Neurobiologist Flavio Frohlich receives transcranial direct-current stimulation.

NEUROSTIMULATION

Bright sparks

As neuroscientists explore the therapeutic prospects of brain stimulation, the amateur community are hoping the technology will enhance their mental faculties or well-being.

BY KATHERINE BOURZAC

Lincoln walks into the neurohacker meeting I am attending in a garage in San Francisco. He takes off his flat-brimmed baseball cap, exposing two small, red burns on the side of his face. The day before, he tried a brain-stimulation method called transcranial direct-current stimulation (tDCS) for the first time. “It was pretty intense,” he says.

Lincoln had one electrode on his right temple, and another at the bottom of his left deltoid. When turned on, 2.5 milliamps of current flowed into his brain, through his medial prefrontal cortex, down to his shoulder. At least, that’s what this set-up was intended to do, he says. The idea was that the stimulation would help Lincoln, a software programmer who has meditated regularly for several years, to achieve a mystic state. That didn’t happen, although he says he did feel a heightened awareness. After 40 minutes of stimulation, he also experienced twitching in his legs.

Neuroscientists who have been studying the use of low-intensity electrical current to stimulate the brain have produced tantalizing results that have, not surprisingly, encouraged amateur use. They have shown boosts in learning, memory and performance on mathematical tests, as well as early success in treating depression and helping the recovery of those who have had a stroke. Brain stimulation is easy to do at home, either by building a tDCS set-up using some simple wiring and a battery, or buying one ready-to-use from any of the ten or so companies selling them online. Some users are seeking cognitive enhancement, whether it’s to achieve mindfulness or a memory boost; others are trying to treat mental illnesses such as depression.

If stimulation is easy, neuroscientists warn, doing it right is not. Companies selling these devices direct to consumers are “smartly circumventing government regulation” in the same way that the supplement industry is, says Flavio Frohlich, a neurobiologist at the University of North Carolina School of

Medicine in Chapel Hill. “People may well be damaging their brains.”

There is a disconnect between carefully done, quantitative research on tDCS, and more exploratory use at home or even, researchers say, in the laboratories of less-experienced scientists. Improper use and some ambiguous meta-analyses — as well as evidence of harm or negative results — have fed into a backlash against the technology within the neuroscience community. Brain-stimulation specialists are calling for a more nuanced understanding of the technology and its uses. Researchers are excited about the possibilities of brain stimulation for cognitive enhancement and therapy. They just want to take their time to validate it.

BIOELECTRIC BOOST

Electric stimulation has come in and out of fashion since the eighteenth century, when Italian physician Luigi Galvani famously made frog’s legs jump with an electric current, and naturalist Alexander Von Humboldt stuck wires in his back with the aim of understanding the excitability of nerves and muscles. In the nineteenth and twentieth centuries, physicians administered shock therapy to patients, inspiring fictional characters from the monster in *Frankenstein* to the horrifying Nurse Ratched in *One Flew Over the Cuckoo’s Nest*. Today’s researchers have tamed both the method and, they hope, the image of electrical stimulation.

A gentler version was popularized by research at the University of Göttingen in Germany led by neurophysiologists Walter Paulus and Michael Nitsche, who began experimenting with low levels of electrical brain stimulation in 1999. Although a typical dose of electroconvulsive therapy (which is used sparingly to treat depression) might approach 1 amp, the tDCS revived by the Göttingen group uses a tiny fraction of that — typically only 1 to 2 milliamps. That is low enough to be done with a standard 9-volt battery.

This weak stimulation cannot directly make neurons fire — instead, it generates a diffuse electrical current that changes their membrane potential. Neurons under the anode, the positive electrode, become more likely to fire when they receive signals from other neurons. Neurons under the cathode, the negative electrode, become less likely to fire. It is very difficult to target a specific region of the brain, especially with simple home set-ups that use wet sponges as the contact points.

In their early work, Paulus and Nitsche used tDCS mainly to study motor learning and working memory. But soon, many other researchers began exploring its potential for cognitive enhancement. They reported that brain stimulation acts a bit like caffeine, and may help people to learn faster. “It seems to give you any kind of benefit you want,” says Frohlich.

Such cheerful pronouncements earned tDCS

SOURCE: REF. 3

a label of ‘too good to be true.’ And indeed, the technique has now reached the backlash point in its hype cycle. Many of the positive tDCS studies have been criticized for a lack of rigour; more carefully controlled experiments are starting to show negative results. Last year, Frohlich and his colleagues wrote a report suggesting that stimulation can actually be detrimental to IQ scores. His team gave a standard IQ test to 40 people, who then received either sham or real tDCS of 2 milliamps for 20 minutes over the left or right prefrontal cortex, or both sides. When people took the IQ test again, everyone’s scores were higher (because of the well-known retest effect), but those who were stimulated actually had a smaller increase than the placebo group¹. The subpar performance came in a particular part of the test that assessed fluid intelligence — the ability to solve new problems on the fly.

A few meta-analyses of tDCS studies have brought the entire field into question — and that includes lab-based research as well as the amateur use. One analysis by a group at the University of Melbourne, Australia, concluded that tDCS had “little-to-no reliable” effects². The authors, whose analysis has been sharply criticized by the brain-stimulation community, declined to speak to *Nature* for this feature.

Nitsche and other prominent brain-stimulation specialists say that the methods used in this — and other — meta-analyses have been poor. In particular, they contend that it does not make sense to pool the results from studies that used different experimental set-ups and equipment, even if they looked at similar cognitive tasks. Marom Bikson, a bioengineer at the City University of New York, says that it would be like doing a meta-analysis of clinical trials for two drugs, only one of which works. The positive and negative results would cancel each other out, but it would be absurd to then conclude that neither drug works. What is important is not to average out the results from different electrical stimulation set-ups in a meta-analysis, but to do work that is reproducible, he says.

Brain stimulation is complicated, says Bikson. Frohlich’s IQ-deficit finding, for example, shows that there may be off-target effects that researchers miss. And the poor spatial resolution of tDCS means that researchers should design experiments carefully to make sure that they are definitely targeting the part of the brain they’re interested in, says Frohlich. Thus, even when a study leads to positive results, researchers may misinterpret the outcome unless they have carefully validated which area of the brain they are stimulating.

STIMULATING MISUNDERSTANDINGS

In the scientific community, Frohlich’s work is respected by both tDCS proponents and doubters. The do-it-yourself community, however, seems to have adopted a more defensive response. One of the most popular blogs, DIY tDCS, pointed to the negative coverage under the headline “Why your

BOYS’ OWN BRAIN BUZZ

Although the over-60s are represented, young men are the most frequent users of transcranial direct-current stimulation kits at home³. Of 121 users, most were looking for cognitive enhancement, but some were treating conditions such as attention-deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD).

USERS

USES

Cognitive enhancement

Medical conditions

brain stimulator is probably not making you stupider”, pointing out the differences between the set-ups for home users and those used in Frohlich’s study. Whether that is the case or not, unavoidable inconsistencies in the use of the home devices — from the intensity of the current to the placement of the electrodes — are troubling for researchers and brain hackers alike.

However, warnings about tDCS seem to be trickling down, at least in the San Francisco hacker community. At a weekly meet-up of the local branch of the international NeurotechX hacker organization, of which Lincoln is a member, I am chatting with six programmers gathered around folding tables and couches. They are talking about a 3D printed electroencephalogram (EEG) cap that is available online, and working on open-source software for brain-computer interfaces.

Computer-science graduate student Damien talks about the excitement of “exploring your own brain” using EEG feedback. But stimulation? No way, say most of them. “It hasn’t been proven that it’s harmless,” says software engineer Marion, who hosts the meet-up. This group takes a read-only approach, recording the brain’s electric signals, but not stimulating them. When Lincoln walks in with the burns on his face, I am not the only one to raise an eyebrow — the side effects he noticed and

the uncertainty about what really happened in his brain reinforces their scepticism. Lincoln says he wouldn’t use that particular set-up again, especially not with the same company’s tDCS device, but he might try another set-up.

It’s difficult to know what people are actually doing at home, and how many home users there are. A tDCS forum on the social-news website Reddit (known as a subreddit) had around 8,000 members at the beginning of 2016, but not all readers are necessarily users of the technology. Posts include tips on electrode placement, links to media coverage of scientific results and some alarming questions, such as one from a reader who asked whether childhood epilepsy makes tDCS more risky as an adult.

Anita Jwa at Stanford Law School in California, whose research focuses on the intersection between law and neuroscience, was the first researcher to survey home users³. Jwa says that tDCS users do not meet up in person very much, as far as she knows, and that the online community has a self-regulating aspect; the reader who asked about epilepsy, for example, was told to ask his doctor or simply not to take the risk. On the basis of surveys posted on two popular websites: the tDCS subreddit and DIY tDCS, Jwa found that users were mostly in their 20s and 30s and 94% were male.

Home tDCS users, says Jwa, tend not to see themselves as experimentalists who are adding to the pool of knowledge. “Most users are doing it for cognitive enhancement,”

“People are desperate, they are driven to these things out of a lack of effective tools.”

L: The burns Lincoln received from a DIY kit. R: Others have more success using a different set up.

she says (see ‘Boys’ own brain buzz’). Most people who sought cognitive enhancement wanted to boost attention, learning or working memory.

SPEAKING THE BRAIN’S LANGUAGE

While repeating the mantra ‘don’t try this at home’, neuroscientists admit that people treating themselves for illnesses such as depression are trying to make up for the real shortcomings of mainstream medicine. “People are desperate, they are driven to these things out of a lack of effective tools,” says Adam Gazzaley, a neuroscientist and psychiatrist at the University of California, San Francisco. Gazzaley is working on combining brain stimulation with brain-training video games for cognitive enhancement.

What’s especially frustrating for neuroscientists is that brain stimulation has real promise for treating conditions and for cognitive enhancement — the very things that companies are implying their machines do (while taking pains to avoid making actual medical claims, which would trigger government regulation). Ultimately, validated devices and stimulation procedures will replace what’s available today. When researchers come up with something better, “the snake oil will go away,” says Gazzaley.

To get there, some researchers are seeking a better understanding of the mechanisms behind tDCS. “We need to find out how it works so we can make it better,” says Frohlich. Bikson agrees, but adds that the technique is too promising to stop and wait for a full mechanism.

For those with a biophysics bent, the mystery about the mechanisms is a great motivation. Cognitive scientists Ludovica Labruna and Richard Ivry, of the University of California, Berkeley, fall into this camp. They hope to use a better-understood brain-stimulation method to try and illuminate the workings of tDCS.

Transcranial magnetic stimulation (TMS) uses a focused magnetic field to cause small numbers of neurons to fire. TMS’s direct effect is much easier to measure in humans than tDCS’s more mysterious influence. Because of this, researchers know that all kinds of things can influence a person’s sensitivity to TMS,

including skin conductivity, skull thickness and even subtle differences in brain anatomy.

Labruna shows me how TMS sensitivity can be quantified. She tapes an electrode near the web of skin between my index finger and thumb. This electrode will measure the voltage in my hand when she stimulates my brain with a TMS paddle. Labruna locates the part of my motor cortex that controls this particular muscle in the hand,

“We need to find out how it works so we can make it better.”

then cranks up the TMS. The machine can focus a magnetic field of about 3 tesla in a small area of the cortex; TMS sensitivity is measured by determining what percentage of this maximum magnetic strength is required to provoke a threshold potential of 1 millivolt in a muscle. After a few tries, my hand jerks like a puppet. My sensitivity is medium-high — whether it’s because my skull is thin, or something else, I respond when the field’s intensity is only 42% of its maximum (most people respond at about 50% maximum intensity; some very sensitive people respond at about 29%, others not until about 60%).

In preliminary results presented at the Society for Neuroscience meeting in October 2015, Labruna, Ivry and their colleagues showed that the more sensitive a person is to TMS, the more readily they respond to tDCS, and the better they do in a motor-learning task compared with both those who had a sham stimulation and those who were less sensitive to TMS. The researchers are now designing an experiment that will test whether this correlation holds in tDCS experiments that look at other types of cognition.

ALTERNATE REALITY

Although tDCS has been getting most of the buzz, there are other kinds of electric brain stimulation that may work better, or at least have different applications. Some researchers, for example, are using alternating current, which targets brain oscillations, instead of direct current, on the basis of the theory that this may be a more natural way to stimulate the brain.

Transcranial alternating current stimulation

(tACS) emerged in 2006, when researchers in Germany showed that stimulating the brains of healthy people at 0.75 hertz (at the lower end of the frequency range of delta waves) during the early stages of sleep encouraged this rhythm and enhanced memory retention⁴. Other frequencies are associated with different cognitive states: theta (5–8 Hz) with working memory and gamma (>30 Hz) with memory maintenance, although these associations are broad and highly dependent on where in the brain the patterns are measured.

When you close your eyes and relax, the brain’s oscillations are about 10 Hz (within the alpha frequency of 7.5–12.5 Hz). In a preliminary study, Frohlich and his colleagues measured a person’s alpha frequency with an EEG, then applied an alternating current at a matching frequency. They found that this enhanced creativity⁵.

Like tDCS, the mechanism of tACS is not clear. One theory is that it might be more targeted because the rhythmic simulations interact with existing brain activity only at a particular frequency. The effects of tACS are also thought to be more short-term than those of tDCS, says Roi Cohen Kadosh, a cognitive neuroscientist at the University of Oxford, UK. That still needs to be proved, but it’s an exciting hypothesis, says Frohlich. Whatever the kind of current, the brain isn’t a simple machine, he cautions, and it isn’t possible to turn a function on like a light switch. “We have to speak the language of the brain and understand how the brain responds,” Frohlich says.

Despite the backlash against tDCS, many neuroscientists have no doubt that transcranial electrical stimulation will come to be an important tool for cognitive health and well-being. “The brain uses both neurotransmitters and electric fields to communicate,” says Sarah Hollingsworth Lisanby, director of the division of translational research at the National Institute of Mental Health in Bethesda, Maryland. Therefore, she says, we should use both channels for therapy. Moreover, she adds, non-invasive stimulation may be a way to intervene earlier in the development of mental illness — perhaps even to prevent it.

Bikson thinks in a similar way. The commonality between brain stimulation for cognitive enhancement and for therapy is that both involve learning. You are “trying to teach the brain,” he says, “either a new trick — or not to be sick.” ■

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