

02 - 30.2 Other Brain Stimulation Methods

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30.2 Other Brain Stimulation Methods Brain stimulation in psychiatric practice and research uses electrical currents or magnetic fields to alter neuronal firing. There is a growing list of tools capable of eliciting such neuromodulation, each with a different spectrum of action. These tools either apply electrical or magnetic fields transcranially or involve the surgical implantation of electrodes to deliver electrical currents to a cranial nerve or to the brain directly. The transcranial techniques include cranial electrical stimulation (CES), electroconvulsive therapy (ECT), transcranial direct current stimulation (tDCS, also called direct current polarization), transcranial magnetic stimulation (TMS), and magnetic seizure therapy (MST). The surgical techniques include cortical brain stimulation (CBS), deep brain stimulation (DBS), and vagus nerve stimulation (VNS). In 1985, nearly 50 years after the first use of ECT, Anthony Barker and colleagues published on the first use of pulsed magnetic fields to stimulate the brain with a procedure called transcranial magnetic stimulation. TMS was initially used in neurology for studies of nerve conduction, but it quickly caught the attention of psychiatrists eager to explore other, less

invasive alternatives to ECT. This nonconvulsive stimulation method through TMS is under active study, with some promising results in the treatment of various psychiatric disorders, including depression, anxiety, and schizophrenia, as described by Sarah H. Lisanby, Leann H. Kinnunen, and colleagues in 2002. In the past decade, a convulsive treatment derived from the application of more powerful magnetic stimulation has been under investigation in nonhuman primates and in human studies in both the United States and Europe. The first MST procedure was performed in an animal in 1998 and in a human in 2000. MST is under development as a more focal means of inducing seizures in an attempt to retain the thus-far-unparalleled efficacy of ECT with fewer cognitive side effects. Two more recent additions to brain stimulation methods, DBS and VNS, were introduced about a decade following the first trials of TMS. Both were first approved by the U.S. Food and Drug Administration (FDA) in 1997 in the realm of treating sequelae of neurological syndromes. DBS was initially approved for the treatment of essential tremor and Parkinson's tremor, whereas VNS was approved for the treatment of epilepsy. Five years later, in 2002, indications for DBS

were expanded to include treatment of all symptoms of Parkinson's disease, including tremor, slowness, and stiffness, as well as involuntary movements induced by medications. TMS, DBS, and VNS originated in the field of neurology. Psychiatrists quickly saw the potential for those tools in the treatment of psychiatric conditions, however, and as a result of clinical trials in depression, VNS subsequently received FDA approval for the adjunctive long-term treatment of chronic or recurrent depression in adults. In addition, human studies are under way to validate the efficacy of DBS in the treatment of depression and obsessive-compulsive disorder. THERAPEUTIC

NEUROMODULATION: TREATING PSYCHIATRIC DISORDERS THROUGH BRAIN STIMULATION

Mechanism of Action Electrical Stimulation—Common Pathway. The brain stimulation modalities just reviewed generate either electrical or magnetic pulses. However, both of these share a common final pathway—they affect the neurons electrically. That electrical effect may either be through the direct application of electricity or through the indirect induction of electricity via magnetic stimulation. The direct forms of electrical stimulation are exemplified in either transcranial delivery, as with ECT, CES, and tDCS, or intracerebral delivery, as in the case of DBS or direct cortical stimulation (epidural or subdural). The indirect forms of electrical stimulation include TMS and MST, which induce electrical fields in the brain through the application of alternating magnetic fields. Of note, both the epidural and intracerebral modalities are more focal than the transcranial application of electricity because electrodes are placed directly in the neuronal tissue, bypassing the impedance of the scalp and skull. The relatively more contemporary magnetic stimulation methods (TMS and MST) also bypass the impedance of the scalp and skull and are thus likewise more focal. However, magnetic stimulation is in fact an example of an indirect method of electrical brain stimulation, in that the changing magnetic fields from these devices induce electricity in the brain, the latter acting as a conductor, according to the principle first described by Michael Faraday in a law that bears his name and later incorporated into James Clerk Maxwell's equations, which unify all of electromagnetism. The magnetic modalities achieve their enhanced focality noninvasively, in contrast to the intracerebral and epidural methods, and are thus at the center of intensive research in that they offer the promise of an unparalleled degree of spatial specificity without the need for surgery. All but one of the brain stimulation modalities described here act by stimulating neurons. The one exception is tDCS, which does not stimulate but rather polarizes. In this sense, the "S" of tDCS is a misnomer. It is more accurate to conceptualize tDCS as exerting a polarizing effect that may alter the likelihood of neuronal firing. The action of the

subconvulsive modalities of stimulation relies on the effects of the repeated stimulation of the targeted neural circuitry. However, in the case of the convulsive modalities (ECT and MST), the action depends on the seizure induced by the stimulation and the effects of repeated seizure induction on brain processes. This is not to say that the form of stimulation that triggers the seizure has no effect on outcome. Indeed, it is well replicated that electrode placement and electrical stimulus parameters have a profound effect on the efficacy and side effects of ECT. Whether the same will be true for MST is under active investigation.

Acute versus Prolonged Effects. Brain stimulation can have immediate or lasting effects. A single electrical pulse delivered at sufficient intensity can induce depolarization, trigger an action potential, release neurotransmitters at the synapse, and result in transsynaptic propagation with subsequent activation of a functional circuit. For example, brain stimulation applied to the hand area of the primary motor cortex may activate the corticospinal tract and induce a muscle twitch in the contralateral hand. Such stimulation can result acutely in the induction of either a positive effect, as in the case of a muscle twitch or visualization of phosphenes, or a disruptive effect, as in the case of visual masking. Repetitive pulses delivered at fixed frequencies can exert even more powerful effects. Epstein and colleagues described in 1999 how repetitive TMS (rTMS) applied to the language-dominant hemisphere induced an arrest of speech. After termination of the stimulation, speech returned to normal. Some more invasive brain stimulation modalities, such as DBS or VNS, are programmed to operate chronically, thus extending the acute action for as long as the stimulation is turned on. In the case of DBS, the pulses are typically given continuously at a high frequency, whereas in the case of VNS the pulses are given in trains lasting up to 30 seconds and typically repeated every 5 minutes. The less invasive modalities, such as rTMS, tDCS, CES, and even ECT, presumably require the induction of some form of neuroplasticity for their effect to become lasting.

TRANSCRANIAL MAGNETIC STIMULATION Definition TMS is the application of a rapidly changing magnetic field to the superficial layers of the cerebral cortex, which locally induces small electric currents, also referred to as eddy currents. This induction was originally discovered by Faraday through his experiments in 1831 and later quantified in Maxwell's equations of electromagnetism. Thus, TMS may be referred to as electrical stimulation without an electrode, in that it uses magnetic fields to indirectly induce electrical pulses. TMS devices deliver strong magnetic pulses via a coil that is held on the scalp. Because magnetic fields are unaffected by the electrical impedance of the scalp and skull, this method of stimulation enables the focal stimulation of smaller areas of the brain than is possible with other noninvasive devices that use either alternating (ECT, CES) or direct (tDCS) electrical current for primary stimulation. TMS is an example of noninvasive stimulation of focal regions of the brain and, as such, can be used for research or therapeutically without the need for anesthesia.

Mechanisms of Action At sufficient intensity, electrical currents will stimulate neuronal depolarization, which can result in an action potential. For example, when the TMS coil is positioned over the hand area of the cerebral cortex's motor strip, the changing magnetic field generated by

the repetitive pulses induces local currents immediately below the site of stimulation that cause the neurons in area M1 to fire. In turn, this action potential propagates through the polysynaptic corticospinal tract and results in a twitch in the contralateral hand muscle. In summary, TMS uses magnetic fields to indirectly induce focal electrical currents in the brain, thereby triggering the firing of functional neuronal circuits that can lead to observable behavioral effects. This effect can be easily demonstrated by single TMS pulses that can be used to map the homunculus simply by

moving the TMS coil across the cortical representation of neighboring muscle groups and simultaneously to study the excitability of the corticospinal system. Single TMS pulses can exert other effects when moved to different cortical areas. When positioned over the primary visual cortex (V1), scotomas, or “blind spots,” are often elicited. This illustrates that TMS can transiently disrupt functions. Activation of motor neurons resulting in a muscle twitch and disruption of visual perception with a single-pulse TMS represent examples of the acute effects of TMS-induced neuronal depolarization, as shown in Table 30.2-1. The effects of single TMS pulses are believed to be immediate and short lived. The muscle twitch as induced by TMS to area M1 is nearly instantaneous, with the hand movement occurring approximately 20 milliseconds after the TMS pulse is applied. The visual masking likewise operates on a similar time scale measured in milliseconds. TMS can, however, exert longer-lasting effects when the pulses are repeated at regular intervals in a process of rTMS or when they are paired with other forms of stimulation in which TMS pulses are coupled with electrical stimulation of a peripheral nerve (as in paired associative stimulation [PAS]) or when TMS is paired with audiovisual stimuli, as in the example of classical conditioning of the brain response to TMS. The mechanisms underlying these lasting effects of TMS have been described by various researchers and are thought to be related to neuroplasticity and alterations in synaptic efficacy. Table 30.2-1 Acute and Prolonged Mechanisms of Action Treatment of psychiatric disorders with rTMS has been informed by attempts to focally alter pathological cortical excitability, believed to be linked to a specific illness. Reduced activity in the left dorsolateral prefrontal cortex has been implicated in several studies as a physiological correlate of affective disorders. To correct this, numerous studies have applied high frequencies of rTMS, which have been reported to increase excitability, to the left dorsolateral prefrontal cortex (DLPFC) in an attempt to normalize activity in this region. In a related approach, some investigators who implicated abnormal interhemispheric balance in activation between the right and left DLPFC applied low-frequency rTMS, which has been reported to be inhibitory, to the right DLPFC in an attempt to normalize this balance. Side Effects, Interactions with Medications, and Other Risks

Administration of TMS is a noninvasive, relatively benign procedure when applied by a knowledgeable professional to a subject who has been properly evaluated. However, it is not entirely without risk. The most serious known risk of TMS is an unintended seizure. There are several factors that may contribute to seizure risk. Primarily, these include the form of TMS, with single-pulse stimulation less likely to result in a seizure than rTMS, and, in an equally important manner, the dose, which is the combination of treatment parameters including frequency, power, train duration, and intertrain interval. In addition, subject factors can be important, such as the presence of a neurological disorder (epilepsy or a focal brain lesion) or use of seizure-lowering medications. Single-pulse TMS is generally considered to be of minimal risk when administered to appropriately screened adults without seizure risk factors. On the other hand, rTMS can induce seizures in individuals without predisposing conditions when given at sufficiently high doses. Patient Selection Patients who have failed a trial of one or more antidepressant medications or have untoward side effects to medications may be good candidates for TMS. However, given the lower effect size of TMS, for urgent or severely refractory cases, ECT would remain the ultimate gold standard treatment. Future Directions and Controllable Pulse Shape TMS TMS and other forms of magnetic stimulation hold a tremendous promise in psychiatric treatment due to their focality and noninvasiveness. However, much research is needed to replicate preliminary findings, improve optimal dosing, establish the patient characteristics that predict response, and examine the influence of concomitant medications on TMS effect. Posttreatment relapse prevention is one of

many areas that have to be properly explored. Other vigorously pursued directions are attempts to develop stimulation coils that will allow deeper brain penetration and work on pulse shapes that may be more physiologically optimal for human stimulation. **TRANSCRANIAL DIRECT CURRENT STIMULATION** Definition Transcranial direct current stimulation is a noninvasive form of treatment that uses very weak (1 to 3 mA) direct electrical current applied to the scalp. Because direct current (DC) polarizes rather than stimulates with discrete pulses, its action does not appear directly to result in action potential firing in cortical neurons. It is also this DC form of electrical stimulation that distinguishes it from devices that use alternating currents (AC) as found in CES, ECT, VNS, and DBS, which produce discrete pulse stimulation. In addition, because tDCS works via polarization and does not affect action potential firing

in cortical neurons, the term transcranial direct current polarization is favored by some modern investigators, and both terms appear interchangeably in the literature today. The small device is very portable and usually operated by readily available DC batteries. **Side Effects** There are no known serious adverse effects of tDCS. It is well tolerated, with reported common side effects in the literature listing mostly minimal tingling at the site of stimulation, with a few reported cases of skin irritation. **Mechanism of Action** Direct current polarizes current, and tDCS is believed to act via the alteration of neuronal membrane polarization, but little is known about the actual mechanism of action of tDCS. Polarization may affect the firing and conductance of neurons by either lowering or raising the threshold of activation. Because tDCS involves the application of low currents to the scalp via cathodal and anodal electrodes, depending on the direction of current flow, polarization can either inhibit (cathodal) or facilitate (anodal) function. **Clinical Studies** Preliminary research suggests that tDCS may enhance certain brain functions independent of mood; however, tDCS technology and its use in psychiatry are in the early stages of exploration. Research is focusing on its potential effectiveness in facilitating recovery from stroke and from certain forms of dementia. **Future Directions** Most of the current tDCS devices use large, saline solution-soaked electrodes. Future device development will most likely investigate electrode shape and contact material to optimize the intended clinical effects and further improve ease of use. However, basic questions of efficacy, indications, and dose-response relationships, as well as predictors of response, will need to be explored first. **CRANIAL ELECTRICAL STIMULATION** Definition CES, like tDCS, uses a weak (1 to 4 mA) current. However, with CES the current is alternating. It is traditionally applied via saline-soaked, felt-covered electrodes clipped onto the earlobes. Other placement strategies are also being investigated. **Mechanism of Action** The exact mechanism of action has not been elicited, and there is no agreement among researchers on the predominant mode of action. Previous hypotheses proposed that the

stimulation with the alternating microcurrent affects the thalamic and hypothalamic brain tissue and facilitates the release of neurotransmitters. Claims have been made that through interaction with cell membranes, the stimulation produces changes in signal transduction associated with classical second-messenger pathways, including calcium channels and cyclic adenosine monophosphate (AMP). There are summary reports that CES causes increases in plasma serotonin, norepinephrine, dopamine, and monoamine oxidase type B (MAOB) in blood platelets and cerebrospinal fluid (CSF), as well as release of 5-hydroxy-indol-acetic acid (DHEA) and enkephalins and reduction of cortisol and tryptophan. However, most of these reports have not been validated through modern research. **Side Effects** It is believed that the CES stimulation is not harmful, primarily due to its low voltage power supply (9-V battery) and lack of any reported adverse event

by the FDA. Local skin effects, as well as a general feeling of dizziness, have been reported, however, and the use of the device during pregnancy, in those with low blood pressure, or in people who have arrhythmias or pacemakers is not advised by device manufacturers. Clinical Studies In a meta-analysis by the Harvard School of Public Health, 18 human clinical trials were examined that used CES to treat depression, anxiety, drug addiction, insomnia, headache, and pain. The overall pooled result showed CES to be better than sham treatment for anxiety at a statistically significant level. Current Status in Treatment Algorithms, Patient Selection, and Dosing The use of CES has not been studied sufficiently in the United States, and it does not have a specific place in any algorithm of standard US psychiatric practice. Future Directions As with tDCS, basic issues of indications, patient selection, dose-response relationship, and efficacy are under active research and remain to be optimized. MAGNETIC SEIZURE THERAPY Definition MST is a novel form of a convulsive treatment that is under development in several research institutions in the United States and Europe. The treatment uses an alternating magnetic field that crosses the scalp and the calvarium bone unaffected by their high electrical impedance, to in turn induce a more-localized electrical current in the targeted regions of the cerebral cortex than is possible with ECT. The aim is to produce a seizure

whose focus and patterns of spread may be controlled. MST is a convulsive treatment, in many ways similar to ECT. It is performed under general anesthesia. It requires approximately the same preparation and infrastructure as ECT. However, MST is given using a modified TMS device, one that can administer higher output than the conventional TMS devices and thus relies on magnetic stimulation, unlike electric stimulation in ECT. The MST procedure is performed under general anesthesia with a muscle relaxant. MST is at the stage of clinical trials and is not FDA approved. Mechanism of Action Induction of a seizure is hypothesized to be the underlying event responsible for the likely multiple specific mechanisms of action of MST treatment. As in ECT, these are not fully understood. However, due to its focality, MST appears to represent a tool better suited than ECT to study the mechanisms of action of convulsive therapy through its potential of inducing seizures initiated in different regions of the brain. Side Effects Adverse effects from MST, like those of ECT, are largely connected to the risks associated with anesthesia and generalized seizure. In addition, the MST magnetic coil produces a clicking noise that may potentially affect hearing. To mitigate that risk and prevent any cumulative damage, earplugs should be worn by both the patient and members of the treating team. Studies suggest that MST results in less retrograde and anterograde amnesia than ECT, although this result should be replicated in a larger trial. Current Status in Treatment Algorithms No clinical algorithms exist for MST, given that it is still an investigational protocol and treatments outside of research are not FDA approved. Assuming that the hypothesis that MST can approach the efficacy of ECT (but with fewer side effects) is correct, this magnetically induced convulsive treatment will play an important role prior to referral for ECT. Future Directions MST is a novel treatment in early phases of clinical testing. Clinical treatment variables, including dosing, optimal coil placement, patient selection, and mechanisms of action, are the topics of ongoing and future studies. VAGUS NERVE STIMULATION Definition

VNS is the direct, intermittent electrical stimulation of the left cervical vagus nerve via an implanted pulse generator, usually in the left chest wall. The electrode is wrapped around the left vagus nerve in the neck and is connected to the generator subcutaneously. Mechanisms of Action The majority of the fibers contained in the left vagus are afferents. It is estimated that as many as 80 percent of these fibers are up-going afferents, and thus chronic stimulation of these nerve fibers

predominantly changes activity in the brainstem nuclei such as the nucleus of the tractus solitarius and other neighboring nuclei (e.g., Raphe) that alter serotonergic activity in cortical and limbic structures. In addition, persistent stimulation of the vagal afferents is anticonvulsant, an effect that appears to depend on the norepinephrine-producing locus ceruleus.

Side Effects and Contraindications

To date, reasonably comprehensive literature confirms that VNS is generally well tolerated. The adverse events that are most frequently reported are voice alteration, dyspnea, and neck pain. Besides the risk of perioperative infection, the surgical implantation carries a small risk of vocal cord paralysis, bradycardia, or asystole.

Current Status in Treatment Algorithms

The FDA indicated VNS for the adjunctive long-term treatment of chronic or recurrent depression in patients 18 years or older experiencing a major depressive episode in the setting of unipolar or bipolar disease who have not had an adequate response to four or more adequate antidepressant treatments. Consultation with another clinician experienced with treatment-resistant depression and VNS is recommended. VNS treatment success rates are lower than those with ECT. Its onset of action is also comparatively slow—typically an approximately 30 percent response rate is observed after 1 year. VNS may be worth considering, therefore, when patients have failed to respond to less invasive treatments, ECT was ineffective, or post-ECT relapse cannot be prevented with less invasive means. VNS might be helpful with longer-term relapse prevention, but results of controlled trials would be useful to guide practice.

Patient Selection

VNS is approved as an adjunctive long-term treatment for chronic or recurrent depressive episodes in adults with a major depressive episode who have not had a satisfactory response to four or more adequate antidepressant trials. The efficacy of VNS in other disorders is unknown. ECT can be safely used in patients with an implant as long as the VNS generator is turned off during the convulsive treatment. This is needed because of the anticonvulsant effects of VNS. It remains to be studied whether VNS could be useful in relapse

prevention post-ECT.

Dosing

The optimal dosing for psychiatric applications of VNS is still largely an area of investigation. The published studies do not identify optimal dosing parameters like time on, time off, frequency, current, or pulse width. However, the epilepsy literature suggests that there is a threshold current for efficacy. Given current knowledge of VNS dosing, electrical current is typically increased up to greater than 1 mA and clinical benefit is assessed over several months. Because the adverse effects of VNS are known to be dose dependent, treatment parameters are often chosen to mitigate specific side effects. For example, lowering pulse width reduces neck pain, allowing patients to tolerate higher currents.

Future Directions

More research is required to establish the dose-response relationships for VNS. Future studies may explore optimal medication strategies to augment responses, test the potential role of VNS for long-term relapse prevention (e.g., after ECT), and study its mechanisms of action.

IMPLANTED CORTICAL STIMULATION

Definition

CBS is a novel neurosurgical approach in which electrodes are implanted over the surface of the cortex to provide electrical brain stimulation in a targeted superficial region. This approach is being studied for treatment of conditions like stroke, tinnitus, and treatment-resistant depression.

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