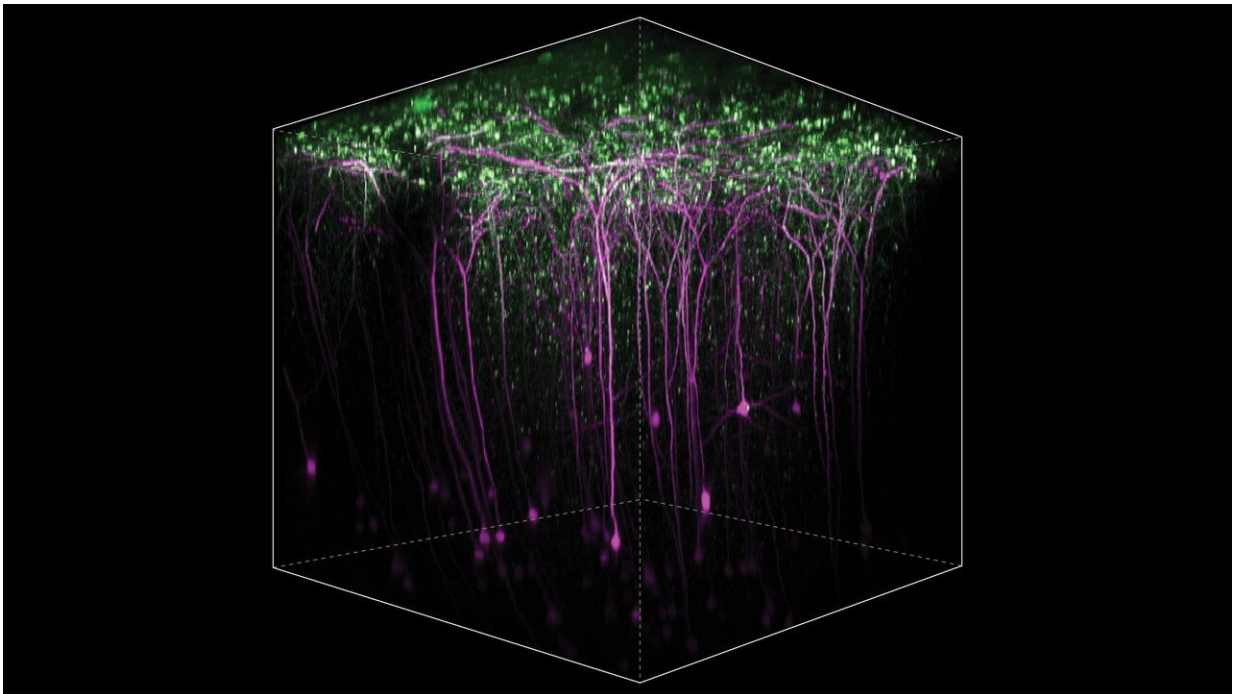


# Some learning is a whole-brain affair, study shows

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AMPA receptors in green on neurons in magenta at one time point in a live mouse. Credit: Richard Roth and Richard Huganir

Researchers at Johns Hopkins Medicine have successfully used a laser-assisted imaging tool to "see" what happens in brain cells of mice learning to reach out and grab a pellet of food. Their experiments, they say, add to evidence that such motor-based learning can occur in multiple areas of the brain, even ones not typically associated with motor

control.

"Scientists should be looking at the entire brain to understand specific types of learning," says Richard Huganir, Ph.D., Bloomberg Distinguished Professor and Director of the Solomon H. Snyder Department of Neuroscience at the Johns Hopkins University School of Medicine. "Different parts of the brain contribute to learning in different ways, and studying brain cell receptors can help us decipher how this works."

The work, say the researchers, may ultimately inform efforts to develop treatments for learning-based and neurocognitive disorders.

In a report on the work, appearing online Dec. 31 in *Neuron*, Huganir and his research team say they focused on AMPA-type glutamate receptors, or AMPARs, key molecules that help send messages between brain cells called neurons. AMPARs function like antennas that form along the surface of a particular spot on neurons called a synapse, where it receives molecular signals from other neurons.

To monitor and measure AMPAR levels in mouse brains, scientists previously had to dissect the organ before and after a learning experiment and compare differences. Now, scientists have ways to directly view the brain during learning, recording thousands of synapses at a time.

In the new experiments, scientists injected DNA-encoding AMPARs carrying a fluorescent tag into the brains of [mice](#), and used an electrical pulse to get neurons to absorb the AMPAR DNA. Next, with a tool called two-photon microscopy, the scientists used a laser—essentially an intensely focused beam of light—to detect and measure the amount of fluorescence coming from the tagged AMPARs.

More fluorescence is an indication of increased AMPAR activity and messaging between neurons, a good sign that learning and memory building is taking place in those neurons, Hugarir says.

To "see" what learning looked like in the test animals' neurons, Hugarir's team trained mice to reach for and grab a food pellet placed just outside their cage using their paws. Normally, mice get pellets with their mouths.

While the mice were learning how to reach for the pellet, the scientists found an approximately 20% increase in the activity of AMPARs in an area of the brain known as the [motor cortex](#), which is known for controlling and precisely moving muscles. On neurons, the AMPARs look like lights on a Christmas tree and glow brighter with increasing activity.

But the experiments also showed the same increase in AMPAR activity levels in the visual cortex too.

"This made sense because vision is very important for [motor control](#)," says Richard Roth, Ph.D., currently a postdoctoral fellow at Stanford University, but who performed experiments for this study as a graduate student in Hugarir's laboratory.

"So, we did the same experiment again, but with the lights switched off," says Roth.

Using infrared light, which the mice couldn't see, the mice eventually learned to successfully grab the food, but there was a smaller increase (10%) in the activity of AMPARs in the visual cortex.

"We believe the mice brains are using different sets of sensory cues in the dark to learn the motor task, including touch and smell, enabling these other senses to take over," says Roth.

Next, the research team repeated the experiments using specialized light-activated modulators to shut down neurons in either the motor or visual cortex.

If the mice were trained to get the pellet with the room lights on, the mice could not complete the task if their visual cortex was shut down. "Clearly, these mice relied on learning centralized in their visual cortex to reach the pellet," says Roth.

However, mice initially trained to grab the pellet in the dark could still complete the task, even if their [visual cortex](#) was shut down.

"We've traditionally thought that motor-based learning happens solely in the motor part of the brain, but our studies and others now show that it's not as specific as we had thought. There is more of a brainwide effect in learning," says Roth.

Huganir notes that among the genes that control neuronal receptors involved in learning is SYNGAP. His and others' research has shown that when the gene is mutated, it contributes to conditions including intellectual disability, autism and schizophrenia—all conditions marked in part by disrupted thinking and learning.

**More information:** Richard H. Roth et al, Cortical Synaptic AMPA Receptor Plasticity during Motor Learning, *Neuron* (2019). [DOI: 10.1016/j.neuron.2019.12.005](#)

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