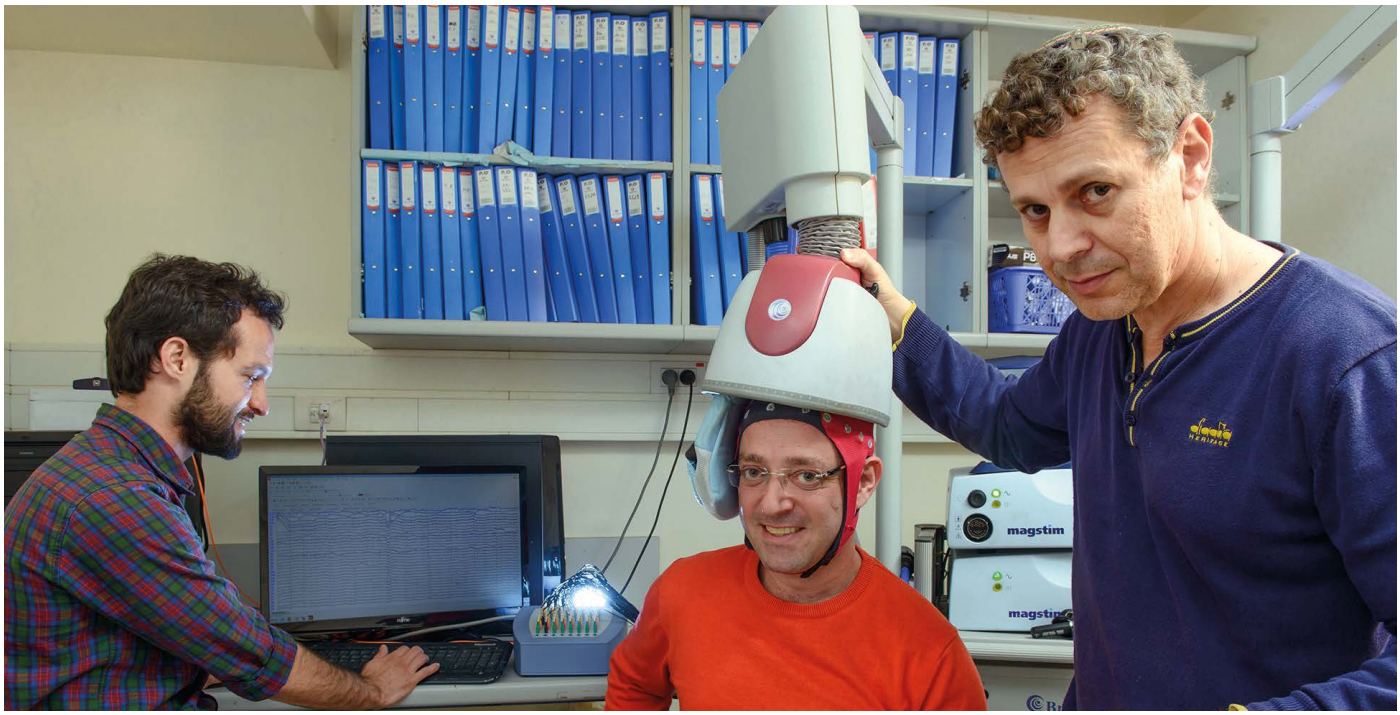

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Neuroscientist Abraham Zangen (right) and two of his students with an early version of their repetitive transcranial magnetic stimulation system.

A stimulating solution to smoking

Magnetic pulses delivered to the brain could help people to overcome addiction to cigarettes, but there is still a lot to learn. **By Simon Makin**

Galit Blecher never wanted to start smoking, but during her service in the Israeli military, she succumbed. "Everyone in Israel smoked in the army," she says. Having held out for more than one year, an especially tedious posting broke her resolve. "I was driving three hours through the desert, several times a week," she says. "I was falling asleep."

After returning to civilian life, she gave up smoking twice with the help of an antidepressant drug called bupropion (also known as Zyban), which reduces cravings and withdrawal, but she started smoking again each time. Then, six years ago, she joined a clinical trial of a new treatment targeted at people who had tried and failed to quit smoking. She hasn't smoked since. "After Zyban, there was always a craving when I saw other smokers," Blecher says. "This time it's a real aversion; I can't stand smelling cigarettes."

The treatment that helped Blecher is called repetitive transcranial magnetic stimulation (TMS), and uses magnetic fields to stimulate regions of the brain involved in addiction. The effect on quit rates in the trial was modest, but comparable to bupropion, which blocks nicotine receptors in the brain. It was enough to convince the US Food and Drug Administration (FDA) to approve, in August 2020, the use of repetitive TMS to help people quit smoking.

However, the scientists working on this new approach to giving up smoking are not finished yet. With so many variables in how repetitive TMS is delivered, researchers from around the world are now aiming to pool their knowledge and standardize methods to help the field move forwards. Understanding of the neural circuitry that underlies addiction is improving, which is helping to find ways to make the treatment more effective. And some researchers are exploring the use of brain imaging to tailor treatment to individuals.

A pivotal trial

Blecher was one of 262 smokers who were recruited to test the treatment. "These were very heavy smokers, for many years," says Abraham Zangen, a neuroscientist at Ben-Gurion University of the Negev in Israel, who led the study[1]. Half of the participants experienced real stimulation of their brains through a coil inside a helmet, whereas the other half received a sham stimulation from a second coil that produced similar sounds and sensations on the scalp but did not produce a magnetic field that affected the brain.

The stimulation was aimed at their lateral prefrontal cortex and the deeper-lying insula, with the intensity set to 120% of the level needed to make each recipient's thumb move. "To make brain stimulation effective, you need to use meaningful intensities and frequencies," Zangen says. This is uncomfortable for patients. "It's like an electric shock to the head, you feel your jaw clamping," says Blecher. "It wasn't that painful, but it wasn't pleasant."

Blecher and her fellow participants initially received the treatment every weekday for three weeks, and then once per week for another three weeks. For people in both the treatment and sham groups, each half-hour

session began with provocation cues designed to elicit cravings, to activate the neural circuitry. "When a circuit is active, it's more liable to change," says Zangen. Afterwards, all participants received a short motivational talk.

Following the treatment period, participants' smoking behaviour was monitored for four weeks, both by self-reporting and by monitoring urine for cotinine — a product formed when nicotine is broken down in the body. Anyone still not smoking at this point was assessed again 12 weeks later. By this time, 28% of people who received the full treatment protocol were still not smoking, compared with 12% of those who received the sham stimulation. People in the treatment group also reported greater reductions in their cravings for cigarettes.

"Looking at the percentage of quitters, it's not that great," says Zangen. Other treatments, such as nicotine replacement therapy, were approved by the FDA on the basis of higher quitting rates, he says. But these treatments were usually tested on less heavy smokers who had not tried and failed to quit in the past as many times as Zangen's participants had. Some of those studies also based their results purely on self-reported behaviour and breath testing for carbon monoxide, which can detect whether a person has smoked only within hours of a cigarette. "You can find traces of cotinine after a single cigarette smoked a week ago," says Zangen. "The numbers are small because our criteria for quitting are very strict, but they're absolutely clinically meaningful."

The side effects of magnetic stimulation also appear to be minor. During the trial, the most common adverse effects were headaches and discomfort. Nevertheless, the now-approved treatment can be carried out only under medical supervision because of the risk of seizures. Although none of the participants experienced seizures during his pivotal trial, Zangen says that reports from treating other conditions suggest that around 1 in 5,000 recipients of TMS might experience a seizure[2].

"If we reduce excitability of the insular cortex, we're going to reduce cravings."

Some health insurance providers in the United States already cover TMS as a treatment for depression, but not yet for smoking, says Zangen. "But they should, because the cost of hospitalization, and lost working days due to chronic obstructive pulmonary disease, and cancers and so on, are much higher," he says. The treatment is currently available in more than 50 centres and psychiatrists' offices, mainly in the United States, with a few in Europe and India. Psychiatrists and physicians can refer someone to a TMS centre, and the centres also market the treatment directly to consumers.

Craving success

TMS was first approved for treating depression in 2008. Approval for treating obsessive-compulsive disorder followed ten years later. Its use in addiction is just beginning: the trial that Blecher participated in was the first multicentre randomized controlled trial of non-invasive brain stimulation as treatment for any form of addiction. "Targeting brain circuits responsible for symptoms has proven valuable for treating a variety of brain disorders," says Michael Fox, a neurologist at Harvard Medical School in Boston, Massachusetts. "We're optimistic it can help patients with addiction."

Addiction is not one behaviour, but a cycling pattern of recurrent relapse. Characteristics of this cycle include increasing sensitivity to drug-associated cues and the anticipation of drug rewards, coupled with decreasing sensitivity to those rewards when they come. People also experience impaired self-control, enhanced stress and negative emotions. Neuroscientists have pinpointed many brain regions involved in these states and behaviours, including the prefrontal cortex, which implements self-control, and the insula, which is thought to integrate autonomic information with motivation and emotion, and so give rise to the experience of cravings.

Early in Zangen's career, he worked on reward processing in animal models at the National Institute on Drug Abuse in Baltimore, Maryland. He learnt that electrically stimulating a rat's brain affected certain receptors involved in reward circuitry in the opposite way to repeated exposure to cocaine. "I thought, we must study whether stimulation in specific areas can induce behavioural changes in addiction," he says. In 2007, then at the Weizmann Institute of Science in Rehovot, Israel, Zangen published a paper demonstrating precisely that[3]. "This was the first ever study showing that brain stimulation, in rats, can reduce drug-seeking behaviour," he says. "At the same time, I started to develop applications of these animal studies to humans."

The first studies of repetitive TMS for smoking cessation, which stimulated the prefrontal cortex, found encouraging but impermanent effects. In search of a longer-lasting impact, Zangen and his colleagues began to look deeper into the brain, towards the insula. Another 2007 study[4] found that people who experienced damage to the insula were more likely to lose their smoking addiction than were people with damage elsewhere in the brain. Zangen's hypothesis was that electrically stimulating the insula could have similar results, by interfering with cravings. "If we reduce excitability of the insular cortex, we're going to reduce cravings," he says.

The standard 'figure-of-eight' coils that were used in the first human trials did not penetrate far enough into the brain to hit the insula. So Zangen used a new design that he had helped to develop during his time in the United States that could reach deeper regions of the brain[5]. The patent for this coil is now held by BrainsWay, a medical technology company in Burlington, Massachusetts, which developed the coil used in the trial and now supplies the equipment to treatment centres (Zangen is a scientific consultant for BrainsWay). Other researchers are now studying how the coils that Zangen and his colleagues developed could be used to target several other brain regions.

Unexpected explanations

Research into TMS has found that high-frequency stimulation typically makes an area of the brain more excitable, whereas low frequencies can reduce activity. Because Zangen and his team were aiming to suppress cravings, they expected that low frequencies directed at the insula would have the desired effect. To their surprise, the opposite was true: high-frequency stimulation proved to be effective[6].

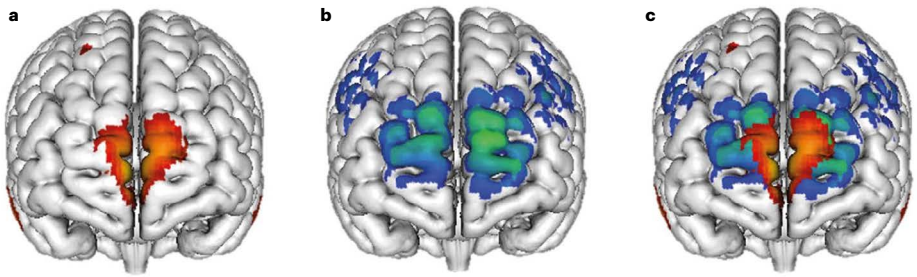
One possible explanation for this counterintuitive result is that, although the acute effect of high-frequency TMS is to increase excitability, the long-term effect of repeated stimulation could instead be suppressive. "If we stimulate the pathological circuitry daily, for several days, we [might] disrupt the processing of information," Zangen says. "That's one way to explain it."

It's not the only theory, however. "The other is that we don't reach all the way to the insula," says Zangen. Support for the idea that the treatment's effect might come from stimulating a different brain region can be found in a study of people with brain damage that was published last year[7]. A team led by neurologist Juho Joutsa at the University of Turku in Finland, mapped the brains of 129 people, all of which had areas of damage. All the participants were smokers at the time they acquired these lesions, but 34 of them had quit immediately after injury and not craved cigarettes since.

The brain lesions in those who had stopped smoking were not all in the insula. "There were many lesions that led to disruption of smoking addiction that didn't hit the insula, indicating it's not the whole story," says Joutsa. All the lesions that led to smoking cessation did, however, share a common brain circuit. Joutsa calls this the addiction remission network, in

ZAPPING AND MAPPING

A study of people with brain damage[7], some of whom quit smoking following their injury, associated activity in the medial frontopolar cortex with remission from addiction (**a**). Analysis of the brain regions that are excited by transcranial magnetic stimulation used to aid smoking cessation (**b**), which is intended to target the insula, shows that it is ideally positioned to stimulate the frontopolar cortex (**c**). This could explain the treatment's effects on addiction.



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which many parts of the brain form different nodes. Some of these areas are positive nodes – that is, activity in these areas is associated with increased activity elsewhere in the network. Other brain regions form negative nodes that are associated with reduced activity elsewhere, probably owing to inhibitory connections to the network.

> **"We need a village of expert people working together to solve this."**

This discovery might have huge consequences for understanding how repetitive TMS helps people to quit smoking. It suggests that to benefit people with addiction, a device that stimulates brain activity should target negative nodes. And after scrutinizing Zangen's work, Joutsa thinks that might be exactly what their TMS therapy is doing. "They were kind enough to share the model of the fields generated by their coil, and the strongest activation was actually in the medial frontopolar cortex," says Joutsa – the largest negative node in their network. "That aligns perfectly with their excitatory stimulation to that region," he says (see 'Zapping and mapping').

Evidence is now pointing to the frontopolar region as being a key treatment target, says Hamed Ekhtiari, a psychiatrist at the University of Minnesota in Minneapolis. "When we expose people to drug-related cues, the frontopolar area is activated," he says. The medial frontopolar cortex connects not just to the insula that Zangen was intending to target, but also to several parts of the limbic system, such as the amygdala and nucleus accumbens. "These are important for arousal, for being excited about drugs," Ekhtiari says. Stimulating this one area of the brain could therefore affect numerous other regions that are involved in addiction. "My idea is that when we target the frontopolar area, we are modulating those subcortical areas in a beneficial way," Ekhtiari says.

Finishing touches

As researchers learn about where and how to optimally stimulate the brain, repetitive TMS treatments could become increasingly sophisticated. Devices that could target multiple regions in different ways are already being developed. "That's where the field is slowly moving," says Joutsa. Some regions could be excited while others are suppressed, for instance. According to Zangen, BrainsWay is working on a multichannel stimulator. "I have a prototype in my laboratory," he says.

The region being targeted is not the only variable associated with TMS: the frequency, intensity, duration and pattern of stimulation could also affect outcomes, as could the number of treatment sessions. Much of this has barely been explored, let alone optimized. "The parameter space is huge," says Joutsa. "I hope our findings help narrow down the spatial part, so we at least know where to target."

The uncertainty in how best to administer TMS for addiction has led to a wide variety of trial designs, which is partly why a generally supportive meta-analysis of the field, published last year[8], carried the caveat that the available evidence enabled the authors to have only a low level of confidence in their evaluation. To address this problem, many researchers working in the field have begun to collaborate under the banner of the International Network of tES/TMS Trials for Addiction Medicine (INTAM). Their aim is to share protocols and propose best practices, identify gaps in their knowledge and accelerate the creation of effective treatments for addiction based on non-invasive brain stimulation. "We need a village of expert people working together to solve this," says Ekhtiari, the lead author on a consensus paper[9] the group published in 2019. "We try to harmonize efforts around the world, to make sure people are informed about what different labs are doing."

Ekhtiari is also pursuing another kind of optimization: personalization. "The brain is very different across different people," he says. This means that exactly where to optimally stimulate the medial frontopolar cortex, for instance, might vary between people. Ekhtiari and his colleagues are looking for ways to use brain imaging to characterize these differences and increase the precision of targeting. A team led by researchers at Stanford University in California are already personalizing repetitive TMS treatment in this way. One clinical trial, using a protocol called SAINT (Stanford accelerated intelligent neuromodulation therapy), found a 53% reduction in symptoms of depression in its active treatment group, compared with 11% in the group that received the sham stimulation[10] – a result that led to FDA approval last September. "That's the idea we have for nicotine, and other types of addiction," says Ekhtiari.

Many researchers hope repetitive TMS will be effective not only for smoking cessation but also for treating a wide range of substance and even behavioural addictions. Already, Joutsa and his colleagues have found that brain lesions that are associated with a lower risk of alcohol abuse show similar connectivity patterns to the smoking network[7]. "It doesn't prove it's exactly the same finding in alcoholism, but it suggests the findings could be relevant for other substances of abuse," says Joutsa.

It is too early to tell whether repetitive TMS will have the impact on addiction medicine that its proponents envisage. But even in its current, nascent form, the technology is already being used to help some people quit smoking. The numbers being helped might be modest so far, but for those people for whom it works, the benefits are significant. "I'm really relieved I stopped smoking, because of the kids, the smell and my husband, who doesn't like it, and of course the health issues," says Blecher. "I'm never going back."

Simon Makin is a freelance writer in Reading, UK.

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