Transcranial Magnetic Stimulation and Cranial Electrotherapy Stimulation

Treatments for Psychiatric and Neurologic Disorders

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Transcranial magnetic stimulation (TMS) and cranial electrotherapy stimulation (CES) are relatively recent alternative or adjunctive approaches to pharmacologic, invasive, and behavioral treatments for psychiatric and neurologic disorders. This article reviews TMS and CES development, current and emerging diagnostic and therapeutic applications, proposed mechanisms of action, and roles as tools used in basic neuroscience research to understand and potentially enhance brain functioning.

Historical Background

The concept of using electrical currents therapeutically dates back to the first century AD, when a Roman physician applied currents from torpedo fish (of the Torpedinidae or other electric ray family) to treat headaches.[1] In the nineteenth century, scientists studying the fundamental principles of electromagnetism began investigating magnetic stimulation of muscles and nerves.[2]

Transcranial Magnetic Stimulation

TMS is a noninvasive technique that utilizes electromagnetic induction to focus electrical currents from a pulsing electromagnet to the brain via the scalp to study or modulate cortical functioning. The effects of the localized current are dependent on stimulation parameters, such as frequency and intensity, and the device's coil configuration and orientation.

In 1985, researchers at the University of Sheffield in England initiated the first clinical studies of TMS, developed the first safety guidelines for the procedure, and encouraged commercial development of the technique. TMS is now used therapeutically and to study the relationship between brain functions and behaviors. TMS is classified as single-pulse or repetitive (rTMS). In this article, the term TMS is used to designate rTMS unless otherwise specified.

In the early 1990s, researchers who adapted technology developed for experimental studies of the brain proposed TMS as a treatment for depression.[3] Clinical trials established that TMS had clinical efficacy with a low side-effect profile for patients with clinical depression.[4] In 2008, the U.S. Food and Drug Administration (FDA) cleared a TMS device (NeuroStar TMS Therapy,® System developed by Neuronetics, Inc., Malvern, PA) for treating adult patients diagnosed with major depressive disorder (MDD) who did not experience clinically significant improvement after a course of antidepressant medication.[5] Up to two-thirds of patients with MDD do not respond to the first medication prescribed, and they are less likely to go into remission with further drug treatment.[6]

Unlike electroconvulsive therapy (ECT)—long and controversially used to treat psychiatric disorders—or deep brain stimulation (DBS)—a recently-developed modality used to treat certain other neurologic conditions such as Parkinson's disease—TMS and other cranial stimulation methods do not involve sedation, anesthesia, or surgery for electrode implantation. Nor do they produce negative cognitive effects as is the case with ECT.

Barriers to wider adoption of TMS include the high cost and lack of portability of the equipment involved. More affordable, compact electromedical devices designed for health care practitioner office or home use by patients address these issues.

Cranial Electrotherapy Stimulation

CES was originally developed in Russia for alleviating insomnia and, thus, was called "electrosleep treatment," and came to the United States in the 1960s. Unlike TMS, which uses high-powered magnets, CES delivers a weak alternating, pulsed electrical current via battery-powered sponge electrodes applied to the scalp under a headband or applied to the earlobes to induce an electrical charge in the brain. Classified as CES in 1978 by the FDA, this agency regulates marketing of these devices for treatment of depression, anxiety, and in-

somnia. A major application of CES has been management of these symptoms in drug-abstinence syndrome. Ongoing studies suggest that CES also has efficacy as an adjunctive therapy for various chronic pain disorders.[7]

Alpha-Stim® (Electromedical Products International, Inc., Mineral Wells, Texas) is a CES device developed in 1981. Patients are instructed to place the electrode clips firmly but gently on their earlobes (Fig. 1). A CES session takes 20–60 minutes, depending on the condition being treated. Many patients report an immediate sense of relief and improvement in their moods. This device is contraindicated for patients who have pacemakers or are pregnant.[8] See Contraindications for TMS and/or CES.

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Another CES device, the Fisher Wallace Stimulator® (Fisher Wallace Laboratories, LLC, New York, New York) was cleared by the FDA in 1991 for treating depression, anxiety, insomnia, and pain. The device, which may be used in conjunction with the patient's usual treatment, requires written authorization from a licensed health care practitioner (acupuncturist, chiropractor, massage therapist, nurse, osteopathic physician, or psychologist). The stimulator is intended to be used twice a day (morning and evening) for 20 minutes per treatment session. Symptoms are said to typically recede after 2 weeks, but it may take up to 45 days for the user to experience results. Rare side-effects include mild headache or restlessness, which ceases after discontinuing use of the device.[9]

A Typical TMS Session

The initial TMS treatment course for MDD typically consists of 5 treatments per week on an outpatient basis over a 4–6 week period, for an average total of 20–30 treatments. Each session lasts ~ 40 minutes. Through a treatment coil placed against the scalp (generally over the left prefrontal cortex), the patient—who is seated in a reclining chair and remains awake and alert—receives highly concentrated magnetic fields that are turned on and off very rapidly. These magnetic fields produce very weak electrical currents that penetrate just 2–3 cm into the brain directly beneath the coil.[10]

Any side-effects during treatment are generally mild and may include discomfort at the stimulation site, headaches, light-headedness, facial twitches, or shifts in hearing thresholds if earplugs are not used. At the Mayo Clinic in Rochester, Minnesota, clinicians track each patient's progress with depression questionnaires administered at the beginning and end of the treatment period and every 2 weeks during treatment. Patients are encouraged to continue treatment with their referring health care providers. Shirlene Sampson, MD, a clinic psychiatrist, said: "Although a > 50% improvement is considered successful, we aim for remission of depression when possible."[11] The Mayo Clinic participated in the multicenter trial (discussed below) that led to FDA approval of TMS.

Mechanisms of Action

Mark A. Demitrack, MD, chief medical officer of Neuronetics, Inc., stated: "We believe that TMS exerts its effects by improving the metabolic activity (i.e., the energy production) in the specific areas of the brain that we know are involved in the regulation of mood."[12] This technique may induce cognitive-enhancing alternations in neural networks involved in cognitive operations.[13]

The TMS coil sends brief electrical pulses that are thought to activate transmission of neurotransmitters (serotonin, norepinephrine, and dopamine) in mood-regulating areas of the brain.[10] TMS is neuromodulating as well as neurostimulating, modulating excitability of the cerebral cortex as well as the activity of deeper neural circuits.[14] TMS has been found to be a reliable method for recording and treating impaired cortical inhibition, mediated by γ-aminobutyric acid (GABA), which is associated with chronic pain.[15]

Similarly, CES has been associated with significant cortical and behavioral processes, apparently synchronizing and enhancing the efficacy of neurophysiologic activity via rhythmic stimulation.[16] Results of a study with healthy subjects indicated that CES causes deactivation in regions that can have significant effects on resting-state brain activity.[17]

Insurance Reimbursement

Although they are not considered to be experimental treatments by the FDA, restrictions on coverage of TMS and CES by some private and public health insurers have been a factor limiting their wider adoption. However, Medicare now provides some coverage of TMS for certain conditions.[18] Fisher Wallace Laboratories notes that insurance companies often reimburse patients for purchase of their CES devices that are used to treat pain.[9]

Empirical Evidence for TMS

Major Depressive Disorder

In the study that served as the basis for FDA approval of TMS devices, a multisite blinded study examined the efficacy and safety of TMS for acute treatment of MDD. Medication-free patients (N = 301) who had not benefited from prior drug treatment for MDD were randomized to active (n = 155) or sham (n = 146) TMS. TMS sessions were conducted 5 times per week for 4–6 weeks. Active TMS was significantly superior to sham TMS with respect to response and remission rates on

standard scales at weeks 4 and 6. Active TMS was well-tolerated with a low dropout rate (4.5%) for mild adverse events, primarily transient scalp discomfort.[19]

In a subsequent prospective sham-controlled study, 199 outpatients with MDD who were not taking antidepressants were randomized to receive TMS daily at intervals in a 37.5-minute session aimed at the left prefrontal cortex for 3 weeks or a simulated treatment. Compared with the sham control and an intention-to-treat (ITT) sample (n = 190), the active TMS group had significantly greater remission of symptoms (14%), compared with what occurred in the control and ITT groups (5%). The researchers noted that this remission rate was comparable to that of antidepressants, without their considerable side-effects. Nearly 30% of the patients who had some improvement remitted in an open-label follow-up phase of this study.[20]

In another post-FDA approval study, the results of TMS treatment for MDD were observed in a clinical cohort of 100 patients who were treated between 2008 and 2011 and for whom other treatment failed. The patients were flexibly dosed in a course of up to 30 sessions adjunctive to their current medications. Enduring benefit was assessed over 6 months in patients receiving TMS maintenance treatment; 62% still had their responder status at the final assessment. TMS was well-tolerated during both acute and maintenance treatment.[21]

After 6 months of TMS maintenance treatment, 62% of patients still had responder status.

A prospective, open pilot trial investigating TMS as an adjunct to selective serotonin reuptake inhibitors in adolescents with MDD whose conditions had not responded sufficiently to medication, found the adult dose of TMS to be effective for some adolescents.[22]

MDD is common during pregnancy, and pregnant women generally prefer nondrug treatment options. In an open-label pilot study, 10 women with MDD in the second or third trimester of pregnancy were treated with 20 sessions of TMS. Antenatal monitoring was performed during treatment sessions 1, 10, and 20. Seven of the 10 subjects showed a decrease of 50% or more in Hamilton Depression Rating Scale scores. Mild headache experienced by 4 of the 10 subjects was the only adverse event, and no adverse pregnancy or fetal outcomes were observed.[23]

Chronic Pain

Dr. Sampson of the Mayo Clinic noted that patients in studies of TMS treatment for depression have also experienced reduction of chronic pain. She stated: "We know that the neural pathways for pain and depression overlap. We hope that future TMS research will help us better understand the pathophysiology of chronic pain."[11]

Figure 1. Alpha-Stim® cranial electrotherapy stimulation device. ©2013, Electromedical Products International, Inc. Reproduced with permission.

For example, on the basis of a systematic review of 9 studies—8 of which were double-blinded, randomized controlled trials—showing significant pain reduction, investigators concluded that TMS (or direct current stimulation which is not discussed here) should be considered when treating patients with fibromyalgia syndrome who are unable to find adequate symptom relief with other therapies. Fewer and milder side-effects occurred, compared to pharmaceuticals for fibromyalgia.[24]

TMS also produced safe, beneficial effects in studies of chronic neuropathic pain,[25] migraine,[26] and phantom-limb pain.[27]

Stroke

Aphasia, the loss of language fluency, is a significant source of functional impairment following stroke. In a test of the effect of TMS on aphasia, TMS was applied to 10 subjects in 10 sessions over 2 weeks at a cortical site that was previously shown to facilitate naming ability in persons who had stroke affecting the left brain hemisphere and nonfluent (expressive) aphasia. Five patients were given sham TMS, then were switched to active TMS 2 months later. Active TMS resulted in a significant increase in many measures of discourse productivity, compared to baseline performance.[28] TMS also reduced another frequent symptom of stroke, visuospatial neglect, in a randomized study of 27 patients.[29]

Traumatic Brain Injury

A review of evidence from animal and human studies suggests that TMS, in conjunction with other rehabilitative therapy, may enhance cortical neuroplasticity to facilitate recovery of function after traumatic brain injury.[30]

Spinal Cord Injury

A randomized trial studied the potential of TMS to help patients with incomplete spinal cord injury (SCI) improve some motor function in their lower extremities. Patients (N = 17) were randomized to receive either high-frequency TMS

Contraindications for TMS and/or CES

- Patients with implanted metal devices or nonremovable metallic objects in or around the head (e.g., metal plates in the skull, aneurysm coils)[10]
- Patients with implants controlled by physiologic signals (e.g., cardiac pacemakers, implantable cardioverter defibrillators, vagus nerve stimulators)[10]
- Patients who are pregnant[a]
- Seizures have been reported with TMS in rare cases,[11] but have not occurred with CES[9]
- CES and TMS are currently approved only for adults
- CES should be used with caution in conjunction with medication for high blood pressure (BP), because BP can become too low.[9]
- TMS may be less effective for patients with psychotic depression or for the elderly[11]
- TMS has not been studied in patients who have not been treated with antidepressants, who have had two or more adequate trials of antidepressants that failed, who have bipolar disorder or depression with psychosis, or who are at high risk for suicide[b]

Note: Superscript numbers denote text references.

[a]Fisher Wallace Laboratories. Frequently Asked Questions. Online document at: www.fisherwallace.com/cranial-stimulator-faq Accessed March 12, 2013.
[b]National Alliance on Mental Illness. Transcranial Magnetic Stimulation (TMS) Fact Sheet. Online document at: www.nami.org/factsheets/TMS_factsheet.pdf Accessed March 12, 2013.

TMS, transcranial magnetic stimulation; CES, cranial electrotherapy stimulation.

or sham stimulation in conjunction with gait-rehabilitation therapy. Active TMS consisted of 15 daily sessions over the leg motor area; 3 patients who began in the sham group were crossed over to the active TMS group after a washout period of more than 3 weeks. Significant improvement was observed from baseline after the last TMS session in the active TMS group on scores for selected lower-extremity motor skills on standard assessment tools. Improvement in walking speed was maintained at the 2-week follow-up period.[31]

Parkinson's Disease

A double-blinded placebo-controlled study evaluated the safety and efficacy of TMS (of 25-Hz) for gait and bradykinesia (slow movements) in 18 patients with Parkinson's disease (PD). Eight TMS sessions were performed over a 4-week period, with 4 cortical sites stimulated in each session. During the 4 weeks, times for executing walking and complex hand movements gradually decreased. The therapeutic effect of TMS lasted for at least 1 month following the end of treatment.[32]

Another randomized, double-blinded, sham-controlled study explored the efficacy and effects of different frequencies of TMS on symptoms of PD ($N = 106$). The effects of weekly interventions of low-frequency (1-Hz), high frequency (10-Hz), and sham TMS stimulations over the supplementary motor area were assessed by changes in scores from baseline on the Unified Parkinson's Disease Rating Scale. Several nonmotor symptoms scales were also used, including one that measured depression. The low-frequency Hz TMS proved effective for reducing motor, but not nonmotor, PD symptoms.[33] On the basis of 84 single-pulse and/or paired-pulse TMS, a recent literature review concluded that single-pulse TMS and rTMS protocols pose no significant threats to patients with PD.[34]

Schizophrenia

Researchers conducted a systematic review of 13 sham-controlled studies, 5 open trials, 2 meta-analyses, and 2 review articles. After conducting the review, the researchers concluded that TMS had a mild-to-moderate effect in reducing the negative symptoms (e.g., lack of expression, will, or activity) of schizophrenia.[35]

Substance Dependence

A review of 8 studies evaluated the use of TMS for treating tobacco, alcohol, or cocaine addiction. Based on what the review showed, the researchers concluded that TMS is a promising modality for treating drug addiction.[36]

Other Disorders

Because preliminary data have suggested that TMS has a positive effect on repetitive behaviors, stimulus hypersensitivity, and social functioning in individuals with high-functioning autism, a planned clinical trial will assess TMS efficacy in children and adolescents with low-functioning autism.[37] Short-term efficacy was found for TMS for treating chronic tinnitus.[38] Studies are also in progress to evaluate the efficacy of TMS for treating Alzheimer's disease, mild cognitive impairment, bipolar disorder, and Tourette syndrome, and to monitor recovery from stroke.[39]

Enhancing Cognitive Processes

Because TMS alters cortical activity and excitability, these approaches are being considered for potentially enhancing cognitive processes including perception, learning, working memory, and long-term memory formation in healthy humans.[40]

Empirical Evidence for CES

Although not as well-researched as TMS, CES has shown promise for treating chronic pain and other conditions. While CES may be used as an adjunctive therapy, it is often used as a stand-alone therapy because results are frequently seen from the first treatment.[41]

Chronic Pain

In a controlled double-blinded study, patients diagnosed with fibromyalgia (N unspecified) were randomized to the following groups: active CES device; sham device; or only usual care. Patients receiving treatment with the active device had a greater decrease in average pain than did the other groups; the decrease in cortical pain-processing regions was shown by magnetic resonance imaging (MRI).[42]

Chronic pain is also a significant problem for many persons following SCI, but SCI-related neuropathic pain is often refractory to analgesic medications. In a multisite, randomized controlled study [*N* unspecified], application of active CES, 1 hour per day for 21 days, resulted in a small but statistically significant reduction of pain intensity and pain interference with few troublesome side-effects, compared to use of sham CES.[43]

PD

Patients with PD may experience musculoskeletal pain in the lower back or lower extremities. In a study to assess the feasibility of using CES for pain in PD, a randomized, controlled double-blinded trial involved a total of 19 participants with PD-related pain. Of these participants, 13 recorded daily pain data and were divided into two groups: 6 receiving active CES and 7 receiving sham CES; the devices were given to the patients to use at home 40 minutes per day for 6 weeks. Patients receiving active CES had, on average, a small decrease in self-reported pre- and postsession pain ratings, compared to patients receiving sham CES.[44]

Other PD Symptoms

The effect of CES on gait and balance in 10 patients with long-standing PD was examined in a pilot study. In week 1, participants received CES for 20 minutes via an electrode placed over the primary motor area. In week 2, participants walked for 20 minutes on a treadmill. Week 3 involved both CES and treadmill use. Based on pre- and post-testing, CES significantly increased stride length and gait velocity, without adverse side-effects. Improving gait and balance can improve quality of life for patients by reducing their risk of falls.[45]

Pain and Other Symptoms in Cancer Treatment

Another pilot study tested CES as a complementary modality for multiple symptom management (pain, fatigue, depression, anxiety, and sleep disturbances) in 36 women with stages I–IIIA breast cancer, who were receiving chemotherapy. Based on data collected from interviews, questionnaires, and biomarkers measured from a blood sample taken from each patient prior to that patient's initial chemotherapy session, CES was found to be a safe and acceptable modality during chemotherapy.[46]

Insomnia

CES has been studied for treatment of insomnia. Active-duty service members receiving mental health care (*N* unspecified) were randomly assigned to receive 60 minutes of either active or sham CES device treatment for 5 days. Following each intervention, and 3 and 10 days later, patients completed a sleep log. A nearly significant increase in total time slept after 3 CES treatments occurred in all study subjects. The researchers concluded that the results were caused by an insufficient dose of CES.[47]

Generalized Anxiety Disorder

A pilot study of CES was conducted in 12 patients with generalized anxiety disorder. CES was associated with a significant reduction in scores on the Hamilton Rating Scale for Anxiety.[48]

Other Disorders

Current research projects are investigating CES as a modality to treat patients with post-traumatic stress disorder, and patients with bipolar disorder, and to identity the mechanism of action of the effects of CES combined with TMS.[49]

Conclusions

TMS has been shown to be a safe, effective, innovative treatment for a significant percentage of patients with clinical depression whose conditions are unresponsive to, or who cannot tolerate, pharmacologic antidepressants. TMS is also a promising technique for a variety of treatment-resistant neuropsychiatric diseases in which cognitive impairment is a core symptom, including Alzheimer's disease, autism, and schizophrenia.

Empirical evidence is emerging for the efficacy of both TMS and CES as noninvasive alternative or adjunctive modalities for treating other psychiatric disorders and chronic pain, and in rehabilitation following stroke and SCI. Further research into the mechanisms of action of such devices should help guide the development of optimal protocols for effective treatment. ■

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