

Repetitive Transcranial Magnetic Stimulation in Depression: A Changing Landscape

June 19, 2013 | [Depression](#) [1], [Transcranial Magnetic Stimulation](#) [2]

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Clinicians can feel confident in the evidence base when referring patients with a moderate level of treatment resistance for rTMS. Preliminary results suggest that deep rTMS may be an effective option in patients who have failed to respond to more than one antidepressant treatment.

Source:

It is estimated that globally 121 million people suffer from clinical depression. Despite an extensive psychotherapeutic and pharmacological arsenal, many affected individuals continue to suffer while the burden on the health care system increases. Of the millions affected worldwide, 20% to 40% are resistant to pharmacological antidepressant treatments while another third show poor response.¹

Many medications are associated with significant adverse effects (eg, weight gain, sexual dysfunction), and there is a recognized need for better treatment options for treatment-resistant depression.



Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive, nonconvulsive neurostimulation treatment. Approval of an rTMS device was granted by the FDA in October 2008. The approval was for 10 Hz stimulation of the left dorsolateral prefrontal cortex (DLPFC) as a treatment for major depression in patients who have not responded to only one antidepressant. rTMS has rather benign adverse effects—the most frequent are mild headache, nausea, and irritation at point of stimulation.² The most serious adverse effect is the induction of a seizure, which is exceedingly rare, with an estimated incidence of less than 1 in 1000 patients.

Mechanism of action

Magnetism and electricity are intrinsically related to each other. Electrical currents generate magnetic fields (eg, magnetic resonance scanners), and conversely, magnetic fields elicit currents in conductors. rTMS takes advantage of this link and makes use of the electromagnetic induction phenomenon to elicit a focal current in brain tissue strong enough to trigger action potentials in neurons. And, it does so in a noninvasive fashion (ie, there is no need for a surgical intervention).

A coil made of an electrical conductor that is isolated by a plastic shell acts as the inductor. When pulses of current pass through the coil, a strong focal magnetic field is generated (on

the order of 1.5 to 2 Tesla). This magnetic field crosses the skull and soft tissue unimpeded; the brain tissue acts as the conductor, and an electrical current is generated parallel to the current in the coil windings and in the opposite direction. The current induced is maximal at the focal point of the coil and diminishes with distance. It is sufficiently strong to cause neuronal polarization and depolarization in the volume lying 3 to 4 cm around the focal point. The entire procedure is carried out with no need for general anesthesia or prior procedural preparation (eg, intravenous line, heart rate or blood pressure monitoring), as opposed to other convulsive neurostimulation techniques, such as magnetic seizure therapy and electroconvulsive therapy.

A brief overview

Beginning in the 1980s, a series of positron emission tomography (PET) studies showed that glucose metabolism is reduced in a number of areas of the prefrontal cortex, including the DLPFC.^{3,4} Additional research using PET demonstrated that effective antidepressant treatment was correlated with reversing the hypoactivity in the prefrontal cortex.^{5,6} More recent studies using functional MRI (fMRI) and electroencephalographic recordings show that it is not only the DLPFC that changes its level of activation.^{7,8} A network of brain regions involved in cognitive control and emotion regulation, including the DLPFC, changes its activity in response to effective antidepressant treatment.

The large body of convergent evidence pointing at the DLPFC as a neuroanatomical location of interest in depression built a compelling and solid rationale for early studies using rTMS to target the DLPFC in depression treatment.⁹⁻¹¹ Pilot studies then showed that rTMS to the left DLPFC was an effective treatment for a proportion of patients with major depressive episodes who had not responded to earlier antidepressant treatments. Indeed, a recent meta-analysis shows that rTMS is effective in 30% to 40% of individuals with treatment-resistant depression.¹²

Conventional rTMS protocols typically target the left DLPFC. The discharge frequency of stimulation (ie, the number of times the magnetic field is generated and the current induced on brain tissue) is usually at a frequency of 10 Hz; this high-frequency stimulation increases cortical excitability. Other protocols have targeted the right DLPFC using low-frequency stimulation at 1 Hz; this protocol decreases cortical excitability.

Recent meta-analyses have shown that stimulation using either protocol provides similar rates of efficacy for treatment-resistant depression.^{13,14} Therefore, in depression, conventional rTMS can be applied either to the left DLPFC with high-frequency stimulation or to the right DLPFC with low-frequency stimulation; both approaches achieve similar rates of efficacy.

Newer stimulation protocols

Brain plasticity is a broad concept that encompasses several neurobiological phenomena; the common denominator of the phenomena is the capacity of the brain to undergo dynamic changes in its function and/or structure. Memory and learning are examples of brain functions in which the neurobiological underpinning at work is brain plasticity. In this regard, long-term potentiation and long-term depression are key mechanisms of brain plasticity at the synaptic level among neurons.

Beginning in the 1970s, in a series of seminal experiments in animal models, it was shown

that stimulating brain slices in bursts of stimuli repeated over a theta frequency (ie, 5 to 7 Hz) was particularly effective in inducing long-term potentiation at neural synapses.¹⁵⁻¹⁸ These findings provided the rationale for the more recent development of patterned rTMS protocols such as theta-burst stimulation (TBS). TBS uses bursts of 3 pulses at 50 Hz, with each burst repeated at 5 Hz of frequency, to mimic the endogenous theta rhythms of the brain. Subsequent studies further demonstrated that TBS paradigms are particularly potent in inducing long-term potentiation and long-term depression in neuroanatomical areas and circuits, with effects persisting long after the stimulation has ceased.¹⁹⁻²¹

In addition, TBS protocols offer the advantage of shortening the time required to deliver a therapeutically effective protocol. Conventional 10-Hz rTMS treatments last 30 to 40 minutes, which imposes a time burden on the patient as well as a limit on the daily treatment capacity of each rTMS device. These limitations restrict the availability of this treatment and increase the cost of treatment. TBS requires a relatively short period of stimulation (eg, 40 to 190 seconds) to produce effects that are similar to much longer conventional protocols. Current TBS protocols for depression require as little as 1 to 7 minutes, rather than the 20 to 40 minutes for conventional protocols. Small pilot studies have suggested that TBS may be an effective antidepressant treatment; however, randomized controlled trials that compare TBS with conventional rTMS protocols are still needed.

Expanding the neuroanatomical targets for rTMS in depression

The earliest functional neuroimaging studies of depression, using PET, identified the DLPFC as hypoactive bilaterally in depressed individuals and found that clinical improvement related to antidepressant treatment was associated with a reversing of this hypoactivity.⁵⁻⁸ On the basis of these studies and later replications using fMRI, the DLPFC was a logical neuroanatomical target for the earliest rTMS protocols and, hence, early studies in clinical samples targeted this location.

An extensive literature of randomized controlled trials supports the efficacy of both excitatory rapid rTMS on the left DLPFC as well as inhibitory slow rTMS on the right DLPFC. However, there remains a significant proportion of individuals who do not respond to conventional rTMS to the DLPFC. Converging lines of evidence from lesion studies, fMRI, and PET suggest other relevant areas in the circuits that regulate and modulate mood, and the cognitive aspects tightly linked to it. Specifically, the dorsomedial prefrontal cortex and ventrolateral prefrontal cortex have been shown to be hypoactive in functional imaging studies, and structural or functional lesions of the dorsomedial prefrontal cortex cause a depressive syndrome presentation.

Areas such as the ventromedial prefrontal cortex and medial frontopolar cortex have been shown to be hyperactive in functional neuroimaging studies, and structural or functional lesions in these neuroanatomical locations can relieve and protect against depressive symptoms. Several case reports describe the complete remission of severe and refractory major depression in individuals who sustained localized brain damage in the ventromedial prefrontal cortex and the medial frontopolar cortex.¹¹ Novel coil designs may lead to superior efficacy because of their ability to target deeper areas, such as the ventromedial prefrontal cortex and medial frontopolar cortex.

Optimizing treatment schedules

Current available evidence for use of rTMS in depression supports its efficacy for the

treatment of acute depressive episodes. For this indication, the most frequent schedule involves daily rTMS sessions on weekdays for 4 to 6 weeks (although longer duration of treatment, as long as 9 weeks, has been investigated and has shown enhanced effectiveness). Of note, the majority of rTMS studies in major depression have investigated rTMS in community-based and outpatient populations.^{12,22}

The limited data available for inpatient samples typically used rTMS schedules with shorter, less effective durations (10 sessions)—perhaps because of the lack of clinical indication for admission and costs associated with maintaining an inpatient admission. Recently, there has been a renewed interest in protocols that concentrate more stimulations in a single day, in the hope of an accelerated response. These protocols would have particularly useful applications in inpatient populations, for whom the acuity of illness is greater and the cost of extended hospitalization is significant.

Following an initial course of treatment, the duration of the clinical response to rTMS is highly variable. Thus, the use of medication for relapse prevention should be considered. There is a scarcity of systematic evidence investigating the role of maintenance rTMS in the prevention of relapse and recurrence of depression. Nonetheless, case series and open-label studies suggest that for those who have responded to an initial course of treatment, a tapering course of maintenance rTMS can be effective in preventing relapse.²³ There is no consensus on a systematic protocol for maintaining response; some groups give no routine maintenance, others provide maintenance treatments less than 4 times per month, while others opt for more frequent maintenance treatments—once or twice weekly.

Future directions

One of the active areas of inquiry in depression is the search for biomarkers to help predict therapeutic response. fMRI has previously been helpful in defining targets for stimulation with rTMS, and it may also prove helpful in predicting the likelihood of response as well as the optimal site of stimulation and the optimal type of stimulation (excitatory or inhibitory). Currently there are no neuroimaging tools that can reliably predict the optimal treatment parameters or likelihood of success in a patient, although efforts to accomplish this are under way.

Conclusion

Based on meta-analyses of studies over the past 15 years and several large multicenter trials, it is clear that rTMS is an effective treatment for depression.²⁴⁻²⁷ The remission rates with rTMS are comparable to those seen in the third and fourth steps of the STAR*D trial: with remission rates of approximately 30% and response rates of approximately 40% to 50%.^{24,25}

Clinicians can feel confident in the evidence base when referring patients with a moderate level of treatment resistance for rTMS using high-frequency left-sided stimulation at 120% motor threshold for 3000 pulses per session. Preliminary results suggest that deep rTMS may be an effective option in patients who have failed to respond to more than one antidepressant treatment.²⁸

Current research efforts are under way to improve remission rates while reducing the time and cost burden of the treatment. Accelerated treatment regimens and theta-burst stimulation protocols could potentially achieve similar remission rates in a shorter or more

efficient time frame. Efforts to establish how best to sustain remission in patients who respond to rTMS are another central area of future work that must be addressed. Finally, the identification of reliable markers for selecting optimal treatment parameters and predicting treatment outcomes is an important goal for future research. These approaches will help establish rTMS as a safe, effective, and accessible treatment option for the large number of patients with treatment-resistant major depression.

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