DE GRUYTER Reviews in the Neurosciences

Theta burst stimulation for enhancing upper extremity motor functions after stroke: A systematic review of clinical and mechanistic evidence

Journal:	*Reviews in the Neurosciences*
Manuscript ID	RNS.2024.0030.R1
Manuscript Type:	REVIEW
Date Submitted by the Author:	11-Apr-2024
Complete List of Authors:	Zhang, Jack; The Hong Kong Polytechnic University, Sui, Youxin; The Hong Kong Polytechnic University Sack, Alexander T; Maastricht University Bai, Zhongfei; Tongji University Kwong, Patrick WH; The Hong Kong Polytechnic University SANCHEZ VIDANA, Dalinda Isabel; The Hong Kong Polytechnic University Xiong, Li; Sun Yat-Sen University Fong, Kenneth N. K.; The Hong Kong Polytechnic University
Keywords:	stroke, upper extremity, theta burst stimulation, neuroplasticity, cortical excitability

Theta burst stimulation for enhancing upper extremity motor functions after stroke: A systematic review of clinical and mechanistic evidence

Jack Jiaqi ZHANG[1*], PhD

Youxin SUI[1], MPhil

Alexander T SACK[2], PhD

Zhongfei BAI[3], PhD

Patrick WH KWONG[1], PhD

Dalinda Isabel SANCHEZ VIDANA[1], PhD

Li XIONG[4], PhD

Kenneth NK FONG[1], PhD

[1]Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong SAR, China.

[2]Department of Cognitive Neuroscience, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, The Netherlands.

[3]Shanghai YangZhi Rehabilitation Hospital (Shanghai Sunshine Rehabilitation Centre), School of Medicine, Tongji University, Shanghai, China.

[4]Clinical Trials Centre, The Eighth Affiliated Hospital of Sun Yat-sen University, Shenzhen, China.

***Corresponding author:**

Jack Jiaqi ZHANG, PhD

Department of Rehabilitation Sciences

The Hong Kong Polytechnic University

Hung Hom, Hong Kong SAR, China

Email: jack-jq.zhang@connect.polyu.hk

Fax: +852-23308656

Word count	
Abstract	~~247~~248
Main text	3492
References	54
Figures	2
Tables	3

Keywords: stroke, upper extremity, theta burst stimulation, neuroplasticity, cortical excitability

Abstract

~~Objective: To~~This systematic review aimed to evaluate the effects of different theta burst stimulation (TBS) protocols on improving upper extremity motor function in patients with stroke, their associated modulators of efficacy, and the underlying neural mechanisms.

~~**Methods**:~~ We conducted a meta-analytic review of 29 controlled trials published from January 1, 2000, to August 29, 2023, that investigated the effects of TBS on upper extremity motor, neurophysiological, and neuroimaging outcomes in poststroke patients.

~~**Results**:~~ TBS significantly improved upper extremity motor impairment (Hedge's g =0.646, p=0.003) and functional activity (Hedge's g=0.500, p<0.001) compared to controls. Meta-regression revealed a significant relationship between the percentage of patients with subcortical stroke and the effect sizes of motor impairment (p=0.015) and functional activity (p=0.018). Subgroup analysis revealed a significant difference in the improvement of upper extremity motor impairment between studies using 600-pulse and 1200-pulse TBS (p=0.002). Neurophysiological studies have consistently found that intermittent TBS increases ipsilesional corticomotor excitability. However, evidence to support the regional effects of continuous TBS, as well as the remote and network effects of TBS, is still mixed and relatively insufficient. In conclusion,

~~**Conclusions**:~~ TBS is effective in enhancing poststroke upper extremity motor function. Patients with preserved cortices may respond better to TBS. Novel TBS protocols with a higher dose may lead to superior efficacy compared with the conventional 600-pulse protocol. The mechanism of poststroke recovery facilitated by TBS can be primarily attributed to the modulation of corticomotor excitability and is possibly caused by the recruitment of corticomotor networks connected to the ipsilesional motor cortex.

1 Introduction

Theta burst stimulation (TBS), originally used as a neuroplasticity-induction paradigm to modulate the activity of hippocampal neurons, was first introduced for research on human motor plasticity in 2005 (Huang et al. 2005, Huang et al. 2004). TBS has the advantage of short conditioning duration and has comparable neuromodulatory effects to conventional repetitive transcranial magnetic stimulation protocols. TBS has been increasingly utilized in neurorehabilitation, particularly in cases of poststroke hemiparetic upper-extremity rehabilitation (Lefaucheur et al. 2020). In 2007, an experimental study by Talelli et al. showed that intermittent TBS (iTBS) and continuous TBS (cTBS) had a ~~bidirectional~~ robust effect on modulating corticospinal excitability and behavioral motor learning in patients who had suffered a stroke (Talelli et al. 2007). In clinical trials, TBS is now frequently used for stimulation-based brain priming before rehabilitation intervention to improve the readiness of the brain to re-learn motor skills during behavioral motor practice, thereby facilitating therapeutic benefits from rehabilitation training for patients after stroke (Cassidy et al. 2014).

Systematic reviews published on the effects of TBS on poststroke upper extremity motor functions generally report positive effects of TBS in promoting hemiparetic upper extremity functions (Chen et al. 2023, Gao et al. 2022, Huang et al. 2022, Tang et al. 2022, Xiang et al. 2019, Zhang et al. 2017). However, these reviews consistently have methodological limitations that need to be addressed. First, several articles mixed different outcomes in the meta-analysis, such as finger-tapping speed and clinical scores (Tang et al. 2022, Xiang et al. 2019, Zhang et al. 2017). Combining norms-based behavioral tests with performance-based clinical measures is unlikely to yield robust results (Moayyedi 2004). The responsiveness of these measures

differed significantly, making it inappropriate to use the pooled effect size as a reference for clinical efficacy. Second, most of the systematic reviews used post-treatment scores rather than improvement scores in the meta-analyses of continuous variables (Chen et al. 2023, Huang et al. 2022, Tang et al. 2022, Xiang et al. 2019). This issue has been investigated in a study by Chhatbar et al., in which the results of a meta-analysis using postscores were not consistent because baseline differences were neglected when using postscores alone in the meta-analysis (Chhatbar et al. 2016). Third, the influence of possible modulators of efficacy, such as patient demographics and clinical profiles as well as the parameters of TBS protocols, on the effect sizes in association with TBS remains largely unexplored. These critical issues that previous meta-analytic reviews have not adequately addressed should be resolved through subgroup analyses and meta-regression. Finally, previous systematic reviews focused on clinical measures and ignored neuroimaging and neurophysiological outcomes, except for a few articles that reviewed TMS-electromyography (EMG) (Chen et al. 2023, Tang et al. 2022, Xiang et al. 2019). However, the neural mechanisms underlying the effects of TBS on poststroke rehabilitation have not been sufficiently described. Therefore, a comprehensive understanding of the neural mechanisms that explain the therapeutic benefits of TBS in poststroke rehabilitation, in terms of its regional, remote, and network effects, is needed.

The current meta-analytic review aims to 1) evaluate the effects of different TBS protocols on improving upper extremity motor impairment and functional activities in patients with stroke; 2) identify any significant associations between various TBS parameters, patient demographics, clinical profiles, and effect sizes using subgroup analyses and meta-regression; and 3) summarize and interpret the mechanisms underlying the therapeutic effects of TBS by qualitatively assessing studies using neuroimaging and/or neurophysiological outcome measurements.

2 Methods

2.1 Literature search

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al. 2009). The protocol for this review was registered in INPLASY (INPLASY202410069) after the initial database literature search and prior to our formal data analysis. ~~The protocol of this review has been pre-registered in INPLASY (INPLASY202410069).~~ A literature search was conducted for studies published between January 1, 2000, to August 29, 2023, which were indexed in four databases: PubMed, EMBASE, Web of Science, and Medline. The keywords used to identify TBS were "theta burst," "theta burst stimulation," and "theta burst transcranial magnetic stimulation." The keywords used for identifying stroke included "stroke," "cerebrovascular accident," and "hemiplegia." Medical subject heading terms were used when performing the PubMed search. Two authors (JZ and YS) independently read and identified all titles and excluded irrelevant studies. In addition, the reference lists of previously published reviews were manually screened to identify relevant articles.

2.2 Inclusion and exclusion criteria

We followed the PICOS framework for the inclusion of studies; that is, studies were considered for this review if they satisfied the following criteria. Population (P): Studies that included adult participants diagnosed with stroke. Intervention (I): Interventions that used TBS applied to the primary motor cortex (M1) cortical representations of the proximal or distal upper extremity. Comparison (C): Sham TBS or no stimulation control. Outcomes (O): Studies that provided at least one outcome assessing upper limb motor impairment, functional activity, or neural functions (neurophysiological or neuroimaging outcomes). According to expert

consensus, motor impairment and activity limitations are deemed primary in poststroke rehabilitation trials (Kwakkel et al. 2017). Therefore, we selected the upper extremity subscores of the Fugl-Meyer Assessment (FMA-UE), which is the gold standard for evaluating upper extremity motor impairment poststroke. For measuring poststroke activity limitations, the action research arm test (ARAT) was considered. If ARAT scores were not available, the Wolf motor function test or the Jebsen-Taylor hand function test were used in the meta-analysis because these two assessments involved a series of gross and fine motor tasks that were relatively comparable to the functional tasks utilized in the ARAT (Chen et al. 2019). A similar meta-analytical methodology has been utilized in a previous review (van Lieshout, 2019). Study design (S): Randomized or pseudorandomized controlled trials with either a parallel or crossover design. Studies meeting any of the following criteria were excluded: 1) the study recruited participants with concomitant neurological disorders other than stroke or neurologically healthy individuals; 2) the study was published as conference abstracts, dissertations, or in books; and 3) studies not published in English.

2.3 Quality assessment and data extraction

Two independent authors (JZ and YS) conducted data extraction and quality assessment of the included studies. The quality assessment was assessed using the Physiotherapy Evidence Database (PEDro) scale - a scoring system for measuring methodological reporting quality of rehabilitation trials (Bhogal et al. 2005). Discrepancies were resolved through discussion with a third author (ZB).

2.4 Data analysis

Statistical analyses were performed using Comprehensive Meta-analysis software version 3.0. The authors were contacted by email if meta-analyzable data were missing. In the case of a

lack of response from the authors, a graph digitizer (http://getdata-graph-digitizer.com/) was used to extract graphically reported data. Hedges' g and 95% confidence interval (CI) were computed for all meta-analyses (Higgins et al.). Reported standard errors were converted to standard deviations (SD) using the formula SD = SEM × √n (n = sample size). Between-study heterogeneity was examined using Higgins I^2 statistic (Higgins et al. 2003). Inverse variance method was applied in the estimation of the weight of each study. Owing to the limited number of studies with follow-up data and the heterogeneity in the length of follow-up, we only focused on the effect of TBS post-intervention in the meta-analysis. Improvement scores, i.e., post-intervention minus baseline, were used to estimate individual effect sizes to minimize the influence of baseline differences between groups (Chhatbar et al. 2016). According to Brydge 2019, effect sizes measured by Hedge's g values of 0.15, 0.40, and 0.75 are typically interpreted as indicating small, medium, and large effects, respectively. Meta-regression analysis was performed to identify any association between effect size and TBS parameters in at least five studies per subgroup (Zhang et al. 2019). Univariate meta-regression was performed with various patients' demographics, i.e., age and sex (expressed by the percentage of male patients), clinical information, i.e., the chronicity of stroke (mean months after stroke), the baseline severity (mean baseline severity scores), the percentage of subcortical patients, the percentage of ipsilesional MEP positive patients, and the percentage of patients with cerebral infarction, as well as TBS parameters, including the total number of applied pulses, the number of sessions, the number of pulses per session, and stimulation intensity (presented as % resting motor threshold [RMT], action motor threshold [AMT] was transformed to RMT using 70% RMT = 80% AMT (Goldsworthy et al. 2012)]. Meta-regression was conducted to investigate the potential association between the aforementioned variables and the weighted Hedges' g values at the study level. Publication bias was investigated using Egger's test. A sensitivity analysis was performed using the leave-one-out method to obtain significant results. The statistical

threshold was set at p <0.05 (two-tailed), except that a two-tailed threshold (p <0.1 (two-tailed) was used for the Egger's test (Egger et al. 1997).

3 Results

3.1 Study selection

The selection process is illustrated in **Figure S1**. We included 29 studies with 779 patients in the systematic review (Ackerley et al. 2016, Ackerley et al. 2010, Ackerley et al. 2014, Bai et al. 2023, Bonnì et al. 2020, Chen et al. 2021, Chen et al. 2019, Di Lazzaro et al. 2016, Di Lazzaro et al. 2013, Diekhoff-Krebs et al. 2017, Ding et al. 2022, Ding et al. 2021, Dionísio et al. 2021, Hsu et al. 2013, Khan et al. 2019, Kuzu et al. 2021, Lai et al. 2015, Meehan et al. 2011, Meng et al. 2020, Neva et al. 2019, Nicolo et al. 2018, Sung et al. 2013, Talelli et al. 2007, Talelli et al. 2012, Vink et al. 2023, Volz et al. 2016, Wadden et al. 2019, Wang et al. 2014, Watanabe et al. 2018, Zhang et al. 2022), of which 20 were included in the meta-analyses of upper extremity motor outcomes (Ackerley et al. 2016, Chen et al. 2021, Chen et al. 2019, Di Lazzaro et al. 2016, Di Lazzaro et al. 2013, Dionísio et al. 2021, Hsu et al. 2013, Khan et al. 2019, Lai et al. 2015, Meehan et al. 2011, Meng et al. 2020, Neva et al. 2019, Nicolo et al. 2018, Sung et al. 2013, Talelli et al. 2012, Vink et al. 2023, Wang et al. 2014, Watanabe et al. 2018, Zhang et al. 2022). The characteristics of the included studies are summarized in **Table 1**.

3.2 Methodological quality assessment

The methodological quality of the included studies was rated using the PEDro scale (**Table S1**). The mean score was 7.83, ranging from 6 to 10, indicating the moderate to high methodological quality of the included articles.

3.3 TBS protocols

Most studies used standard 600-pulse iTBS for the ipsilesional M1 or 600-pulse cTBS for the contralesional M1. A bilateral TBS protocol (cTBS to the contralesional M1 + iTBS to the ipsilesional M1) was used by Khan et al. (Khan et al. 2019), while another two studies utilized low-frequency rTMS to the contralesional M1 before iTBS to the ipsilesional M1 (Meng et al. 2020, Wang et al. 2014). cTBS was applied to the ipsilesional M1 in two studies by Di Lazzaro et al. (Di Lazzaro et al. 2016, Di Lazzaro et al. 2013) to induce a metaplastic interaction between cTBS and subsequent motor training, while another study applied a priming iTBS protocol, which involved applying cTBS to the ipsilesional M1 before iTBS over the ipsilesional M1 to induce a stronger facilitative effect of iTBS via therapeutic beneficial metaplasticity (Zhang et al. 2022). A 1200-pulse iTBS protocol to the ipsilesional M1 was applied in Hsu et al. (Hsu et al. 2013) and Meng et al. (Meng et al. 2020).

3.4 Upper extremity motor impairment

A total of 12 studies with 14 units of analysis were included in the meta-analysis of FMA-UE scores (Chen et al. 2021, Chen et al. 2019, Di Lazzaro et al. 2016, Hsu et al. 2013, Khan et al. 2019, Meng et al. 2020, Nicolo et al. 2018, Sung et al. 2013, Vink et al. 2023, Wang et al. 2014, Watanabe et al. 2018, Zhang et al. 2022). Overall, improved upper extremity impairment was found after TBS intervention compared to the control group (Hedge's g = 0.646, p = 0.003, I^2 = 76.15%; Figure 1A), and the overall significance was robust to leave-one-out sensitivity analysis (Hedge's g from 0.402 to 0.715, which consistently indicated medium effect sizes during sensitivity analysis). Subgroup analysis showed that excitatory and bilateral TBS protocols significantly improved upper extremity motor impairment (excitatory: Hedge's g = 0.470, p = 0.001, I^2 = 44.97%; bilateral: Hedge's g = 3.521, p <0.001, I^2 = 0.00%), but the effect of inhibitory TBS protocols was not significant (Hedge's g = 0.300, p = 0.122, I^2 = 0.00%).

Between-subgroup differences (excitatory vs. inhibitory) were not statistically significant (Q = 0.34, p = 0.56). There was no sign of publication bias according to the non-significant results of the Egger's test (p = 0.12). Univariate meta-regression analysis revealed that the percentage of patients with subcortical lesions (p = 0.015) was a significant predictor of the effect size of TBS (Figure 2A). Furthermore, the Q-test revealed a significant between-group difference between studies with 600-pulse TBS and 1200-pulse TBS (Q = 9.59, p = 0.002; Figure 2C).

3.5 Upper extremity functional activity

A total of 14 studies with 19 units of analysis were included in the meta-analysis of upper extremity functional activity (Ackerley et al. 2016, Chen et al. 2021, Chen et al. 2019, Di Lazzaro et al. 2013, Dionísio et al. 2021, Hsu et al. 2013, Lai et al. 2015, Meehan et al. 2011, Neva et al. 2019, Sung et al. 2013, Talelli et al. 2012, Vink et al. 2023, Wang et al. 2014, Zhang et al. 2022). A meta-analysis demonstrated that TBS significantly improved upper limb functional activity compared with sham stimulation (Hedges' g = 0.500, p <0.001, I^2 = 34.12%; Figure 1B). The overall significance was also robust to leave-one-out sensitivity analysis (Hedge's g from 0.408 to 0.528, which consistently indicated medium effect sizes during sensitivity analysis). The subgroup analysis showed that both excitatory and inhibitory TBS protocols yielded a more significant effect than sham stimulation on improving upper limb functional activity (excitatory: Hedges' g = 0.609, p <0.001, I^2 = 52.68%; inhibitory: Hedges' g = 0.344, p = 0.021, I^2 = 0.00%). Between-subgroup differences were not statistically significant (Q = 1.32, p = 0.251). There was no sign of publication bias according to Egger's test (p = 0.964). Univariate meta-regression revealed a significantly positive relationship between the percentage of subcortical patients and the effect size (p = 0.018; Figure 2B). **Table S2 and S3** summarize the results of the univariate meta-regression.

3.6 Neural modulatory effects of TBS

A total of 22 studies included in this review used neuroimaging or neurophysiological outcomes (Ackerley et al. 2016, Ackerley et al. 2010, Ackerley et al. 2014, Bai et al. 2023, Di Lazzaro et al. 2013, Diekhoff-Krebs et al. 2017, Ding et al. 2022, Ding et al. 2021, Dionísio et al. 2021, Hsu et al. 2013, Khan et al. 2019, Lai et al. 2015, Meng et al. 2020, Neva et al. 2019, Nicolo et al. 2018, Sung et al. 2013, Talelli et al. 2007, Volz et al. 2016, Wadden et al. 2019, Wang et al. 2014, Watanabe et al. 2018, Zhang et al. 2022). TMS-EMG outcomes were the most frequently used (Ackerley et al. 2010, Ackerley et al. 2014, Bai et al. 2023, Di Lazzaro et al. 2013, Diekhoff-Krebs et al. 2017, Khan et al. 2019, Lai et al. 2015, Meng et al. 2020, Neva et al. 2019, Talelli et al. 2007, Wang et al. 2014, Watanabe et al. 2018), followed by electroencephalography (EEG)/TMS-EEG/magnetoencephalography (MEG) (Bai et al. 2023, Ding et al. 2022, Ding et al. 2021, Dionísio et al. 2021, Hsu et al. 2013, Nicolo et al. 2018, Zhang et al. 2022), and structural and functional magnetic resonance imaging (fMRI) (Ackerley et al. 2016, Volz et al. 2016, Wadden et al. 2019). Overall, iTBS over the ipsilesional M1 increased ipsilesional corticomotor excitability, whereas cTBS over the contralesional M1 decreased contralesional corticomotor excitability, as measured by the amplitude of MEP (Ackerley et al. 2010, Ackerley et al. 2014, Bai et al. 2023, Diekhoff-Krebs et al. 2017, Meng et al. 2020, Talelli et al. 2007, Wang et al. 2014, Watanabe et al. 2018), motor map area (Lai et al. 2015, Sung et al. 2013, Wang et al. 2014), input-output curve (Talelli et al. 2007), P30 in the TMS-evoked potential on EEG (Bai et al. 2023), and movement event-related desynchronization (ERD) (Dionísio et al. 2021). Furthermore, iTBS or iTBS priming over the ipsilesional M1 enhances the sensory permissiveness of M1, as measured by short-interval afferent inhibition (Ackerley et al. 2014) and mirror visual feedback-induced ERD (Zhang et al. 2022).

Apart from the regional effects, TBS demonstrated remote effects in poststroke brains. Specifically, iTBS over the ipsilesional M1 was found to increase the functional connectivity between the ipsilesional M1 and other parts of the cortical motor system over the bilateral hemispheres, as measured by resting-state fMRI (Volz et al. 2016) and intra-and interhemispheric sensorimotor coherence (Ding et al. 2021). Moreover, cTBS over the contralesional M1 decreases directional connectivity from the contralesional to ipsilesional M1 (Nicolo et al. 2018). Regarding network effects, one study using iTBS on the ipsilesional M1 showed an increase in global efficacy (defined as the reciprocal of the shortest path length between whole-brain connections) in subacute stroke patients (Ding et al. 2021). However, another study using the same protocol did not find any significant effects of modulating network properties in chronic stroke patients (Bai et al. 2023).

4 Discussion

The here presented meta-analysis revealed that 1) both ipsilesional iTBS and contralesional cTBS significantly improved upper limb functional activities in patients after stroke, as compared sham stimulation. 2) iTBS~~, but not cTBS,~~ significantly improved upper limb motor impairment after stroke compared to sham stimulation or no stimulation; however, the evidence to support the effect of cTBS was still limited. 3) A significant association was found between the number of patients with subcortical lesions and the magnitude of the effect size of TBS, indicating that lesion location may be a factor determining individual treatment responsiveness to TBS with pure subcortical stroke patients benefitting most from the cortical TBS therapy. 4) TBS with a higher number of pulses, e.g., 1200-pulse, seems to lead to superior efficacy compared to conventional 600-pulse protocols. 5) The neural mechanisms underlying TBS in poststroke rehabilitation can be attributed to the modulation of corticomotor excitability and may be related to the recruitment of corticomotor networks connected to the ipsilesional M1.

TBS is frequently used for cortical conditioning (stimulation intensity <100% RMT) in poststroke rehabilitation (Huang et al. 2005), and the level of the structural reserve of the cortical motor system appears to be important for responsiveness to TBS (Ding et al. 2023). The enhanced excitability of the M1 through iTBS or decreased interhemispheric inhibition from the contralesional to the ipsilesional M1 through contralesional cTBS can potentially increase the chances of activating specific cortico-subcortical neural circuits that are crucial for task-specific rehabilitation training. This, in turn, may result in more favorable therapeutic outcomes (Ding et al. 2023). Impairment of the cortical region, particularly the stimulated M1 region, can potentially nullify the impact of cortical conditioning during the TBS, thereby restricting facilitation along the corticospinal descending pathway (Ameli et al. 2009). Therefore, individuals with an intact cortex, specifically a preserved motor cortex, may exhibit a more favorable response to cortical conditioning using TBS.

Accelerated TBS protocols with more stimulation pulses (e.g., 1200-pulse) seemed to be more efficacious than the conventional 600-pulse protocol. However, it is worth mentioning that there are three types of 1200-pulse TBS protocols that have been reported in the previous literature: a higher dose iTBS (two sessions of 600-pulses iTBS delivered to the ipsilesional M1) (Hsu et al. 2013, Meng et al. 2020), priming iTBS (applying 600-pulse cTBS before 600-pulse iTBS, and both were applied to the ipsilesional M1) (Zhang et al. 2022), and bilateral TBS (cTBS over the contralesional M1 and iTBS over the ipsilesional M1) (Khan et al. 2019). The underlying rationale for the use of different 1200-pulse TBS protocols differs; however, in general, novel TBS protocols have demonstrated improved efficacy compared to conventional protocols with lower number of overall pulses. It is, however, important to interpret the results with caution because all novel protocols have only been tested in small-

scale clinical studies and have not been externally validated (Hsu et al. 2013, Khan et al. 2019, Meng et al. 2020, Zhang et al. 2022).

The timing of TBS intervention is a potentially influential factor in post-stroke rehabilitation outcomes (Vink et al., 2023). A previous review on rTMS reported a signficantly larger effect size in the acute stroke subgroup compared to the subacute and chronic stroke subgroups (van Lieshout, 2019). This finding aligns with the results in the present focused review of TBS literature, as we observed numerically higher effect sizes in studies involving patients in the earlier stages of stroke compared to those in later stages. However, due to variations in the literature regarding the specific cutoffs used to define the acute and post-acute phases post-stroke, we employed a meta-regression analysis to investigate the relationship between time since stroke and effect size. However, no significant results were found, highlighting the lack of consistent evidence to determine the optimal timing of TBS intervention in post-stroke patients.

The regional modulatory effect of TBS has been well-documented in the literature, primarily derived from neurophysiological evidence using EEG/MEG (Dionísio et al. 2021, Hsu et al. 2013, Zhang et al. 2022), TMS-EMG (Ackerley et al. 2014, Diekhoff-Krebs et al. 2017, Khan et al. 2019, Lai et al. 2015, Meng et al. 2020, Talelli et al. 2007, Wang et al. 2014, Watanabe et al. 2018), and TMS-EEG outcomes (Bai et al. 2023, Ding et al. 2022). However, the modulatory effect of single-target TBS on connectivity and networks is still under investigation, with limited evidence. Preliminary evidence using EEG or fMRI suggests that TBS (iTBS or cTBS) affects the corticomotor network connected to the ipsilesional M1 (Ding et al. 2021, Nicolo et al. 2018, Volz et al. 2016), although the underlying neural circuit remains unknown. The remote and network effects of single-target M1 TBS are largely unpredictable in healthy

adults (Zhang 2024) and can be even more complicated in poststroke patients with impaired neural connectivity and networks. Studies may further explore the association between poststroke impairments of neural networks and the effect of TBS, and then optimize the network effect of TBS through the use of multifocal TBS or combined with specific motor training that can recruit task-specific neural circuits.

The present study was not free from limitations. Firstly, due to our inability to access the individual datasets from each study, i.e., individual participant data meta-analysis, we were unable to conduct a comprehensive analysis on the percentage of patients who achieved improvement scores exceeding the minimal clinically important difference. On the other hand, the heterogeneity of neural outcomes used across the different studies prevented us from conducting a quantitative analysis. The current discussion regarding the neural mechanisms underlying TBS in poststroke rehabilitation was based on a qualitative interpretation of the findings.

5 Conclusion

TBS is an efficacious brain stimulation therapy that enhances the therapeutic benefits of poststroke upper extremity rehabilitation training. Patients with subcortical stroke show better responsiveness to TBS. Accelerated TBS protocols using higher doses may have superior efficacy. The mechanisms of recovery facilitated by TBS in poststroke rehabilitation can be attributed to the excitability modulation of the M1 and descending motor pathways and possibly to the recruitment of corticomotor networks connected to the ipsilesional M1.

Funding

The study was partially supported by the Start-up Fund for RAPs under the Strategic Hiring

Scheme, The Hong Kong Polytechnic University (Grant number: P0048866) to JZ, the Science and Technology Commission of Shanghai Municipality (23Y11900600) and the Shanghai Hospital Development Center (SHDC12023618) to ZB

Declarations of conflicting interests

Alexander T Sack is chief scientific advisor for PlatoScience Medical, scientific advisor for Alpha Brain Technologies, Founder and CEO of Neurowear Medical, scientific director of the International Clinical TMS Certification Course and president of the Academy of Brain Stimulation. He also received equipment support from MagVenture, Magstim, and Deymed Diagnostics. These activities and roles do not influence the work reported in this paper. Other authors also declare that there are no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper, and there are no additional relationships, patents, or activities to disclose.

Data availability statement

Data supporting the findings of this study are available from the corresponding author on request.

Ethical approval

Not applicable. The study was a review.

Protocol registration

The protocol of this review has been ~~pre-~~registered in the International Platform of Registered Systematic Review and Meta-analysis Protocols (Reference number: INPLASY202410069)

References:

Ackerley, S.J., Byblow, W.D., Barber, P.A., MacDonald, H., McIntyre-Robinson, A., and Stinear, C.M. (2016) Primed Physical Therapy Enhances Recovery of Upper Limb Function in Chronic Stroke Patients. Neurorehabil Neural Repair. 30:339-48.

Ackerley, S.J., Stinear, C.M., Barber, P.A., and Byblow, W.D. (2010) Combining theta burst stimulation with training after subcortical stroke. Stroke. 41:1568-72.

Ackerley, S.J., Stinear, C.M., Barber, P.A., and Byblow, W.D. (2014) Priming sensorimotor cortex to enhance task-specific training after subcortical stroke. Clin Neurophysiol. 125:1451-8.

Ameli, M., Grefkes, C., Kemper, F., Riegg, F.P., Rehme, A.K., Karbe, H., Fink, G.R., and Nowak, D.A. (2009) Differential effects of high-frequency repetitive transcranial magnetic stimulation over ipsilesional primary motor cortex in cortical and subcortical middle cerebral artery stroke. Ann Neurol. 66:298-309.

Bai, Z., Zhang, J.J., and Fong, K.N.K. (2023) Immediate Effects of Intermittent Theta Burst Stimulation on Primary Motor Cortex in Stroke Patients: A Concurrent TMS-EEG Study. IEEE Trans Neural Syst Rehabil Eng. 31:2758-2766.

Bhogal, S.K., Teasell, R.W., Foley, N.C., and Speechley, M.R. (2005) The PEDro scale provides a more comprehensive measure of methodological quality than the Jadad scale in stroke rehabilitation literature. J Clin Epidemiol. 58:668-73.

Bonnì, S., Motta, C., Pellicciari, M.C., Casula, E.P., Cinnera, A.M., Maiella, M., Picazio, S., Tramontano, M., Sallustio, F., and Koch, G. (2020) Intermittent Cerebellar Theta Burst Stimulation Improves Visuo-motor Learning in Stroke Patients: a Pilot Study. Cerebellum. 19:739-743.

Brydges C. R. (2019). Effect Size Guidelines, Sample Size Calculations, and Statistical Power in Gerontology. Innovation in aging, 3(4), igz036.

Cassidy, J.M., Gillick, B.T., and Carey, J.R. (2014) Priming the brain to capitalize on metaplasticity in stroke rehabilitation. Phys Ther. 94:139-50.

Chen, P.M., Kwong, P.W.H., Lai, C.K.Y., and Ng, S.S.M. (2019) Comparison of bilateral and unilateral upper limb training in people with stroke: A systematic review and meta-analysis. PLoS One. 14:e0216357.

Chen, S., Zhang, S., Yang, W., Chen, Y., Wang, B., Chen, J., Li, X., Xie, L., Huang, H., ~~Zeng, Y., Tian, L., Ji, W., Wei, X., Lan, Y., Li, H~~et al. (2023) The effectiveness of intermittent theta burst stimulation for upper limb motor recovery after stroke: a systematic review and meta-analysis of randomized controlled trials. Frontiers in Neuroscience. 17.

Chen, Y.H., Chen, C.L., Huang, Y.Z., Chen, H.C., Chen, C.Y., Wu, C.Y., and Lin, K.C. (2021) Augmented efficacy of intermittent theta burst stimulation on the virtual reality-based cycling training for upper limb function in patients with stroke: a double-blinded, randomized controlled trial. J Neuroeng Rehabil. 18:91.

Chen, Y.J., Huang, Y.Z., Chen, C.Y., Chen, C.L., Chen, H.C., Wu, C.Y., Lin, K.C., and Chang, T.L. (2019) Intermittent theta burst stimulation enhances upper limb motor function in patients with chronic stroke: a pilot randomized controlled trial. BMC Neurol. 19:69.

Chhatbar, P.Y., Ramakrishnan, V., Kautz, S., George, M.S., Adams, R.J., and Feng, W. (2016) Transcranial Direct Current Stimulation Post-Stroke Upper Extremity Motor Recovery Studies Exhibit a Dose-Response Relationship. Brain Stimul. 9:16-26.

Di Lazzaro, V., Capone, F., Di Pino, G., Pellegrino, G., Florio, L., Zollo, L., Simonetti, D., Ranieri, F., Brunelli, N., Corbetto, M., ~~Miccinilli, S., Bravi, M., Milighetti, S., Guglielmelli, E., Sterzi, S~~et al. (2016) Combining Robotic Training and Non-Invasive Brain Stimulation in Severe Upper Limb-Impaired Chronic Stroke Patients. Front

Neurosci. 10:88.

Di Lazzaro, V., Rothwell, J.C., Talelli, P., Capone, F., Ranieri, F., Wallace, A.C., Musumeci, G., Dileone, M. (2013) Inhibitory theta burst stimulation of affected hemisphere in chronic stroke: a proof of principle, sham-controlled study. Neurosci Lett. 553:148-52.

Diekhoff-Krebs, S., Pool, E.M., Sarfeld, A.S., Rehme, A.K., Eickhoff, S.B., Fink, G.R., and Grefkes, C. (2017) Interindividual differences in motor network connectivity and behavioral response to iTBS in stroke patients. Neuroimage Clin. 15:559-571.

Ding, Q., Chen, J., Zhang, S., Chen, S., Li, X., Peng, Y., Chen, Y., Chen, J., Chen, K., Cai, G~~., Xu, G., Lan, Y.~~, et al. (2023) Neurophysiological characterization of stroke recovery: A longitudinal TMS and EEG study. CNS Neurosci Ther.

Ding, Q., Chen, S., Chen, J., Zhang, S., Peng, Y., Chen, Y., Chen, J., Li, X., Chen, K., Cai, G., et al~~Xu, G., Lan, Y~~. (2022) Intermittent Theta Burst Stimulation Increases Natural Oscillatory Frequency in Ipsilesional Motor Cortex Post-Stroke: A Transcranial Magnetic Stimulation and Electroencephalography Study. Front Aging Neurosci. 14:818340.

Ding, Q., Zhang, S., Chen, S., Chen, J., Li, X., Chen, J., Peng, Y., Chen, Y., Chen, K., Cai, G., et al. ~~Xu, G., Lan, Y.~~ (2021) The Effects of Intermittent Theta Burst Stimulation on Functional Brain Network Following Stroke: An Electroencephalography Study. Front Neurosci. 15:755709.

Dionísio, A., Gouveia, R., Castelhano, J., Duarte, I.C., Santo, G.C., Sargento-Freitas, J., Duecker, F., and Castelo-Branco, M. (2021) The Role of Continuous Theta Burst TMS in the Neurorehabilitation of Subacute Stroke Patients: A Placebo-Controlled Study. Front Neurol. 12:749798.

Egger, M., Davey Smith, G., Schneider, M., and Minder, C. (1997) Bias in meta-

analysis detected by a simple, graphical test. Bmj. 315:629-34.

Gao, B., Wang, Y., Zhang, D., Wang, Z., and Wang, Z. (2022) Intermittent theta-burst stimulation with physical exercise improves poststroke motor function: A systemic review and meta-analysis. Front Neurol. 13:964627.

Goldsworthy, M.R., Pitcher, J.B., and Ridding, M.C. (2012) The application of spaced theta burst protocols induces long-lasting neuroplastic changes in the human motor cortex. Eur J Neurosci. 35:125-34.

Higgins, J.P., Thompson, S.G., Deeks, J.J., and Altman, D.G. (2003) Measuring inconsistency in meta-analyses. Bmj. 327:557-60.

Higgins, J.P.T., and Green, S. Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011, http://handbook.cochrane.org.

Hsu, Y.F., Huang, Y.Z., Lin, Y.Y., Tang, C.W., Liao, K.K., Lee, P.L., Tsai, Y.A., Cheng, H.L., Cheng, H., Chern, C.M., ~~Lee, I.H~~et al. (2013) Intermittent theta burst stimulation over ipsilesional primary motor cortex of subacute ischemic stroke patients: a pilot study. Brain Stimul. 6:166-74.

Huang, W., Chen, J., Zheng, Y., Zhang, J., Li, X., Su, L., Li, Y., and Dou, Z. (2022) The Effectiveness of Intermittent Theta Burst Stimulation for Stroke Patients With Upper Limb Impairments: A Systematic Review and Meta-Analysis. Front Neurol. 13:896651.

Huang, Y.Z., Edwards, M.J., Rounis, E., Bhatia, K.P., and Rothwell, J.C. (2005) Theta burst stimulation of the human motor cortex. Neuron. 45:201-6.

Huang, Y.Z., and Rothwell, J.C. (2004) The effect of short-duration bursts of high-frequency, low-intensity transcranial magnetic stimulation on the human motor cortex. Clin Neurophysiol. 115:1069-75.

Khan, F., Rathore, C., Kate, M., Joy, J., Zachariah, G., Vincent, P.C., Varma, R.P., and Radhakrishnan, K. (2019) The comparative efficacy of theta burst stimulation or functional electrical stimulation when combined with physical therapy after stroke: a randomized controlled trial. Clin Rehabil. 33:693-703.

Kuzu, Ö., Adiguzel, E., Kesikburun, S., Yaşar, E., and Yılmaz, B. (2021) The Effect of Sham Controlled Continuous Theta Burst Stimulation and Low Frequency Repetitive Transcranial Magnetic Stimulation on Upper Extremity Spasticity and Functional Recovery in Chronic Ischemic Stroke Patients. J Stroke Cerebrovasc Dis. 30:105795.

Kwakkel, G., Lannin, N.A., Borschmann, K., English, C., Ali, M., Churilov, L., Saposnik, G., Winstein, C., van Wegen, E.E., Wolf, S.L., ~~Krakauer, J.W., Bernhardt, J~~et al. (2017) Standardized measurement of sensorimotor recovery in stroke trials: Consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable. International Journal of Stroke. 12:451-461.

Lai, C.J., Wang, C.P., Tsai, P.Y., Chan, R.C., Lin, S.H., Lin, F.G., and Hsieh, C.Y. (2015) Corticospinal integrity and motor impairment predict outcomes after excitatory repetitive transcranial magnetic stimulation: a preliminary study. Arch Phys Med Rehabil. 96:69-75.

Lefaucheur, J.P., Aleman, A., Baeken, C., Benninger, D.H., Brunelin, J., Di Lazzaro, V., Filipović, S.R., Grefkes, C., Hasan, A., Hummel, F.C~~., Jääskeläinen, S.K., Langguth, B., Leocani, L., Londero, A., Nardone, R., Nguyen, J.P., Nyffeler, T., Oliveira-Maia, A.J., Oliviero, A., Padberg, F., Palm, U., Paulus, W., Poulet, E., Quartarone, A., Rachid, F., Rektorová, I., Rossi, S., Sahlsten, H., Schecklmann, M., Szekely, D., Ziemann, U.~~, et al. (2020) Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018). Clin Neurophysiol. 131:474-528.

Meehan, S.K., Dao, E., Linsdell, M.A., and Boyd, L.A. (2011) Continuous theta burst stimulation over the contralesional sensory and motor cortex enhances motor learning post-stroke. Neurosci Lett. 500:26-30.

Meng, Y., Zhang, D., Hai, H., Zhao, Y.Y., and Ma, Y.W. (2020) Efficacy of coupling intermittent theta-burst stimulation and 1Hz repetitive transcranial magnetic stimulation to enhance upper limb motor recovery in subacute stroke patients: A randomized controlled trial. Restor Neurol Neurosci. 38:109-118.

Moayyedi, P. (2004) Meta-analysis: Can we mix apples and oranges? Am J Gastroenterol. 99:2297-301.

Moher, D., Liberati, A., Tetzlaff, J., and Altman, D.G., The, P.G. (2009) Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLOS Medicine. 6:e1000097.

Neva, J.L., Brown, K.E., Wadden, K.P., Mang, C.S., Borich, M.R., Meehan, S.K., and Boyd, L.A. (2019) The effects of five sessions of continuous theta burst stimulation over contralesional sensorimotor cortex paired with paretic skilled motor practice in people with chronic stroke. Restor Neurol Neurosci. 37:273-290.

Nicolo, P., Magnin, C., Pedrazzini, E., Plomp, G., Mottaz, A., Schnider, A., and Guggisberg, A.G. (2018) Comparison of Neuroplastic Responses to Cathodal Transcranial Direct Current Stimulation and Continuous Theta Burst Stimulation in Subacute Stroke. Arch Phys Med Rehabil. 99:862-872.e1.

Sung, W.H., Wang, C.P., Chou, C.L., Chen, Y.C., Chang, Y.C., and -Tsai, P.Y. (2013) Efficacy of coupling inhibitory and facilitatory repetitive transcranial magnetic stimulation to enhance motor recovery in hemiplegic stroke patients. Stroke. 44:1375-82.

Talelli, P., Greenwood, R.J., and Rothwell, J.C. (2007) Exploring Theta Burst

Stimulation as an intervention to improve motor recovery in chronic stroke. Clin Neurophysiol. 118:333-42.

Talelli, P., Wallace, A., Dileone, M., Hoad, D., Cheeran, B., Oliver, R., VandenBos, M., Hammerbeck, U., Barratt, K., Gillini, C., ~~Musumeci, G., Boudrias, M.H., Cloud, G.C., Ball, J., Marsden, J.F., Ward, N.S., Di Lazzaro, V., Greenwood, R.G., Rothwell, J.C~~et al. (2012) Theta burst stimulation in the rehabilitation of the upper limb: a semirandomized, placebo-controlled trial in chronic stroke patients. Neurorehabil Neural Repair. 26:976-87.

Tang, Z., Han, K., Wang, R., Zhang, Y., and Zhang, H. (2022) Excitatory Repetitive Transcranial Magnetic Stimulation Over the Ipsilesional Hemisphere for Upper Limb Motor Function After Stroke: A Systematic Review and Meta-Analysis. Front Neurol. 13:918597.

van Lieshout, E. C. C., van der Worp, H. B., Visser-Meily, J. M. A., and Dijkhuizen, R. M. (2019). Timing of Repetitive Transcranial Magnetic Stimulation Onset for Upper Limb Function After Stroke: A Systematic Review and Meta-Analysis. Frontiers in neurology, 10, 1269.

Vink, J.J.T., van Lieshout, E.C.C., Otte, W.M., van Eijk, R.P.A., Kouwenhoven, M., Neggers, S.F.W., van der Worp, H.B., Visser-Meily, J.M.A., and Dijkhuizen, R.M. (2023) Continuous Theta-Burst Stimulation of the Contralesional Primary Motor Cortex for Promotion of Upper Limb Recovery After Stroke: A Randomized Controlled Trial. Stroke. 54:1962-1971.

Volz, L.J., Rehme, A.K., Michely, J., Nettekoven, C., Eickhoff, S.B., Fink, G.R., and Grefkes, C. (2016) Shaping Early Reorganization of Neural Networks Promotes Motor Function after Stroke. Cereb Cortex. 26:2882-2894.

Wadden, K.P., Peters, S., Borich, M.R., Neva, J.L., Hayward, K.S., Mang, C.S., Snow,

N.J., Brown, K.E., Woodward, T.S., Meehan, S.K., et alBoyd, L.A. (2019) White Matter Biomarkers Associated with Motor Change in Individuals with Stroke: A Continuous Theta Burst Stimulation Study. Neural Plast. 2019:7092496.

Wang, C.P., Tsai, P.Y., Yang, T.F., Yang, K.Y., and Wang, C.C. (2014) Differential effect of conditioning sequences in coupling inhibitory/facilitatory repetitive transcranial magnetic stimulation for poststroke motor recovery. CNS Neurosci Ther. 20:355-63.

Watanabe, K., Kudo, Y., Sugawara, E., Nakamizo, T., Amari, K., Takahashi, K., Tanaka, O., Endo, M., Hayakawa, and Y., Johkura, K. (2018) Comparative study of ipsilesional and contralesional repetitive transcranial magnetic stimulations for acute infarction. J Neurol Sci. 384:10-14.

Xiang, H., Sun, J., Tang, X., Zeng, K., and Wu, X. (2019) The effect and optimal parameters of repetitive transcranial magnetic stimulation on motor recovery in stroke patients: a systematic review and meta-analysis of randomized controlled trials. Clin Rehabil. 33:847-864.

Zhang, J.J. (2024) Cortico-cortical paired associative stimulation: a novel neurostimulation solution for modulating brain connectivity and networks. Frontiers in Neuroscience. 17.

Zhang, J.J., Bai, Z., and Fong, K.N.K. (2022) Priming Intermittent Theta Burst Stimulation for Hemiparetic Upper Limb After Stroke: A Randomized Controlled Trial. Stroke. 53:2171-2181.

Zhang, J.J.Q., Fong, K.N.K., Ouyang, R.G., Siu, A.M.H., and Kranz, G.S. (2019) Effects of repetitive transcranial magnetic stimulation (rTMS) on craving and substance consumption in patients with substance dependence: a systematic review and meta-analysis. Addiction. 114:2137-2149.

Zhang, L., Xing, G., Fan, Y., Guo, Z., Chen, H., and Mu, Q. (2017) Short- and Long-term Effects of Repetitive Transcranial Magnetic Stimulation on Upper Limb Motor Function after Stroke: a Systematic Review and Meta-Analysis. Clin Rehabil. 31:1137-1153.

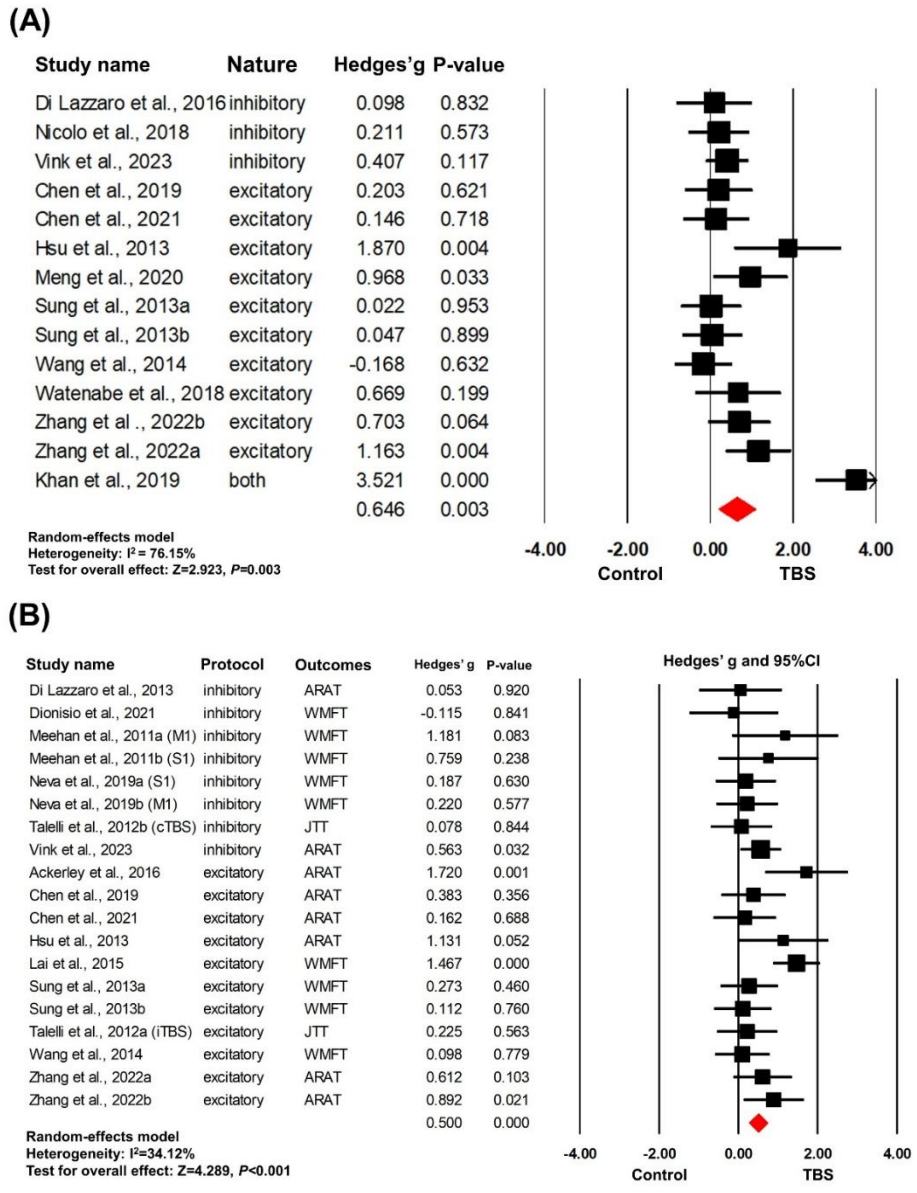

Figure 1. Meta-analysis of the effect of theta burst stimulation on (A) upper extremity motor impairment and (B) functional activity. The studies were represented by symbols whose area was proportional to the study's weight in the analysis.

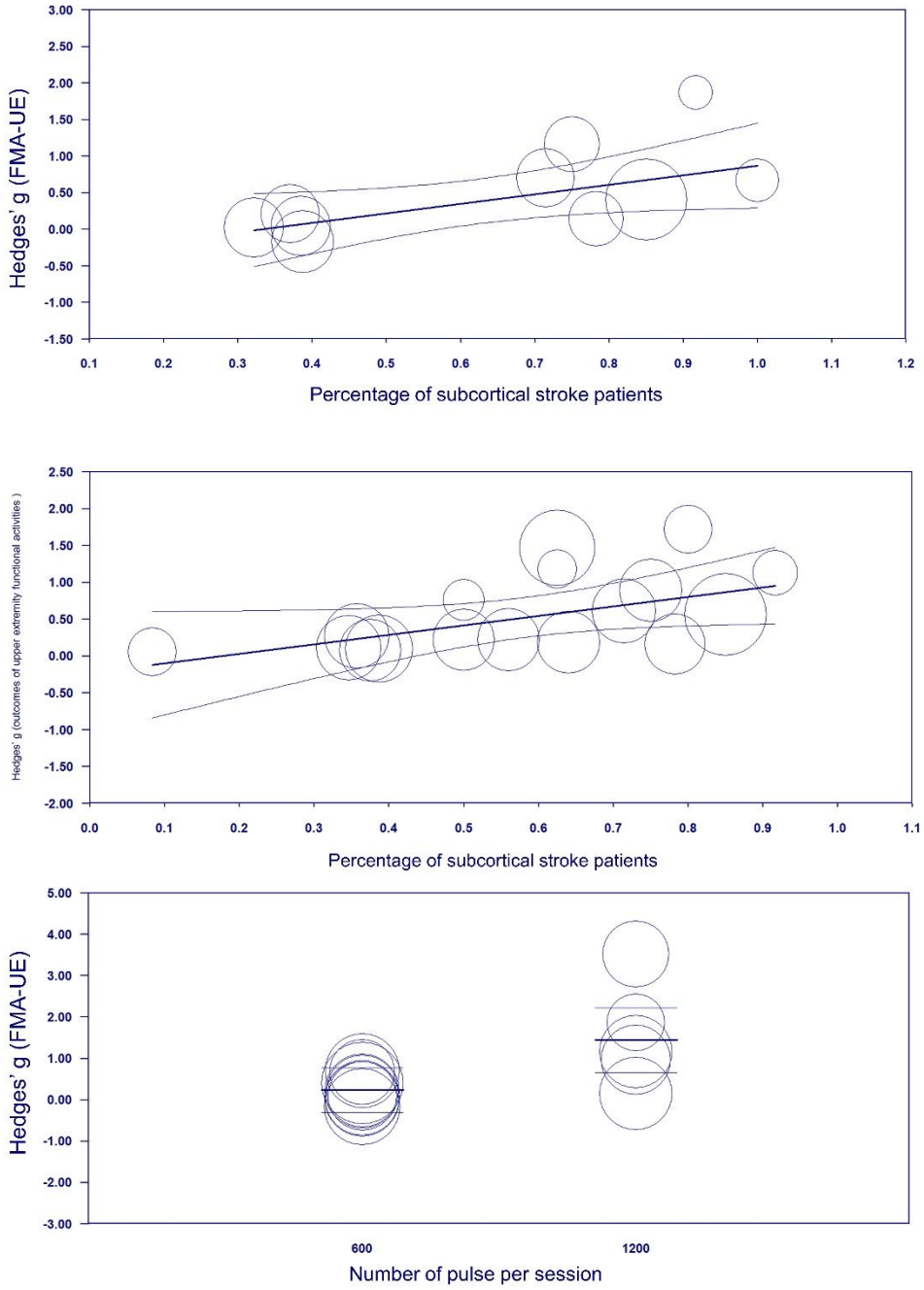

Figure 2. Meta-regression of the association between (A) the percentage of subcortical stroke patients and the effect sizes of FMA-UE and (B) the percentage of patients with subcortical lesions and the effect sizes of the outcomes assessing functional activity. (C) Between-group differences in the effect sizes of FMA-UE using 600-pulse protocols and 1200-pulse protocols. Each study was represented by a circle proportional to its weight in the analysis. FMA-UE: Fugl-Meyer Assessment-Upper Extremity.

Table 1. Characteristics of the included studies

	Population					TBS protocol						Motor outcomes			Timepoints
Study	Design	Group size	Chronicity	Severity of hemiplegia	Nature of lesion and the status of ipsilesional MEP	Protocol	Intensity	Duration	Stimulation target	Control	Combined intervention	Clinical	Behavioral	Neural (by technique)	
Talelli et al., 2007	Cross-over	iTBS-ipsi M1 (n=6) cTBS-contra M1 (n=6) Sham (n=6)	Chronic (≥12 months)	Mild (ARAT: 41-57/57)	MCA infarction, 3 cortical involved/3 pure subcortical ipsi-MEP+: 100.00%	iTBS-600 cTBS-300	80% AMT	1 session	Ipsi-M1 (iTBS) Contral-M1 (cTBS)	90°flipped coil with 50% MMO	No	No	RT; Grip strength	TMS-EMG	Baseline, Post
Ackerley et al., 2010	Cross-over	iTBS-ipsi M1 (n=10) cTBS-contra M1 (n=10) Sham (n=10)	Chronic (≥6 months)	Mild to moderate (FMA-UE wrist/hand subscores 12-28/32)	8 ischemic and 2 hemorrhagic stroke, 2 cortical involved/8 pure subcortical ipsi-MEP+: 100.00%	iTBS-600 cTBS-600	90% AMT	1 session	Ipsi-M1 (iTBS) Contral-M1 (cTBS)	Sham coil	Precision grip movements	ARAT	Preload force and duration	TMS-EMG	Baseline, Post
Kleehan et al., 2011	Parallel	cTBS-contra M1 (n=4) cTBS-contra S1 (n=4) Sham (n=4)	Chronic (≥12 months)	Mild to severe (FMA-UE≥15/66)	Ischemic stroke Unclear nature ipsi-MEP+: 100.00%	cTBS-600	80%AMT	3-session	Contral-M1 (cTBS) Contral-S1 (cTBS)	Sham coil	Serial targeting task	WMFT	Movement kinematics	No	Baseline, 1 day post
Talelli et al., 2012	Parallel	iTBS-ipsi M1 (n=13) cTBS-contra M1 (n=12) Sham iTBS (n=12) Sham cTBS (n=12)	Chronic (≥12 months)	Mild to moderate hand weakness[#]	Ischemic stroke, 26 Cortical involved/23 pure subcortical ipsi-MEP+: 83.67%	iTBS-600 cTBS-600	80% AMT	10 sessions	Ipsi-M1 (iTBS) Contral-M1 (cTBS)	90° flipped coil with 50% MMO	Upper limb physical therapy	NHPT; JTT; Grasp and pinch grip strength	No	No	Baseline, 4-day post, 30-day post, 90-day post
Sung et al., 2013	Parallel	LF rTMS+iTBS (n=15) iTBS-ipsi M1 (n=12) LF rTMS+sham iTBS (n=13) Sham (n=14)	Subacute (3-12 months)	Moderate to severe hand weakness (MRC in the finger flexor of the paretic hand≤3/5)	35 ischemic and 19 hemorrhagic stroke, 35 Cortical involved/19 pure subcortical ipsi-MEP+: 51.85%	iTBS-600	80% AMT	20 sessions	Ipsi-M1 (iTBS)	Sham coil	Conventional rehabilitation	FMA-UE WMFT MRC	RT, Finger tapping	TMS-EMG	Baseline, Mid, Post
Hsu et al., 2013	Parallel	iTBS-ipsi M1 (n=6) Sham (n=6)	Acute (2-4 weeks)	Mild to moderate hand weakness (NIHSS arm score: 1-3)	Ischemic stroke, MCA infarction, Unclear nature ipsi-MEP+: 75.00%	iTBS-1200	80% AMT	10 sessions	Ipsi-M1 (iTBS)	90° flipped coil	Conventional rehabilitation	NIHSS ARAT FMA-UE	No	MEG, TMS-EMG	Baseline, Post, 2-4 weeks post
Di Lazzaro et al., 2013	Parallel	cTBS-ipsi M1 (n=6) Sham (n=6)	Chronic (≥12 months)	Moderate hand weakness*	Ischemic stroke, 11 cortical involved/1 pure subcortical ipsi-MEP+: 66.67%	cTBS-600	80% AMT	10 sessions	Ipsi-M1 (cTBS)	Sham coil	Physical therapy	ARAT JTT NHPT	Grasp and pinch grip strength	TMS-EMG	Baseline Post 30-day post 90-day post
Ackerley et al., 2014	Cross-over	cTBS-contra M1 (n=13) iTBS-ipsi M1 (n=13) Sham (n=13)	Chronic (≥6 months)	Mild to severe (FMA-UE: 25-55/66; ARAT: 6-57/57)	10 ischemic and 3 hemorrhagic stroke, 11 subcortical/2 MCA territory involved. ipsi-MEP+: 100.00%	iTBS-600 cTBS-600	90%AMT	1 session	Ipsi-M1 (iTBS) Contra-M1 (cTBS)	Sham coil	Precision grip movements	ARAT	Preload force and duration	TMS-EMG	Baseline Post
Wang et al., 2014	Parallel	LF rTMS-contra-M1 prior to iTBS-ipsi M1 (n=17) iTBS-ipsi M1 prior to LF rTMS-contra-	Subacute (2-6 months)	MRC≤3	Ischemic stroke, 22 subcortical/23 cortical/3 unknown ipsi-MEP+: unclear	iTBS-600	80%AMT	10 sessions	Ipsi-M1 (iTBS)	Sham coil	Conventional Physiotherapy	WMFT MRC FMA-UE	No	TMS-EMG	Baseline Post 10sessions Post 20 sessions

		M1 (n=16) Sham (n=15)													3-month post
Lai et al., 2015	Parallel	iTBS-ipsi M1 (n=55) Sham (n=17)	Chronic (10.5±5 months after stroke)	Unclear	45 subcortical/27 cortical involved ipsi-MEP+: 29.17%	iTBS-600	80%AMT	10 sessions	Ipsi-M1 (iTBS)	Sham coil	Conventional physiotherapy	WMFT	RT; FT	TMS-EMG	Baseline Mid Post
Ackerley et al., 2016	Parallel	iTBS-ipsi M1 (n=9) Sham (n=9)	Chronic (≥6 months)	Mild to severe (FMA-UE: 21-63)	Subcortical ipsi-MEP+: 72.22%	iTBS-600	90%AMT	10 sessions	Ipsi-M1 (iTBS) Contra-M1 (cTBS)	Sham coil	Upper limb physical therapy	ARAT FMA-UE	No	TMS-EMG; fMRI	Baseline Mid Post 1 month post 3 months post
Di Lazzaro et al., 2016	Parallel	cTBS-ipsi M1 (n=8) Sham (n=9)	Chronic (≥12 months)	Severe (FMA-UE: 3-28)	Ischemic stroke Unclear nature ipsi-MEP+: unclear	cTBS-600	80% AMT	10 sessions	Contra-M1 (cTBS)	90°flipped coil	Robot-assisted shoulder and elbow training	FMA-UE	Movement kinematics	No	Baseline Post 1 month post 3 months post
Volz et al., 2016	Parallel	iTBS-ipsi M1 (n=13) Sham (n=13)	Acute (within 2 weeks)	Unclear	Ischemic stroke (21 subcortical and 5 cortical involved) ipsi-MEP+: 73.08%	iTBS-600	70%RMT	5 sessions	Ipsi M1 (iTBS)	Parieto-occipital cortex	Physiotherapy	JTT	Hand grip	TMS-EMG; fMRI	Baseline Post 3-6 months post
Diekhoff-Krebs et al., 2017	Cross-over	iTBS-ipsi M1 (n=14) Sham (n=14)	Chronic (≥12 months)	Mild to severe ARAT: 24-57	Ischemic stroke ipsi-MEP+: 96.43%	iTBS-600	80%AMT	1 session	Ipsi M1 (iTBS)	Parieto-occipital cortex	No	JTT	Finger tapping, Grip strength	TMS-EMG; fMRI	Baseline Post
Nicolo et al., 2018	Parallel	cTBS-contra M1 (n=14) Sham (n=13)	Acute to subacute (<10 weeks)	Mild to severe (FMA-UE: 3-48)	23 ischemic/4 hemorrhagic stroke, 10 subcortical/17 cortical involved ipsi-MEP+: unclear	cTBS-600	80% RMT	9 sessions	Contra-M1 (cTBS)	Sham coil	physical therapy	FMA BBT NHPT	No	EEG	Baseline Post 30 days post
Watanabe et al., 2018	Parallel	iTBS-ipsi M1 (n=8) Sham (n=6)	Acute (<7 days)	Moderate to severe (Brunnstrom stage for the upper extremity: I-III)	Ischemic stroke, capsular infarction only ipsi-MEP: unclear	iTBS-600	80% RMT	10 sessions	Ipsi-M1 (iTBS)	Separated by a 10-cm plastic band	Conventional rehabilitation	FMA	Grip strength	TMS-EMG	Baseline 12 week post
Chen et al., 2019	Parallel	iTBS-ipsi M1 (n=12) Sham (n=11)	Chronic (≥6 months)	Unclear	5 ischemic and 17 hemorrhagic stroke, 7 supratentorial/15 infratentorial ipsi-MEP+: unclear	iTBS-600	80% AMT	10 sessions	Ipsi-M1 (iTBS)	Reversed coil+60%AMT	Conventional rehabilitation	FMA-UE ARAT BBT	No	No	Baseline Post
Wadden et al., 2019	Parallel	cTBS-contra M1 (n=9) cTBS-contra S1 (n=11) Sham (n=8)	Chronic (≥6 months)	Mild to severe (FMA-UE:7 to 63)	7 cortical involved/21 subcortical ipsi-MEP+: NR	cTBS-600	80% AMT	5 sessions	Contra-M1 (cTBS) Contra-S1 (cTBS)	Sham coil	Skilled motor practice	No	RTT	DTI	Baseline During 1 day post
Khan et al., 2019	Parallel	cTBS-contraM1+iTBS-ipsiM1 (n = 20) Control (n=20)	Acute (within 10-30 days)	Moderate to severe (MRC of the upper limb muscle <3)	Ischemic stroke, MCA infarction Unclear nature ipsi-MEP+: 47.50%	cTBS-600 iTBS-600	60% RMT	12 sessions	Contra-M1 (cTBS) Ipsi-M1 (iTBS)	No TBS	Physical therapy	FMA-UE	Noo	TMS-EMG	Baseline Post 1 month post 3-month post 6-month post 1 year post
Neva et al., 2019	Parallel	cTBS-contra M1 (n=12) cTBS-contra S1	Chronic (≥6 months)	Mild to severe (FMA-UE: 7 to 66)	6 cortical/20 subcortical/3 cerebellar/7 unclear	cTBS-600 iTBS-600	80% AMT	5 sessions	Contra-M1 (cTBS) Contra-S1	Sham coil	Skilled motor practice	WMFT	RTT	TMS-EMG	Baseline During 1-2 days post

		(n=13) Sham (n=12)			ipsi-MEP+: 72.00%				(cTBS)						
Meng et al., 2020	Parallel	LF rTMS+iTBS (n=10) LF rTMS+sham iTBS (n=10) Sham (n=8)	Acute (30-60 days)	NIHSS: 1-15 points	16 ischemic/12 hemorrhagic stroke; 18 basal ganglia/10 others ipsi-MEP+: 71.43%	iTBS-1200	60-80% RMT	10 sessions	Ipsi-M1 (iTBS)	Flipped coil	Conventional rehabilitation	FMA-UE	No	TMS-EMG	Baseline Post
Chen et al., 2021	Parallel	iTBS-ipsi M1 (n=12) Sham (n=11)	Subacute and chronic	Mild to moderate (Brunnstrom stage ≥ 3)	8 ischemic and 15 hemorrhagic stroke, 5 cortical involved/18 subcortical ipsi-MEP+: 65.22%	iTBS-600	80% AMT	15 sessions	Ipsi-M1 (iTBS)	Reversed coil+60%AMT	VCT	FMA-UE ARAT BBT NHPT MAL	No	No	Baseline Post
Bionísio et al., 2021	Parallel	cTBS-contra M1 (n=5) Sham (n=5)	Acute (within 7±3 days)	Unclear	Ischemic stroke, MCA stroke ipsi-MEP+: 70.00%	cTBS-600	100%AMT	Single-session	Contra-M1 (cTBS)	Intensity reduction and sham noise generator	No	WMFT	No	TMS-EMG; EEG	Baseline Post 3-month post
Ging et al., 2021	Parallel	iTBS-ipsi M1 (n=15) Sham (n=15)	Acute to chronic (1-18 months)	Mild to severe (FMA-UE: 4-64)	24 ischemic/6 hemorrhagic stroke ipsi-MEP+: 43.33%	iTBS-600	70%RMT	Single-session	Ipsi M1 (iTBS)	90°flipped coil	No	No	No	EEG	Baseline Post
Kuzu et al., 2021	Parallel	cTBS-contra M1 (n=7) Sham (n=6)	Chronic (6 months-2 years)	Mild to moderate (Brunnstrom stage for the upper extremity 3-5)	Ischemic stroke, 6 cortical involved/ 7 subcortical ipsi-MEP+: NR	cTBS-600	80%AMT	10 sessions	Contra-M1 (cTBS)	Sham coil	Physical therapy	FMA MAL	No	No	Baseline Post 4-week post
Ding et al., 2022	Parallel	iTBS-ipsi M1 (n=11) Sham (n=11)	Acute to chronic (1-18 months)	Mild to severe (FMA-UE: 4-66)	18 ischemic/4 hemorrhagic stroke ipsi-MEP+: 50.00%	iTBS-600	70%RMT	Single-session	Ipsi M1 (iTBS)	90°flipped coil	No	No	No	TMS-EEG	Baseline Post
Zhang et al., 2022	Parallel	cTBS+iTBS-ipsi M1 (n=14) iTBS-ipsi M1 (n=14) Sham (n=14)	Chronic (≥12 months)	Mild to severe (FTUHE: 2-7)	24 ischemic and 18 hemorrhagic stroke, 10 cortical involved/ 31 subcortical/1 unknown ipsi-MEP+: unclear	cTBS-600 iTBS-600	70% RMT	10 sessions	Ipsi M1 (cTBS+iTBS and iTBS)	Intensity reduction	Robot-assisted arm and hand training	FMA-UE ARAT	Movement kinematics	EEG	Baseline Mid Post 2-week post
Bai et al., 2023	Cross-over	iTBS-ipsi M1 (n=20) Sham (n=20)	Chronic stroke (≥6 months)	Mild (FMA-UE: 56-66)	12 ischemic /8 hemorrhagic stroke ipsi-MEP+: 100.00%	iTBS-600	70% RMT	1 session	Ipsi M1 (iTBS)	Coil away from the scalp	No	No	No	TMS-EEG	Baseline Post
Vink et al., 2023	Parallel	cTBS-contra M1 (n=28) Sham (n=31)	Acute (≤3 weeks)	Mild to severe (MI: 9-99)	50 ischemic stroke and 9 hemorrhagic stroke ipsi-MEP: 33.90%	cTBS-600	70% RMT	10 sessions	Contra-M1 (cTBS)	Intensity reduction	Individualized upper limb exercises	ARAT; FMA-UE; JTT; NHPT;	No	No	Baseline 1-week 1-month 3-month 6-month 1-year

Abbreviations: AMT: Active motor threshold; ARAT: Action research arm rest; BBT: Box and block test; BI: Barthel Index; cTBS: Continuous theta burst stimulation; EEG: Electroencephalography; FMA-UE: Upper extremity scores of Fugl-Meyer assessment; fMRI: Functional magnetic resonance imaging; FT: Finger tapping; iTBS: Intermittent theta burst stimulation; JTT: Jebsen-Taylor test; M1: Primary motor cortex; MAL: Motor activity log; MEG: Magnetoencephalography; MEP+: Motor-evoked potential positive; MI, Motricity Index; MMO: Maximal machine output; NHPT: Nine hole peg test; RT: Reaction time; S1: Primary somatosensory cortex; TMS-EMG: Transcranial magnetic stimulation-electromyography; VCT, virtual reality-based cycling training; WMFT: Wolf motor function test.

#defined as grasp strength ≥5% of the unaffected hand, preserved extension at the wrist (≥20°), and baseline score in Nine Hole Peg Test (NHPT) ≤70% of the unaffected hand

*defined as grasp strength ≥1% of the unaffected hand, preserved extension at the wrist (≥20◦), and baseline score in Nine Hole Pegboard Test (NHPT) ≤70% of the unaffected hand.

Table 2. Summary of modulatory effects of TBS in people with stroke

Study	Comparisons	Outcome measurements	Significant results
Tallelli et al., 2007	iTBS (ipsi-M1) vs. cTBS (contra-M1) vs. sham	***TMS-EMG:*** (1) MEP; (2) Area under the I/O curves	***iTBS (ipsi-M1):*** MEP (ipsi-M1) ↑ Area under the I/O curves↑ ***cTBS (contra-M1):*** No significant finding was found in TMS-EMG outcomes
Ackerley et al. 2010	iTBS (ipsi-M1) vs. sham cTBS (contra-M1) vs. sham	***TMS-EMG*:** (1) MEP	***iTBS (ipsi-M1)*:** MEP (ipsi-M1) ↑ ***cTBS (contra-M1):*** MEP (contra-M1) ↓
Hsu et al., 2013	iTBS (ipsi-M1) vs. sham	***TMS-EMG:*** (1) AMT; (2) MEP ***MEG*:** (1) Post movement ERS (2) Movement-related ERD	***iTBS (ipsi-M1)*:** Post movement ERS (ipsi-M1)↑
Di Lazzaro et al., 2013	cTBS (ipsi-M1) vs. sham	***TMS-EMG:*** (1) AMT; (2) MEP	***cTBS (ipsi-M1):*** No significant finding was found in TMS-EMG outcomes
Sung et al., 2013	iTBS (ipsi-M1) vs. sham	***TMS-EMG:*** (1) RMT; (2) MEP; (3) Motor map area	***iTBS (ipsi-M1):*** Motor map area (ipsi-M1) ↑ Motor map area (contra-M1) ↓
Ackerley et al. 2014	iTBS (ipsi-M1) vs. sham cTBS (contra-M1) vs. sham	***TMS-EMG:*** (1) MEP; (2) SAI	***iTBS (ipsi-M1)*:** MEP (ipsi-M1) ↑ SAI (ipsi-M1) ↑ MEP (contra-M1) ↓ ***cTBS (contra-M1):*** MEP (ipsi-M1) ↑
Wang et al., 2014	iTBS (ipsi-M1) vs. sham	***TMS-EMG:*** (1) RMT; (2) MEP; (3) Motor map area	***iTBS (ipsi-M1*):** MEP (ipsi-M1) ↑

			Motor map area (ipsi-M1) ↑ Motor map area (contra-M1) ↓
Lai et al., 2015	iTBS (ipsi-M1) vs. sham	***TMS-EMG:*** (1) MEP; (2) Motor map area	***iTBS (ipsi-M1)*:** Motor map area (contra-M1) ↓
Ackerley et al. 2016	iTBS (ipsi-M1) vs. sham	***fMRI:*** Activation over M1, S1, PMC, and SMA during paretic hand movement.	***iTBS (ipsi-M1)*:** No significant pre-post change in laterality index of activation over all ROIs.
Volz et al., 2016	iTBS (ipsi-M1) vs. control stimulation	***fMRI:*** (1) rsFC ***TMS-EMG:*** (1) MEP	**iTBS *ipsi-M1*:** rsFC ↑ (Ipsi-M1 with ipsi-SMA, ipsi-MCC, contra-SMA, contra-dPMC, and contra-M1)
Diekhoff-Krebs et al., 2017	iTBS (ipsi-M1) vs. sham	***TMS-EMG:*** (1) MEP	***iTBS ipsi-M1*:** MEP (ipsi-M1) ↑ MEP (contra-M1) ↓
Nicolo et al., 2018	cTBS (contra-M1) vs. sham	***EEG:*** (1) EC (PDC); (2) FC (imagery part of coherence); (3) Node strength	***cTBS (contra-M1):*** PDC (from contra-M1 to ipsi-M1, beta rhythm) ↓
Watanabe et al., 2018	iTBS (ipsi-M1) vs. sham	***TMS-EMG:*** (1) MEP	***iTBS (ipsi-M1)*:** MEP (ipsi-M1) ↑
Wadden et al., 2019	cTBS (contra-M1) vs. sham cTBS (contra-S1) vs. sham	***MRI:*** (1) DTI of constrained motor connectome	No significant finding was reported in DTI outcomes
Neva et al., 2019	cTBS (contra-M1) vs. sham	***TMS-EMG:*** (1) RMT; (2) SICI; (3) ICF; (4) iSP	***cTBS (contra-M1):*** No significant finding was reported in TMS-EMG outcomes
Khan et al., 2019	Bilateral TBS vs. No TBS	***TMS-EMG:*** (1) RMT	***Bilateral TBS:*** RMT (ipsi-M1) ↓

			RMT (contra-M1) ↑
Meng et al., 2020	LF rTMS (contra-M1)+iTBS (ipsi-M1) vs. LF rTMS (contra-M1)+sham	***TMS-EMG:*** (1) MEP (abductor brevis pollicis, extensor digitorum communis, and biceps brachii)	***LF rTMS (contra-M1)+iTBS (ipsi-M1) vs LF rTMS (contra-M1)+sham:*** MEP (ipsi-M1) ↑
Ding et al., 2021	iTBS (ipsi-M1) vs. sham	***EEG:*** (1) Spectral power; (2) Sensorimotor FC-coherence; (3) Global efficiency	***iTBS (ipsi-M1):*** Sensorimotor FC (delta and theta rhythms)↑ Global efficiency (delta and beta rhythms) ↑
Dionísio et al., 2021	cTBS (contra-M1) vs. sham	***EEG:*** (1) Movement-related ERD ***TMS-EMG:*** (1) MEP	***cTBS (contra-M1)*** *Movement-related ERD over the ipsilesional hemisphere*↑
Ding et al., 2022	iTBS (ipsi-M1) vs. sham	***TMS-EEG:*** (1) Local Mean Field Power; (2) Global Mean Field Power; (3) TMS-induced ERS/ERD; (4) Natural Frequency	***iTBS (ipsi-M1):*** Natural Frequency (ipsi-M1)↑
Zhang et al., 2022	Priming iTBS (ipsi-M1) vs. sham iTBS (ipsi-M1) vs. sham	***EEG:*** (1) MVF-induced ERD; (2) Movement-related ERD	***Priming iTBS (ipsi-M1):*** MVF-induced ERD (ipsi-M1, high beta rhythm)↑ ***iTBS (ipsi-M1):*** No significant finding in the EEG outcomes.
Bai et al., 2023	iTBS (ipsi-M1) vs. sham	***TMS-EEG:*** (1) TEP; (2) TMS-induced ERS/ERD; (3) TMS-induced network properties ***TMS-EMG:*** (1) MEP; (2) CSP; (3) ICF; (4) SICI	***iTBS (ipsi-M1):*** MEP (ipsi-M1)↑ P30 in TEP (ipsi-M1)↑

Abbreviations: AMT: Active motor threshold; CSP: Cortical silent period; cTBS: Continuous theta burst stimulation; DTI: Diffusion tensor imaging; EC: Effective connectivity; ERD: Event-related desynchronization; ERS: Event-related synchronization; FA: Fractional anisotropy; FC:

Functional connectivity; fMRI: Functional magnetic resonance imaging; I/O curve: Input–Output curve; ICF: Intracortical facilitation; ISP: Ipsilateral silent period; iTBS: Intermittent theta burst stimulation; LF rTMS: Low-frequency repetitive transcranial magnetic stimulation; M1: Primary motor cortex; MEP: Motor evoked potential; MRI: Magnetic resonance imaging; PDC: Partial directed coherence; PMC: Premotor cortex; RMT: Resting motor threshold; ROI: Region of interest; rsFC: Resting-state functional connectivity; S1: Primary somatosensory cortex; SAI: Short-latency afferent inhibition; SICI: Short-interval intracortical inhibition; SMA: Supplementary motor cortex; TMS-EEG: Transcranial magnetic stimulation-Electroencephalography; TMS-EMG: Transcranial magnetic stimulation-Electromyography, TEP: Transcranial magnetic stimulation evoked electroencephalography potential.

Table 3. Results of meta-analysis

Protocol	Outcome	n	Effect size			Heterogeneity	
			Hedges' g	95% CI	*p*	I^2	*p*
All TBS protocols	FMA-UE	14	0.646	0.213 to 1.079	0.003**	76.15%	<0.001***
Excitatory TBS		10	0.470	0.121 to 0.818	0.001**	44.97%	0.060
Inhibitory TBS		3	0.300	-0.080 to 0.680	0.122	0.00%	0.812
Bilateral TBS		1	3.521	2.539 to 4.503	<0.001***	0.00%	>0.999
All TBS protocols	Functional activity	19	0.500	0.272 to 0.729	<0.001***	34.21%	0.072
Excitatory TBS		11	0.609	0.270 to 0.948	<0.001***	52.68%	0.020*
Inhibitory TBS		8	0.344	0.053 to 0.636	0.021	0.00%	0.747

Abbreviations: TBS: Theta burst stimulation; FMA-UE: Fugl-Meyer Assessment Upper Extremity.

*p<0.05; **p<0.01; ***p<0.001