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# Transcranial magnetic stimulation: A review of its evolution and current applications

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## Abstract

Repetitive transcranial magnetic stimulation (rTMS) is a recently developed noninvasive brain stimulation method for the treatment of psychiatric and neurological disorders. Although, its exact mechanism of action is still not clear, current evidence points toward its role in causing long-term inhibition and excitation of neurons in certain brain areas. As evidence steadily grows in favor of rTMS as a therapeutic tool; there is a need to develop standardized protocols for its administration. There have been no reports of any serious side effects with rTMS, though its use is restricted in those having magnetic implants or recent adverse neurological or cardiac event. Of all the psychiatric indications of rTMS, the evidence is most robust for treatment of refractory unipolar depression. This paper reviews contemporary literature highlighting the evolution of rTMS as a diagnostic and therapeutic tool, especially in the management of treatment-resistant depression.

**Keywords:** Long-term potentiation, repetitive transcranial magnetic stimulation, treatment-resistant depression

Energy is dynamic, has a frequency, can change its form and is electromSagnetic (EM) in nature. All atoms, chemicals and cells produce EM fields (EMFs) of their own and all 70 trillion cells in the body communicate via EM exchanges.[1] Disruption of EM flow of energy in cells can causes impaired cell metabolism and its role and that may be the underlying cause of any disease process. These principles have led to an explosion of information pertaining to understanding of normal and abnormal brain in the past few decades. Barker *et al.* discovered the induction of finger and foot movements through the use of magnetic coil placed on the motor cortex.[2] Transcranial magnetic stimulation (TMS) is a neurophysiological procedure for noninvasive stimulation of the nervous system. It involves the application of rapidly changing magnetic field to the superficial layers of the cerebral cortex, which locally induces small electric currents, known as “Eddy or Foucault currents.” Cerebral cortex acts as a secondary coil in this situation.[3] TMS has an advantage over electroconvulsive therapy (ECT) as it is focused and bypasses the impedance of skull and superficial tissues.

Therefore, it needs lesser stimulus strength and need for a true seizure or any form of anesthesia is completely obviated. However, despite the plethora of evidence supporting its usefulness in selected cases, skeptics continue to question its efficacy and the usage of repetitive TMS (rTMS) is still less. Therefore, a need was felt to systematically review the data on evolution and use of TMS in the treatment of refractory depression. We searched the PubMed/MEDLINE, EMBASE, PsycInfo, and Web of Science from inception up until July 2018. Two authors (AC and RKS) independently performed the search. Disagreements were discussed with other authors (PSB and KS) and resolved by consensus.

## THE DEVELOPMENT OF MODERN TRANSCRANIAL MAGNETIC STIMULATION

Experiments on electrical stimulation of cerebral cortex started somewhere in 1874 in which contralateral motor response was elicited. The laws of electro-magnetic induction were given by Faraday in 1881.[4] d'Arsonval (1896) pioneered the use of magnetic fields to induce cortical stimulation.[5] In 1959, Kolin *et al.* [6] achieved nerve stimulation by using magnetic energy in frogs which laid the foundation for EM stimulation of neural tissue for diagnostic and therapeutic purposes. In the past few years, there have been rapid advances in the development of shape of coils to ensure concentrated magnetic field to achieve better control over the spatial extent of excitation. While the old form of treatment took up to 37 min per session, with high-frequency (HF) theta-burst stimulation the session may last for few minutes only.[7] It is likely that treatment protocols will undergo further refinements in the years to come making it more comfortable for patients.

### Mechanism of action

TMS uses principles of EM induction. According to the principle of EM induction when an electric current is passed through a coil (primary coil), a magnetic field is generated. When the magnetic flux flows to the secondary coil (neural tissue), a secondary electrical field is induced, and this causes stimulation of the same. [5] Neurons have bent or curved axonal processes, passing at right angles to the lines of force of the magnetic field. They act like secondary coils and thus experience electrical effects.[8,9] Therefore, by changing the direction of current flow at HFs, rapidly alternating magnetic fields can be generated which in turn stimulate the underlying neurons and their fibers. The phenomenon of applying such stimulation in pulses is known as pulsed EMF stimulation which causes persistent depolarization. These pulsed stimulations are known to correct impaired functioning of cells and aid healing. Repetitive TMS works on similar principles and thus leads to observable clinical effects.[10]

## EFFECTS OF TRANSCRANIAL MAGNETIC STIMULATION

The effect of rTMS stimulation on the cortical surface depends on the frequency of pulses of stimulation. At low frequency (LF), i.e., <1 Hz, rTMS is inhibitory to the underlying cortex while stimulation at HF, i.e., >5 Hz, it is excitatory.[11,12] In TMS studies, cortical excitability (CSE) can be assessed by either calculation of resting motor threshold (RMT) or by calculation of Motor evoked potential (MEP). RMT is the minimal stimulation intensity required to produce a reliable motor response (twitch) in a peripheral muscle. The strength of the stimulus is then calculated based on RMT and normally, it is 120% of the RMT. In the other method to calculate CSE, the test stimulus is adjusted to produce MEP responses up to 0.5 mV. MEP size is the averaged response to a series of pulses applied at consistent stimulator intensity. HF rTMS (i.e., >5 Hz) appears to produce a persistent increase in MEP size and a reduction in cortical inhibition.[13]

The effects of TMS can be acute or prolonged depending on the mode of stimulation.

### Acute effects

Acute effects of TMS will depend on the area of the cortex being stimulated. In the primary motor cortex, it produces a muscle activity referred to as motor evoked potential (MEP). In the occipital cortex, it generates flashes of light or visual distortions also known as phosphenes. In other areas, it may lead to slowed cognition or speech arrest.[14]

## Prolonged effects

rTMS can increase or decrease the excitability of the cortical neurons depending on the frequency of stimulation. The mechanism of these effects is believed to reflect changes in synaptic efficacy akin to long-term potentiation or long-term depression. Other proposed mechanisms include alteration in levels of neurotrophic factors such as BDNF, modulation of CSE, and functional connectivity among brain circuits.[8] In a systematic review of patients treated with ECT, Fidalgo *et al.* reported a correlation of clinical outcome with changes in BDNF levels.[15] Although the study was conducted on patients undergoing ECT, the underlying biological mechanisms are akin to rTMS.

## Depth of stimulation

Depending on the type of coil and intensity of stimulus used, depth of stimulation can vary from 2 to 4 cm below the cortical surface. This means that only superficial brain structures can be stimulated.[13] Therefore, achieving equilibrium in depth-focality trade-off is a matter of intense research. Figure-8 type coils exhibit superior depth-focality than other coils.[16,17]

## Administration of transcranial magnetic stimulation

Informed consent – All patients are to be informed about the procedure, role in treatment, and expected adverse effects.

Transcranial magnetic stimulation safety screen – It is a standard set of 13 questions proposed by Rossi *et al.* [18] on behalf of the International Federation of Clinical Neurophysiology.

Food and Drug Administration (FDA) recommends at least 20 sessions spread over 4–6 weeks at a frequency of at least 5 times a week for treatment-resistant depression (TRD). It is also important to measure the symptoms with the help of a standardized questionnaire to monitor weekly progress or lack of it. A self-rated questionnaire in local vernacular (like Beck's Depression Inventory) is a useful instrument as it eliminates observer bias.[19,20]

## Scalp position of coil

While administering TMS, it is important to determine the position of the scalp and coil orientation for optimal therapeutic effects. In experimental models, the growing cells respond differently to moving electric fields. They tend to align preferentially either parallel or antiparallel to the field vector, a process known as galvanotaxis.[21] Forces in the direction perpendicular and parallel to the electric field are in competition with one another in a voltage-dependent manner, which ultimately govern the trajectories of the cells in the presence of an electric field.[22] Since hypofunctioning of the left dorsolateral prefrontal cortex (DLPFC) has been implicated in the pathophysiology of several psychiatric illnesses including depressive disorder; it remains the preferred area for stimulation in most of the studies.[23] There are two ways of determining surface landmark of DLPFC:

5 cm technique – About 05 cm toward the left of the vertex a point is marked and about 02 cm ahead of that lies the motor cortex. The motor cortex is functionally localized as a scalp position where TMS evokes a motor movement and a measurable motor-evoked potential (MEP) in the contralateral hand. The prefrontal cortex stimulation site is determined as 5 cm anterior further ahead of the motor strip in the parasagittal line. It corresponds to an area between F3 and F5 position of 10–20 system of EEG recording.[24]

Neuro-navigational method – This method is theoretically more precise and employs MRI scan to pinpoint DLFPC with live video navigation. Fitzgerald *et al.*[25] studied 51 patients with treatment-resistant depression using this method and compared matched controlled subjects with standard 5 cm technique and found the superior response at the end of 3 weeks. However, the method is yet to gain popularity probably owing to the high costs of equipment involved.[26]

According to existing literature, 5 cm method remains fairly reliable and popular method as far as daily rTMS sessions are concerned.

## Coil orientation in repetitive transcranial magnetic stimulation

In routine clinical and experimental models with rTMS, the amplitude of muscle evoked potential (MEP) is an indicator of the maximum effect of a particular orientation with reference to head position. Optimal stimulation has been reported if coil current was at an angle of 45° with respect to the sagittal plain.[27,28]

## Terminologies and dosing considerations associated with transcranial magnetic stimulation

These are the terms frequently encountered while using rTMS in either experimental or treatment models. A detailed description of these terms is given in Table 1. It is to be noted that modern rTMS machines have inbuilt software which automatically do most of these calculations though RMT has to be determined by one of the above-mentioned methods and pre-selected protocol has to be mentioned to the machine.[8,9]

## Treatment protocols and their efficacy

A brief summary of these protocols and the results are given in a tabular form as per Table 2. In the past two decades, research has focused on establishing sound protocols which could be replicated across various studies. However, the field is still wide open and newer protocols are being proposed.

## Indications/applications of transcranial magnetic stimulation

What initially started as a purely noninvasive diagnostic tool is slowly emerging as an effective tool in the hands of a harried clinician dealing with intractable and chronic psychiatric and neurological conditions. The discussion below is restricted to the psychiatric applications, especially for TRD.

## Investigational/diagnostic applications

Initially, the role of TMS was restricted to experimental brain research to localize motor and sensory areas. When combined with functional magnetic resonance imaging, positron-emission tomography or single-photon emission computed tomography, TMS indicates the functional integrity of intracortical neuronal structures and gives information about the conduction along various fibers, the function of nerve roots and peripheral motor pathways. It can also help in localizing level of the lesion within the nervous system in conditions such as stroke, injury, or demyelination/sclerosis.[39]

## Therapeutic uses

TMS is slowly gaining popularity as a useful therapeutic tool in many psychiatric disorders though FDA has cleared its role in Major unipolar depression and obsessive-compulsive disorder only. This paper focuses primarily on current evidence supporting its role in the treatment of unipolar depression. The findings are summarized in Table 3. George and Wassermann[40] first reported the benefits of daily rTMS to left PFC in resistant depression which were further corroborated by Pascual-Leone *et al.*[41] in 1996 and Liu *et al.*[42] In their meta-analysis, the pooled rates for rTMS group were 46.6% and 22.1% for response and remission, respectively. The pooled odds ratio was 5.12 (95% confidence interval; 2.11–12.45, $P = 0.0003$). The number needed to treat in their analysis was 3.4. However, there was marked variability in terms of number of treatments and the stimulus intensity. Padberg *et al.*[43] provided evidence of relation between antidepressant

efficacy and stimulation intensity. They found clinical improvement at 100% RMT as compared to sub-threshold at 90% RMT. Avery *et al.*[44] reported results of their double-blind sham-controlled RCT done on 68 TRD patients (35 in rTMS and 33 in the sham arm). Patients with medication-resistant depression were randomized to receive 15 sessions of active or sham rTMS delivered to the left DLPFC at 110% RMT. Each session consisted of 32 trains of 10 Hz rTMS delivered in 5-s trains. They concluded that by adjusting the protocol to therapeutic levels in terms of stimulation intensity, pulse frequency and number of treatments, rTMS is an effective strategy to treat-resistant depression. The probability of adverse effects besides clinical improvement was the focus of research by O'Reardon *et al.*[45] They found a significant reduction in HAMD score after 4 weeks of treatment with rTMS and reported minimal side effects such as scalp pain (35%) and local discomfort (10%). These effects were transient and resolved spontaneously within a few minutes or hours. Long-term efficacy of rTMS in the prevention of recurrence and relapse has been topic of intense debate. Dunner *et al.*[46] studied long-term effectiveness of TMS across many sites and concluded that TMS demonstrates a statistically and clinically meaningful durability of acute benefit over 12 months of follow-up. Cost-benefit ratio was another area of research, which warranted systematic analysis. Nguyen and Gordon[47] concluded that rTMS was statistically superior and cost-effective antidepressant for patients with TRD. However, web results in this area did not reveal many references. In brief, research about long-term efficacy and cost-benefit ratio is sparse and continues to be hotly debated, especially in third world countries where resources are limited. Regarding who may benefit more from rTMS therapy, Fregni *et al.*[48] concluded that rTMS may be most suited for younger and less treatment-resistant patients. Head-to-head comparison of rTMS with ECT was done by Slotema *et al.*,[49] who reported that ECT was superior to rTMS in the treatment of depression (mean weighted effect size −0.47, $P < 0.004$). However, comparative acceptability and side effect profile were superior for rTMS. Chen *et al.*,[50] conducted head-to-head comparison of ECT and rTMS as augmentation strategy for TRD. They included 25 studies with 1288 individuals with MDD. They reported that ECT was more efficacious than bilateral-PFC rTMS, however, differences were not statistically significantly. Razza *et al.*[51] reported that though there may be placebo response to rTMS in depression trials, pooled data reveal that current protocols achieve 29%–49% response and 19%–34% remission in TRD, indicating intermediate efficacy between medication and ECT. In 2014, the International Federation of Clinical Neurophysiology gave guidelines for therapeutic use of rTMS.[13] They gave three levels of evidence for the efficacy of rTMS in various neuro-psychiatric disorders, i.e., level A (definite efficacy) was for antidepressant effect of HF-rTMS of left DLPFC, level B (probable efficacy) for antidepressant effect of LF rTMS of the right DLPFC and HF-rTMS of the left DLPFC for the negative symptoms of schizophrenia; whereas level C (possible efficacy) was for LF-rTMS of the left temporoparietal cortex for auditory hallucinations in Schizophrenia. The most recent approval by US FDA for rTMS has been for obsessive-compulsive disorders in Aug 2018.[52]

## Use of repetitive transcranial magnetic stimulation in special population

Although a lot of data and best practice recommendations for TMS usage in adults are largely available, there is a dearth of similar data for the pediatric population. However, its practice in children continues to grow. Its minimal risk, excellent tolerability and increasingly sophisticated ability to interrogate neurophysiology and plasticity make it an easy technology for use in pediatric research, with future extension into therapeutic trials. While adult trials show promise in using TMS as a novel, noninvasive, nonpharmacologic diagnostic and therapeutic tool in a variety of neurological disorders, its use in children is only just emerging.[53,54] Its use in pregnancy is safe and effective and pregnancy *per se* is not a contraindication.[55] rTMS was well tolerated and found to be statistically and clinically effective in pregnant patients with TRD. It may be preferred choice of treatment in the elderly population owing to the lack of cognitive side effects and very little chance of drug interactions. Cognitive impairment has been researched the most in this population and evidence so far suggests that TMS may, in fact, have therapeutic benefits.[56] However, additional research that specifically includes older subjects is needed to replicate findings and to optimize treatment protocols for this population.

### Other psychiatric indications of transcranial magnetic stimulation

There are reports of the role of rTMS in chronic schizophrenia in controlling intractable hallucinations and negative symptoms. The US FDA and NICE guidelines (UK) have included rTMS a therapy for treating migraine.[57,58] There are also reports of its role in treatment of anxiety disorder like PTSD and substance use disorders. However, detailed description of these indications is beyond the purview of this article and reader is advised to refer to other sources of information.[59,60]

## CONCLUSION

The field of diagnostics and therapeutics in psychiatry is still in a state of flux. As research in neurosciences moves at a rapid pace, there is a need to translate the findings into treatment methods. rTMS is a big step in this direction and offers a therapeutic approach without serious and long-lasting side effects. It is slowly emerging as an effective tool in managing TRD, though evidence in favor of its role in other psychiatric conditions is still sparse. It is safe and well tolerated by most patients. There is a need to develop well-standardized protocols for its application and to establish it as an affordable therapeutic tool.


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### Conflicts of interest

There are no conflicts of interest.

## REFERENCES


1. Muehsam D, Ventura C. Life rhythm as a symphony of oscillatory patterns: Electromagnetic energy and sound vibration modulates gene expression for biological signaling and healing. Glob Adv Health Med. 2014;3:40–55. [PMCID: PMC4010966] [PubMed: 24808981]

2. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet. 1985;1:1106–7. [PubMed: 2860322]

3. Horvath JC, Perez JM, Forrow L, Fregni F, Pascual-Leone A. Transcranial magnetic stimulation: A historical evaluation and future prognosis of therapeutically relevant ethical concerns. J Med Ethics. 2011;37:137–43. [PubMed: 21106996]

4. Cohen Kadosh R, Elliott P. Neuroscience: Brain stimulation has a long history. Nature. 2013;500:529. [PubMed: 23985862]

5. Hasey GM. Transcranial magnetic stimulation: Using a law of physics to treat psychopathology. J Psychiatry Neurosci. 1999;24:97–101. [PMCID: PMC1188989] [PubMed: 10212551]

6. Kolin A, Brill NQ, Broberg PJ. Stimulation of irritable tissues by means of an alternating magnetic field. Proc Soc Exp Biol Med. 1959;102:251–3. [PubMed: 14410710]

7. Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): A randomised non-inferiority trial. Lancet. 2018;391:1683–92. [PubMed: 29726344]

8. Klomjai W, Katz R, Lackmy-Vallée A. Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS) Ann Phys Rehabil Med. 2015;58:208–13. [PubMed: 26319963]

9. Mishra BR, Sarkar S, Praharaj SK, Mehta VS, Diwedi S, Nizamie SH, et al. Repetitive transcranial magnetic stimulation in psychiatry. Ann Indian Acad Neurol. 2011;14:245–51. [PMCID: PMC3271460] [PubMed: 22346010]

10. Sorrell RG, Muhlenfeld J, Moffett J, Stevens G, Kesten S. Evaluation of pulsed electromagnetic field therapy for the treatment of chronic postoperative pain following lumbar surgery: A pilot, double-blind, randomized, sham-controlled clinical trial. J Pain Res. 2018;11:1209–22. [PMCID: PMC6018879] [PubMed: 29950893]

11. Chen M, Deng H, Schmidt RL, Kimberley TJ. Low-frequency repetitive transcranial magnetic stimulation targeted to premotor cortex followed by primary motor cortex modulates excitability differently than premotor cortex or primary motor cortex stimulation alone. Neuromodulation. 2015;18:678–85. [PMCID: PMC5154674] [PubMed: 26307511]

12. Berlim MT, Van den Eynde F, Jeff Daskalakis Z. Clinically meaningful efficacy and acceptability of low-frequency repetitive transcranial magnetic stimulation (rTMS) for treating primary major depression: A meta-analysis of randomized, double-blind and sham-controlled trials. Neuropsychopharmacology. 2013;38:543–51. [PMCID: PMC3572468] [PubMed: 23249815]

13. Lefaucheur JP, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS) Clin Neurophysiol. 2014;125:2150–206. [PubMed: 25034472]

14. Fitzgerald PB, Fountain S, Daskalakis ZJ. A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. Clin Neurophysiol. 2006;117:2584–96. [PubMed: 16890483]

15. Fidalgo TM, Morales-Quezada JL, Muzy GS, Chiavetta NM, Mendonca ME, Santana MV, et al. Biological markers in noninvasive brain stimulation trials in major depressive disorder: A systematic review. J ECT. 2014;30:47–61. [PMCID: PMC4260176] [PubMed: 23845938]

16. Deng ZD, Lisanby SH, Peterchev AV. Electric field depth-focality tradeoff in transcranial magnetic stimulation: Simulation comparison of 50 coil designs. Brain Stimul. 2013;6:1–3. [PMCID: PMC3568257] [PubMed: 22483681]

17. Suchorska B, Ruge MI. Deep brain stimulation: Current applications and future prospects. Discov Med. 2015;20:403–11. [PubMed: 26760984]

18. Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Screening questionnaire before TMS: An update. Clin Neurophysiol. 2011;122:1686. [PubMed: 21227747]

19. Basker M, Moses PD, Russell S, Russell PS. The psychometric properties of beck depression inventory for adolescent depression in a primary-care paediatric setting in India. Child Adolesc Psychiatry Ment Health. 2007;1:8. [PMCID: PMC1976414] [PubMed: 17688697]

20. Wang YP, Gorenstein C. Psychometric properties of the beck depression inventory-II: A comprehensive review. Braz J Psychiatry. 2013;35:416–31. [PubMed: 24402217]

21. Li Y, Gu Y, Wang H, Liu Z, Song B, Yin T, et al. Electric pulses can influence galvanotaxis of *Dictyostelium discoideum*. Biomed Res Int. 2018;2018:2534625. [PMCID: PMC6112078] [PubMed: 30186854]

22. Huang YJ, Samorajski J, Kreimer R, Searson PC. The influence of electric field and confinement on cell motility. PLoS One. 2013;8:e59447. [PMCID: PMC3608730] [PubMed: 23555674]

23. Paillère Martinot ML, Galinowski A, Ringuenet D, Gallarda T, Lefaucheur JP, Bellivier F, et al. Influence of prefrontal target region on the efficacy of repetitive transcranial magnetic stimulation in patients with medication-resistant depression: A [(18)F]-fluorodeoxyglucose PET and MRI study. Int J Neuropsychopharmacol. 2010;13:45–59. [PubMed: 19267956]

24. Beam W, Borckardt JJ, Reeves ST, George MS. An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. Brain Stimul. 2009;2:50–4. [PMCID: PMC2882797] [PubMed: 20539835]

25. Fitzgerald PB, Hoy K, McQueen S, Maller JJ, Herring S, Segrave R, et al. A randomized trial of rTMS targeted with MRI based neuro-navigation in treatment-resistant depression. Neuropsychopharmacology. 2009;34:1255–62. [PubMed: 19145228]

26. Vaghefi E, Cai P, Fang F, Byblow WD, Stinear CM, Thompson B, et al. MRI guided brain stimulation without the use of a neuronavigation system. Biomed Res Int. 2015;2015:647510. [PMCID: PMC4564628] [PubMed: 26413537]

27. Herwig U, Padberg F, Unger J, Spitzer M, Schönfeldt-Lecuona C. Transcranial magnetic stimulation in therapy studies: Examination of the reliability of "standard" coil positioning by neuronavigation. Biol Psychiatry. 2001;50:58–61. [PubMed: 11457424]

28. Richter L, Neumann G, Oung S, Schweikard A, Trillenberg P. Optimal coil orientation for transcranial magnetic stimulation. PLoS One. 2013;8:e60358. [PMCID: PMC3623976] [PubMed: 23593200]

29. Boutros NN, Gueorguieva R, Hoffman RE, Oren DA, Feingold A, Berman RM. Lack of a therapeutic effect of a 2-week sub-threshold transcranial magnetic stimulation course for treatment-resistant depression. [Last cited on 2018 Oct 08];Psychiatry Res [Internet] 2002 113:245–54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12559481 . [PubMed: 12559481]

30. Couturier JL. Efficacy of rapid-rate repetitive transcranial magnetic stimulation in the treatment of depression: A systematic review and meta-analysis [Internet] [Last cited 2018 Oct 08];J Psychiatry Neurosci. 2005 30 Available from: www.cochrane.org . [PMCID: PMC551158] [PubMed: 15798783]

31. George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: A shamcontrolled randomized trial. Arch Gen Psychiatry. 2010 [PubMed: 20439832]

32. Hadley D, Anderson BS, Borckardt JJ, Arana A, Li X, Nahas Z, et al. Safety, Tolerability, and Effectiveness of High Doses of Adjunctive Daily Left Prefrontal Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression in a Clinical Setting. [Last cited on 2018 Oct 08];J ECT [Internet] 2011 27:18–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21343710 . [PubMed: 21343710]

33. Mantovani A, Aly M, Dagan Y, Allart A, Lisanby SH. Randomized sham controlled trial of repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex for the treatment of panic disorder with comorbid major depression. [Last cited on 2018 Oct 08];J Affect Disord [Internet] 2013 144:153–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22858212 . [PubMed: 22858212]

34. Sayar GH, Ozten E, Tan O, Tarhan N. Transcranial magnetic stimulation for treating depression in elderly patients. Neuropsychiatr Dis Treat. 2013 [PMCID: PMC3666544] [PubMed: 23723700]

35. Bulteau S, Sebille V, Fayet G, Thomas-Ollivier V, Deschamps T, Bonnin-Rivalland A, et al. Efficacy of intermittent Theta Burst Stimulation (iTBS) and 10-Hz highfrequency repetitive transcranial magnetic stimulation (rTMS) in treatment-resistant unipolar depression: Study protocol for a randomised controlled trial. Trials. 2017 [PMCID: PMC5237321] [PubMed: 28086851]

36. Pamela D SS. US FDA report on HORIZON TMS therapy system [Internet] Maryland: 2018. [Last cited on 2018 Sep 10]. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf18/K180907.pdf .

37. Royal College of Psychiatrists C on E and related treatment. Statement on Repetitive Transcranial Magnetic Stimulation for Depression. 2017. [Last cited on 2018 Oct 08]. Available from: https://www.rcpsych.ac.uk/pdf/Repetative%20Transcranial%20Magnetic%20Stimulation%20-%20ECT%20ctee%20statement%20May18.pdf .

38. Wilson MT, St George L. Repetitive Transcranial Magnetic Stimulation: A Call for Better Data. [Last cited on 2018 Oct 08];Front Neural Circuits [Internet] 2016 10:57. Available from: www.frontiersin.org . [PMCID: PMC4971102] [PubMed: 27536222]

39. Cortes M, Black-Schaffer RM, Edwards DJ. Transcranial magnetic stimulation as an investigative tool for motor dysfunction and recovery in stroke: An overview for neurorehabilitation clinicians. Neuromodulation. 2012;15:316–25. [PMCID: PMC3760962] [PubMed: 22624621]

40. George MS, Wassermann EM, Williams WA, Callahan A, Ketter TA, Basser P, et al. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. Neuroreport. 1995;6:1853–6. [PubMed: 8547583]

41. Pascual-Leone A, Rubio B, Pallardó F, Catalá MD. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. Lancet. 1996;348:233–7. [PubMed: 8684201]

42. Liu B, Zhang Y, Zhang L, Li L. Repetitive transcranial magnetic stimulation as an augmentative strategy for treatment-resistant depression, a meta-analysis of randomized, double-blind and sham-controlled study. BMC Psychiatry. 2014;14:342. [PMCID: PMC4264336] [PubMed: 25433539]

43. Padberg F, Zwanzger P, Keck ME, Kathmann N, Mikhaiel P, Ella R, et al. Repetitive transcranial magnetic stimulation (rTMS) in major depression: Relation between efficacy and stimulation intensity. Neuropsychopharmacology. 2002;27:638–45. [PubMed: 12377400]

44. Avery DH, Holtzheimer PE, 3rd, Fawaz W, Russo J, Neumaier J, Dunner DL, et al. A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. Biol Psychiatry. 2006;59:187–94. [PubMed: 16139808]

45. O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: A multisite randomized controlled trial. Biol Psychiatry. 2007;62:1208–16. [PubMed: 17573044]

46. Dunner DL, Aaronson ST, Sackeim HA, Janicak PG, Carpenter LL, Boyadjis T, et al. A multisite, naturalistic, observational study of transcranial magnetic stimulation for patients with pharmacoresistant major depressive disorder: Durability of benefit over a 1-year follow-up period. J Clin Psychiatry. 2014;75:1394–401. [PubMed: 25271871]

47. Nguyen KH, Gordon LG. Cost-effectiveness of repetitive transcranial magnetic stimulation versus antidepressant therapy for treatment-resistant depression. Value Health. 2015;18:597–604. [PubMed: 26297087]

48. Fregni F, Marcolin MA, Myczkowski M, Amiaz R, Hasey G, Rumi DO, et al. Predictors of antidepressant response in clinical trials of transcranial magnetic stimulation. Int J Neuropsychopharmacol. 2006;9:641–54. [PubMed: 16939662]

49. Slotema CW, Blom JD, Hoek HW, Sommer IE. Should we expand the toolbox of psychiatric treatment methods to include repetitive transcranial magnetic stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. J Clin Psychiatry. 2010;71:873–84. [PubMed: 20361902]

50. Chen SJ, Chang CH, Tsai HC, Chen ST, Lin CC. Superior antidepressant effect occurring 1 month after rTMS: Add-on rTMS for subjects with medication-resistant depression. Neuropsychiatr Dis Treat. 2013;9:397–401. [PMCID: PMC3617929] [PubMed: 23576870]

51. Razza LB, Moffa AH, Moreno ML, Carvalho AF, Padberg F, Fregni F, et al. A systematic review and meta-analysis on placebo response to repetitive transcranial magnetic stimulation for depression trials. Prog Neuropsychopharmacol Biol Psychiatry. 2018;81:105–13. [PubMed: 29111404]

52. US FDA. Press Announcements – FDA Permits Marketing of Transcranial Magnetic Stimulation for Treatment of Obsessive Compulsive Disorder. [Last accessed on 2018 Aug 31];Office of the Commissioner. Avaialble from: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm617244.htm .

53. Rajapakse T, Kirton A. Non-invasive brain stimulation in children: Applications and future directions [Internet] [Last accessed on 2018 Oct 08];Translational Neuroscience. 2013 4:217–33. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3807696/pdf/nihms-510197.pdf .

54. Allen CH, Kluger BM, Buard I. Safety of transcranial magnetic stimulation in children: A systematic review of the literature HHS public access. [Last accessed on 2018 Oct 08];Pediatr Neurol. 2017 68:3–17. Avaialble from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5346461/pdf/nihms-840696.pdf . [PMCID: PMC5346461] [PubMed: 28216033]

55. Hızlı Sayar G, Ozten E, Tufan E, Cerit C, Kağan G, Dilbaz N, et al. Transcranial magnetic stimulation during pregnancy. Arch Womens Ment Health. 2014;17:311–5. [PubMed: 24248413]

56. Iriarte IG, George MS. Transcranial magnetic stimulation (TMS) in the elderly. Curr Psychiatry Rep. 2018;20:6. [PubMed: 29427050]

57. [Last accessed on 2018 Aug 31];US FDA. Consumer Updates – Treating Migraines: More Ways to Fight the Pain. Office of the Commissioner. Avaialble from: https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm414707.htm .

58. National Institute for Health and Care Excellence. Transcranial Magnetic Stimulation for Treating and Preventing Migraine. National Institute for Health and Care Excellence. 2014:1–8.

59. Gorelick DA, Zangen A, George MS. Transcranial magnetic stimulation in the treatment of substance addiction. Ann N Y Acad Sci. 2014;1327:79–93. [PMCID: PMC4206564] [PubMed: 25069523]

60. Dilkov D, Hawken ER, Kaludiev E, Milev R. Repetitive transcranial magnetic stimulation of the right dorsal lateral prefrontal cortex in the treatment of generalized anxiety disorder: A randomized, double-blind sham controlled clinical trial. Prog Neuropsychopharmacol Biol Psychiatry. 2017;78:61–5. [PubMed: 28533148]

## Figures and Tables

## Table 1

Various terms used in transcranial magnetic stimulation[5,8]

| Term | Description |
|---|---|
| Stimulus strength | A measure of magnetic field, generally expressed in terms of percentage of maximum machine capacity (about 1-3 T) |
| MT | Minimum stimulus strength that produces 5 motor responses out of 10 stimuli when applied over a specified muscle area e.g., thumb area |
| Frequency | Number of stimuli given in 1 s |
| Single pulse | Single stimulus given after fixed interval, for example, after every 5 s |
| Frequency | The number of stimuli in a given pulse |
| Pulse train | Several pulses administered continuously in a given period of time |
| Inter-train interval | The time gap between two trains |
| Repetitive TMS | Trains of pulses applied to one brain area, slow: Low frequency <1 Hz, fast (high frequency) >1 Hz |
| Theta burst | Three magnetic pulses with an inter-stimulus interval of 20 m (50 Hz) were applied repeatedly every 200 m representing the theta rhythm of 5 Hz. (Hence named theta as it corresponds to theta rhythm of EEG) |
| Session | A time period in a day when rTMS is administered; typically in one session several trains are administered (1200-3000) |

MT - Motor threshold; TMS - Transcranial magnetic stimulation; EEG - Electroencephalography; rTMS - Repetitive TMS

**Table 2**

Various protocols used for treatment resistant depression

| Years | Authors | Protocol/procedure/finding/remarks |
|---|---|---|
| 2002 | Boutros *et al*. [29] | Open label singe-blind study. Twenty one patients treated with sub-threshold (80% RMT) for 10 sessions over 2 weeks (20 Hz, 2-s trains, 20 trains). No meaningful clinical gain achieved |
| 2005 | Couturier[30] | Systematic meta-analysis and review of various protocols. rTMS is no different from sham treatment in major depression |
| 2010 | George *et al*. [31] | Sham controlled randomized trial. 199 TRD patients. Left prefrontal cortex at 120% MT (10 Hz, 4-s train duration, and 26-s intertrain interval) for 37.5 min (3000 pulses per session) using a figure-eight solid-core coil. The odds of attaining remission were 4.2 times greater with active rTMS than with sham |
| 2011 | Hadley *et al*. [32] | Open-label study. Nineteen patients received daily left prefrontal rTMS at 120% resting MT, 10 Hz, 5 s on, and 10 s off and for a mean of 6800 stimuli per session (34,000 stimuli per week), these higher rTMS doses were well tolerated without significant adverse effects or adverse events. All measured dimensions showed improvement, with many showing improvement in 1-2 weeks. Of perhaps most importance, suicidal ideation diminished in 67% of the patients after just 1 week |
| 2013 | Mantovani *et al*.[33] | Twenty five patients compared with matched controls. Cases received 1800 stimuli/day, 1-Hz, at 110% of RMT; Five times/week. At 4 weeks, response rate for panic disorder was 50% with active rTMS and 8% with sham. After 8 weeks of active rTMS, response rate was 67% for panic and 50% for depressive symptoms. A longer course of treatment resulted in better outcomes for both panic disorder and major depression |
| 2013 | Hizli Sayar *et al*.[34] | Prospective open study. 65 depressed elderly patients, 6 days/week, for 3 weeks. 100% RMT, 25 Hz, 2 s duration, 20 times with 30 s interval. Total 1000 pulses. Treatment safe and effective |
| 2017 | Bulteau *et al*. [35] | Randomized, controlled, double-blind, single-center study with two parallel arms. Intermittent theta burst, 80% MT, 50Hz, burst frequency 5Hz, 3 pulses, number of bursts 3, cycle time 10 s, number of cycles 20, 600 pulses. Ongoing study |
| 2011/2017 | FDA (USA) [36] 2011 and RC Psych (UK) [37] | 120% above MT, 10 Hz, pulse duration: 4 s, 10 pulses per second, 26 s off, number of trains 75, 3000 pulses, total actual treatment time: 37.5 min |
| 2016 | Wilson and St George[38] | The authors reviewed existing protocols and their efficacy and called for uniformity and standardization of the procedure. They also acknowledged rapid advances and advocated collaing the data |
| 2018 | Blumberger | Randomized, multicenter, double-blind, clinical trial in which 205 patients received |

The protocols for delivering TMS are gradually evolving and keeping pace with technology and research in biosciences. The table shows evolution and refinement of protocols for TMS. It is noteworthy that latest protocols favor the role of TMS in TRD and are less time consuming. Dominant (left) DLPFC is the preferred site for stimulation in most studies. MT - Motor threshold; RMT - Resting MT; TMS - Transcranial magnetic stimulation; rTMS - Repetitive TMS; TRD - Treatment resistant depression; iTBS - Intermittent theta burst stimulation; DLPFC - Dorsolateral prefrontal cortex

**Table 3**

Summary of evidence for therapeutic uses of repetitive transcranial magnetic stimulation

| Author | Methodology | Year of publication | Measures | Outcome | Additional remarks |
|---|---|---|---|---|---|
| Pascual-leone *et al*. [41] | Multiple cross-over, randomised placebo controlled trial | July 1996/The Lancet | HDRS<br>BQ | Significant improvement in HDRS and BQ scores after real rTMS over left DLPFC<br>11/17 patients showed pronounced improvement that lasted for 2 weeks after 5 days of daily rTMS sessions | No patient experienced any significant undesirable side-effects |
| Liu *et al*. [42] | Meta-analysis | 2014/BMC Psychiatry | Pooled OR<br>NNT | Pooled response and remission rate for the rTMS and sham group was 46.6% and 22.1%, respectively; pooled OR was 5.12 (95% CI 2.11-12.45, $Z$=3.60, $P$=0.0003), NNT was 3.4<br>Pooled SMD of change from baseline was 0.86 (95% CI 0.57-1.15, $Z$=5.75, $P$<0.00001) | rTMS was a safe strategy with relatively low adverse events and low dropout rate |
| Padberg *et al*.[43] | Parallel design controlled study | 2002/Neuro psychopharmacology | HDRS<br>MADRS<br>Duration of hospital stay | HRSD decrease by 30% after 100% MT rTMS<br>For MADRS scores, the antidepressant effect significantly increased from sham rTMS<br>over 90% MT rTMS to 100% MT rTMS ($P$<0.05)<br>rTMS at MT | No severe side effects of rTMS were observed |

Open in a separate window

TMS - Transcranial magnetic stimulation; rTMS - Repetitive TMS; LF - Low-frequency; dTMS - Deep TMS; BQ - Beck questionnaire; DLPFC - Dorsolateral prefrontal cortex; OR - Odds ratio; NNT - Number needed to treat; CI - Confidence interval; SMD - Standardized mean difference; MT - Motor threshold; ECT - Electroconvulsive therapy; RCT - Randomized controlled trial; HF - High-frequency; HDRS - Hamilton depression rating scale; MADRS - Montgomery-asberg depression rating scale; HRSD - Hamilton rating scale for depression; AD - Anti-depressant medication; CGI-S - Clinical Global Impression- severity scale; IDS-SR - Inventory of Depressive Symptomatology (Self-Report); PHQ-9 - Patient health Questionnaire-9; QALY - Quality Adjusted LifeYear; US FDA - United States Food and Drug Administration; YBOCS -Yale-Brown Obsessive Compulsive Scale