Study reveals set of brain regions that control complex sequences of movement

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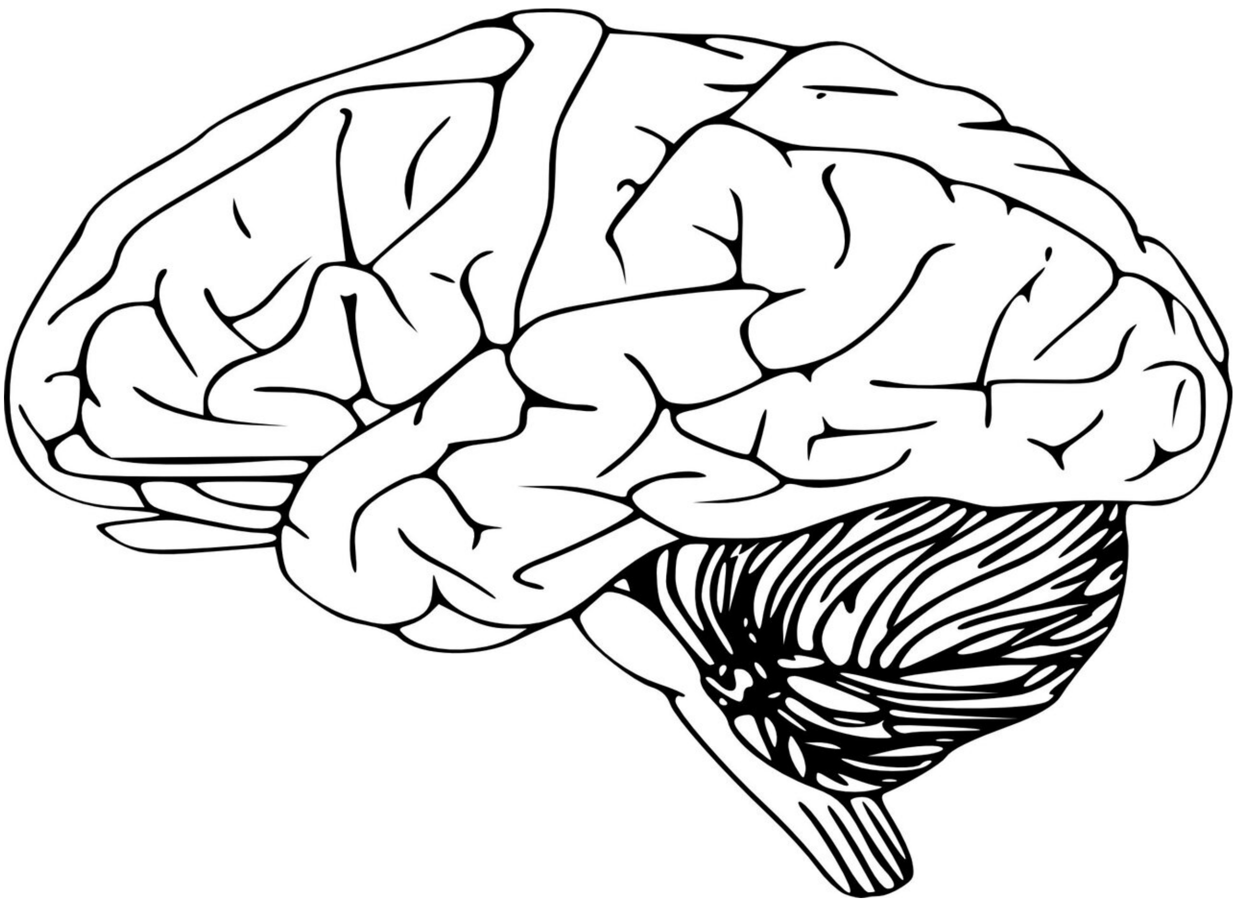

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In a novel set of experiments with mice trained to do a sequence of movements and "change course" at the spur of the moment, Johns

Hopkins scientists report they have identified areas of the animals' brains that interact to control the ability to perform complex, sequential movements, as well as to help the mice rebound when their movements are interrupted without warning.

The research, they say, could one day help scientists find ways to target those regions in people and restore motor function caused by injury or illness.

Results of the Johns Hopkins-led experiments were published March 9 in *Nature*.

Based on brain activity measurements of the specially trained rodents, the investigators found that three main areas of the cortex have distinct roles in how the mice navigate through a sequence of movements: the premotor, primary motor and primary somatosensory areas. All are on the top layers of the mammals' brains and arranged in a fundamentally similar fashion in people.

The team concluded that the primary motor and primary somatosensory areas are involved in controlling the immediate movements of the mice in real time, while the premotor area appears to control an entire planned sequence of movements, as well as how the mice react and adjust when the sequence is unexpectedly disrupted.

As the animals perform sequential movements, the researchers say, it's likely that the premotor area sends electrical signals via special nerve cells to the two other sensorimotor cortex areas, and more studies are planned to chart the paths of those signals between and among the cortical layers.

"Whether it's an Olympian practicing a downhill ski run or a person doing an everyday chore such as driving, many tasks involve learned sequences of movements made over and over," says Daniel O'Connor, Ph.D., associate professor of neuroscience at the Johns Hopkins University School of Medicine. O'Connor led the research team. Such sequential movements may seem commonplace and simple, he says, but they involve complex organization and control in the brain, and the brain must not only direct each movement correctly but also organize them into an entire series of linked movements.

When unexpected things happen to interrupt an ongoing sequence, O'Connor says, the brain must adapt and direct the body to re-configure the sequence in real time. Failure of this process can result in disaster—a fall or car accident, for example.

Neuroscientists have long studied how mammals compensate when an individual movement—such as reaching for a coffee cup—is disrupted, but the new study was designed to address the challenges of tracking what happens when complex sequences of several movements must be reorganized in real time to compensate for unexpected events.

In the case of the Olympic skier, for example, the skier expects to perform a planned series of movements to approach and pass through gates along a downhill run, but there will likely be moments when an obstacle disrupts the skier's trajectory and forces a change of course.

"How the mammalian brain can take a sensory cue and, almost instantly, use it to completely switch from one ongoing sequence of movements to another remains largely a mystery." O'Connor worked with Duo Xu, Ph.D., a former graduate student in O'Connor's laboratory, to design a set of experiments in mice to track the brain regions that process the "change course" cue.

For the study, the researchers first created a "course" for mice that were trained to stick out their tongues and touch a "port"—a metal tube. When the investigators moved the port, the mice learned to touch the port again. Over the span of the course, when the port was moved to its final location, the mice that touched it with their tongues got a reward. All of this training was meant to simulate a repeated and expected sequence of learned movements, much as the skier's downhill run.

To study how an unexpected cue can prompt the brain to change course, the researchers had the mice perform what scientists call a "backtracking trial." Instead of moving the port to the next in-sequence location, the researchers moved the port to an earlier location, so that when the mice extended their tongues, they failed to find the port, prompting them to reverse course, find the port, and progress through the course to get the treat.

"Each sequence of port licks involves a series of complex movements that the mouse's brain needs to organize into a movement plan and then perform correctly, but also to rapidly reorganize when they find that the expected port isn't there," says O'Connor.

During the experiments, the researchers used brain electrodes to track and record electrical signals among neurons in the sensorimotor cortex, which controls overall movement. An increase in electrical activity corresponds to increased brain activity. Because many areas of the cortex could be activated when the mice moved through the course in the experiment, the researchers used mice bred with genetically engineered brain cells that, in certain parts of the cortex, can be selectively "silenced" or deactivated. Thus, the scientists could narrow down the location of brain areas directly involved in the movements.

"The results provide a new picture of how a hierarchy among neural networks in the sensorimotor cortex are managing sequential movements," says O'Connor. "The more we learn about these interacting neural networks, the better positioned we are to understand sensorimotor dysfunction in humans and how to correct it."

More information: Duo Xu et al, Cortical processing of flexible and context-dependent sensorimotor sequences, *Nature* (2022). DOI: 10.1038/s41586-022-04478-7

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