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Newly found 'volume control' in the brain promotes learning, memory

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Scientists have long wondered how nerve cell activity in the brain's hippocampus, the epicenter for learning and memory, is controlled—too much synaptic communication between neurons can trigger a seizure, and too little impairs information processing, promoting neurodegeneration. Researchers at Georgetown University Medical Center say they now have an answer. In the January 10 issue of *Neuron*, they report that synapses that link two different groups of nerve cells in the hippocampus serve as a kind of "volume control," keeping neuronal activity throughout that region at a steady, optimal level.

"Think of these special synapses like the fingers of God and man touching in Michelangelo's famous fresco in the Sistine Chapel," says the study's senior investigator, Daniel Pak, PhD, an associate professor of pharmacology. "Now substitute the figures for two different groups of neurons that need to perform smoothly. The touching of the fingers, or synapses, controls activity levels of neurons within the hippocampus."

The hippocampus is a processing unit that receives input from the cortex and consolidates that information in terms of learning and memory. Neurons known as granule cells, located in the hippocampus' dentate gyrus, receive transmissions from the cortex. Those granule cells then pass that information to the other set of neurons (those in the CA3 region of the hippocampus, in this study) via the synaptic fingers.

Those fingers dial up, or dial down, the volume of neurotransmission from the granule cells to the CA3 region to keep neurotransmission in

the learning and memory areas of the hippocampus at an optimal flow—a concept known as homeostatic plasticity. "If granule cells try to transmit too much activity, we found, the synaptic junction tamps down the volume of transmission by weakening their connections, allowing the proper amount of information to travel to CA3 neurons," says Pak. "If there is not enough activity being transmitted by the granule cells, the synapses become stronger, pumping up the volume to CA3 so that information flow remains constant."

There are many such touching fingers in the hippocampus, connecting the so-called "mossy fibers" of the granule cells to neurons in the CA3 region. But importantly, not every one of the billions of neurons in the hippocampus needs to set its own level of transmission from one nerve cell to the other, says Pak.

To explain, he uses another analogy. "It had previously been thought that neurons act separately like cars, each working to keep their speed at a constant level even though signal traffic may be fast or slow. But we wondered how these neurons could process learning and memory information efficiently, while also regulating the speed by which they process and communicate that information.

"We believe, based on our study, that only the mossy fiber synapses on the CA3 neurons control the level of activity for the hippocampus—they are like the engine on a train that sets the speed for all the other cars, or neurons, attached to it," Pak says. "That frees up the other neurons to do the job they are tasked with doing—processing and encoding information in the forms of learning and memory."

Not only does the study offer a new model for how homeostatic plasticity in the hippocampus can co-exist with learning and memory, it also suggests a new therapeutic avenue to help patients with uncontrollable seizures, he says.

"The CA3 region is highly susceptible to seizures, so if we understand how homeostasis is maintained in these neurons, we could potentially manipulate the system. When there is an excessive level of CA3 neuronal activity in a patient, we could learn how to therapeutically turn it down."

Provided by Georgetown University Medical Center