The expanding evidence base for rTMS treatment of depression

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Purpose of review
Daily left prefrontal transcranial magnetic stimulation (TMS) for several weeks was first proposed as an acute treatment for depression in the early 1990s, and was Food and Drug Administration (FDA) approved in 2008. In the past year, several important studies have been published that extend our understanding of this novel treatment approach.

Recent findings
The first round of multisite clinical trials with TMS addressed whether prefrontal rTMS has efficacy and were conducted in carefully selected depressed patients who were antidepressant medication free. Several more recent studies assess the clinical effectiveness of TMS and report that about 35–40% of real-world patients who are commonly taking adjunctive antidepressants reach remission with a modest side effect profile. There are also new studies examining the durability of the TMS-induced antidepressant effect. Fifty-eight percent of TMS remitters remain remitted at 3-month follow-up.

Summary
These recent studies suggest that daily left prefrontal TMS over several weeks as a treatment for depression not only appears to have efficacy in rigorous randomized controlled trials, but is effective in real-world settings, with remission in 30–40% of patients. The TMS antidepressant effect, once achieved, appears to be as durable as with other antidepressant medications or interventions. Much more research is needed, particularly with issues such as the TMS coil location, stimulation intensity and frequency, and dosing strategy.

Keywords
depression, magnetic, stimulation, transcranial magnetic stimulation, transcranial, treatment

INTRODUCTION

Transcranial magnetic stimulation (TMS) is perhaps the most popular of the new brain stimulation techniques because its clinical effects are produced without the need for a craniotomy [as with deep brain stimulation (DBS)] or seizure induction [as with electroconvulsive therapy (ECT)]. As a focal, noninvasive form of brain stimulation, TMS produces limited side effects and can be used as either a therapy or a research tool (e.g., to measure how excitable the brain is or to produce a temporary lesion) [1–3].

TMS uses an electromagnetic coil on the scalp to create an extremely potent (near 1.5 T) but brief (μs) magnetic field. This magnetic field enters the surface of the brain without interference from the skin, muscle, and bone. In the brain, the magnetic pulse encounters nerve cells and induces electrical current to flow. Thus, the magnetic field created from electrical energy in the coil passes through the skull and is converted back into electrical energy in the brain [4]. It is for this reason that TMS is sometimes called 'electrodeless electrical stimulation'.

Brief history

The idea of using TMS, or something akin to it, to alter neural function goes back to at least the early 1900s. In 1902 Pollacsek and Beer, psychiatrists working down the street from Sigmund Freud in Vienna, filed a patent to treat depression and

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KEY POINTS

- TMS is an exciting research tool and is FDA approved for treating depression.
- Repeated daily prefrontal TMS has acute antidepressant effects similar to medications or ECT, with few side effects.
- More research on the fundamental neurobiological effects of brain electrical stimulation will help these new techniques continue to improve and evolve.

neuroses with an electromagnetic device that looks surprisingly like today's TMS machines [5]. The modern TMS era began in 1985 when Barker *et al.* [6,7], working in Sheffield, England, created a focal electromagnetic device with sufficient power to induce currents in the spine. They quickly realized that their device could also directly and non-invasively stimulate the human brain, launching the modern TMS era.

Seizure risk

Repetitive TMS or rTMS can create behaviors not seen with single pulses, including the potential risk of causing an unintended seizure. Worldwide, out of the 300 000 or more treatment or research sessions in the history of TMS, approximately 20 seizures have occurred [8]. In the United States, since market introduction of the NeuroStar TMS Therapy system in October 2008, seven seizures have been reported out of 250 000 NeuroStar TMS treatment sessions in over 8000 patients. In five of the seven seizures, patients had concurrent use of medications that may have altered seizure threshold. The estimated risk of seizure under ordinary clinical use is approximately one in 30 000 treatments (0.003% of treatments) or one in 1000 patients (0.1% of patients) (M. Demitrack, Neuronetics, personal communication). This risk is less than or comparable to the risk of seizure associated with antidepressant medications [9,10]. All TMS seizures have occurred during stimulation, rather than later, and have been self-limited with no sequelae. rTMS seizures are more likely to occur with certain combinations of TMS intensity, frequency, duration and interstimulus interval [11,12].

TRANSCRANIAL MAGNETIC STIMULATION FOR ACUTE TREATMENT OF DEPRESSION

In 2008, the NeuroStar TMS Therapy system (Neuronetics, Inc., Malvern, PA, USA) received Food and Drug Administration (FDA) clearance for the treatment of adult patients with Major Depressive Disorder (MDD) who have failed to receive satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode. FDA clearance was based on a large, multisite, sham-controlled randomized study that showed that daily prefrontal TMS was a well-tolerated and effective treatment for certain patients with major depression. The observed effect sizes in both the original study population ($N = 301$, [13]) and in the subset of patients who met the FDA approved indication for use of the NeuroStar TMS Therapy system ($N = 164$, [14]) are of similar or greater magnitude than those observed with the majority of currently approved antidepressant medication treatments.

George *et al.* in a 190 patient National Institute of Mental Health-sponsored multisite, randomized controlled trial [called optimised TMS (OPT-TMS)] demonstrated that rTMS, as drug-free monotherapy, produced statistically significant antidepressant effects with a remission rate four times that of sham patients [15]. This study provided industry-independent class I evidence of safety and efficacy in a well-studied and carefully controlled cohort. Recently, two additional publications resulted from this trial. McDonald *et al.* [16▪] reported on an open-label extension phase. They found that 43 of 141 (30.5%) patients who enrolled in the open-phase study eventually met criteria for remission. Some patients took up to 6 weeks to fully remit [16▪]. Most recently Mantovani [17▪] reported on the 3-month durability of the TMS antidepressant response in this trial. Of the 50 patients who remitted and agreed to participate in follow-up, at 3 months, 29 of 50 (58%) were classified as in remission [Hamilton depression rating scale (HDRS)-24 $\leq$ 10], two of 50 (4%) as partial responders (30% $\leq$ HDRS-24 reduction $<$50% from baseline), and one of 50 (2%) met criteria for relapse [17▪].

Several other recent studies describe the effectiveness of TMS in modern clinical practice. The first was a multisite observational study in 307 real-world patients receiving Neurostar TMS in clinical practice settings [18▪▪]. With an acute course of TMS treatments [average 28.3 (SD: 10.1) treatment sessions], symptom severity ratings decreased significantly. With categorical outcomes, 58% of the participants were responders of the primary outcome measure [clinical global impression-subject (CGI-S)], and 37% had reached remission, with similar findings on the secondary measures. Given that over half of the participants met criteria for resistance to two or more antidepressant trials in the current episode, outcomes were stratified by level of treatment resistance (<2 vs. ≥ 2 treatment failures); response and

remission rates were similar between groups (e.g., 59.4 vs. 56.8% response for low vs. high levels of resistance; 39.9 vs. 34.9% remission rates).

Connolly *et al.* [19▪] reported data from the first 100 patients treated at their university-based TMS clinical service following FDA approval. Their cohort was also treatment resistant, with a mean of 3.4 failed adequate antidepressant trials in the current episode. Thirty-one individuals had received prior lifetime ECT, and 60% had a history of psychiatric hospitalization. The clinical global impression-investigator response rate was 50.6% and the remission rate was 24.7% at 6 weeks. The HDRS response and remission rates were 41.2 and 35.3%, respectively. Forty-two patients (49%) entered 6 months of maintenance TMS treatment. Sixty-two percent (26/42 patients) maintained their responder status at the last assessment during the maintenance treatment. These data from care-seeking patients suggest that TMS, unlike many therapies in medicine, does not suffer from an efficacy/effectiveness gap between clinical trials and clinical treatments.

Clinically relevant research

Much research is underway to determine exactly which neurons TMS affects and to elucidate the cascade of neurobiological events that follow stimulation. We do know that factors like gyral anatomy, brain atrophy and nerve fiber orientation relative to coil all impact how TMS affects neurophysiology.

Single nerve cells form themselves into functioning circuits over time through repeated discharges. Externally stimulating a nerve cell with low or high frequency electrical stimulation can cause long-term depression (LTD) or long-term potentiation (LTP), respectively. These phenomena are thought to be involved in learning, memory, and dynamic changes in neuronal networks. A very exciting aspect of TMS research is whether noninvasive stimulation can change brain circuits over time in a manner analogous to LTD or LTP. Many studies have shown that TMS can inhibit or potentiate motor-evoked potentials for several hours beyond the time of stimulation [20–22]. The clinical implications of such TMS-induced neuroplasticity are profound. If functional imaging can be used to identify faulty brain networks, then TMS or other techniques might be useful for resculpting them. Recent research indicates that TMS can induce neurogenesis [23–25]. Some basic physiological studies also suggest that neuroplastic changes are more robust when the cells being stimulated are acting as a circuit [26–28]. These findings raise the possibility that TMS could be combined with cognitive-behavioral or physical therapy.

Home transcranial magnetic stimulation?

Exciting research at the cellular level has revealed that, when bundles of neurons fire in the same direction, the electricity flowing through them creates a magnetic field as Maxwell's equations would suggest. This brain-generated magnetic field can synchronize neuronal firing and is called ephaptic coupling [29,30]. Studies in cell cultures and nonhuman animals have shown that weak electrical or magnetic fields produced by the brain itself can entrain neurons in widespread cortical areas. This finding opens up the possibility of influencing this meta-electrical field with 'weak' TMS. One company has created such an oscillatng weak TMS device, with positive studies in small trials of schizophrenia and depression [31,32]. This device (Neosync) is currently being tested in a multisite pivotal study. If successful, this device might enable home delivery of TMS (under a doctor's prescription) because it would likely not be able to cause a seizure.

Combining transcranial magnetic stimulation with functional imaging

A critically important technique that might ultimately guide clinical parameters is the use of functional imaging to directly monitor TMS effects on the brain. Since different frequencies of TMS produce divergent effects on brain activity, combining TMS with functional brain imaging will better delineate not only the behavioral neuropsychology of various psychiatric syndromes, but also some of the underlying pathophysiologic brain circuits. In contrast to imaging studies with ECT, which have found that ECT shuts off global and regional activity following the seizure [33], most studies using serial scans in depressed patients undergoing TMS have found increased activity in the cingulate and other limbic regions [34,35].

When a neuron fires or discharges, different neurotransmitters are released in the synaptic cleft. Thus, brain stimulation methods are in one view simply 'focal pharmacology'. This link between brain stimulation and traditional pharmacological views of psychiatric illnesses has been highlighted by studies using radioligands. Baeken and colleagues examined the neurobiologic impact of 10 rTMS sessions applied to the left dorsolateral prefrontal cortex (DLPFC) on postsynaptic 5-HT(2A) receptor binding indices measured with (1)(2)(3)I-5-I-R91150 single photon emission computed tomography (SPECT). Compared with controls, patients displayed significantly less bilateral DLPFC and significantly higher left hippocampal baseline 5-HT(2A) receptor binding. Successful rTMS treatment correlated positively with 5-HT(2A) receptor binding in the DLPFC bilaterally and correlated negatively with

right hippocampal 5-HT(2A) receptor uptake values. Strafella *et al.* [36] used PET to show that prefrontal cortex TMS causes dopamine release in the caudate nucleus and has reciprocal activity with the anterior cingulate gyrus [37].

Work with interleaved TMS/functional MRI has shown that prefrontal TMS at 80% motor threshold produces much less local and remote blood flow change than does 120% motor threshold TMS [38]. Our group at Medical University of South Carolina [39], as well as others in Scotland [35] and Australia [40], has shown that lateral prefrontal TMS can alter the function of the anterior cingulate gyrus and other limbic regions in depressed patients. Changing the site of prefrontal stimulation (lateral vs. medial) produces different secondary activations. The effects of TMS also differ as a function of mood, cortical excitability, and other factors that alter resting brain activity [41,42]. These results highlight the notion that cortical TMS is 'opening a window' to different cortical–subcortical networks.

Where is depression in the brain?

Although more work is needed, certain brain regions have been consistently implicated in the pathogenesis of depression and mood regulation [43–50]. These include the medial and dorsolateral prefrontal cortex, the cingulate gyrus, and other regions commonly referred to as limbic (amygdala, hippocampus, parahippocampus, septum, hypothalamus, limbic thalamus, insula) and paralimbic (anterior temporal pole, orbitofrontal cortex). A widely held theory over the last 20 years has been that depression results from a dysregulation of these prefrontal and limbic regions [47,50–52]. In 1995, George and colleagues performed the first open trial of daily prefrontal TMS as an antidepressant [53], followed immediately by a cross-over double-blind study [54]. The reasoning was that chronic, frequent, sub-convulsive stimulation of the prefrontal cortex might initiate a therapeutic cascade of events that rebalances and normalizes the dysregulated prefrontal and limbic circuitry [55]. The imaging evidence previously discussed now shows that this hunch was largely correct. Thus, modern TMS was specifically designed as a focal, nonconvulsive, circuit-based approach to therapy.

Unresolved issues

There are many unresolved issues with TMS therapy for depression. One issue is finding the best target to enhance the antidepressant effects of TMS. Moreover, it is also important to determine if this region can be found with a group algorithm or if individual imaging guidance improves results. Positioning of the TMS coil is typically based on an algorithm that researchers (including MSG) developed in early studies [53]. However, this method was shown to be imprecise, depending largely on the subject's head size [56].

Another issue is determining the optimal dose over the optimal time period for alleviating depression. Most studies have stimulated patients at or above motor threshold. This is particularly important in elderly patients, in whom prefrontal atrophy may outpace motor cortex atrophy [57–60]. There have never been dose-finding studies with rTMS. Thus, some groups are studying whether higher doses of TMS might produce more rapid or more effective results [61]. Also, there are a few case series suggesting that weekly or monthly rTMS can serve as maintenance therapy for acute responders [62–64].

One interesting development with TMS is different coil designs [65▪,66]. Most studies use a figure eight coil, which is quite focal in terms of the field created in the brain [67]. Zangen and colleagues in Israel have designed a series of TMS coils that penetrate more deeply and broadly into the brain than do traditional coils [68,69]. A company now manufactures these coils (Brainsway). A multisite clinical antidepressant trial using such a coil showed positive results compared with sham. The FDA is currently reviewing these results for potential approval to market this coil for treating depression.

Transcranial magnetic stimulation as a treatment for other psychiatric conditions

TMS has also been investigated as a possible treatment for a variety of neuropsychiatric disorders. The literature in these conditions is much less extensive than for TMS as an antidepressant, and therefore conclusions about the clinical significance of effects must remain tentative until large sample studies are conducted.

Transcranial magnetic stimulation and pain

Mood-regulating centers in the brain overlap significantly with the neural pathways involved in pain regulation, especially the regions involved in determining whether a pain is really bothersome. Thus, researchers are exploring whether TMS might have a therapeutic role in treating acute, chronic or perioperative pain. There are exciting reports that TMS over prefrontal cortex or motor cortex acutely decreases pain in healthy adults or patients with chronic pain [70–75,76▪▪]. A recent randomized controlled trial found that a single 20-min session of left prefrontal rTMS given to patients in the recovery

room following surgery reduced self-administered morphine by 40% [77]. In the lab, a 20-min dose of prefrontal TMS can also increase pain thresholds. This effect is blocked in healthy volunteers by pretreatment with naloxone, suggesting that opiate receptors play a necessary role in the anti-nociceptive effects of TMS [78▪,79].

CONCLUSION

Overall, TMS is a promising new therapy and a powerful research tool. The body of TMS literature suggests that daily left prefrontal TMS for 3–6 weeks has antidepressant effects that are significantly greater than sham, and that these effects in open-label studies are clinically meaningful (30% remission), with low side effects and no drug–drug interactions. The remission outcomes are at least as robust as next choice antidepressant medication. Since FDA approval TMS has been generally safe and well tolerated with a low incidence of treatment discontinuation, and the therapeutic effects once obtained appear at least as durable as other antidepressant treatments. TMS also shows promise in several other psychiatric disorders, particularly treating acute and chronic pain.

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Conflicts of interest

Dr George is a nonpaid consultant to several TMS companies (Brainsway, Cervel, Neosync, Neuronetics). Dr George serves or has served as a paid consultant to several non-TMS device and pharmaceutical companies. He owns no equity in any device or pharmaceutical company.

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- ▪ of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 125).

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