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Novel combination of techniques reveals new details about the neuronal networks for memory

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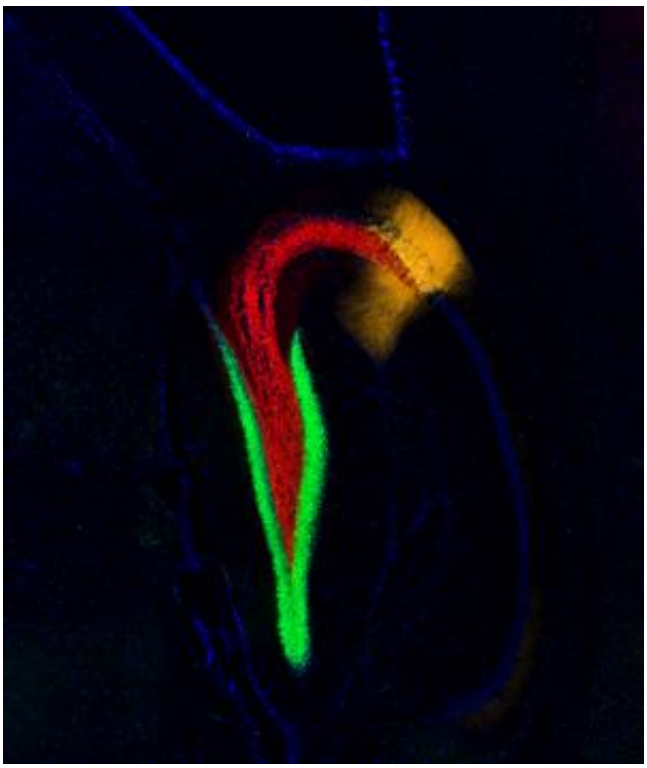

Figure 1: Fluorescent labeling reveals mossy fibers (red) projecting from the dentate gyrus (green) into the CA2 subregion (orange). Credit: Keigo Kohara, RIKEN–MIT Center for Neural Circuit Genetics

Learning and memory are believed to occur as a result of the strengthening of synaptic connections among neurons in a brain structure

called the hippocampus. The hippocampus consists of five subregions, and a circuit formed between four of these is thought to be particularly important for memory formation. Keigo Kohara and colleagues from the RIKEN–MIT Center for Neural Circuit Genetics and RIKEN BioResource Center have now identified a previously unknown circuit involving the fifth subregion.

For a hundred years, memory research has typically focused on the main circuit, which projects from layer II of the entorhinal cortex via the dentate gyrus to subregion CA3 and then CA1. Subregion CA2 lies between CA3 and CA1 but its cells are less elaborate than those of its neighbors and were thought not to receive inputs from the dentate gyrus.

Kohara and his colleagues combined anatomical, genetic and physiological techniques to analyze the connections formed by neurons in the CA2 subregion of the hippocampus in unprecedented detail. First, they identified the CA2 subregion by examining the expression of three genes that encode proteins called RGS14, PCP4 and STEP using a fluorescent marker to label nerve fibers—a technique called fluorescent immunohistochemistry. They were surprised to discover that, contrary to expectations, CA2 neurons receive extensive inputs from cells in the dentate gyrus (Fig. 1).

The researchers reinforced their anatomical observations by performing a series of experiments in genetically engineered mice expressing light-sensitive algal proteins in their mossy fibers. They stimulated the fibers with pulses of laser light and simultaneously recorded activity in the other subregions with microelectrodes. This procedure showed that stimulation caused neurons in both CA2 and CA3 to fire quickly, followed by neurons in CA1 after a brief delay.

Another set of experiments revealed that neurons in CA2 also send fibers to the CA1 subregion, forming an alternative circuit. The

researchers found that, unlike CA3 neurons, the fibers of CA2 neurons preferentially enter the deeper layers of CA1. They also found that cells in layer III of the entorhinal cortex do not project to CA2, again contrary to previous reports.

"It was previously unclear how memory is transferred from the dorsal hippocampus, which is involved in spatial memory, to the ventral hippocampus, which is involved in emotional memory," says Kohara. "Our findings tell us that the CA2-linked circuit may be the route by which spatial information combines with emotional information because it relays information from the dorsal to the ventral hippocampus."

More information: Kohara, K., Pignatelli, M., Rivest, A. J., Jung, H.-Y., Kitamura, T., Suh, J., Frank, D., Kajikawa, K., Mise, N., Obata, Y. et al. "Cell type–specific genetic and optogenetic tools reveal hippocampal CA2 circuits." *Nature Neuroscience* 17, 269–279 (2014). dx.doi.org/10.1038/nn.3614

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