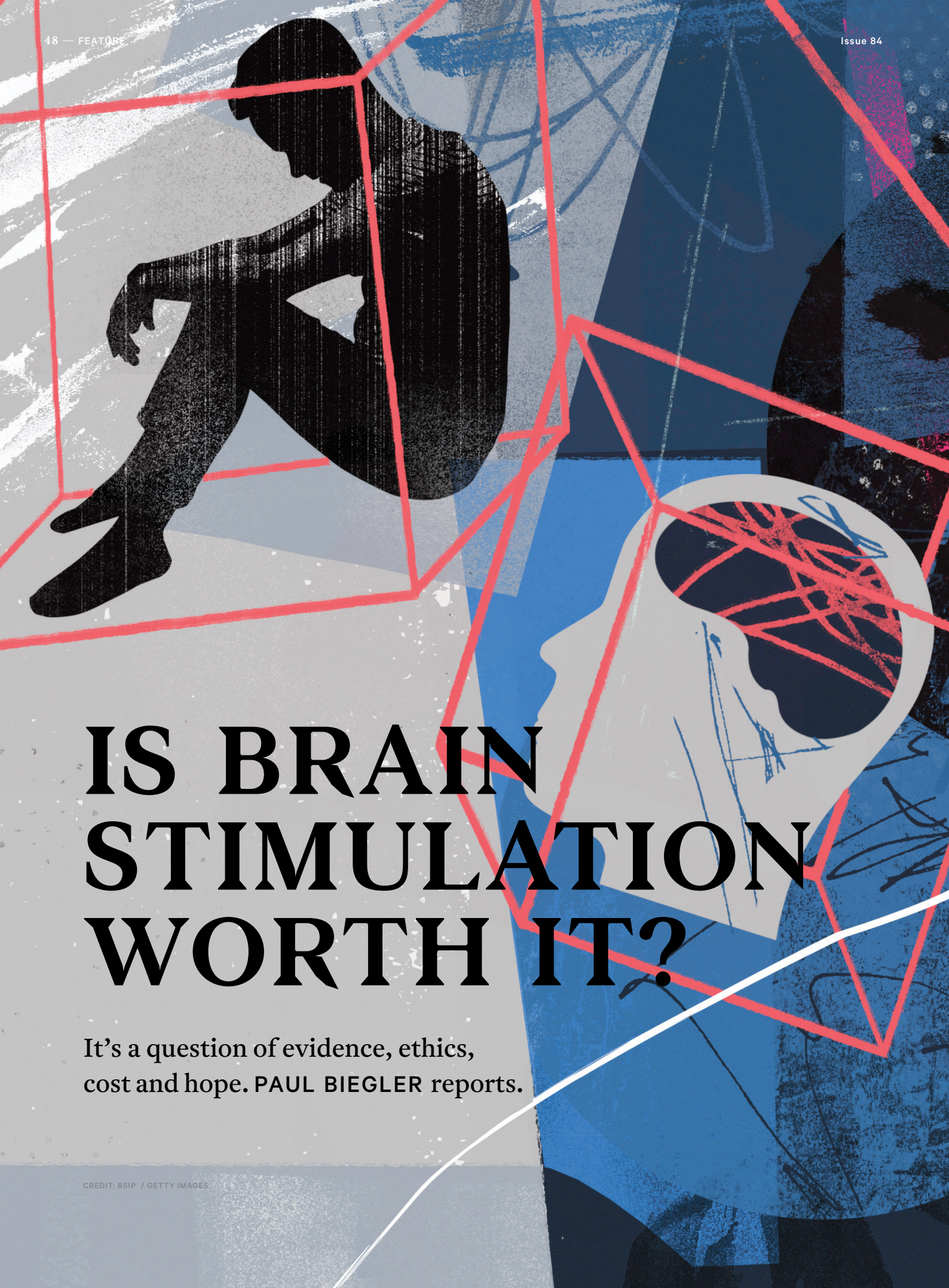

# IS BRAIN STIMULATION WORTH IT?

It's a question of evidence, ethics, cost and hope. PAUL BIEGLER reports.

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**PETER SIMPSON-YOUNG IS TORN.** The Sydney-based technologist has been contacted by a father desperate to find a solution to his daughter's depression. She's in her early twenties and has run the gamut of medication and psychotherapy but is still suffering.

**"SHOULD SHE TRY** brain stimulation at home?" the dad asked. He's talking about transcranial direct current stimulation (tDCS), the passing of a small electric current through the brain by a device worn on the head, something that's been racking up evidence points as a treatment for depression, early dementia and even stroke.

It's a technology that has also, in recent years, been well and truly democratised. Anybody can pick up a model such as the Brain Driver, Focus V3 or the snappy Halo Sport online for around US$400.

Why then is Simpson-Young, who has a science degree and a Masters in Health Technology Innovation from the University of Sydney, wavering on whether to recommend one to the young woman?

"I've used all of the devices, I think, at least all the types of devices. I'm a technologist. They're all shit. Like, it's the 21st century, yet tDCS is glorified nine-volt batteries hooked up to dish sponges connected to elastic bands on our heads," says the side-burned, youthful Simpson-Young over Skype.

"We are now at a position where the evidence is ahead of the technology. No-one has made the product that can deliver on the evidence."

The precise state of that evidence and technology is critical information, not just for the worried dad, but for the sizeable bunch of people wondering if sending current through their cranium is what it is cracked up to be; the market for these devices and related neurotech is tipped to pass US$3 billion by 2020.

All in all, it's a very mixed bag.

In June, a pilot study led by Colleen Loo from Sydney's Black Dog Institute found depression got significantly better in 34 patients using tDCS at home. And in May, research led by Robert Reinhart at Boston University in the US found that stimulating the noggins of a group of adults over 60 gave them, briefly, the short-term memory of 20-year-olds.

Back in December, a study of people who lost their speech after a stroke found those who got tDCS had more than double the improvement of controls who didn't get their brains tickled.

But a 2018 review concluded tDCS had only modest and sometimes negative effects in depression. And in 2016, Dutch and German researchers testing the Focus tDCS device on healthy volunteers found their short-term memory actually got worse.

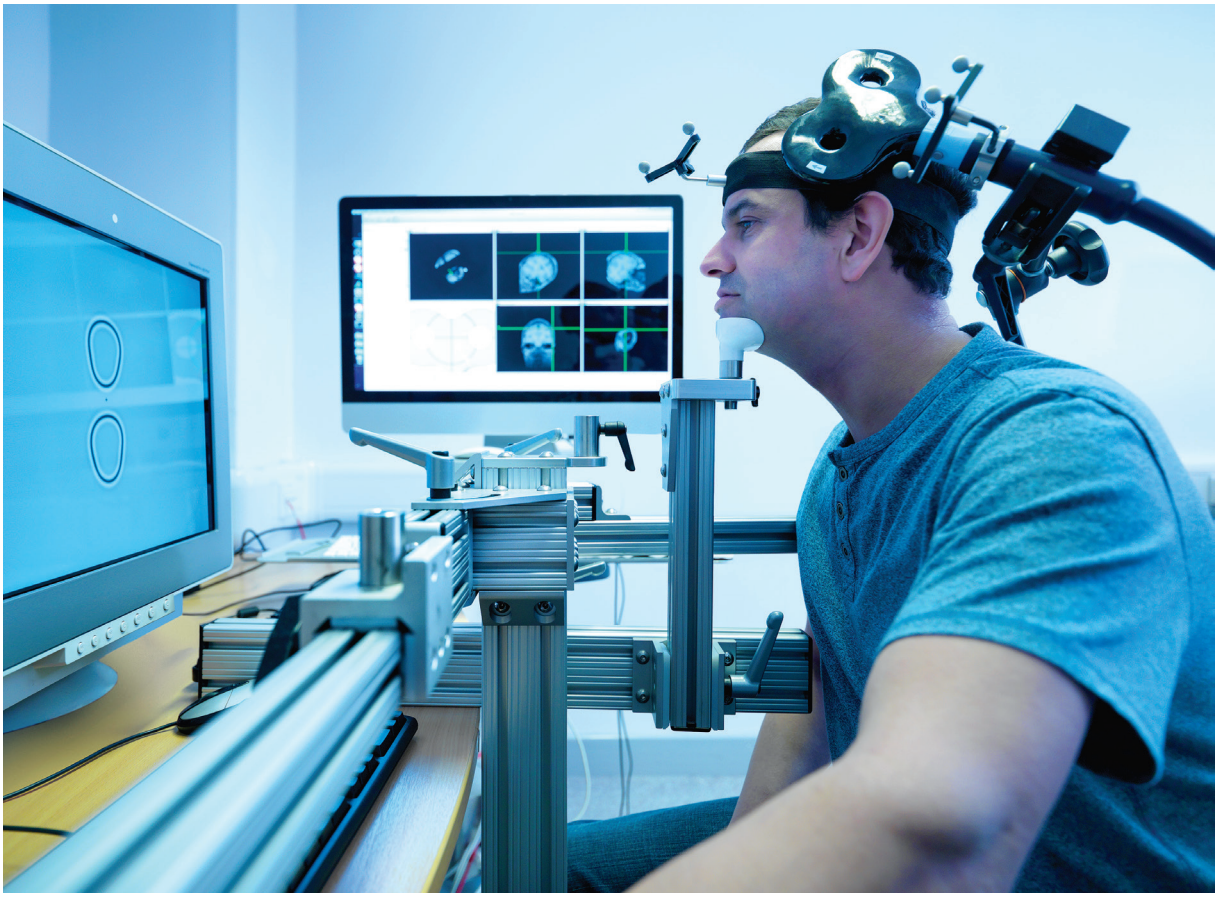
Which is a lot of noise to cut through.

To help find the signal, I went to see Paul Fitzgerald, a Professor of Psychiatry at Monash University in Melbourne. He is also director of the Epworth Centre for Innovation in Mental Health, which has digs in an anonymous, glass-fronted cube of a building in Melbourne's leafy Camberwell, where I visit on a drizzly winter day.

Fitzgerald is tallish, neatly groomed and serious, speaking with the just discernible tension of someone who has a lot on his plate. He is admirably patient as I fire off my first question: "how do these things actually work?"


Peter Simpson-Young with a 3D printing farm used to fabricate bespoke tDCS headgear.

CREDIT: PETER SIMPSON-YOUNG



TMS treatment for depression has become more widely available, but is not yet ready for home-based treatment.

CREDIT: TIER UND NATURFOTOGRAFIE J UND C SOHNS

"tDCS works through producing some very subtle changes in the likelihood that nerve cells will fire," he says. "If those areas of the brain are being activated, through being involved in doing something, those nerve cells will fire more and the circuits are likely to be reinforced."

Imagine you're swotting hard on a new language, or maybe re-learning the old one you lost after a stroke. The theory, Fitzgerald explains, is that by lowering the threshold for brain cells to fire, it gets easier to forge the new pathways that will bring forth the patter.

The process is called neuroplasticity, something of a buzzword since Norman Doidge made it famous in his bestselling book *The Brain that Changes Itself*.

How tDCS might help in depression is not quite so clear; one review suggests buzzing the circuitry might boost control over negative thinking.

But this may all be academic for Fitzgerald, who says tDCS, at least in his own practice, is fast becoming yesterday's tech.

"I'm of the view that direct current stimulation is probably going to have a relatively low ceiling," he says.

"So as an antidepressant, as something that might improve cognition, it looks like it probably has effects, but I think those effects that are shown in studies so far are pretty modest."

The mainstay of Fitzgerald's electrical treatment of depression is called transcranial magnetic stimulation (TMS), which uses a magnet placed on the skull to induce current in the brain. TMS has been approved since 2008 by the US Food and Drug Administration (FDA) for treatment-resistant depression, the kind that doesn't budge with drugs or psychotherapy.

But TMS has, literally, a very big drawback, one I see firsthand when Fitzgerald leads me to a room where his patients get the brain-zapping tech. The machine is the size of a largish bar fridge on wheels. That means in current form it doesn't fit the bill for what many clinicians, Fitzgerald included, are dreaming of – home-based treatment.

And that's part of the reason he has swivelled his sights to another type of current. It's the one Reinhart used to turbocharge the memory of his seniors and it's already an option on some home brain stimulators, including the Focus V3. It is called transcranial alternating current stimulation (tACS), and it works by eavesdropping on, then tweaking the brain's own silent chatter.

"The language of processing of information in the brain is frequency-dependent so our nerve cells, when they interact with one another, fire at specific frequencies," says Fitzgerald.

THE THEORY IS THAT BY LOWERING THE THRESHOLD FOR BRAIN CELLS TO FIRE, IT GETS EASIER TO FORGE THE NEW PATHWAYS THAT WILL BRING FORTH THE PATTER

He is talking about brainwaves. The firing of neurons tends to be synchronised and to happen at regular intervals, a kind of pulsing electrical backbeat that sets the tone for what happens on the brain's dance floor.

Brainwaves range from the slow delta waves of sleep, through to the slightly faster theta waves of deep relaxation and, quicker again, the alpha waves of wakeful rest. Up the cha cha further and you have the beta waves that signify goal-oriented tasks.

Depression, it seems, has its very own brainwave signature, which differs slightly between people. Fitzgerald measures this with EEG recorded from scalp electrodes. He then uses tACS, which can be applied at different frequencies, to try to shift the rhythm and kick the owner out of the blues.

"If you have a lack of firing at a particular frequency, say at theta or alpha frequency, then by stimulating repeatedly over time at that frequency… we can entrain that frequency," he says.

Fitzgerald is running a trial of home tACS for people aged 15-30 with treatment-resistant depression. Results are pending, so in the meantime the TMS bar fridge is the mainstay of treatment, and patients have to spend precious hours traipsing in and out of the clinic.

But research underway in Western Australia might just unchain TMS from the consulting rooms.

Jennifer Rodger heads up research into brain plasticity at the Perron Institute in Perth. Among recent endeavours she has designed a TMS device to fit the petite skulls of mice and, in so doing, has discovered that when it comes to zapping brains, less may well mean more. Rodger has been studying mice with an animal version of depression. Mini caps in place, some received a high-intensity dose of TMS, equivalent to what depressed people might get, and some a very low intensity hit, around one hundredth of that.

"The main finding we're really excited about is that low intensity stimulation seems to have the potential to have much longer lasting effects," says Rodger.

Both groups of mice got better, but the low intensity group had structural changes in their brains that hold promise they will get better for longer.

"We find that low-intensity magnetic stimulation has some very interesting effects on plasticity," she says.

Rodger explains that neuroplasticity – a mechanism by which TMS probably helps in depression – happens in two main ways. One is by altering the strength of connections between existing neurons. The other is by creating new brain cells altogether.

"We've shown that the low-intensity stimulation increases the number of newly generated neurones in the brain and the high-intensity doesn't," she says.

Low-intensity stimulation, she explains, puts in train a raft of changes that increase the excitability of neurones and set the scene for plasticity. Calcium is released within cells, altering gene expression to up production of a protein called Brain Derived Neurotrophic Factor, something of a fertiliser for growing neurones.

But why is higher-intensity stimulation less effective?

"It's a big volume of the brain that gets a massive discharge of neurones firing and we know that when that happens the brain takes a while to recover," says Rodger.

"We think that by giving very high stimulation we are almost exhausting the neurons in that particular place."

All this, she adds, could have major implications.

"With the higher-intensity stimulation used in humans the effects tend to last maybe half an hour or so. We think that our low intensity stimulation effects will last weeks or months because they cause structural changes to the neurons."

To that end, Rodger is part of a trial just now under way at Perth's Sir Charles Gairdner Hospital that will add low-intensity TMS to the standard treatment for people with major depression. If it works, the machinery needed for TMS might just get downsized.

"If we can show that the low intensity has efficacy… I think that you could redesign the devices and make them much more portable," she says.

It's a way off but, if a recent survey of home users of brain stimulation in the US is any guide, there could be plenty of takers for such a device.

Anna Wexler, Assistant Professor of Medical Ethics and Health Policy at the University of Pennsylvania in the US, recently finished a doctorate on direct-to-consumer brain stimulation.

She teamed up with seven manufacturers and sent an online survey to people who had bought one of their tDCS devices, to gauge who was buying them and why. The results, published last year, featured responses from 339 users, mostly from North America.

But they were not the ones Wexler was expecting.

"One of the most interesting things about our findings was that it was assumed, up until this point, that the typical user was kind of like this twenty-something male on Reddit, trying to hack his brain," she says.

Wexler's quarry, however, had bucked the youthful biohacker stereotype. "We found that the typical respondent was a wealthy, highly educated, liberal, forty-something male living in the US, who reported being an early adopter of technology," she says.

Wexler is not sure why, but thinks media attention on the devices may have hooked in more intrepid members of the middle-aged cohort. But what is clear, and troubling, is why people were buying the sets.

"Most people, 75%, reported using it for cognitive enhancement. About 40% reported using it for treatment," she says.

"One of the interesting things about the treaters, and this was one of the very surprising things, was that almost all of them were using it to self-treat depression."

Home tDCS is not FDA-approved to treat depression, which raises big questions about how the marketing and sale of the devices are regulated.

"It basically comes down to whether these devices are considered medical devices," says Wexler. To be considered a medical device, she explains, the product must be intended for the diagnosis or treatment of disease. That "intention" boils down to what the maker says the device will do in the marketing blurb. And that's critical, because as soon as something becomes a "medical device" it has to meet a range of FDA requirements around safety and effectiveness.

Nailing down medical claims is relatively cut and dried, says Wexler, but there is another, altogether murkier area.

"It gets much more complicated when you talk about claims that are just 'enhance your brain' or 'unlock the potential of your mind'," she says.

These claims can mean brain stimulators become "medical devices" under another prong of the FDA's definition if, in its rather archaic terms, they are "intended to affect the structure or any function of the body of man". Applying electric current to the brain would seem to fit that category but, according to Wexler, the FDA has not, thus far, seen fit to crack down on manufacturers making such claims.

All those carefully chosen words caught the spotlight big time in May, with the publication of a study in the journal *Neuron* that put the spruiking of 41 "neurowearables", 19 of which are brain stimulators, under the microscope.

Thirty-one devices made wellness claims. For example, the blurb for the Omni tDCS machine says, "If you want to improve your mood... Omni is for you". Twenty-eight made claims about enhancement. One, the Halo Sport, which is also a tDCS device, promises to accelerate "how fast people learn skills like golf, piano, triathlon, clarinet, and CrossFit".

There were also medical claims. Bellabee, which uses a technology related to TMS called "pulsed electromagnetic fields", informs potential buyers that "some conditions where Bellabee has been used include: Anxiety problems, Sleep disorders...ADD and ADHD issues [attention deficit disorders]".

The report's authors were nonplussed. "It is unclear then how eight DTC devices that claim medical benefit appear to have escaped the requirement to provide FDA confirmation of the safety and efficacy of their stated function," they wrote.

The article's lead author is Judy Illes, who holds the Canada Research Chair in Neuroethics at the University of British Columbia in Vancouver. She is clearly troubled by the marketing tactics.

"They tout benefits and downplay, if not completely omit, any reference to risks. When there are risks, we found some very mild language about safety, such as skin burning," Illes told me by phone.

"This is not the kind of information we really would like to see when it comes to brains."

Of particular concern, says Illes, was the failure to warn people, such as those with a psych disorder, not to stop their usual meds and not to use the device as a substitute for seeing a doctor.

I asked Illes what needs to change to make the marketing of these devices ethical.

"They must give as much warning information as promise information. Completely balanced. And that includes what companies don't know about what the device may be doing, as in 'we don't know how this will affect your child's still developing brain'," she says.

Illes's comment is a disturbing reminder that ADD and ADHD, targets of some of the devices, are almost entirely disorders of childhood.

Studies show tDCS is being used to self-treat depression, in spite of its non-medical classification – and testing.

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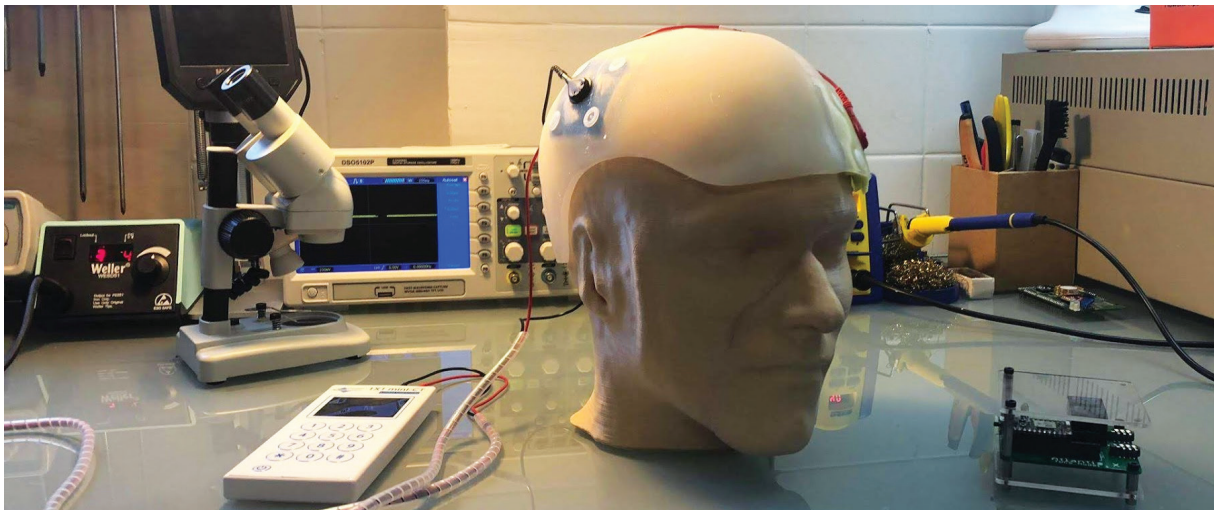

Simpson-Young is developing next-gen tACS that senses brainwaves in real time and sends a personalised response.

CREDIT: PETER SIMPSON-YOUNG

But there are encouraging signs. Illes says manufacturers are very much coming to the table, meeting with her and colleagues to discuss how they can hit ethical benchmarks.

"To be a responsible innovator you have to own your ethics and many neurotechnology companies are actually doing that today. There has been a wave shift in responsible innovation and attention to ethics," she says.

Nonetheless, pressure to keep upping the hype is likely to intensify as companies jockey for position in an increasingly congested field. And if it's a race, Peter Simpson-Young is very much hoping to be a frontrunner.

We've been chatting for a good while when the self-described scientific entrepreneur, who works two days a week at his own startup, vacates his seat to return with what looks like a bicycle helmet made out of jelly, deforming and rippling as he holds it up to the web cam. It is a silicone cap that, he says, will become the next generation brain stimulator.

"Everyone in this space knows that closed loop brain stimulation is how you're going to get, like, the 'killer app," he says – stressing later that "killer" does mean "superior" not "fatal".

The loop will be closed, he explains, by using the device to sense brainwaves with EEG in real time, and then shoot back personally calibrated tACS to alter our neural frequencies.

"Anti-depressants haven't reduced the prevalence or suicide rate of depression. And so we want to make a device that does," he says.

"We want to make a device that allows a patient to walk into a clinic, walk into a GP, then walk out with a bespoke headset that they can connect to their phone and turn down the depression."

The innovator plans to use MRI scans to pin down each person's brain areas to enable more precise positioning of electrodes. The applications, he says, go beyond depression to stemming the cognitive decline of Alzheimer's and rewiring the brains of returned soldiers with PTSD.

Simpson-Young's passion for the field goes back to his neuroscience student days, when he moonlighted as a technician in a sleep lab, monitoring the brain waves of slumbering subjects.

"I would spend all night watching the electrical activity of their brains... I could tell immediately by looking at someone's brainwaves the stage of sleep they were in. So someone in deep sleep has totally different brain waves, compared to if they are awake or in light sleep," he says.

"I kept thinking, if I put these electrodes on the head that are measuring the brain's activity, can't I just reverse the signal?"

Those ponderings led to a Google search for "brain stimulation" and the discovery of a series of conference videos on the subject.

"I just binge-watched eight hours of the conference," he says.

Simpson-Young's viewing habits might prompt some to think he got in line twice when the nerd genes were handed out. There is another interpretation, however, which I'm more inclined to accept, and that is that he's just driven to make tech that improves lives.

For the sake of many people, and one in particular, it can only be hoped that his wibbly-wobbly jelly cap is fit for purpose in the very near future.

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