Neurons coordinate to fine-tune motor control

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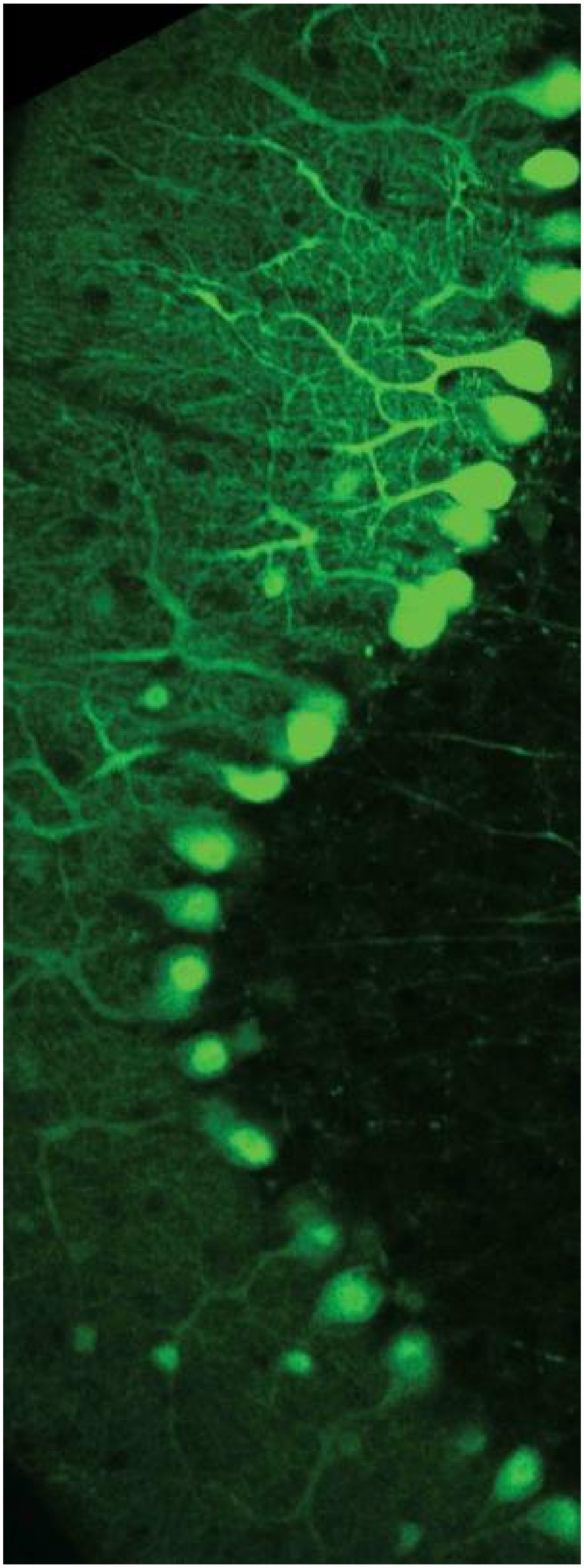

A two-photon microscopy image of a mouse's Purkinje cells. Credit: Andrea Giovannucci

Whether it is playing a piano sonata or acing a tennis serve, the brain needs to orchestrate precise, coordinated control over the body's many muscles. Moreover, there needs to be some kind of feedback from the senses should any of those movements go wrong. Neurons that coordinate those movements, known as Purkinje cells, and ones that provide feedback when there is an error or unexpected sensation, known as climbing fibers, work in close concert to fine-tune motor control.

A team of researchers from the University of Pennsylvania and Princeton University has now begun to unravel the decades-spanning paradox concerning how this feedback system works.

At the heart of this puzzle is the fact that while climbing fibers send signals to Purkinje cells when there is an error to report, they also fire spontaneously, about once a second. There did not seem to be any mechanism by which individual Purkinje cells could detect a legitimate error signal from within this deafening noise of random firing.

Using a microscopy technique that allowed the researchers to directly visualize the chemical signaling occurring between the climbing fibers and Purkinje cells of live, active mice, the Penn team has for the first time shown that there is a measurable difference between "true" and "false" signals.

This knowledge will be fundamental to future studies of fine motor control, particularly with regards to how movements can be improved with practice.

The research was conducted by Javier Medina, assistant professor in the Department of Psychology in Penn's School of Arts and Sciences, and Farzaneh Najafi, a graduate student in the Department of Biology. They collaborated with postdoctoral fellow Andrea Giovannucci and associate professor Samuel S. H. Wang of Princeton University.

It was published in the journal *Cell Reports*.

The cerebellum is one of the brain's motor control centers. It contains thousands of Purkinje cells, each of which collects information from elsewhere in the brain and funnels it down to the muscle-triggering motor neurons. Each Purkinje cell receives messages from a climbing fiber, a type of neuron that extends from the brain stem and sends feedback about the associated muscles.

"Climbing fibers are not just sensory neurons, however," Medina said. "What makes climbing fibers interesting is that they don't just say, 'Something touched my face'; They say, 'Something touched my face when I wasn't expecting it.' This is something that our brains do all the time, which explains why you can't tickle yourself. There's part of your brain that's already expecting the sensation that will come from moving your fingers. But if someone else does it, the brain can't predict it in the same way and it is that unexpectedness that leads to the tickling sensation."

Not only does the climbing fiber feedback system for unexpected sensations serve as an alert to potential danger—unstable footing, an unseen predator brushing by—it helps the brain improve when an intended action doesn't go as planned.

"The sensation of muscles that don't move in the way the Purkinje cells direct them to also counts as unexpected, which is why some people call climbing fibers 'error cells,'" Medina said. "When you mess up your tennis swing, they're saying to the Purkinje cells, 'Stop! Change! What you're doing is not right!' That's where they help you learn how to correct your movements.

"When the Purkinje cells get these signals from climbing fibers, they change by adding or tweaking the strength of the connections coming in from the rest of the brain to their dendrites. And because the Purkinje cells are so closely connected to the motor neurons, the changes to those synapses are going to result in changes to the movements that Purkinje cell controls."

This is a phenomenon known as neuroplasticity, and it is fundamental for learning new behaviors or improving on them. That new neural pathways form in response to error signals from the climbing fibers allows the cerebellum to send better instructions to motor neurons the next time the same action is attempted.

The paradox that faced neuroscientists was that these climbing fibers, like many other neurons, are spontaneously activated. About once every second, they send a signal to their corresponding Purkinje cell, whether or not there were any unexpected stimuli or errors to report.

"So if you're the Purkinje cell," Medina said, "how are you ever going to tell the difference between signals that are spontaneous, meaning you don't need to change anything, and ones that really need to be paid attention to?"

Medina and his colleagues devised an experiment to test whether there was a measurable difference between legitimate and spontaneous signals from the climbing fibers. In their study, the researchers had mice walk on treadmills while their heads were kept stationary. This allowed the researchers to blow random puffs of air at their faces, causing them to blink, and to use a non-invasive microscopy technique to look at how the relevant Purkinje cells respond.

The technique, two-photon microscopy, uses an infrared laser and a reflective dye to look deep into living tissue, providing information on both structure and chemical composition. Neural signals are transmitted within neurons by changing calcium concentrations, so the researchers used this technique to measure the amount of calcium contained within the Purkinje cells in real time.

Because the random puffs of air were unexpected stimuli for the mice, the researchers could directly compare the differences between legitimate and spontaneous signals in the eyelid-related Purkinje cells that made the mice blink.

"What we have found is that the Purkinje cell fills with more calcium when its corresponding climbing fiber sends a signal associated with that kind of sensory input, rather than a spontaneous one," Medina said. "This was a bit of a surprise for us because climbing fibers had been thought of as 'all or nothing' for more than 50 years now."

The mechanism that allows individual Purkinje cells to differentiate between the two kinds of climbing fiber signals is an open question. These signals come in bursts, so the number and spacing of the electrical impulses from climbing fiber to Purkinje cell might be significant. Medina and his colleagues also suspect that another mechanism is at play: Purkinje cells might respond differently when a signal from a climbing fiber is synchronized with signals coming elsewhere from the brain.

Whether either or both of these explanations are confirmed, the fact that individual Purkinje cells are able to distinguish when their corresponding muscle neurons encounter an error must be taken into account in future studies of fine motor control. This understanding could lead to new research into the fundamentals of neuroplasticity and learning.

"Something that would be very useful for the brain is to have information not just about whether there was an error but how big the error was—whether the Purkinje cell needs to make a minor or major adjustment," Medina said. "That sort of information would seem to be necessary for us to get very good at any kind of activity that requires precise control. Perhaps climbing fiber signals are not as 'all-or-nothing' as we all thought and can provide that sort of graded information."

Provided by University of Pennsylvania

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