Research team reveals underpinnings of how motor memory forms

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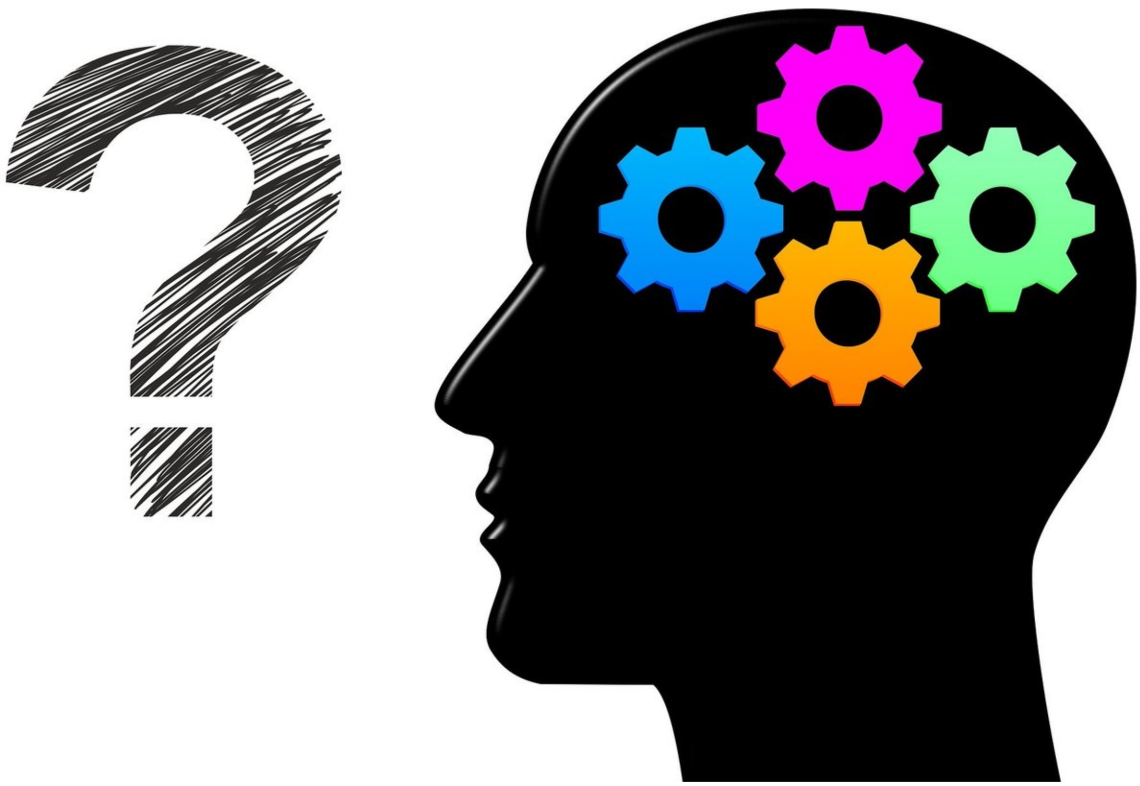

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When you are first learning how to ride a bicycle or play a musical instrument, your physical movements are uncoordinated at best. But with time and lots of repetition, your brain's motor neurons create a kind of shorthand between mind and muscle. The associated motions eventually become so ingrained that jumping on a bike or playing scales feels nearly automatic.

What are the cellular underpinnings of how this motor learning process works? In a study published this week in *Neuron*, a research team led by Dr. Simon Chen of the uOttawa Faculty of Medicine offers new and valuable insights into this enduring mystery of neuroscience.

His lab is focused on unraveling how memories are encoded and stored in the brain, particularly with motor learning, the complex process of how we move and coordinate the muscles of our bodies. With this latest study, Dr. Chen's research team explored the mechanisms involved in regulating the process of motor memory acquisition and consolidation during repetitive practice.

Dr. Chen, the Canada Research Chair in Neural Circuits and Behavior, says the study's findings could prove useful for developing therapeutic targets that can help recover motor functions in patients suffering from Parkinson's disease, a stroke or a brain injury. This is significant because restoring gross motor coordination and regaining lost movements is a very difficult battle for these individuals.

"If we understand how the acquisition of motor skills is regulated in the brain then perhaps one day we can help patients with stroke or Parkinson's disease regain those skills during the rehabilitation process," he says.

The study focused on mice, not people. But since scientists believe that the mechanisms of memory formation are very similar in mice and human beings, the findings likely have deep relevance for people.

So how did the experiments work?

By restricting the head movements of mice on the imaging stage, which allows scientists to probe the brain at single-cell resolution, the team trained the animals to perform a specific motor task: Reach and grasp a food pellet from a motorized delivery holder.

Initially, the head-restrained mice were tentative and clumsy when grabbing the pellet. The researchers conducted detailed analysis of the animals' movements using DeepLabCut, a deep-learning software toolbox combining motion-capture video with artificial intelligence. They found that with repetition and time, mice formed stereotyped reach-and-grasp movements that allowed them to eventually secure the food easily.

The team wanted to see the activation of neurons specific to these reach-and-grasp movements—and view the formation of synaptic pathways in the brain as they occurred.

"We were able to monitor the brain changes while mice were actually learning this task," says Dr. Chen, an associate professor at the Faculty of Medicine's department of Cellular and Molecular Medicine.

Using two-photon imaging, a type of microscopy that permits the visualization of living tissue at micrometer scale, his team was able to view the reorganization of dendritic spines among the excitatory neurons in the primary motor cortex as the head-fixed mice performed these pellet-grabbing actions over time. Dendritic spines—neural structures at synapses resembling lollipops with skinny sticks and bubble-like tops—are key for memory formation and storage.

Zooming in to the cellular level, the researchers discovered that motor learning selectively induces the expression of an activity-dependent "transcription factor" called NPAS4 in the primary motor cortex.

What these novel findings unveil, says Dr. Chen, is that the expression of this transcription factor triggers the emergence of a learning-associated inhibitory neuron ensemble that modulates inhibition in the primary motor cortex. That regulates the dendritic spine reorganization process among excitatory neurons during learning.

Essentially, NPAS4 regulates the gene changes in the inhibitory neurons that control the activity of these neurons similar to the way a volume slider controls a laptop's speakers. Dr. Chen says these findings "also demonstrate that inhibitory neuron-specific induction of a transcription factor acts as a defining feature underlying the formation of neuronal ensembles engaged by an act of learning."

In other words, repeating the movements over time changed the inner workings of the animals' primary motor cortex—the part of the brain that only mammals possess, and which controls complex movements.

The team found that the expression of the NPAS4 transcription factor in inhibitory neurons is key to how your brain winnows down options to form the strongest motor memories for specific movements—and it needs to be consistently re-expressed for those memories to get lodged and refined in your brain while doing repetitive practices.

More information: Jungwoo Yang et al, Functionally distinct NPAS4-expressing somatostatin interneuron ensembles critical for motor skill learning, *Neuron* (2022). DOI: 10.1016/j.neuron.2022.08.018

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