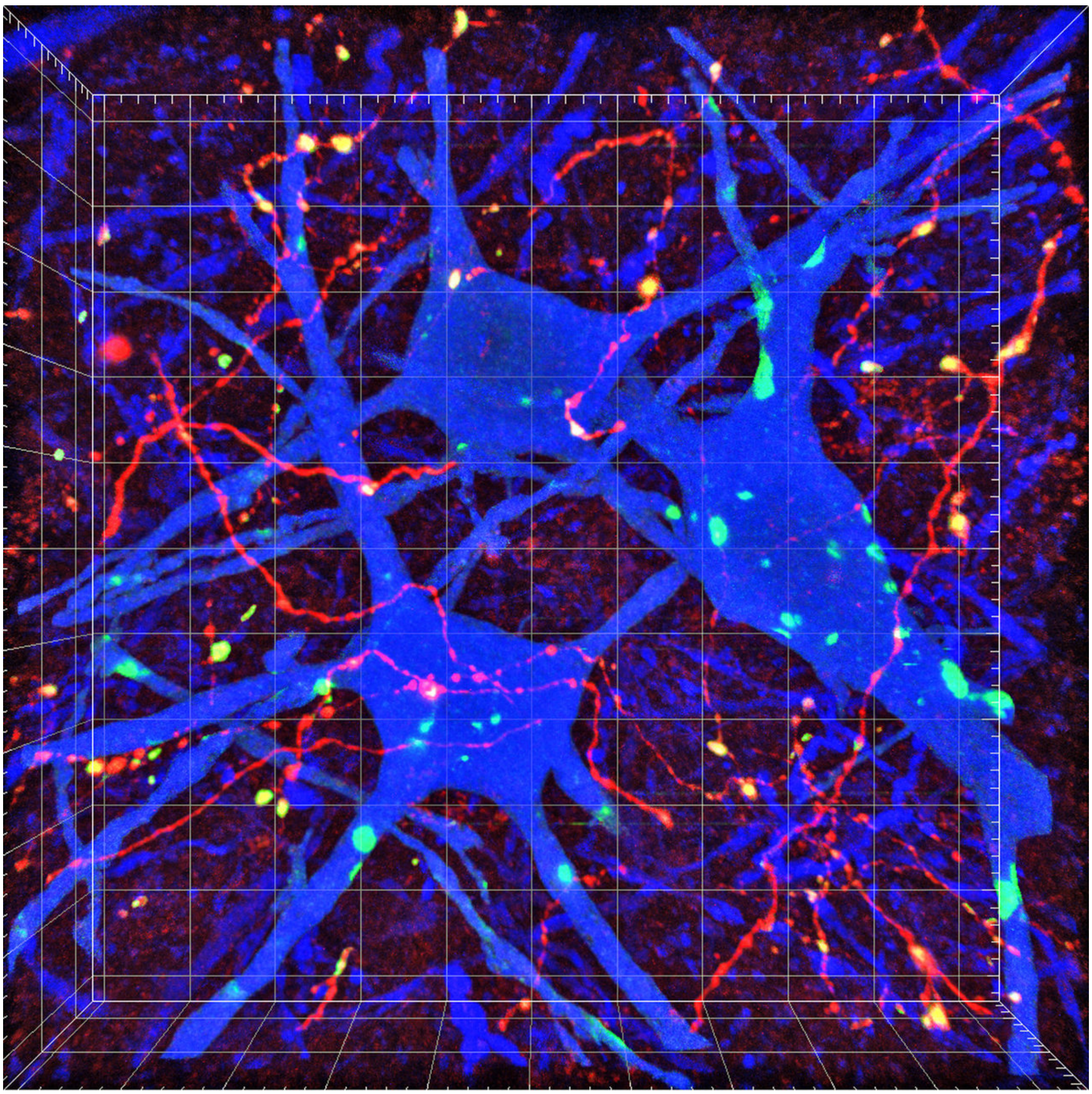
Scientists map key brain-to-spinal cord nerve connections for voluntary movement

May 1 2018



This microscopic image shows corticospinal neurons and synaptic connections to the spinal cord in a mouse. Spinal interneurons (blue) show synaptic connections (in green) with corticospinal axons (red). Researchers report in *Cell Reports* the mapping of critical nerve connections to the spine that drive voluntary movement in forelimbs. The gridlines allow scientists to plot the neuron locations along the spinal cord. Scientists say the information will be useful as they begin searching in future preclinical studies for specific repair strategies to help people who had a stroke or spinal cord injury. Credit: Cincinnati Children's

Researchers trying to help people suffering from paralysis after a spinal cord injury or stroke mapped critical brain-to-spinal cord nerve connections that drive voluntary movement in forelimbs, a development that scientists say allows them to start looking for specific repair strategies.

The study by Yutaka Yoshida, PhD, and colleagues at Cincinnati Children's Hospital Medical Center is an important step toward rehabilitating motor circuits to help motor function recover after an injury or disease damages the central nervous system, the scientists report in *Cell Reports*.

"The map described in this study should allow us to explore which corticospinal-spinal interneuron connections are good targets for repair and restoration of voluntary movement," says Yoshida, lead investigator in the Division of Developmental Biology. "More research is necessary before human therapies are possible, but this information is very helpful for future repair strategies. We now know which circuits need to be repaired."

The scientists said it will take years for additional investigative work to make the current findings therapeutically relevant. Yoshida and colleagues are conducting new studies to build on the basic neuronal architecture identified in the current study. They want to reach a point where these circuits can be reconstructed to stimulate the recovery of motor function central nervous system injuries.

Corticospinal Schematics

Little has been known about how the corticospinal network of nerve connections between the brain and spinal cord are organized and function together. Seemingly simple tasks like reaching or grabbing require precise coordination between sensory and motor information transmitted through these coordinated connections, according to the researchers.

To map this connectivity in the current study, the scientists study these circuits in laboratory mice—taking advantage of similar corticospinal connections in primates, cats, and rodents.

Working initially from previous studies by his research team and others, Yoshida and colleagues were able to track corticospinal connections from the brain's cerebral cortex near the top of the head down to the spinal cord. They also traced the organization and function of corticospinal circuits using mouse genetics, and a viral tracer (a de-armed rabies virus) that allowed investigators to highlight and capture images of these links.

The connections trace down through what's called the brain's internal capsule, then arrive at the caudal medulla of the brain just above the spinal cord. From there they enter the spinal cord, crisscrossing deep inside the spine as they continue to protrude downward and make additional connections.

Yoshida said his team was able to develop a map of corticospinal neurons that control forelimb and sensory nerve impulses. They also identified specific neurons that control different skilled movements.

In these areas, the scientists show how the nerve fibers connect onto certain premotor interneurons and transmit impulses between neurons to trigger skilled movements. This includes nerve fibers that express a transcription factor called Chx10 (a regulator gene that instructs other genes to turn on or off to initiate biological functions).

Chx10 is linked to nervous system function in other parts of the body, including the eyes. When the researchers silenced Chx10 only in the cervical spinal cord, it hampered the animals' ability to reach for food.

The Importance of Sensing

The researchers also highlighted the connections of corticospinal neurons in the forelimb sensory cortex—which control the animals' ability to sense and convert external stimuli into electrical impulses. They said that in contrast to corticospinal neurons in the motor cortex that directly trigger certain skilled movement, corticospinal neurons in the sensory cortex do not connect directly to premotor neurons. Instead, they connect directly to other spinal interneurons that express a gene called Vglut3.

This is important because when the scientist inhibited neurons expressing Vglut3 in the cervical spinal cord, it also caused deficits in the animals' ability to grab and release food pellets, as well as other goal-oriented tasks.

Key collaborators on this study include scientists at the Precursory Research for Embryonic Science and Technology (PRESTO) at the Japan Science and Technology Agency, the Brain Research Institute at Niigata University in Japan and the University of Cincinnati Medical Center.

More information: *Cell Reports* (2018). DOI: 10.1016/j.celrep.2018.03.137

Provided by Cincinnati Children's Hospital Medical Center