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Transcranial Magnetic Brain Stimulation: Therapeutic Promises and Scientific Gaps

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Abstract

Since its commercial advent in 1985, transcranial magnetic stimulation (TMS), a technique for stimulating neurons in the cerebral cortex through the scalp, safely and with minimal discomfort, has captured the imaginations of scientists, clinicians and lay observers. Initially a laboratory tool for neurophysiologists studying the human motor system, TMS now has a growing list of applications in clinical and basic neuroscience. Although we understand many of its effects at the system level, detailed knowledge of its actions, particularly as a modulator of neural activity, has lagged, due mainly to the lack of suitable non-human models. Nevertheless, these gaps have not blocked the therapeutic application of TMS in brain disorders. Moderate success has been achieved in treating disorders such as depression, where the U.S. Food and Drug Administration has cleared a TMS system for therapeutic use. In addition, there are small, but promising, bodies of data on the treatment of schizophrenic auditory hallucinations, tinnitus, anxiety disorders, neurodegenerative diseases, hemiparesis, and pain syndromes. Some other nascent areas of study also exist. While the fate of TMS as a therapeutic modality depends on continued innovation and experimentation, economic and other factors may be decisive.

Keywords

Brain stimulation; neuromodulation; neurology; psychiatry; depression

1. Introduction

Since becoming widely available in the late 1980s, transcranial magnetic stimulation (TMS) has evolved from an almost magical curiosity and a simple tool for neurophysiologists to a mainstay of noninvasive neuromodulation, gaining acceptance as a candidate treatment in psychiatry, neurology, and perhaps, other clinical specialties. This evolution has come as the result of some very interesting research, but with surprisingly little direct understanding of how TMS produces lasting physiological, let alone behavioral, effects. This review will cover the points necessary for a basic understanding of how TMS causes neuronal firing and resulting simple phenomena, as well as the theories for how it alters neural states and behaviors in a lasting way. It also identifies the widest gaps in our knowledge of how this actually occurs. This is followed by a survey of the clinical literature, focusing on areas where there are sufficient data to form an impression of its therapeutic potential. We also

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encourage the curious reader to look into the literature on other forms of transcranial stimulation currently in vogue, but with long and interesting histories, i.e., transcranial direct current stimulation and its alternating counterpart, cranial electrotherapy stimulation.

2. Basic mechanisms

2.1 Physical considerations

Put simply, TMS harnesses the principle of induction to transport electrical current across the resistive layers of the scalp, skull, and meninges, into the brain, where it can alter the electrical environment of neurons, causing them to fire. The basic apparatus consists of a wire coil encased in plastic, which is placed on the subject's head over the brain target. The coil is attached by an electric cable to a box containing one or more large capacitors, charged by a power source and discharged through the coil when the device is triggered. The first coils were large rings, which, when centered near the vertex, could stimulate the hand motor areas in either or both hemispheres, depending on whether the current pulse was uni- or biphasic. An early advance was to use two adjacent coils forming a figure-8 where the junction contains twice the number of windings as the "wings". This permits focal stimulation when the junction is placed tangentially over the cortical target. Some designs, including that of the only U.S. Food and Drug Administration (FDA)-cleared device for TMS treatment, increase the efficiency of stimulation and reduce the power demand by adding a solid, ferromagnetic core to the coil. Firing of neurons by induction requires a strong and very brief current pulse in the stimulating coil, because, according to Faraday's law, the induced current is proportional to the rate of change of the stimulating magnetic field. This places stringent demands on stimulator design and was one reason why TMS became commercially available many decades after the principles were understood and why the technology remains relatively expensive (on the order of tens of thousands of U.S. dollars).

While the underlying principles are simple and the magnetic field is not affected significantly by passing through the tissues of the head, the topology of the induced electrical field in the brain is determined by the complex shape and variable conductivity of the cranial contents. This complexity greatly hinders an anatomically precise understanding of where TMS acts to produce any of its behavioral effects. Ohm's law states that the current induced in the head is divided among the infinite number of possible pathways according to their conductances. This means, for instance, that regardless of where the current is "aimed", it will flow preferentially through areas containing cerebrospinal fluid, which has a much higher conductance than brain. Therefore, the current may concentrate at points that do not lie directly below the coil. It has also been observed that holes in the low-conductance cranial bone, i.e., neural foramina, the orbits, etc., concentrate current and may direct it in unanticipated ways. Finite element models (Silva, et al., 2008; Wassermann, et al., 1996) provide detailed predictions of current flow under given conditions, but definitive biological validation would require intracranial recordings during TMS. Aspects of brain ultrastructure can determine where TMS acts. For instance, axons are especially susceptible to stimulation at bends in their courses (Amassian, et al., 1992). Given these sources of uncertainty, it is sometimes surprising how well effects can be targeted in practice.

2.2 Single-pulse stimulation

The first TMS systems (Barker, et al., 1985) were able to charge their capacitors only once every few seconds. This proved sufficient for simple experiments in the central motor system, analogous to clinical nerve conduction studies. The electrically recorded muscle twitch, or compound motor action potential, in response to cortical stimulation is called the motor evoked potential (MEP). MEPs were first produced by stimulating the motor cortex

through the head with electrical shocks (Merton & Morton, 1980). This technique, while simpler than TMS, is painful and has been largely relegated to monitoring during spinal surgery.

Single-pulse TMS of the motor cortex proved a fertile area for research on the human corticospinal motor system. Cleverly designed experiments (e.g., Rothwell, et al., 1991) permitted strong inferences about elements of the system between the stimulated cortex and twitching muscle. The most important and relevant principle to come from this work is that the amplitude of the MEP is an aggregate measure of the excitation state of output cells in the motor cortex, assuming spinal activity is held constant. This principle underlies virtually all of the physiological research on which therapeutic TMS is based. Inferences from physical and physiological data have also established that firing of axons by TMS occurs in the cerebral cortex, within 1–2 cm from the coil (Epstein, et al., 1990). It may be possible to stimulate deeper structures when they lie adjacent to cerebrospinal fluid-containing spaces, e.g., the ventricles, whose high conductance could provide privileged current pathways, but only one potential instance of this has been reported (Marg & Rudiak, 1994). Some have implied that specially constructed coils can reach deeper into the brain because they can produce MEPs when displaced further from the scalp than conventional coils (Zangen, et al., 2005). However, these experiments failed to consider the extent of the cortical area stimulated by each coil type and a careful comparison with conventional coils (Fadini, et al., 2009) showed no evidence of deeper stimulation, such as the shift in MEP latency expected with subcortical stimulation of the pyramidal tract.

Among other basic discoveries with implications for the therapeutic use of TMS is the fact that it preferentially depolarizes axons running in the plane of the stimulating current, which is, in turn parallel to the plane of the coil. Consequently, TMS has a preference for tangentially oriented axons, whereas radially oriented cortical output (pyramidal) neurons tend to be activated indirectly. This fact and the evidence that TMS activates axons quite near the brain surface, make it safest to assume that any effects of TMS on deep structures or radially oriented fibers result mainly from synaptic transmission of the stimulus. Another consequence is that the figure-8 coil, energized with a monophasic pulse, permits differential targeting of axon populations simply by rotating the coil around the center of the junction (Werhahn, et al., 1994). This property has not been exploited or often considered in therapeutic trials.

The advent of paired-pulse techniques, using two stimulators discharging through the same coil, allowed investigators to examine excitatory and inhibitory processes within the cortex itself (Ziemann, et al., 1996) and to explore the effects of drugs and the correlates of genes and behavioral traits in cortical physiology (Kapogiannis & Wassermann, 2008).

Single magnetic pulses delivered to the occiput produce phosphenes (Marg & Rudiak, 1994) and, although this has never been explored, motor cortex stimulation produces a powerful somatosensory phenomenon, independent of the muscle twitch (personal observation). Single pulses can disrupt sensory processes very briefly (Amassian, et al., 1998), and produce facilitatory and disruptive effects in cognitive domains, such as language (Devlin & Watkins, 2008). However, because of the uniquely quantifiable nature of the MEP, virtually all we know about the local brain effects of TMS comes from studies in the human motor cortex where, within a few years, easy, inexpensive neurophysiological experimentation produced important additions to a literature arduously gathered in surgically prepared animals over previous decades.

2.3 Repetitive TMS (rTMS)

The advent, in the late 1980s, of stimulators able to deliver long trains of closely spaced pulses increased the scope of TMS from a neurophysiological probe to a tool with the potential for altering cortical activity and connectivity. The first published use of rTMS was an unsuccessful attempt to activate epileptic foci in patients being evaluated for surgical resection for intractable epilepsy (Dhuna, et al., 1991). However, it did produce a focal seizure in an uninvolved area of cortex. The first unique effect was arrest of ongoing speech in healthy subjects when stimulation in the 10 Hz range was applied near the motor speech area of the language-dominant hemisphere (Pascual-Leone, et al., 1991). This did not outlast the stimulating train. Insights into the mechanisms of these acute effects of rTMS on cortical function came, unsurprisingly, from rTMS studies in the motor cortex (Pascual-Leone, et al., 1994b) where the physiological effects of stimulus trains could be observed in the amplitude of the MEP.

2.3.1 Disruptive effect—Motor cortex data suggested that speech arrest and related disruptive phenomena result from hypersynchrony of output cell firing, produced when stimuli are delivered at multiples of the MEP recovery cycle (about 200 ms). That is, when a strong stimulus causes a large fraction of the output neuron pool to fire, it synchronizes their refractory periods. A subsequent stimulus delivered during the refractory period causes little response, but when the neurons have recovered, they are artificially synchronized and ready to fire simultaneously. In the motor cortex, strong trains of pulses at 10 Hz (every 100 ms or about one-half the MEP recovery cycle) produce huge MEPs alternating with little or no response (Pascual-Leone, et al., 1994b). Induced hypersynchrony likely prevents normal processing in the stimulated area. These disruptive phenomena were mainly interesting to investigators of cognitive processes and have been largely replaced with “offline” paradigms (see *Inhibitory effect*, below) for reasons of subject safety and comfort.

2.3.2. Facilitatory effect—The observation responsible for the first adoption of rTMS as a treatment was that trains of stimuli delivered at about 5 Hz or more caused MEP amplitude to increase, either late in the train, when the stimuli were delivered above MEP threshold, or to subsequent test stimulation (Fig. 1), implying an increase in the excitability of the output cells. This was presumably related to the epileptic phenomena produced when the safe limits on stimulus intensity, frequency, and train length were exceeded (Wassermann, 1998). The effect underlying the increase in MEP amplitude with high-frequency rTMS was thought to be a change in the sensitivity of the motor cortex output cells to excitatory influences (Wassermann & Lisanby, 2001), perhaps via a change in the efficacy of excitatory synapses, i.e., an early stage of long-term synaptic potentiation (LTP; McNaughton, 1982). While this is a sensible conjecture, there is only circumstantial evidence to support the theory. A key piece of this comes from experiments showing that rTMS, delivered with the so-called, theta burst pattern of stimulation (Larson, et al., 1986) is effective for altering cortical excitability (Huang, et al., 2005). This frequency-modulated stimulation pattern, where high frequency bursts (in this case at 50 Hz) are delivered at a lower carrier frequency (in this case 5 Hz), is particularly potent both for inducing LTP in animal synapses and increased MEP amplitude in humans, suggesting that the two phenomena are closely related (Huang, et al., 2007). Perhaps the best thing about theta burst stimulation is that it is effective when delivered at intensities below the MEP threshold and is, therefore, considered less likely to produce epileptic seizures than other rTMS paradigms for increasing cortical excitability. At the time of this writing, no seizures have been reported from theta burst TMS below the MEP threshold.

An implication of the foregoing is that excitatory rTMS should produce facilitatory effects on behavior. This idea formed the basis for rTMS treatment in depression (George, et al.,

1995b) and, indeed, there are reports of improved cerebral functions after high-frequency rTMS in healthy subjects (e.g., Boroojerdi, et al., 2001).

2.3.4. Inhibitory effect—Another important effect of rTMS on the motor cortex was depression of the MEP after trains of stimuli delivered at frequencies in the 1 Hz range (Fig. 2; Wassermann, et al., 1996). Because the seizure induction was not a concern with this technique (Wassermann, 1998), strong stimulation could be delivered for long periods to produce relatively robust and long-lasting inhibitory effects (Chen, et al., 1997). Just as the facilitatory effect of high frequency rTMS was considered analogous to LTP, this opposite phenomenon with low frequency stimulation was inevitably compared to synaptic long-term depression. Again, there is indirect evidence in favor of the analogy: A prominent characteristic of long-term depression is that it is easier to produce in synapses treated previously with very subtle potentiating stimulation (Holland & Wagner, 1998), an instance of the phenomenon referred to as “metaplasticity” (Abraham & Bear, 1996). The depressant effect of low-frequency rTMS on the MEP shows metaplasticity; i.e., “priming” with 6 Hz rTMS greatly increases the depth and duration of the MEP depression from 1 Hz rTMS delivered immediately afterward (Iyer, et al., 2003). “Continuous” theta burst rTMS, where the 50 Hz bursts are delivered continuously every 200 ms, also effectively depresses cortical excitability (Di Lazzaro, et al., 2005). Interestingly, these dramatic physiological effects on the motor cortex do not come with clinically apparent changes in measures, such as simple reaction time (Iyer, et al., 2003), although they have been employed to good effect in treatment studies, as described below.

Inhibitory effects of rTMS have also been of great interest to investigators of cognition and perception. Low frequency and continuous theta burst rTMS have provided a means of safely, focally and temporarily disabling cortical areas in order to define their role in behavior. Appropriately designed rTMS paradigms have proven useful in resolving uncertainties in the interpretation of functional brain imaging studies (Cohen, et al., 1997).

2.4. (Lack of) Animal and in vitro data

One of the historical features of TMS that distinguish it from most other scientifically and clinically accepted treatments, is the near absence of non-human data. There are several reasons for this, the most important of which is that the technique is fundamentally noninvasive and was first adopted by a community of basic and clinical neurophysiologists who had a decades long tradition of shocking and needling experimental subjects, including themselves. The basic, single-pulse technique was thereby demonstrated to be safe enough even for casual experimentation long before it was considered as a treatment for disease. Animal safety studies were further obviated by the fact that magnetic stimulators were approved for peripheral nerve stimulation in the U.S., greatly smoothing the regulatory path to experimental and off-label clinical use on the brain. Another reason is that the animal models are not reliable: For basic physical reasons, human TMS equipment, techniques and paradigms do not scale down easily to smaller brains because of greatly decreased electrical coupling in smaller volumes (Weissman, et al., 1992) and it is a matter of common sense that standard, human-sized, stimulating coils would deliver stimulation, not only to the entire brain of a small animal, but to an appreciable portion of the body, making generalizations to focal cortical stimulation in humans invalid.

One theoretically possible approach to studies in small animals would be to construct appropriately sized coils, but, particularly with repetitive stimulation, the problems of heat dissipation and mechanical stability are not easily surmounted (Cohen & Cuffin, 1991) and miniaturization to anything approaching rat size has not been accomplished. Nevertheless, there are many studies on the effects of TMS with human coils on rats. Appropriately sized

coils have been made for use in monkeys (e.g., Lisanby, et al., 2001a), but the circumstances and purposes of the experiments in which they have been used did not permit much exploration. To complicate the issue further, definitive answers to detailed questions about which neuronal populations are activated by TMS would certainly involve intracerebral recordings, but breaching the skull might affect the current distribution, if coil position were not tightly controlled. Highly valuable recordings of TMS-evoked activity in the human corticospinal tract have been made in patients undergoing spinal surgery (Di Lazzaro, et al., 2002; Nakamura, et al., 1997) and cranial neurosurgery for resection of tumors and epileptic foci provides another potential opportunity to obtain direct neural recordings; however, this has not yet been done.

While neurophysiologists speculated about the underlying mechanisms of neural modulation by TMS, it was being adopted in fields, such as clinical psychiatry and cognitive neuroscience, where users were motivated more by pragmatic concerns than curiosity about how it works. Adoption of conservative dosing guidelines for rTMS (Wassermann, 1998) reduced accidental seizures to a level that most investigators and ethics panels found acceptable even for purely experimental uses. Encouraging data from therapeutic trials created enthusiasm in the clinical community and attracted public notice. The recent clearance of an rTMS device by the FDA to treat depression without animal safety data further decreased the incentive for animal studies that might reveal its mode of action.

Many assume that TMS techniques have been developed and optimized in animals and humans by a large, well-funded enterprise and are surprised to hear how insubstantial the scientific founding of the technique remains. Thus, users, particularly of rTMS, operate on assumptions and incomplete knowledge, which are often propagated uncritically by users unfamiliar with its history. One might ask, "What's the problem, as long as it's safe and it works?" However, the apparent success of TMS may ensure that the full potential of this promising technology is never exploited: It would be surprising if current techniques, particularly for clinical treatment, were optimal, but without a basic understanding of the physical and physiological mechanisms, significant advances are less likely.

3. Therapeutic applications

3.1. Depression

Treatment of depression was the first major therapeutic goal set for TMS. In targeting a phenotypically heterogeneous, spontaneously remitting behavioral disorder with no biological surrogate markers or agreed-upon anatomical or physiological basis, and where the clinical endpoints are subject to subtle behavioral influences, pioneering investigators subjected therapeutic TMS to a very hard first test.

The era of TMS treatment opened in 1993, when an Austrian group reported a beneficial effect in two profoundly depressed patients who underwent a course of repeated single-pulse TMS before electroconvulsive therapy (Höflich, et al., 1993). They followed up with a single-blind trial of 0.3 Hz TMS, delivered with a round coil centered at the vertex, (Kolbinger, et al., 1995), producing additional encouraging results. George et al. (1995b) were the first to try rTMS in depression: They delivered rTMS at 20 Hz, a frequency in the range for increasing motor cortex excitability, to a location on the scalp estimated to lie over the left dorsolateral prefrontal cortex (DLPFC). This area showed decreased metabolic activity in positron emission tomography studies of induced sadness (George, et al., 1995a) and the rationale was that repeated administration of a treatment able to increase the excitability of the motor cortex should have a tonic effect on the frontal circuitry whose apparent sluggishness was thought to underlie the disorder. In healthy subjects, similar treatment had produced small but significant mood elevations (George, et al., 1996; Pascual-

Leone, et al., 1996). The stimulation frequency range, putative cortical target, and technique for estimating its scalp location (measuring 5 cm on the scalp, anterior to the location for causing a twitch in the hand), and the 2–3 week duration of treatment became standard procedure for a large number of trials following up on these results (see George, 2010 for review).

While studies have used low-frequency (e.g., 1 Hz) rTMS, some with the goal of reducing right prefrontal activity (e.g., Kauffmann, et al., 2004), single pulse and low-frequency TMS have been essentially abandoned for depression treatment. However, apart from small trials comparing high and low stimulation frequencies and right vs. left DLPFC targeting (Wassermann & Lisanby, 2001), there have been very few attempts to validate the somewhat arbitrary paradigm. While there is convincing evidence (see below) that this treatment is effective in certain patient populations, in our opinion, the rationale and its supporting scientific and clinical evidence are insufficient to justify freezing the paradigm at this point. However, systematically exploring the multi-dimensional stimulation parameter space (frequency, intensity, pulse train duration, train number, inter-train interval, duration of treatment, etc.) and the many potential brain targets would be a task of discouraging magnitude. Attempts to optimize the paradigm would be greatly aided by biological surrogates for the brain response to rTMS and there is at least one viable candidate: rTMS of the DLPFC releases dopamine, measured as displacement of the dopamine radioligand, raclopride, in the putamen in healthy subjects (Strafella, et al., 2001) and this has been proposed as a mechanism for its effect on mood. Other methodological challenges and considerations in rTMS trial design are outlined by Demitrack and Lisanby (2008).

Despite the uncertainties surrounding the paradigm and mechanism, there is a growing body of evidence that rTMS improves mood in depression, at least in patients not on antidepressant medication. In a 2003 meta-analysis (Martin, et al., 2003) of 14 randomized, controlled trials, rated by the authors as low quality, found an effect size of 0.35, which was statistically significant, for two weeks of left DLPFC treatment vs. sham. However, the effect was nonsignificant two weeks later. However, in a more recent meta-analysis of 34 randomized, sham-controlled studies (Slotema, et al., 2010), rTMS delivered to the DLPFC produced a mean effect size of 0.55 ($P < 0.001$), regardless of hemisphere stimulated or concurrent antidepressant medications. Trials in patients not on drug treatment yielded a higher mean effect size (0.96, $P < 0.001$) than those where rTMS was added to existing pharmacotherapy (0.51, $P < 0.001$) or started concurrently with antidepressants (0.37, $P < 0.03$). This meta-analysis is the only one to include either of the two, large, longer-term, multicenter trials that have been influential in acceptance of rTMS depression treatment by the clinical community and regulators. The first of these (O'Reardon, et al., 2007; included in Slotema, et al., 2010), industry-sponsored study, randomized 301 antidepressant medication-free, previously treatment-resistant, patients to sham TMS or 10 Hz rTMS at 120% of hand twitch threshold, delivered to the left prefrontal area in 75 4 second trains, five times a week for 4–6 weeks. Outcome was assessed with the Montgomery–Asberg Depression Rating Scale (MADRS) and the Hamilton Depression Rating Scale (17 and 24 question versions; HAMD). Active rTMS was significantly superior to sham on the MADRS at week 4 and on the HAMD scales at weeks 4 and 6. Response rate, defined as a 50% reduction in scale score, was significantly higher with active TMS on all scales at weeks 4 and 6. Remission rate was also significantly higher in the active rTMS group. The second study (George, et al., 2010), randomized 199, antidepressant-free, moderately treatment-resistant, patients to sham or active treatment similar to that used by O'Reardon et al. (2010). All patients underwent a fixed, 3-week period of treatment. In a second, 3-week period, patients showing evidence of remission were routed to an unblinded, tapering, rTMS treatment regimen and initiation of pharmacotherapy. Non-remitting patients were given another three weeks of unblinded, active treatment, screened for remission in a second

variable treatment period and, if in remission, routed to the tapering regimen. HAMD score, the primary outcome measure, indicated remission in 14% of the active group and 5% in the sham group after blinded treatment. However, approximately 30% of both groups remitted in the open treatment phase. The study included an important innovation in the delivery of sham rTMS: that is, adding electrodes under the sham coil to produce a somatosensory artifact roughly matching that of the active coil. Blinding was assessed carefully and shown to be effective for both patients and experimenters. Both of the multi-center studies employed the Neurostar® TMS system, which has been cleared by the FDA, but whose use is not yet widely reimbursed by third-party payers in the U.S.

It is noteworthy that not a single patient in either of these studies or, indeed in the vast majority of those before suffered a seizure or any other serious adverse event unrelated to the underlying disease. Seizures are certainly dangerous and undesirable. However, all of the 17 or so reported seizures with rTMS (Gomez, et al., 2011; Rossi, et al., 2009) have occurred under observation and resolved rapidly and spontaneously without serious sequelae. Therefore, we question whether the optimal risk-benefit balance for a severely depressed population undergoing rTMS treatment requires a seizure rate of virtually zero and substantially less than that of conventional antidepressant medications (Mula, et al., 2008). We urge the cautious easing of guidelines on rTMS for therapeutic applications, especially where there are convincing indications of efficacy.

rTMS-induced seizures may, in fact, be therapeutic. So-called, magnetic seizure therapy (Lisanby, et al., 2001b) was conceived as a way to produce the antidepressant effect of traditional electroconvulsive therapy with milder side effects by producing seizures with a focal origin and partially controlled spread (Rowny, et al., 2009). Clinical experience with this technique is limited; however, results indicate that it does produce milder seizures and side effects and that its antidepressant efficacy may be comparable to that of electroconvulsive therapy (Kirov, et al., 2008; Lisanby, et al., 2003).

3.2. Schizophrenic hallucinations and tinnitus

One of the earliest and most successful applications of inhibitory, low frequency rTMS was to treat schizophrenic auditory hallucinations. Functional neuroimaging shows activity in the temporoparietal cortex during auditory hallucinations (Silbersweig, et al., 1995), providing an accessible target and a compelling physiological rationale for a treatment producing local neural depression. Hoffman et al. (2000; 2005) were the first to show that repeated sessions of 1 Hz rTMS delivered to the left temporoparietal area suppressed auditory hallucinations, in some cases for weeks after stopping treatment. Largely overlapping meta-analyses (Slotema, et al., 2010; Tranulis, et al., 2008) found average effect sizes of just over 0.5 ($P < 0.001$, in both cases). TMS has also been tried therapeutically for the, so-called, negative symptoms of schizophrenia, e.g., impaired performance on neuropsychological tests of frontal lobe function (Hoffman & Stanford, 2008) that are thought to be causally associated with signs of hypofunction seen on functional imaging (Andreasen, et al., 1997). There, however, the motivating rationale and results (Slotema, et al., 2010) are less convincing.

Like schizophrenic auditory hallucinations, tinnitus is associated with activity in temporoparietal cortex on functional imaging studies (Moller, 2003), providing a similar target and rationale for intervention with inhibitory rTMS. However, 10 Hz rTMS was chosen for a trial in 14 tinnitus patients, comparing stimulation of various scalp sites, with procedures to control for the auditory and somatosensory effects of rTMS (Plewnia, et al., 2003). While the results were not dramatic, transient reductions in tinnitus were significantly greater when rTMS was delivered to temporal and temporoparietal than to frontal and parietal sites. One Hz rTMS was later tested in a crossover trial where active or sham rTMS was targeted at each of 14 patients' individual locus of activation in auditory cortex (left

hemisphere in 12), using a frameless stereotactic procedure (Kleinjung, et al., 2005). After five days of active treatment, there was significant improvement of symptoms, which was still present at six months. Sham did not produce statistically significant effects, but, unfortunately, the authors did not report a direct statistical comparison between the effects of sham and active treatment. A study in 62 patients (Khedr, et al., 2010) found that rTMS, delivered to the temporoparietal cortex contralateral to the symptomatic ear, was more effective than arbitrary left-sided treatment and that it didn't seem to matter whether the stimulation was delivered at 1 or 25 Hz. The latter finding is somewhat surprising, given the dogma of frequency-specific effects and the putative mechanism of rTMS treatment for tinnitus. It should create some skepticism in the minds of clinical investigators. Continuous theta burst rTMS and "primed" 1 Hz rTMS (Iyer, et al., 2003) produce enhanced inhibitory effects, which may be effective in hallucinations and tinnitus.

3.3. Anxiety: Obsessive compulsive disorder (OCD) and posttraumatic stress disorder (PTSD)

Somewhat better understood than depression (Menzies, et al., 2008), OCD also provided an early target for rTMS. Greenberg et al. (1997), influenced by the initial success in depression, were the first to try it in an acute, "challenge" study, intended more as a physiological probe than a therapeutic trial. Their anatomical target, based on functional imaging studies in OCD (Menzies, et al., 2008), was the DLPFC, where they delivered single sessions of 20 Hz rTMS to each side on different days. Occipital stimulation was used as a control. Right DLPFC treatment significantly reduced patient-rated compulsions, but not obsessions, for several hours and improved mood transiently in this non-depressed sample. The authors' interpretation was that right DLPFC stimulation might have disrupted activity related to the generation of compulsive urges. Several subsequent therapeutic trials of frontal rTMS (Alonso, et al., 2001; Prasko, et al., 2006; Sachdev, et al., 2007; Sachdev, et al., 2001) failed to find beneficial effects. However, a study targeting the supplementary motor area, a cortical region found hyperactive in OCD, with inhibitory, 1 Hz rTMS in 21 patients found a significant improvement, relative to sham, after four weeks of daily treatment (Mantovani, et al., 2010). It may be possible to target and activate the supplementary motor area, a paired structure lying on the medial surfaces of the hemispheres in the interhemispheric fissure, with a conventional coil placed on the overlying scalp "15% of the distance between inion and nasion anterior to [the] vertex", the procedure described in this study. However, independent evidence of this ability does not exist. So, while the therapeutic effects may be real, clinically valuable, and spatially selective, the nominal target in this and many other otherwise well-conceived trials should be taken as representing a procedure and a scalp location, rather than anatomical reality. This particularly true when only one or even a few scalp sites are tested and critical when such studies are cited in support of pathogenetic theories.

PTSD has also been treated with 1 Hz rTMS delivered to the right prefrontal area with the goal of reducing hyperactivity seen there on functional imaging studies of patients recalling triggering events (McCann, et al., 1998). An open trial in two patients produced encouraging results, but the findings of a subsequent controlled study by the same group proved less impressive (Osuch, et al., 2009). In a trial in 24 PTSD patients (Cohen, et al., 2004) comparing 1 Hz, 10 Hz, and sham rTMS, there was a reduction of symptoms with 10 Hz relative to 1 Hz and sham. These investigators, however, used a circular coil, whose center hole was apparently placed over the target in the right prefrontal area, virtually ensuring that the stimulus was delivered somewhere else. Finally, in a study of 30 PTSD patients randomized to receive 20 Hz rTMS delivered to the right or the left prefrontal area or sham (Boggio, et al., 2010), investigators found a stronger therapeutic effect on anxiety with

treatment delivered to the right side after 10 sessions delivered over two weeks. Beneficial effects were reported to persist at 3-month follow-up.

One potentially important consideration, which seems largely to have escaped psychiatrists, but not neurorehabilitation specialists (see below), is that the best use of rTMS may be to augment the benefit of behavioral treatment by promoting the desired neural change, rather than remodeling brain pathways on its own. Anxiety spectrum disorders are typically and successfully treated with behavioral techniques, e.g., cognitive-behavioral and exposure therapy, aimed at altering maladaptive responses to internal and environmental stimuli. The combination of rTMS, as a modulator of plasticity, with a proven behavior modification technique might yield useful synergy. The concept of enhancing the effects of exposure therapy pharmacologically has already been proven in acrophobia (Ressler, et al., 2004).

3.4. Neurodegenerative disorders: Parkinson Disease (PD) and Alzheimer disease (AD)

Neurophysiological models of PD indicate decreased excitatory drive on the motor cortex from the basal ganglia, via thalamic relays (DeLong, 1990). This was part of the rationale for directing high frequency rTMS to the motor cortex in PD patients (Pascual-Leone, et al., 1994a). Using continuous 5 Hz rTMS of the motor cortex below the MEP threshold, this group found beneficial effects on reaction time, movement time, and performance on the Grooved Pegboard test, a measure of fine finger control and psychomotor speed, in six PD patients. These effects were smaller, absent, or reversed in a larger group of elderly controls. Others (Ghabra, et al., 1999), however, could not replicate this finding. Mally and coworkers (Mally & Stone, 1999) were the first to report a lasting beneficial effect of “offline” TMS in PD patients. In an open trial, they delivered 30, single TMS pulses, at a range of very moderate intensities, either once or twice a day, for 7–10 days. Their twice-a-day groups showed statistically significant, intensity-dependent improvements that persisted for months after treatment, a phenomenon difficult to explain in physiological terms. There are no large or definitive studies in this area, where pharmacological and surgical approaches have been comparatively successful. However, these and several other trials of varying quality, where TMS was delivered at assorted frequencies and intensities with round or 8-shaped coils, are reviewed in a meta-analysis (Fregni, et al., 2005), which found an effect size of 0.62 on Unified Parkinson’s Disease Rating Scale scores and concluded that TMS might be an effective treatment for PD. A later study of intermittent theta-burst rTMS of the motor cortex (Benninger, et al., 2011) found no effect on motor measures, but a beneficial effect on mood. The same group (Benninger, et al., 2009) completed a safety study of 50 Hz rTMS in PD patients, laying the groundwork, perhaps, for a new generation of rTMS treatment studies. Interestingly, rTMS of the motor cortex, like the DLPFC, can stimulate dopamine secretion in the caudate nucleus (Strafella, et al., 2003), providing a plausible explanation for at least some beneficial effects in PD and a potential surrogate outcome measure.

rTMS has also been tried as an “online” intervention in dementia (Cotelli, et al., 2006; Cotelli, et al., 2008). These investigators applied brief trains of 20 Hz rTMS during presentation of a picture stimulus, which the patients were asked to name. Facilitatory effects on naming were found with stimulation of the left and right DLPFC, but not with sham. Given the non-lateralized effect and the fact that the sham was delivered with the coil held with its narrow edge to the top of the head, greatly reducing its somatosensory effect, caution is required in interpreting the results: Sensory stimulation in multiple channels can facilitate behavior, a phenomenon called, intersensory facilitation (Nickerson, 1973) and the sensory artifact of TMS can produce the effect (Terao, et al., 1997).

A later, “offline” study (Cotelli, et al., 2011), 10 AD patients were assigned to 20 Hz rTMS delivered in 20 sessions over four weeks or 10 sessions of sham, followed by 10 sessions of the active treatment. At the 2-week point, the active group had improved significantly from

baseline on a measure of auditory sentence comprehension and there was a smaller, but significant, performance difference between the groups at that point. The effect on naming, found in the on-line studies, was not present, nor did other cognitive measures appear to improve. The increase in comprehension appeared to last for 12 weeks in the active group. Another group (Bentwich, et al., 2011), combined 10 Hz rTMS, delivered to a number of scalp sites, with cognitive training in 8 AD patients in an open study. No significant improvements were found after 6 weeks or 4.5 months of treatment.

3.5. Neurorehabilitation

Based on its potential to produce plastic change in synapses (see sections on facilitatory and inhibitory effects, above), researchers and clinicians have wondered whether rTMS could be used to drive or augment adaptive plasticity, aiding the process of recovery from brain damage. Interestingly, the most successful experiments in this area used 1 Hz rTMS to reduce neural “competition” from the intact hemisphere, presumably liberating suppressed capacity on the injured side. This principle was tested in a study of 10 hemiparetic, chronic stroke patients and 10 healthy controls (Mansur, et al., 2005). All subjects underwent three sessions each of 1 Hz rTMS and sham, delivered to the primary motor and premotor cortex, contralateral to the lesion, in a single day. Outcome measures, including reaction time, finger-tapping speed, and the Purdue Pegboard Test were administered after each treatment session. In contrast to the healthy group, the stroke patients’ performance improved after active motor cortex stimulation. In a case-controlled trial (Kirton, et al., 2008), 10 very carefully selected children and young adults, aged 9–20 years, with chronic ischemic hemipareses involving the upper extremity, were paired for age and severity and randomized to 1 Hz rTMS over the motor cortex contralateral to the lesion, 10 minutes a day for 8 days, or sham. At 10 days, there was a significant increase in grip strength in the active rTMS group, which persisted at day 17. A more global test of function, the Melbourne Assessment of Upper Extremity Function, showed improvements, which did not persist after the end of treatment. In another trial in 23 chronic stroke patients (Takeuchi, et al., 2008), physiological measures were added to the clinical outcome variables: One Hz rTMS of the motor cortex contralateral to the stroke produced increased excitability (tested with TMS) in the affected motor cortex along with statistically significant clinical improvements. In a rare, subacute study, stroke patients, treated 7–20 days after onset of hemiparesis with 5 days of 1 or 3 Hz rTMS, performed better on motor testing three months later than patients treated with sham and there appeared to be an advantage of 1 Hz treatment (Khedr, et al., 2009). The inhibitory approach has also been taken in nonfluent aphasia after stroke, where inhibitory rTMS was delivered to the homolog of the motor speech area in the intact hemisphere with encouraging results (Naeser, et al., 2010).

A different strategy suggested by the laboratory data is to use the putative ability of higher frequency rTMS to strengthen synaptic connections, to promote remodeling of pathways on the affected side and/or boost the effect of concurrent behavioral treatment. This has been tried with some success, as well (e.g., Kim, et al., 2006). There, 10 Hz rTMS or sham was delivered to the affected motor cortex immediately before a motor training task involving the paretic fingers. rTMS produced an increase in MEP amplitude, which was associated with improved motor performance in the active stimulation group.

3.6. Migraine and chronic pain

The results of an industry-funded, multi-center, randomized, double-blind, sham-controlled trial (Lipton, et al., 2010), indicate that single TMS pulses, delivered by patients to their own occiputs with a battery-powered device, can abort migraine attacks. Theoretical support for this treatment comes from evidence that TMS can disrupt the phenomenon of cortical spreading depression, which is believed to be a precursor of pain in the disorder (Lipton &

Pearlman, 2010). These authors also present data indicating that TMS-based migraine prophylaxis may be feasible.

The observation that epidural stimulation of the motor cortex can reduce chronic pain (Tsubokawa, et al., 1993) stimulated interest in doing the same procedure noninvasively with rTMS. Surprisingly, no large trials have been run in this area where the need for new treatments would seem to be great. A meta-analysis of five controlled studies of motor cortex rTMS (Leung, et al., 2009), including 149 patients with pain from a variety of sources, found a significant overall beneficial effect. Lower frequencies (≤ 10 Hz) seemed to be most effective and the techniques in general seemed better for pain of central than peripheral origin. However, a more recent meta-analysis of 17 rTMS studies in chronic pain (O'Connell, et al., 2011) found evidence of no effectiveness of low frequency (< 5 Hz) rTMS in providing even short-term relief from chronic pain; whereas, single treatments with rTMS at > 5 Hz may have had a short-term beneficial effect. Still more recently, and to conclude on an encouraging note, the first trial of prolonged rTMS treatment for pain (Mazzoni, et al., 2007) was reported. These investigators randomized 40 fibromyalgia patients either to 10 Hz rTMS or sham treatment, first delivered daily for five days, then weekly for three weeks, bi-weekly for six weeks, and then monthly for three months. Thirty patients completed the trial and the analysis was on the intent-to-treat cohort. Pain ratings in the sham and active groups began to diverge after the first treatment and remained significantly different one month after the last treatment. Secondary outcome measures related to mood, quality of life, and disease impact showed parallel and significant treatment effects.

4. Discussion and conclusions on the clinical outlook

In the 25 years since TMS has been commercially available, it has gained prominence as a research tool for noninvasive stimulation and neuromodulation of the human cortex. However, despite some solid therapeutic successes, many encouraging leads, and the clearance of a device for therapeutic use, its future in the clinic is uncertain. A major consideration is the appropriate business model for a durable medical device, potentially able to deliver thousands of treatments. One case is the device tested for migraine (Lipton, et al., 2010), where one or two single pulses appear sufficient to abort an attack and there is little danger of harm from inappropriate use. A simple device capable of delivering isolated pulses could be disseminated among sufferers of a common disorder, such as migraine, where conventional pharmacological therapies have significant side effects and risks. In contrast, there is depression treatment, where rTMS, with its complex equipment and risks of seizures and even, theoretically, abuse, is required. There, a device is sold or leased to the provider, who could, potentially, use it to treat hundreds of patients with little further return to the supplier. The vendor of the FDA-cleared system (www.neuronetics.com), has adopted the following strategy: In addition to purchasing or leasing a suite of equipment, including a chair and a computer and proprietary clinical data management system, the provider is required to place a pad, containing electronic components, between the coil housing and the patient's head, in order to operate the device. Each pad permits only a limited number of pulses, after which it must be replaced and returned to the manufacturer; several are required for each course of treatment. According to company material, this item provides "contact sensing to ensure the treatment coil is properly positioned; magnetic field confirmation to ensure patient receives desired treatment; surface field cancellation to reduce stimulation of the scalp, and a hygiene barrier from patient to patient" (www.neuronetics.com/Prod-Components.aspx?q=senstar). These technical merits have not been subjected to independent evaluation. Resort to such a design suggests that at the business analysis did not find sufficient commercial potential in therapeutic rTMS without such enhancement, even for a common disease, inadequately treated by conventional

therapies. It is indicative of current health care economics that an effective treatment, which could be delivered at a low cost per patient, must be made more costly in order to be commercially viable. Three economic comparisons have been made between ECT and rTMS treatment for depression, one in the United States (Kozel, et al., 2004), which found a cost advantage for rTMS, and two in the United Kingdom (Knapp, et al., 2008; McLoughlin, et al., 2007), both of which found an advantage for ECT.

As mentioned above, magnetic stimulators, including those able to deliver rTMS, are FDA approved for peripheral nerve stimulation, making them legal to use “off-label” for other purposes. However, without specific clearance or approval, third party reimbursement is generally unavailable and providers providing off-label treatment are exposed to greater liability and regulatory burdens. Manufacturers, in turn, are unlikely to pursue approval or clearance for new indications without solid indications of profitability. The same considerations apply, at least in part, to adoption by providers. Thus, in our opinion, there is no reason to expect widespread adoption of therapeutic TMS, at least in the U.S., without a structural change in the health care market or a spectacular demonstration of efficacy in a common disorder.

Nevertheless, we expect TMS to continue attracting the interest of innovative clinicians and scientists and to continue to advance. There are many potential opportunities to improve TMS treatment, in addition to those mentioned above. For instance:

- Analysis of the local sulcation and fiber directions in cortical target areas would allow optimization of coil placement and current direction.
- Adopting theta burst paradigms or primed low-frequency rTMS, instead of conventional, unpatterned stimulation, would increase the effectiveness and safety of rTMS treatments.

These are among the easiest innovations to implement in existing clinical paradigms. Other more speculative possibilities include the following:

- While hyper-focal coils are difficult to produce, there may be simpler ways to improve the spatial and functional focality of TMS: Experiments in visual cortex have shown that behavioral pre-activation and adaptation of particular populations of neurons within the stimulated area can alter the response to single pulse (Silvanto, et al., 2007b) and theta burst (Silvanto, et al., 2007a) TMS. This could be a way of refining the targeting of therapeutic interventions without changing the hardware.
- Endophenotypes for neurobehavioral disease and surrogate markers for clinical endpoints are actively being sought and discovered. These should improve the ability to define the most effective protocols for TMS treatment.

This is but a sample of the potential ways in which TMS treatment might be improved. Given the opportunities, new interventions are sure to be attempted and one may yet provide that spectacular demonstration.

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Abbreviations

DLPFC Dorsolateral prefrontal cortex

FDA	(US) Food and Drug Administration
LTP	Long term potentiation
MEP	Motor evoked potential
OCD	Obsessive compulsive disorder
PTSD	Posttraumatic stress disorder
PD	Parkinson disease
rTMS	Repetitive transcranial magnetic stimulation
TMS	Transcranial magnetic stimulation

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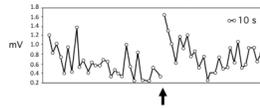


Fig. 1.

The effect of a short train of high frequency rTMS on MEP amplitude. Baseline MEP amplitude is measured by giving test stimuli, once every 10 s; then a 2 s train of 20 Hz rTMS is delivered (arrow). After a brief pause, test stimulation is resumed every 10 s. MEP amplitude is shown on the y-axis.

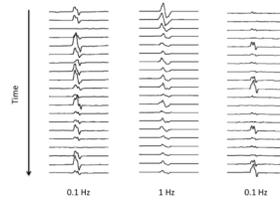


Fig. 2.

The effect of low frequency rTMS on MEP amplitude. In the first panel, test stimuli are delivered every 10 s (0.1 Hz). Then rTMS is delivered at 1 Hz (second panel); MEP amplitude decreases gradually during the stimulus train. 0.1 Hz stimuli are then resumed (third panel) and MEPs remain suppressed. The sequence of traces is from top to bottom in each panel.