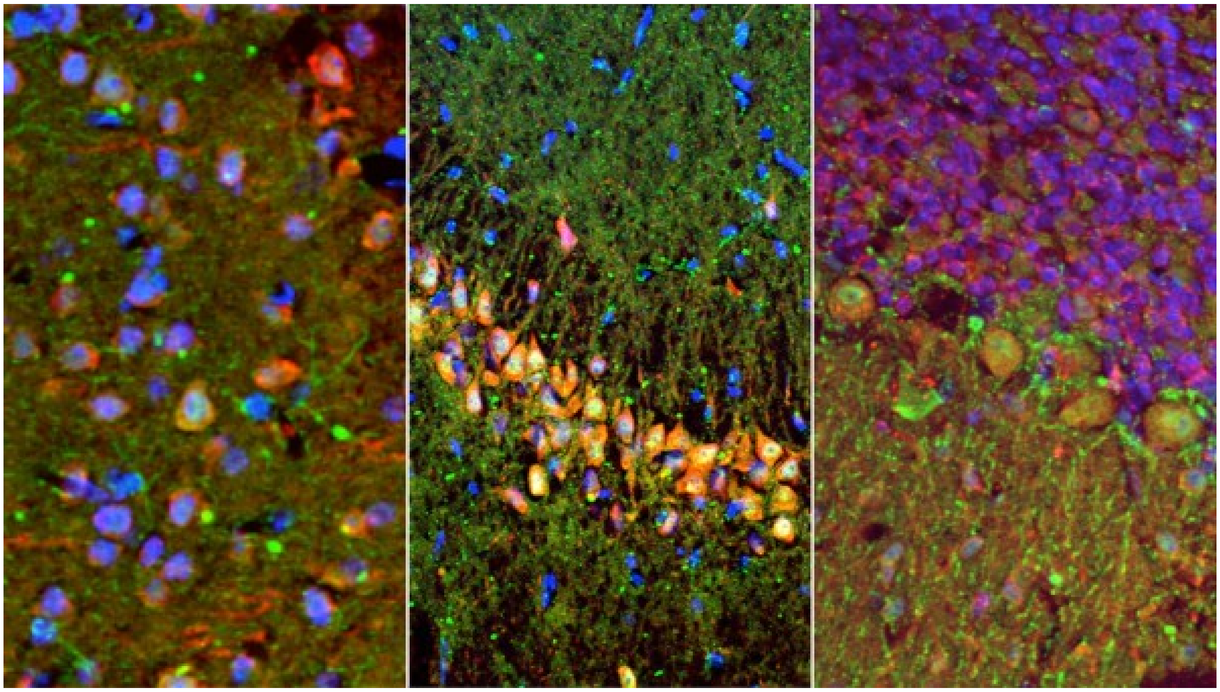

S.F. PALIDA ET AL.

Three regions of the mouse brain in which perineuronal nets (green) are found.

Mysterious 'holes' in neuron net may help store long-term memories

Tweet Share 289 G+1 15

By Emily Underwood (/author/emily-underwood) | 20 October 2015 6:45 pm | 0 Comments (/brain-behavior/2015/10/mysterious-holes-neuron-net-may-help-store-long-term-memories#disqus_thread)

CHICAGO—In 1898, Italian biologist Camillo Golgi found something odd as he examined slices of brain tissue under his microscope. Weblike lattices, now known as "perineuronal nets," surrounded many neurons, but he could not discern their purpose. Many dismissed the nets as an artifact of Golgi's staining technique; for the next century, they remained largely obscure. Today, here at the annual meeting of the Society for Neuroscience, researchers offered tantalizing new evidence that holes in these nets could be where long-term memories are stored.

Scientists now know that perineuronal nets (PNNS) are scaffolds of linked proteins and sugars that resemble cartilage, says neuroscientist Sakina Palida, a graduate student in Roger Tsien's lab at the University of California,San Diego, and co-investigator on the study. Although it's still unclear precisely what the nets do, a growing body of research suggests that PNNs may control the formation and function of synapses, the microscopic junctions between neurons that allow cells to communicate, and that may play a role in learning and memory, Palida says.

One of the most pressing questions in neuroscience is how memories —particularly long-term ones—are stored in the brain, given that most of the proteins inside neurons are constantly being replaced, refreshing themselves anywhere from every few days to every few hours. To last a lifetime, Palida says, some scientists believe that memories must somehow be encoded in a persistent, stable molecular structure. Inspired in part by evidence that destroying the nets in some brain regions can reverse deeply ingrained behaviors (http://www.sciencemag.org/content/298/5596/1248.short) , Palida's adviser Tsien, a Nobel-prize-winning chemist, recently began to explore whether PNNs could be that structure. Adding to the evidence were a number of recent studies linking abnormal PNNs to brain disorders including schizophrenia and Costello syndrome, a form of intellectual disability.

At the meeting, Palida and colleagues attracted a crowd with several new findings that support the hypothesis that PNNs are, indeed, key to learning and long-term memory storage. Given the lack of knowledge about PNNs, Tsien's group first tried to answer basic questions about how long they last, and where—precisely—they are located. Using a stable isotope labeling techniques that can determine whether a protein were present in early life, the team confirmed that proteins contained in the PNNs of rodents are not constantly recycled, but can survive for at least 180 days. "We found that [proteins contained in] PNNs are highly stable, and can last throughout an animal's lifetime," Palida says. The researchers also found—using a new florescent labeling technique developed by Palida—that they are pervasive throughout the brain, instead of being limited to just a few brain areas, as previous studies have suggested.

Next, Palida and colleagues explored how PNNs interact with synapses. These connectors are thought to form and grow stronger as memories are created and reinforced, and weaken and even disappear as memories fade. No one yet knows how many synapses—or neurons, for that matter—are involved in any one memory. After growing neurons in a petri dish and allowing the PNNs surrounding them to develop, Palida treated them with BDNF, a chemical that stimulates neurons to form new connections with other cells. Using electron microscopy to examine the neurons at nanoscale resolution, the group found that wherever synapses had emerged, the PNN's tight-knit lattice had developed holes, as if to accommodate the new connections. The new data suggest that the PNN is an "ideal substrate for very long term maintenance of memory over time," Palida says. In a separate experiment, the group found that knockout mice missing an enzyme that normally degrades the PNN performed badly on a basic fear-association task: The animals failed to associate a shock with a beep.

The results fit well with growing evidence that loose or degraded PNNs increase neural plasticity, says John Wesley Paylor, a master's student at the University of Alberta, in Edmonton.

"The idea is that if the net is loose, any synapse can come in and make contact," whereas a tight net prevents new synapses from forming, preserving connections that were established before, he says. Further support for the hypothesis comes from studies showing that PNN formation is correlated with critical periods—set windows of time in which functions, such as vision, develop. But given that many other factors are known to influence memory formation, "it's a bit of a stretch to say that the hole itself is encoding info," he cautions.

Although PNNs do seem to limit plasticity, it's still not clear how much they change throughout life, notes Barbara Sorg, a neuroscientist at Washington State University in Vancouver. A number of environmental factors seem to be able to loosen up or tighten PNNs, she notes: Cocaine addiction, for example, seems to trigger an over-expression of PNNs in animals, suggesting a potential mechanism for the intense and persistent memories that form as a result of drug abuse, she says. At the meeting, Sorg's group presented evidence that destroying the PNN in some regions can erase drug-associated memories, suggesting that the process may be reversible. Don't look for PNN-dissolving therapies anytime soon, however, she says: The enzyme used to break down the PNN in animals is a "very blunt tool," and there's no knowing what would happen to a person if they were exposed to it, she says.

Ultimately, scientists will need a way to watch how PNNs change over time in living animals to determine their true role in memory, says Takao Hensch, a molecular biologist at Harvard University. Next, Palida says, Tsien's group plans to create transgenic rodents with the florescent PNN marker, and watch how the nets change over time in the laboratory.

Posted in Brain & Behavior (/category/brain-behavior)

Science | DOI: 10.1126/science.aad4740
