

# The association of total pulses with the efficacy of repetitive transcranial magnetic stimulation for treatment-resistant major depression: A dose-response meta-analysis

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## Abstract

**Aim:** This study aimed to examine dose-effects of total pulses on improvement of depressive symptoms in patients with treatment-resistant depression (TRD) receiving repetitive transcranial magnetic stimulation (rTMS) over the left dorsal lateral prefrontal cortex (DLPFC). **Materials and methods:** The MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, PsycINFO, and ClinicalTrials.gov databases were systematically searched. We included randomized, double-blind, placebo-controlled trials (RCT) that used rTMS over left DLPFC in patients with TRD. Excluded studies were non-TRD, non-RCTs, or combined other brain stimulation interventions. The outcome of interest was the difference between rTMS arms and sham controls in improvement of depressive symptoms in a dose-response manner. A random-effects meta-analysis and dose-response meta-analysis (DRMA) was used to examine antidepressant efficacy of rTMS and association with total pulses.

**Results:** We found that rTMS over left DLPFC is superior to sham controls (reported as standardized mean difference [SMD] with 95% confidence interval: 0.77; 0.56–0.98). The best-fitting model of DRMA was bell-shaped (estimated using restricted cubic spline model;  $R^2 = 0.42$ ), indicating that higher doses (>26,660 total pulses) were not associated with increased improvement of depressive symptoms. Stimulation frequency ( $R^2 = 0.53$ ) and age ( $R^2 = 0.51$ ) were significant moderators for the dose-response curve. Furthermore, 15–20 Hz rTMS was superior to 10 Hz rTMS (0.61, 0.15–1.10) when combining all doses.

**Conclusions:** Our findings suggest higher doses (total pulses) of rTMS were not always associated with increased improvement of depressive symptoms in patients with TRD, and that the dose-response relationship was moderated by stimulation frequency and age. These associations emphasize the importance of determining dosing parameters to achieve maximum efficacy.

## 1. Introduction

Major depressive disorder (MDD) is a high prevalent, recurring, and debilitating mental disorder causing functional impairment and a decrease in quality of life. (Steel et al., 2014; Whiteford et al., 2013) However, substantial number of patients do not respond to antidepressant treatment, leading to what is known as treatment-resistant depression (TRD). Patients with TRD have higher healthcare costs, more psychiatric and medical comorbidities, and an increased risk of hospitalization. (Crown et al., 2002; Rush et al., 2006) In addition to electroconvulsive therapy, the United States (U.S.) Food and Drug Administration (FDA) has approved repetitive transcranial magnetic stimulation (rTMS) as a treatment option for TRD. (O'Reardon et al., 2007) The approved protocol for rTMS targets the left dorsal lateral prefrontal cortex (DLPFC) with 10 pulses/second (10 Hz), 120% of the motor threshold, 3000 pulses/session for 4–6 weeks (5 sessions/week). (O'Reardon et al., 2007) Many clinical trials and meta-analytic studies have demonstrated the antidepressant efficacy of rTMS in TRD. (Hyde et al., 2022; Mutz et al., 2019).

Recent meta-analytic studies have reported remarkably heterogeneous antidepressant efficacy for rTMS ( $I^2$ : 79.5–88%). (Hyde et al., 2022; Mutz et al., 2019; Teng et al., 2017) The application of rTMS protocols varied substantially across different trials and clinical settings. Modifiable dosing parameters of rTMS include stimulation frequency, intensity (power), pulse/session, session/day, session/week, and total sessions (treatment duration). (Hyde et al., 2022; Mutz et al., 2019) A meta-analysis using subgroup analysis explored potential moderators of high frequency (HF)-rTMS over the left DLPFC, suggesting that efficacy was positively associated with the total number of sessions, and that 1200–1500 pulses per day provided the best antidepressant effects for MDD. (Teng et al., 2017) Other reviews suggested that more than 1000 pulses/session and more than 10 sessions of treatment are predictors of a positive response to rTMS. (Beuzon et al., 2017; Kar, 2019) However, in 2008, the U.S. FDA-approved protocol recommends 60,000 or more total pulses for TRD. (Cotovio et al., 2023; O'Reardon et al., 2007).

To date, researchers and clinicians are still unaware of the dose-response curve between dosing parameters and antidepressant effects of rTMS for patients with TRD. We aimed to fill this gap by conducting a dose-response meta-analysis (DRMA), which may help determine the comparative efficacy of rTMS at different dose levels. For the analysis of homogeneity, this study focuses on conventional rTMS treatment protocols, meaning that other protocols, such as TBS (theta burst stimulation) and dTMS (deep transcranial magnetic stimulation), were not included. In the current study, we defined the dose as total numbers of pulses in the DRMA and we would also assess other potential confounding factors affecting the antidepressant efficacy of rTMS.

## 2. Methods

The protocol of the current study was a priori registered with Open Science Framework (OSF) (10.17605/OSF.IO/S2FYX). This study followed the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions (Appendix 1). (Page et al., 2021) The need for ethical approval was waived in this study.

### 2.1. Search strategy

The PICOS (population, intervention, comparison, outcome, and study) were as follows: (i) P: patients with TRD; (ii) I: rTMS over the left DLPFC; (iii) C: sham control; (iv) O: changes in depressive symptoms; and (v) S: blinded randomised controlled trials (RCT). We excluded: (i) treatment-naïve patients (medication naïve); (ii) open-label trials or non-RCT studies; (iii) other external aetiologies of depression, such as post-stroke depression or Parkinson-related depression; (iv) maintenance treatment or relapse prevention studies; (v) combination treatment with other brain stimulation sites (e.g. right DLPFC, bilateral DLPFC, or medial PFC) or protocols (e.g. TBS or dTMS); and (vi) head-to-head studies without any sham controls. The MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, PsycINFO, and ClinicalTrial.gov databases were systematically searched without language restrictions from database inception to December 13, 2022. Screening and selection of studies were performed independently by four of the authors and each study was

assessed by a minimum of two authors. Disagreements were resolved by consulting with the corresponding author.

## 2.2. Outcome definition and data extraction

The primary outcome was the change in depressive symptoms at the end of treatment with rTMS compared with sham controls. We extracted baseline, post-treatment, or change in score for depressive symptoms (means and standard deviation) for both active and sham groups, as measured using the Hamilton Rating Scale for Depression (17, 21, 24, 25, 28-items), (Hamilton, 1967) Montgomery-Åsberg Depression Rating Scale, (Montgomery and Asberg, 1979) or Beck Depression Inventory (second edition). (Beck et al., 1996) If two measures met the criteria, we extracted the measure with the lower p-value.

Intention-to-treat datasets were used when available. We also extracted sex, age, hospitalisation status, parameters of rTMS (frequency, pulses per session, total sessions, intensity, methods of sham control, and treatment duration), definitions of TRD, treatment strategy (augmentation with medication, monotherapy, or mixed), and diagnoses (MDD or bipolar depression). For studies that reported effect estimates graphically, a web plot digitiser ([www://plotdigitizer.sourceforge.net/](http://www.plotdigitizer.sourceforge.net/)) was used to estimate the effect estimates from the graphs.

At least two of the authors double checked the data-transfer accuracy and calculations.

## 2.3. Quality assessment

The Cochrane Risk of Bias Assessment Tool-2 (Sterne et al., 2019) was utilised to evaluate the quality of the RCTs. The included studies were classified as having high, low, or unclear risk of bias (ROB) according to the following domains: randomisation process, intended intervention, missing outcome data, measurement of the outcome, selection of the reported result, and overall bias. Two authors independently conducted this assessment and discrepancies were resolved by consensus.

## 2.4. Statistical analysis

The dose of rTMS was defined as total pulses (a result of multiplying pulse/session, session/week, and treatment weeks). A dose-response relationship was modelled using a one-stage weighted mixed effects meta-analysis, (Crippa et al., 2019) and a near-maximum effective dose (ED<sub>max</sub>) was estimated using the proposed method. (Crippa and Orsini, 2016) The effect size of the primary outcome was standardised mean difference (SMD), with 95% confidence interval (CI) calculated using a random-effect model (fitted through restricted maximum likelihood [REML]). Effect sizes were defined as small ( $d=0.2$ ), medium ( $d=0.5$ ), and large ( $d\geq 0.8$ ). (Sullivan and Feinn, 2012) We modelled the dose-response relationships using restricted cubic splines (RCSs) with three knots according to Harrell's recommended centiles (10%, 50%, and 90%) of distribution. (Harrell et al., 2015) We also modelled linear and quadratic models to determine the best-fitting models according to goodness-of-fit statistics (deviance test and adjusted R-squared). A leave-one-out dose-response meta-analysis was performed to examine the robustness of the dose-response curve and identify influential studies.

We conducted a dose-response meta-regression to examine potential moderators for the dose-response relationships, including frequency, power (motor threshold), total sessions, type of TRD (1 or >1 failure of antidepressant trial), sample size, age, female proportion, year, daily sessions (1 or >1), type of sham control, outpatient group, blinding (single or double), TRD population (pure TRD or mixed TRD and non-TRD participants), diagnosis (bipolar depression or MDD), treatment strategies (rTMS monotherapy or augmentation with rTMS), type of rating scale, and risk of bias. Sensitivity analyses included three knots with different centiles and a four-knots model.

A random-effects meta-analysis using the REML method was also conducted for the primary outcome.

Heterogeneity was quantified employing the  $I^2$  statistic. (Higgins et al., 2019) Publication bias and small-study

effect were examined utilising funnel plots and Egger's test. The robustness of the pooled results was examined using excluding high ROB trials and leave-one-out influence analysis as sensitivity analyses.

Finally, we examined the geographic difference in the effect size, exploring how the estimates differ as a function of geographical location. Data analyses were conducted using R-Project (version 4.1.1, R Foundation). The p-values for all statistical tests were two-tailed, with a cut off value of 0.05.

### 3. Results

#### 3.1. Study characteristics

Our searches resulted in 2394 potentially relevant citations (eFigure 1). The complete search strategies and reasons for the exclusion of certain studies can be found in Appendices 2 and 3. After removing duplicates, 50 eligible RCTs ( $n = 2494$ ) were included. There were 1280 participants in rTMS arms (mean age: 44.4 (10.5) years; females: 60.2%) and 1214 in the sham groups (mean age: 44.3 (10.3) years, females:

56.8%). The details of the characteristics of the included studies are provided in eTable 1.

#### 3.2. Quality of evidence

Only seven studies ( $7/50 = 14\%$ ) were rated as having a high overall ROB (eFigure 2 and eFigure 3). The percentage of studies with high, unclear, and low ROB for the individual items were as follows: 0%, 70%, and 30% for randomisation process; 6%, 30%, and 64% for intended intervention; 8%, 2%, and 90% for missing outcome data; 6%, 12%, and 82% for measurement of the outcome; and 0%, 0%, and 100% for selection of the reported result.

#### 3.3. Dose-response curve and potential moderators

Without considering the dose-effect, the rTMS compared with sham was associated with a medium-to-large effect size (reported as SMD with 95% CI: 0.78, 0.57–0.99;  $I^2 = 74\%$ ) (Fig. 1). The leave-one-out analysis did not reveal any influential studies (eFigures 5 and 6). The dose-response analysis showed that the best-fitting model was a RCS model (Fig. 2; bell-shaped, adjusted  $R^2 = 0.42$ ), and the  $ED_{max}$  was 26,660 (22,380–89,980) pulses with a maximum SMD ( $SMD_{max}$ ) of 1.07. Visual inspection of the dose-response curve did not suggest that higher doses would be more effective in improving depressive symptoms. The leave-one-out dose-response analysis did not find any influential studies for this dose-response curve (eFigure 7). Sensitivity analyses of three knots with different centiles and a four-knots model showed similar model fitting (eTable 2). For potential moderators of the dose-response curve (Table 1), stimulation frequency (continuous:  $R^2 = 0.53$  or categorical:  $R^2 = 0.56$ ) and age ( $R^2 = 0.51$ ) were potentially important moderators since their explained variances were increased compared to other potential moderators. Higher stimulation frequency and younger mean age of studies were associated with better treatment efficacy. Other moderators, including inpatients ( $R^2 = 0.43$ ) and augmentation therapy ( $R^2 = 0.39$ ) were considered less important for minimal changes of the  $R^2$  value.

#### 3.4. Subgroup analysis

Stimulation frequency was categorised into three groups:  $\leq 5$  Hz, 10 Hz, and  $> 10$  Hz. Without considering the dose-effect, rTMS  $> 10$  Hz compared with sham had a large effect size (eFigure 8; 1.12, 0.68–1.56;  $I^2 = 74\%$ ), while rTMS 10 Hz compared with sham had a small-to-medium effect size (eFigure 9; 0.47, 0.32–0.61;  $I^2 = 48\%$ ). For rTMS  $\leq 5$  Hz (eFigure 10), the size was not significant (0.55, –0.04–1.15;  $I^2 = 28\%$ ).

Fig. 3 shows the dose-response curves of the six subgroups. The rTMS  $> 10$  Hz group had a  $SMD_{max}$  of 2.50, achieved at an  $ED_{max}$  of 59,990, and the dose-response curve did not appear to plateau (Fig. 2a). The rTMS 10

Hz group had a SMD<sub>max</sub> of 0.69 and an ED<sub>max</sub> of 31,740, and the dose-response curve was bell-shaped (Fig. 2b). The rTMS ≤ 5 Hz group had a SMD<sub>max</sub> of 0.98 and an ED<sub>max</sub> of 24,000, while the 95 CI was very wide. The group aged < 40 years had a SMD<sub>max</sub> of 2.56 and an ED<sub>max</sub> of 31,790, and the dose-response curve was bell-shaped. The group that was between the age of 40 and 50 years had a SMD<sub>max</sub> of 0.87 and an ED<sub>max</sub> of 15,880, and the dose-response curve was bell-shaped. The group aged > 50 years had a SMD<sub>max</sub> of 0.88 and an ED<sub>max</sub> of 59,990, while the dose-response curve approached a plateau quickly and seemed to increase slightly at larger doses.

Considering the FDA-approved protocol (10 Hz, 3000 pulses/session for 20 sessions), the pooled effect size was small to medium (eFigure 11; 0.46, 0.12–0.80;  $I^2 = 60\%$ ). When compared the FDA-approved protocol with a similar protocol using 15 Hz, the 15 Hz group produced a large effect size (eFigure 12, 2.67, 1.89–3.45;  $I^2 = 18\%$ ), and the group difference was significant ( $p < 0.01$ ).

### 3.5. Geographic difference in effect size and sample size

To date, 20 countries from four continents (Asia, Europe, North America, and Oceania) have conducted RCTs meeting our inclusion criteria (Fig. 4). The U.S. had the most RCTs ( $k = 17$ ) and participants ( $n = 938$ ), with a medium effect size (reported as SMD with 95CI: 0.54, 0.25–0.82). Large effect sizes were observed in seven countries, and four out of these seven originated in Asia. Subgroup analysis by continent showed significant group difference (eFigure 13,  $p = 0.02$ ), demonstrating the largest effect sizes (1.22, 0.77–1.68,  $I^2 = 71\%$ ) in Asian countries.

### 3.6. Sensitivity analyses and publication bias for primary outcomes

In the sensitivity test of excluding high ROB studies, rTMS had a medium-to-large effect size (eFigure 14; reported as SMD with 95CI: 0.74, 0.52–0.96;  $I^2 = 74\%$ ) when dose-effects were not considered. The dose-response curves after excluding high ROB studies were similar, and the RCS model was still the best fitting model (adjusted  $R^2 = 0.41$ ) (eFigure 15). The leave-one-out dose-response curve did not find any influential studies (eFigure 16). The detailed parameters of model fitting were similar after excluding studies with high ROB (eTable 3). Funnel plots and Egger's test showed no significant publication bias (eFigure 17).

## 4. Discussion

The main findings are as follows: First, the dose-response curve was bell-shaped with maximum efficacy achieved at approximately 26,660 total pulses, suggesting that higher doses would not be always more effective than lower doses. Second, stimulation frequency and age were significant moderators of the dose-response curve. The dose-response curve of rTMS > 10 Hz did not reach a plateau, while the dose-response curve for rTMS 10 Hz was bell-shaped. This suggests that

higher doses would be more efficacious in rTMS at 15 Hz or 20 Hz, while such relationship was not observed at 10 Hz. Finally, the effect sizes differed as a function of geographical location, indicating that RCTs conducted in Asia were associated with the largest effect size.

The most widely proposed mechanism of rTMS is the neural plasticity effect, which could lead to long-term potentiation/depression (LTP/LTD) of excitatory synaptic transmission. (Ma et al., 2014) The function of rTMS is frequency dependent. Low-frequency (usually 1 Hz or less) induces an inhibitory effect, while high-frequency (more than 5 Hz) induces a facilitative effect in the brain. (Noda et al., 2015) Previous studies usually combined 10 Hz and > 10 Hz (e.g. 15 Hz or 20 Hz) together as "HF-rTMS". Few studies compared the difference between 10 Hz and > 10 Hz in the antidepressant effects or in other biological markers. A retrospective study on MDD using rTMS on the left DLPFC reported that the 20 Hz group had a higher remission rate than the 10 Hz group. (DeBlasio and Tendler, 2012) When considering the density of pulses in a session, intermittent

theta-burst stimulation (iTBS) delivered higher density stimulation than 20 Hz rTMS. A previous NMA showed that iTBS over the left DLPFC did not demonstrate better anti-depressant efficacy than traditional HF-rTMS in patients with MDD. (Mutz et al., 2019) However, this finding was limited by the inclusion of non-TRD participants and the combining of 10 Hz and > 10 Hz as

HF-rTMS. Further research is encouraged to investigate the association between stimulation frequency and antidepressant efficacy in patients with TRD, along with its associated molecular and physiological mechanisms.

Our study findings provide a different understanding of the application of rTMS for TRD. The FDA-approved protocol of rTMS for TRD is 10 Hz, with a minimum of 60,000 total pulses. We found that the efficacy of rTMS at 10 Hz decreased after approximate 30,000 total pulses, while the efficacy did not approach a plateau in the rTMS > 10 Hz group between 30,000–60,000 total pulses. When considering the dose effects, both rTMS 10 Hz and rTMS > 10 Hz groups showed a dose-dependent relationship in antidepressant efficacy before 30,000 total pulses. Without considering the dose-effects, rTMS > 10 Hz was superior to rTMS 10 Hz for TRD. Indeed, the efficacy of rTMS using the FDA-approved protocol is inferior to the similar protocol with 15 Hz. However, 15–20 Hz rTMS studies generally employed a lower total number of pulses. If there are studies with a higher total number of pulses, it is possible to observe a plateau phenomenon at higher total pulses as well. More 15–20 Hz studies with high total number of pulses were needed to strengthen our findings.

We suggest several mechanisms to explain why there may be a maximal or plateau effect of rTMS at a certain dose in treating TRD. First, the antidepressant effects of rTMS may be associated with several biophysiological changes, such as increasing frontal cerebral blood flow, (Kinney and Hanlon, 2022), increasing glucose metabolism in the anterior cingulate cortex (Kinney and Hanlon, 2022), increasing low theta activity, (Bailey et al., 2018) and improving connectivity and network between brain regions. (Liston et al., 2014) However, neurons and other brain tissues may not react to these biophysiological effects in a total pulse-dependent manner. Second, rTMS may induce homeostatic structural plasticity in the stimulated and connected neuronal networks, which means that the synapses and dendritic spines are dynamically adjusted to maintain a stable level of activity. This may result in reaching a plateau effect after a certain level of stimulation, as the

network adapts to the increased input and reduces its excitability (Anil et al., 2023). Last, in clinical practice, the etiology of depression is multifactorial, and this is also true in patients with TRD. (Murphy et al., 2017) There are several biological factors that may contribute to the development of TRD, such as activation of inflammatory system, abnormal neural activity, neurotransmitter dysfunction, and other non-biological factors, such as personality, other comorbid psychiatric diseases, traumatic experiences, interpersonal relationships, and supportive systems. (Murphy et al., 2017) Therefore, the rTMS-associated biological factors may not affect every biological domain in patients with TRD, suggesting a plateau at certain dose levels.

In addition to stimulation frequency, our study found age is another significant moderator for the antidepressant effect rTMS in TRD. Older age has been regarded as a factor associated with poorer therapeutic response to rTMS. (Dumas et al., 2012; Kar, 2019) Cortical atrophy was the most widely investigated etiological factor. Several studies have reported that a greater frontal cortex volume is associated with a better antidepressant effect of rTMS. (Manes et al., 2001; Sabesan et al., 2015) In an atrophied brain, the distance between the cortex and scalp increases, potentially reducing the energy from the coil reaching the cortex, and consequently, the antidepressant effect of rTMS could also decrease correspondingly. (Sabesan et al., 2015) Furthermore, older individuals with a thinner motor cortex tended to have a lower resting motor threshold. (List et al., 2013) Consequently, the intensity of rTMS may be underestimated for older individuals, which might contribute to a poorer antidepressant response. Current evidences suggested that the response and remission rates in geriatric patients are similar to younger adults when the stimulus intensity (e.g. 110% MT) and number of pulses are increased. (Cappon et al., 2022; Jorge et al., 2008; van Rooij et al., 2020) Protocols specifically designed for older patients and personalized brain navigation are expected to be the future directions in the development of TMS for geriatric depression. (Cappon et al., 2022; van Rooij et al., 2020).

#### 4.1. Strengths and limitations

The present study was the first dose-response analysis of rTMS in treating TRD by using DRMA and examining multiple potential moderators. However, our findings must be interpreted with the following limitations: First, only patients with TRD were included in the study. Our study findings cannot be generalized to treatment-naïve depression, clinical depression, non-TRD MDD, and non-TRD bipolar depression. Additionally, the definitions of TRD varied among those trials. Second, we could only use the aggregated data to examine the dose-response curves, and only a few studies included doses of more than 60,000 total pulses. Third, the 95% CIs of the spline curves for rTMS  $\leq$  5 Hz, reflecting substantial uncertainty and variability. In addition, for homogeneity, we did not include accelerated TMS protocols or other types of TMS, such as theta-burst stimulation or deep TMS. Fourth, the best fitting model for the dose-response relationship could only explain 42% of the variance in the data. When considering the significant moderators of age and stimulation frequency, the explained variance increased to 51% and 53%, respectively. Therefore, other potential moderators warrant further investigation. Fifth, we only assessed the depressive symptom scale at the end of treatment. Some studies have suggested that a superior antidepressant effect would occur two to four weeks after rTMS. (Chen et al., 2013; Stern et al., 2007) Therefore, the dose-response curve might not apply to the after-effects of rTMS during the follow-up period. Sixth, the current analysis is based on a large number of very small RCTs, and the heterogeneity and small sample size limit the statistical power. Finally, our finding needs to be considered preliminary since there are only three RCTs (Baeken et al., 2013; Peng et al., 2012; Zheng et al., 2010) that utilized 15 Hz with more than 30,000 total pulses.

#### 5. Conclusions

In conclusion, for patients with TRD receiving rTMS over the left DLPFC, higher doses may not always be associated with greater efficacy in the treatment of depressive symptoms. Stimulation frequency might be an important moderator for the dose-response curves. These associations highlight the importance of determining dosing parameters of rTMS to achieve maximum efficacy among patients with TRD. Further studies are necessary to investigate other important dosing parameters for this difficult-to-treat population.

#### Ethical approval

Not required; analysis of aggregated de-identified clinical trial data.

#### Funding

The study was supported by MacKay Medical College, Taiwan (MMC- RD-111-1B-P003, for SLC), and the funder had no conflict of interest in this study.

#### Declaration of Competing Interest

None.

#### Data Availability

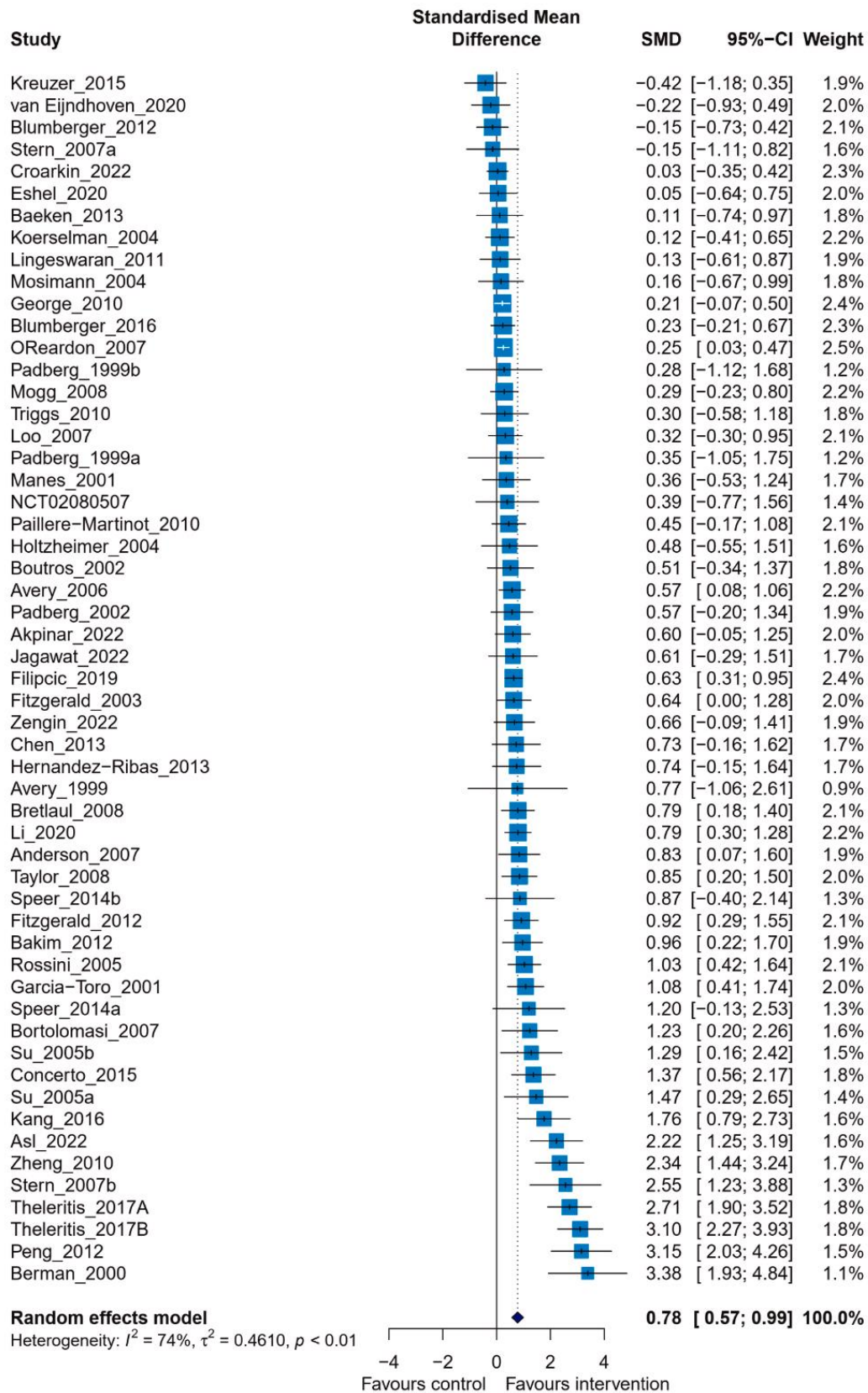
The data that support the findings of this study are available from the corresponding author (CSL) upon reasonable request.

#### Acknowledgements

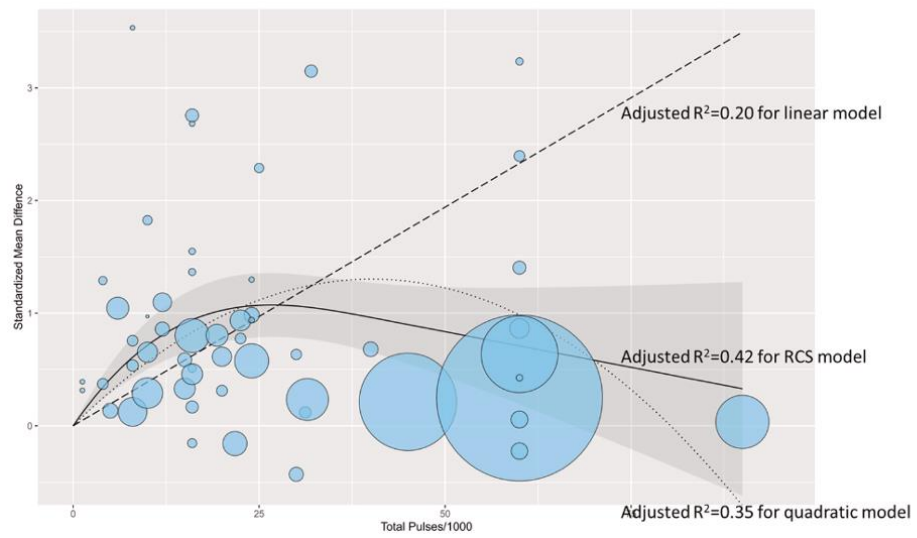
The study was supported by MacKay Medical College, Taiwan (MMC- RD-111-1B-P003, for SLC).

#### Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ajp.2023.103891](https://doi.org/10.1016/j.ajp.2023.103891).

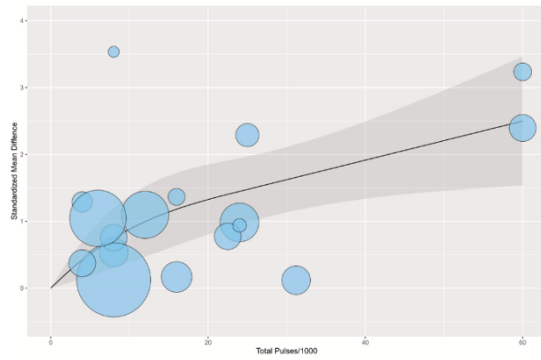


**Fig. 1.** Forestplot of all rTMS RCTs for TRD without considering a dose-effect Abbreviation: CI, confidence interval; RCT, randomized controlled trial; rTMS, re- petitive transcranial magnetic stimulation; SMD, standardized mean difference; TRD, treatment-resistant depression.

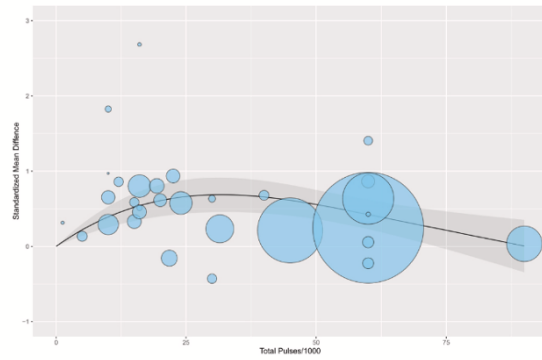


**Fig. 2.** Dose-response curve of rTMS for TRD, with dose of total pulses<sup>a</sup>,<sup>b</sup> a The dose was defined as the total pulses divided by 1000, and the total pulses was the product of pulses per session and total sessions. b The maximum standardized mean difference was 1.07 when using total pulses of 26660 (95CI: 22380–89980). Abbreviation: RCS, restricted cubic spline; rTMS, repetitive transcranial magnetic stimulation; TRD, treatment-resistant depression.

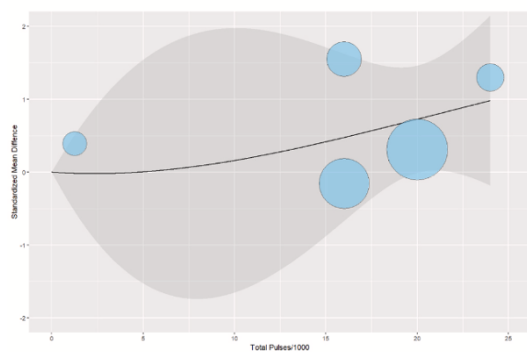
(a) >10Hz (ED<sub>max</sub>: 59990 (59990-59990); SMD<sub>max</sub>:2.50)



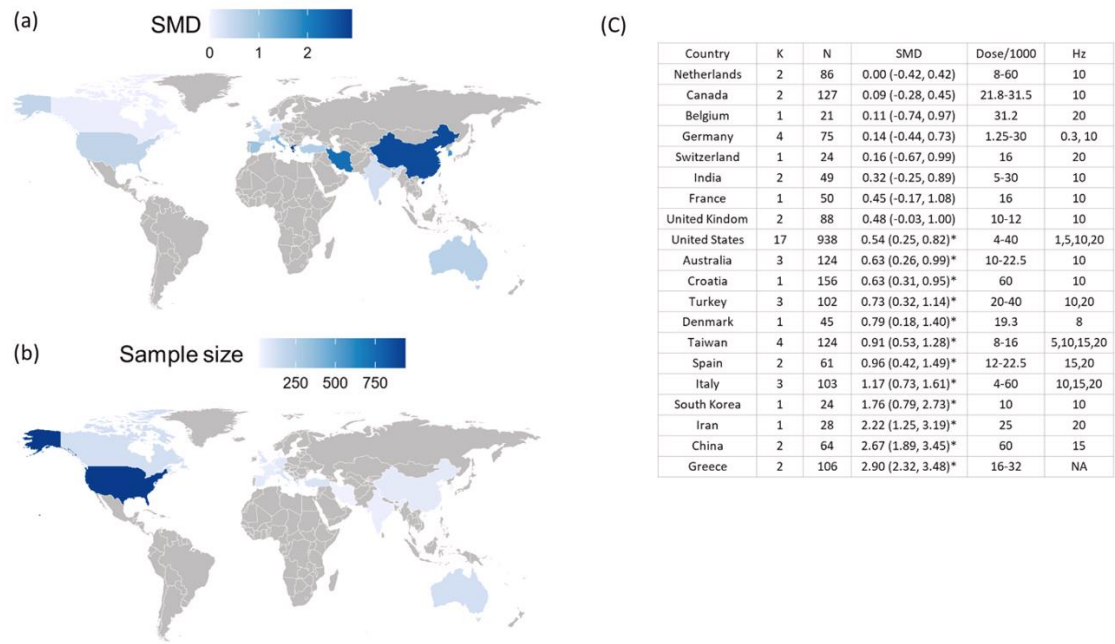
(b) 10Hz (ED<sub>max</sub>: 31740 (28660-37880); SMD<sub>max</sub>:0.69)



(c) ≤5Hz (ED<sub>max</sub>: 24000 (9400-24000); SMD<sub>max</sub>:0.98)



**Fig. 3.** Dose-response curve stratified by stimulation frequency ( $\leq 5$  Hz, 10 Hz, and  $>10$  Hz) and age ( $<40$ ,  $40-50$ ,  $>50$ ) a)  $> 10$  Hz (ED<sub>max</sub>: 59990 (59990–59990); SMD<sub>max</sub>:2.50) b) 10 Hz (ED<sub>max</sub>: 31740 (28660–37880); SMD<sub>max</sub>:0.69) c)  $\leq 5$  Hz (ED<sub>max</sub>: 24000 (9400–24000); SMD<sub>max</sub>:0.98). a The dose was defined as total pulses divided by 1000, and total pulses was the product of pulse per session and total sessions. Abbreviation: CI, confidence interval; ED<sub>max</sub>: maximum effective dose; rTMS, repetitive transcranial magnetic stimulation; TRD, treatment-resistant depression; SMD<sub>max</sub>: maximum standardized mean difference.



**Fig. 4.** Geographic differences in effect size and sample size Abbreviation: K, number of studies; N, number of participants; SMD, standardized mean difference.

**Table 1**

Moderator for dose-response meta-analysis using restricted cubic spline of 3 knots .

Moderator (M)	Dose	P1	Dose'	P2	Dose:M	P3	Dose': M	P4	Adjusted R <sup>2</sup>	Log- likelihood	AIC	BIC
Original model without moderator	0.09	< 0.001 *	-2.31	< 0.001 *					0.42	-73.95	157.90	167.76
Hz (continuous variable)*	0.08	0.01 *	-4.02	< 0.001 *	-0.001	0.66	0.21	0.04 *	0.53	-67.87	149.74	162.99
Hz (categorical variable: ≤5, 10, >10) <sup>b</sup> *	0.06	< 0.001 *	-1.68	< 0.001 *					0.56	-60.46	138.92	155.57
Power (muscle threshold)	0.26	0.07	-2.15	0.69	-0.18	0.18	0.95	0.84	0.49	-70.14	154.28	167.80
Total sessions	0.14	0.002 *	-4.11	0.02 *	-0.003	0.32	0.12	0.25	0.40	-80.78	175.56	189.08
TRD type (two vs one)	0.11	0.0001 *	-2.93	0.0004 *	-0.03	0.33	1.43	0.18	0.46	-68.83	151.65	164.45
Total sample size	0.12	< 0.001 *	-2.90	0.005 *	-0.0006	0.39	0.017	0.02	0.44	-85.07	184.15	197.67
Age*	0.38	0.0002 *	-7.47	0.001 *	-0.006	0.006 *	0.11	0.03	0.51	-76.34	166.69	180.07
Female	0.05	0.75	0.10	0.96	0.08	0.51	-3.78	0.21	0.44	-70.07	154.14	167.53
Year	0.07	0.52	-1.41	0.74	0.02	0.86	-0.92	0.83	0.41	-74.75	163.49	177.02
Daily once session vs multiple	0.07	0.52	-1.41	0.74	0.02	0.86	-0.92	0.83	0.41	-74.75	163.49	177.02
Baseline depression severity score	-0.08	0.44	1.55	0.63	0.007	0.10	-0.15	0.28	0.46	-77.92	169.85	183.37
Sham (rotation vs low stimuli)	0.04	0.74	-0.76	0.76	0.07	0.54	-1.06	0.68	0.43	-76.29	170.57	187.60
Sham (sham coil vs low stimuli)	0.04	0.74	-0.76	0.76	0.04	0.72	-0.83	0.75	0.43	-76.29	170.57	187.60
Outpatient vs inpatient	0.18	0.006 *	-2.27	0.01 *	-0.07	0.32	1.45	0.12	0.43	-63.27	144.53	158.78
Outpatient+inpatient vs inpatient*	0.18	0.006 *	-2.27	0.01 *	-0.16	0.049 *	2.41	0.01 *	0.43	-63.27	144.53	158.78
Single blind vs double blind	0.09	< 0.001 *	-0.65	0.0008 *	0.14	0.24	-1.11	0.27	0.43	-75.91	165.82	179.48
Pure TRD vs mixed TRD	0.07	0.30	-3.00	0.32	0.04	0.56	0.49	0.16	0.43	-73.07	160.15	173.67
Mixed (BD+MDD) vs MDD	0.10	< 0.001 *	-2.02	< 0.001 *	0.02	0.59	-0.93	0.42	0.41	-74.73	163.46	176.85
Monotherapy vs augment therapy	0.04	0.20	-0.18	0.55	0.02	0.73	-0.34	0.51	0.39	-66.87	151.75	166.00
Monotherapy+augment vs augment	0.04	0.24	-1.59	0.16	0.11	0.03 *	-0.95	0.03 *	0.39	-66.87	151.75	166.00
Scale (MADRS vs HDRS)	0.09	< 0.001 *	-2.27	< 0.001 *	0.01	0.89	-0.50	0.85	0.39	-73.45	160.91	174.29
Risk of bias (high vs low)	0.09	< 0.001 *	-2.38	< 0.01 *	0.06	0.28	-1.27	0.44	0.42	-77.03	172.07	189.09

Abbreviation: AIC, Akaike's Information Criteria; BIC, Bayesian Information Criteria; BD, bipolar depression; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation; TRD, treatment-resistant depression.

<sup>a</sup> The dose was defined as the total pulses divided by 1000, and the total pulses was the product of pulses per session and total sessions.

<sup>b</sup> The stimulation frequency was categorized into ≤ 5 Hz, 10 Hz, and > 10 Hz.