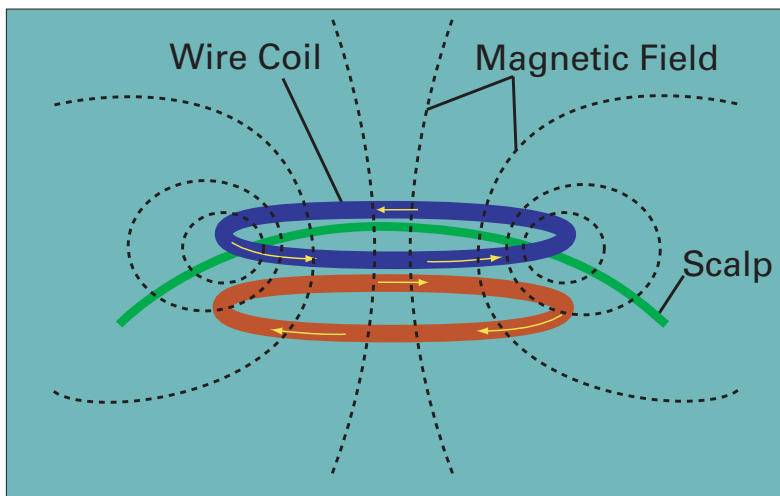


Snap, Crackle, and Feel Good?

Magnetic fields that map the brain may also treat its disorders

By JOHN TRAVIS



Utopia

In TMS, an electric current in a coil above the head generates a magnetic field that penetrates the skull. This field, in turn, stimulates an electric current (orange) within a small brain region.

its own accord.

Welcome to transcranial magnetic stimulation (TMS), one of the hottest research tools in neuroscience. Since its invention 15 years ago, TMS has become a relatively simple, noninvasive, and usually painless way to electrically stimulate specific brain regions. It's power tantalizes investigators who want to unravel how the human mind works. More recently, TMS has also grabbed the attention of physicians and psychologists, who predict that it has the potential to treat conditions ranging from epilepsy to stuttering to depression.

There's preliminary evidence, for example, that TMS offers a less drastic alternative to electroconvulsive therapy (ECT), the treatment of last resort for people with severe depression. At the same time, investigators acknowledge that there's much they don't know about how TMS affects the brain.

"These are all pioneering studies," says David Avery of the University of Washington School of Medicine in Seattle, who studies TMS' use for depression. "As pioneers were crossing the prairie, some took one valley and others took another route. At this point, we don't know which is the easiest route, or the best route."

The first attempts to alter brain activity with magnetism occurred around a century ago when it wasn't yet possible to produce very strong magnetic fields. Researchers could magnetically stimulate nerve cells in retinas, causing test subjects to perceive flashes of light, but they couldn't fire up brain cells.

Until 1985, that is. That's when Anthony T. Baker of the University of Sheffield and his colleagues reported the first success at triggering brain cells with TMS. The principle behind TMS

A sharp sound, like a snapping rubber band, rings out. "Anything?" queries the neuroscientist standing behind my seat.

I shake my head, which the researcher, Eric Wassermann, takes as "No." In response, he tweaks a knob on a nearby machine, which connects via a black cord to a paddle-like object that he holds to the back of my head.

Snap!

Hmm, did my right arm twitch a bit that time?

Another small twist of the knob.

Snap!

No doubt about it this time. My right arm jerks.

Snap!

I don't feel any pain or notice anything unusual other than the sound, but my arm jumps again, seemingly of

is relatively simple. If an electrical current suddenly courses through a wire coil, it momentarily generates a magnetic field. Unlike a direct electrical current, a magnetic field penetrates a skull easily and painlessly, as if it were a ghost passing through a wall. Within the brain, this field induces an electrical current perpendicular to itself and parallel to the coil. It's this current that stimulates brain-cell activity.

The original coils used by Baker were doughnut-shaped and could only deliver a single stimulation per experiment. Many investigators now work with a figure-eight coil because the magnetic field generated by its two circles focuses on smaller regions of the brain than the simpler coil does. TMS devices today create magnetic fields with strengths up to 2 Tesla, about 40,000 times the Earth's natural magnetic field.

By the 1990s, technology had advanced to the point where repetitive TMS, or rTMS, also became available to most researchers. In rTMS, scientists deliver repeated magnetic pulses at frequencies up to 50 times a second (50 hertz). As a result, the targeted brain region receives a barrage of brief electric stimulations.

The early uses of TMS were the neurological equivalent of testing a person's reflexes with a hammer. By sending single magnetic pulses into the motor cortex, which is just under the scalp and easy for a magnetic field to reach, scientists found they could map how this brain region controls the body's muscles. Pulses directed to different spots on the motor cortex would make a thumb twitch, an arm jerk, or a leg kick. Physicians now employ this capability of TMS to check that the nerves conveying such orders from the brain are operating properly. In illnesses such as multiple sclerosis, that's not always the case.

TMS began to show its true potential, however, when scientists probed beyond the motor cortex. After magnetic stimulation of a brain region, that area temporarily becomes unresponsive to the normal input from the rest of the brain.

"What TMS allows you to do is transiently inactivate an area and evaluate the behavioral consequences," says Leonardo G. Cohen of the National Institute of Neurological Diseases and Stroke (NINDS) in Bethesda, Md. "Nothing else can do that in humans."

Those consequences depend on where scientists direct the magnetic pulse. For example, we can use TMS to prevent people from seeing a visual stimulus or make it hard for them to speak, says Wassermann, who, like Cohen, conducts TMS studies at NINDS.

Scientists who study how the human brain works have long desired this kind of control. Using technologies such as magnetic resonance imaging (MRI) and positron emission tomography (PET), they've been able to watch the human brain in action, recording which regions act up or quiet down during various cognitive tests. Yet these scans can't prove a specific brain region is integral to such tasks as counting, reading, or seeing. An activated brain region may simply reflect a nervous volunteer tensing his muscles whenever he does a task in the laboratory.

Instead of merely watching the brain in action, TMS can intervene, enabling investigators to more easily test hypotheses about the human brain. For example, Cohen and his colleagues have found that TMS applied to a brain region called the primary visual cortex impairs the ability of blind people to read Braille. That result supports a hypothesis, derived from MRI and PET studies, that blind people recruit parts of the brain normally used for vision to boost their sense of touch.

A TMS study by Stephen Kosslyn of Harvard University and his colleagues confirmed the claim that a brain area known to process visual signals plays a similar role when a person imagines a mental picture. Future TMS research, says Wassermann, will look into the involvement of specific brain regions in many cognitive activities, including mathematical reasoning, visual attention, and memory.

Even as they use TMS to probe brains, investigators have begun to examine whether it can also help brains. They've found that beyond the temporary disruption, rTMS treatments may bring about lasting changes in brain activity. This influence can last days, weeks, even months after the treatments stop. The type of change varies with the specifics of the stimulations. One rule of thumb among many researchers is that slow rTMS (1 Hz or lower) makes brain regions less easily excited, while fast rTMS has the opposite effect.

Cohen and other researchers speculate that rTMS trained on specific brain areas can encourage recovery from strokes, spinal cord injuries, and even amputations, that cause so-called phantom limb pain. Such therapies would depend upon the brain's plasticity, its ability to adapt to trauma or experiences.

Many neuroscientists used to imagine the brain as a microchip with fixed wiring, but they've learned that the brain is far more flexible. With rigorous training, for example, a person who's had a stroke and lost use of a limb can regain control by enlisting undamaged parts of the brain.

Cohen has turned to TMS in several ways to probe such plasticity. The ultimate goal of such work, he says, is to enhance any brain plasticity that aids recovery from stroke or other trauma.

The finding that rTMS can have lasting effects on the human brain has turned the technology into a potential therapeutic tool for several serious disorders. Take epilepsy, an illness in which the brain's nerve cells begin firing wildly, leading to seizures.

In the June 26, 1999 LANCET, a group at the University of Göttingen in Germany reported promising results from the use of rTMS on nine people with epilepsy who were unresponsive to drugs. All but one described a reduction in number and severity of seizures after receiving five daily treatments of rTMS at a slow rate, one stimulation every 3 seconds.

William H. Theodore, who heads the epilepsy research branch at the National Institutes of Health in Bethesda, cautions that the German trial was an "open study," meaning it involved no comparison group that didn't receive treatment. He points out that a placebo effect could just as well explain the success.

Nevertheless, the data were provocative enough that NIH has begun its own study of rTMS for epilepsy. To create a control group, says Theodore, NIH scientists will angle the TMS coil so that some subjects don't receive brain stimulation. He expects the study to take a year to complete.

Researchers also propose that TMS may help treat schizophrenia, a brain disorder for which few effective drugs exist. In the March 25 LANCET, investigators at the Yale University School of Medicine, report that rTMS significantly reduced auditory hallucinations experienced by a dozen people with schizophrenia.

The hallucinations, usually perceived as voices in the head, afflict 50 to 70 percent of such people and are often difficult to eliminate with antipsychotic drugs. "These voices can be very disruptive and produce some really bad consequences," notes study leader Ralph E. Hoffman.

Brain scans of people with schizophrenia suffering auditory hallucinations have revealed abnormal activity in a speech-related brain region—the left temporalparietal cortex. Scientists suspect, says Hoffman, that "these auditory hallucinations arise from parts of the brain that are ordinarily involved with processing spoken speech."

To test that theory, Hoffman and his colleagues directed magnetic pulses at the left temporalparietal cortex of schizophrenia patients for 4 to 16 minutes daily for 4 days.

In most cases, the severity and frequency of auditory hallucinations decreased more with the real TMS treatment than with sham applications. In one person, the improvement lasted 2 months.

"Some patients don't respond at all, but the majority do," says Hoffman. One woman has "been free of hallucinations for the first time in many, many years. It's a miracle for her," he says.

"It's a very interesting study. I think they may be onto something," says Wassermann. He

praises the work for pursuing a clear hypothesis. Some investigators, he says, just blast rTMS at various brain regions and hope for an effect.

Peter Fox of the University of Texas Health Science Center at San Antonio has concerns of his own about rTMS use. He worries that some investigators are prematurely applying it to disorders without understanding why the brain goes awry in the conditions or how the treatments alter neural circuitry.

Moreover, he charges that many investigators simply hold the TMS coil above a person's scalp, a crude technique that doesn't allow precise targeting. "How do they really know what they're stimulating?" he asks. "I consider that about the same as having a neurosurgeon operate on your brain blindfolded."

Fox further contends that the field's rule of thumb—that rTMS at 1 Hz suppresses brain regions, while higher frequency treatments excite them—rests on weak evidence primarily stemming from work on the motor cortex. So, researchers can't be certain whether they're exciting or suppressing a brain region when they treat a patient.

"We really want to go about this in a more rational way," says Fox.

Fox studies stuttering with Roger Ingham and Janet Ingham, both of the University of California, Santa Barbara. Stuttering offers fertile ground for scientists because they can image brain activity both while a person stutters and while he or she speaks normally. People who stutter can often overcome the problem by singing, extending vowels, or speaking in unison with others.

The investigators already have identified a set of brain areas that are abnormally active during stuttering. They're now combining TMS and PET scans to determine how areas involved in speech production connect to each other and to the rest of the brain.

"One of the most powerful ways to map connectivity is TMS," says Fox. "Once you trigger an area—fire its neurons—that activity will propagate in quite a normal way. We've been stimulating areas in stutterers to see if their connectivity patterns are different."

Using 1 to 3 Hz rTMS and a robotic apparatus to precisely position the stimulus, the investigators have established that they can alter activation and connectivity patterns in the brain for up to several days. They haven't yet tried to stop a person's stuttering because they don't yet know all the brain circuitry involved. Any attempt at treatment now could just as easily increase a person's stuttering, says Fox.

The clinical condition that has brought TMS the most attention is depression. In some of the earliest studies, investigators noticed that applying the magnetic fields to the brain's temporal lobes, which are regions just above the eyebrows, induced temporary mood changes in healthy volunteers. Zap above the right eyebrow and elation results. Targeting the left temporal lobe instead leads to sadness and apathy. These feelings last only a few hours, but that was enough to intrigue researchers.

There was another major reason to think that TMS might have a chance at treating depression. Both TMS and ECT induce electrical activity in the brain. Despite its horrifying reputation—think Jack Nicholson in *One Flew Over the Cuckoo's Nest*—ECT has proven its capability to help severely depressed people time and time again. "ECT unquestionably works. It's the gold standard for treating depression," says Wassermann.

The problem with ECT is that it must shoot a strong current through the skull into the brain. This can cause painful seizures, which is why people having ECT undergo general anesthesia. Since the massive burst of electricity hits the hippocampus, a seat of memory formation and recall, ECT also frequently produces partial amnesia. People receiving ECT may not recall the months leading up to a treatment.

“Despite its often-remarkable efficacy, ECT remains a crude technique, analogous to sculpting rock with explosive charges,” Gary M. Hasey of the Hamilton Psychiatric Hospital in Ontario, Canada, noted in the March 1999 *JOURNAL OF PSYCHIATRY AND NEUROSCIENCE*.

The hope is that TMS can be a kinder, gentler version of ECT. So far, the data have nourished that hope. Several small studies have now compared TMS with sham treatments and even ECT.

“In small, controlled studies of people who fail to respond to antidepressant medication, transcranial magnetic stimulation continues to show effectiveness,” says Avery, who has created a database to consolidate TMS depression studies. He suggests that TMS could become an intermediate stage of treatment between antidepressants and ECT. He also notes that some investigators are also testing whether TMS combined with drugs works better than antidepressants alone.

Investigators have begun to tease out why some people may not benefit from TMS. “We found that the longer the duration of the current episode of depression, the worse the response. Those whose current episode had lasted 5 years or longer didn’t respond well,” says Avery.

Several studies hint that TMS may rival ECT in effectiveness, at least for depressed people with no other psychological problems. In one trial, Leon Grunhaus of the Sheba Medical Center in Ramat Gan, Israel, and his colleagues compared ECT with 10-Hz rTMS treatments in 40 people with severe depression. The investigators randomly assigned each patient to one of the two therapies.

“Our results indicate that rTMS is as effective as ECT in the treatment of patients with major depressive disorder without psychosis,” the research team concluded in the Feb. 15 *BIOLOGICAL PSYCHIATRY*.

In an even more radical effort, a few researchers have begun to use TMS as a form of ECT. In other words, they use the magnetic stimulation to deliberately induce seizures in people with severe depression. These scientists argue that the seizures produced by ECT may be integral to its success and that TMS can generate seizures in targeted regions of the brain without affecting others areas, such as those involved in memory.

On May 1, a woman in Switzerland became the first person to receive such “magnetic seizure therapy.” A team led by Thomas Schlaepfer of the University of Bern in Switzerland and Sarah Lisanby and Harold Sackeim, both of Columbia University, was able to trigger seizures in the anesthetized woman in four separate trials. The group used 40 Hz rTMS and administered stronger magnetic pulses than those of standard rTMS treatments.

The woman scored lower on depression assessments after the seizures and reported that she recovered more quickly from TMS than traditional ECT. Still, it’s too early to gauge TMS’ effectiveness as a seizure therapy, warns Schlaepfer.

“The field has not been helped by overenthusiastic interpretations of studies,” says Schlaepfer. “My general reading of the field is that up to now there’s no convincing proof of antidepressant effects, but there are certainly hints. What we really need are large, multicenter trials.” □