New Frontier for Deep Brain Stimulation Therapy Is Recovery From Stroke

Researchers testing the effects of DBS on the brains of rats hope to begin testing its effects in humans

Dr. Andre Machado, director of the Cleveland Clinic's Center for Neurological Restoration Photo: Center for Medical Art and Photography at Cleveland Clinic

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Researchers at the Cleveland Clinic are testing whether electrical stimulation of the brain helps improve the effectiveness of physical rehabilitation after a stroke. Strokes leave hundreds of thousands of people in the U.S. debilitated each year.

With deep brain stimulation, or DBS, electrodes are surgically implanted into the brain, and a neurostimulator, typically implanted in the chest, stimulates the brain with mild electrical current.

Approved by the Food and Drug Administration to reduce symptoms of Parkinson’s disease, among other conditions, DBS is used primarily to treat or reduce tremors, stiffness and slowness. The technique [1] also has been studied for use in a variety of ailments, including depression and chronic pain.

**New Use for a Pacemaker in the Brain**

Deep brain stimulation sends electrical impulses to the brain, typically to interrupt faulty brain circuits thought to cause a number of disorders.

**How It Works**

Thin coated wires carry an electrical current from a battery-powered implant to electrodes in the brain.

**Area targeted in stroke: Dentate Nucleus**

- Researchers at the Cleveland Clinic are experimenting with animals to find the appropriate electrical current frequency and optimal timing of DBS to help restore function after a stroke.
- Recent evidence indicates DBS may prompt the growth of new neurons in animals.
- Researchers are applying to the Food and
Andre Machado, director of the Center for Neurological Restoration at the Cleveland Clinic, and his team are experimenting with the treatment in animals, to find the appropriate electric current and stimulation frequency that will help restore function after a stroke. They are applying to the FDA for permission to begin testing the technique in humans although they don’t have an estimated start date for the work.

The hope with human stroke patients is that DBS would be able to help healthy brain regions compensate for the damaged ones and facilitate new connections.

The Cleveland Clinic group found that using electrical stimulation in rats after stroke appears to promote the growth of new neurons in the brain. Dr. Machado presented his findings in June at the world congress of the International Neuromodulation Society[2], whose members are clinicians, scientists and engineers.

“The expectation is that by applying stimulation, it will augment or boost the effects of physical rehabilitation,” Dr. Machado says. “We have no expectation that it will cure stroke.”

In a stroke, blood supply to the brain is cut off. The damaging effects occur because some areas in the brain shut down or die, and communication is disrupted between other brain regions.
The Cleveland Clinic's Dr. Machado is testing whether deep brain stimulation helps rats recover brain function after stroke, and he is hoping to test it in human stroke patients. Photo: Center for Medical Art and Photography at Cleveland Clinic

Of the nearly 800,000 people in the U.S. each year who survive a stroke, 10% recover almost completely and 25% experience only minor impairment. Half of survivors are debilitated severely and require special care, according to the National Stroke Association. (The other 15% die shortly after the stroke.)

With a type of stroke called ischemic stroke, caused by blockage of an artery to the brain, a drug called tissue plasminogen activator can improve chances of recovery if given within three hours of the stroke. But patients often don’t get the medicine in time. Physical rehabilitation can help improve strength and functioning weeks or months later, but often there isn’t a 100% return to pre-stroke levels, and improvement often plateaus after a few months.

The aim is that treatment with DBS will augment the benefit of physical therapy. DBS, the thinking goes, is unlikely to bring back the dead portions of the human brain but may help facilitate new connections.

In particular, stimulating the brain's cerebellum, the region controlling voluntary muscle movements, will “re-establish some flow of neurological input” after a stroke, Dr. Machado says.
Efforts to stimulate the brain electrically make sense, says Steven Ojemann, professor of neurosurgery and director of stereotactic and functional neurosurgery at the University of Colorado School of Medicine in Aurora, who isn’t involved in the DBS research. The brain is an electrical organ, and movement of ions and current through neurons drives biologic changes that promote growth, connectivity between brain regions and the brain’s ability to learn and change.

Restoring function with electrical stimulation has been pursued for a long time. Researchers have studied cortical stimulation and transcranial direct current stimulation, two less-invasive therapies. Cortical stimulation, where electrodes are placed on the surface of the brain, showed early promise in post-stroke recovery but didn’t demonstrate a benefit in a large clinical trial.

Transcranial direct current stimulation, a noninvasive technique that involves passing current between two electrodes over the head, has shown some benefit as a possible add-on therapy to physical rehabilitation after stroke in studies involving a small number of humans.

Researchers are exploring applications for deep brain stimulation beyond treatment for Parkinson’s disease. Here’s how it works. Graphic: Adele Morgan/The Wall Street Journal

Deep brain stimulation theoretically overcomes some of the limitations of cortical stimulation, Dr. Ojemann says. With cortical stimulation, the periphery of the brain area that has died is stimulated, but that area can be hard to define and difficult to cover with a surface electrode, and cerebral spinal fluid can divert the current. DBS, on the other hand, can potentially stimulate regions more broadly and deeply, which may more effectively influence brain functions.

In general, DBS is safe and well tolerated, experts say. As with any brain surgery, there are risks and potential complications, including stroke, infection and seizures.

Dr. Machado’s team at the Cleveland Clinic began work on the question about seven years ago. In 2009, the team showed that after inducing a stroke in rats, then implanting an electrode and stimulating the cerebellum, brain activity in the stimulated region improved. Their research, funded by the National Institutes of
Health, was published in a series of papers beginning in 2010.

In animals that were stimulated, motor functioning improved in the weeks after the stroke compared with animals whose electrodes were implanted but not turned on.

Early on, the researchers had to figure out which frequency of current to use. While a high frequency of 200 Hz (electrical pulses per second) seems to interrupt tremors, a lower frequency of 30 to 50 Hz appears to promote activity, according to Dr. Machado.

Three years ago, his group began evaluating the combination of stimulation plus physical training. In a study published in Neurosurgery in 2013, they found that animals that were stimulated could reach and grasp with their anterior paws better than unstimulated rats.

Recently the Cleveland Clinic researchers found stimulation improved the number of synaptic connections, presumably enhancing communication between neurons in animals. Last month, they presented data showing stimulation appears to promoted neurogenesis; this work isn’t published yet.

Many questions remain to be answered before DBS can become a clinically useful treatment. The biggest: Will its effects hold in humans? Promoting the formation of new neurons is probably harder in humans than in rats. To date, there isn’t direct evidence that electrical stimulation of the cerebellum will promote the formation of new neurons in humans, although that remains a possibility and a hope, says Dr. Machado.

And there is the question of timing: At what point during the recovery process would DBS do the most good? Scientists are trying to determine whether patients would need continuous DBS, or if the improvement will linger if the stimulation is stopped, Dr. Machado says.

Another potential consideration is that stroke survivors aren’t a homogenous group. It’s unclear whether patients with a certain type of stroke, or damage in a particular area of the brain, would be the best candidates, says Konstantin Slavin, a neurosurgery professor at the University of Illinois at Chicago who wasn’t involved in
“Right now, brain damage from stroke is considered irreversible,” Dr. Slavin says. The ultimate goal would be to regrow the brain and reestablish connections and original function. But for now, he says, “we can wake up parts of brain that can modify activity to compensate for dead regions.”

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