The brain hackers

Non-invasive stimulation of the brain is being touted to promote health and well-being and for ‘curing’ disease, but the mechanistic underpinnings of the devices remain unclear.

Emily Waltz

Both clinicians and companies are touting the allure of painlessly zapping the brain with electrical or magnetic energy to promote mental health and ameliorate disease. Consumers are gobbling up one particular type of non-invasive device—transcranial direct current stimulators—by the tens of thousands in the hope of making themselves smarter or happier. Researchers are producing hundreds of studies on brain stimulation techniques each year in the hope of finding therapeutic benefit for dozens of diseases. Many global regulators have even given some of these devices a green light.

But the literature surrounding these technologies remains contradictory and muddled. To sort out the confusion, researchers are returning to basic science to better understand the mechanisms underlying non-invasive brain stimulation.

Impulse treatments
Researchers have long been drawn to the idea of hacking into the brain’s electrical communication system to modulate brain activity, behavior and disease. Electroconvulsive therapy, which dates back to at least the 1930s, involves sending a fairly strong current into the brain in anesthetized patients and, according to the American Psychiatric Association, works in 50–90% of people with severe major depression. Deep brain stimulation, which involves surgically implanting electrodes in the brain to stimulate precise structures or circuits, can ease motor symptoms in people with Parkinson’s disease. But the invasiveness and side effects of the treatments often limit them to patients with the most severe, and otherwise untreatable, symptoms or disabilities.

Naturally, researchers are looking to non-invasive techniques with the hope of reaching a wider range of patients and conditions. These technologies gently deliver electromagnetic fields to the brain without penetrating the skin or requiring anesthesia. Transcranial magnetic stimulation, or TMS, for example, stimulates neurons by delivering short, repetitive pulses of concentrated magnetic fields. Sessions typically last up to 40 min, delivered daily over the course of a few weeks, although the regimen varies by patient or study.

A TMS stimulator, which is about the size of a microwave, delivers current to a plastic-enclosed coil of wire placed over the scalp. Pulses of current through that wire generate a magnetic field, which induces electrical currents in the brain of about 100–200 milliamps. That’s enough energy to induce neurons to fire. The area reached by the stimulation is relatively shallow—typically only reaching the cortex—and broad, fanning one to two centimeters from the focal point of the energy. Compared with the complexity of the brain, and its billions
of cells and connections, the stimulation amounts to an electrical slap to the brain. And yet it provides relief to a sizable number of patients with major depressive disorder who have previously failed to respond to medication, with remission rates in some studies reaching 30% (ref. 2). The US Food and Drug Administration (FDA) first cleared a TMS system in 2008 with a product called NeuroStar by Neuronetics, for the treatment of depression. In 2012, the company also received Europe’s CE mark.

Since 2008, at least eight different companies have received FDA clearance for TMS systems, most of them for depression (Table 1). BrainsWay, based in Jerusalem, in August 2018 received the first FDA approval to market the technique as a treatment for obsessive-compulsive disorder. The company has clearances from European regulators for a dozen indications, including post-traumatic stress disorder (PTSD) and autism. An independent study from Croatia, published in April, found that 60% of people with depression treated with a combination of medication and BrainsWay’s TMS technology achieved remission, compared with 11% in a control group who received medication alone. TMS is popular enough that specialty clinics devoted to providing the therapy have popped up globally. Even established institutions, such as Johns Hopkins Medicine and Massachusetts General Hospital, offer the service.

But the road to the first regulatory clearance and reimbursement proved long, bumpy and full of drama. Attempts to replicate early TMS studies produced confounding results. “There was a lot of hope, then some setbacks, a moment when people questioned whether it would work at all, and then redemption with an NIH [US National Institutes of Health]-sponsored multisite trial” and FDA approval, says Marom Bikson, a biomedical engineer at the City College of New York (CUNY) and co-founder of Soterix Medical, a neuromodulation device developer.

It’s still not smooth sailing. An advisory committee for the FDA in March voted unanimously that Neuronix, in Yokoam, Israel, had not proven efficacy of its NeuroAD TMS system for Alzheimer’s disease. The company’s US pivotal study did not demonstrate a clinically meaningful benefit and lacked objective outcome measures, the committee decided. The device is approved for use in Alzheimer’s disease in Europe, Australia and Israel, according to the company.

**Booming beyond TMS**

TMS systems tend to be expensive—typically thousands of dollars—and bulky. That has prompted many researchers to turn to more accessible stimulation technologies, such as transcranial electrical stimulation (TES). This type of therapy includes transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS), which cost a few hundred dollars and are portable. These devices deliver very weak stimulation to the brain—typically one to two milliamperes of either direct or alternating current through electrodes placed on the scalp. The FDA has not approved a tDCS or tACS therapy for any condition.

The safety of TES is well established, many scientists say. Manufacturers for years have been selling tDCS and variations of these technologies directly to consumers on the open market in the United States. Some TES makers claim that the devices can make people smarter or more athletic. That’s legally acceptable, as long as manufacturers don’t claim that their devices treat a medical condition. A medical claim, by statute, would trigger FDA oversight.

Some clinicians recommend tDCS treatment for their patients. For example, Leigh Charvet, a neuropsychologist who directs the research program at New York University’s Langone Multiple Sclerosis Comprehensive Care Center, says she plans to launch a telemedicine-based tDCS service open to patients with any type of medical condition. Charvet says her group is not making any medical claims about what the treatment can achieve. The program will run with approval from her institution.

Charvet’s service is a response to overwhelming patient demand for tDCS, she says. “My worst fear is that [drugstores] will start selling tDCS devices and everyone will start using them, but without the right parameters,” she says. Her program provides a way for people to try the technology in a “research-informed context,” she says.

Charvet’s willingness to provide the treatment stems from promising results from her research, which includes several pilot and case studies in multiple sclerosis and other conditions that were published in peer-reviewed journals. Her team has two large randomized, sham-controlled clinical trials underway that pair tDCS with either motor rehabilitation or cognitive training in people with multiple sclerosis. They also have an ongoing open-label study of tDCS paired with rehabilitation that has included people with traumatic brain injury, mild cognitive impairment, hypersonnia, post-stroke aphasia, and ataxia.

In fact, TES has been investigated by researchers globally in over 70 neuropsychiatric conditions, including depression, tinnitus, Parkinson’s disease, pain, stroke rehabilitation and addiction. Hundreds of studies are published in

### Table 1 | Selected companies with approved TMS devices

<table>
<thead>
<tr>
<th>Company (location)</th>
<th>Indication</th>
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<tbody>
<tr>
<td>Magstim (Whitland, UK)</td>
<td>Depression</td>
</tr>
<tr>
<td>Nexstim (Helsinki, Finland)</td>
<td>Depression</td>
</tr>
<tr>
<td>Tonica Elektronik (Farum, Denmark)</td>
<td>Depression</td>
</tr>
<tr>
<td>MAG &amp; More (Munich, Germany)</td>
<td>Depression, obsessive-compulsive disorder</td>
</tr>
<tr>
<td>BrainsWay (Jerusalem)</td>
<td>Depression</td>
</tr>
<tr>
<td>TeleEMG</td>
<td>Depression</td>
</tr>
<tr>
<td>Neuronetics</td>
<td>Depression</td>
</tr>
<tr>
<td>eNeura</td>
<td>Migraine</td>
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</table>
Electrical devices to patients for at-home use.

Post-market clinical trials and dole out in Korea, where the company can conduct centers, all located at university hospitals, founder and CEO of the company. Lee treatment to be listed as an official treatment Assessment program, which allows the schizophrenia7,8. The company's device in cognitive impairment, dementia, and for depression that it is testing in other Korea, has developed a tDCS system to consumers. She says. The company does not sell directly devices for Charvet's telemedicine service, and several smaller markets, according to Australia, Brazil, Singapore, China, Mexico pain with regulatory approvals in Europe, Soterix Medical, cofounded by Bikson, has developed a tDCS system for depression and spinning out of university research (Table 2).

Developers of commercially marketed devices come from many backgrounds, some working out of their garages and some spinning out of university research (Table 2). Soterix Medical, cofounded by Bikson, has developed a tDCS system for depression and pain with regulatory approvals in Europe, Australia, Brazil, Singapore, China, Mexico and several smaller markets, according to the company. Soterix will supply the tDCS devices for Charvet’s telemedicine service, she says. The company does not sell directly to consumers.

Ybrain in Seongnam-si, Republic of Korea, has developed a tDCS system for depression that it is testing in other psychiatric conditions, including mild cognitive impairment, dementia, and schizophrenia24. The company's device in April received a "conditional allowance" from Korea's New Health Technology Assessment program, which allows the treatment to be listed as an official treatment option for depression, says Kiwon Lee, founder and CEO of the company. Lee says he plans to open 25 neurostimulation centers, all located at university hospitals in Korea, where the company can conduct post-market clinical trials and dole out devices to patients for at-home use.

Electric irreproducibility

Although there are many successes, there are a lot of failures—enough, some researchers say, to have muddled the science. "There's a big problem with reproducibility in the field," says Anli Liu, a neurologist at New York University's Langone Comprehensive Epilepsy Center. Studies with positive results often can't be replicated, and that has led some scientists back to the drawing board.

Liu saw the replication problem firsthand in her experiments. She had been encouraged by a 2006 study in Nature in which TES successfully enhanced sleep rhythms to improve memory in healthy students. "That was a high-impact study that got people excited," says Liu. The paper inspired several replication studies, about half of which found positive effects and the other half of which found no effects, she says. She wondered whether the technique could be applied to remediate memory in people with epilepsy, who often suffer from memory impairment. But when she and her colleagues applied a TACS protocol to this population during sleep, they found no effects. "To our disappointment, there was nothing," says György Buzsáki, a neuroscientist at Langone, who collaborated with Liu on the project. "Of the 17,000 electrodes tested in a dozen or so patients, not one showed entrainment," he cautions.

"The story illustrates the problem with the field in general," adds Liu. "You have high impact, but often underpowered, studies that show a large effect and then all these replication studies that try to follow it because it's so appealing and exciting," she says. But often the follow-on studies show smaller effects, or none at all, "and no one knows why," she says. The original studies may have been rigorously performed, but the lack of mechanistic understanding means there may be aspects critical to replication that are being missed, she says.

Part of the challenge to reproducibility has been keeping variables consistent from one study to the next. "What's holding the field back is that you have labs all over the world using slightly different parameters," says Colleen Hanlon, an associate professor at the Medical University of South Carolina, who studies the effects of brain stimulation on addiction. "So when one of us doesn't replicate the other, we don't know if it was variable A or variable B or the technique in general," she says.

The intensity of the stimulation, the location of the electrodes, the length of stimulation session, the number of stimulation sessions, the patient's medical history—all of these affect the outcome. It has become increasingly apparent that what's going on in the patient's brain during stimulation—what the person is thinking about or the task she is performing—affects the results as well. "If you change one of these parameters, you are changing the intervention," says Bikson. "This is a bigger problem in tDCS than it is in TMS."

It doesn't help that, unlike in TMS, there's no easy biomarker for determining the dose of TES. TMS delivers a 100- to 200-fold stronger electromagnetic field to the brain, compared with TES, and when applied over the motor cortex, TMS causes the thumb to twitch. This shows that the treatment is strong enough to produce an effect and helps determine the dose for each patient.

"If we didn't know that, I don't know that TMS would be approved [by the FDA] for any kind of treatment," says Mark George, director of the Brain Stimulation Lab at the Medical University of South Carolina. TES, however, doesn't do anything immediate or obvious to the body, so it's hard to tailor the dose to the patient, or prove, on the spot, that it's doing something.

Coming up with solid placebo controls and sham conditions has also proven tricky. A good sham must have the same look, feel and sound of the real device. And, critically, researchers need to know what to expect from the placebo group in that therapeutic area. "The reason we have TMS as a treatment for depression is because we absolutely understood the sham response," says George, who is credited with developing some of the earliest TMS treatments in the 1980s.

In those early years, he and his colleagues knew from studies of Prozac and other antidepressants that in people with new cases of depression, about 60% of the placebo group will show improvement, George says. But the placebo response drops to 20% among depression patents who have tried two or more medications. "That's why with TMS we only enrolled people who have failed two drugs," says George. "That strategy allowed the team to find effects using hundreds of subjects, rather than thousands, he says.

### Table 2 | Selected tDCS device companies

<table>
<thead>
<tr>
<th>Company (location)</th>
<th>Status and market</th>
</tr>
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<tbody>
<tr>
<td>Soterix</td>
<td>Registered in Europe, Australia, Brazil, Singapore, China, Mexico; sold to researchers and medical professionals</td>
</tr>
<tr>
<td>Ybrain (Seongnam-si, Republic of Korea)</td>
<td>Registered in Republic of Korea; available through specialized clinics</td>
</tr>
<tr>
<td>Neuroelectrics (Barcelona, Spain)</td>
<td>Sold to researchers and medical professionals</td>
</tr>
<tr>
<td>Sooma (Helsinki, Finland)</td>
<td>CE-marked and sold as investigational device globally to researchers and medical professionals</td>
</tr>
<tr>
<td>Halo Neuroscience</td>
<td>Direct to consumer</td>
</tr>
<tr>
<td>TCT Research (Hong Kong)</td>
<td>Direct to consumer</td>
</tr>
<tr>
<td>Omni Stimulator</td>
<td>Direct to consumer</td>
</tr>
<tr>
<td>Super Specific Devices</td>
<td>Direct to consumer</td>
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News Feature | Focus

Box 1 | Next-generation brain stimulation

Compared with the complexity of the brain, such non-invasive stimulation techniques as TMS and TES modulate brain activity in woefully rudimentary ways. Researchers working on the next generation of neuromodulation techniques aim to improve precision using computer mapping, artificial intelligence, new techniques, and smart combinations of tools.

One increasingly popular approach is the combination of electroencephalography (EEG), functional magnetic resonance imaging (fMRI), and machine learning algorithms to monitor brain activity with more precision. This allows scientists to time the delivery of TMS or TES stimulation in ways that synchronize or build on native brain rhythms. "EEG has really great temporal precision, but its spatial precision is not good, and fMRI has good spatial precision, but its temporal precision isn't very good," says Hanlon. By combining them, "you get this extra special thing," she says.

BrainsWay scientists have combined EEG and TMS with machine learning to help them find optimal stimulation parameters and are studying the combination in populations with ADHD, depression and PTSD. The company's algorithm can predict, with 94% accuracy, whether a subject with ADHD is going to respond to treatment, says Aron Tendler, chief medical officer at BrainsWay. "We'll know after the first treatment if we should change the protocol," he says.

Ultimately, researchers would like to reach deeper regions of the brain in more focal ways, without surgery. TES and TMS in their current form can't do that. One promising alternative is low-intensity focused ultrasound, or LIFU. The technology sends focused beams of ultrasonic energy to deep targets in the brain, causing them to fire.

In another effort to reach the deep brain non-invasively, engineers at the MIT Media Lab in 2017 proposed a technique they call temporal interference. It involves sending two high frequency electrical signals that differ by a small amount to a single deep target. When the two signals meet at the target, they create an electric field with an amplitude that oscillates at a frequency equal to the difference between the two signals. That frequency is low enough to engage neurons in mice.

But it isn't always that straightforward. A 2018 study of TMS on 164 veterans with depression found that nearly equal numbers of participants—about 40%—in the active and sham groups experienced significant improvement in their symptoms. We assumed [the sham rate] would be in the range of 10 to 15%, like in other TMS pivotal studies," says George, who coauthored the study. "But the sham rate was huge, and the trial failed to find a difference," he says. For depressed veterans, participation in the trial itself was a behaviorally activating experience, George says. And the patients may have been more compliant with their medications during the trial, he says.

It's possible that, unlike TMS, TES systems don't induce neuronal firing in the brain at all and that the technology works by some other mechanism. And that's the elephant in the room. A TES current is weak, and about 75% of it is shunted by skin and skull. The small amount of energy that actually reaches the brain—electric fields of about 0.4 to 0.8 volts per meter—likely isn't enough to cause silent neurons to start firing, or entrain neurons that are already firing. "It's possible we're doing something to the brain, but we need to be more open-minded about what the possibilities are," Liu says. "It's overly simplistic to think you are only targeting the part of the brain that the electrode is placed over," she says.

Instead of inducing neuronal firing, TES may prime the brain, putting it in a more excitatory state. "We do have a lot of evidence that's been replicated to show that tDCS absolutely changes cortical excitability," says Hanlon. "It does not, however, seem to fire neurons. It just changes the likelihood that they will fire," she says. For example, if neurons are already close to firing when a person is performing a specific cognitive or motor task, a weak current applied to the head might tip the balance or reinforce that brain activity. Or perhaps stimulation applied at just the right time, synced with the native rhythms of the brain, will bias firing (Box 1).

The brain and beyond

Perhaps it's actually peripheral nerves in the face, scalp or neck, rather than the brain, that are responsible for the therapeutic effects of TES. Researchers at Exp ORL in Leuven, Belgium, in January provided evidence for this idea, with a study on tremors. In those experiments, neurophysiologist Myles McLaughlin and colleagues applied tACS to people with essential tremor. Surprisingly, whether the stimulation was applied over the motor cortex or to the arm, it caused tremors in the finger to sync with the stimulation. A topical anesthetic applied to the scalp significantly reduced the effect of tACS on the tremor, suggesting that the peripheral nerves in the skin, not direct cortical stimulation, modulated the tremor.

Peripheral nerves, such as the occipital, vagal and trigeminal nerves, have all been investigated to understand how direct stimulation to those circuits affects behavior and disease. The FDA in April approved marketing of a non-invasive trigeminal nerve stimulator, developed by NeuroSigma, for the treatment of attention deficit hyperactivity disorder (ADHD). ElectroCore sells a handheld, non-invasive vagus nerve stimulator for the treatment of migraines and other conditions; the device received approval from European regulators in 2011 and from the FDA in 2017.

The challenges have led researchers to look for answers by trying to better understand mechanisms underlying TES. The US National Institute of Mental Health, for example, is directing much of its TES funding to mechanisms. "We've had decades of funding clinical trials that didn't explore mechanisms, and when they failed, we didn't learn that much from them," says David McMullen, program chief of the agency's neuromodulation program. "By focusing on mechanisms, even trials that fail are still informative," he says.

Liu, in her work on mechanisms, is continuing to measure the effects of TES stimulation in the cortical surface of patients with epilepsy who are undergoing invasive electroencephalography (EEG). "Until we understand how we get the behavioral effects, we're not going to be able to replicate published findings to a point where we can actually use them reliably for clinical purposes," she says.

The challenges have also led some groups to eschew TES altogether to pursue other technologies. DARPA (Defense Advanced Research Projects Agency), the research arm of the US Department of Defense, which has, for the past five years, funded a wide range of neuromodulation projects, won't be focusing on TES or TMS, says Justin Sanchez, who was until June the director of the agency's Biological Technologies Office. These technologies "do not have the right resolution or functionality to truly produce a functional effect," he says. "The signals are so coarse that it's really hard to interact with the brain in the way that the brain is designed to function."
DARPA wants the next generation of non-invasive devices to match the precision of invasive stimulation, he says. To that end, the agency in May announced funding for six groups through a new program called N³. The chosen projects employ nanoparticles, optical techniques, ultrasound, and combinations of some of those technologies with electromagnetic fields.

**The neuromarketing bonanza**

Despite the challenges and unknowns, sales of TES directly to consumers in the United States are growing rapidly. And as long as the manufacturers don’t claim that a device treats a medical condition, they don’t need FDA clearance to sell them on the open market. “There are well-established regulations for what constitutes a medical claim and what doesn’t,” says Bikson. For example, a device that treats insomnia would require FDA oversight, but a device that provides a “sweeter night’s sleep” would not, he says. That means that claiming that a tDCS device makes a healthy person smarter or more athletic is free game.

One metric for the growth among consumers is Caputron, the Amazon of neuromodulation devices. This online device distributor has grown 60–70% per quarter since it was founded in 2014, according to Robin Azzam, CEO at Caputron and former engineer at Soterix. The company moves tens of thousands of items per year, and consumer sales comprise 94% of the world’s market for consumer tDCS products. The company’s biggest seller, a tDCS device called ActivaDose, retails for about $350.

Caputron tests every device before distributing it and doesn’t make any claims about what effects the devices are supposed to achieve in the body, says Azzam. “We make sure everything that is delivered to the customer performs exactly to the specifications listed by the manufacturer,” he says. “We take a very conservative approach in how we market these devices. On our website, we don’t make any claims about wellness or neurological disorders or treatment of any kind,” he says. “We’re not telling consumers to use anything for a specific purpose. We’re just giving them the best information for the device that is available.”

Other sellers are less cautious with their marketing. Many device makers say their TES technology enhances human capabilities. Halo Neuroscience, for example, says its tDCS device increases the brain’s plasticity and that wearing it during training will improve athletic and musical skills, as well as accelerate recovery from sports injuries. The company on its website points to the company’s white papers and several small peer-reviewed studies of Halo and other tDCS devices to support these claims. For example, a group from China found that Halo’s device enhanced sprint cycling performance in a study of nine men.

Others go further by referencing medical benefits. A company called The Brain Stimulator says on its website that tDCS “has been documented as having impressive potential to treat depression, anxiety, PTSD, as well as chronic pain.” The website runs a small-print disclaimer along the bottom of its webpages, saying that the company “does not claim to diagnose, assist, treat, improve, cure, or prevent any medical condition or ailment whatsoever.”

**Anything goes**

In a survey published in May of direct-to-consumer TES and EEG products, researchers found nine devices with marketing language related to the treatment of a medical condition, including depression, PTSD, chronic pain, insomnia and amyotrophic lateral sclerosis (ALS).

The quality of these direct-to-consumer devices varies greatly. “People see it as this really trivial technology,” says Bikson. “It’s a 9-volt [battery] connected to sponges. That unfortunately promotes a cavalier attitude among some manufacturers and some do-it-yourselfers, where they think anything goes,” he says. “But it’s not trivial. Anyone who understands medical device standards understands that the difference between reliable 99% of the time and reliable 100% of the time is a huge amount of work.”

The growth of the do-it-yourself brain stimulation movement compelled researchers from four institutions to write an open letter listing reasons why people shouldn’t try this at home. Among the authors’ concerns is that “enhancement of some cognitive abilities may come at the cost of others.” There are too many unknowns for people to be randomly zapping themselves or their children, they wrote. Some researchers interviewed by *Nature Biotechnology* echoed those sentiments. Says George: “Anything that has the power to heal has the power to harm.”

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Published online: 12 August 2019
https://doi.org/10.1038/s41587-019-0238-4

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