New study sheds light on brain's ability to orchestrate movement

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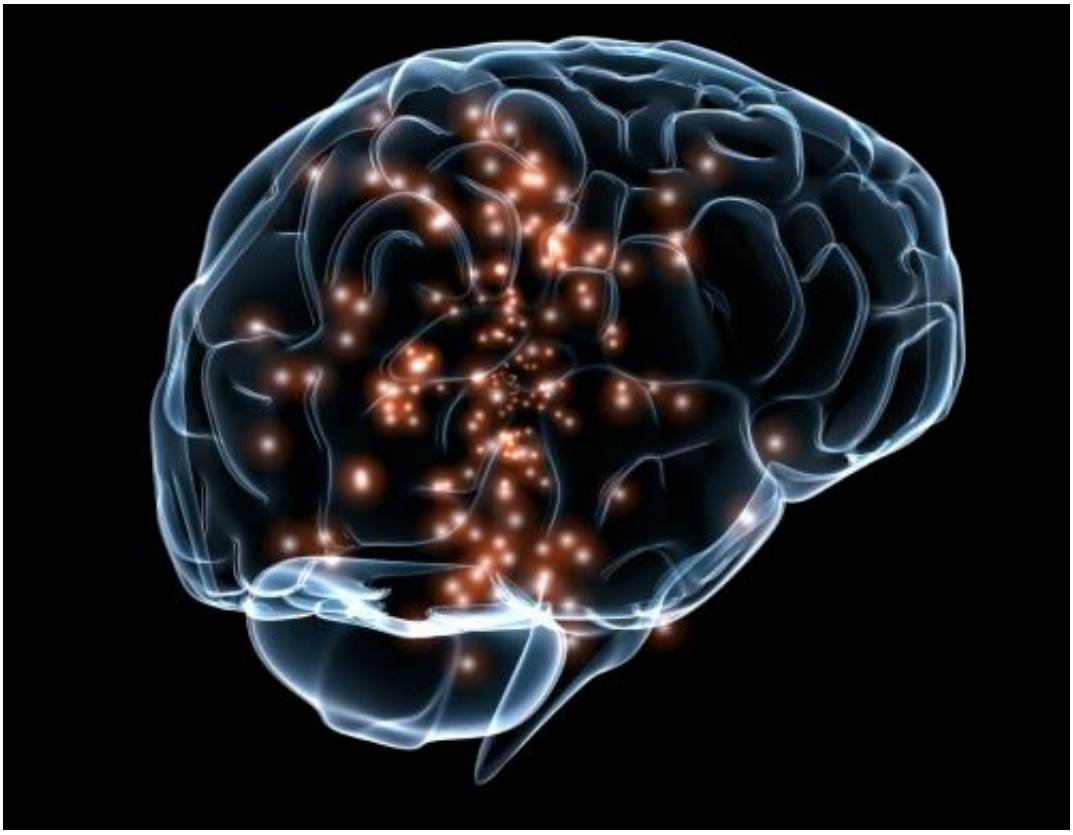

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To carry out any action, whether playing the piano or dancing the jitterbug, the brain must select and string together a series of small, discrete movements into a precise, continuous sequence.

How exactly the brain achieves this remarkable feat has been a mystery, but a new study in mice, led by scientists from Harvard Medical school, brings much needed insight into this process.

Results of the study, published online May 17 in *Cell*, reveal that the brain relies on an exquisite balance between the activity of two populations of neurons in a part of the brain called the striatum, the coordinating center for motor and action planning. The findings could help researchers better understand conditions that dramatically impact movement—such as Parkinson's disease and Huntington's disease—and eventually develop new ways to treat them.

"We believe our observations set the stage for both unraveling how movement gets translated into desired action, and propel us forward in our ability to understand and, eventually, treat devastating neurodegenerative disorders where this process goes awry," said the study's senior author Sandeep Robert Datta, associate professor of neurobiology at Harvard Medical School.

Scientists have long known that the striatum, a spiral-shaped region buried in the forebrain, is a critical component of the motor system, which houses the neurons that die out in both Parkinson's and Huntington's diseases.

Previous research identified two populations of cells in the striatum—spiny projection neurons arranged into what are called the direct and the indirect pathways—that control key aspects of movement.

However, precisely how these two pathways interact to modulate and guide movement has remained unclear. Some evidence suggests that the direct pathway selects and initiates the expression of actions, while the indirect pathway inhibits unwanted actions. Other studies, however, have found that both pathways are often activated at the same time.

"That didn't make sense based on what we've long thought each pathway did," explained the study's lead author Jeffrey Markowitz, a postdoctoral fellow in the department of Neurobiology.

To better define the dynamic between these pathways, the research team took advantage of technology developed by the Datta lab called MoSeq, short for motion sequencing. The system films animals' three-dimensional movements and uses machine learning to fine-splinter, or precisely parse, the movements into basic patterns lasting only a few hundred milliseconds apiece. The researchers dubbed those ultra-fast movements "syllables."

Teaming up with neural imaging experts from Bernardo Sabatini's lab, the researchers genetically altered neurons in the direct and indirect pathways to fluoresce, or glow, in different colors when activated. Combining neural imaging, genetic engineering and MoSeq allowed the scientists to observe and analyze the neural activity simultaneously in both pathways as mice performed a variety of actions.

Corroborating previous studies, the researchers found that every time mice switched behaviors—from running to stopping, for example—the activity of both pathways increased.

When they looked at syllables identified by MoSeq, however, they found that the balance of activity between the two pathways differed. For some syllables, the direct pathway dominated; for others, the indirect pathway did. Even for highly similar syllables, such as two different types of "scrunching," or curling up in a ball, the two pathways could be distinguished. Each syllable yielded a particular balance between the two pathways. The relationship between neural activity and syllables was so pronounced that the researchers could successfully identify specific syllables expressed based on the pathway activity alone.

The activity ratios between the pathways were so constant that the researchers successfully identified specific syllables being expressed based on the activity of the pathways alone. Using imaging techniques, they could also observe ensembles of neurons that displayed regular and predictable patterns of activity during particular syllables.

In a final set of experiments, the scientists wanted to understand what happened when activity in these pathways was disrupted or went awry. To do so, they induced lesions in the striatums of a handful of mice. After a week of recovery, they placed the mice into an arena-like space that had the scent of a fox wafting through one side. With an inborn instinct to avoid predation, mice with an intact striatum immediately raced to the other side of the arena. Mice with lesions in their striatums were also able to display all the separate syllables seen in normal mice, such as sniffing, running, rearing and turning, but their brains somehow failed to sequence these movements correctly rendering the animals incapable of reaching the arena's opposite side.

"This underscores the importance of order in piecing movements together toward a desired outcome," Datta said. "Even if you're able to move your body correctly, if you can't put actions in the correct order, it's hard to do even the most basic of things."

If replicated in further studies, the findings could help inform new treatments for Parkinson's disease and Huntington's disease, conditions in which even basic movements become extremely difficult as these diseases progress, the researchers said.

Currently, Parkinson's disease is treated by giving patients a form of the neurotransmitter dopamine, which stimulates both the direct and indirect pathways. However, the efficacy of the treatment wanes over time. There is still no effective treatment for Huntington's disease.

"We hope that future work emanating from these findings would address more specifically what exactly happens in these cell types when neurodegenerative disorders rob people's brains of their ability to generate actions and action sequences," Datta said.

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