NEUROSCIENCE:

Boosting Brain Activity From the Outside In

Laura Helmuth

Stimulating the brain with magnetic fields is not only a useful research tool but can apparently alter cognition and ease depression. But exactly how it works is a bit of a mystery

Recent claims about the powers of a brain stimulation technique might sound like testimonials for healing crystals. Fights depression! Speeds reaction times! Enhances reasoning abilities! But despite the link to magnets, which have long inspired goofball theories, so-called repetitive transcranial magnetic stimulation (rTMS) is being described not in the back of astrology magazines but in articles in journals such as *The Lancet*, *Neurology*, and *Science*.

A slew of recent clinical trials in the United States and abroad has indicated that rTMS can lift depression in some patients who are resistant to other types of therapy. Canada's Health Ministry is convinced; in March it approved the technique for treating people with major depression. The U.S. Food and Drug Administration is considering a similar move; for now, the treatment is only available in the United States in clinical trials. So far, no one is claiming that rTMS will help you lose weight fast, but a few studies have suggested that it can also ease symptoms of schizophrenia, obsessive-compulsive disorder, and Parkinson's disease, although these findings aren't as well established as those on depression. And one recent study even shows that well-aimed rTMS can speed one's ability to solve puzzles.

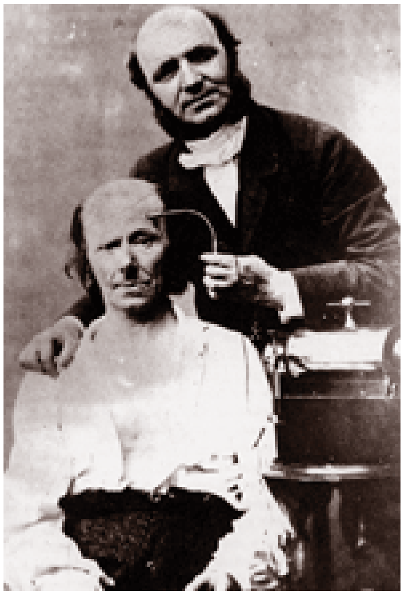
Since it was introduced in 1985, rTMS has been used mostly as a research tool to figure out what different parts of the brain are doing and how they interact. Researchers still don't completely understand how rTMS modifies brain activity, but its ability to do so is well established. "This is a great neuroscience tool for testing the relationship between brain and behavior," says neurologist and psychiatrist Mark George of the University of South Carolina, Charleston. George helped conduct the first study showing rTMS can relieve depression, and that has opened the door to using this therapy as a potential treatment for other psychiatric disorders. "We're just beginning to understand how to use it," says George.

Charging neural batteries

The rTMS technique is a fairly noninvasive way to stimulate brain tissue, George says. It works because neurons are in some sense electric creatures: They fire in response to changes in the concentration of charged particles inside and outside the cell. People have known for years that direct electrical stimulation can cause neurons to fire (see photo below). The trouble is that it hurts; direct electrical stimulation zaps pain-sensitive neurons in the scalp and thus tends to scare away research subjects.

In contrast, rTMS gooses neurons indirectly and painlessly. Repeated pulses of electric current are sent through a metal wire, which is usually round or figure-eight-shaped. This electric current generates a perpendicular magnetic field. (Remember the right-hand rule from physics class.) The magnetic field, in turn, generates another electric current in nearby material--in the case of rTMS, the current runs through brain tissue just below where the coil is placed on the scalp (see illustration).

If the induced electric current is strong enough, it can overwhelm neural communication in the tissue where it is focused and cause a "temporary lesion." Many single-burst (as opposed to repetitive) TMS studies marshal this power to test whether a specific brain region contributes to a given task; for instance, zapping the visual cortex has been shown to interfere with visual imaging (*Science*, 2 April 1999, p. 167).



Beta version. Direct electrical stimulation alters brain activity (and raises eyebrows, as in this 1861 demonstration by Guillaume Armand Duchenne), but rTMS is more comfortable.

CREDIT: COURTESY OF VINCENT WALSH

Under the right circumstances, however, repeated applications have a longer lasting effect than a single burst of stimulation. To get this effect, researchers first calibrate the intensity of the magnetic stimulation by placing the coil over a person's motor cortex. They move the coil around and adjust the intensity until they find what George calls "the sweet spot"--a region of motor cortex that, when stimulated, causes the thumb to twitch. The researchers then use the twitch-inducing intensity to deliver repeated pulses to other parts of the scalp. In general, low-frequency stimulation of about 1 to 5 pulses per second tends to depress brain activity afterward; higher frequency stimulation of about 25 pulses per second increases excitability. Both effects last about twice as long as the initial stimulation, that is, for a few minutes to about an hour.

Why different stimulation frequencies trigger different responses in nearby neurons is "absolutely unclear," says Eric Wassermann, chief of the brain stimulation unit at the National Institute of Neurological Disorders and Stroke (NINDS) in Bethesda, Maryland. But researchers and clinicians can take advantage of the lingering buzz.

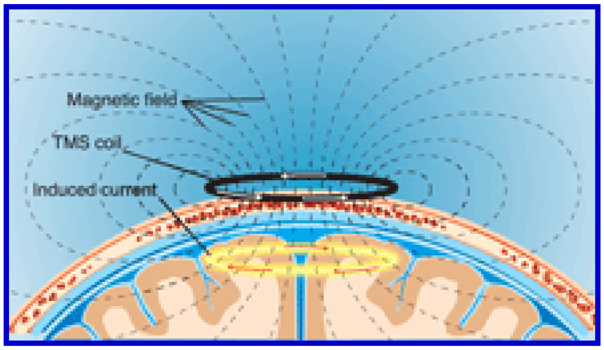
Detour for depression circuits

Although rTMS can spark an electric current in the brain, it's nowhere near as powerful as a better known treatment for depression: electroconvulsive therapy (ECT). Shock therapy fell out of favor because of its often severe side effects, but it can cure stubborn cases of depression. It works by causing a seizure. "After a seizure, all brain function is radically changed," Wassermann explains, and somehow that kicks the brain out of its depressive rut. In testing rTMS, says Wassermann, "our idea was to [change brain function] in a focal way, incrementally."

Wassermann and others have found that, compared to sham stimulation, tickling the left prefrontal cortex with rTMS relieves depression in some people who haven't responded to drugs or other treatments. The target, near the top of the forehead, isn't arbitrary; in functional imaging studies "the lateral prefrontal cortex comes up again and again as part of the mood circuit underlying depression," says psychiatrist Holly Lisanby of Columbia University in New York City, who has conducted rTMS studies on Parkinson's disease and other disorders. The left prefrontal cortex is less active in people with depression, and neuroimaging studies show that rTMS gives it a boost.

In a standard clinical trial, a depressed patient receives rTMS over the left prefrontal cortex for 20 to 30 minutes once a day for 2 to 4 weeks. Most studies to date have used this model, even though it's "based on something Mark George and I pulled out of a hat," says Wassermann. "It's implausible that we stumbled on the most effective combination" of stimulation frequency, intensity, timing, and location, cautions George. But as Wassermann points out, there's not a lot of funding directed at perfecting clinical rTMS techniques. Unlike drug companies, Wassermann says, "the equipment manufacturers' [pockets] are not deep." Most studies have been funded by private institutions or the National Institutes of Health.

In this and other applications, the stimulation is probably not easing depression simply by juicing up the neurons directly below the coil. As neurologist Alvaro Pascual-Leone of Harvard Medical School in Boston points out, rTMS is "not a light form of ECT but a way of modulating a circuit." In depression, the left prefrontal cortex is connected to a network of maladjusted brain areas. "I think a lot of the therapeutic effect we're seeing is not related to stimulation of the area we're targeting," speculates Pascual-Leone. "But through there, we're getting access to the limbic system," which decades of research have implicated in the regulation of emotions.



Indirect stimulation. With rTMS, researchers can induce a shadow current in the brain a few centimeters below the coil.

ILLUSTRATION: C. SLAYDEN

If rTMS can indeed jump-start--or calm-- entire neural circuits, many disorders might yield to targeted stimulation, Lisanby says. Researchers can determine through functional neuroimaging where a circuit rises to the surface of the brain and focus treatment there. In schizophrenia, for example, a study reported last year in *The Lancet* showed that low-frequency rTMS to the temporoparietal cortex (above the ear) reduced auditory hallucinations. Such studies are in their early stages, but "the field is aggressively pursuing" the strategy, Lisanby says.

Faster thinking with rTMS·

Neurological and psychiatric disorders aren't the only brain processes that affect wide-ranging neural circuits. Speaking, seeing, and problem solving, along with most mental tasks, activate some tissue deep in the brain and other bits at the surface. Once researchers showed that rTMS could alter mood, the logical next step was to see whether "we could do the same thing for any process stored in the brain," says cognitive neuroscientist Jordan Grafman of NINDS.

In the past few years, for instance, researchers have found that delivering rTMS to speech areas of the brain can take the words right out of someone's mouth; specifically, people name pictures faster after the treatment. And rTMS applied to motor areas facilitates lightning-fast movements. Grafman's group has turned its attention to more abstract brain processes, as they reported in *Neurology* this year. They asked people to solve analogy puzzles, in which they had to figure out the relationship among a group of colored geometric shapes and then pick out the analogous pattern in other sets of shapes. Positron emission tomography (PET) studies show that the prefrontal cortex, among other areas, lights up when people perform such a task. Sham stimulation or rTMS to other areas of the brain shortly before presenting the puzzles didn't help people solve them, but rTMS to the prefrontal cortex speeded subjects' insights. So far, no studies have answered just how rTMS might facilitate thinking, Grafman says. He suggests that rTMS might raise the baseline level of neural activity in a region just enough so that neurons don't have to work as hard to retrieve a memory or a problem-solving strategy.

Modern version. Eric Wassermann demonstrates rTMS technique on Jordan Grafman.

CREDIT: ERIC WASSERMANN

One of the barriers to figuring out how neurons respond to rTMS is the lack of animal models, says George. Whereas researchers can easily dilute a drug to rat strength, they can't yet make an effective miniature rTMS coil. At smaller sizes, the coil can't create a magnetic field strong enough to induce a current in the rat or monkey brain that's as strong as the current induced by a full-size coil. "It's a real materials science problem," says George.

In addition to neurobiology, Wassermann notes, plenty of other effects of rTMS aren't well understood. The procedure appears to be safe at the mild intensities used in the lab, and rTMS passed all its safety studies shortly after it was introduced. But if the technique is powerful enough to ease depression and have other possibly long- lasting clinical effects, researchers should be more diligent about including safety studies whenever they use it, Wassermann cautions: "Anything that works well can cause significant side effects."

But if researchers can live with a certain amount of neurobiological ambiguity and are willing to test the safety of the technique as they go, rTMS is a fairly affordable and therefore democratic tool--especially for neuroscience hardware. A complete setup runs $30,000 to $40,000, compared to $1.5 million and up for functional magnetic resonance imaging. It's still a young field with plenty of unanswered questions and wide-open neural territory to explore. But if the words "brain stimulation" and "inexpensive" bring improper thoughts to mind, be warned: Those neurons that buzz when someone takes euphoria-inducing drugs or eats ice cream are buried deep in the brain, beyond the reach of rTMS. "We've tried," jokes George, "but there's no way to get a pleasure-center stimulation with the current technology."