Transcranial Magnetic Stimulation: Basic Principles and Clinical Applications in Migraine

Anthony T. Barker, PhD, FIET, FIPEM; Kevin Shields, MB, PhD, MRCPI

Purpose.—Transcranial magnetic stimulation (TMS) is a neurophysiological technique with a long established pedigree of safety, tolerability, and efficacy. Initially TMS was used to study the function of the cerebral cortex, but it has now become a treatment for migraine, one of the most common and debilitating neurological conditions. In this review we discuss the scientific background and development of the technique. We explore its application for the treatment of migraine and ponder the possible mechanisms of action in this most common neurological condition.

Overview: The generation of brief magnetic pulses by a suitable coil can induce electrical fields in the body. When applied to the cerebral cortex, currents are painlessly induced in cortical neurons. These currents can lead to neuronal depolarization and may influence cortical excitability by means that are as yet not fully understood. This ability to modulate cortical excitability has been exploited as a treatment for migraine with aura. Aura is implicated in the pathophysiology of migraine. Experimental studies have shown that transcranial magnetic pulses can block waves of cortical spreading depression – the experimental equivalent of migrainous aura.

Discussion.—Migraine is a debilitating condition characterized by headache, nausea, and sensory hypersensitivity. It may affect up to 15% of the population, yet current drug treatments are often poorly tolerated. Clinical studies have shown that TMS is an effective treatment for migraine. In addition, it has the added advantages of being safe and well tolerated by patients.

Key words: transcranial magnetic stimulation (TMS), single-pulse transcranial magnetic stimulation (sTMS), migraine, aura, cortical spreading depression (CSD)

Abbreviations: CSD cortical spreading depression, MA migraine with aura, sTMS single-pulse transcranial magnetic stimulation, TMS transcranial magnetic stimulation

Formerly Consultant Clinical Scientist in the Department of Medical Physics and Clinical Engineering at Sheffield Teaching Hospitals NHS Foundation Trust, Professor Associate at the University of Sheffield Medical School, UK (A.T. Barker); Consultant Neurologist and Clinical Neurophysiologist at The National Hospital for Neurology and Neurosurgery, Queen Square, London, UK (K. Shields).

Address all correspondence to: Corresponding Author (Basic Principles): Anthony T. Barker, PhD, email: a.t.barker@sheffield.ac.uk; Corresponding Author (Clinical Applications): Kevin Shields, MB, PhD, MRCPI, email: kshields@doctors.net.uk

Accepted for publication November 4, 2016.

Headache

INTRODUCTION

Transcranial magnetic stimulation (TMS) occurs when an external pulsed magnetic field near tissue leads to induction of electrical current within the brain. Since its introduction in the early 1980s, the technology has been applied to diagnosis and treatment in many areas of healthcare. One such area is treatment of migraine.

TMS is by no means a new topic of conversation in the scientific literature. A 2015 search of PubMed yielded nearly 11,000 papers that mention TMS following its first description in 1985.[1] In an effort to make this expansive body of knowledge more manageable, the authors of this TMS paper have divided it into three sections. The first section introduces the mechanism of action of TMS. The second section provides a brief history of the development of TMS technology. And the third section addresses the applications of TMS within the clinical setting for treatment of migraine. Although the authors make no claim that this paper is a definitive resource for TMS, our intent is to provide a useful overview of technology and application.

MECHANISM OF ACTION OF TMS

In TMS, the magnetic stimulation induces electrical fields (voltages measured between two points) which, in turn, cause electric currents to flow in the body. More specifically, a magnetic stimulator comprises a capacitor discharge system connected to an external coil of wire, which generates a pulse of current within the coil and hence a pulse of magnetic field. When this coil is placed near the body, this causes currents to flow in the tissue (Fig. 1). If these currents are of suitable size, duration, and location, they will depolarize neural tissue and generate an action potential, which then propagates by the body's normal nerve conduction mechanisms.

Conflict of Interest: Both authors are paid scientific advisors for eNeura. Dr Barker is a Scientific Advisor to the Magstim Company, Ltd, in addition to his work with eNeura. Dr Shields has no other consultancies to report.

Financial support for research. Drs Barker and Shields are scientific advisors to eNeura (see Disclosures). They are compensated for their counsel.

Disclosures: Drs Barker and Shields serve as scientific advisors to eNeura (Sunnyvale, CA, USA) and are compensated for their counsel. eNeura is the manufacturer of the SpringTMS®, a portable single-pulse transcranial magnetic stimulation device. In the US, it is indicated for the treatment of pain associated with migraine headache with aura. In the UK, the SpringTMS is intended for therapeutic treatment and prevention of migraine headache.

Headache registration policy of the ICMJE. Not applicable since no new original research is reported here.

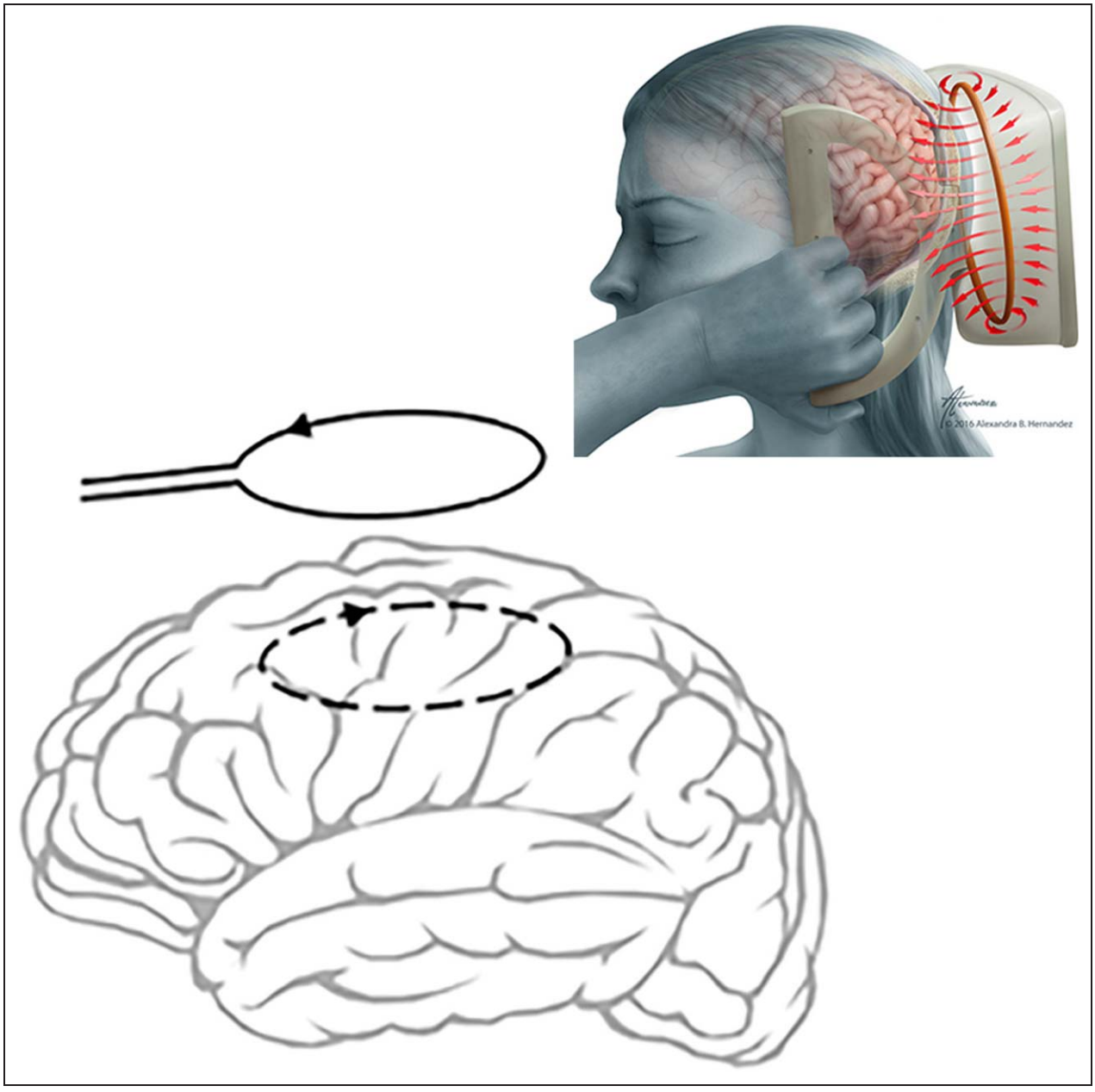

Fig. 1.—The basic principle of transcranial magnetic stimulation, showing a time-varying pulse of current in an external coil inducing currents in the brain. Inset: Time-varying pulse in TMS, with coil at occiput. (Courtesy of Anthony Barker, PhD; inset by Alexandra Hernandez.).

Strictly speaking, the term "magnetic stimulation" is a misnomer, as the stimulation at the neuronal level is actually electrical. However, in the clinical setting, the terminology provides "convenient shorthand"[2] to distinguish it from conventional electrical stimulation, where current is injected into the tissue via electrodes. The physiological effects of these currents are addressed in the last section of the paper.

Variables to be considered in the deployment of TMS include repetition rate of stimulation, risetime, coil geometry and position, depth penetration, and safe stimulator design.

RATE OF STIMULATION

Early versions of magnetic stimulators were essentially designed to provide single pulses and could only be fired once

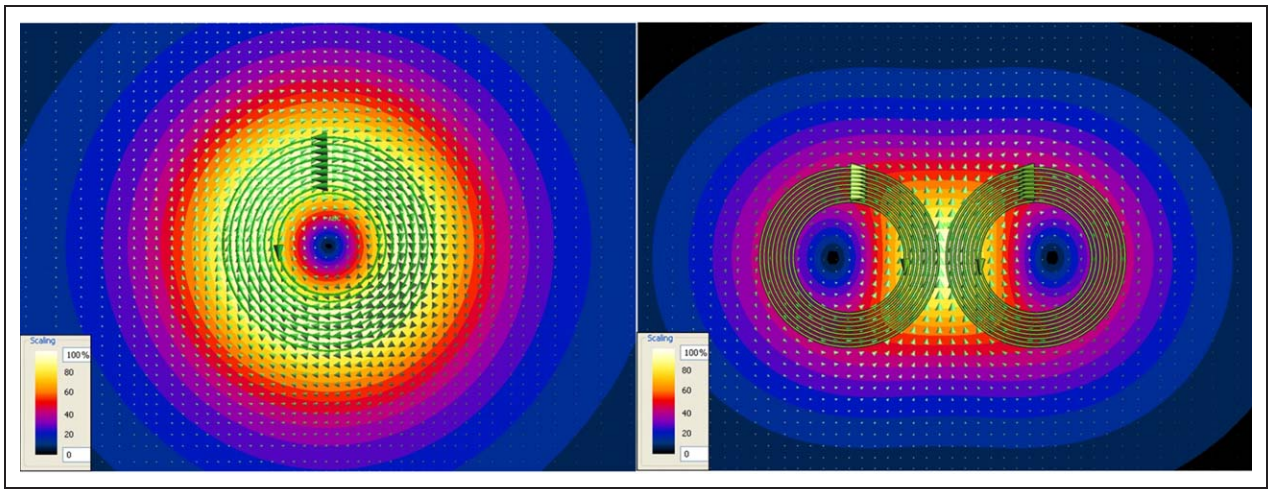

Fig. 2.—Comparison of electric fields induced in a homogeneous tissue slab underneath the plane of a circular and a figure-of-eight coil. Colour scale shows field intensity; arrows show the direction of the induced current.[1] (Figure courtesy of Anthony Barker, PhD).

every several seconds. They generated monophasic magnetic field pulses with risetimes of approximately 100 μs and decays of approximately 800 μs. Improvements in design and technology have led to so called "repetitive" stimulators (rTMS) that can stimulate, for short periods, at up to tens of pulses per second. By substituting an oscillatory field output for a monophasic one, efficiency can be improved by reusing some of the energy in each pulse (an important consideration, as TMS stimulators use considerable amounts of electrical energy), and stimulation can be induced at lower levels of the peak magnetic field due to the interaction between the neural membrane time constant and the TMS waveform.[3]

RISETIME

This term refers to the time taken for a magnetic (or electrical) stimulation pulse to reach its peak amplitude. Generally speaking, risetime of the pulse from a single pulse stimulator is proportional to the square root of the product of two electrical parameters, the inductance of the coil (measured in Henries), and the capacitance of the capacitor (measured in Farads).[4] Typically, several hundred joules of energy need to be delivered to the stimulating coil, in close proximity with the patient and in roughly 100 μs.[4,5]

Using magnetic stimulation, in volunteer subjects, peripheral and cortical stimulation has been achieved over a tested range of risetimes of 59 to 175 μs in one of our studies.[4] This study showed that the shortening of risetime decreases the stored energy in the stimulator that is needed to achieve stimulation. This is because charge leaks from the nerve membrane with time and, hence, the faster the charge is applied, the less leaks away. This is analogous to pouring water into a leaky bucket to make it overflow. The faster the water is poured, the less volume of water is needed to make it overflow – equivalent to triggering a nerve action potential.

COIL GEOMETRY AND DEPTH OF PENETRATION

Because of the nature of the physics of magnetic fields, stimulation at a precise focal point is not possible – magnetic fields cannot be focused to a point as can light with a lens. Instead of precise stimulation, one thinks of areas where stimulation is likely to occur, especially when one is referring to the use of a single circular coil. Counterintuitively, one does not stimulate under the center of a circular coil. Quite the contrary is true; the level of induced fields directly under the center of a circular coil is zero, and the currents are induced in circular loops, with their maximum value occurring approximately under the mean diameter of the coil.[6]

In contrast, a figure-of-eight coil[7] in which two coils are placed beside each other, wired such that the stimulator current rotates in opposite directions in the two coils, produces a more localized peak induced field and can decrease the uncertainty as to the site of stimulation.[5] Indeed, the area directly under the center of the side-by-side coils experiences approximately twice the induced electric fields that occur elsewhere in the vicinity of the coils. Figure 2 shows a comparison of the location and size of the electric fields under a single circular coil and a figure-of-eight coil in a simple, homogeneous, model of tissue. In transcranial stimulation, as opposed to stimulation of other anatomical regions such as the wrist and arm for which the

single coil may be more appropriate, a figure-of-eight coil allows more focal stimuli to be delivered to the target area.

Depth of penetration of magnetic stimulation into the tissue is dependent on several variables, including coil geometry and size, local anatomy, stimulus strength, and perhaps even gravitational effects on the brain within the skull space.[8] While it is not possible to give a specific figure for depth of penetration because of these variables, a few generalizations can help understand the issues involved:

1. Induced fields from conventional coils decrease with distance from the coil. Hence stronger stimuli will occur in superficial tissue than at depth.
2. Modeling studies show that the induced fields from typical commercial coils are some 2-5 times greater in the superficial cortex than at a target depth of 5 cm,[9] depending on their size, configuration, and proximity to the head.
3. Larger coils stimulate to a greater depth as the decrease in stimulus intensity with distance from the coil is less.
4. Circular coils stimulate deeper than figure-of-eight coils that have the same overall dimensions or "footprint" on the head.

STIMULATOR DESIGN

Two key factors in stimulator design are the amount of energy involved and the speed with which the energy is delivered. Several hundred joules of energy need to be delivered to the stimulating coil, in close proximity to the patient, in a time of roughly 100 μs.[5,6] To deliver the peak energy required in such a short time, voltages in the stimulator need to be high (typically several kilovolts). To generate the required peak magnetic fields, peak coil currents of several thousand amps can be required. These large values of electrical parameters present some interesting engineering challenges, but improvements in semiconductor design and other electrical components have made modern stimulators somewhat easier to build than were the early devices.

DEVELOPMENT OF TMS TECHNOLOGY

In 1831, Michael Faraday discovered electromagnetic induction with a simple experiment in which he wound two coils of wire on opposite sides of an iron ring. He connected a battery to one coil via a switch and a voltmeter to the other. When he closed the switch, he saw the voltmeter needle deflect momentarily in one direction and then return to its resting position. When he opened the switch, it moved in the opposite direction and then returned to zero. He realized that, when the switch was closed, current flowed from the battery into one coil, generating an increasing magnetic field and an induced voltage in the other coil. When the magnetic field reached its peak and stopped varying, the induced voltage ceased. Similarly, when the switch was opened, the current – and hence the magnetic field – collapsed and a voltage of the opposite polarity was induced in the other coil for a brief time. He soon realized that the iron core, whilst a convenient way of routing the magnetic field between the two coils, was not necessary and demonstrated that the same effect could be achieved by two coils placed close to each other in air.

However, the empirical trajectory from injecting electrical currents into tissue via electrodes to stimulate nerves to using magnetic stimulation to induce current in the tissue has not been linear. Studies of the effects of electricity on nerves and muscles by Galvani and Volta in the 1790s demonstrated that neuromuscular tissue was electrically excitable.[10] With this knowledge as a pre-cursor, investigators sought to utilize Faraday's discovery to explore the physiological effects of induced current stimulation. d'Arsonval noticed that placing a person's head within an electromagnet led to the subject reporting seeing flickering lights (magnetophosphenes) and feeling vertigo.[11] Cessation of current led to cessation of both the lights and the vertigo, a finding reinforced by the work of Thompson in 1910.[12] Research efforts by Kolin et al[13] and Bickford and Freeming[14] expanded the knowledge base of noninvasive induced current stimulation with in vivo and in vitro settings.

These efforts all presaged the work that would be done by Anthony T. Barker, first as a doctoral candidate at the University of Sheffield in the mid-1970s and then with colleagues at the Royal Hallamshire Hospital in Sheffield (UK) in the mid-1980s. In 1974, Barker created an early magnetic stimulator comprising two capacitor banks, charged to 200 V, and a "C" shaped laminated steel electromagnet steel core with a 50 mm air gap. He reported that firing the stimulator resulted in "sensation and slight muscular contraction of the hand when the wrist was placed in the airgap."[6,15] Later experiments with colleagues yielded a more powerful air-cored magnetic design, with a capacitor bank charged to 340 V and a peak discharge current of 6800 A.[16] Stimulation of superficial nerves in the wrist resulted in supramaximal evoked potentials being observed in the thenar eminence at the base of the hand and thumb, thus forming the first practical demonstration of peripheral magnetic nerve stimulation.

Advances in design and power levels continued at a rapid rate. In 1985, a more efficiently designed, high-voltage stimulator designed by Barker and colleagues in the Sheffield group was used to demonstrate magnetic stimulation in the human cortex, resulting in distinct hand movements and evoked action potentials from the abductor digiti minimi.[17] Subjects

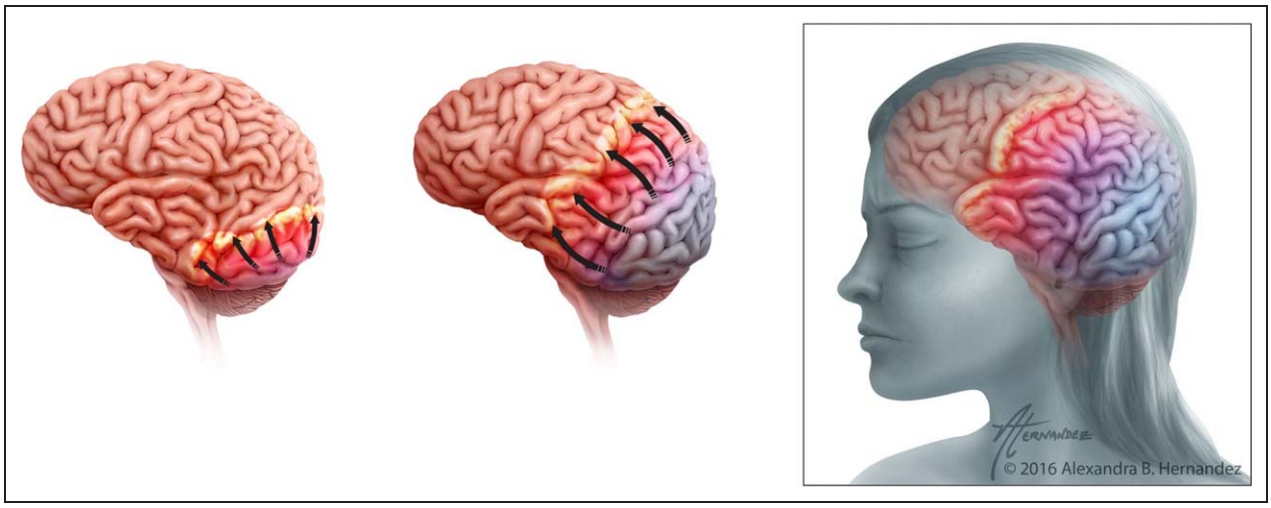

Fig. 3.—Propagating cortical spreading depression. (Figure courtesy of Alexandra Hernandez).

reported no "pain or discomfort with the first cortical magnetic stimulation."[6] The importance of the absence of pain cannot be overstated since subject discomfort was an ongoing complaint with earlier studies of motor cortex stimulation using current injected through surface electrodes in the technique pioneered by Merton and colleagues.[18]

The absence of pain and discomfort heightened clinical interest in magnetic stimulation by professionals in neurophysiology and clinical neurology throughout the UK and worldwide. Responding to inquiries by clinicians, the Sheffield group at the Royal Hallamshire Hospital built six magnetic stimulators for research groups to use not only to demonstrate proof of concept but, more importantly, to explore possible applications in clinical settings.[19,20] Requests for stimulators continued to flood in; rather than patent the device, the Sheffield group introduced a number of manufacturers to the technique to encourage its uptake. In the 30+ years since the early experiments and successes, medical device manufacturers have successfully explored commercial development of magnetic stimulators. By the late 1990s, at least three commercial stimulators were in widespread use.[6] By 2016, some 10 manufacturers were producing commercial magnetic stimulator systems for a variety of clinical and research applications.

TMS IN THE CLINICAL SETTING

Single pulse TMS has been used for many years for routine diagnostic purposes. It is regularly used in clinical neurophysiology departments to non-invasively study the functional integrity of the corticospinal tracts. It is a safe and painless technique, which is well tolerated with minimal side effects.

CORTICAL ACTIVITY IN TMS

In their expansive and well-researched article, "Transcranial Magnetic Stimulation in the Treatment of Migraine," authors Lipton and Pearlman cite several important findings from colleagues in the field to offer a rationale for the use of TMS in the migraine population.[21] Migraine can be characterized as a condition that is chronic in nature but that appears episodically.[22] Fluctuations in neuronal excitability may play in the pathogenesis of migraine though the precise mechanisms are still not fully understood.[23,24]

It has been recognized for some time that TMS can influence cortical activity. There is evidence that it may alter the levels of neurotransmitters, regulate synaptic plasticity, and effect changes in neuronal networks.[25] TMS pulses may therefore modulate the very neuronal excitability that leads to attacks of migraine. How long the effects of TMS last is uncertain but it is possible that repeat stimulation may increase the duration of the effect.[1] The model for modulating brain excitability may have a precedent in pharmacology. Pharmaceutical treatments for migraine may modulate the neuronal excitability that leads to attacks of migraine.[26,27] However, how neuronal excitability induces clinical effects is not yet well identified.[28] The same principle may apply to TMS in the cortex, though, again, the neuromodulatory mechanism has not been well defined.

Migraine aura may be experienced by up to 20% and 30% of migraineurs. It usually, although not always, precedes the onset of headache and is the clinical manifestation of cortical spreading depression (CSD; Fig. 3). This phenomenon can involve any part of the cerebral cortex but the occipital (visual) cortex is most commonly affected. Unfortunately, no explanation has been found for this predilection. During CSD, a

wave of excitation propagates across the cortex at a constant rate. This is followed by a period of electrical silence. CSD has been implicated by some as the source of pain during the migraine attack.[29,30]

TMS pulses can block waves of CSD once initiated but not prevent them.[31] TMS may thus disrupt CSD by interrupting its progression across the cortex. It may also influence thalamocortical sensory traffic. Such disruption and modulation would then thus obviate the ensuing consequences of CSD, namely, sensory hypersensitivity, and other migraine symptoms such as headache and dizziness.

CLINICAL TRIALS WITH sTMS FOR MIGRAINE

In 2010, Lipton et al published the results of their two-part randomized, double-blind, parallel-group, sham-controlled US trial of sTMS in treatment of migraine with aura (MA).[28] In Part one, 267 patients with MA were enrolled, screened, and trained in the use of personal electronic diaries. No treatment was administered in this phase. In Part two, 201 of these individuals were randomized to receive either sTMS or sham stimulation with a device identical in appearance to the device used for sTMS. (Sixty-six of the original patients did not proceed to Part two.) Study participants were trained in the use of the sTMS (or sham device), with instructions to apply the sTMS portable device just underneath the area of the occipital bone. The sTMS device used was the Cerena Transcranial Magnetic Stimulator, a predecessor to the current SpringTMS (eNeura, Sunnyvale, CA, USA). Both the sSTM device and the sham device vibrated, rather than made any sound, to maintain blinding. Participants first pressed a button on the device to recharge the capacitors and then, when charged, another button was pressed to activate the magnetic field pulse. Patients repeated the process a second time, directly following the first pulse.

Participants were allowed use of the device for up to three attacks over a period of three months. During the study period, participants recorded their attack first at baseline and then post two-pulse delivery at 30 minutes, 1 hour, 2 hours, 24 hours, and 48 hours. Baseline pain and symptoms within the first hour of onset of aura were recorded, as was use of rescue drugs. Rescue drugs were permitted 2 hours post treatment; pharmaceutical formulations that could confound assessment of efficacy and safety, eg, pain medications, anti-nausea meds, triptans, and ergots, were not permitted. At 48 hours, patients provided global assessment of pain relief on a 5-point scale (excellent, very good, good, fair, poor).

The primary efficacy endpoint was pain freedom 2 hours post treatment. Other primary endpoints assessed were photophobia, nausea, or phonophobia at the 2 hour time point. Secondary endpoints were presence of mild pain or absence of pain (headache response) 2 hours post first aura episode, sustained pain-free

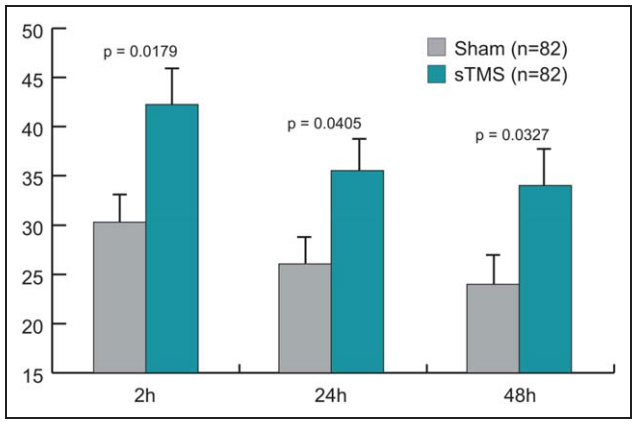

Fig. 4.—Differences in pain-free response in patients treated with sham device and patients treated with sTMS device. (Figure courtesy of *The Lancet* [*Lancet Neurol*. 2010;9:373-380]).

response at 24 hours and 48 hours, use of rescue drugs during the attack, proportion of pain free responses in 2 out of 3 episodes, and the aforementioned global assessment.

A total of 164 patients used either the sTMS device or the sham device for treatment of at least one attack. (Of the 201 patients enrolled, 37 did not report a migraine and were thus excluded from analysis.) The pain-free results for the sTMS device were statistically significant compared to the sham device at 2 hours, 24 hours, and 48 hours (Fig. 4).

Non-inferiority of symptoms other than pain was also shown. Safety profiles of the subjects were broadly similar between the device and the sham group. Researchers concluded that "sTMS could be a promising acute treatment for some patients with migraine with aura."

In a smaller nonblinded, hospital-based trial in Canada,[32] a total of 42 individuals (10 with aura, 25 without aura, and 6 with "headache with migraine components") received at least one treatment of sTMS, using a device different from the one in the study cited earlier (Caldwell Stimulator, model #MES-10). Some individuals received up to three treatments. Pain and suffering were noted at baseline and then at 5-minute intervals for 20 minutes post treatment. Efficacy varied, as 69% evidenced improvement after the first trial, 87% after the second trial, and 83% after all three trials. In the individuals with MA, some relief was experienced by 100% of the subjects. There was an overall mean decrease in pain intensity of 75%.Researchers concluded that "TMS meets the criteria of immediate, sustained pain relief with no known side effect." This last point is in agreement with the general observation that sTMS is well tolerated.[33] This is relevant clinically, as some acute treatments, such as triptans, may be contraindicated or not be tolerated by all patients. Indeed, it is an interesting and rather telling observation that many neurologists do not actually use triptans to treat

their own migraines.[34] In addition, individuals in special populations, eg, patients with vascular disease (myocardial infarctions and ischemic strokes) and gastrointestinal disease (ulcers and irritable bowel syndrome) must be mindful of contraindications for acute therapies. sTMS appears safe and well tolerated in these special populations.

Two other sTMS articles in the clinical literature warrant special mention. In the first article, a UK study in 2015, investigators sought to assess patient response to sTMS in conventional clinical settings.[35] The study allowed migraine patients with and without aura to participate. Three-month data were reported on 190 patients; of these, 59 experienced episodic migraine and 131 experienced chronic migraine. Sixty-two percent of all participants reported pain relief. Slightly more than half of the participants reported reductions in nausea, photophobia, and phonophobia. Occurrences of episodic migraine were reduced by 25% across subjects and chronic pain by 33%. In their conclusions section, the researchers mention a possible cost-advantage of sTMS in the preventive setting, citing a cost comparison of sTMS and botulinum toxin type A.[36]

In the second article, researchers reviewed two decades of available literature on adverse events during treatment of migraine with sTMS.[33] Variables examined include brain tissue and cardiovascular levels, seizures, and cognitive and psychomotor parameters. Researchers determined that "no discernable evidence exists to suggest that sTMS causes harm to humans," adding, "Single-pulse sTMS may offer a safe nonpharmacologic, nonbehavioral therapeutic approach to the currently prescribed drugs for patients who suffer from migraine."

SUMMARY

Transcranial magnetic stimulation (TMS) refers to the induction of electrical current in the cerebral cortex, by an externally applied pulse of magnetic field. If the induced currents are of sufficient size and duration, depolarization of neural tissue, resulting in an action potential, can occur.

TMS was first introduced into medical environments in the mid-1980s, although experiments with the neural stimulation technology date back to the 1790s, with work by Galvani and Volta. In 1974, Anthony Barker developed a fully operational magnetic stimulator, which he and his colleagues in England continued to refine into the mid-1980s. In 1985, Barker and colleagues demonstrated magnetic stimulation in the cortex.

One relatively recent area of study of TMS is its use in treatment of migraine. TMS pulses may affect neuronal excitability, one factor associated with the onset of migraine. How excitability modulates neuronal changes is not yet well characterized, either for pharmaceutical formulations or for TMS.

Cortical spreading depression (CSD) is the experimental equivalent of migraine aura. This phenomenon propagates through the cortex and may have a role in the genesis of head pain in migraine. TMS can inhibit waves of CSD, thus potentially mitigating the severity of attack.

A well-designed US trial of single-pulse TMS (sTMS), a two-part, randomized, double-blind, parallel group and sham-controlled study by Lipton and colleagues was reported in 2010.[28] In that study, 201 subjects were randomized to TMS and sham TMS devices. Subjects placed the device below the occipital bone. They could use the device for device for a three month period. The primary efficacy endpoint was absence of pain at 2 hours. Secondary endpoints were degree of pain at various time points over the course of the study. Baseline and post two-pulse delivery data were recorded at 30 minutes, 1 hour, 2 hours, 24 hours, and 48 hours. At the end of the 48 hours, patients assessed their levels of pain on a 5-point scale. Pain-free results were statistically significant for TMS device compared to sham at all time points. In addition, a comprehensive review of the adverse events literature[33] published that same year could find "no discernible evidence" of harm from sTMS. Other trials have also supported the efficacy of TMS in migraine.[12,35]

Thirty years after the initial British work in Sheffield, UK, TMS has achieved a place of prominence in research and in clinical practice. We look forward to reading reports that extend the body of knowledge on migraine and on other diseases as well. Even at this stage of exploration, TMS offers a safe, viable, and noninvasive alternative to conventional pharmaceutical and neuromodulatory treatment options that have long been the mainstay of migraine treatment protocol.

Acknowledgments: The authors sincerely appreciate the editorial contributions by David J. Howell, PhD (San Francisco, CA) in the development of this paper. Dr Howell is a self-employed medical writer.

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