participants, just like other people with Parkinson's, are assessed only a few times a year. With such sparse data collection, as DeMello discovered, it is difficult to quantify someone's symptoms and disease progression, let alone gain any detail about how a drug affects them under real-world conditions. What's more, assessments can be affected by the disposition of everyone involved on that particular day. "They're highly subjective," says Christian Gossens, who heads the early development informatics team at Roche. Technology is free of such whims. The app, Gossens notes, "takes away all influence of mood or stress" for both the patient and the physician, and eliminates differences between observing physicians.

The app is being informally assessed as part of a current trial, and the Roche researchers are already seeing benefits. "If you want to zoom into an individual patient, and zoom into disease progression a certain way, now you can," Gossens says. When you look at a group of patients, or general properties of a disease, he says, "things look like they're on a continuum. But the more you zoom in, the more they become discrete." Such granularity allows researchers to find and analyse more specific aspects of both drugs and disease.

If the app proves useful, Roche will consider including it in future trials in order to file for US Food and Drug Administration (FDA) approval. For now, the FDA remains curious, Gossens says. It wants to know what is technically possible, how it could be valuable, and how future trials of such an app could be regulated.

Bootstrapping existing technologies and using them in ways for which they were not intended can yield game-changing results. There are no biomarkers for Parkinson's that definitively identify the disease in its earliest stages. But Little says that he and his colleagues have preliminary evidence that the same smartphone tools can detect sleep issues, which are emerging as useful early warning signs for Parkinson's (see page S5).

And then there are applications in countries with less-developed health-care infrastructure. "More than 2 million Parkinson's patients haven't been diagnosed in China," Zhan says. "Some don't know they have it, and some can't access good health-care resources for diagnosis or treatment." Zhan imagines a day when a smartphone app could be used in countries such as China and India as an inexpensive, simple way to monitor people who have the disease — or even to help with diagnosis.

Smartphones have huge potential, Little says. "We're really only beginning to scratch the surface of what it's possible to do with this technology." ■

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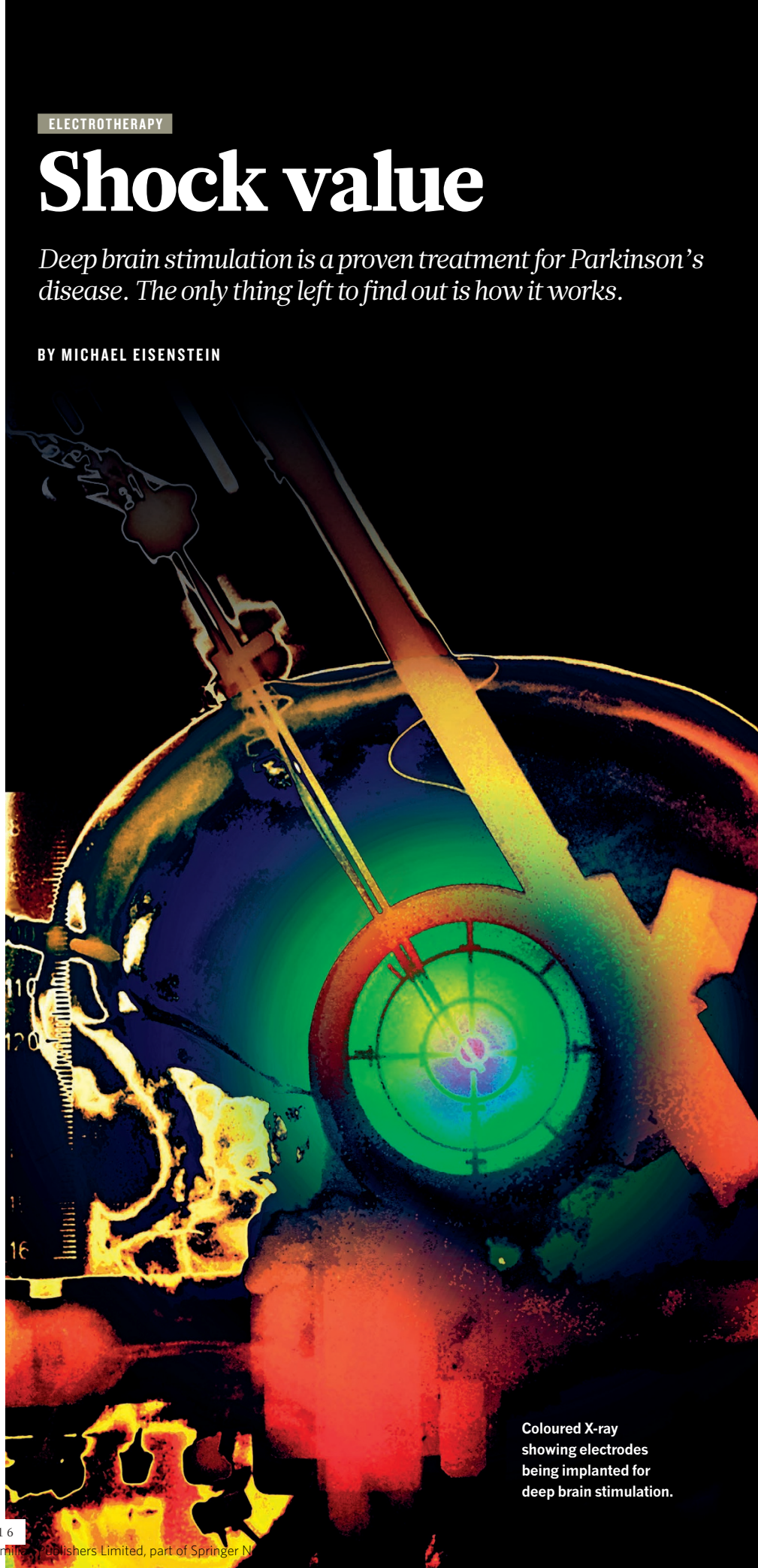
ELECTROTHERAPY

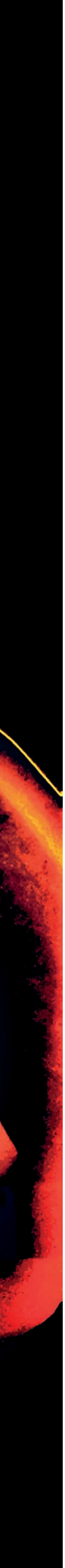
Shock value

Deep brain stimulation is a proven treatment for Parkinson's disease. The only thing left to find out is how it works.

BY MICHAEL EISENSTEIN



Coloured X-ray showing electrodes being implanted for deep brain stimulation.



SOVEREIGN, ISM/SPL

Before your doctor starts sticking electrodes into your brain, it would be reasonable to hope that he or she knows precisely what will happen and why. But when it comes to deep brain stimulation (DBS) for Parkinson's disease, the only thing the experts can agree on is that it works.

In DBS, millimetre-thin electrodes are implanted into the brain, aimed at a target smaller than a corn kernel, the location of which has been painstakingly mapped from imaging data. The electrodes deliver a mild stream of electrical jolts to the subthalamic nucleus that can control the debilitating motor symptoms that patients experience.

Over the past few decades, the medical community has embraced this treatment. "The procedure is very safe and effective," says Andres Lozano, a neurosurgeon at the University of Toronto in Canada. He estimates that around 10,000 people worldwide undergo DBS surgery for Parkinson's every year, with more than 140,000 people receiving implants so far. Yet little is known about how DBS restores normal function to the brain's motor circuitry.

Progress is being made, however, and any advance in the understanding of the disease could yield major dividends in patient-specific care. "We are just blasting the brain with continuous stimulation at the moment, and it's amazing that such a crude intervention helps so much," says Jill Ostrem, a neurologist at the University of California, San Francisco (UCSF). "Imagine what we could do if we could be more sophisticated and individualistic about this."

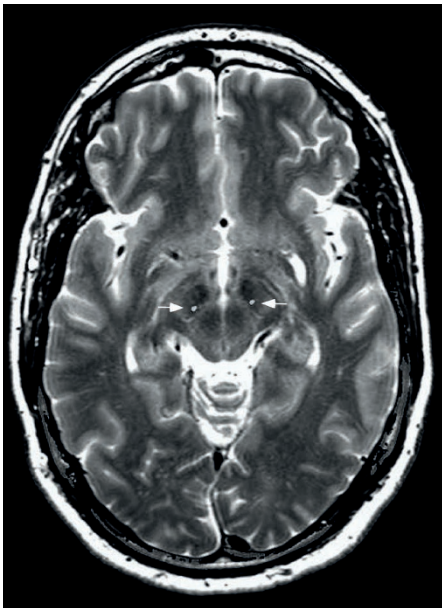
CIRCUIT BREAKER

Perhaps the biggest obstacle is the continuing uncertainty about how Parkinson's causes the brain's circuits to malfunction. Most research into the neurophysiology of the disease has focused on the brain's 'motor circuit', which consists of the basal ganglia, the thalamus and part of the cortex that governs movement. As Parkinson's progresses, neurons in the basal ganglia that produce the neurotransmitter dopamine die, derailing the function of the motor circuit. "Dopamine plays the major role in setting the rules for neural activity," says Lozano. "In the absence of that influence, the neurons start misbehaving and firing in a pattern that is pathological."

At first, researchers seeking an explanation for the neurons' misbehaviour favoured what was known as the 'rate model', which was developed in the 1980s. Neurologist Mahlon DeLong at Emory University in Atlanta, Georgia, proposed that parkinsonian symptoms arise from a higher rate of signalling in a region of the basal ganglia known as the subthalamic nucleus. DeLong thought that this increased neuronal firing was inhibiting other areas in the motor circuit, and reported that surgical disruption of the subthalamic nucleus relieved parkinsonian motor symptoms in monkeys[1].

In the 1990s, Alim-Louis Benabid and his colleagues, then at the University Hospital of Grenoble in France, used DeLong's findings as a foundation for the development of DBS for Parkinson's. Benabid's team demonstrated that high-frequency electrical stimulation, delivered by electrodes positioned near the subthalamic nucleus, eased motor symptoms such as rigidity[2].

Although the fundamentals of how DBS is given to people with Parkinson's have changed little since then, the rate model has largely fallen by the wayside. Instead, it seems that symptoms arise from a change in the normal firing patterns across the motor circuitry, rather than excessive firing at one point. The concept now is that the circuit is excessively synchronized, says Philip Starr, a neurosurgeon at UCSF. "Individual cells in the motor cortex and the basal ganglia that normally tend to fire independently now fire together," Starr explains. In particular, Parkinson's researchers have identified high levels



COURTESY OF LUDVIC ZRINZO

The electrodes are targeted to the tiny subthalamic nuclei (white arrows) for deep brain stimulation.

of β-band oscillation — brainwave activity occurring at around 15–30 hertz — within the basal ganglia. Such frequencies also occur in the healthy brain but become exaggerated in Parkinson's and seem to be associated with delayed or impaired conscious movement.

Normally, dopamine-producing neurons in the basal ganglia prevent such synchronized rhythms from becoming established; in this 'pattern model', the loss of these neurons removes this safeguard. But researchers are still unclear how the disruptive β activity arises. One possibility is that the activity spills over from other connected regions of the brain. Neurologist Helen Bronte-Stewart, at Stanford University in California, says that the β activity that occurs routinely in the motor cortex could be transmitted by the long axons that extend from neurons in this region to the basal ganglia. Also unclear is how the β rhythm interferes with voluntary movement. Starr's group is exploring a phenomenon known as phase–amplitude coupling, which might have an important role in the process. According to this model, the parkinsonian motor cortex is forced to march in lockstep with β rhythms that emanate from the basal ganglia, rather than fire independently to enable normal physical movement.

"We're taking this pathological behaviour and quashing it."

MAKE SOME NOISE

Against this backdrop, neuroscientists are at a loss as to why DBS works so well. When the rate model prevailed, researchers thought that DBS was directly inhibiting the excessive activity that DeLong, Benabid and their colleagues observed. But researchers have since shown that the electrical stimulation excites rather than inhibits neurons in the basal ganglia, sending neuroscientists back to the drawing board. "We had a situation where subthalamic stimulation was a mainstream therapy that had been done all over the world for ten years with great supporting evidence, but we didn't know how it worked anymore," says Starr.

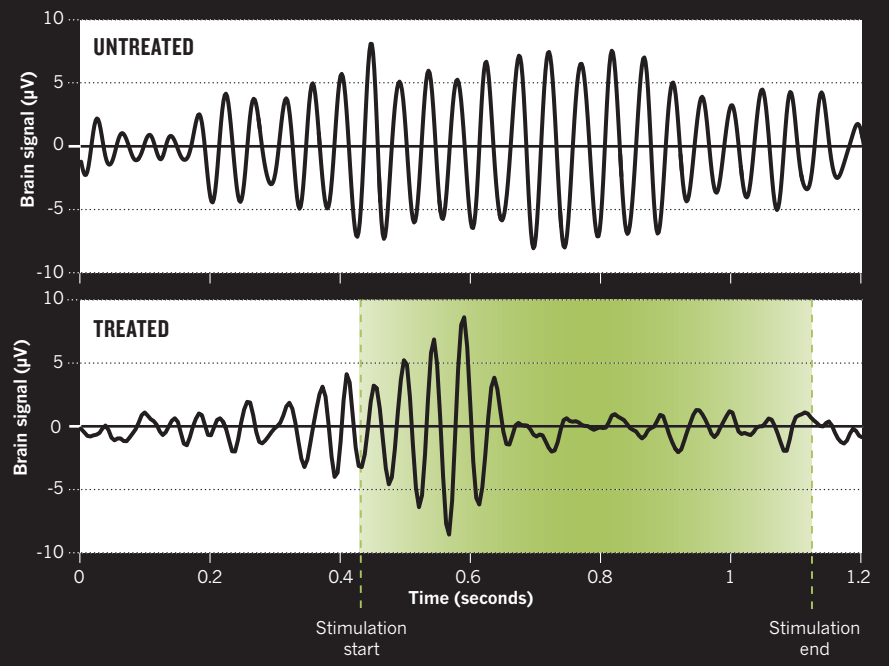
Most current pattern-model theories go back to the idea that DBS breaks up the unhealthy rhythms in the motor circuitry by introducing irregular patterns of neuronal activity in the basal ganglia. "We're taking this pathological behaviour and quashing it," says Lozano. "You seem to be better off with no output than with output that causes trouble." But researchers are still struggling to understand how this loss of synchronization occurs, and the model is not yet universally accepted.

Whatever the mechanism, the general belief is that the β-band-busting activity of DBS comes from stimulating the cells within the subthalamic nucleus of the basal ganglia. But neuroscientist Gordon Arbuthnott at the Okinawa Institute of Science and Technology in Japan and his colleagues have an alternative theory. They posit that stimulation excites the long axons that connect neurons in the motor cortex with those in the subthalamic nucleus, and that the effect is transmitted 'backwards' along these wires to the motor cortex, rather than 'forwards' into the basal ganglia. The hypothesis is that DBS disrupts unhealthy activity patterns in the motor cortex, and this region, in turn, stops the abnormal synchronization of β activity seen in the basal ganglia[3,4].

"It seems as though there is a link between motor cortical activity, the loss of β rhythm and recovery," Arbuthnott says. This would favour a model in which Parkinson's is driven by the motor cortex rather than by the basal ganglia. But research is still at an early stage — the supporting data have mostly come from animal

DEEP BRAIN THERMOSTAT

To correct the aberrant brain waves shown in the top panel, deep brain stimulation is typically applied constantly, like a radiator that is always left on to heat a room. But some researchers are developing a system that delivers stimulation only when aberrant brain waves are detected (bottom), and delivers only the dose (green) needed to correct the problem, like a thermostat that activates the heating only when needed to keep the temperature constant.



COURTESY OF PETER BROWN

models. Efforts to alleviate Parkinson's symptoms in humans with direct electrical stimulation of the motor cortex, rather than the basal ganglia, have proven disappointing.

A TREATMENT WITH POTENTIAL

Unsolved mysteries about the mechanism aside, DBS works — and researchers are now customizing its delivery to individuals through a combination of clinical experience and technological progress.

One of the hot questions concerns when during the course of the disease can DBS do the most good. Most people receive an implant after they have lived with medically managed Parkinson's for more than a decade, when disease progression has made their symptoms more difficult to control. A 2013 clinical trial called EARLYSTIM concluded that intervening a few years earlier might be beneficial[5]. The following year, a pilot study led by researchers at Vanderbilt University in Nashville, Tennessee, went further: they gave DBS to people who had been receiving medication for as little as six months[6]. Both studies provoked a backlash, partly because of the risks associated with neurosurgery, but also owing to fears that such patients might have been misdiagnosed and instead have a different, non-Parkinson's motor disorder.

But some clinicians believe it is possible to identify those who are most likely to benefit from early intervention. "These are usually patients with early-onset, tremor-dominant Parkinson's disease," says Bronte-Stewart. After DBS, she says, "many of them quit their meds and have a very good and stable response, and some of them are lucky enough to never develop cognitive impairment."

At the moment, DBS is an all-or-nothing proposition. It comprises a continuous dose of electrical stimulation at a fixed frequency that can be adjusted only by a specialist. More flexible approaches that are designed to fine-tune the timing, frequency and spatial distribution of the current could both boost the efficacy and reduce the downsides of DBS.

"After DBS, many people quit their meds and have a very good and stable response."

Peter Brown, a neurologist at the University of Oxford, UK, is investigating patterned stimulation. Changing the timing of the electrical pulses can radically alter the effect of DBS on dysfunctional motor-circuit rhythms, he contends: "You can impede them by timing the stimulation appropriately, or you can worsen them by timing it wrong."

Peter Tass and colleagues at the Jülich Research Centre in Germany are pursuing a version of this approach called coordinated reset, which delivers stimulation sequentially to distinct subpopulations of subthalamic neurons. This approach has shown early promise, and Brown is impressed. "You can treat for a few sessions and there can be this prolonged, sustained improvement for several weeks," he says.

There are side effects with DBS, such as impaired speech, involuntary movements and cognitive impairment, and these can become especially problematic when stimulation is delivered non-stop. Brown likens it to "heating a room in your house all the time, come summer or winter". His team is among several that are developing adaptive DBS, in which stimulation changes in response to physiological signals — essentially, installing a thermostat for the brain (see 'Deep brain thermostat'). The hard part is picking the right trigger. Brown's team is focusing on excessive β-band activity in the basal ganglia, and has shown that the adaptive approach delivers symptom relief that is equivalent to conventional DBS, while reducing the side effects[7]. Adaptive systems also consume less power — an important benefit given that standard batteries for current DBS last only 3–4 years and require a surgical procedure to replace.

Meanwhile, Starr's team has identified signatures in the activity of motor-cortex neurons that predict the onset of parkinsonian symptoms, and devised an algorithm that initiates stimulation when these patterns are detected[8]. And Bronte-Stewart's team has developed an adaptive DBS platform that uses Bluetooth-enabled smartwatches to detect the onset of tremor and then signal to the stimulator to respond accordingly[9].

These adaptive approaches could also help to unlock some mysteries of the parkinsonian brain. Ostrem, for example, has been working with a new DBS system from Medtronic called the Activa PC+S, which allows flexible monitoring of brain activity before, during and after the onset of symptoms. Ostrem notes that these kinds of technologies, combined with accumulating data from high-resolution brain imaging and modelling efforts, could allow treatment regimens that target specific neurological malfunctions. "Parkinson's patients have similar symptoms, but there are probably many reasons why they develop," she says. "It may be that DBS should not be applied in the exact same way to everyone."

Although it is important to uncover the mystery of how DBS works, improving the precision of treatment will at least remove some of the urgency from answering such questions. ■

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