Accelerated TMS for Depression: A Systematic Review and Meta-Analysis

Ayse Irem Sonmez, Deniz Doruk Camsari, Aiswarya L. Nandakumar, Ammar Almorsy, Jennifer L. Vande Voort, Simon Kung, Charles P. Lewis, Paul E. Croarkin
Mayo Clinic Depression Center, Department of Psychiatry & Psychology, Mayo Clinic, Rochester, MN, USA

Abstract

Background: Repetitive transcranial magnetic stimulation (TMS) is now widely available for clinical treatment of depression, but the associated financial and time burdens are problematic for patients. Accelerated TMS (aTMS) protocols address these burdens and attempt to increase the efficiency of standard TMS. This systematic review and meta-analysis aimed to examine accelerated TMS studies for depressive disorders in accordance with PRISMA guidelines.

Methods: Inclusion criteria consisted of studies with full text publications available in English describing more than one session of TMS (repetitive or theta burst stimulation—TBS) per day. Studies describing accelerated TMS protocols for conditions other than depression or alternative neuromodulation methods, preclinical studies, and neurophysiology studies regarding transcranial stimulation were excluded. 18 articles describing 11 distinct studies (7 publications described overlapping samples) met eligibility criteria. A Hedges' g effect size and confidence intervals were calculated.

Results: The summary analysis of 3 suitable randomized control trials revealed a cumulative effect size of 0.39 (95% CI 0.005-0.779). A separate analysis including open-label trials and active arms of suitable RCTs revealed a g of 1.27 (95% CI 0.902-1.637).

Conclusion: Overall, the meta-analysis suggested that aTMS improves depressive symptom severity. In general, study methodologies were acceptable, but future efforts could enhance sham techniques and blinding.

Background

- Major depressive disorder (MDD) is a chronic condition, affecting more than 300 million people (World Health Organization, 2018).
- Mortality from suicide in depression is a major public health concern. Every year, more than 800,000 people die from suicide worldwide (World Health Organization, 2014).
- Repetitive transcranial magnetic stimulation (rTMS) is an evidence-based MDD treatment.
- Accelerated TMS (aTMS) protocols are increasingly under study to address the practical limitations of conventional daily rTMS for MDD.

Objective

- We aimed to systematically review existing studies of aTMS (including both accelerated rTMS and accelerated TBS protocols) for efficacy for depression.
- A meta-analysis was performed to determine the cumulative antidepressant effect size of L-DLPFC aTMS.

Methods

- A systematic review of the literature on aTMS protocols in patients with depressive disorders was executed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.
- Search terms: transcranial magnetic stimulation OR trans-cranial magnetic Stimulation OR rtms OR tms AND repetitive AND accelerated OR OR fast* OR quick* OR condensed OR rapid AND depressed OR dysphoria OR melancholia OR antidepressant
- Data Sources: EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Ovid MEDLINE(R) Epub Ahead of Print In-Process & Other Non-Indexed Citations, Ovid MEDLINE 1946 to December 29, 2017, PsycINFO, SCOPUS, and Web of Science

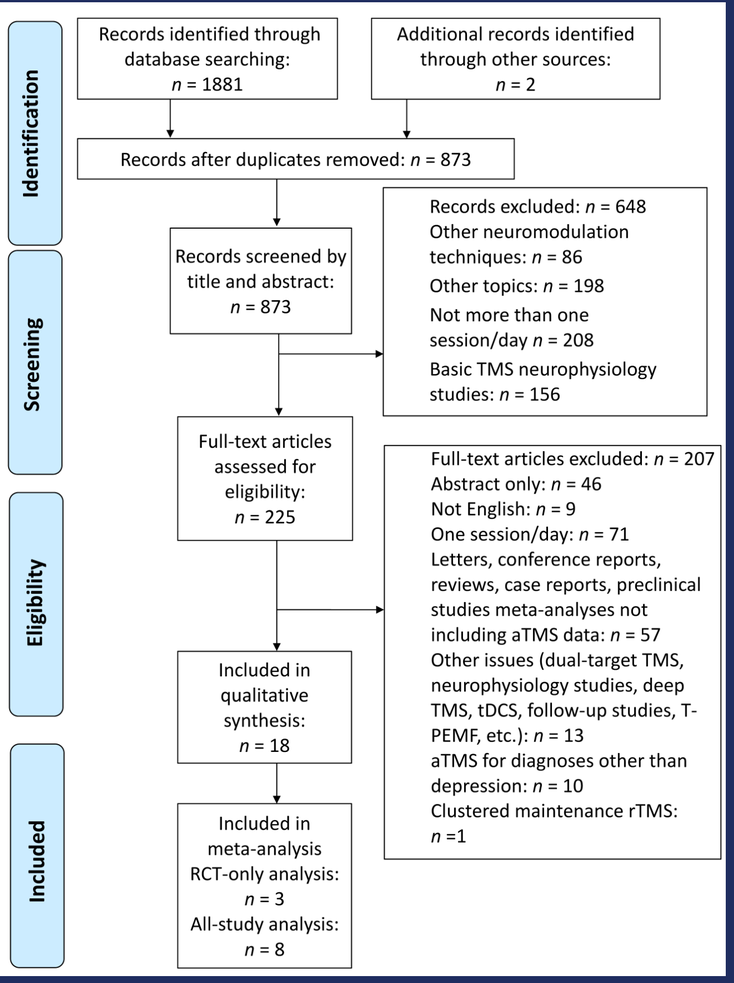
References

World Health Organization, 2014. Preventing suicide: A global imperative. WHO Press, Geneva

World Health Organization, 2018. Depression. Available from www.who.int/mediacentre/factsheets/fs369/en/ (accessed 11 April 2018)

Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive Meta-Analysis Version 3. Biostat, Englewood, NJ, 2013

Figure 1: PRISMA Flow Diagram



Meta-Analysis

- Analyses were conducted using Comprehensive Meta-Analysis (Borenstein et al., 2013), and IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA) was used for data processing.
- Change in depression severity scores (typically HDRS) comprised the primary outcome. Hedges' g, standardized mean difference (d) multiplied by a correction factor (J), was computed as an index of effect size for continuous outcome data. Another meta-analysis of response rates was computed.

Results

A total of 18 publications from 11 unique studies (6 randomized controlled trials and 5 open-label trials) met inclusion criteria (Fig. 1).

Discussion

- In eleven unique studies, aTMS sessions were administered at a frequency ranging between 2 and 10 sessions per day. Intersession interval varied from 12 minutes to 2 hours. The total stimuli delivered ranged between 15,000 and 90,000.
- The number of aTMS studies to date is small, and thus the results of this systematic review and meta-analysis must be interpreted with caution.
- The optimal TMS dosing strategy for aTMS is unknown. Additional research is required to assess whether the total stimuli, number of sessions per day, intersession intervals, or any other stimulation parameter is the most influential in generating clinical benefit.
- Common limitations were small sample size, limited statistical power, and maintaining the integrity of blinding due to sham techniques.
- Existing work suggests that aTMS is safe, tolerable, and feasible. Larger, systematic trials with enhanced blinding and sham delivery are urgently needed.

Acknowledgments

The authors acknowledge the efforts of Mayo Clinic Libraries, who assisted in the development and execution of the literature search. This research was supported by grants from the Brain and Behavior Research Foundation (Young Investigator Award 20883) and the National Institute of Mental Health (R01MH113700). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Figure 2: Forest Plot of RCT-Only Meta-Analysis on Continuous Outcomes

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Loo et al., 2007	0.369	0.328	0.107	-0.273	1.011	1.126	0.260
Baeken et al., 2013	0.334	0.453	0.205	-0.554	1.223	0.737	0.461
Duprat et al., 2016	0.435	0.296	0.088	-0.145	1.016	1.471	0.141
Overall (I-squared =0.0%, p = 0.979)	0.392	0.198	0.039	0.005	0.779	1.983	0.047

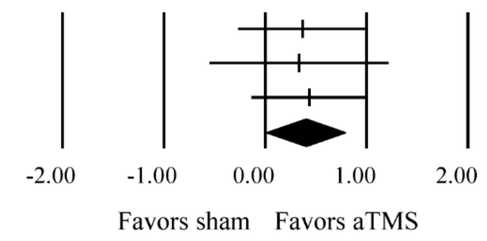


Figure 3: Forest Plot of All Study Meta-Analysis on Continuous Outcomes

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Baeken et al., 2013*	0.735	0.295	0.087	0.157	1.313	2.494	0.013
Duprat et al., 2016*	0.737	0.198	0.039	0.349	1.126	3.719	0.000
Fitzgerald et al., 2018*	0.826	0.128	0.016	0.576	1.076	6.466	0.000
Loo et al., 2007*	1.369	0.272	0.074	0.836	1.903	5.034	0.000
McGir et al., 2015	1.656	0.317	0.100	1.035	2.277	5.230	0.000
Dardenne et al., 2018	1.715	0.407	0.166	0.916	2.513	4.208	0.000
Holtzheimer et al., 2010	1.742	0.378	0.143	1.001	2.483	4.607	0.000
Williams et al., 2018	3.322	0.864	0.747	1.627	5.016	3.843	0.000
Overall (I-squared=71%, p =0.001)	1.269	0.188	0.035	0.902	1.637	6.767	0.000

*active arms only

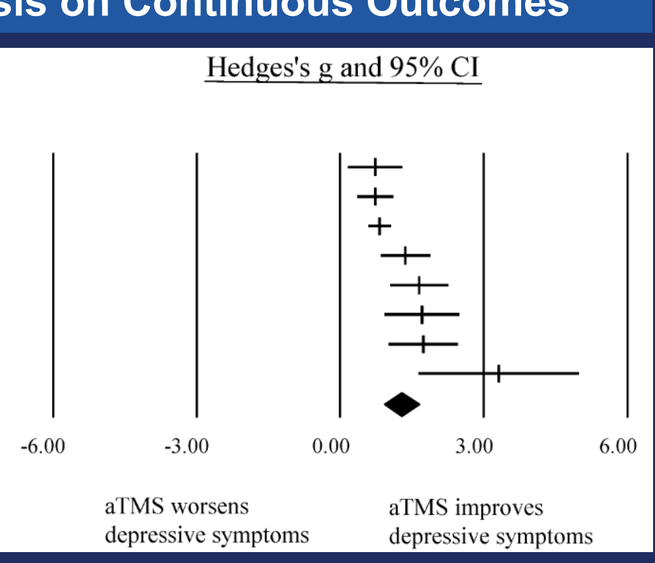


Figure 4: Forest Plot of RCT Response Rate Meta-Analysis

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Loo et al., 2007	2.500	0.515	12.139	1.137	0.256
Baeken et al., 2013	2.857	0.215	37.990	0.795	0.426
Duprat et al., 2016	5.333	0.548	51.879	1.442	0.149
Overall (I-squared = 0.0, p = 0.864)	3.127	0.980	9.976	1.926	0.054