

ABOLT TO THE BRAIN

Although depression is a worldwide epidemic, the various drugs used to treat it don't work well or come with a load of side effects. Cate Montana reports on a new non-drug way to stimulate healing

We are a sad species. According to the World Health Organization, major depressive disorder (MDD) is the most common of all psychiatric disorders, affecting nearly 322 million people globally. It's a chronic condition that is usually episodic—coming and going over the course of a lifetime, with episodes lasting from two weeks to several months or more at a time.

Stressful events such as the death of a loved one, divorce, a traumatic event such as a sexual attack or a sudden loss of income can cause both temporary and ongoing clinical depression. But childhood abuse has been highlighted as clearly related to the development of major depressive episodes later in life.

Changes in brain chemistry, such as a decrease in neurotransmitter production; a drop in serotonin, dopamine, endorphins or oxytocin levels (the happy hormones); and a general decrease in metabolism or blood flow in several areas of the brain are also directly related. But whether these biochemical imbalances and reductions in metabolic function are triggered by events, happen independently or both is uncertain.

“There’s increasing understanding that depression is not a monolith, that there are different subtypes of depression,” says Dr Colleen Hanlon, a neuroscientist and vice president of medical affairs with BrainsWay (brainsway.com), a company that develops noninvasive neurostimulation techniques to treat mental and cognitive health disorders.

“This is perhaps the reason some people respond to one type of therapy and others respond differently or not at all. It’s like little mini diseases in there.

“Some people have anhedonic depression and tend to sleep more and eat more, and they don’t get excited. They don’t get sad. They’re just kind of low, versus a more anxious type of depression that often looks like anxiety to the untrained eye. These are people that sleep less and eat less and are a little more activated.”

MDD has traditionally been treated with psychotherapy accompanied by the prescription of tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)—all different kinds of antidepressant medications that are also used to treat anxiety disorders, social phobia, chronic neuropathic pain and other issues.¹¹

Studies suggest the more severe the depression, the greater the benefits of antidepressant medications, but they also show that antidepressants often don’t work. Some people experience depressive symptoms even after trying several different medications.

And the statistics paint a gloomy picture. Anywhere between 10 and 30 percent of patients suffering from

MDD do not improve or only partially improve by following the traditional treatment route.¹² And many patients experience initial relief of symptoms only to have the medication they’re on gradually lose efficacy. Approximately 25 percent of people who take antidepressants for major depression relapse within one to two years.¹³

Another downside to antidepressants is that it might easily take a couple of weeks or far longer to experience any initial effects. For patients resistant to antidepressants, multi-drug experimentation may drag on for a year or more without diminishing symptoms.

Meanwhile, side effects such as drowsiness and fatigue, nausea, sexual dysfunction, weight gain, insomnia and various gastrointestinal issues are common. As well, there is an increased risk of suicide from taking these drugs.¹⁴

TMS to the rescue

Into this rather bleak treatment picture comes repetitive transcranial magnetic stimulation (TMS or rTMS), a noninvasive brain stimulation therapy developed for use in treatment-resistant depression that started garnering attention in the mid-1990s. The understanding that the brain is electrical in its function had already produced a radical treatment for depression, schizophrenia and other severe mental disorders called electroconvulsive shock therapy (ECS).

First used in 1938 on a homeless man with schizophrenia, ECS involves inducing a seizure by directing a mild electric current through the brain, thus flooding the whole brain with neurotransmitters that change its fundamental chemistry. Today the procedure is conducted only under general anesthesia.

A few decades later, based on the discovery by English scientist Michael Faraday in the mid-1800s that the movement of electricity through a coil creates magnetic fields, experimentation with applying magnetic fields to the brain commenced. It quickly established that applying a coil to the motor-cortex area of the brain stimulated hand and foot responses.

Research and increasingly sophisticated brain mapping, which nowadays include computed tomography scans and functional magnetic resonance imaging, showed researchers what areas of the brain are related to functions such as memory and learning as well as to mental and emotional dysfunction—areas where a coil should be placed. And thus TMS was born.

“The old idea that you had to have a seizure that affected both hemispheres along with a huge flooding of neurotransmitters and growth factors has been replaced with the understanding that accurate treatment is really quite focal,” says Dr Ian Cook, founder of the

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Los Angeles TMS Institute Inc., former professor of psychiatry and director of the UCLA Depression Research Program.

“We pulse magnetic fields through a small coil to induce electrical currents in brain tissue in highly specific areas. If a person has too much anxiety, there are certain circuits that we would stimulate to bring down the activity in those circuits. And if a person has depression, there are other circuits that we would want to increase the activity in to improve their mood, retraining circuits to function in a different, healthier way.”

Several regions of the brain are targets for treating depression.¹ According to Cook, the orbital frontal cortex over the eye on the forehead is useful for treating OCD and mitigating intrusive thoughts. The supplemental motor area on the top, a little bit closer to the nose than the motor strip itself, is also an OCD target. Heschel’s gyrus, which is located in the primary auditory cortex, is a target in people with schizophrenia who have auditory hallucinations.

Cook says there is growing interest in using some targets over the motor sensory strip for pain. As well, the hippocampus can be targeted as a treatment area in people with minor memory problems and may prove effective in treating dementia.

How it works

When a magnetic field passes into the brain, the axons of the neurons in the brain in that area (the tiny fibers responsible for neuron communications) act like secondary coils, creating electrical currents in the brain that stimulate biochemical releases as well as increased neuronal activity and growth.

The effect of TMS depends on the frequency of the pulses. At a low frequency, less than 1 Hz (one pulse per second), rTMS has an inhibitory effect. At higher frequencies of 5 Hz and above, the effect is excitatory.² According to Hanlon, who conducted clinical research programs in transcranial magnetic therapy at the Medical University of South Carolina and Wake Forest School of Medicine, two common frequencies currently in use are 18 Hz and 20 Hz.

“Stimulating the brain at frequencies closer to about 20 Hz, it’s possible to induce cellular changes in the brain that are associated with plasticity or learning and memory,” she says.

Another very interesting pulse rhythm that’s now being used for treatment is something called theta burst. It aligns with our endogenous theta brainwave rhythm of 4–8 Hz, a frequency associated with entrainment, learning and memory.

“If you deliver that rhythm with TMS, you can have particularly fast response rates in terms of changing the motor cortex and possibly changing depression,” Hanlon says.

“So this has become a big trend in the field because you only need about 600 pulses of theta bursts

The sad statistics



ONE IN THREE WOMEN AND ONE IN FIVE MEN IN THE UNITED STATES DEVELOP MDD AT SOME POINT IN THEIR LIVES

Persistent depressive disorder is depression that lasts for at least two years. Treatment-resistant depression affects as many as 30 percent of patients with MDD and is classified as lingering depression symptoms even after taking multiple antidepressants or antidepressant classes as directed.

About one in three women and one in five men in the United

States develop MDD at some point in their lives.⁴ In the UK, clinical depression affects an average of one in six adults (16 percent, a rise of about 10 percent since before the Covid pandemic).² There are several subtypes of MDD, such as panic attacks, substance use disorder (SUD) and social anxiety disorder.

As well, depression is frequently accompanied by obsessive-compulsive disorder (OCD), which is characterized by uncontrollable (usually negative) thoughts and repetitive behaviors. Anxiety is also a common aspect of the disorder.

MDD is twice as common in women as it is in men, and it’s estimated that close to 50 percent of people who have it don’t receive an official diagnosis or treatment. Symptoms include persistent low mood and a sense of poor self-worth, negative emotions such as guilt and hopelessness, low energy and exhaustion, poor concentration, disrupted sleep cycles, changes in appetite and lowered cognitive ability.



IN THE UK, CLINICAL DEPRESSION AFFECTS AN AVERAGE OF ONE IN SIX ADULTS

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compared to 2,000 to 3,000 pulses of the standard high-frequency 18 Hz.”

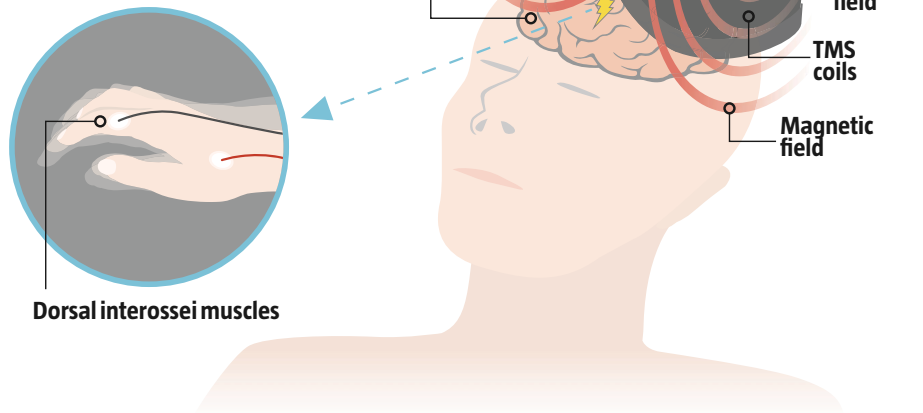
The success of TMS has led to widespread experimentation and the use of different coil shapes and methods of approach. The original US Food and Drug Administration (FDA)-approved protocol for TMS is daily sessions for 36 consecutive days using a coil.

The simplest transcranial magnetic stimulation coil is circular and has good penetration but lacks precision. However, a figure-eight coil—which looks just like it sounds—placed on the area requiring stimulation has better focality and penetration.

“Figure-eight coils are used a lot in academic research institutions because, as a researcher, you often want to ask a very specific scientific question,” says Hanlon. “But in clinical practice, treating volumes of patients, we know that all individuals are unique. Like, there’s not a single brain pattern for depression, right?”

“If we put you in a scanner and me in a scanner and somebody else who is suicidal in a scanner, you’re going to notice there are a lot of similarities and differences between our brains.

TMS electromagnetically stimulates particular areas of the brain, which causes muscle movement in the hand on the opposite side of the body



A typical TMS session

Whether it involves a standard or accelerated protocol and whether it uses a figure-eight coil or an H coil and helmet, the TMS session is fundamentally the same. The patient sits in a comfortable chair while the coil is secured at the appropriate spot on their scalp. Standard sessions last about 20 minutes and accelerated sessions take five minutes, with an hour in between to allow the brain to “reset itself.”

While stimulating neuron function in the brain, TMS also stimulates the muscle tissue and nerves in the scalp. When Dr Ian Cook got the first TMS machine for research purposes at UCLA back in 2009, he says he didn’t think it would be ethical to have his staff practicing on each other. So, they all practiced on him instead.

“I got a lot of experience with what it’s like,” he says. “And frankly it’s more weird than uncomfortable. It feels like something’s tapping on your head. Sort of like a percussive tap that ends as soon as the treatment session is over.”

For those with any anxiety about the experience, Hanlon advises having a chat with their psychiatrist about what it entails. Many psychiatric clinics have TMS centers available for patients. A patient can just go sit in the chair and experience a single pulse to the motor function area and feel/see their hand move.

“If that freaks people out too much, then they just don’t have to have the treatment,” says Hanlon. “But a lot of times, just easing people into it to show them that it’s really not scary—not like the movie *One Flew over the Cuckoo’s Nest* or anything—makes all the difference. Young people used to tech just think it’s really cool.”

See page 64 for how to find a TMS provider.

“One of the challenges that has really been talked about a lot recently with figure-eight coils is that, because the field they produce is small, if you don’t use neural navigation, you could miss the target,” he explains. “That’s why the H coil, which exhibits flexibility and a broader targeted area, was created.”

Developed by BrainsWay, the H coil is used in a protocol known as deep TMS. It’s held inside a helmet that fits entirely over the patient’s head, emitting magnetic pulses that reach deeper into a broader area of brain structures. It eliminates the need for neuro-navigation equipment while effectively influencing neural activity.

The Stanford protocol, known as SAINT (Stanford Accelerated Intelligent Neuromodulation Therapy) uses neuroimaging (MRI) to guide precision placement of the coil—providing accuracy within 1 mm—and calls for 10 five-minute treatments a day for five days in a row.

“So far they have reported much better outcomes than with conventional TMS,” says Cook. A double-blind controlled SAINT study conducted in 2021 showed remission in 79 percent of participants who suffered from severe depression.⁴

Up to now, there has been little understanding of why the SAINT protocol works so well. “Is it the higher number of pulses per treatment?” questions Cook. “Is it the higher number of pulses combined with neuro-navigated MRI placement of the coil?”

“Is it the schedule itself? Is there some sort of synergy created from doing more than one session in a day? The relative importance of each of those factors is unclear.”

Despite the unknowns, one thing is very clear: TMS works exceedingly well for mitigating clinical depression as well as OCD, anxiety, schizophrenia and bipolar disorder. Whether a figure-eight coil is used once a day for 20 minutes for 36 days, or 10 times a day for five minutes for five days straight, TMS achieves far better results than talk therapy and drugs. It can produce total remission of symptoms within a matter of weeks instead of partial reduction of symptoms over a span of years. And side effects are minimal.

Although many people worry about the possibility of seizures, studies show seizure rates are incredibly low. Hanlon says about two patients out of 10,000 might experience a seizure while using TMS.

“The primary side effect is a temporary headache—which tends to resolve within that day—in about a third of people during the treatment,” she says. “Also, about a third of people will have pain or discomfort at the site of stimulation at least one time during the treatment course.”

“So, these are anticipated adverse events. We’ve looked at things like changes in cognitive function and changes in hearing, and we haven’t found anything. Actually, if anything, using TMS—both the figure-eight and the H coil—people with depression tend to have a nonsignificant improvement in cognitive function.”

Studies

Increasing evidence shows that TMS is successful in treating a range of mental conditions. Studies show that



Bye-bye, bipolar

Because clinical depression is such a sensitive diagnosis, no patients were willing to talk directly to *WDDTY* about their TMS treatments. However, BrainsWay has numerous patient testimonials on its website (brainsway.com/knowledge-center/video-gallery). And Dr Ian Cook has lots of stories to tell.

Early on he worked with a graduate student in her early 30s diagnosed with bipolar disorder type 2, meaning she had periods of full-blown depression but without experiencing full-blown mania. In her manic phase, she would sleep less and be more active, but nothing over the top.

"She came to us after she had tried a long list of medications for a number of years," says Cook. "At the recommendation of her primary psychiatrist, who had worked with her for a number of years, we initially tried ketamine (an extremely fast-acting dissociative antidepressant).

"This really helped the depressions to get better. But she never felt like she got totally well. There was always some degree of darkness lurking in the corners, as it were. So, we tried TMS, and her comment to me early on, almost with disbelief, was, 'So, this is what normal people feel like every day?'

"After she had gotten well with the TMS, she said she had to rethink a lot of things about her life. How she thought about herself, for example, and the way that she related to people. All of it was really just a habit she had gotten into from years of depression.

"I need to figure out how to live differently in my body because my whole life is different now," she said. She finished her PhD degree and is now healthy and gainfully employed."

daily TMS treatments are safe and effective for the acute phase of depression in people who are treatment resistant or intolerant.¹³ Accelerated TMS treatment “appears to hold promise to reduce treatment time and achieve rapid reduction in depressive symptoms.”¹⁴

TMS is also a good option for treating OCD.¹⁵ It effectively treats posttraumatic stress disorder (PTSD) and generalized anxiety disorder (GAD).¹⁶ In a study of bipolar disorder, 41 percent of subjects who completed at least 25 TMS treatments experienced remission.¹⁷

Although there is a paucity of studies of anxiety disorder, preliminary results show that TMS might be a satisfactory intervention.¹⁸ Three studies show positive results of treating people with severe social phobia symptoms.¹⁹ Finally, TMS appears to be a successful option for patients suffering with schizophrenia.²⁰

Transcranial magnetic stimulation is FDA approved in the US and covered by most insurance policies. However, it is rarely approved as a first-line treatment. Standard treatment involving antidepressants must have failed—at least once and often numerous times—before TMS is considered.

In the UK, the National Institute for Health and Care Excellence (NICE) approved TMS in 2015. However, the NHS offers it only for depression and anxiety and only to patients in certain areas who haven’t found success with antidepressants and electroconvulsive therapy (ECT). Some providers offer it through other referral and/or payment routes.

Initial response and post-treatment care

Hanlon says typically the nurse or other TMS providers notice a patient’s improvement even before the patient themselves. “They start coming in wearing nicer clothes, or they tuck their shirt into their pants, or they brush their hair nicely that day,” says Hanlon. “It usually takes about 16 sessions before the patient starts noticing their own improvement.”

There are some things patients can do to support their TMS treatments, like making sure they hold to regular sleep schedules. Maintaining or increasing social connections—physical connections, not online—is also extremely helpful. Exercise is another way to bolster the positive effects.

Cook says using light therapy, such as stimulating yourself with intense light early in the morning, can make a positive difference. Also, making sure to keep track of mood is very important. At the end of treatment, Cook gives patients copies of the rating scales they have used during treatment and asks them to rate themselves every few weeks.

“We’ve had some people whom we treated soon after I left UCLA back in 2018 who are still well,” says Cook. “And we’ve had other people who have come back in once in a while when their numbers started to go up and they started experiencing a symptom burden again. Additional TMS is helpful if we catch it early. Just an afternoon of three or four five-minute sessions is enough to get the train back on the tracks.”



“Those thoughts are gone!”

A woman in her mid-60s was diagnosed with bipolar disorder and was actively suicidal when Ian Cook conducted her first TMS treatment. “Toward the end of that first treatment,” Cook remembers, “she suddenly said, ‘Those thoughts are gone!’”

“When she came out of treatment, her partner took one look at her and said, ‘You’re back!’ When I asked her partner to explain, she said my patient’s facial expressions were different, her body language was different, and she was much like herself again.

“A few weeks later, after we did a full series of treatments, my patient said, ‘You know, if this had been around 30 years ago, I would have been spared God knows how many psychiatric hospitalizations, a suicide attempt, two rounds of ECT, and on and on and on.’”

Depression banished

Cook’s last story is about a college student with a genetic predisposition to depression. A handful of relatives had committed suicide, and the boy had been struggling with depression since he was age 12 or so.

His family quickly got him into traditional talk therapy and onto prescription antidepressants. But nothing truly worked.

“We did a so-called accelerated TMS where we did more than one treatment a day,” says Cook. “At that time, we didn’t have access to the Stanford targeting algorithms, so we used a more traditional way to set the focal targets for treatment.

“But after a few days, he said, ‘I feel different. I feel hopeful.’ His family was reporting at the same time that he seemed to be brighter and that he was making jokes for the first time in several years.”

“By the time the TMS course was finished, the patient was in remission to the point that he scored in the same range that people who have never had depression scored. Last I knew, he had finished college and was looking at grad school.”

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