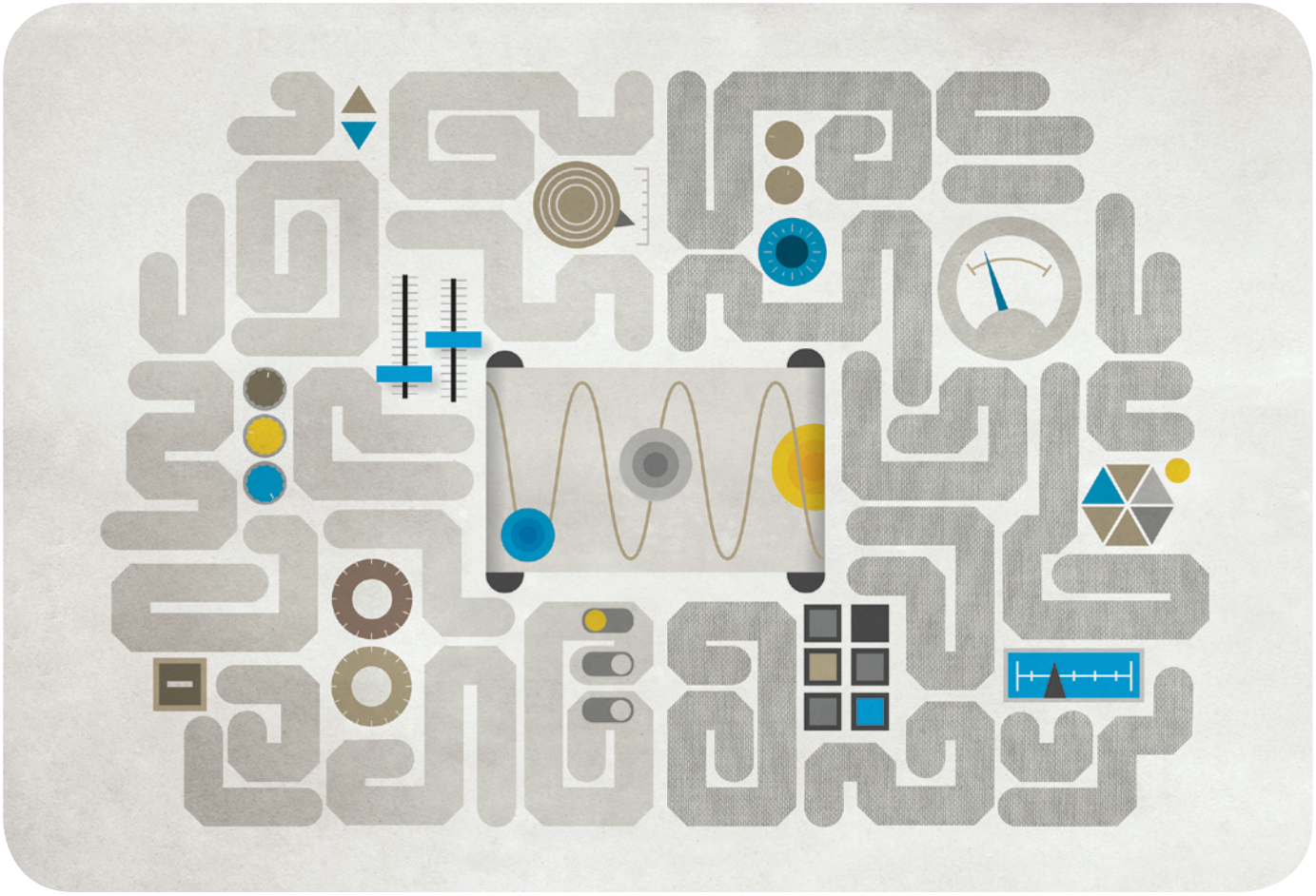


Tuning THE BRAIN

Deep brain stimulation has shown promise in treating conditions such as Parkinson's disease. Now scientists are using the technology to eavesdrop on problem neural circuits.

BY HELEN SHEN

For Frank Donobedian, sitting still is a challenge. But on this day in early January, he has been asked to do just that for three minutes. Perched on a chair in a laboratory at Stanford University in California, he presses his hands to his sides, plants his feet on the floor and tries with limited success to lock down the trembling in his limbs — a symptom of his Parkinson's disease. Only after the full 180 seconds does he relax.

Other requests follow: stand still, lie still on the floor, walk across the room. Each poses a similar struggle, and all are watched closely by Helen Bronte-Stewart, the neuroscientist who runs the lab.

"You're making history," she reassures her patient.

"Everybody keeps saying that," replies the 73-year-old Donobedian, a retired schoolteacher, with a laugh. "But I'm not doing anything."

"Well, your brain is," says Bronte-Stewart.

Like thousands of people with Parkinson's before him, Donobedian is being treated with deep brain stimulation (DBS), in which an implant quiets his tremors by sending pulses of electricity into motor areas of his brain. Last October, a team of surgeons at Stanford threaded the device's two thin wires, each with four electrode contacts, through his cortex into a deep-seated brain region known as the subthalamic nucleus (STN).

But Donobedian's particular device is something new. Released to researchers in August 2013 by Medtronic, a health-technology firm in Minneapolis, Minnesota, it is among the first of an advanced generation of neurostimulators that not only send electricity into the brain, but can also read out neural signals generated by it. On this day, Bronte-Stewart and her team have temporarily turned off the stimulating current and are using some of the device's eight electrical contacts to record abnormal neural patterns that might correlate with the tremors, slowness of movement and freezing that are hallmarks of Parkinson's disease.

Until now, such data have been accessible only when a patient's brain is exposed briefly during surgery. But being able to make long-term

ILLUSTRATION BY CHAD HAGEN

neural recordings from human patients may become increasingly important — especially because researchers are experimenting with using DBS as a treatment for many other neurological conditions, including depression, obsessive–compulsive disorder and Tourette's syndrome. The networks involved in such disorders are even less well understood than those involved in Parkinson's disease, says Helen Mayberg, a neurologist at Emory University in Atlanta, Georgia. Devices such as Donobedian's could change that, allowing scientists to start to understand just how unhealthy neural networks misfire in different diseases, and what DBS actually does to the brain. "Every disease will be different and one size won't fit all," Mayberg says. "The new technology is going to enable progress exponentially."

Eventually, adds Bronte-Stewart, engineers could use the new-found knowledge about brain networks to build even more-advanced brain implants — devices that could interpret the neural signals they record, monitor their own effectiveness and generate personalized treatments.

"This is such an exciting time," she says. "This is the first time we're really getting a window into the brain."

> *"This is the first time we're really getting a window into the brain."*

'BLACK BOX' BEGINNINGS

The roots of DBS reach back to the 1960s, when Parkinson's disease was commonly treated with surgery to remove or destroy certain brain regions. To pinpoint which areas to target in each patient, some neurosurgeons began to experiment with electrical stimulation. They discovered that the delivery of rapid pulses to the basal ganglia — a cluster of structures including the STN — could markedly reduce the patient's tremors. By the late 1980s, long-term brain stimulation started to emerge as an alternative treatment to surgery[1]. DBS has since been approved for the treatment of Parkinson's and other movement disorders by both the US Food and Drug Administration (FDA) and European regulators, and has been used in more than 100,000 people.

The biological mechanism underlying DBS remains mysterious, and is a subject of controversy. "We've been guessing a lot over the last decade or two," says Michael Okun, a neuroscientist at the University of Florida in Gainesville. "It would be premature for anyone to claim they know exactly how the therapy works."

There are some clues, however. For example, DBS is not thought to mimic any natural signals in the brain. The high-frequency pulses — delivered at 130–180 times per second for Parkinson's disease — exceed the 1–100-hertz frequency range of most natural neural communications. Furthermore, with each 60–90-microsecond burst, DBS typically delivers several orders of magnitude more current than any neuron or groups of neurons can produce.

And it does not seem to produce permanent changes in the brain, at least not when applied to Parkinson's disease, currently one of the most common targets of the technology. Turning on the current can produce immediate relief from symptoms such as tremor and rigidity. But in many people, symptoms return seconds or minutes after the device is turned off, or the battery runs out — which happens every 3–5 years. Nor does the therapy halt the progressive neurodegeneration associated with the disease; in the long run, patients will typically succumb to symptoms that are not well treated by DBS, such as cognitive deterioration.

From the evidence gleaned so far, researchers suspect that DBS does more than affect neural tissue at the site of the electrodes: it somehow disrupts pathological signals that reverberate through multiple brain regions, corrupting their communications (see 'Circuit training').

That theory meshes with the emerging view that Parkinson's disease, as well as depression and many other neuropsychiatric conditions are best understood as network dysfunctions. "That's a really important realization that has caught on in the last five years," says Cameron McIntyre, a biomedical engineer at Case Western Reserve University in Cleveland, Ohio. Indeed, it has helped to launch two major neuroscience efforts in the past year: the US Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, and the European Union's Human Brain Project.

The primary target of DBS for Parkinson's disease, for example — the STN — sits in the middle of a highly interconnected brain network that helps an individual to control his or her motions. There is some evidence[2] that as Parkinson's destroys neurons in the basal ganglia, the activity of groups of cells in the STN and across this sensorimotor network becomes abnormally synchronized, locking at certain frequencies. DBS seems to release them from these activity patterns, as do some of the drugs that relieve Parkinson's symptoms[3,4].

Recordings from the new generation of neurostimulators are poised to elucidate these mechanisms, not just for Parkinson's but also — as DBS applications broaden — for psychiatric conditions. The data could help to resolve concerns about the wisdom of expanding the treatment's usage. Although the sensorimotor network involved in Parkinson's disease has been mapped in great detail, says Joseph Fins, a medical ethicist at Weill Cornell Medical College in New York City, much less guidance is available on how best to apply the technology to other disorders. "There has got to be a biological rationale for what you're intending to do," he says.

But others argue that controlled testing of DBS in humans need not wait for complete or near-complete understanding of the relevant networks. "As a clinician, that's not really the important question," says Benjamin Greenberg, a psychiatrist at Brown University in Providence, Rhode Island. "The real questions are: do these treatments help people? Are they safe?"

Okun adds that, unlike the field of movement disorders, the mechanistic study of neuropsychiatric disorders has been slowed by a lack of realistic animal models. "If we're going to move forward with some of these human diseases, we are going to have to use humans — in a very careful way, of course," he says.

ZOOMING IN

Mayberg has been doing just that for more than a decade. In 2005 she published one of the first studies on the use of DBS to alleviate severe, treatment-resistant depression[5]. Since then, she has mainly focused her experiments on a structure known as the subgenual cingulate, in which elevated metabolism has been shown to correlate with the severity of a patient's depression[6]. She estimates that the use of DBS in this region and elsewhere has successfully eased symptoms in 40–60% of the roughly 150 cases of depression reported on so far. But in recent years, her group has begun to do better by using brain imaging to map the dense web of nerve fibres zigzagging through and around the subgenual cingulate, which connects to regions involved in learning, motivation, appetite and sleep. Combining this information with the effects seen in patients, Mayberg is zeroing in on millimetre-scale differences in electrode placement that can make the difference between success or failure.

Potentially, she says, new implants such as the device being tested by Bronte-Stewart could help her team to do even better, allowing researchers to monitor patients' condition in real time and fine-tune the stimulation pulses to maximize benefit. "There may be an optimal tuning frequency for a given person, and it may not be the same for everyone," she says.

Creating personalized DBS treatments is a top priority in this field. Just before Donobedian's meeting with Bronte-Stewart, his neurologist, Camilla Kilbane of Stanford University, spends half an hour tuning the device's stimulation settings to address his symptoms.

Using a short-range radio device, she programs a pulse generator implanted in Donobedian's upper chest. The generator — about half the size of a deck of cards — sends electrical pulses through insulated wires that run under the skin of his neck and scalp, and into his brain. Kilbane has already determined during a previous visit the subset of electrode

contacts she wants to tweak, and Donobedian has stopped taking his supplementary Parkinson's drugs overnight so that Kilbane can cleanly isolate the effects of neurostimulation.

As she drops the voltage and the implant can no longer overcome Donobedian's tremors, his hands and feet begin to quiver again. Within seconds, the tremors grow and spread, until his arms clap against his sides and his shoes tap the linoleum floor. Kilbane clicks the voltage up again, and Donobedian's limbs calm down — but then his arms begin to tingle, a common side effect of DBS. At intermediate voltages, his right leg stops shaking, but the other continues to tremble.

"It's stubborn, that left foot!" remarks Kilbane. She spends another 10 minutes inching the voltage up and down, gradually homing in on an optimal setting. Even after this, Donobedian may need to return in the coming months for further fine-tuning.

"What we have right now for DBS works, but it's very much the first generation," says Bronte-Stewart. She and others are using the new recording-capable DBS implants as a stepping stone towards 'closed-loop' neurostimulators — devices that can continuously track an individual's brain activity and automatically optimize settings as needed in real-time. As a first step, the Stanford group is beginning to mine the electrical recordings downloaded wirelessly from the implants in Donobedian and other patients to find patterns that correlate with different Parkinsonian symptoms. They are also looking to see how these patterns might change in the context of different actions, such as sitting, standing and walking — data that could not be obtained with bulky hospital machines. Indeed, Bronte-Stewart says, there may not be just one set of 'optimal' stimulation parameters. "We may find out there are different frequency ranges that are better for different functions," she says.

SMARTER STIMULATION

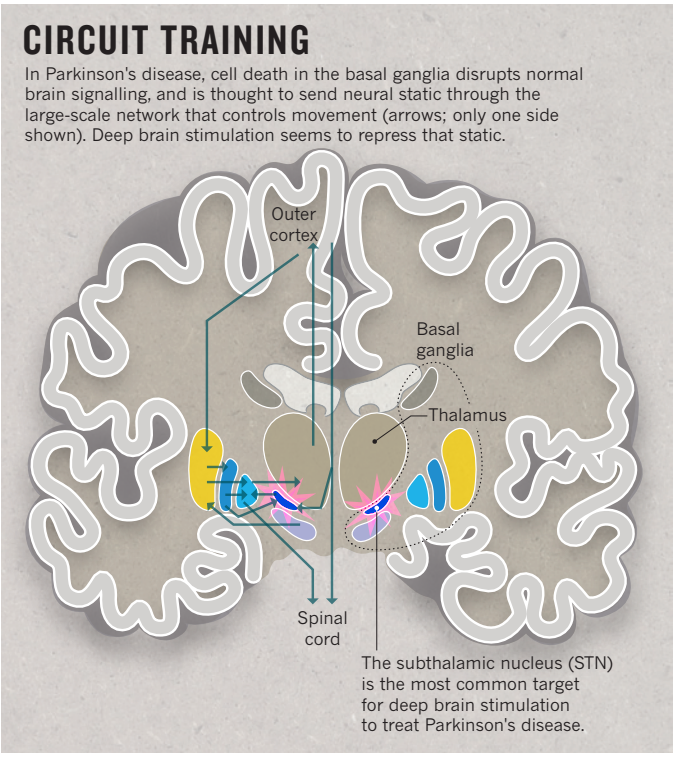
As scientists collect more data, some manufacturers are already starting to make strides in closed-loop technology. Last November, the FDA approved the first closed-loop, implantable neurostimulator for intractable epilepsy, another disorder attributable to network dysfunction. The device, made by NeuroPace in Mountain View, California, monitors neural networks for the first sign of abnormal activity — which in some patients originates again and again at one or a few 'epileptic foci' — then responds with a pulse of electrical current to prevent a seizure. "We use stimulation to disrupt that abnormal activity so that it doesn't get picked up by the adjacent neurons," explains Frank Fischer, the company's chief executive.

But Fischer concedes that, whatever the device might do for epilepsy treatment, the technology is not immediately applicable to other conditions. Epilepsy is a comparatively simple disorder, generally consisting of discrete episodes of abnormal brain activity. By contrast, Parkinson's disease involves a mishmash of symptoms that rise, fall and morph over time. Researchers are still searching for the relevant neural signatures in Parkinson's and other diseases, and developing the computational tools required to keep up with changing symptoms.

The first laboratory demonstration of a closed-loop DBS system for Parkinson's disease was reported last year by experimental neurologist Peter Brown at the University of Oxford, UK, for a group of eight patients[7]. Brown plugged the patients' DBS implants into an external machine, which triggered stimulation of the STN only when certain abnormal brain rhythms were detected. This selective stimulation improved the symptoms by almost 30% compared with standard DBS treatments, which stimulate the brain at regular intervals.

"It's far short of being introduced into patients," says Brown of the bulky experimental system, but the demonstration does provide an important proof that the closed-loop concept could work for Parkinson's disease.

In an effort to accelerate the move towards closed-loop technology, the US Defense Advanced Research Projects Agency (DARPA) last October announced a 5-year, US$70-million programme to support the development of novel brain stimulators. As part of the BRAIN Initiative, the project aims to foster brain implants to treat conditions such as post-traumatic stress disorder, anxiety and traumatic brain injury. The agency is looking for implantable devices that can monitor and manipulate neural activity not just at one or a few sites at a time, but across entire functional networks of neurons. Accomplishing this goal will require the development of new types of miniaturized sensor, as well as detailed network models of brain function to interpret data streaming in from multiple brain areas, says DARPA programme manager Justin Sanchez.



Some of those models may eventually grow out of data from researchers such as Kendall Lee, a neurosurgeon at the Mayo Clinic in Rochester, Minnesota. At last year's Society for Neuroscience meeting, he presented a prototype DBS system called Harmoni that can deliver current to one area of the brain while recording electrical and neurochemical responses elsewhere (see *Nature* http://doi.org/rvj; 2013). Because the brain uses both electrical and chemical signals to communicate, explains Kevin Bennet, the lead engineer on the project, monitoring each type of data could provide more complete information about what is going on. The group intends to test Harmoni first in patients with movement disorders. But, ultimately, the scientists hope to extend combined chemical and electrical monitoring to psychiatric disorders. "Those will be the most difficult to treat," says Bennet. "The symptoms are harder to detect and quantify."

Bronte-Stewart projects that testing might begin in about five years for the first implantable, closed-loop DBS devices for Parkinson's disease, with psychiatric applications following close behind. It is not clear whether Donobedian and other current research volunteers could be easily upgraded to those systems; much depends on the precise design of the devices. But even if he does not benefit directly from the data he is generating, Donobedian is glad to participate.

"Somebody had to give to me, to get this far," he says. "If there's a chance for me to give something back without too much effort, I'd like to help." ■ SEE EDITORIAL P.273

Helen Shen *is a freelance writer in Mountain View, California.*

1. Benabid, A. L., Pollak, P., Louveau, A., Henry, S. & de Rougemont, J. *Appl. Neurophysiol.* **50,** 344–346 (1987).
2. Weinberger, M. *et al. J. Neurophysiol.* **96,** 3248–3256 (2006).
3. Whitmer, D. *et al. Front. Hum. Neurosci.* **6,** 155 (2012).
4. Levy, R. *et al. Brain* **125,** 1196–1209 (2002).
5. Mayberg, H. S. *et al. Neuron* **45,** 651–660 (2005).
6. Osuch, E. A. *et al. Biol. Psychiatry* **48,** 1020–1023 (2000).
7. Little, S. *et al. Ann. Neurol.* **74,** 449–457 (2013).