Old habit-controlling neurons may also help the brain learn new tricks

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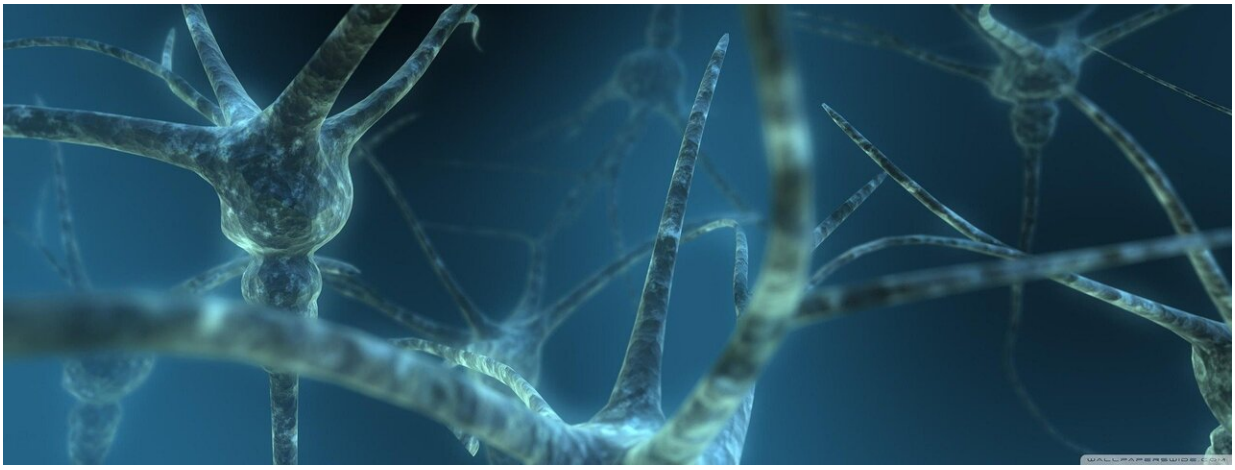

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Imagine working on your computer and typing the same long password you have used for years to access your email. By habit, you perform this sequence almost unconsciously. But then, one day, you stumble upon a shortcut. It's faster but involves learning and remembering a new set of keystrokes.

In a study of rodents, scientists at the Icahn School of Medicine at Mount Sinai discovered that a part of the brain traditionally thought to control typing the old sequence may also play a critical role in learning the new one. The results, published on August 25th in *Nature*

Communications, suggest that this process involves a delicate balance in the activity of two neighboring neural circuits: one dedicated to new actions and the other to old habits.

"For years scientists thought that habits and learning new, rewarding actions were most likely controlled by different parts of the brain. Surprisingly, we found that a brain area traditionally thought to specialize in the expression of old habits may also help the brain learn new actions," said Paul J. Kenny, Ph.D., the Ward-Coleman Professor and Chair of the Nash Family Department of Neuroscience at Mount Sinai and the senior author of the paper. "Ultimately, we hope that these results provide new insights into the brain cells and circuits which underlie a variety of disorders that involve abnormalities in how our actions are controlled, including Parkinson's disease and drug addiction."

The study was led by Alexander C. W. Smith, Ph.D., an instructor in the Kenny lab, and Sietse Jonkman, Ph.D., a former postdoctoral fellow at Mount Sinai.

Action learning happens when doing something, like moving an object, produces a benefit, such as finding food or avoiding a foe. In this study, the researchers examined the role that the striatum plays in this type of learning. Located deep inside the brain, the striatum is known to be involved with controlling movements and actions.

"Although scientists have hypothesized that the striatum is involved in action learning, few have actually tested this idea," said Dr. Jonkman. "We wanted to take an in-depth look at the striatal circuits that may be involved with action learning."

To do this, the researchers tested the ability of hungry rodents to find food. On day one of the experiments, the rodents were put into a special cage and trained to earn food by pressing a dispenser lever. Each time an

experimental rodent pressed the lever it received a food pellet whereas control rodents received none. Two days later, the researchers tested learning by putting the rodents back into the special cage. Once in the cage, the experimental rodents vigorously pressed the lever even though it no longer delivered food, indicating they had successfully learned the new action, whereas the control rodents would search all around and only press the lever a few times.

At various times during the experiments, the researchers examined neural activity in the rodents' brains. They found that immediately after a training session, neurons in specific areas of the striatum were more active in experimental rodents than those in the control group. This was a period when the memory of the newly learned action is known to be stored, or encoded, in the brain for later use. Most notably, this was seen in the dorsolateral striatum, the posterior dorsomedial striatum, and the nucleus accumbens, suggesting these areas played a role in learning.

To test this further, the researchers injected into each area a drug, anisomycin, which prevents cells from manufacturing the proteins required for long-term memory storage. The drug was injected either immediately after a training session or six hours later, a time when the new proteins required for memory storage should already have been produced. Unexpectedly, the researchers found that the drug only disrupted the ability of the animals to remember the new action when it was injected into the dorsolateral striatum immediately after the training session. Injections into any other areas had no effect on learning.

"We were surprised by these results. Traditionally, it is thought that action learning is encoded by the posterior dorsomedial striatum while the dorsolateral striatum only takes care of habits. But that is not what we saw," said Dr. Smith. "Instead our results suggested that in addition to regulating habits, the dorsolateral striatum also consolidates action learning immediately after the new action has been learned."

Further experiments supported this idea. For instance, chemically blocking the activity of neurons in the dorsolateral striatum soon after a training session also prevented the rodents from remembering to use the lever to retrieve food.

Finally, when the researchers took a closer look at this area, they found that learning may be controlled by two neighboring and counteracting neural circuits known to respond to the neurotransmitter dopamine. In one circuit, the activity of cells called D1 receptor medium spiny neurons rose immediately after training, and inhibiting these cells hindered learning. In contrast, the activity of the other cells, called D2 receptor medium spiny neurons, quieted after training and blocking their activity enhanced the ability of the animals to remember the new action. In a separate set of experiments the researchers found that blocking D2 neuron activity prevented the rodents from displaying previously learned habits.

"Our results suggest that there is a delicate balance between new action learning and the expression of old habits, which is controlled by the yin-yang activity of two different populations of neurons in the dorsolateral striatum," said Dr. Kenny. "In the future, we plan to study how disruption of this balance contributes to maladaptive actions in brain disorders."

More information: Alexander C. W. Smith et al, Opposing roles for striatonigral and striatopallidal neurons in dorsolateral striatum in consolidating new instrumental actions, *Nature Communications* (2021). DOI: 10.1038/s41467-021-25460-3

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