

STIMULATING THE BRAIN

ACTIVATING THE BRAIN'S CIRCUITRY WITH PULSED MAGNETIC FIELDS MAY HELP EASE DEPRESSION, ENHANCE COGNITION, EVEN FIGHT FATIGUE

BY MARK S. GEORGE

BLEARY-EYED, THE PILOT STARES AT THE INSTRUMENTS while sipping stale coffee. The cup is nearly empty, as is the radar screen. So, he realizes, are the airplane's fuel tanks, not to mention his own energy reserves. Another cup certainly won't help much. His co-pilot dozes beside him, having already flown several legs of their long mission to deliver sorely needed humanitarian aid to the other side of the world. The pilot considers, then rejects popping a pep pill. Uppers make him jumpy, a bad feeling to have during the tricky nighttime aerial-refueling maneuver he will soon have to execute. Suddenly the radar shows a blip orbiting up ahead. Scanning the cloudy sky for the tanker's navigation lights, the pilot knows he has to get focused fast. He flips a switch. A "rat-a-tat-tat" sound, like that of a staple gun, echoes through his helmet, and fatigue abruptly flees his mind. Clear-headed for the first time in what seems days, the pilot almost immediately spies lights flashing in the murky distance. He nudges the co-pilot, who absently toggles his own switch as he stifles a yawn. Muffled snapping noises follow. Fully awake, the aviators steer for the flying gas station circling overhead.

In the scenario above, sharp sounds emerge when electromagnets inside the helmets generate

magnetic fields to excite particular parts of the pilots' brains—areas that govern tiredness and wakefulness. Neuroscientists developing this novel noninvasive technique call it transcranial magnetic stimulation (TMS). TMS employs head-mounted wire coils that send strong but very short magnetic pulses directly into specific brain regions, thus safely and painlessly inducing tiny electric currents in a person's neural circuitry.

This scenario is still speculative, but research to make this promising technology a reality is advancing steadily. The Defense Advanced Research Projects Agency (DARPA) is funding several studies to investigate the use of TMS to improve the performance of U.S. service personnel exhausted by protracted field operations. And DARPA is not alone in its interest in TMS, because the procedure offers one of the most promising technological (nonpharmaceutical) methods to literally turn particular parts of the human brain on and off.

Some TMS researchers, for example, are inducing temporary brain "lesions" in healthy subjects to gain insight into fundamental neuronal mechanisms such as speech and spatial perception: they inhibit a basic brain function with a magnetic pulse stream and then compare the "before"

Wire coil containing time-varying electric currents generates brief magnetic pulses that cause brain cells to fire. Transcranial magnetic stimulation is being evaluated at Columbia University's College of Physicians and Surgeons.

condition with the “after.” Other investigators are trying to determine whether the hyperactive brain regions that create epileptic seizures might be quieted with magnetic fields. Still other neuroscientists are attempting to employ TMS to alter the operation of specialized nerve cell networks to enhance people’s memory and learning. Many of my colleagues are looking for ways to use the technology as an alternative to seizure-causing electroconvulsive therapy (ECT) to ease depression. Whatever the goals, TMS holds great potential as a tool for understanding how the brain works, correcting its dysfunctions and even augmenting its abilities.

The Electric Brain

TMS TAKES ADVANTAGE of the fact that the brain is fundamentally an electrical organ that transmits electrical signals from one nerve cell to the next. When a TMS coil is activated near the scalp, an ex-

TMS offers a PROMISING METHOD
to turn particular parts of the
BRAIN ON AND OFF without drugs.

remely powerful and rapidly changing magnetic field travels unimpeded through skin and bone. Although the field reaches a strength of nearly 1.5 tesla—tens of thousands of times that of the earth’s magnetic field—each pulse lasts for less than a millisecond. The popping sound it generates when it is operating arises from the passing of current through the insulated coil [see illustration on opposite page].

OVERVIEW/*Electromagnetic Excitation*

- Neuroscientists utilize a variety of electromagnetic stimuli to directly activate neurons in the brain. Electroconvulsive therapy (ECT), a procedure in which electrodes are attached to the scalp, is the best known of these techniques. Its use, however, remains somewhat problematic for various reasons.
- For a decade, researchers have been experimenting with pulsed magnetic fields that induce electrical activity in specific areas of the brain safely and painlessly. The ability of transcranial magnetic stimulation (TMS) to target specific brain regions is key to many new applications.
- TMS offers potential treatments for depression and other neurophysiological disorders. The technology may also provide a nonpharmaceutical method to rouse people from the effects of severe fatigue or to teach them a new skill.

In the brain, the magnetic field encounters resting nerve cells and induces small electric currents to flow in them. Thus, electrical energy in the copper-wire coil (typically encased in a paddlelike wand) is converted into magnetic energy, which is then changed back into electric current in the neurons of the brain. The \$30,000 to \$40,000 TMS machines are manufactured by the Magstim Company Limited in Whitland, Wales, by Dantec/Medtronic in Denmark and in Shoreview, Minn., and by Neuro-netics in Malvern, Pa.

Unlike purely electrical techniques—such as ECT and others [see box on page 73], which involve attaching electrodes to the scalp or even to brain or nerve tissue—TMS creates a magnetic field that enters the brain without any interference or direct contact. The technique can be thought of as electrodeless electrical stimulation. Although magnetism does interact with biological tissue to some degree, the majority of TMS effects most likely derive not from the magnetic fields directly but from the electric currents they produce in neurons.

Magnetic Excitation

THE IDEA OF USING electromagnetic fields to alter neural function goes back to at least the early 1900s. Psychiatrists Adrian Pollacsek and Berthold Beer, who worked down the street from Sigmund Freud in Vienna, filed a patent to treat depression and neuroses with an electromagnetic device that looked surprisingly like a modern TMS apparatus.

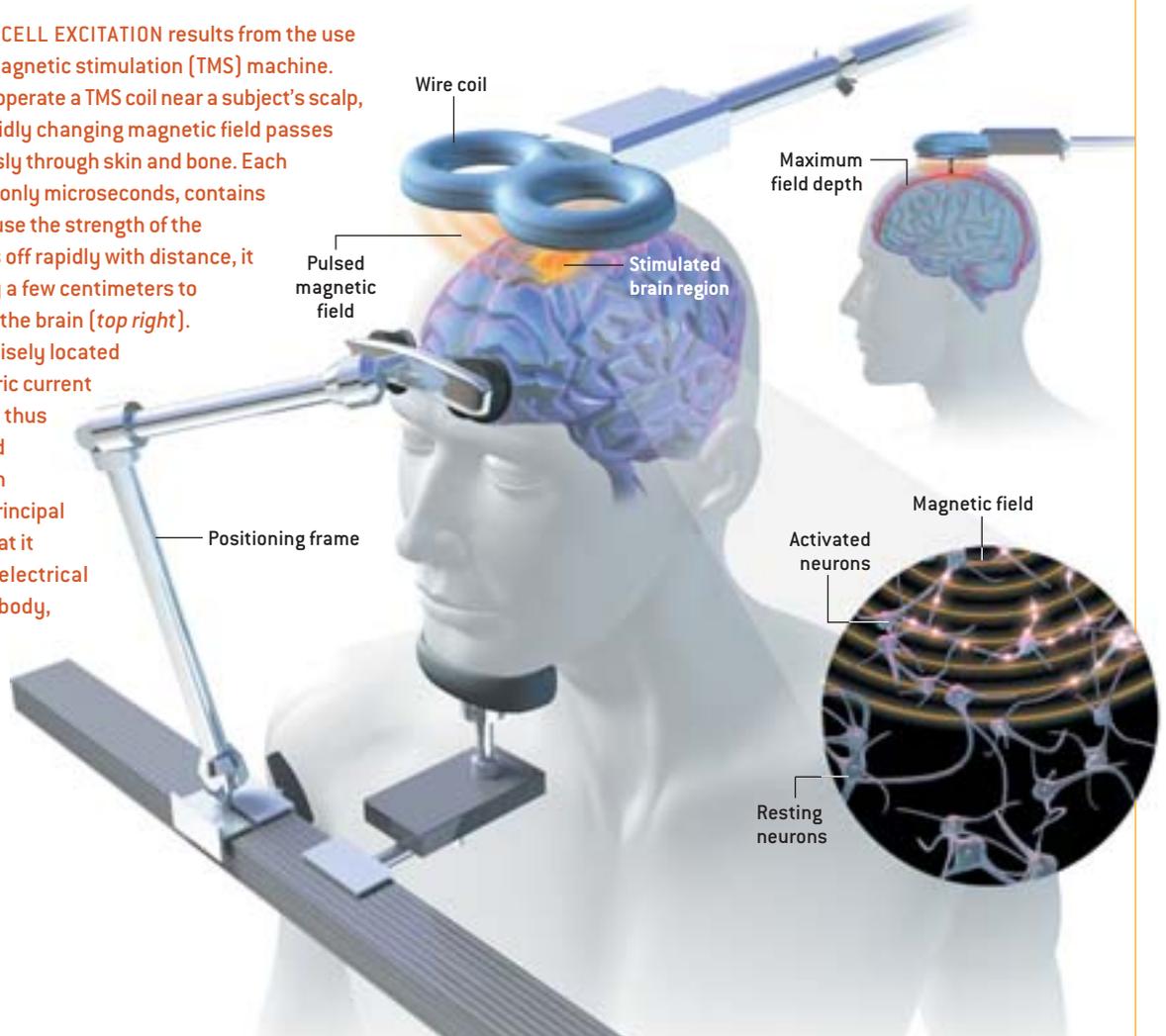
Today’s TMS technology took shape in 1985, when medical physicist Anthony T. Barker and his colleagues at the University of Sheffield in England created a focused electromagnetic device with enough power to create currents in the spinal cord. They quickly realized that their equipment could also directly and noninvasively stimulate the brain itself. Since then, the field of TMS research has exploded.

Unfortunately, TMS devices can excite only the surface cortex of the brain because magnetic field strength falls off sharply with distance from the coil (maximum range: two to three centimeters). A magnetic field that can safely penetrate and activate the brain’s central structures continues to be the Holy Grail of TMS research because it offers the possibility of treating difficult conditions such as Parkinson’s disease [see box on page 72].

When researchers send a single magnetic pulse into the motor cortex of a subject’s brain, it produces a jerk in the hand, arm, face or leg, depending on where the coil is placed. One pulse directed to the back of the brain can generate a flash of light in the eyes. That is the extent of the immediate effects of single-pulse TMS, however. Magnetic field pulses

TRANSCRANIAL MAGNETIC STIMULATION

LOCALIZED BRAIN-CELL EXCITATION results from the use of a transcranial magnetic stimulation (TMS) machine. When researchers operate a TMS coil near a subject's scalp, a powerful and rapidly changing magnetic field passes safely and painlessly through skin and bone. Each brief pulse, lasting only microseconds, contains little energy. Because the strength of the magnetic field falls off rapidly with distance, it can penetrate only a few centimeters to the outer cortex of the brain (*top right*). On arrival, the precisely located field induces electric current in nearby neurons, thus activating targeted regions of the brain (*bottom right*). A principal benefit of TMS is that it requires no direct electrical connection to the body, as is required for electroconvulsive therapy.



emitted in rhythmic succession, which neuroscientists call repetitive TMS, or rTMS, though, can induce behaviors not seen with the use of single pulses. These results are now the subject of intense study.

For brief periods during stimulation, rTMS can block or inhibit a brain function. Repetitive TMS application over the speech-control motor area, for instance, can leave the subject temporarily unable to speak. Cognitive neuroscientists have employed this so-called functional knockout capability to re-explore and confirm our knowledge about which part of the brain controls which part of the body, insights that have been gleaned from decades of studying stroke patients.

Field Learning

WHEN SINGLE NERVE CELLS are made to discharge repeatedly, they can form themselves into functioning circuits. Researchers have found that stimulating a neuron with a low-frequency electrical signal can produce what they call long-term de-

pression (LTD), which diminishes the efficiency of the intercellular links. High-frequency excitation over time can generate the opposite effect, which is known as long-term potentiation (LTP). Scientists believe that these cell-level behaviors are involved in learning, memory and dynamic brain changes associated with neural networks. The chance that one could use magnetic brain stimulation to alter brain circuitry in a manner analogous to LTD or LTP fascinates many researchers. Although this controversial notion remains unresolved, several studies have

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shown nerve cell network inhibition or excitation lasting for up to a few hours after rTMS application. The implications of these results could be enormous. If one could employ rTMS techniques to change learning and memory by resculpting brain circuits, the possibilities are nearly endless. TMS might be used on a stroke patient to teach the remaining, intact parts of the brain to pick up the functions formerly conducted by the damaged region. Or overactive brain circuits that drive epilepsy might be toned down, resulting in fewer seizures.

Recent experiments in our laboratory at the Medical University of South Carolina (MUSC) and elsewhere hint that rTMS might temporarily enhance cognitive performance, either during application or for short periods afterward. Investigators at the National Institute of Neurological Disorders and Stroke, for example, found that TMS applied to the prefrontal cortex can enable subjects to solve geometric puzzles more rapidly.

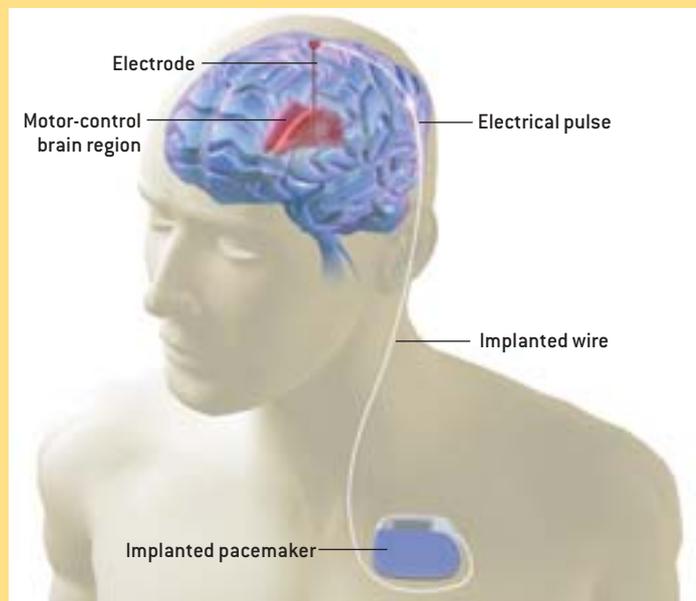
Most researchers working in this area stimulate subjects' brains over the prefrontal cortex or pari-

ZAPPING THE BRAIN

WHEREAS TRANSCRANIAL MAGNETIC STIMULATION of the human brain came into modern use in the 1980s, electrical excitation has been around for at least a century. David Ferrier and others in the 1880s showed that direct electrical brain stimulation could change behavior and that activation of specific regions correlated with certain behavioral changes. For the past 100 years, neurosurgeons have stimulated the brain electrically during brain surgery, cataloguing the resulting effects along the way.

Physicians have long known that electrical stimulation could be therapeutic as well. During electroconvulsive therapy (ECT), a doctor applies electrodes directly to the scalp of an anesthetized subject with the goal of inducing a generalized seizure. For reasons that are still unclear, repeated ECT sessions over the course of several weeks is an effective treatment for depression, mania and catatonia. The technique is, however, associated with memory loss and requires repeated general anesthesia. Because the skull acts as a large resistor that spreads direct electric current, ECT cannot be focused on or directed to specific targets within the brain.

Persistent shaking (*dyskinesia*) caused by Parkinson's disease can be lessened by electrical deep brain stimulation, imparted by implanted electrodes.



Of late, neuroscientists have explored other methods to electrically stimulate the brain. These new techniques tend to be either more focused or less invasive, or both, than the older ones. Employed in conjunction with the advanced brain-imaging technologies developed over the past two decades, these approaches are being used to build on our recently assembled understanding of how the brain works (see table on page 73).

Two direct electrical brain-stimulation techniques have been approved for therapeutic use. In deep brain stimulation (DBS), a neurosurgeon guides a small electrode into the brain through a small hole in the skull with the help of three-dimensional images (left). The surgeon then connects the electrode to a pacemaker (signal generator) implanted in the chest. The pacemaker sends high-frequency electrical pulses directly into the brain tissue. DBS is approved by the U.S. Food and Drug Administration for the treatment of Parkinson's disease, typically in patients who no longer respond to medication.

Within the motor-control circuitry of the brain, several regions (including the internal globus pallidus, thalamus and subthalamic nucleus) are inhibitory in function and so act as brakes on movement. In current practice, neurosurgeons place DBS electrodes in those regions and then stimulate them at high frequencies to arrest the shaking (*dyskinesia*) that characterizes Parkinson's. The technique is being explored as a treatment for depression as well. Little information exists concerning what happens when DBS is applied to other brain regions or when low-frequency pulses are used.

Theoretically, DBS electrodes can be removed with no lasting damage. Thus, the procedure represents an advance over traditional ablative brain surgery in which neural tissue is lost forever. In rare cases, DBS can, however, lead to infections, strokes and even death, so it is largely restricted to patients who have failed to respond to other therapies.

Another electrical brain-excitation technique now in use is vagus nerve stimulation (VNS). The vagus nerve is an important cranial nerve that connects the brain with the body's viscera. Eighty years of research has shown that stimulation of the vagus nerve in the chest or neck can alter the operation of brain regions involved in the control of bodily functions. In the 1980s Jake Zabara of Temple University discovered that excitation of the

etal cortex while they perform a task. To control for testing bias, neuroscientists also use deactivated (“sham”) rTMS coils. Our lab is funded by DARPA to study whether rTMS might temporarily energize sleep-deprived individuals so they can perform better over the short term. Early results are promising. Another DARPA-supported group at Columbia University, led by Yaakov Stern and Sarah H. Lisanby, is exploring whether rTMS might be used to retrain subjects to accomplish a task in a different manner by shifting neural activity to an alternative

cellular network that might be more resilient to stress or sleep deprivation.

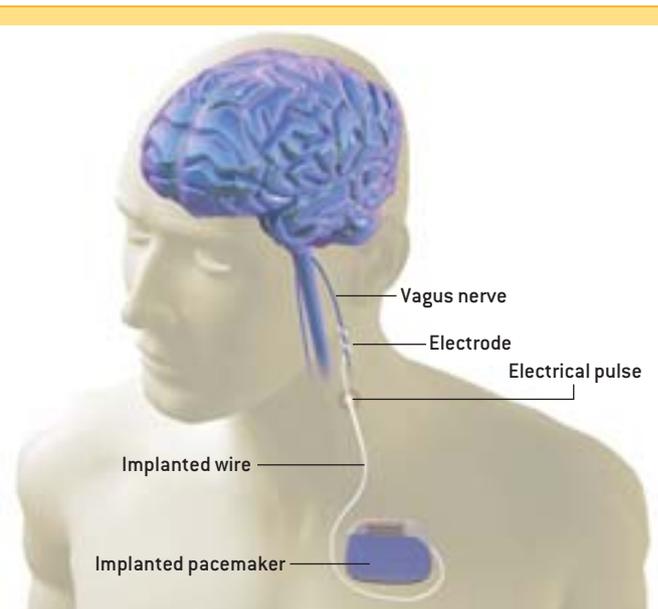
Recent media reports have made public Australian claims that TMS might be used to unleash nascent savant skills (mastery of difficult tasks without training) in healthy subjects by temporarily disabling one brain hemisphere. This work has not yet been published in the scientific press. In fact, most neuroscientists believe that the reported effects are unlikely to be true. Researchers have supervised TMS sessions involving thousands of subjects and have yet to witness any so-called savant skill changes. Although existing artistic talents occasionally improve with the onset of dementia, we have not seen savant abilities emerge after TMS-like stimuli such as focal brain disability caused by trauma, stroke or surgery or after brain areas are injected with anesthetics.

What Excites What

INTRIGUING AS THESE POTENTIAL applications might be, they raise difficult questions. Scientists would like to ascertain exactly which neurons rTMS affects as well as the detailed neurobiological events that follow stimulation. In addition to figuring out which electromagnetic frequencies, intensities and dose regimens might produce different behaviors, researchers must decide (for each individual) exactly where to place the rTMS coil and whether to activate it when someone engages in a task. Scientists also need more knowledge about what rTMS is doing at both the cellular level—the effects on neurotransmitters, gene expression, synaptic changes—as well as at the circuit level.

Further complication occurs because each person’s brain is wired differently, so the location for behaviors varies. If one’s motor area is close to one’s skull, TMS might have a large effect. In someone else, whose motor area lies deeper in, TMS may have little or no effect on movement.

To better understand the effects of rTMS on brain circuits, physicist Daryl E. Bohning and others in our group at MUSC developed the ability to perform rTMS testing in combination with a functional magnetic resonance imaging (fMRI) scanner. Many researchers had thought that generating the powerful TMS magnetic fields within an fMRI machine was impossible or unwise. By applying rTMS within the scanner as subjects perform a task, however, one can know exactly where the stimulation is occurring and can image alterations to the neural circuit taking place because of the stimulus. Our group has shown that the brain changes that TMS causes when it makes your thumb move are very much the same as when you move your thumb in a



Direct electrical excitation of the vagus nerve in the neck can suppress the onset of brain seizures.

vagus nerve could abort a seizure occurring in a dog. This finding led to clinical trials of the technique and eventual FDA approval of VNS for suppressing seizures.

Surgeons typically wrap the VNS electrode around the left vagus nerve in the neck and connect it to a pacemaker they have implanted in the patient’s chest wall (*above*). The VNS apparatus can be programmed to produce electrical stimuli in various intermittent patterns.

Researchers are now conducting studies to determine if VNS has therapeutic value for other disorders such as depression and anxiety. As with the other stimulation approaches, we do not know if changing how the VNS electrical signals are delivered would produce different brain effects. Our group at the Medical University of South Carolina has investigated VNS within a functional magnetic resonance imaging scanner to determine whether altering VNS parameters achieves different results. If it is confirmed, one might modulate brain regions by varying the VNS pulse pattern at the neck. No brain surgery would be needed. —M.S.G.

DEEP BRAIN MAGNETIC STIMULATION

TRANSCRANIAL MAGNETIC STIMULATION fields extend only a few centimeters to the surface of the cortex. Although TMS is promising for certain applications, the procedure could find much wider use if it could reach to the central structures of the brain.

High-intensity TMS fields could penetrate farther into the brain, but they can cause seizures, tissue damage or discomfort. Thus, a magnetic field that can safely penetrate and activate the brain's inner regions has remained the Holy Grail of TMS research for some time. Creation of such a field offers the possibility of treating difficult conditions such as Parkinson's disease. Though unlikely, it might even make it possible to energize the brain's "pleasure center" directly (think "Orgasmatron," from Woody Allen's film *Sleeper*).

An interdisciplinary team at the U.S. National Institutes of Health has invented a new TMS coil configuration that is designed to generate sufficient magnetic field strength to stimulate neurons deep inside the brain mass without posing a hazard. The research group included Abraham Zangen, Roy A. Wise, Mark Hallett, Pedro C. Miranda and Yiftach Roth.



According to Zangen, now a neurobiologist at the Weizmann Institute of Science in Israel, the prototype device is designed to maximize the electric field deep in the brain by summing separate fields projected into the skull from several points around its periphery. The device also minimizes the accumulation of electrical charge on the surface of the brain, which would give rise to an electrostatic field that reduces the magnitude of the induced electric field both at the surface and inside. The unique, form-fitting shape of the base of the new stimulator positions wire coils containing several wire strips that is set tangentially to the scalp's surface. Each set of strips is connected in series and contains current flowing in the same direction. Therefore, each set generates a field that extends into the brain in a specified orientation from each location along the scalp.

The prototype apparatus underwent an initial round of clinical evaluations this summer. Investors have recently established a company called Brainsway in Delaware to carry on the research and development effort and to commercialize the deep brain magnetic stimulator. —The Editors

similar pattern of your own accord. Two research groups in Germany have also succeeded in conducting rTMS studies within an fMRI scanner.

Magnet Therapy

IN THEORY, TMS could be a useful therapy for any brain disorder involving dysfunctional behavior in a neural circuit. Researchers have tried employing the technique as a treatment for obsessive-compulsive disorder, schizophrenia, Parkinson's, dystonia (involuntary muscle contractions), chronic pain and epilepsy. For most of these conditions, only a few inconclusive or contradictory studies currently exist, so the jury is still out regarding the effectiveness of TMS as therapy for them.

Most of these inquiries have concentrated on relieving depression. In the mid-1990s I was among the first researchers (along with several European groups) to investigate the use of daily rTMS sessions to treat depression. Perhaps, we thought, one could accomplish what ECT does for depressed individuals with TMS while avoiding seizures. My studies (at the National Institute of Mental Health) focused on stimulating the prefrontal cortex because that region appears abnormal in many internal images of depressed patients and because it governs deeper limbic regions involved in mood and emotion regulation. Double-blind studies soon indicated a small but significant antidepressant effect. A few patients at the NIH who had not responded to any other treatments had emerged from their depression and returned home.

Since then, more than 20 randomized and controlled trials of prefrontal rTMS as a treatment for depression have been published. Most of these studies show antidepressant effects significantly greater than sham electrode application, a conclusion that has been further confirmed by subsequent meta-analyses of the results. Whereas current consensus holds that rTMS offers a statistically significant antidepressant effect, controversy continues over whether these effects are sufficient to be clinically useful.

Because no commercial industry yet exists to promote TMS as an antidepressant therapy and because most of the studies have been relatively small (with considerable variation in rTMS methods and patient selection), the use of rTMS as a treatment for depression is still considered experimental by the U.S. Food and Drug Administration. The technique has, however, already been sanctioned for use in Canada, where it is now available. A large industry-sponsored trial designed to garner FDA acceptance is being planned. Even if the approach is approved, much additional research remains to refine it.

Repetitive TMS can, it should be noted, cause seizures or epileptic convulsions in healthy subjects, depending on the intensity, frequency, duration and interval of magnetic stimuli. In the history of the technique's use, TMS has led to eight unintended seizures, but since the publication of safety guidelines several years ago, no new seizures have been reported. Some scientists are investigating the potential positive application of this result. Harold A. Sackeim and Sarah H. Lisanby of Columbia have shown that a supercharged version of TMS, which they call magnetic seizure therapy (MST), can produce beneficial seizures in depressed patients (who are first anesthetized). Unlike ECT, MST allows users to focus on the site where the seizure is triggered. Better control over the seizure should block its spread to the regions of the brain responsible for

ELECTROMAGNETIC BRAIN-STIMULATION TECHNIQUES

Neuroscientists employ electricity and magnetism to treat brain disorders. Each method offers different degrees of targeting accuracy.

	TREATMENT USE	PULSE DELIVERY	TARGETING ABILITY	ADVANTAGES	DISADVANTAGES
Electroconvulsive therapy (ECT)	Depression, mania, catatonia	Skin electrodes	Fair	Effective for depression; side effects reduced with newer systems	Nonfocal; can lead to memory side effects; requires repeated general anesthesia
Transcutaneous electrical nerve stimulation (TENS)	Pain, spasticity	Skin electrodes (attached to peripheral nerves)	Good	Does not require surgery	Limited access to brain
Vagus nerve stimulation (VNS)	Approved for epilepsy; FDA trials under way for depression and anxiety	Electrodes (attached to vagus nerve)	Fair	Does not involve brain surgery	Effects modest (to date); unclear how to tune pulses to alter brain function
Deep brain stimulation (DBS)	Approved for Parkinson's disease; under investigation for pain and obsessive-compulsive disorder	Electrodes (embedded in brain regions)	Excellent	Discrete targeting; marked effects	Potential side effects if incorrectly positioned; invasive brain surgery
Transcranial direct current stimulation (tDCS)	Under investigation for Parkinson's disease	Electric field	Unfocused	Noninvasive	Scalp irritation; nonfocal
Transcranial magnetic stimulation (TMS)	Under investigation for depression; FDA trials under way	Magnetic field	Excellent	Noninvasive and safe; potential for many applications	Limited to surface brain stimulation; effect on neural function still unclear
Magnetic seizure therapy (MST)	Under investigation for depression	Magnetic field	Fair	May offer better targeting and might avoid side effects of ECT	No efficacy data yet; requires repeated general anesthesia

the memory loss seen with ECT. Preliminary data indicate that MST has fewer cognitive side effects than traditional ECT techniques. More needs to be done to determine whether the MST really works and for which disorders it might be beneficial.

The technology of TMS is evolving as well. Our group at MUSC, for instance, has recently developed a portable TMS machine—an advance that may someday translate into the fatigue-fighting flight helmets depicted earlier. Extensive development is also proceeding on new designs and prototypes for coils that can stimulate more deeply inside the brain, that can be focused more finely or that operate in coordinated arrays. Most of our actions

and thoughts arise not from activity in a single brain region but rather through the coordinated firing of many brain regions. If one could make several TMS coils, distributed over various key regions and fired in a coordinated way, new vistas might open up for TMS as a neuroscience tool and treatment.

After more than a decade of experimentation, TMS is still not FDA-approved to alleviate any disorder. Nevertheless, interest remains high among researchers who continue to believe in the intuitive aptness of using safe magnetic fields to turn specific brain regions on and off. If TMS proves itself, it could even lend some credence to the folk wisdom that humans use only a small portion of their brains. 

MORE TO EXPLORE

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For more information on transcranial magnetic stimulation, visit pni.unibe.ch/TMS.htm