Lateral inhibition keeps similar memories apart

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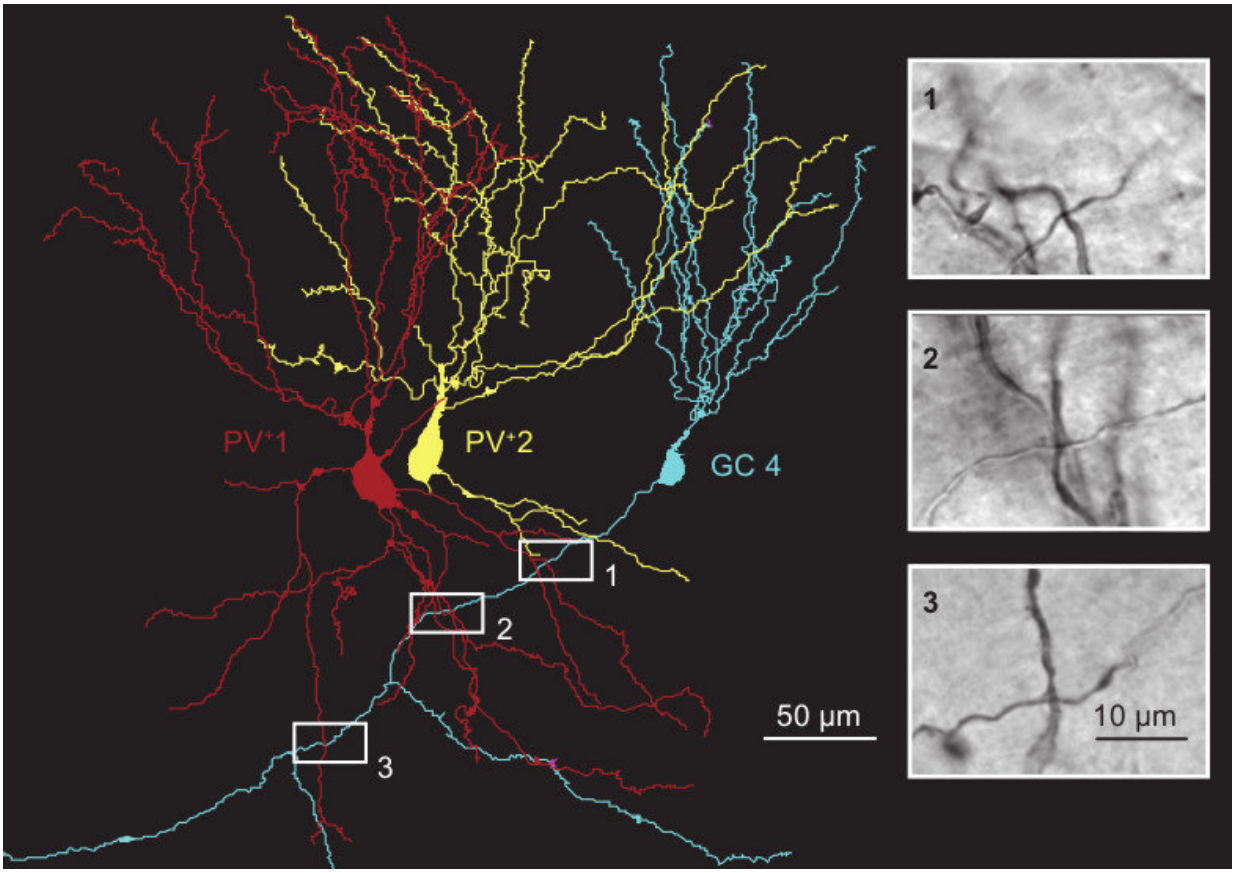

Digital reconstruction of the two parvalbumin-expressing interneurons (red and yellow) and one granular cell (blue) and visualization of the synaptic connections (black & white photographs). Credit: Espinoza et al

When you park in the office car park, you usually have no problem

finding your car again at the end of the day. The next day, you might park a few spots further away. However, in the evening, you find your car, even though the memories of both days are very similar. You find your car (also) because our brains are able to store memories of very similar events as distinct memories in a process called pattern separation. Researchers at the Institute of Science and Technology Austria (IST Austria) are deciphering how the brain computes this pattern separation in a brain region called the dentate gyrus. Results of their work are published today in *Nature Communications*.

Peter Jonas and his team, including first author and Ph.D. student Claudia Espinoza, Jose Guzman and Xiaomin Zhang sought to understand how the connections between neurons in the dentate gyrus, a part of the hippocampus, enable the separation of patterns in mice.

In the dentate gyrus, two types of neurons send signals: principal neurons send excitatory signals, while interneurons send inhibitory signals. The researchers sought to decipher the rules of connectivity between them—which neurons send signals to each other, whether connections between neurons are reciprocal, and whether many neurons converge to send signals to one main neuron. They recorded signaling between neurons to understand how the neurons are connected and how the local circuit works to support pattern separation. Espinoza performed octuple whole-cell recordings, in which she stimulated one neuron in a slice of the dentate gyrus, and recorded how the other seven neurons responded. By labeling all stimulated neurons, she could then reconstruct the morphology of the circuit.

The researchers found that the parvalbumin-expressing interneurons are connected in a specific way only in the dentate gyrus. In the dentate gyrus, parvalbumin-expressing interneurons mainly inhibit the activity of nearby neurons in a process called lateral inhibition. In other brain regions, such as the neocortex, parvalbumin-expressing interneurons are

not connected in this manner. "We think that the unique connectivity rules established by parvalbumin-expressing interneurons, such as lateral inhibition, represent a circuit adaptation to specific network functions that occur in this brain region," says Claudia Espinoza. "Our experimental data supports the idea that pattern separation works through a mechanism called 'winner-takes-all,' achieved via lateral inhibition in the dentate gyrus. However, this has not been proven yet. We need behavioral data and computational models, which we are working on."

After the dentate gyrus separates similar memories to avoid an overlap between them, the CA3 region of the hippocampus then stores these memories. In a previous article published in *Science* in 2016, Peter Jonas and Jose Guzman showed that the connectivity in the CA3 region of the hippocampus is designed to recall information of stored memories in a process called pattern completion. "At a biological level, our group found the connectivity rules that support the computational function of a brain region," says Espinoza, "Our work contributes to showing how local circuits are optimized for the specific function of a brain area. While the input that reaches the dentate gyrus is important, the way in which the dentate gyrus then computes this information to achieve pattern separation is crucial."

Claudia Espinoza is a Ph.D. student in the group of Peter Jonas. Before she joined IST Austria for her Ph.D. studies in 2013, she worked with patients with neurological disorders. This experience motivated Espinoza to pursue a Ph.D. in neuroscience: "I realized that my work as a therapist was very limited because the treatment that we could offer to our patients was very scarce, and actually most of the available treatments are palliative and not curative. The main reason is that the information available about how the nervous system works is very limited, more than what most people believe. This fact motivated me the most for changing my career from a therapist to a researcher. I think that creating

knowledge is a beautiful way of contributing something to our society and indirectly to helping people."

More information: Claudia Espinoza et al, Parvalbumin+ interneurons obey unique connectivity rules and establish a powerful lateral-inhibition microcircuit in dentate gyrus, *Nature Communications* (2018). DOI: 10.1038/s41467-018-06899-3

S. J. Guzman et al. Synaptic mechanisms of pattern completion in the hippocampal CA3 network, *Science* (2016). DOI: 10.1126/science.aaf1836

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