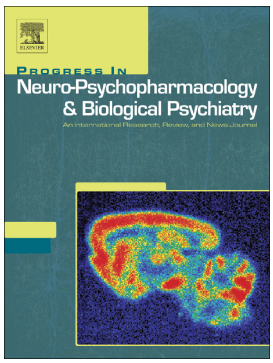

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Efficacy and tolerability of theta-burst stimulation for major depression: A systematic review and meta-analysis

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Abstract

Background: Repetitive transcranial magnetic stimulation (rTMS) is the current treatment option for major depression (MD). Theta-burst stimulation (TBS), a variation of rTMS, affords a short stimulation duration, low stimulation pulse intensity, and possibility to improve rTMS efficiency. This systematic review and meta-analysis examined the studies on efficacy and tolerability of TBS in patients with MD.

Methods: This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We searched the literature from 1990 until May 24, 2020, and performed a random-effects meta-analysis by including response and remission rates of depression and dropout rates as main outcome measures.

Results: In total, 10 studies including 6 randomized controlled trials (RCTs; n = 294) and 4 uncontrolled clinical trials (non-RCTs; n = 297) were included. The overall effect size of response rate and remission rates were 0.38 (95% confidence interval [CI]: 0.29–0.48) and 0.20 (95% CI: 0.13–0.29), respectively. Notably, the TBS group showed favorable efficacy without major adverse events.

Conclusions: TBS treatment was more efficient in terms of time and energy than the standard rTMS was. Our meta-analysis provided evidence that the application of TBS to the dorsolateral prefrontal cortex is associated with significant antidepressant effects along with favorable tolerability.

Keywords: Efficacy, major depression, meta-analysis, theta-burst stimulation, tolerability.

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a US Food and Drug Administration (US FDA)-approved treatment option for patients with major depressive episodes without satisfactory responses to adequate pharmacotherapy or psychotherapy. The antidepressant efficacy of high-frequency (e.g., 10-Hz) rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) has been demonstrated by considerable evidence, and thus, it is widely used in clinical settings (Perera et al., 2016). Different rTMS protocols with varying parameters (e.g., location and frequency of the stimulation, orientation of the magnetic field, number of stimuli, intensity, and duration of treatment) and various individual characteristics (e.g., age, right/left handedness, age at onset of depression, scalp-cortical space, seriousness of depression, treatment resistance and concurrent medication, baseline neural activity) are potential to influence each individual's treatment effect. (Atkinson et al., 2014; Holtzheimer et al., 2001; O'Reardon et al., 2007). Left prefrontal hypoactivity and right prefrontal hyperactivity were noted in patients with major depression (Grimm et al., 2008), and prefrontal hypoactivity was observed to be a characteristic feature in refractory patients (Li et al., 2015). Depending on the major depression(MD) asymmetrical prefrontal activity hypothesis, that is left DLPFC hypoactivity and right DLPFC hyperactivity(Mayberg et al., 2000). Therefore, the most common parameters

for depression treatment are high-frequency transcranial magnetic stimulation (TMS), which increases cortical excitability, and low-frequency TMS, which decreases cortical activity to apply over the left and right DLPFC respectively to achieve its therapeutic effects (Fitzgerald et al., 2009; Höppner et al., 2003). However, not every patient responds to rTMS treatment (Berlim et al., 2013; Brunoni et al., 2017), and the antidepressant efficacy of rTMS is less prominent in patients with higher treatment resistance (Li et al., 2010; Lisanby et al., 2009).

Theta-burst stimulation (TBS), a variation of rTMS, consists of a 50-Hz triplet pulse burst with a 200-ms interburst interval typically at 80% of the active motor threshold, corresponding to theta brain oscillations. Two major TBS protocols have been developed, namely continuous TBS (cTBS), uninterrupted TBS trains for 40 s (600 pulses), or intermittent TBS (iTBS) involving 2 s of TBS trains repeated every 10 s for a total of 20 cycles (600 pulses), and each with increased and decreased cortical excitability, respectively (Huang et al., 2005). cTBS with 300 pulses decreases cortical excitability beyond its stimulation period by almost 20 min, and up to 1 hour by 600 pulses (Huang et al., 2005). By contrast, iTBS could have excitatory effects on motor cortex that persist for 15 min after the stimulation. Compared with conventional rTMS protocols, TBS protocols use shorter stimulation duration and lower stimulation pulse intensity and have more impact on synaptic plasticity

(Daskalakis, 2014). Randomized sham-controlled evidence has revealed that iTBS to the left and cTBS to the right DLPFC and consecutive bilateral cTBS and iTBS to the DLPFC have the potential to treat refractory depression (Chung et al., 2015b), whereas the antidepressant effect of iTBS appear to be comparable to that of 10-Hz rTMS (Blumberger, D. M. et al., 2018; Li, C.T. et al., 2020). Many studies have indicated that TBS has antidepressant effects on patients with treatment-resistant depression (Daskalakis, 2014; Li et al., 2014; Plewnia et al., 2014; Prasser et al., 2015a). In addition, studies have demonstrated the safety of TBS (Grossheinrich et al., 2009), even when applied with a stimulation intensity (120% resting motor threshold) higher than the standard threshold (80% active motor threshold) (Blumberger, D. M. et al., 2018). However, the aftereffects of TBS are not dose-dependent, and most of the hypothetical effects of TBS are derived from motor cortical experiments by using subthreshold stimulation intensity (Li et al., 2019). Therefore, the most optimal TBS parameters remain elusive.

A meta-analysis included five randomized controlled trials (RCTs), reporting that TBS reduced the severity of depression in patients with MD (Berlim, Marcelo T. et al., 2017). Recently, more TBS trials on MD have been published, including one RCT (Li, C.-T. et al., 2020), two non-RCTs (Blumberger, Daniel M. et al., 2018; Fitzgerald, P. B. et al., 2020), and one open-label trial (Dhami et al., 2019). Updating

the summarized effects of TBS in patients with MD therefore becomes crucial.

To summarize the best available evidence on the use of TBS for treating MD, we aimed to quantitatively review RCTs and non-RCTs analyzing the efficacy of TBS. Furthermore, little is known about the tolerability of different TBS protocols. The present study aimed to examine (a) the rates of response and remission following TBS treatment and (b) its overall acceptability (as indexed by dropout rates) (Berlim et al., 2014).

2. Methodology

2.1. Search strategy

We searched the Internet databases of PubMed, Embase and Cochrane Central Register of Controlled Trials for articles on TBS for MD published from 1990 until May 24, 2020, following the recommendations of the Preferred Items for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). The keywords used for our search were "(theta burst stimulation) and ((major depressive disorder or unipolar depression) or (bipolar depression or bipolar disorder))." We also checked the reference listing from selected articles in search of papers that could be neglected. Only the original articles published in English were included. All duplicates were excluded, and each title and abstract was screened and filtered regarding the significance for the clinical research question. The

study selection process is illustrated in the PRISMA flow diagram (Fig. 1). Thus, open-label studies and randomized controlled studies (compared with sham treatment) and uncontrolled studies (without sham treatment) on TBS in patients with MD were identified. The search strategies are described in detail in the supplementary materials.

2.2. Eligibility criteria and study selection

2.2.1. Inclusion criteria

Candidate studies (judged by their title and abstract) had to satisfy the following criteria (Higgins et al., 2019):

2.2.1.1. Study validity

The study used random allocation, both sham control (i.e., coil angled on the scalp or use of a sham coil) and no control (without sham treatment), a parallel or crossover design (with data from only the initial randomization being extracted for the uncontrolled studies to avoid carryover effects and possible loss of blinding integrity), or ≥5 participants with MD randomized per study arm.

2.2.1.2. Sample characteristics

The participants were aged 16–75 years having a diagnosis of primary MD (unipolar or bipolar) according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (APA, 2000) or the tenth revision of the International

Classification of Diseases (Organization, 1992).

2.2.1.3. Treatment characteristics

Unilateral iTBS to the left DLPFC, unilateral cTBS to the right DLPFC or consecutive bilateral iTBS and cTBS were provided to the DLPFC for ≥10 sessions either as a monotherapy or as an augmentation strategy for MD.

2.2.1.4. Publication related

The study was written in English.

2.2.2. Exclusion criteria

Articles were excluded if they were

1. studies starting TBS protocol concomitantly with new psychotropics (e.g., antidepressants, antipsychotics),
2. nonclinical trials such as case series or observational studies, and
3. conference abstracts and studies published in languages other than English.

2.2.3. Study selection

Two authors (H.T. Chu and C.M. Cheng) selected controlled studies or open-label studies with or without randomization by evaluating titles and abstracts. They also assessed full papers to confirm eligibility whenever necessary, and divergences

were solved through consensus.

2.3. Data extraction

We recorded the following data extracted from the included studies in a structured principle as follows:

- Sample characteristics: mean age, sex, treatment strategy (i.e., augmentation or monotherapy), and presence of treatment-resistant MDD
- TBS related: stimulation parameters (including the total number of stimuli delivered), brain target(s) and coil placement method, number of treatment sessions, treatment duration, and type of sham
- Primary outcome measure: response rate (≥50% reduction in Hamilton Depression Rating Scale (HDRS) scores after acute TBS treatment)
- Secondary outcome measure: remission rate (according to definitions used in individual studies – final HDRS scores of ≤10 or final Montgomery-Asberg Depression Rating Scale scores of ≤7 after acute TBS treatment)
- Treatment acceptability: overall dropout rates

2.4. Data synthesis and analysis

We used an inverse-variance-weighted, random-effects model to estimate summary effect sizes for each outcome. For the analysis of all TBS studies,

proportions of response, remission, and all-cause discontinuation in the active group of each study were calculated to a pooled prevalence. For the analysis only the included RCTs, pooled odds ratios (ORs) were calculated to evaluate the response, remission, and all-cause discontinuation rates of TBS. All results are presented using 95% confidence intervals (CIs) and weights of each study. Sensitivity analyses were performed using leave-one-out and cumulative analysis to examine if any study had a significant effect on the pooled results.

A funnel plot was performed to evaluate publication bias. The Egger's test was also used to test the asymmetry of the funnel plot where P <.05 represents existence of publication bias. The trim-and-fill technique detects potentially missing studies by adjusting for funnel plot asymmetry (Duval and Tweedie, 2000). Considering the lack of statistical power to detect bias, the Egger's test would not present when the number of studies is <10. A graphical L'Abbé plot can visually demonstrate the overall heterogeneity among the various studies.

Subgroup analyses were performed to examine the influence of number of pulses in each session, stimulation intensity, treatment period, as well as the pattern of TBS. We performed meta-regression to analyze whether the effect size has changed over the treatment period and number of pulses in each session. Analyses were performed using the meta package in R 3.6.3 (Viechtbauer, 2010), at a two-tailed

alpha level of.05.

We will evaluate the risk of bias in included studies by using the Revised Cochrane risk-of-bias tool for randomised trials(RoB 2)(Sterne et al., 2019) and the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool(Sterne et al., 2016). Two authors (H.T. Chu and C.M. Cheng) independently conducted this assessment, and discrepancies were resolved by consensus.

3. Results

3.1. Literature search

We retrieved 177 articles (after discarding duplicates) from PubMed, MEDLINE, EMBASE (Fig. 1 (Moher et al., 2009); see Supplementary Material for a detailed description of the study selection procedures). After the selection procedure, 10 articles met the eligibility criteria of articles that assessed TBS as a treatment for MD (Blumberger, Daniel M. et al., 2018; Chistyakov et al., 2015a; Chistyakov, Andrei V. et al., 2010; Dhami et al., 2019; Duprat et al., 2016; Fitzgerald, P. B. et al., 2020; Li et al., 2014; Li, C.-T. et al., 2020; Plewnia et al., 2014; Prasser et al., 2015a).

3.2. Overview

In total, 10 studies that used TBS to treat MD were included in this meta-analysis (Blumberger, Daniel M. et al., 2018; Chistyakov et al., 2015a;

Chistyakov, Andrei V. et al., 2010; Dhami et al., 2019; Duprat et al., 2016; Fitzgerald, P. B. et al., 2020; Li et al., 2014; Li, C.-T. et al., 2020; Plewnia et al., 2014; Prasser et al., 2015a). Of these, six were randomized, sham-controlled (Chistyakov et al., 2015a; Duprat et al., 2016; Li et al., 2014; Li, C.-T. et al., 2020; Plewnia et al., 2014; Prasser et al., 2015a), one was crossover (Duprat et al., 2016), two were randomized, non–sham-controlled (Blumberger, Daniel M. et al., 2018; Fitzgerald, P. B. et al., 2020), and two were open-label (Chistyakov, Andrei V. et al., 2010; Dhami et al., 2019). The details of these studies, including TBS protocol parameters and validated questionnaires used, and methods for target identification are shown in Table 1.All the included RCTs recruited 294 patients with MD, with 156 of them receiving active TBS protocols. The four non-RCTs included 297 patients with MD. The results of our risk of bias assessment are presented in the supplementary materials (Supplementary Table 4-5). All 10 studies reported response and remission rates, except one open-label trial (Chistyakov, Andrei V. et al., 2010), which did not report the remission rates.

3.3. Meta-analysis of TBS effect on response rate in all studies

An exploratory analysis was performed using data from both the active arms of RCTs and non-RCTs to determine the proportion of achieving response to the TBS intervention after the course of treatment. Fig. 2 presented the unbiased weighted

estimates of Hedges effect sizes using a random-effects model. The overall effect size of the response rate was 0.38 (95% CI: 0.29–0.48), which favors TBS and suggests a modest treatment effect. The response rate after receiving TBS was robust to leave-one-out and cumulative sensitivity analysis. The heterogeneity was medium (I^2 = 68.0%, P <.01). The funnel plot is symmetric (P =.115, Egger's test), suggesting no publication bias.

3.4. Meta-analysis of TBS versus sham on response rate in RCTs

Data regarding response rates were available from all six RCTs. In total, 58 (37.9%) of 153 and 19 (13.8%) of 138 participants receiving active and sham TBS, respectively, were classified as responders. The pooled OR was 3.64 (95% CI: 1.61–8.23, z = 3.11, P <.01), indicating a significant difference in outcomes favoring active TBS (Fig. 3). The response rate after receiving TBS was robust to leave-one-out and cumulative sensitivity analysis. The test for heterogeneity provided nonsignificant results (Q = 9.2, degrees of freedom [df] = 6, P =.16, I^2 = 35%), implying that the variance among the effect sizes was not greater than expected by sampling error. In addition, the associated funnel plot was reasonably symmetrical. Publication bias was assessed more conservatively using the Egger's regression intercept, which may lack the statistical power to detect bias when the number of studies is small (i.e., k < 10).

3.5. Meta-analysis of TBS effect on remission rate in all studies

An experimental analysis was performed using data from both the active arms of RCTs and non-RCTs to figure out the remission rate of depression by TBS treatment. One open-label trial was excluded because it did not evaluate the outcome on remission (Chistyakov, A. V. et al., 2010); the remaining three non-RCTs were included. Fig. 4 presents the unbiased weighted estimates of Hedges effect sizes using a random-effects model. The overall effect size of response rate was 0.20 (95% CI: 0.13–0.29), which favors TBS and implies a medium treatment effect. The remission rate after receiving TBS was robust to the leave-one-out and cumulative sensitivity analysis. The heterogeneity was medium (I^2 = 61%, P <.01). The funnel plot is asymmetrical (P =.0195, Egger's test), suggesting evidence of publication bias.

3.5. Meta-analysis of TBS versus sham on remission rate in RCTs

Data relating to remission rates were available from all six RCTs. Overall, 31 (20.3%) of 153 and 12 (9.0%) of 138 participants receiving active and sham TBS, respectively, were classified as remitters. The pooled OR was 2.45 (95% CI: 1.11–5.42, z = 2.22, P =.03; Fig. 5). Heterogeneity between RCTs was nonsignificant (Q = 5.39, df = 6, P =.49, I^2 = 0%), implying that the variance among the effect sizes was not greater than expected by sampling error. The remission rate after receiving TBS was robust to the leave-one-out and cumulative sensitivity analysis. Moreover, the

associated funnel plot was reasonably symmetrical. Publication bias was assessed more conservatively using Egger's regression intercept, which may lack the statistical power to detect bias when the number of studies is small (i.e., k < 10).

3.6. TBS treatment tolerability

Data regarding the dropout rate were available from six RCTs. Overall, no differences in dropout rates were observed at the end of the study between active and sham TBS groups (6.4% [10/156] vs. 5% [7/138], respectively; OR = 1.51, 95% CI: 0.39–5.80, z = 0.60, P =.46; Fig. 6). Of the 453 patients receiving active TBS in all trials (RCTs and non-RCTs), 31 did not complete the stimulation protocols (Fig. 7). Four participants in two trials withdrew because of adverse events (Blumberger, Daniel M. et al., 2018; Chistyakov, A. V. et al., 2010).

3.7. Subgroup analyses: stimulation parameters

We performed subgroup analyses to explore the potential confounding factors, such as number of pulses per session, stimulation intensity, treatment period, and TBS pattern. With regard to the response rate in RCTs, the antidepressant effect of TBS may be higher, with the following parameters: ≥1800 pulses/session (OR = 4.13, 95% CI = 1.32–12.95), subthreshold intensity (OR = 3.56, 95% CI = 1.41–8.95), ≤2-week treatment duration (OR = 5.26, 95% CI = 1.71–16.19), and protocol involving iTBS

(OR = 5.10, 95% CI = 1.75–14.85), than the other subgroup which showed no difference in OR with controls (Fig. 8). Similar findings were observed in the response rate of all studies.

4. Discussion

The present meta-analysis examined the antidepressant effects, including response rates and remission rates, of TBS and reported results separately for all RCTs and for RCTs and non-RCTs combined. The results of RCTs revealed that active TBS was associated with higher response and remission rates (pooled ORs = 3.64 and 2.45, respectively) than sham TBS (Figs. 2 and 4, respectively), indicating favorable antidepressant efficacy of TBS for MD treatment. Likewise, in the meta-analysis for all RCTs and non-RCTs, TBS was favored with medium treatment effect of response rates and remission rates (overall effect size = 0.38 and 0.2, respectively; Figs. 3 and 5, respectively). In addition, TBS has exceptional tolerability. The supporting evidence demonstrated no differences in discontinuation rates between active and sham TBS groups (Fig. 6). Furthermore, our subgroup analysis revealed that the antidepressant parameters associated with favorable response rates of TBS were low stimulation intensity, high pulses/session, short treatment period, and iTBS (Fig. 8).

The most vital finding of our study was that the antidepressant effects of TBS

were associated with higher response and remission rates than sham treatment for depression treatment. Consitent with previous meta-analyses(Berlim, M. T. et al., 2017), it demonstrated active TBS with higher response rates than sham TBS. In spite of lower number of TBS studies, iTBS showed improved response in network meta-analysis(Brunoni et al., 2017; Mutz et al., 2019), while bilateral theta burst stimulation was associated with higher response.; however, the optimum TBS protocol based on different parameters has yet to be determined. This finding warrants further clinical investigation, so our study included more RCTs and non-RCTs by now for clinical investigation.

Few studies thus far have compared TBS with standard rTMS for MD treatment. A large multicenter, noninferiority clinical trial performed lately including 414 patients with treatment-resistant depression demonstrated that the efficacy and acceptability of iTBS was comparable with that of the standard FDA-approved 10-Hz rTMS protocol to the DLPFC (20 daily sessions), and shared a similar adverse event profile (Blumberger, Daniel M. et al., 2018). Similarly, in a recent study, we found that prolonged iTBS over the left prefrontal cortex for 2 weeks demonstrated better antidepressant efficacy than sham treatment and the efficacy was not inferior to the 10-Hz rTMS (Li, C.-T. et al., 2020). TBS required much less time in each session than

did standard rTMS (George and Aston-Jones, 2010), and this advantage could not only increase its capacity for clinical treatment and flexible treatment scheduling but also improve adherence (Daskalakis, 2014).

The optimal treatment parameters of TBS for MD (e.g., total number of pulses and sessions, effective stimulus intensity, duration of stimulation) remain to be determined (Gamboa et al., 2011). Our results revealed that low stimulation intensity, high number of pulses per session, short treatment period, and iTBS were possibly associated with better antidepressant responses. To date, only few studies of TBS have evaluated the effects of varied lengths of stimulation. In line with our findings, a study demonstrated dose-dependent effects of iTBS (1800 vs. 600 pulses) for enhancing cortical excitability on the motor cortex (Nettekoven et al., 2014). By contrast, Gamboa et al. (Gamboa et al., 2011) revealed that longer stimulation sessions (1200 vs. 600 pulses) might not certainly strengthen TBS-induced neuroplastic aftereffects but may demonstrate few or converse effects in healthy participants. Regarding the RCTs included in the present meta-analysis, a long-stimulation duration of TBS protocols was associated with better treatment outcomes on MD. For instance, Li et al. reported the antidepressant efficacy of iTBS (1800 pulses) for refractory depression in two RCTs (Li et al., 2014) (Li, C.-T. et al., 2020). Antidepressant effects of TBS were also demonstrated in studies applying more than 1800 pulses/session (Chistyakov et

al., 2015b; Li et al., 2014; Prasser et al., 2015b). Several elements might explain the inconsistency of dose-dependent effects of TBS across studies. For example, the TBS findings may not be consistent in the prefrontal cortex with those in the motor cortex (Chung et al., 2015a). Moreover, the baseline cortical excitability and threshold for facilitating synaptic plasticity may vary considerably among healthy controls and clinical patients.

Duprat et al. (Duprat et al., 2016) revealed that multiple consecutive sessions of iTBS separated by 15 min did not reverse the antidepressant effects as well as that demonstrated by Fitzgerald et al. (Fitzgerald, Paul B et al., 2020). Therefore, adding a rest between consecutive TBS sessions (an approach known as priming or preconditioning) may avoid the opposite effects over the primary motor cortex (Gamboa et al., 2011). However, the appropriate duration of the pause and ideal number of consecutive sessions must be examined. In general, the structured evaluation on clinical outcomes, including the objective neurophysiological and neuroimaging measurements, might be helpful in choosing the optimal stimulation protocols for MD, and predict that TBS will be beneficial to different patients with depression (Arns et al., 2012).

In addition, the stimulation intensity seems safe and tolerable at a suprathreshold level (>100% of the motor threshold) through the course of treatment

(Blumberger, Daniel M. et al., 2018; Duprat et al., 2016; Fitzgerald, Paul B et al., 2020). Li et al. showed that 2 weeks of daily iTBS treatment had similar response rates for MD (40% and 45.7%) (Li et al., 2014; Li, C.-T. et al., 2020), not as long as that using the recommended standard rTMS course (4–6 weeks) (McClintock et al., 2018). From the studies mentioned earlier, TBS treatment may have more capacity and tolerability to produce the same clinical effects as standard rTMS therapy courses.

Our study has a few limitations. First, the recruited participants with MD demonstrated varying degrees of therapy resistance in our RCTs. High levels of baseline treatment resistance have demonstrated an association with poor clinical outcomes (Li et al., 2014). However, this correlation was not demonstrated consistently in other research (Li, C.-T. et al., 2020). Second, most of our included studies applied TBS as an augmentation therapy combined with medications, which limited the interpretation of the efficacy of TBS by monotherapy. Third, the present study focused on analyzing the acute treatment effects of TBS on depression. The optimal maintenance duration of TBS remains unclear. Therefore, future long-term TBS studies on MD are still required. Finally, meta-analyses have often been criticized for the potential of publication bias (Borenstein et al., 2011). In the present study, however, these questions were addressed by the comprehensive and systematic review of the literature, use of strict inclusion criteria, and objective examination of

publication bias.

5. Conclusion

TBS treatment is more efficient in terms of time and energy than is standard rTMS. Our meta-analysis provided evidence that TBS applied to the DLPFC is associated with significant antidepressant effects and favorable tolerability. Low stimulation intensities, high number of pulses per session, short treatment periods, and iTBS might be the optimal parameters of TBS protocols, whose effects must be examined by performing more RCTs.

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Contributors

Hsuan-Te Chu and Chih-Ming Cheng prepared the manuscript. Chih-Sung Liang, Jia-Shyun Jeng, and Cheng-Ta Li conceived and designed the study. Chih-Ming Cheng analyzed the data. Chi-Hung Juan, Ying-Zu Huang, Ya-Mei Bai, Shih-Jen Tsai, and Mu-Hong Chen critically read the manuscript and made important suggestions. Cheng-Ta Li, the corresponding authors, take all the responsibility of collecting all the information from the other authors, revise the manuscript, and submit the manuscript. All authors reviewed the manuscript and had full access to all study data.

Declaration of Competing Interest

None of the authors in this study has any conflict of interest to declare.

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Study	Randomized (Y/N)	Sham-controlled (Y/N)	Active TBS			Sham TBS				TBS Parameters							Scale	Main Diagnosis	Treatment Strategy	Resistant MD
			n	Age (mean±SD,years)	Female/Male(n)	n	Age (mean±SD,years)	Female/male(n)	Strategy	Treatment Protocol	Brain Target	Target method	Duration(weeks)	Sessions	MT (%)	pulses/session				
Li et al., 2014	Y	Y	15	49.2 ± 10.0	10/5	15	46.9 ± 10.9	11/4	90 coil angulation	cTBS	R-DLPFC	Neuronavigation	2	10	80% aMT	1800	HDRS-17	Unipolar MD	Augmentation	Yes, >=2 AD
Li et al., 2014	Y	Y	15	42.4 ± 11.6	8/7					iTBS	L-DLPFC	Neuronavigation	2	10	80% aMT	1800	HDRS-17	Unipolar MD	Augmentation	Yes, >=2 AD
Li et al., 2014	Y	Y	15	42.5 ± 12.1	11/4					bilateral TBS	L-DLPFC + R-DLPFC	Neuronavigation	2	10	80% aMT	3600	HDRS-17	Unipolar MD	Augmentation	Yes, >=2 AD
Plewnia et al., 2014	Y	Y	16	46.9 ± 13.2	8/8	16	49 ± 13.6	12/4	45 coil angulation	bilateral TBS	L-DLPFC + R-DLPFC	F3 and F4 in 10/20 EEG System	6	30	80% aMT	1200	HDRS-17	Unipolar MD	Augmentation	N/A
Prasser et al., 2015	Y	Y	20	48.2 ± 10.9	10/10	17	42.6 ± 12.4	9/8	Inactive coil	bilateral TBS	L-DLPFC + R-DLPFC	Anterior to the motor hotspot(6 cm)	3	15	80% rMT	2400	HDRS-21	Unipolar MD and Bipolar MD	Augmentation	N/A
Chistyakov et al., 2015	Y	Y	15	52.7 ± 11.1	5/10	14	50.9 ± 17.3	6/8	Inactive coil	cTBS	R-DLPFC	5 cm rule	2	10	100% aMT	3600	HDRS-21	Unipolar MD and Bipolar MD	Augmentation	Yes, >=1 AD
Duprat et al., 2016	Y	Y	22	40.1 ± 11.4	16/6	25	43.2 ± 12.1	17/8	Inactive coil	iTBS	L-DLPFC	Neuronavigation	1	20	110% rMT	1620	HDRS-17	Unipolar MD	Monotherapy	Yes, >=1 AD
Li et al., 2020	Y	Y	35	47.1 ± 14.2	23/12	35	47.1 ± 12.4	24/11	Inactive coil	iTBS	L-DLPFC	Neuronavigation	2	10	80% aMT	1800	HDRS-17	Unipolar MD	Monotherapy	Yes, >=1 AD
Blumberger et al., 2018	Y	N	209	41.6 ± 10.8	127/82					iTBS	L-DLPFC	Neuronavigation	4	20	120% rMT	600	HDRS-17	Unipolar MD	Augmentation	Yes, >=2 AD
Fitzgerald et al., 2020	Y	N	36	44.4 ± 12.1	19/17					iTBS	L-DLPFC	F3 beam method	4	21	120% rMT	600	MADRS	Unipolar MD and Bipolar MD	Augmentation	Yes, >=2 AD
Chistyakov et al., 2010	N	N	7	54.1±17.2	5/2					iTBS	L-DLPFC	5 cm rule	2	10	90% aMT	1200	HDRS-17	Unipolar MD and Bipolar MD	Augmentation	Yes, >=1 AD
			6	55.3±13.5	6/0					cTBS	R-DLPFC	5 cm rule	2	10	90% aMT	1200	HDRS-17			
			5	52.3±16.2	5/1					cTBS	R-DLPFC	5 cm rule	2	10	100% aMT	1800	HDRS-17			
			14	61.4±13.0	11/3					cTBS	R-DLPFC	5 cm rule	2	10	100% aMT	3600	HDRS-17			
Dhami et al., 2019	N	N	20	20.9 ± 2.6	10/10					bilateral TBS	L-DLPFC + R-DLPFC	Neuronavigation	2	10	80% aMT	3600	HDRS-17	Unipolar MD	Augmentation	Yes, >=1 AD

Table1 Demographic data of include studies.

Abbreviations: AD = Antidepressant medication; aMT = Active motor threshold; HDRS= Hamilton Depression Rating Scale; MADRS= Montgomery-Asberg Depression Rating Scale; MD = Major depression; MT = Motor threshold; N/A = Not available; rMT = Resting motor threshold; R-DLPFC = Right dorsolateral prefrontal cortex; L-DLPFC = Left dorsolateral prefrontal cortex.

Fig. 1. PRISMA flowchart of study selection.

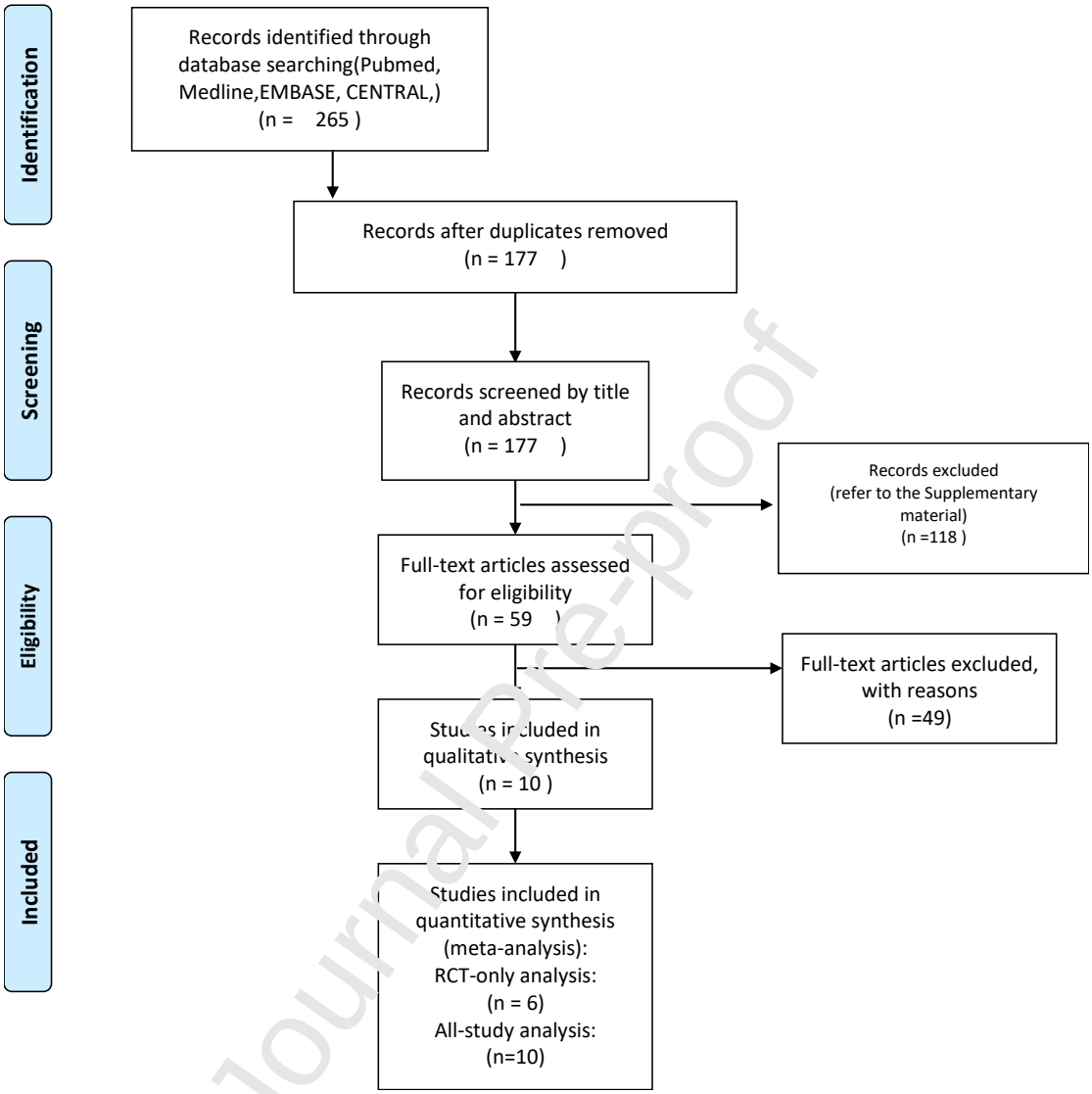


Fig. 2. ***Meta-analysis of TBS for MD (All studies): Response rate.***

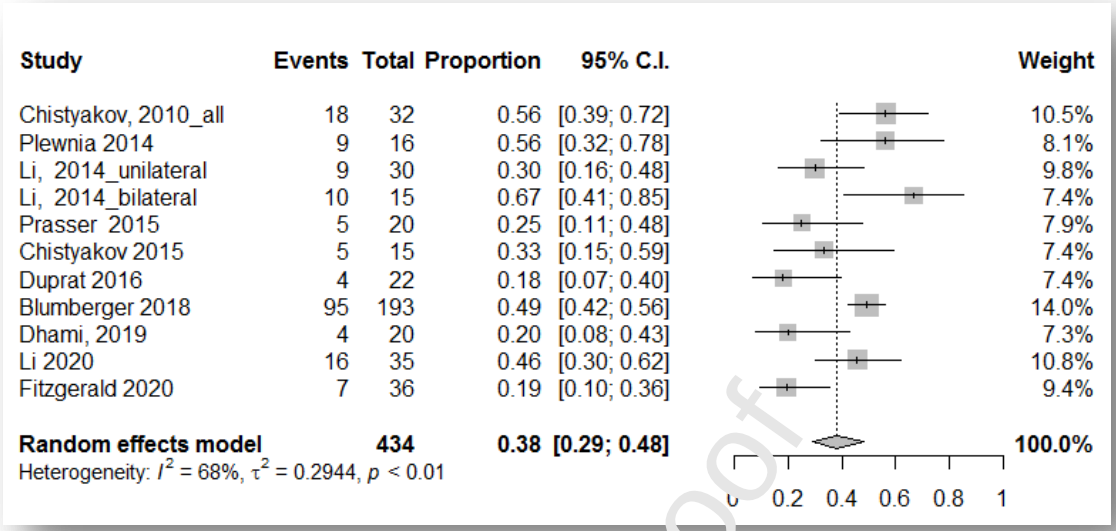


Fig. 3. ***Meta-analysis of Active vs. Sham TBS for MD: Response rate.***

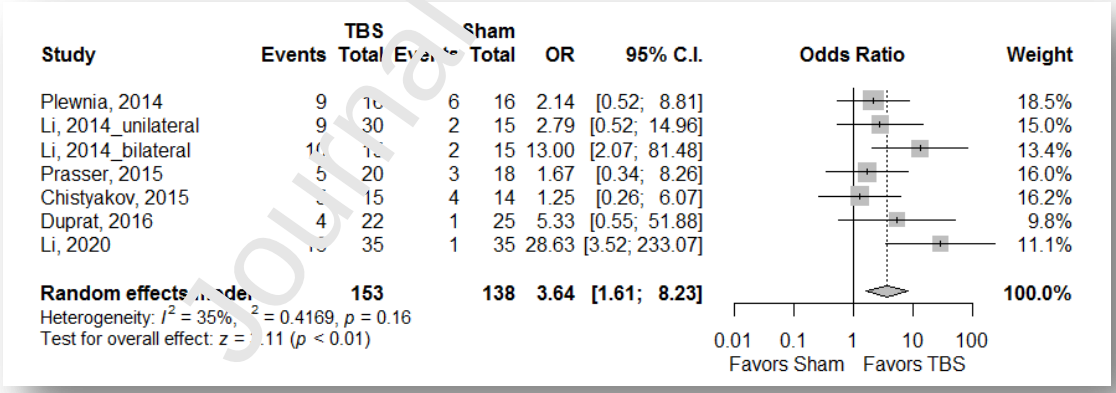


Fig. 4. ***Meta-analysis of TBS for MD (All studies): Remission Rate.***

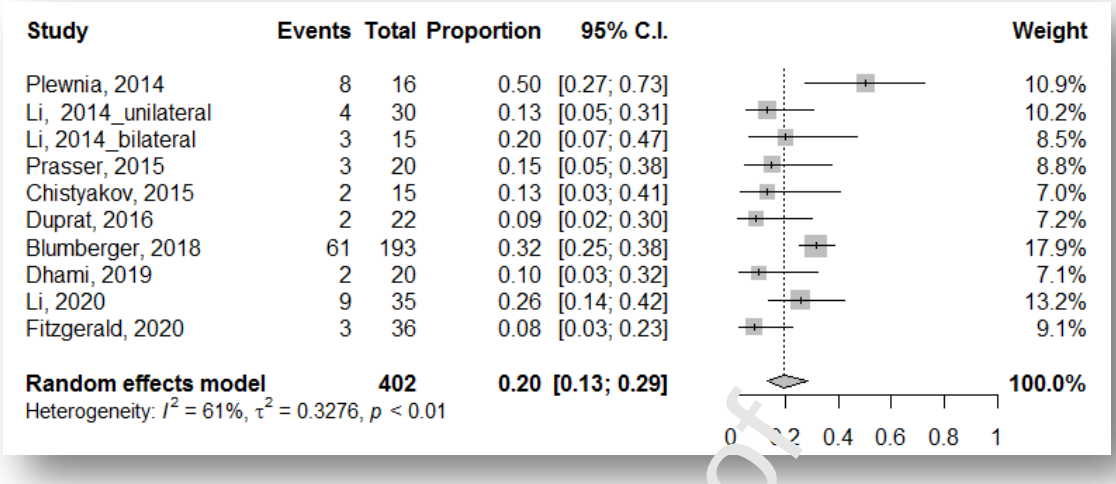


Fig. 5. ***Meta-analysis of Active vs. Sham TBS for MD: Remission rate.***

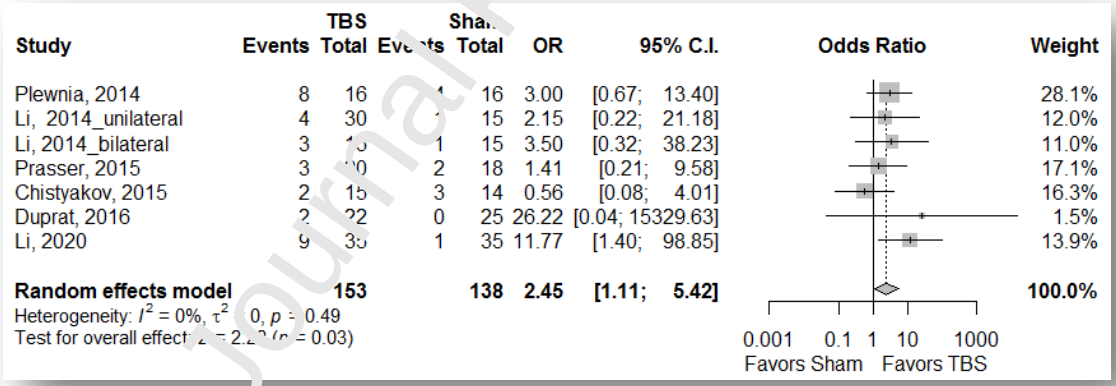


Fig. 6. ***Meta-analysis of Active vs. Sham TBS for MD: All-cause discontinuation Rate.***

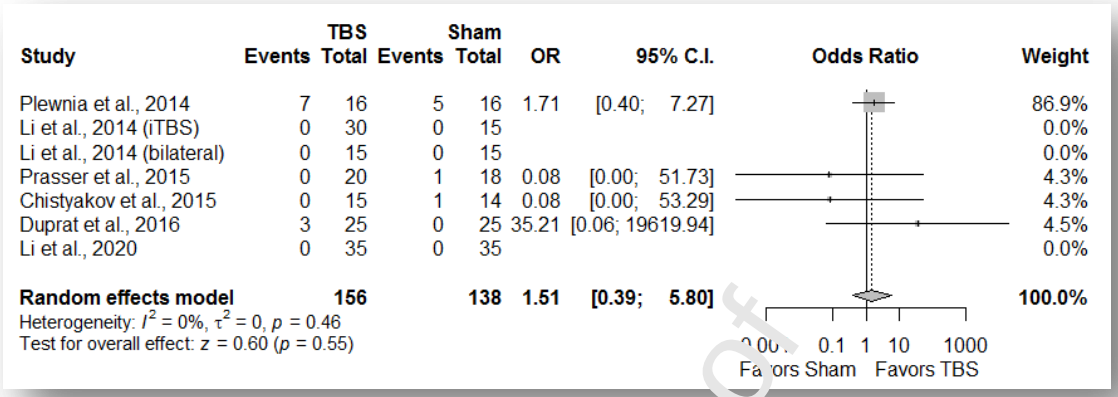


Fig. 7. ***Meta-analysis of TBS for MD (All studies): All-cause discontinuation Rate.***

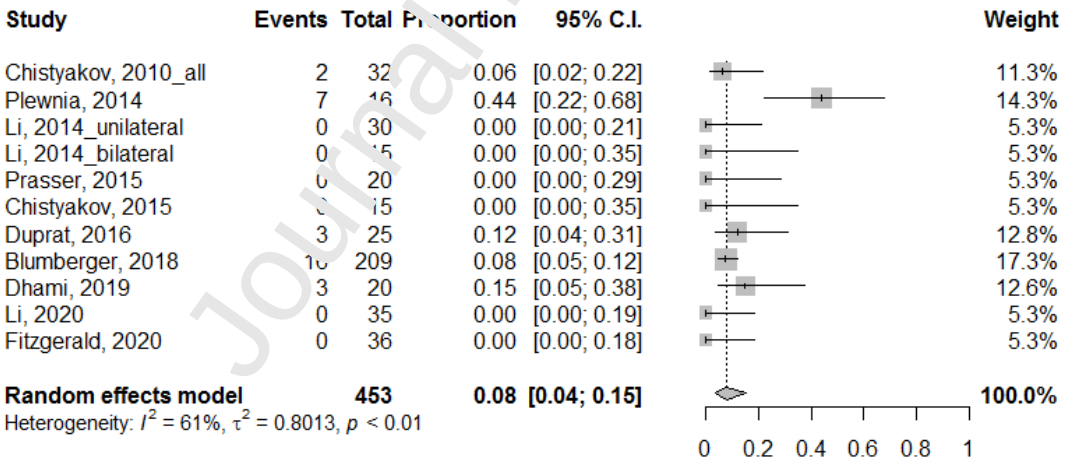
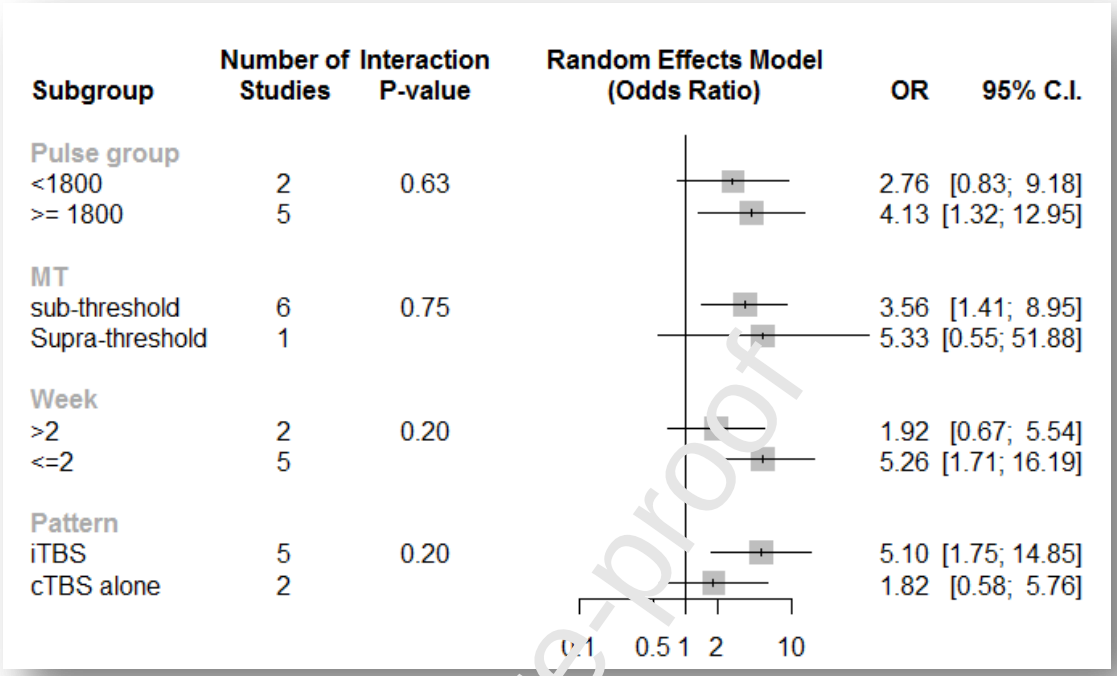


Fig. 8 Subgroup analysis- Parameters *vs.* Response Rate *(RCTs)*



None of the authors in this study has any conflict of interest to declare.

Study	Randomized (Y/N)	Sham-controlled(Y/N)		Active TBS			Sham TBS							
			n	Age (mean±SD, years)	Female/ Male(n)	n	Age (mean±SD, years)	Female/ Male(n)	Strategy	Treatment Protocol	Brain Target	Target method	Duration (weeks)	Sessions
Li et al., 2014	Y	Y	15	49.2 ± 10.0	10/5	15	46.9 ± 10.9	11/4	90◦coil angulation	cTBS	R-DLPFC	Neuronavigation	2	10
Li et al., 2014	Y	Y	15	42.4 ± 11.6	8/7					iTBS	L-DLPFC	Neuronavigation	2	10
Li et al., 2014	Y	Y	15	42.5 ± 12.1	11/4					bilateral TBS	L-DLPFC + R-DLPFC	Neuronavigation	2	10
Plewnia et al., 2014	Y	Y	16	46.9 ± 13.2	8/8	16	49 ± 13.6	12/4	45◦coil angulation	bilateral TBS	L-DLPFC + R-DLPFC	F3 and F4 in 10/20 EEG System	6	30
Prasser et al., 2015	Y	Y	20	48.2 ± 10.9	10/10	17	42.6 ± 12.4	9/8	Inactive coil	bilateral TBS	L-DLPFC + R-DLPFC	Anterior to the motor hotspot (6 cm)	3	15
Chistyakov et al., 2015	Y	Y	15	52.7 ± 11.1	5/10	14	50.9 ± 17.3	6/8	Inactive coil	cTBS	R-DLPFC	5 cm rule	2	10
Duprat et al., 2016	Y	Y	22	40.1 ± 11.4	16/6	25	43.2 ± 12.1	17/8	Inactive coil	iTBS	L-DLPFC	Neuronavigation	1	20
Li et al., 2020	Y	Y	35	47.1 ± 14.2	23/12	35	47.1 ± 12.4	24/	Inactive coil	iTBS	L-DLPFC	Neuronavigation	2	10
Blumberger et al., 2018	Y	N	209	41.6 ± 10.8	127/82					iTBS	L-DLPFC	Neuronavigation	4	20
Fitzgerald et al., 2020	Y	N	36	44.4 ± 12.1	19/17					iTBS	L-DLPFC	F3 beam method	4	21
Chistyakov et al., 2010	N	N	7	54.1±17.2	5/2					iTBS	L-DLPFC	5 cm rule	2	10
			6	55.3±13.5	6/0					cTBS	R-DLPFC	5 cm rule	2	10
			5	52.3±16.2	5/1					cTBS	R-DLPFC	5 cm rule	2	10
			14	61.4±13.0	11/3					cTBS	R-DLPFC	5 cm rule	2	10
Dhami et al., 2019	N	N	20	20.9 ± 2.6	10/10					bilateral TBS	L-DLPFC + R-DLPFC	Neuronavigation	2	10

Table1 Demographic data of include studies.

Abbreviations: AD = Antidepressant medication; aMT = Active motor threshold; BA = Brodmann Area; HDRS= Hamilton Depression Rating Scale; MADRS= Montgomery-Asberg Depression Rating Scale; MD = Major depression; MT = Motor threshold; N/A = Not available; rMT = Resting motor threshold; R-DLPFC = Right dorsolateral prefrontal cortex; L-DLPFC = Left dorsolateral prefrontal cortex.

1. TBS applied to the dorsolateral prefrontal cortex is associated with significant antidepressant effects and favorable tolerability.
2. Low stimulation intensities, high number of pulses per session, short treatment periods, and iTBS might be the optimal parameters of TBS protocols.