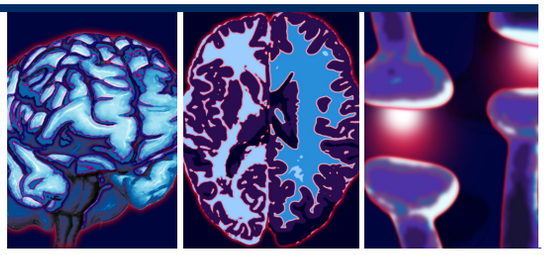
EDITORIAL



Is there a place for transcranial magnetic stimulation in the treatment of depression?



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Some patients with depression fail to respond to psychotherapy or medications, or may develop undesirable side effects to these interventions. Repetitive transcranial magnetic stimulation (rTMS) is a valuable clinical option for such patients. The neurobiological effects of rTMS remain unclear, yet evidence for the efficacy and utility of rTMS in treatment-resistant depression is rapidly growing. TMS involves a powerful magnetic field that is rapidly modulated, creating an electrical current that focally stimulates the brain. If safety guidelines and recommendations are followed, rTMS is safe and well tolerated. In the coming decades, we will likely learn more about how the disruption of identifiable neural systems underlie specific psychopathologies, and techniques such as rTMS offer a rare opportunity for psychiatrists to directly modulate these systems to diagnose and treat specific mental illnesses with truly individually tailored interventions.

Since the advent of psychopharmacological interventions, psychiatry has primarily been focused on neurotransmitter imbalances rather than a neural systems framework. However, over the past decades, it has become increasingly apparent that complex brain capacities depend critically on dynamic interactions between brain areas. This insight has led to the concept of functional connectivity networks: distributed brain regions transiently interacting to perform a particular neural function. Abnormalities in the interactions of network components play a critical role in psychiatric and neurological disorders ranging from depression to epilepsy. Damage to specific functional connectivity networks can lead to distinct neurological syndromes, and both the deficits and functional recovery after damage from strokes or traumatic brain injury may be a function of the architecture and adaptability of these networks. Therefore, therapeutic interventions that modulate

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neural networks in a specific and targeted fashion carry exciting potential. In this realm, the currently available neuromodulatory interventions include, among others, electroconvulsive therapy (ECT), deep brain stimulation, vagus nerve stimulation and rTMS, as well as transcranial direct current stimulation and high-field pulsing ultrasound. Each of these neuromodulatory techniques has its own strengths and weaknesses in terms of invasiveness, cost, efficacy and ability to selectively stimulate focal brain regions. rTMS offers the appeal of low invasiveness, good spatial resolution, exquisite temporal resolution and excellent tolerability.

Early studies of rTMS in major depressive disorder featured small numbers of patients for short durations of time and different stimulation parameters, leading to variable results. The first sham stimulation-controlled trial revealed that high-frequency, intermittent rTMS to the left, but not the right, prefrontal cortex could result in sustained antidepressant benefits in patients with medication-resistant depression [1]. Subsequent studies confirmed that rTMS of sufficiently high frequency, intensity and duration over the left prefrontal cortex does provide statistically significant improvement compared with sham treatment in patients with depression. Interestingly, similar beneficial effects appear achievable with low-frequency, continuous rTMS to the right prefrontal cortex [2]. One hypothesis is that high-frequency rTMS results in a facilitation of activity in the targeted brain region, while low-frequency rTMS suppresses activity in the targeted brain region. Presumably, the targeted prefrontal region is a window into a distributed bi-hemispheric, cortico–subcortical network, the modulation of which defines the antidepressant efficacy. Apparently, distinct modulation of different nodes of this network can yield therapeutic efficacy, although more work is needed to clarify such neurobiological issues. Of more immediate clinical relevance, newer stimulation protocols and technology yield better clinical efficacy and longer lasting benefits [3], and patient characteristics associated with treatment success appear to be youth, absence of psychosis and a low number of failed antidepressant trials [4,5].

Three well-powered, properly controlled and carefully conducted studies on the effects of rTMS in medication-resistant depression have been completed to date. One large-scale, multisite European trial featuring 127 patients with treatment-resistant depression failed to demonstrate efficacy of treatment. It is not clear why no significant benefit of rTMS was found in that trial. However, length of treatment, statistical power of the trial and rTMS stimulation parameters have been raised as potential factors that could have contributed synergistically to mask an effect [6]. Conversely, O'Reardon and colleagues, in an industry-sponsored, double-blind, multisite randomized controlled trial involving 301 patients, did demonstrate more improvement in the active treatment group than the sham group [7]. The active group showed significant decreases in Hamilton Rating Scale for Depression (HAMD)24 scores, as well as higher remission rates. Although the decrease in Montgomery–Åsberg Depression Rating Scale scores was only of borderline significance ($p = 0.056$) in the entire sample, the effects of active rTMS were clearly superior to sham in patients with a lesser number of failed medication trials. At 6 weeks, the active treatment group was twice as likely to achieve full remission of depressive symptoms as its sham counterpart [7]. Most recently, George and colleagues' NIH-sponsored, multisite study also found a statistically significant and potentially clinically meaningful antidepressant effect of daily left prefrontal rTMS, in which the odds of attaining remission were 4.2-times greater with active rTMS than sham treatment. Nearly 30% of patients remitted in the open-label follow-up to the study. This study also found that low antidepressant treatment resistance was associated with likelihood of remission [8].

A fourth rTMS study featuring 300 depressed veterans sponsored by the Department of Veterans Affairs is currently underway. Subjects in this study will be allowed to remain on stable antidepressant medications – this was notably true of the European study as well – and will include subjects with more diverse comorbid disorders than in other studies [9].

Similar to all relatively new technologies, broad acceptance of rTMS faces the obstacle of establishing clinically relevant efficacy, achieving availability in more communities and overcoming the relatively high cost of treatment when compared with medications alone. Deploying rTMS requires training, purchase of costly equipment and a specialized clinical work space. Few patients can absorb the costs of treatment without assistance from the insurance carriers and most payers have

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not yet established policies to cover rTMS. The field is moving quickly, however, as rTMS has a number of cost advantages in medication-refractory depression. For example, rTMS costs substantially less than ECT (a typical course of rTMS costs approximately a third as much as a course of ECT at our facility), rTMS is performed on an out-patient basis and it allows patients to continue a regular work schedule without driving restrictions. In a cost–benefit analysis, Simpson and colleagues applied a Markov model to estimate the long-term outcomes versus costs [10]. The authors concluded that rTMS is cost–effective compared with standard of care in subjects who have failed antidepressant trials, and especially in patients who have only failed one antidepressant prior to the start of rTMS treatment.

Thus, overall, meta-analyses and the available larger clinical trials support the utility of rTMS in treatment-resistant depression. However, the overall effect size is discrete, and there is a need to consider the conditions that may maximize rTMS efficacy. Certainly, growing clinical experience with rTMS demonstrates that for some patients who have failed many other treatment approaches, rTMS can be a well tolerated and extremely effective therapy. So, who is an appropriate patient for rTMS treatment and what are the best rTMS parameters to apply?

Studies that examine approaches to improve patient selection, individually tailor rTMS paradigms and define ways to predict efficacy of rTMS are needed. It is already known that age is important – older patients tend not to respond as well, although the reason for this remains unclear. The severity of the depression is also important. The US FDA approval for rTMS in depression is for patients who have failed one adequate antidepressant medication trial, but not more. Perhaps rTMS should be considered earlier, but the evidence that rTMS can help in mild depression is insufficiently examined. In patients who do not tolerate or fail one medication trial, established clinical practice often leads clinicians towards the trial of a second agent or coadministration of an adjuvant medication. Only when multiple medication resistance is established are ECT or rTMS considered. In the choice between rTMS and ECT, one should consider patient characteristics – for instance, psychotic depression responds more clearly to ECT – as well as cost and side effect profile, which certainly favor rTMS. Thus, the choice between rTMS and ECT is currently best made on a case-by-case basis with a comprehensive discussion between psychiatrists and their patients of the potential benefits and costs of each option. For each approach, maintenance treatments can be administered to lessen the likelihood of a relapse, although the most effective schedule for rTMS maintenance remains to be established.

Wider use of rTMS will require more centers with the appropriate training for effective administration and more regular coverage from insurance carriers. Neuronetics (PA, USA), the company behind the FDA-approved Neurostar TMS Therapy® System, is making a significant and important effort in this regard. Comprehensive training courses (such as the one offered at Harvard, MA, USA) and efforts to define training requirements for clinicians and technicians who prescribe and deliver rTMS are crucial.

Ongoing studies will likely result in improvement in the rTMS technology itself, leading to different current pulses, better brain target selection using MRI guidance and more advanced consideration of adjunct pharmacological modulators and therapeutic interventions. Better targeting through the use of stereotactic guidance and electrophysiology or functional imaging promise to increase the efficacy of rTMS and to better ascertain the brain mechanisms underlying the improvement, enabling individualization of treatment schedules. Optimized stimulation paradigms might also be developed based upon better understanding of the neurobiological effects (e.g., time of day for stimulation and number of sessions per day). This effort requires human as well as more basic studies in animal models, but promises to ultimately increase the therapeutic yield of rTMS. Finally, investigators are rapidly exploring new indications for rTMS including chronic pain, anxiety disorder, post-traumatic stress disorder and auditory hallucinations. Each disorder will likely best respond to a different protocol in terms of location, frequency and intensity of stimulation. As the changes in brain networks are defined in these and other conditions, rTMS targeted at specific nodes in the network represents a unique therapeutic opportunity. What is presently clear is that TMS represents a valuable technology with the potential to meaningfully contribute to the psychiatric treatment of major mental illness and that while patients can already benefit from the advances made, more research is needed to realize its full potential.

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