Alpha Psychiatry

EDITORIAL COMMENT
Alpha Psychiatry 2023;24(6):270-272
DOI: 10.5152/alphapsychiatry.2023.231401

Optimization Strategies of Transcranial Magnetic Stimulation in Major Depressive Disorder

Major depressive disorder (MDD), a widely prevalent and incapacitating illness, imposes a significant burden on individuals and society.[1–3] Alongside pharmacological and psychological interventions, nonsurgical brain stimulation techniques, such as transcranial magnetic stimulation (TMS), are frequently employed to treat MDD.[4] Conventional repetitive TMS (rTMS) includes low-frequency (LF) and high-frequency (HF) magnetic stimulation to the right and left dorsolateral prefrontal cortex, respectively. However, standard rTMS protocols may not be effective for all patients with MDD. Hence, optimization strategies of conventional rTMS, such as deep, priming, accelerated, or synchronized TMS or theta burst stimulation (TBS), including intermittent, continuation, and bilateral TBS, have been developed to enhance the treatment outcomes.[4]

Transcranial Magnetic Stimulation

Repetitive Transcranial Magnetic Stimulation

In rTMS, HF-rTMS is an U.S. Food and Drug Administration (FDA)-approved technique for the treatment of treatment-resistant depression (TRD).[5] Bilateral rTMS[6] and accelerated rTMS[7] are promising techniques for treating MDD. A meta-analysis reported that bilateral rTMS is a potentially effective treatment for MDD, offering clinically significant benefits over standard antidepressant medications and unilateral rTMS.[6] Furthermore, daily multiple treatment sessions of accelerated rTMS can reduce the overall treatment duration, enhance clinical efficiency, and expedite the onset of antidepressant effects.[7] Notably, 4 sessions per day of accelerated rTMS were found to be more effective than intranasal esketamine.[8]

Deep Transcranial Magnetic Stimulation

Deep TMS is an FDA approved technique for treating TRD.[9] Using a specific coil configuration (helmet-like H-coil), wider cortical penetration and deeper brain region stimulation can be achieved by deep TMS, thereby augmenting its therapeutic effectiveness.[10] A multicenter study reported that deep TMS is a promising intervention for MDD and its therapeutic effects last for at least 3 months during the maintenance phase of the treatment.[11] Furthermore, accelerated deep TMS protocols involving multiple sessions per day (2, 3, 5, or 10 times per day), are safe and effective therapeutic options for MDD.[12] These protocols offer a treatment alternative with a rapid onset of action and prolonged durability.[12]

Priming Transcranial Magnetic Stimulation

Priming TMS is a variant of LF-rTMS with a specific protocol that involves a brief administration of low-intensity HF-rTMS or "priming stimulation," followed by the main treatment of LF-rTMS targeted to the right dorsolateral prefrontal cortex (DLPFC).[4] Iyer et al[13] discovered that a more pronounced depression of motor cortex excitability through 1 Hz treatment can be achieved when it is preceded by a priming rTMS at 6 Hz.[13] Research indicates that the utilization of low-intensity, HF priming stimulation may enhance the efficacy of LF-rTMS stimulation.[4,14] Additionally, a network meta-analysis revealed that priming TMS exhibits a greater response compared to continuous TBS.[4] Notably, compared to sham stimulation, priming TMS also exhibited lower rates of participant attrition.[4]

Synchronised Transcranial Magnetic Stimulation

Synchronized TMS is a therapeutic technique that is synchronized with the alpha frequency of an individual's electroencephalogram .[15] This technique has been reported to offer greater advantages for patients with more pronounced depression severity and heightened anxiety levels at baseline compared to sham synchronized TMS.[15] Conversely, a network meta-analysis

Kai-Si Wen[1]
Wei Zheng[2]

[1]Guangxi University of Traditional Chinese Medicine, Nanning, China
[2]The Affiliated Brain Hospital of Guangzhou Medical University, Guangzhou, China

Corresponding author:
Wei Zheng
zhengwei0702@163.com

Received: October 30, 2023
Accepted: November 13, 2023
Publication Date: December 29, 2023

Cite this article as: Wen K-S, Zheng W. Optimization strategies of transcranial magnetic stimulation in major depressive disorder. *Alpha Psychiatry.* 2023;24(6):270-272.

Copyright@Author(s) - Available online at alpha-psychiatry.com.
Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

has also reported that synchronized TMS does not exhibit superior antidepressant efficacy compared to sham for treating MDD.[4]

Theta Burst Stimulation

Intermittent Theta Burst Stimulation

Intermittent TBS is a recently developed TMS technique (3 minutes and 9 seconds) that has demonstrated comparable effectiveness to HF-rTMS (37.5 minutes) in treating MDD[16] and has been approved by the FDA for treating TRD.[17] A study reported that Stanford neuromodulation therapy (SNT) through resting-state functional connectivity magnetic resonance imaging to specifically target high-dose intermittent TBS comprising 10 daily sessions of 18 000 pulses per day for 5 consecutive days, totaling 90 000 pulses, demonstrated superior effectiveness compared to sham stimulation for TRD.[18] A recent systematic review found that SNT is effective in the treatment of TRD.[19] Similarly, a recent meta-analysis revealed that active accelerated intermittent TBS protocols of ≥2 sessions per day exhibited a greater study-defined response compared to sham stimulation,[20] indicating that faster treatment protocols can reduce treatment duration while maintaining comparable efficacy.

Continuation Theta Burst Stimulation

In contrast to LF-rTMS (e.g., 1 Hz), which requires >20 minutes of continuous stimulation, continuous TBS produces 20 minutes of suppression with 20-second stimulation.[21] A single-arm prospective study determined that continuous TBS is a safe, well-tolerated, and effective treatment for patients with depression.[22] However, 3 randomized controlled trials (RCTs) investigating the efficacy and safety of active continuation TBS compared to sham stimulation in individuals with depression did not reveal any significant advantage in improving depressive symptoms.[23-25] A recent meta-analysis found that cTBS is not effective for treating major depressive episodes.[26]

Bilateral Theta Burst Stimulation

In addition to unilateral TBS, the application of left facilitatory and right inhibitory stimulation from bilateral TBS seems to be equally effective in the treatment of MDD.[24,27] A recent meta-analysis of RCTs (n = 285) revealed that bilateral TBS, specifically intermittent TBS over the left DLPFC and continuous TBS over the right DLPFC, is a well-tolerated form of rTMS that exhibits significant antidepressant effects, particularly in individuals with MDD.[28] Notably, bilateral TBS showed similar improvement in depressive symptoms when compared to standard bilateral rTMS in older adults.[29] Presently, no head-to-head studies have been published comparing bilateral TBS with bilateral rTMS for the treatment of depression in adults or adolescents.

Beyond pharmacological and psychological interventions, non-surgical brain stimulation techniques, including rTMS, represent a tertiary approach to managing MDD. The latest Canadian Network for Mood and Anxiety Treatments guidelines regard rTMS as the primary recommendation for individuals with MDD who exhibited an insufficient response to at least 1 trial of antidepressant medication.[30] The generalizability and treatment capacity of standard rTMS protocols have been limited by their long treatment sessions (37.5 minutes). To address this limitation, optimization strategies, such as the use of intermittent TBS with shorter sessions (3 minutes and 9 seconds), have been implemented clinically. Further research is warranted to explore the most effective dosing regimen for each optimization strategy of standard rTMS, including the determination of the optimal frequency of daily sessions, total sessions, and temporal distribution of treatment days.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – W.Z.; Design – W. Z., K-S. W.; Supervision – W.Z.; Resources – W.Z.; Materials – W.Z.; Data Collection and/or Processing – W.Z.; Analysis and/or Interpretation – W.Z.; Literature Search – W.Z.; Writing – K-S.W., W.Z.; Critical Review – W.Z.

Declaration of Interests: Wei Zheng is serving as one of the Editors in Chief of this journal. We declare that Wei Zheng had no involvement in the peer review of this article and has no access to information regarding its peer review. The authors have no conflict of interest to declare.

Funding: This study was funded by the National Natural Science Foundation of China (82101609), China International Medical Exchange Foundation (Z-2018-35-2002), the Science and Technology Program of Guangzhou (2023A03J0839, 2023A03J0436), Science and Technology Planning Project of Liwan District of Guangzhou (202201012), National Clinical Key Specialty Construction Project [(2023) 33], The Natural Science Foundation Program of Guangdong (2023A1515011383), Guangzhou Municipal Key Discipline in Medicine (2021-2023), Guangzhou Municipal Key Discipline in Medicine (2021-2023), Guangzhou High-level Clinical Key Specialty, Department of Emergency Medicine of National Clinical Key Specialty and Guangzhou Research-riented Hospital. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

1. Shim IH, Yi JM, Ha SH, Kwon KA, Bae DS. Glucocorticoid Receptor Gene (NR3C1) Expression in the Pathogenesis of Depression in Cancer. *Alpha Psychiatry*. 2022;23(6):294-297. [CrossRef]
2. Canlı D, Karaşar B. Predictors of Major Depressive Disorder: The Need for Social Approval and Self-Esteem. *Alpha Psychiatry*. 2021;22(1):38-42. [CrossRef]
3. GBD 2013 DALYs and HALE Collaborators, Murray CJ, Barber RM, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: quantifying the epidemiological transition. *Lancet*. 2015;386(10009):2145-2191. [CrossRef]
4. Mutz J, Vipulananthan V, Carter B, Hurlemann R, Fu CHY, Young AH. Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: systematic review and network meta-analysis. *BMJ (Clin Res Ed)*. 2019;364:l1079. [CrossRef]
5. Holtzheimer PE, 3rd, McDonald WM, Mufti M, et al. Accelerated repetitive transcranial magnetic stimulation for treatment-resistant depression. *Depress Anxiety*. 2010;27(10):960-963. [CrossRef]
6. Berlim MT, Van den Eynde F, Daskalakis ZJ. A systematic review and meta-analysis on the efficacy and acceptability of bilateral repetitive transcranial magnetic stimulation (rTMS) for treating major depression. *Psychol Med*. 2013;43(11):2245-2254. [CrossRef]
7. Chen L, Klooster DCW, Tik M, et al. Accelerated repetitive transcranial magnetic stimulation to treat major depression: the past, present, and future. *Harv Rev Psychiatry*. 2023;31(3):142-161. [CrossRef]
8. Pettorruso M, d'Andrea G, Di Carlo F, et al. Comparing fast-acting interventions for treatment-resistant depression: an explorative study of accelerated HF-rTMS versus intranasal esketamine. *Brain Stimul*. 2023;16(4):1041-1043. [CrossRef]
9. Cheng CM, Li CT, Tsai SJ. Current updates on newer forms of transcranial magnetic stimulation in major depression. *Adv Exp Med Biol*. 2021;1305:333-349. [CrossRef]

10. Levkovitz Y, Harel EV, Roth Y, et al. Deep transcranial magnetic stimulation over the prefrontal cortex: evaluation of antidepressant and cognitive effects in depressive patients. *Brain Stimul*. 2009;2(4):188-200. [CrossRef]
11. Levkovitz Y, Isserles M, Padberg F, et al. Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. *World Psychiatry*. 2015;14(1):64-73. [CrossRef]
12. Roth Y, Hanlon CA, Pell G, et al. Real world efficacy and safety of various accelerated deep TMS protocols for major depression. *Psychiatry Res*. 2023;328:115482. [CrossRef]
13. Iyer MB, Schleper N, Wassermann EM. Priming stimulation enhances the depressant effect of low-frequency repetitive transcranial magnetic stimulation. *J Neurosci*. 2003;23(34):10867-10872. [CrossRef]
14. Fitzgerald PB, Hoy K, McQueen S, et al. Priming stimulation enhances the effectiveness of low-frequency right prefrontal cortex transcranial magnetic stimulation in major depression. *J Clin Psychopharmacol*. 2008;28(1):52-58. [CrossRef]
15. Leuchter AF, Cook IA, Feifel D, et al. Efficacy and safety of low-field synchronized transcranial magnetic stimulation (sTMS) for treatment of major depression. *Brain Stimul*. 2015;8(4):787-794. [CrossRef]
16. Blumberger DM, Vila-Rodriguez F, Thorpe KE, 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(10131):1683-1692. [CrossRef]
17. Caulfield KA. Is accelerated, high-dose theta burst stimulation a panacea for treatment-resistant depression? *J Neurophysiol*. 2020;123(1):1-3. [CrossRef]
18. Cole EJ, Phillips AL, Bentzley BS, et al. Stanford Neuromodulation Therapy (SNT): A double-blind randomized controlled trial. *Am J Psychiatry*. 2022;179(2):132-141. [CrossRef]
19. Lan XJ, Cai DB, Qin ML, et al. Stanford Neuromodulation Therapy (SNT) for treatment-resistant depression: a systematic review. *Front Psychiatry*. 2023;14.
20. Cai DB, Qin ZJ, Lan XJ, et al. Accelerated intermittent theta burst stimulation for major depressive disorder or bipolar depression: A systematic review and meta-analysis. *Asian J Psychiatry*. 2023;85:103618. [CrossRef]
21. Brückner S, Kiefer M, Kammer T. Comparing the after-effects of continuous theta burst stimulation and conventional 1 Hz rTMS on semantic processing. *Neuroscience*. 2013;233:64-71. [CrossRef]
22. Chistyakov AV, Rubicsek O, Kaplan B, Zaaroor M, Klein E. Safety, tolerability and preliminary evidence for antidepressant efficacy of theta-burst transcranial magnetic stimulation in patients with major depression. *Int J Neuropsychopharmacol*. 2010;13(3):387-393. [CrossRef]
23. Chistyakov AV, Kreinin B, Marmor S, et al. Preliminary assessment of the therapeutic efficacy of continuous theta-burst magnetic stimulation (cTBS) in major depression: a double-blind sham-controlled study. *J Affect Disord*. 2015;170:225-229. [CrossRef]
24. Li CT, Chen MH, Juan CH, et al. Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized sham-controlled study. *Brain*. 2014;137(7):2088-2098. [CrossRef]
25. Mallik G, Mishra P, Garg S, Dhyani M, Tikka SK, Tyagi P. Safety and efficacy of continuous theta burst "intensive" stimulation in acute-phase bipolar depression: a pilot, exploratory study. *J ECT*. 2023;39(1):28-33. [CrossRef]
26. Cai DB, Qin XD, Qin ZJ, et al. Adjunctive continuous theta burst stimulation for major depressive disorder or bipolar depression: A meta-analysis of randomized controlled studies. *J Affect Disord*. 2023;346:266-272. [CrossRef]
27. Plewnia C, Pasqualetti P, Große S, et al. Treatment of major depression with bilateral theta burst stimulation: a randomized controlled pilot trial. *J Affect Disord*. 2014;156:219-223. [CrossRef]
28. Qin ZJ, Huang SQ, Lan XJ, et al. Bilateral theta burst stimulation for patients with acute unipolar or bipolar depressive episodes: A systematic review of randomized controlled studies. *J Affect Disord*. 2023;340:575-582. [CrossRef]
29. Blumberger DM, Mulsant BH, Thorpe KE, et al. Effectiveness of standard sequential bilateral repetitive transcranial magnetic stimulation vs bilateral theta burst stimulation in older adults with depression: the FOUR-D randomized noninferiority clinical trial. *JAMA Psychiatry*. 2022;79(11):1065-1073. [CrossRef]
30. Kennedy SH, Lam RW, McIntyre RS, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological treatments. *Can J Psychiatry Rev Canadienne Psychiatr*. 2016;61(9):540-560. [CrossRef]