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# Study improves insights into Parkinson's disease and possible treatments

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About the only thing doctors have understood about deep-brain stimulation, which is widely used to treat Parkinson's disease symptoms, is that somehow it works for many patients. In a new study that will be published March 19 in the online journal *Science Express*, Stanford University researchers used light to illuminate how the treatment works, generating surprising insights into the diseased circuitry and also suggesting new ideas to improve Parkinson's therapy.

Parkinson's disease is a brain disorder that affects an estimated 1.5 million Americans, causing tremors, stiffness and difficulty balancing. In those who undergo deep-brain stimulation, pulses of electricity are applied to the circuitry of a tiny brain region called the subthalamic nucleus. Naturally, researchers suspected that cells within that region are somehow stimulated, or calmed, by the shocks, leading to reduced Parkinson's symptoms.

In the new study, which will also appear in an upcoming print issue of *Science*, the medical and engineering researchers found that by far the biggest effect in "Parkinsonian" rodents occurs not by stimulating cells in the subthalamic nucleus, but by stimulating the neural wires, called axons, that connect directly to it from areas closer to the surface of the brain.

"Pointing to these axons that converge on the region opens the door to targeting the source of those axons. This insight leads to deeper understanding of the circuit and could even lead to new kinds of

treatments," said senior author Karl Deisseroth, MD, PhD, associate professor of bioengineering and of psychiatry and behavioral sciences. "Because these axons are coming from areas closer to the brain's surface, new treatments could perhaps be less invasive than deep-brain stimulation."

**A spotlight on** brain circuits

To perform the research, Deisseroth's team, which included students and faculty from bioengineering, neuroscience and neurosurgery, used a technique his lab has pioneered called "optogenetics." They genetically engineered specific types of cells, or neurons, in the subthalamic nucleus regions of different rodents to become controllable with light. A blue-colored laser pulse makes the neurons more active, while a yellow laser light suppresses activity.

In a separate paper published in the journal *Nature* on March 18, Deisseroth and another cadre from within his research group show that the optogenetic technique can be applied not only to the electrical behavior of neurons, but also to the much broader biochemical activity of other cell types in the body.

"Using the technology allowed us to separate the different circuit elements by placing them under optical control," Deisseroth said. "It allowed us to systematically move through the circuit, turning on or off different elements and finding out which modifications of the circuit corrected the symptoms."

This result also required a complementary method invented in the Deisseroth lab, namely delivering light via a thin, flexible fiber-optic cable deep into the brain of the animals, so that they can move and behave freely during the experiment.

The team tried every kind of neuron they could think of within the brain region itself, and found no effect. Out of persistence and desperation, like a person who has searched the whole house for the keys and finally finds them in the doorknob, the team decided to investigate the incoming axons. In rodents with cells that had been made light-sensitive, the researchers found dramatic results both with high-frequency and low-frequency pulses.

"The [high-frequency stimulation] effects were not subtle," the researchers wrote in the *Science Express* paper. "In nearly every case these severely Parkinsonian animals were restored to behavior indistinguishable from normal, and in every case the therapeutic effect immediately and fully reversed…upon discontinuation of the light pulse."

Low-frequency stimulation, meanwhile, caused the Parkinson's symptoms to become worse.

## Future progress

Deisseroth said the work raises even more interesting questions than it answers, such as what types of cells the axons target.

In addition, he asked, "In what way can we team up with other clinicians to help guide therapies capitalizing on this insight?"

Deisseroth said the most important outcome of the work, primarily carried out by graduate students Viviana Gradinaru and Murtaza Mogri, who are the first authors of the paper, is the new information about the role of the axons. He cautioned that, while the optogenetic technique had a therapeutic effect on the rodents and has worked well in every species tried so far, it still might not be the best therapy for people.

"There may be better or simpler ways to get that therapeutic value now that we have this key insight," he said.

This study is the first showing that optogenetics can be applied to brain disease. Deisseroth said another of this group's hopes is to extend the understanding of deep-brain stimulation to how it affects different diseases, such as depression and obsessive-compulsive disorder.

"Our goal is to better understand this disease and its treatment, and to help refine and generalize therapies by elucidating basic mechanisms," he said.

Source: Stanford University Medical Center (news : web)