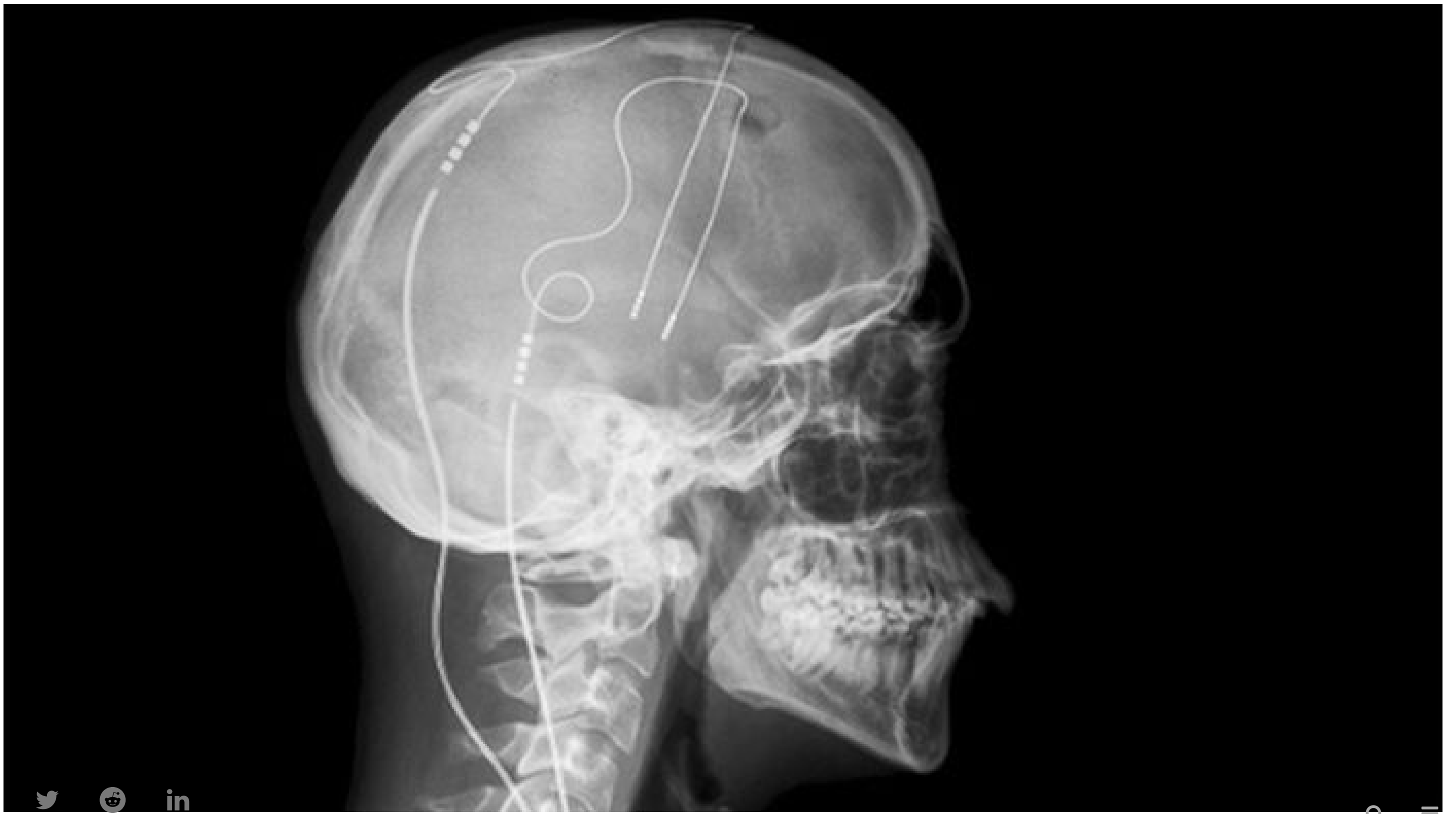

A new, noninvasive method could one day replace treatments for Parkinson's disease and—experimentally—Tourette syndrome that rely on electrodes implanted deep in the brain.
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Electric fields tease buried brain cells into action

By **Meredith Wadman** | Jun. 1, 2017 , 12:15 PM

Using "freshman physics," neuroscientists have deployed electric fields to stimulate neurons buried deep in the brains of mice—a method that could one day lead to noninvasive therapies for people with Parkinson's disease and other brain disorders. The new technique could also become a valuable research tool, allowing scientists to selectively prod deep-brain neurons into action.

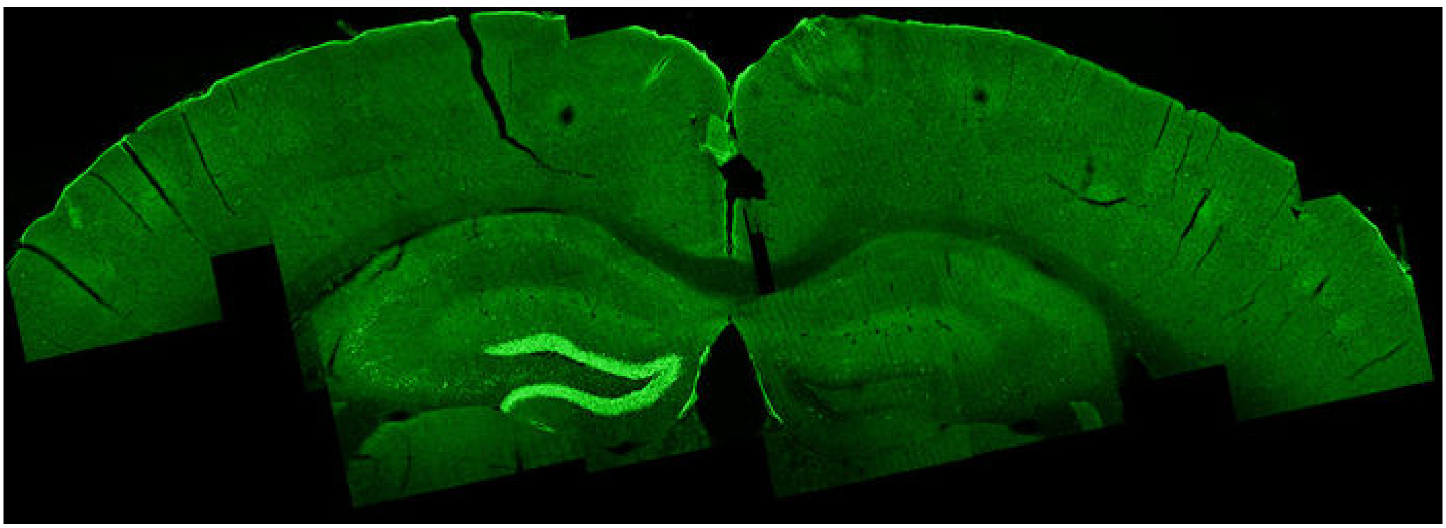
"[It's] very exciting," says Antonio Sastre, a neurobiologist who oversees research in the Division of Applied Science and Technology at the National Institute of Biomedical Imaging and Bioengineering in Bethesda, Maryland. "This has true potential for translation [to patients] in a way that some of the other approaches [to neurostimulation] don't."

For decades, scientists have electrically stimulated specific neurons below the brain's surface layers with implanted electrodes connected through spaghettilike wires to a pacemakerlike device under the skin of the chest. This deep brain stimulation (DBS) has won approval from the U.S. Food and Drug Administration for treating Parkinson's disease, other movement disorders, and obsessive-compulsive disorder. Though the method has produced some striking therapeutic successes, infection, stroke, and the migration of electrodes are rare but real risks.

Neuroscientists have also developed transcranial magnetic stimulation (TMS), which uses magnets held against the scalp to induce electric fields inside the brain, turning on neurons. It is used in research and is approved in the United States and elsewhere to treat depression, but it has trouble selectively stimulating targets buried in the brain. With TMS, says Ed Boyden, a neuroscientist at the Massachusetts Institute of Technology's (MIT's) Media Lab and McGovern Institute for Brain Research in Cambridge, "You can always stimulate deep neurons but you stimulate superficial neurons as well."

Seeking to combine DBS's deep-brain targeting with TMS's noninvasiveness, Boyden's MIT team, led by bioengineer Nir Grossman, took advantage of a well-known property of neurons: They respond only to low-frequency electrical signals. (High-frequency signals pass through the brain, leaving neurons untriggered.) They also applied a basic principle of physics. Two electric fields that differ in frequency only slightly will interfere with each other to produce an "envelope" electric field when they cross paths, whose frequency is the difference between the frequencies of the original fields. It stood to reason, then, that two high-frequency fields—say, 2000 hertz and 2010 hertz—directed from different angles at a deep-brain target should produce a 10 hertz envelope field that would activate neurons at the target but not in the layers of the brain above. The scientists named the new technique "TI" for "temporally interfering" electric fields.

The team found their predictions bore out in computer modeling and an actual mockup of the brain—a plastic cylinder filled with saline and wired with electrodes. So they turned to living, anesthetized mice, attached electrodes to their scalps, and directed 2000 and 2010 hertz signals so that they produced a low-frequency, 10 hertz stimulation at the hippocampus, a deep-brain structure involved in learning and memory. Neurons in the hippocampus—which are affected in Alzheimer's disease, epilepsy, and other illnesses—**were strongly activated, but the neurons above them were not affected**, the group reports today in *Cell.*



An area of the mouse hippocampus glows green, indicating that the new method of electrical stimulation excited neural activity in this deep brain structure.

N. Grossman *et. al., Cell* 169 (1 June 2017) © 2017 Elsevier Inc.

In a separate experiment in anesthetized mice, the scientists "steered" the target area of the TI, without moving the electrodes on the animals' scalps, by altering the relative amount of current in each of the two high-frequency fields. By stimulating different areas of the motor cortex, they were able to selectively prod into motion the mice's forepaws, whiskers, and ears. The ability to change targets with such ease and precision could be a boon for research and potential therapies,Sastre says. At the same time, the procedure didn't change brain temperature beyond its normal range or induce seizures, both standard safety concerns. The MIT team also found no markers indicating that the electric fields caused abnormal inflammation, DNA damage, or cell death in the targeted tissue.

But University of Toronto in Canada neurosurgeon Suneil Kalia, who implants DBS electrodes in the brains of people with Parkinson's disease, cautions that the study is just a first step. "They have turned on some neurons deep in the brain, but there's a lot more that needs to be done."

He notes, for instance, that the TI stimulated patches several millimeters across in the rodent's brains—far larger than the precise spots targeted by implanted electrodes. Boyden and his colleagues hypothesize that using more than two interfering electric fields could pinpoint smaller regions, though they haven't tried that yet. Boyden adds that the method, by targeting larger areas, might also be used one day to treat traumatic brain injury, stroke, or memory loss.

The MIT group is not wasting time, already exploring if TI works in healthy volunteers. "The [MIT Institutional Review Board (IRB)] has approved and we have already begun human subject experiments," Boyden says. "We are planning lots of studies."

Applying principles of "freshman physics" the way they have done, he says, "is one of those elegant, simple things that could have been thought of a long time ago."

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