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The Science of Transcranial Magnetic Stimulation

William M. Sauvé, MD; and Lawrence J. Crowther, MEng

ABSTRACT

Transcranial magnetic stimulation (TMS) is a noninvasive method for stimulating neural tissue based on the principles of electromagnetic induction. The technique is becoming an established treatment for drug-resistant major depressive disorder and is a promising tool for a variety of psychiatric and neurological disorders. Stimulation is achieved by pulsed magnetic fields inducing electric fields with the necessary characteristics to depolarize neurons, generating action potentials. In this article, the underlying principles and mechanisms of TMS are explored and an overview of the development of stimulator devices is provided. **[*Psychiatr Ann*. 2014; 44(6):279–283.]**

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William M. Sauvé, MD, is Medical Director, TMS NeuroHealth Centers, Richmond. Lawrence J. Crowther, MEng, is Graduate Research Assistant, Department of Electrical and Computer Engineering, Iowa State University.

Address correspondence to: William M. Sauvé, MD, TMS NeuroHealth Centers, 5231 Hickory Park Drive, Suite C, Glen Allen, VA 23059; email: william.sauve@viptms.com.

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Since the days of Pliny, humans have been curious about the effects of electrical stimulation on the body, and since Michael Faraday famously developed the concept of electromagnetic induction, it has been understood that changing magnetic fields can cause current to flow in conductive material,[1] including the brain. Although the ability to stimulate the brain using magnetic pulses was established by Jacques d'Arsonval in 1896,[2] this phenomenon has only recently been used as a therapeutic modality in psychiatry. Known as repetitive transcranial magnetic stimulation (rTMS), it was approved for the treatment of major depressive disorder by the U.S. Food and Drug Administration in 2008. What follows is a very basic overview of the underlying physics of TMS, how it impacts the neurons in the brain, some of the methods of application, and the various stimulation devices in use.

FARADAY'S LAW OF ELECTROMAGNETIC INDUCTION

Both Michael Faraday and Joseph Henry independently discovered the concept of electromagnetic induction in 1831, but Faraday was the first to publish his findings. Simply put, a magnetic field that is in motion relative to a conductor brings about a current in said conductor. Hence, a changing magnetic field induces a flow of electric current in nearby conductors that, for the purposes of this article, include human tissue.[3] The most commonly used form of expression for this concept is the Maxwell-Faraday equation, also referred to as Faraday's Law.

Electromagnetic induction is the key principle in transcranial magnetic stimulation (TMS), taking advantage of the fact that every electric current has a magnetic field surrounding it, with alternating currents bringing about fluctuating magnetic fields. Fluctuating magnetic fields in turn cause electric current to flow in conductors placed within them; the conductors in the case of TMS being neurons in the brain, thus allowing for electrical stimulation of neurons within the brain in a noninvasive fashion.

DIRECT NEURONAL EFFECTS OF TMS

It has been demonstrated that a magnetic field pulsed adjacent to a volume conductor (such as the brain) induces an electrical field in that conductor. Although the brain is truly a heterogeneous conductor, with the white and gray matter as well as cerebrospinal fluid all having different conductivities (0.48, 0.7 and 1.79 siemens/m, respectively),[3] the resultant differences in the induced electric field are small enough that the brain can be thought of as a homogeneous volume conductor. Furthermore, the induced current is small enough so as not to have any effect on the magnetic field, thus eddy currents are not significant in this case, making the induction of an electric field within the brain via TMS a one-way proposition.

When discussing the effect of TMS on a neuron, two major factors include chronaxie and rheobase. *Chronaxie* is defined as the minimum time for an electric current to double the strength of the rheobase of a neuron; *rheobase* is defined as the lowest intensity of current that can cause an action potential in said neuron.[4]

Thus, when a magnetic field pulses adjacent to the volume conductor, which in this case is the brain, an electrical field is generated at sufficient strength and duration to cause the neuron to depolarize, resulting in an action potential. When the motor cortex is stimulated in this way, the result is a motor evoked potential (MEP), leading to motor activity. Similar single or paired pulse TMS delivered over the occipital cortex has also resulted in flashes of light being perceived by the subject. Pulses delivered over other parts of the brain may not be experienced on the conscious level but have resulted in measurable changes, such as on the subject's performance in a cognitive task. Practical application of TMS, however, is largely focused on rTMS, where such pulses are being delivered in trains at certain frequencies that have been shown to generate more lasting effects. Generally, by mechanisms that are not well understood, low-frequency stimulation (≤1 Hz) is thought to bring about reduced cortical excitability, whereas high-frequency stimulation (>5 Hz) increases cortical excitability and, in each case, the effect is maintained for some time after a number of pulse trains have been completed. Again, the mechanism is not well understood but may be partly explained by the phenomena of long-term potentiation (LTP) and long-term depression (LTD).[5]

LONG-TERM POTENTIATION/ DEPRESSION

LTP refers to a process by which synaptic communication between neurons is made more efficient when said neurons fire in sequence. Often remembered in school by the saying "neurons that fire together, wire together," LTP is thought to be an important part of learning.[6] LTP was first described by Terje Lømo in 1966, showing that while a single electric stimulus delivered to presynaptic fibers resulted in excitatory postsynaptic potentials in the postsynaptic cells, high-frequency trains of stimuli delivered to the same resulted in an enhanced response over an extended period of time. He called this phenomenon "long-lasting potentiation,"[7] which was later changed to "long-term potentiation" by Douglas and Goddard in 1975.[8]

LTD is the opposing process to LTP, with the efficacy of neuronal synapses being decreased after certain stimuli. LTD is thought to result mainly from a decrease in postsynaptic receptor density, with L-glutamate interacting with multiple receptors to selectively weaken receptor strength. Some examples of the utility of LTD can be the possible clearing of old memory traces in the hippocampus[9] and the concept of neuroplasticity in general, with LTP and LTD occurring in concert to selectively strengthen and weaken synaptic connections in the brain. It is the possible modulation of these phenomena by rTMS that may explain some of its lasting effects and clinical utility.

DEFINING PULSE SEQUENCES

Determining pulse sequences requires that decisions be made about frequency, intensity, and duration of stimulation. Frequency of stimulation will be chosen based on the desired effect, either an increase or decrease in cortical excitability in the area being stimulated, with an increase typically brought about by high-frequency pulse trains, and a decrease brought about by low-frequency pulse trains. For example, the approved treatment for depression consists of 4-second pulse trains at 10 Hz delivered to the left-side dorsolateral prefrontal cortex and is thought to generate an increase in cortical excitability in this area. Conversely, some small studies in the treatment of Tourette syndrome have used a frequency of 1 Hz stimulation over the supplementary motor area (SMA), with

the expectation that cortical excitability will be decreased as a result.[10]

Intensity of stimulation is affected by many variables but is largely dictated by the baseline excitability of the cortex, which can be measured by the minimum stimulation required to bring about an MEP. In clinical practice, this is often determined by the observation of muscle movement in the subject being stimulated and is called the resting motor threshold (RMT). Stimulus intensity in various protocols will then be expressed as a percentage of RMT (eg, the approved treatment for depression is typically performed at an intensity of 120% of RMT).

The duration of a pulse train may have an effect on the duration of the after effects. In the motor cortex, a 15-minute train of rTMS at approximately 1 Hz reduces cortical excitability for at least the subsequent 15 minutes, whereas single-pulse stimulations have been shown to only change cortical excitability for approximately 200 ms.[11]

It is important to note, however, that many studies on cortical excitability following pulse sequences varying in frequency, intensity, and duration are either inconsistent or even contradictory. For practical purposes it is useful to work with the paradigm that high-frequency tends to increase cortical excitability and low frequency tends to decrease it, and longer durations of stimulus may increase the duration of after effects; the exact mechanisms of all the above are not completely understood.[5]

THETA BURSTS

Theta burst stimulation (TBS) protocols consist of very high-frequency (approximately 2500 Hz) pulses delivered in 100-Hz bursts at 5-Hz intervals, which is consistent with theta rhythm as measured on electroencephalography.[12] TBS protocols can be divided into two main categories, intermittent and continuous, with the effects being excitatory and inhibitory, respectively. Intermittent TBS is defined as 1840 ms of stimulation repeated every 10 seconds for a total of 191.84 seconds, or a total of 600 pulses, with continuous TBS being defined as three pulses at 50 Hz repeated every 200 ms for 20 or 40 seconds for a total of 300 or 600 pulses. TBS protocols remain in the investigational stage, with the main potential advantage being that similar effects to rTMS may be achieved with considerably shorter protocols leading to similar or even greater duration of either excitatory or inhibitory after effects.

TMS STIMULATOR DESIGN

TMS stimulators generate the pulsed electrical current needed by TMS coils to produce the transient magnetic field necessary for stimulation of neural tissue. Energy is stored within a large capacitor that is discharged by a silicon-controlled rectifier switch designed to minimize losses and be capable of carrying currents of thousands of amps. The nature of the discharged current depends on the resonant frequency of the stimulator circuitry. In the case of TMS, the rate of change of current and subsequent magnetic field with respect to time is the primary consideration. Two main types of magnetic stimulators exist and are distinguished by the characteristics of the pulse they produce: monophasic and biphasic. Monophasic stimulators are simpler in design and inadequate for generating the repetitive pulses required for therapeutic use. Biphasic stimulators enable shorter interpulse periods by using nonpolarized capacitors, allowing energy to be returned to the capacitor during each pulse. These stimulators have become more widely used, offering pulse repetition rates of up to 100 Hz[13] as required for TBS.

EARLY TMS COIL DESIGNS

Following the first demonstration of noninvasive stimulation of the human motor cortex by Barker et al.[14] in 1985, TMS stimulator coils were predominantly of flat circular type. The greatest electric field is induced directly below the coil windings, meaning circular coils do not produce a single area of maximum field. Circular coils do, however, offer the ability to stimulate both hemispheres at the same time to some degree by placing the coil at the cranial vertex, although the direction of induced current has an influence over the extent to which neuronal activation can be achieved in the motor cortex, with a preference for currents flowing from posterior to anterior. Flat circular coils are still used and commercially produced[15,16] but have been succeeded by more complex designs for therapeutic implementation. In 1998, Ueno et al.[17] proposed the figure-8 coil, also known as a butterfly coil, as a method of achieving localized stimulation by placing two coils side by side with currents flowing in the same direction where the two coils meet. The resulting induced electric fields add together, allowing focused stimulation. Although the localization of stimulation can be greatly increased with a figure-8 coil, the decay of electric field within a homogeneous volume conductor has been shown to occur more rapidly for a figure-8 coil compared to a circular coil,[18,19] reducing its ability to stimulate deeper brain regions.

MODIFICATIONS TO TMS COILS AND USE OF IRON CORES

The double-cone coil is similar in geometry to the figure-8 coil but rather than being flat, each side of the coil is rotated to form an angle. The coil is able to create higher intensities of electric field at depth than is possible with a standard figure-8 coil, with some studies showing it to be capable of stimulating the leg motor area, located 30 to 40 mm below the surface of the scalp.[20,21] Roth et al.[22] estimate the stimulation threshold of neurons to be 20 to 60 V/m, requiring 30% to 50% of the maximum output achievable with a common commercial magnetic stimulator, when used with the double-cone coil. It is indicated that attempting stimulation of deeper-lying regions can be painful because of the high-intensity field being

induced in higher cortical areas and the possible stimulation of facial muscles. A drawback of the geometry of the double-cone coil is that it produces larger field intensities at the sides of the head. The field in these regions can approach 50% of the maximum field produced below the coil center when stimulator output is 150%.[3] In this case, the field below the side loops is theoretically capable of stimulating brain tissue. Therefore, care must be taken when using the double-cone coil to ensure that only brain regions below the center of the coil are affected. Although the double-cone coil will improve the depth at which stimulation can be achieved, it will also increase the volume of tissue that is stimulated.

To reduce the field intensity away from the coil center in figure-8 coils, double-butterfly coils and later, eccentrically wound coils have been proposed.[23,24] Other methods for manipulating the field produced by figure-8 coils have included the use of a conductive shielding plate[25] and "active" shielding by magnetic fields produced by secondary coils.[26] Layering multiple figure-8 coils has also been proposed.[27] To achieve an effective "sham" coil for use in clinical studies, coils with the ability to engage a reverse-current mode have been developed,[28] providing the sensation of stimulation without producing a field of sufficient intensity for neuronal activation. Many TMS coils rely solely on the magnetic field produced by the current carrying conductor (typically copper) in the coils to produce the stimulating field. However, coils making use of ferromagnetic iron cores have been proposed in coils of varying designs and sizes[29-32] and used in widely used commercial systems.[33]

COILS FOR DEEP TMS

The ability to noninvasively stimulate deep brain regions has proved challenging as the intensity of electric field in the brain decays rapidly as a function of distance from the stimulator coil.[18,19,34-36] If commonly used coil designs are used for stimulation of deep brain regions, the intensity of field that is required stimulates cortical regions and also facial nerves to an extent that can cause pain.[22] However, the ability to stimulate deep brain regions noninvasively could lead to the development of various therapeutic applications for neurobehavioral disorders[37] and noninvasive treatment of tremor arising from Parkinson's disease and dystonia in place of deep brain stimulation where electrodes are inserted into the brain. When designing stimulator coils for this purpose, various factors must be considered. The stimulation threshold of neurons needs to be fully understood to ensure new coil designs are capable of achieving stimulation where desired. Conflicting values of stimulation threshold can be found in the literature,[22,38] with values of required intensity ranging from 20 to 100 V/m. Variations in this value are likely to occur due to the alignment of the neurons and the overlying gyral folding pattern. The limitations of the available magnetic stimulators must also be taken into account, meaning new coils must conform to existing inductance values, typically in the range of 15 to 25 μH.

The Halo coil, a large circular coil capable of being placed over the head, was developed to increase the magnetic field at depth in the brain when used together with an existing circular or figure-8 coil.[39] The Halo coil has been shown to provide less decay of field as a function of distance than a figure-8 coil. Magnetic field measurements revealed that the Halo coil in combination with a circular coil increases the magnetic field strength by 10% at a depth of 20 mm and by 50% at a depth of 50 mm, when compared to the circular coil energized alone. Roth et al.[22] have also proposed a coil design, termed the Hesed Coil (H-Coil), for the stimulation of deep brain regions, identifying that previously used coils mainly stimulate the cortical brain regions only. The electric field induced by several of these coil designs was calculated using the method proposed by Eaton,[34] assuming a current discharge of 10 kA in 100 μsec, resulting in an optimized design for deep brain stimulation. Crucially, Roth et al.[22] identified the effect of coil orientation on induced electric field, stating that coil elements that are perpendicular to the brain tissue surface create an accumulation of surface charge, which adversely effects or cancels the perpendicular component of the induced electric field. For this reason, the H-Coil minimizes the presence of coil elements not tangential to the tissue surface. Zangen et al.[40] report on use of a modified H-Coil for stimulation of the abductor pollicis brevis (APB) area of the motor cortex to test the efficacy of the coil. The motor threshold was measured in patients as the H-Coil was progressively moved away from the surface of the head. The intensity that was required for stimulation of the APB at various distances from the scalp using the H-Coil and a figure-8 coil were compared. As distance from the scalp increases, the stimulator output that is required to achieve stimulation was shown to be reduced when using the H-Coil. When using the maximum stimulator output available, the figure-8 coil was able to stimulate the APB at a distance of 20 mm from the scalp, whereas the H-Coil was able to stimulate the APB at a distance of 55 mm. A comprehensive comparison of the H-Coil and a standard figure-8 coil is provided by Fadini et al., [41] indicating "no advantage of this coil with regard to depth of stimulation in comparison to the figure-of-eight coil," but also noting that more study is indicated.

CONCLUSION

Although the practice of using changing magnetic fields to stimulate the brain has been taking place for many years, using this phenomenon to modulate the brain and provide therapy is a practice still very much in infancy. The technology to do so is rapidly evolving and proliferating, and it now will behoove psychiatrists

to become ever more facile with providing a procedure-based treatment and maintaining the technical know-how that goes with it. Although the entire field of brain stimulation is far too expansive to cover in just a few pages, we hope this overview has provided a good starting point.

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