Repetitive transcranial magnetic stimulation for lower extremity motor function in patients with stroke: a systematic review and network meta-analysis

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Abstract

Transcranial magnetic stimulation, a type of noninvasive brain stimulation, has become an ancillary therapy for motor function rehabilitation. Most previous studies have focused on the effects of repetitive transcranial magnetic stimulation (rTMS) on motor function in stroke patients. There have been relatively few studies on the effects of different modalities of rTMS on lower extremity motor function and corticospinal excitability in patients with stroke. The MEDLINE, Embase, Cochrane Library, ISI Science Citation Index, Physiotherapy Evidence Database, China National Knowledge Infrastructure Library, and ClinicalTrials.gov databases were searched. Parallel or crossover randomized controlled trials that addressed the effectiveness of rTMS in patients with stroke, published from inception to November 28, 2019, were included. Standard pairwise meta-analysis was conducted using R version 3.6.1 with the "meta" package. Bayesian network analysis using the Markov chain Monte Carlo algorithm was conducted to investigate the effectiveness of different rTMS protocol interventions. Network meta-analysis results of 18 randomized controlled trials regarding lower extremity motor function recovery revealed that low-frequency rTMS had better efficacy in promoting lower extremity motor function recovery than sham stimulation. Network meta-analysis results of five randomized controlled trials demonstrated that high-frequency rTMS led to higher amplitudes of motor evoked potentials than low-frequency rTMS or sham stimulation. These findings suggest that rTMS can improve motor function in patients with stroke, and that low-frequency rTMS mainly affects motor function, whereas high-frequency rTMS increases the amplitudes of motor evoked potentials. More high-quality randomized controlled trials are needed to validate this conclusion. The work was registered in PROSPERO (registration No. CRD42020147055) on April 28, 2020.

Key Words: cortical excitability; lower extremity; motor function; network meta-analysis; noninvasive brain stimulation; stroke; systematic review; transcranial magnetic stimulation

Introduction

Stroke is the dominant cause of disability among adults worldwide (Lavados et al., 2007; Zhou et al., 2019), often causing motor impairment. Motor impairment is related to a higher risk of falling because of gait impairments (Kim et al., 2014a), as well as limitations in activities of daily life and poor quality of life (Robinson et al., 2011). Clinical therapists therefore normally focus on improving walking ability and lower extremity motor function in patients with stroke (Winstein et al., 2016; Hankey, 2017). As a result of abnormally increased transcallosal inhibition from the contralateral to ipsilateral hemisphere, an imbalance in interhemispheric inhibition often occurs after stroke (Calautti et al., 2001; Zappasodi et al., 2019). This imbalance is associated with the degree of motor impairment and the limitation of sensorimotor recovery (Murase et al., 2004; Peters et al., 2018).

Based on the concept of disrupting interhemispheric balance after stroke, transcranial magnetic stimulation (TMS), a type of noninvasive brain stimulation, has become an essential ancillary therapy for motor function rehabilitation, modulating cortical excitability and inducing neural plasticity (Nowak et al., 2009). TMS can either increase or decrease excitability of the stimulated cerebral cortex site, and of remote regions via functional anatomical connections (Kobayashi and Pascual-Leone, 2003; Gu et al., 2013; Yang et al., 2020). Theoretically, repetitive TMS (rTMS) can induce different changes in cortical excitability that vary with the stimulated frequency. High-frequency rTMS (HF-rTMS) increases brain activity, whereas low-frequency rTMS (LF-rTMS) induces the opposite effect (Benussi et al., 2019). Lately, novel forms of rTMS therapies have emerged, such as deep TMS (dTMS), which uses a different coil type (Hesed coil) that can purportedly stimulate deeper cortical and subcortical regions (Chieffo et al., 2013), and theta-burst stimulation (TBS), including continuous TBS and intermittent TBS (iTBS) (Harrington and Hammond-Tooke, 2015; Strzalkowski et al., 2019).

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Previous meta-analyses have examined the efficacy of rTMS compared with sham therapy, and have demonstrated that rTMS can improve motor function, balance, and walking speed compared with the sham group (Li et al., 2018; Ghayour-Najafabadi et al., 2019; Tung et al., 2019). However, these meta-analyses did not compare the effectiveness of different modalities of rTMS (e.g., HF-rTMS, LF-rTMS, and iTBS) on lower extremity motor function. Furthermore, pairwise meta-analyses provide limited insights into overall treatment hierarchies because treatment effects are only estimated from relevant treatment comparisons. In contrast to standard pairwise meta-analyses, network meta-analysis (NMA) allows the comparison of different modalities of rTMS, although it does not allow direct comparisons of head-to-head trials (Mills et al., 2013). Thus, NMA provides a more complete insight into the efficacy of rTMS interventions, and should be considered as the highest level of evidence in treatment guidelines (Leucht et al., 2016). The objective of this systematic review and NMA was to compare the efficacy of different rTMS interventions for lower extremity motor function in patients with stroke, and to obtain clinical significance levels of these interventions from the perspective of motor function improvement. Furthermore, this review aimed to explore the effectiveness of rTMS on cortical excitability.

Data and Methods

We established the protocol of this systematic review, registered in PROSPERO (registration No. CRD42020147055) on April 28, 2020, in line with guidance from the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) statement (**Additional file 1**) (Moher et al., 2015; Shamseer et al., 2015). This review was also in accordance with the PRISMA statement (Liberati et al., 2009) and its extension for NMA (Hutton et al., 2015), and with the Cochrane Collaboration recommendations (Higgins and Green, 2011).

Eligibility criteria

The inclusion criteria were stroke patients with lower extremity dysfunction who were diagnosed according to the stroke diagnostic criteria formulated by The Fourth National Cerebrovascular Disease Conference in 1995 (Chinese Society of Neuroscience and Chinese Neurosurgical Society, 1996), and parallel or crossover randomized controlled trials (RCTs) that explored the effectiveness of rTMS on lower extremity recovery in stroke patients. Quasi-randomized trials or studies including adolescents (under 18 years of age) with stroke, bilateral stroke patients, or subtentorial stroke patients were excluded. Outcome measures included lower extremity motor function and cortical excitability. The primary outcome was motor recovery of the lower extremity, measured by the Fugl-Meyer assessment (FMA). Secondary outcomes included balance function, speed, motor evoked potential (MEP), and the Barthel Index (BI). Balance function was measured using the Berg Balance Scale (BBS) along with the Timed Up and Go Test (TUG). Post-treatment values of motor function and similar measurements were pooled.

Data sources and searches

The following online electronic databases were searched for eligible studies from inception to November 28, 2019: MEDLINE, Embase, Cochrane Library, ISI Science Citation Index, Physiotherapy Evidence Database (PEDro), and China National Knowledge Infrastructure Library (CNKI). Keywords included transcranial magnetic stimulation or TMS, stroke, cerebrovascular accident, and the combination of these words. We also searched for studies in progress, unpublished research, and research reported in the gray literature and ClinicalTrials.gov. The full search strategy is illustrated in **Additional file 2**. We re-ran the searches just before the final analysis, and further studies were retrieved for inclusion.

Data collection and analysis

Study selection

Two reviewers (YJX and YC) independently screened the titles and abstracts of the included studies using the search strategy, to identify studies that potentially met the predefined inclusion criteria. The full text versions of these potential studies were then retrieved and evaluated independently by two reviewers (YJX and YC). Any disagreements were settled by discussion or by reaching a consensus with a third reviewer.

Data extraction and management

Based on predefined criteria, relevant information from the eligible studies was extracted independently by two reviewers (YJX and YC) using electronic data collection forms. Discrepancies were resolved by consensus with a third reviewer (QFG). The main components of the identified studies (sample size, population characteristics, and study design), rTMS modalities, and outcome measures were extracted. We contacted the authors for any unpublished data that was necessary for the data analysis.

Risk of bias assessment

The PEDro scale was applied to appraise the methodological quality of the included studies (de Morton, 2009). The final score on the PEDro scale is the number of positive answers to 11 questions. An excellent-quality study was defined by a score of 9 to 10, a good-quality study by a score of 6 to 8, a normal-quality study by a score of 4 to 5, and a poor-quality study by a score of less than 4 (Maher et al., 2003). We excluded poor-quality studies (scores lower than 4). Two independent reviewers conducted the quality assessment, and any divergences between the reviewers were resolved by discussion or agreement with a third reviewer.

Quality of evidence

The global quality of our results was evaluated using an approach to extend the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system (Atkins et al., 2004) to NMAs. In this way, we were able to integrate quality ratings for direct comparisons to evaluate the certainty of the evidence (confidence in evidence/quality of evidence) from an NMA (Brignardello-Petersen et al., 2018). According to the GRADE rating standards, which contain five categories—limitations in study design, inconsistency, indirectness, imprecision, and publication bias (Atkins et al., 2004)—the quality of evidence can be graded as high, moderate, low, or very low (Puhan et al., 2014). The evidence profiles were generated using GRADEpro GDT (https://gdt.gradepro.org/app/) (Brignardello-Petersen et al., 2019).

Measures of treatment effect

When diverse measures were used to appraise identical outcomes, the data were presented as standardized mean differences (SMDs) for continuous outcomes. Effect measures for continuous outcomes of included studies were calculated by the means and standard deviations of post-intervention values. The findings of every possible therapy derived from the NMA were presented as summary relative effect sizes. The ranking probabilities for all possible levels of therapy per intervention were also estimated (Salanti et al., 2011).

Dealing with missing data

Corresponding authors were contacted for more information about missing data. If there was no reply, two reviewers (YJX and YC) attempted to measure the data using the available coefficients. These missing data may potentially influence the results of the review; this was determined using a sensitivity analysis.

Assessment of clinical assumptions

The variability of participants, continuation of outcome

measures, and intervention protocols and curative effects can result in multiple heterogeneities in the included studies, such as clinical, methodological, and statistical heterogeneity. Clinical and methodological heterogeneity within each pairwise comparison was evaluated by qualitatively comparing the study and population characteristics across the eligible studies.

The term "transitivity" means that there are no differences between two experiments regarding the distribution of effect modifiers (Salanti, 2012). The elementary presumption underlying NMAs is the assumption of transitivity, which needs to be carefully evaluated. The believability of transitivity can be appraised by originally assessing the resemblance of the competitive interventions in different design studies, and then comparing the distribution of the possible effect modifiers in different direct comparisons (Jansen and Naci, 2013). Quantitative synthesis may not be conducted when various comparisons exist in intransitivity, with considerable variation on effect modifiers (Rouse et al., 2017).

Statistical analysis

Methods for direct treatment comparisons

Standard pairwise meta-analysis was conducted using a random-effects model to calculate the direct relative effects of the competitive interventions in R version 3.6.1 (https://www.r-project.org/) (Salanti et al., 2011; Shim et al., 2019) using the "meta" package. Effect sizes were represented as SMD to determine whether the mean effect size was significant. For all statistical analyses, $P < 0.05$ implies that the effect size is significant. SMDs with 95% confidence intervals (CIs) were used to indicate the mean effect. A mean effect size of 0 was taken to indicate no effect (unchanged), while 0.2, 0.5, and 0.8 indicated small, medium, and large effects, respectively. For each subsequent treatment comparison, direct and indirect evidence was integrated into a single summary estimate to synthesize the evidence from the network of trials.

Methods for indirect and mixed comparisons

Bayesian network analysis using the Markov chain Monte Carlo algorithm was conducted to investigate the effectiveness of different rTMS protocol interventions (Madden et al., 2016). This requires convergence of the Markov chain Monte Carlo chain to its stationary distribution (Toft et al., 2007; Warren et al., 2017). The burn-in period was defined as 5000 simulations for each chain, and posterior summaries are based on 200 000 subsequent simulations. Convergence of chains was verified visually by observing trace plots and inspecting diagnostic statistics, as well as potential scale reduction factors obtained from Brooks–Gelman–Rubin plots (Brooks and Gelman, 1998; van Valkenhoef et al., 2012). When potential scale reduction factors are closer to 1, the simulated observations are closer to the target distribution. The deviance information criterion was then selected to determine the model fitness. A model with a lower deviance information criterion is considered a better fit and is the preferred choice (Dias et al., 2013). The results from NMA were indicated as SMD with 95% credible intervals (CrIs) (Roever and Biondi-Zoccai, 2016), which were presented as a league table (Mavridis et al., 2015). The square matrix contained all of the data about relative efficacy and their ambiguities for all probable interventions. Statistical analysis was performed using GeMTC (version 0.14.3) and R (version 3.6.1) software (Salanti et al., 2011; Shim et al., 2019) using the "gemtc" and "rjags" package (Neupane et al., 2014).

Assessment of statistical heterogeneity and inconsistency

The I2 statistics were used to assess statistical heterogeneity in standard pairwise meta-analysis. Effect sizes were calculated using the fixed-effects model when various independent studies maintained homogeneity ($P > 0.05$ or $I^2 < 50\%$) (Fleiss, 1993). Notwithstanding, when there was heterogeneity between eligible studies ($P < 0.05$ or $I^2 > 50\%$), we conducted a sensitivity analysis or stratified analysis to analyze the source of heterogeneity. The random-effects model was used for the analysis when the included studies remained non-homogeneous after the heterogeneity analysis (Borenstein et al., 2010). The heterogeneity variance parameter (τ^2) was used to assess the statistical heterogeneity of the NMA models (Turner et al., 2012). Presuming the comparability of direct and indirect evidence in NMAs may engender incorrect conclusions when there is prevailing statistically significant inconsistency (White et al., 2012). The node-splitting method was used to locally check inconsistency between direct and indirect evidence (Bucher et al., 1997; Dias et al., 2010). If inconsistency was identified, the potential effect modifiers of included studies within inconsistent loops came under scrutiny by fitting network meta-regression models and/or conducting sensitivity analyses to exclude studies that may possess sources of inconsistency (Higgins et al., 2012; Rouse et al., 2017).

Additional analyses and small study effects

If the necessary data were available, we conducted a subgroup analysis for different outcome measures. Funnel plots and the Egger's test were used for estimating publication bias. Within the outcomes of motor function and cortical excitability, we performed a sensitivity analysis to determine whether our results changed. Studies with lower quality, no blind evaluation, or a dropout rate of more than 10% were excluded.

Results

Study selection

Of 4432 identified references, 4217 articles were excluded after systematically screening the titles and abstracts and removing duplicates. The full texts of 215 articles were retrieved for further exploration. Of these, 189 articles were omitted for several reasons, as described in **Figure 1**. Finally, 26 studies (Chang et al., 2010; Wang et al., 2012, 2016, 2019; Kakuda et al., 2013; Cha et al., 2014; Chieffo et al., 2014; Elkholy et al., 2014; Ji et al., 2014; Kim et al., 2014b; Cha and Kim, 2015; Ji and Kim, 2015; Lin et al., 2015, 2019; Choi et al., 2016; Du et al., 2016; Rastgoo et al., 2016; Cha and Kim, 2017; Forogh et al., 2017; Guan et al., 2017; Meng and Song, 2017; Chen, 2018; Huang et al., 2018; Zhao et al., 2018; Koch et al., 2019; Liu et al., 2019) were included (24 two-arm and 2 three-arm trials) in the quantitative synthesis, providing information on 30 comparisons among five different rTMS interventions (**Figure 1**).

Study characteristics and assessment of clinical assumptions

Of the 26 enrolled studies, 22 (Chang et al., 2010; Wang et al., 2012; Cha et al., 2014; Elkholy et al., 2014; Ji et al., 2014; Kim et al., 2014b; Cha and Kim, 2015; Ji and Kim, 2015; Lin et al., 2015, 2019; Du et al., 2016; Wang et al., 2016; Cha and Kim, 2017; Forogh et al., 2017; Guan et al., 2017; Meng and Song, 2017; Chen, 2018; Huang et al., 2018; Zhao et al., 2018; Koch et al., 2019; Liu et al., 2019; Wang et al., 2019) were RCTs, while the remaining studies were crossover trials (Kakuda et al., 2013; Chieffo et al., 2014; Choi et al., 2016; Rastgoo et al., 2016). Overall, 943 participants (aged 57.17 ± 11.95 years; 610 [65%] men) were randomized to treatment. The baseline characteristics were equivalent between competing treatments. Among 18 studies (Chang et al., 2010; Wang et al., 2012, 2016, 2019; Chieffo et al., 2014; Elkholy et al., 2014; Lin et al., 2015, 2019; Du et al., 2016; Rastgoo et al., 2016; Forogh et al., 2017; Guan et al., 2017; Meng and Song, 2017; Chen, 2018; Huang et al., 2018; Zhao et al., 2018; Koch et al., 2019; Liu et al., 2019) that reported the FMA as the primary outcome measure, the group comparing LF-rTMS *versus* sham was the most accepted comparison (**Figure 2**). Additionally, 11 studies (Wang et al., 2012, 2019; Kakuda et al., 2013; Chieffo et al., 2014; Elkholy et al., 2014; Ji et al.,

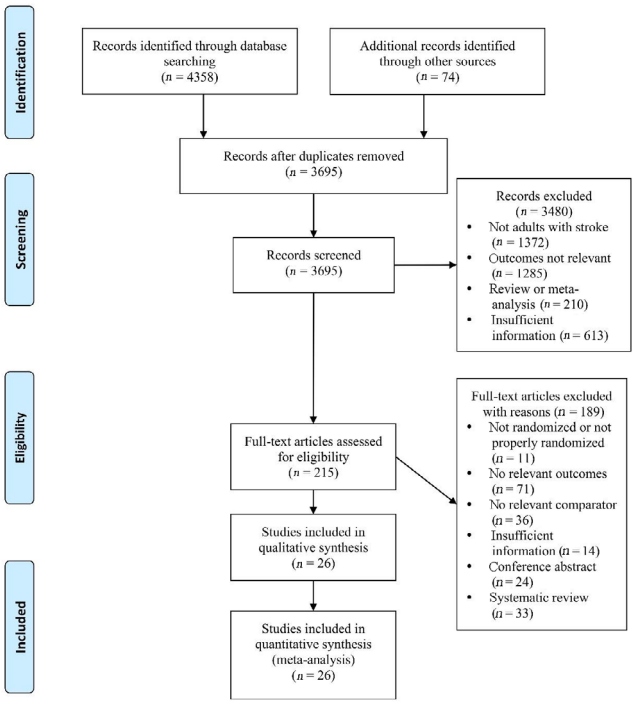

Figure 1 | **Flow diagram of the study selection.**

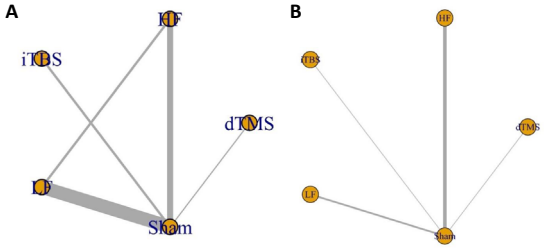

Figure 2 | **Network diagrams of treatments in patients with stroke.**
(A) Network diagram for the Fugl-Meyer assessment. (B) Network diagram for speed. The nodes were linked by a line when the treatments were directly comparable. The width of each line is proportional to the number of randomized controlled trials, and the size of each node is proportional to the number of patients (sample size). dTMS: Deep transcranial magnetic stimulation; HF: high-frequency repetitive transcranial magnetic stimulation; iTBS: intermittent theta-burst stimulation; LF: low-frequency repetitive transcranial magnetic stimulation.

2014; Kim et al., 2014b; Cha and Kim, 2015, 2017; Ji and Kim, 2015; Lin et al., 2019) used speed as a measure of lower extremity function, while 12 studies (Cha et al., 2014; Elkholy et al., 2014; Kim et al., 2014b; Choi et al., 2016; Rastgoo et al., 2016; Wang et al., 2016; Forogh et al., 2017; Chen, 2018; Huang et al., 2018; Zhao et al., 2018; Koch et al., 2019; Lin et al., 2019) also reported balance function. Cortical excitability (MEP amplitude) was assessed in six studies (Wang et al., 2012, 2019; Cha et al., 2014; Du et al., 2016; Cha and Kim, 2017; Huang et al., 2018). The principal characteristics of the included studies are listed in **Tables 1** and **2**. There were no significant discrepancies concerning baseline characteristics or total intervention sessions among the direct comparisons. This finding indicates a strong possibility that the underlying assumption of transitivity is correct in this review.

Quality assessment

The quality levels of all involved studies were appraised as good to excellent according to the PEDro results (**Additional Table 1**). All included studies specified eligibility criteria, and a majority of the studies were determined to be at low risk of bias for random allocation, blinding of outcome assessment, and incomplete outcome data, although they had a high risk of bias for concealed allocation. Of all included studies, 50% presented blinding of participants and outcome assessments, 88% reported adequate random sequence generation, and 77% performed intention-to-treat analysis, showing a low risk of bias. Only 30% presented blinding of therapists, and 27% presented allocation concealment.

According to the GRADE system, the FMA was assessed as being high-quality evidence, while speed outcome was classified as moderate-quality evidence. In contrast, MEP amplitude and BI outcomes were classified as low-quality evidence (**Additional Table 2**).

Relative effects and relative rankings of interventions

Details regarding convergence and priors are given in **Additional Figure 1**.

FMA

The NMA for lower extremity motor recovery included 18 RCTs. According to the direct evidence, only LF-rTMS was significantly more effective than sham simulation with respect to motor function (SMD, 0.34; 95% CI, 0.11 to 0.58) (**Additional Table 3**). In contrast, dTMS, HF-rTMS, and iTBS appeared to have no better efficacy than sham stimulation (SMD, 0.01 [95% CI, –0.91 to 0.94]; SMD, 0.16 [95% CI, –0.29 to 0.61]; and SMD, 0.40 [95% CI, –0.67 to 1.47]; respectively).

On the basis of the NMA results, there were no significant differences between interventions on motor function. After carefully scanning the quality of the included studies, we conducted a sensitivity analysis by excluding one study (Forogh et al., 2017) whose baseline characteristics were significantly different between the experimental and control groups. Results from the NMA then indicated that LF-rTMS (SMD, 2.28; 95% CrI, 0.92 to 3.62) was more effective than sham, which was consistent with the direct evidence. In contrast, HF-rTMS (SMD, 0.85; 95% CrI, –0.98 to 2.80), iTBS (SMD, 2.53; 95% CrI, –1.46 to 6.68), and dTMS (SMD, 0.55; 95% CrI, –6.48 to 7.04) were not more effective than sham (**Table 3**), similar to the results from the direct evidence. Additionally, no active interventions appeared to exert a better effect than any other intervention group.

Speed

For the secondary outcome of speed, 11 RCTs (307 participants) were included. The outcomes from the pairwise meta-analysis suggested a significant difference between HF-rTMS and sham stimulation (SMD, 0.70; 95% CI, 0.37 to 1.03). However, dTMS, LF-rTMS, and iTBS were not significantly more effective than sham stimulation (SMD, 0.15 [95% CI, –0.77 to 1.08]; SMD, 0.91 [95% CI, –0.01 to 1.83]; and SMD, –0.36 [95% CI, –1.24 to 0.53]; respectively) (**Additional Table 4**). The NMA for speed indicated that there were no significant differences between the different interventions (**Additional Table 5**).

Balance

For the investigation of balance, 13 RCTs were included. Direct evidence indicated that LF-rTMS was significantly more effective than both HF-rTMS (SMD, 1.23; 95% CI, 0.34 to 2.12) and sham (SMD, 0.28; 95% CI, 0.03 to 0.52) (**Additional Table 6**). Furthermore, the NMA suggested that HF-rTMS was more effective than LF-rTMS in the inconsistency model (SMD, 8.54; 95% CrI, 0.72 to 17.40). There was no significant difference in the improvement of balance between HF-rTMS, LF-rTMS, or iTBS compared with sham (SMD, 3.31 [95% CrI, –3.41 to 10.43]; SMD, 2.07 [95% CrI, –0.75 to 4.22]; and SMD, 5.59 [95% CrI, –0.58 to 10.06]; respectively) (**Additional Table 7**).

The results of the node-splitting analysis suggested an inconsistency in the NMA relative to balance (**Additional Table 8**). The direct and indirect evidence between HF-rTMS *versus* LF-rTMS, HF-rTMS *versus* sham, and LF-rTMS *versus* sham

Table 1 | **Characteristics of participants in the included studies**

Study	Study design	Sample size (E/C)	Age (yr)	Gender (M/F)	Onset time	Hemiparesis (R/L)	Stroke type (infarction/hemorrhage)
Cha et al. (2014)	RCT	12/12	53.08±7.65	11/13	2.92±1.31/3.58±0.90 mon	10/14	9/15
Cha and Kim (2015)	RCT	15/15	60.72±12.36	13/27	14.45±3.14/14.13±1.55 mon	12/18	10/20
Cha and Kim (2017)	RCT	10/10	54.8±14.56	10/10	3.90±1.59/4.20±1.22 mon	11/9	7/13
Chang et al. (2010)	RCT	10/18	56.61±12.21	11/17	12.9±5.2/14.4±5.9 d	13/15	NR
Chen (2018)	RCT	70/70	53.25±11.92	105/35	31.6±17.9/27.6±19.3 mon	72/68	97/41
Chieffo et al. (2014)	Crossover	10	62.2±9.70	NR	212±6.91 d	6/4	5/5
Choi et al. (2016)	Crossover	30	67.9±4.59	3/27	49.6±28.3/44.0±29.9 mon	15/15	30/0
Du et al. (2016)	RCT	23/23/23	55.72±11.6	45/24	7(4–16)/6(5–12)/8(3–24) d[#]	NR	69/0
Elkholy et al. (2014)	RCT	30/15	44.59±3.93	23/22	2.53±0.52/2.53±0.52 mon	0/45	NR
Forogh et al. (2017)	RCT	13/13	53–79[*]	10/16	NR	8/18	NR
Guan et al. (2017)	RCT	21/21	58.55±10.93	12/30	3.8±3.4/4.8±4.1 d	19/23	42/0
Huang et al. (2018)	RCT	18/20	61.67±9.76	23/15	31.3±25.5/25.9±18.1 d	17/21	25/13
Ji et al. (2014)	RCT	15/14	46.68±10.01	12/17	6.26±2.65/6.35±2.97 mon	14/15	15/14
Ji and Kim (2015)	RCT	20/19	56±9.58	23/16	1.9±0.72/1.68±0.58 mon	20/19	12/27
Kakuda et al. (2013)	Crossover	18	52.1±11.9	5/13	52.8±30.7 mon	12/6	5/13
Kim et al. (2014b)	RCT	10/22	66.59±9.08	17/15	16.2±13.0/15.1±5.1 d	NR	32/0
Koch et al. (2019)	RCT	17/17	64±11.3	21/13	13.06±16.94 mon	20/14	34/0
Lin et al. (2015)	RCT	16/16	60.3±11.26	11/21	40.6±29.1/33.5±23.8 d	15/17	10/22
Lin et al. (2019)	RCT	10/10	60.95±8.7	3/17	359±171/384±270 d	9/11	4/16
Liu et al. (2019)	RCT	18/18/18	59.33±6.52	37/17	NR	NR	54/0
Meng and Song (2017)	RCT	10/10	65±9.35	3/17	NR	NR	20/0
Rastgoo et al. (2016)	Crossover	20	52.15±11.51	4/16	30.2±18.3/27.4±20.1 mon	7/13	5/15
Wang et al. (2012)	RCT	12/12	63.9±11.44	9/15	1.84±1.16/2.00±1.23 yr	10/14	NR
Wang et al. (2016)	RCT	15/15	64.6±14.32	16/14	2.05±1.35/1.98±1.12 yr	NR	NR
Wang et al. (2019)	RCT	8/6	54.01±12.6	11/3	31.8±24.0/25.3±15.7 mon	8/6	6/8
Zhao et al. (2018)	RCT	36/39	55.14±12.06	47/28	4.0±2.0/4.3±3.1 mon	36/39	38/37

Data are expressed as the mean ± SD for age and onset time, while other data are expressed as numbers. *Age range. #Mean (range). C: Control group; E: experimental group; F: female; M: male; NR: not reported; RCT: randomized controlled trial.

were not in agreement (inconsistency factor, 1.24 [95% CrI, 0.14 to 5.07]; 1.31 [95% CrI, 0.11 to 4.87]; and 1.43 [95% CrI, 0.24 to 5.30]; respectively). We therefore closely examined the potential effect modifiers of the included studies, and conducted a subgroup analysis by separating the BBS and TUG results. This analysis revealed no significant associations with balance of HF-rTMS, LF-rTMS, or iTBS relative to sham, for either BBS or TUG.

MEP amplitude

The NMA for the MEP of corticospinal excitability contained five RCTs. The NMA model of the competing interventions for MEP amplitude suggested that HF-rTMS was significantly more effective than LF-rTMS (SMD, 0.27; 95% CrI, 0.04 to 0.58) and sham (SMD, 0.19; 95% CrI, 0.00 to 0.47) (**Additional Table 5**). The direct relative effects indicated that HF-rTMS performed better than LF-rTMS (SMD, 0.77; 95% CI, 0.15 to 1.38) (**Additional Table 9**), which is in accordance with the results of the NMA.

BI

Direct evidence suggested that HF-rTMS and LF-rTMS were more effective than sham for improving BI (SMD, 0.83 [95% CI, 0.09 to 1.56] and SMD, 0.63 [95% CI, 0.28 to 0.97], respectively). In contrast, iTBS was not significantly different compared with sham (SMD, 1.55; 95% CI, –1.36 to 4.46) (**Additional Table 10**).

The NMA for activities of daily life contained eight RCTs, and the results indicated that iTBS was significantly more effective than sham (SMD, 16.77; 95% CrI, 5.47 to 25.33). There was no evidence to suggest that other active treatments were more powerful than sham stimulation (**Additional Table 7**).

Assessment of statistical heterogeneity and inconsistency

According to the results of the node-splitting method for statistical inconsistency, the direct evidence and indirect evidence were not significantly consistent for balance, but they were consistent for motor function, speed, MEP amplitude, and activities of daily life.

Small study effects

No publication bias was observed among the included studies for the FMA using the Egger's test (P = 0.159) (**Additional Figure 2A**). The comparison-adjusted funnel plots appeared symmetrical for both speed (P = 0.248) and balance (P = 0.132), suggesting that small studies had similar effects compared with large studies regarding speed and balance functions (**Additional Figure 2B** and **C**).

Discussion

To the best of our knowledge, this is the first NMA to explore the effects of TMS on lower extremity motor function, and it is currently the most comprehensive review. This systematic review and NMA of TMS for patients with stroke included data from 26 RCTs, including 943 participants who were randomized to one of four rTMS interventions (deep, high-frequency, low-frequency, and intermittent theta-burst rTMS) or sham stimulation. Only LF-rTMS was superior to sham stimulation for motor function improvement, as measured by the FMA. Although direct evidence suggested that HF-rTMS was more effective than sham stimulation for speed, this result was not replicated in the NMA. In addition, HF-rTMS appeared to be more effective than LF-rTMS for MEP amplitudes.

The quality of the evidence used for the primary outcome was typically categorized as high quality. Nonetheless, the summary treatment effect estimates were imprecise for most comparisons. Furthermore, there was large uncertainty regarding novel treatments or those with little or no sham-controlled trials. Therefore, there was no conclusive evidence

Table 2 | **Characteristics of rTMS variables in included studies**

Study	Coil type	rTMS site	rTMS frequency (Hz)	Intensity (%)	No. of pulses	Treatment duration	Outcome measures
Cha et al. (2014)	F8	Ipsi-hotspot/ contra-hotspot	10/1	90 RMT/90 RMT	2000×20/1200×20	4 wk	BBS, MEP
Cha and Kim (2015)	F8	Vertex	10	90 RMT	2000×20	4 wk	Speed
Cha and Kim (2017)	F8	Ipsi-M1	10	90 RMT	1000×40	8 wk	Speed, MEP
Chang et al. (2010)	F8	Ipsi-M1	10	90 RMT	1000×10	10 d	FMA, BI
Chen (2018)	F8	Contra-M1-LL	1	90 RMT	1000×5	5 d	FMA, TUG
Chieffo et al. (2014)	H	Vertex	20	90 RMT	1500×11	3 wk	FMA, speed
Choi et al. (2016)	F8	Trunk motor spot	10	90 RMT	1000×10	2 wk	BBS
Du et al. (2016)	F8	Ipsi/contra	3/1	80–90 RMT/110–120 RMT	1200×5/1200×5	5 d	FMA, BI
Elkholy et al. (2014)	NR	Ipsi	1	2 G	NR×18	6 wk	TUG, FMA, speed
Forogh et al. (2017)	F8	Contra-M1	1	90 RMT	1200×5	5 d	FMA, BBS
Guan et al. (2017)	F8	Ipsi-M1	5	120 MT	2000×10	10 d	FMA, BI
Huang et al. (2018)	Double-cone	Contra-M1	1	120 AMT	900×15	3 wk	TUG, FMA, BI
Ji et al. (2014)	F8	Ipsi-hotspot	10	NR	1500×18	6 wk	Speed
Ji and Kim (2015)	F8	Ipsi-hotspot	10	NR	2000×20	4 wk	Speed
Kakuda et al. (2013)	Double-cone	Bi-M1-LL	10	90 RMT	2000×2	2 d	Speed
Kim et al. (2014b)	F8	Ipsi-cerebellar	1	100 RMT	900×5	5 d	Speed, BBS
Koch et al. (2019)	F8	Contra-cerebellar	iTBS	80 AMT	1200×15	3 wk	BBS, FMA, BI, speed, MEP
Lin et al. (2015)	F8	Contra-M1-LL	1	130 MT	900×15	15 d	BI, TUG, FMA, BI
Lin et al. (2019)	F8	Bi-M1-LL	iTBS	100 MT	1200×10	5 wk	BBS, TUG, speed, FMA, BI
Liu et al. (2019)	NR	Contra-M1/ Ipsi-M1	0.5/10	80 MT/80 MT	600×15/12000×15	3 wk	FMA, MEP
Meng and Song (2017)	F8	Contra-M1	1	90 MT	1800×14	14 d	BI, FMA
Rastgoo et al. (2016)	F8	Contra-M1-LL	1	90 MT	1000×5	5 d	FMA, TUG
Wang et al. (2012)	F8	Contra-M1-LL	1	90 RMT	600×10	2 wk	FMA, MEP, speed,
Wang et al. (2016)	F8	Contra-M1	1	80 RMT	900×20	4 wk	FML, BBS
Wang et al. (2019)	F8	Vertex	5	90 RMT	900×9	3 wk	FMA, speed, MEP
Zhao et al. (2018)	F8	Contra-M1	1	80–120 RMT	1000×20	20 d	FMA, BBS

AMT: Active motor threshold; BBS: Berg Balance Scale; BI: Barthel Index; bi: bilateral; contra: contralateral; F8: figure of 8; FMA: Fugl-Meyer assessment; H: H-coil; ipsi: ipsilateral; iTBS: intermittent theta-burst stimulation; M1: primary motor cortex; M1-LL: primary motor cortex of lower limb; MEP: motor evoked potential; MT: motor threshold; NR: not reported; RMT: resting motor threshold; rTMS: repetitive transcranial magnetic stimulation; TUG: Timed Up and Go Test.

Table 3 | **Relative effects estimated from the network meta-analysis and from a sensitivity analysis comparing every pair of the five interventions with respect to the Fugl-Meyer assessment**

HF	1.02 (–1.72, 3.64)	–0.44 (–2.87, 1.96)	–0.39 (–5.88, 4.84)	2.32 (–3.05, 7.74)
–1.48 (–3.52, 0.79)	LF	–1.46 (–3.27, 0.28)	–1.45 (–6.38, 3.71)	1.30 (–3.73, 6.53)
0.85 (–0.98, 2.80)	2.28 (0.92, 3.62)	Sham	–0.00 (–4.70, 4.86)	2.79 (–1.95, 7.65)
0.34 (–6.47, 7.65)	1.81 (–4.93, 8.94)	–0.55 (–7.04, 6.48)	dTMS	2.70 (–3.92, 9.71)
–1.63 (–6.17, 2.75)	–0.19 (–4.66, 4.04)	–2.53 (–6.68, 1.46)	–2.23 (–10.04, 5.89)	iTBS

Upper triangle: network meta-analysis; lower triangle: sensitivity analysis. dTMS: Deep transcranial magnetic stimulation; HF: high-frequency repetitive transcranial magnetic stimulation; iTBS: intermittent theta-burst stimulation; LF: low-frequency repetitive transcranial magnetic stimulation.

of the superiority of any particular intervention.

LF-rTMS was superior to sham stimulation with respect to motor function. Evidence-based guidelines on the therapeutic use of rTMS also recommend LF-rTMS, applied to the contralesional motor cortex, in the chronic phase of stroke recovery (Lefaucheur et al., 2014). This intervention can theoretically reduce contralesional cortical excitability and thus increase ipsilesional activity under the mechanism of long-term depression. Ueda et al. (2019) reported that intra-voxel directional coherence was greatly increased in some white matter structures bordering on lesioned regions after intervention, suggesting that white matter participates in the motor recovery of stroke patients after LF-rTMS interventions (Takeuchi et al., 2008; Bolognini and Ro, 2010).

Previous standardized meta-analyses have drawn contradictory conclusions regarding balance function and the lower extremity subscale of the FMA in patients with stroke. Tung et al. (2019) revealed the benefit of rTMS on walking speed but not on balance function, which was consistent with previous results (Li et al., 2018). Moreover, Tung et al. (2019) demonstrated improvement in the lower extremity subscale of the FMA after rTMS intervention. In contrast, Ghayour-Najafabadi et al. (2019) reported that rTMS improved balance function but did not have a positive effect on the lower extremity subscale of the FMA. In addition, none of these meta-analyses provided an overall treatment hierarchy of the different modalities of rTMS. The findings of the present NMA in terms of our primary outcome—motor function measured by the FMA—are in line with a previous systematic review and meta-analysis examining the effects of rTMS on walking and balance function after stroke (Li et al., 2018). Furthermore, we found that LF-rTMS was superior to other rTMS interventions. However, the findings regarding speed in the present NMA do not support those of previous standard meta-analyses, which might stem from an insufficient number of studies exploring the effects of novel forms of TMS.

Direct evidence demonstrated the superiority of HF-rTMS versus LF-rTMS for MEP amplitude, and network evidence revealed that HF-rTMS was also preferable to sham. The magnitude of MEP amplitude is considered to be a measure of corticospinal excitability, which denotes the strength or physiological integrity of the corticospinal pathway (Rothwell et al., 1999). Typically, the MEP amplitude of stroke patients lacking voluntary motor control is smaller than that of healthy individuals. Nevertheless, the MEP is an inherently variable measure, and can be affected by the subtle position of the coil or by multiple converging inhibitory and excitatory inputs (Maeda et al., 2000; Carroll et al., 2001). Larger high-quality RCTs are therefore needed to further explore the effectiveness of HF-rTMS. In future studies, the disruption of experimental operations should be minimized by maintaining a consistency of the participants' characteristics and a stable position of the coil.

In the present study, there was statistical inconsistency in the network for balance function, which suggests an inappropriate combination of different measurements (BBS and TUG). Moreover, there were inadequate numbers of studies to explore the efficacy of TMS on balance, and more RCTs are needed to confirm its effectiveness. In the future, researchers should unify the outcome measurements used for balance. We did not investigate the ranking probability of these outcomes here because only a few trials reported these data.

TBS, a novel form of TMS that lasts approximately 5 minutes only, is potentially useful because of its short session duration and induction of neuroplasticity. However, few studies have investigated the efficacy of TBS. Cerebellar iTBS might be a potential treatment to improve balance and gait functions in patients with stroke because the cerebellum is involved in motor control (Popa et al., 2010; Manto et al., 2012) through the disynaptic cerebello-thalamocortical pathway (Bostan et al., 2013). The results of our NMA suggested that iTBS may be beneficial for improving the activities of daily life; this finding merits further clinical investigation.

Finally, dTMS was not more effective than sham stimulation, according to our statistical approach. dTMS is delivered using the Hesed coil, which can effectively stimulate deep brain regions without bringing about greater stimulation of the superficial cortical regions (Roth et al., 2002; Zangen et al., 2005). Various experiments have explored the efficacy of dTMS in recent years (Kranz et al., 2010; Harel et al., 2011; Levkovitz et al., 2011). Nonetheless, the exact coil configuration and placement may vary with different applications, and there is scarce evidence to demonstrate its effectiveness in patients with stroke. More high-quality RCTs investigating the efficacy of dTMS are needed in the near future.

Our study had several limitations. Most studies presented an unclear risk of bias on allocation concealment, which is a renowned methodological drawback in rTMS interventions. Properly assigning concealment, preventing contamination bias, and reporting all results would have improved the included studies. Furthermore, some nodes were not well connected, which may lead to the inaccurate estimation of relative effects, especially when comparing different active interventions. Nevertheless, iTBS and dTMS lacked sufficient evidence to support their effects in stroke patients, and more controlled studies should be conducted to confirm their effectiveness.

The available data suggested that there are differences in clinical effects between the different rTMS modalities, but this was unable to be confirmed. Our findings suggest that LF-rTMS can improve motor function and that HF-rTMS can increase MEP amplitude. Moreover, this finding implies that LF-rTMS is superior to other interventions for stroke rehabilitation. Novel forms of rTMS interventions (dTMS and iTBS) were not more effective than sham stimulation. However, there is little available evidence for rTMS interventions other than LF-rTMS and HF-rTMS. Hence, new high-quality RCTs for novel rTMS interventions are needed to establish their efficacy with higher reliability. In the future, we encourage clinical therapists to include LF-rTMS as a supplementary therapy for stroke rehabilitation in clinical practice.

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Additional files:

Additional file 1: *PRISMA 2009 checklist.*
Additional file 2: *Search strategy.*
Additional file 3: *Open peer reviewer reports 1 and 2.*
Additional Table 1: *Risk of bias assessment according to Physiotherapy Evidence Database scale.*
Additional Table 2: *Levels of evidence according to Grades of Recommendation, Assessment, Development, and Evaluation scale.*
Additional Table 3: *Pairwise meta-analysis results of Fugl-Meyer assessment.*
Additional Table 4: *Pairwise meta-analysis results of speed.*
Additional Table 5: *Relative effects estimated from the network meta-analysis with respect to speed and motor evoked potential amplitude.*
Additional Table 6: *Pairwise meta-analysis results of balance.*
Additional Table 7: *Relative effects estimated from the network meta-analysis with respect to balance and Barthel Index.*
Additional Table 8: *Node-splitting approach for balance.*
Additional Table 9: *Pairwise meta-analysis results of motor evoked potential amplitude.*
Additional Table 10: *Pairwise meta-analysis results of Barthel Index.*
Additional Figure 1: *Trace plot and density plot.*
Additional Figure 2: *Comparison-adjusted funnel plot of Fugl-Meyer assessment (A), speed (B), and balance (C).*

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11-12
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13-16
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-16
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12-13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	16
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20-21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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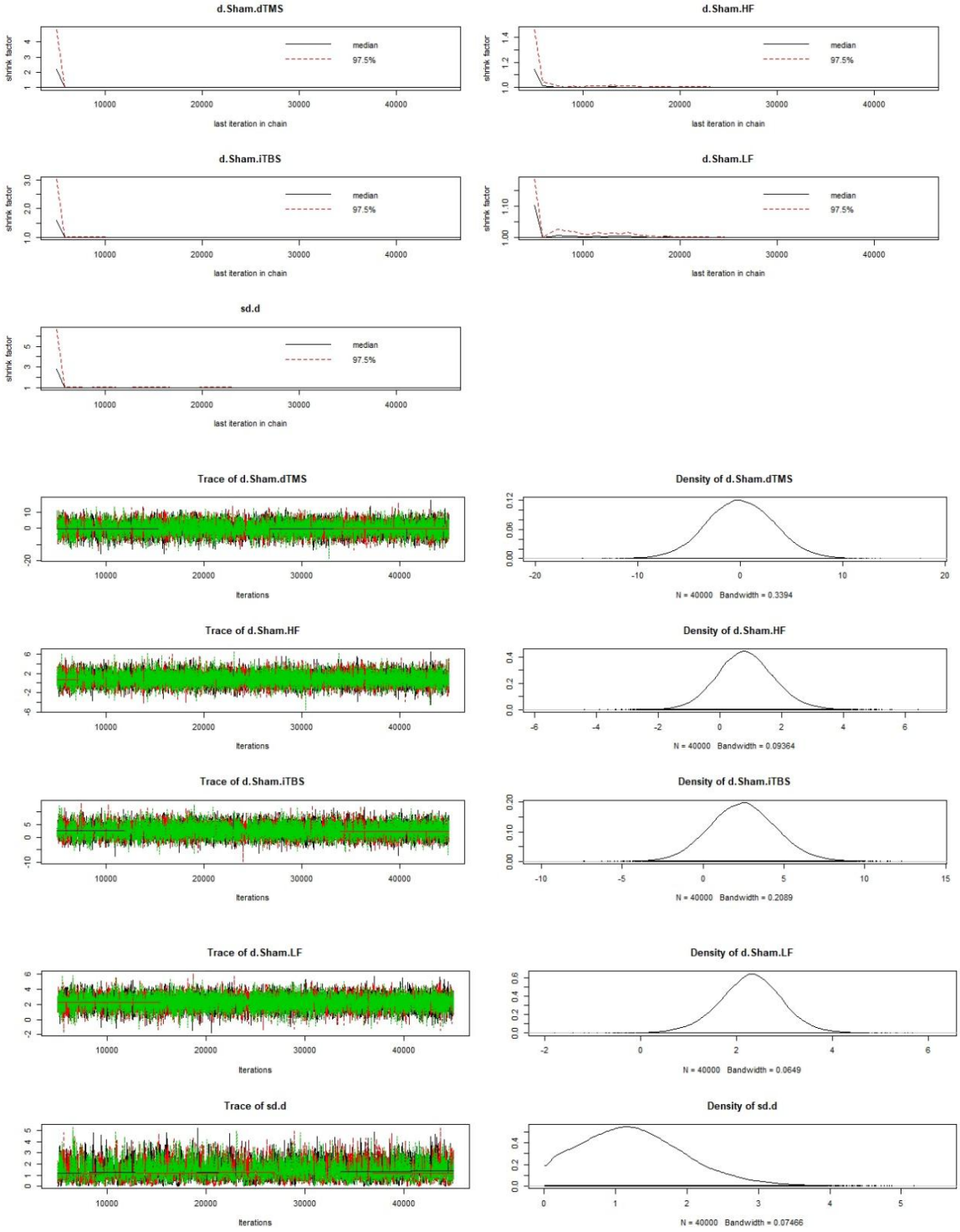
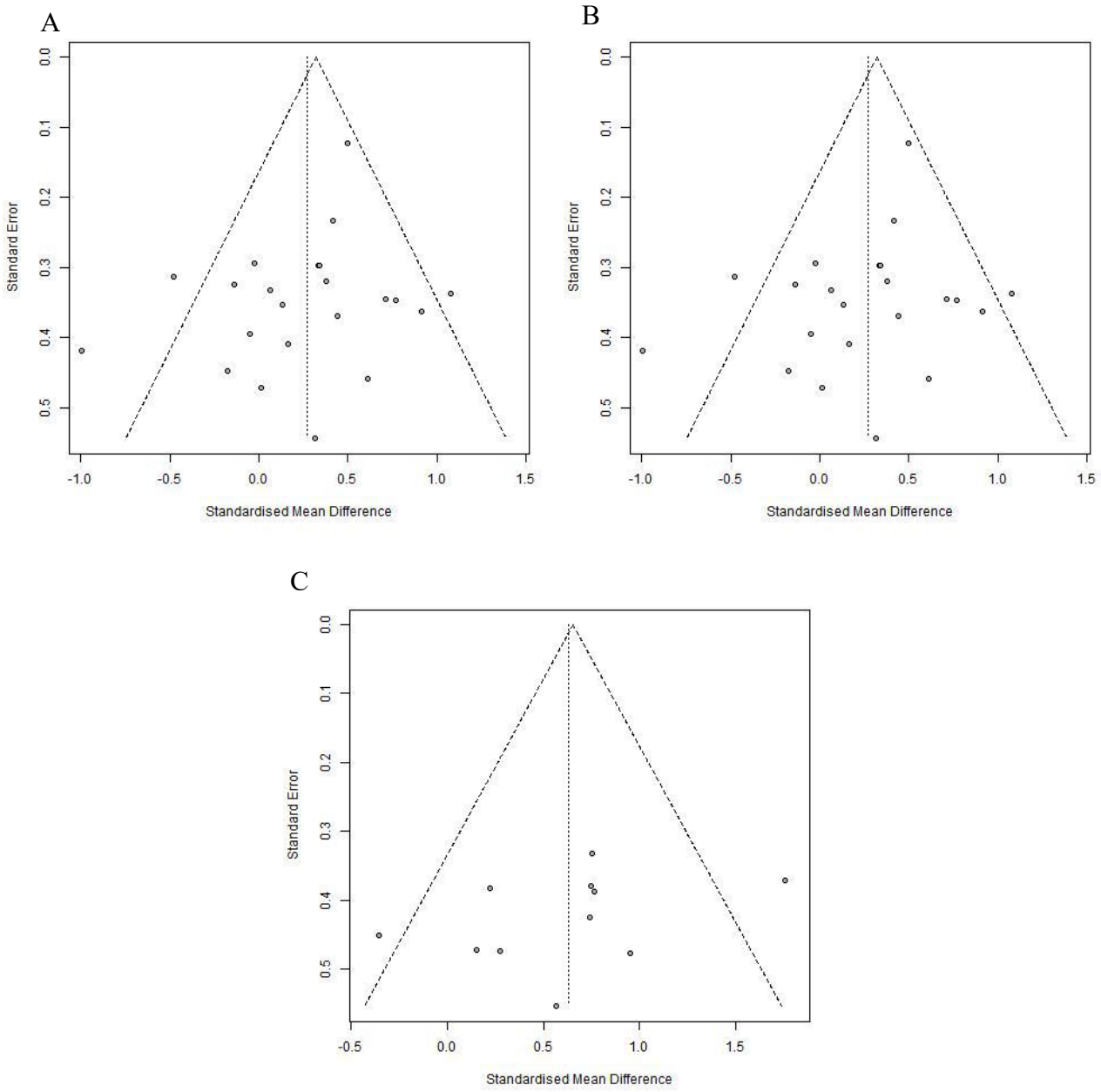


Additional Figure 1 Trace plot and density plot.

The potential scale reduction factor (PSRF) were 1.00, 1.32 and 1.01 separately for Fugl-Meyer assessment, speed and balance. The PSRF is less than 1.2 can be acceptable, which means simulated observations are close to the target distribution. Heterogeneity standard deviation (τ^2) has been estimated using the methods of moments and is reported only for comparisons for which is estimable and larger than 0. dTMS: Deep transcranial magnetic stimulation; HF: high-frequency repetitive transcranial magnetic stimulation; iTBS: intermittent theta-burst stimulation; LF: low-frequency repetitive transcranial magnetic stimulation; sd: standard deviation



Additional Figure 2 Comparison-adjusted funnel plot of Fugl-Meyer assessment (A), speed (B), and balance (C).

Heterogeneity standard deviation (τ^2) has been estimated using the methods of moments and is reported only for comparisons for which is estimable and larger than 0.

Additional Table 1 Risk of bias assessment according to Physiotherapy Evidence Database scale

Study	Eligibility criteria specified (0/1)	Random allocation (0/1)	Concealed allocation (0/1)	Comparable at baseline (0/1)	Blinded subjects (0/1)	Blinded therapists (0/1)	Blinded assessors (0/1)	Adequate follow-up (0/1)	Intention-totreat analysis (0/1)	Between group comparisons (0/1)	Point estimates and variability (0/1)	Summary
Cha et al. (2014)	1	1	1	1	0	0	0	1	1	1	1	8
Cha and Kim (2015)	1	1	0	1	0	0	0	1	1	1	1	7
Cha and Kim (2017)	1	1	1	1	0	1	1	1	1	1	1	10
Chang et al. (2010)	1	1	0	1	1	0	1	1	1	1	1	9
Chen (2018)	1	1	0	1	1	0	0	1	0	1	1	7
Chieffo et al. (2014)	1	1	0	1	0	0	0	1	0	1	1	6
Choi et al. (2016)	1	1	0	1	0	0	0	1	1	1	1	7
Du et al. (2016)	1	1	1	1	1	1	1	1	1	1	1	11
Elkholy et al. (2014)	1	0	0	1	0	0	0	1	1	1	1	6

Forogh et al. (2017)	1	1	0	0	1	0	0	1	1	1	1	7
Guan et al. (2017)	1	1	1	1	1	1	1	1	1	1	1	11
Huang et al. (2018)	1	1	0	1	1	0	1	1	0	1	1	8
Ji et al. (2014)	1	1	0	1	0	0	0	1	1	1	1	7
Ji and Kim (2015)	1	1	0	1	0	0	0	1	1	1	1	7
Kakuda et al. (2013)	1	1	0	1	0	1	1	1	1	1	1	9
Kim et al. (2014b)	1	1	0	1	1	1	1	1	1	1	1	10
Koch et al. (2019)	1	1	0	1	1	0	1	1	0	1	1	8
Lin et al. (2015)	1	0	0	1	1	1	0	1	0	1	1	7
Lin et al. (2019)	1	1	1	1	1	1	1	1	1	1	1	11
Liu et al. (2019)	1	1	0	1	0	0	0	1	1	1	1	7
Meng and Song (2017)	1	1	0	1	1	0	0	1	1	1	1	8

Rastgoo et al. (2016)	1	1	0	1	0	1	1	1	1	1	1	9
Wang et al. (2012)	1	1	1	1	1	0	1	1	0	1	1	9
Wang et al. (2016)	1	0	0	1	0	0	0	1	1	1	1	6
Wang et al. (2019)	1	1	1	1	1	0	1	1	1	1	1	10
Zhao et al. (2018)	1	1	0	1	0	0	0	1	1	1	1	7

0 indicates the criterion was not satisfied; 1 the criterion was satisfied.

1 **Additional Table 2 Levels of evidence according to Grades of Recommendation, Assessment, Development, and Evaluation scale**

Certainty assessment							No. of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TMS	Sham	Relative (95% CI)	Absolute (95% CI)		
Motor function (follow up: range 1 weeks to 3 months; assessed with: Fugl-Meyer assessment)												
18	Randomised trials	Serious[a]	Not serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	431	411	-	SMD 0.27 SD higher (0.09 higher to 0.45 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Speed (follow up: range 1 months to 3 months; assessed with: walking speed)												
11	Randomised trials	Serious[a]	Not serious	Not serious	Not serious	None	169	138	-	SMD 0.63 SD higher (0.3 higher to 0.96 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
Balance (assessed with: Berg Balance scale and Timed up and go test)												
12	Randomised trials	Serious[a]	Serious[b]	Not serious	Not serious	None	360	338	-	SMD 0.39 SD higher (0.11 higher to 0.67 higher)	⊕⊕◯◯ LOW	IMPORTANT
Motor evoked potential amplitude (assessed with: motor evoked potential)												
6	Randomised trials	Serious[a]	Serious[c]	Not serious	Not serious	None	83	83	-	SMD 0.32 SD higher (0.02 lower to 0.67 higher)	⊕⊕◯◯ LOW	IMPORTANT
Barthel Index (assessed with: Barthel Index)												
8	Randomised	Serious[a]	Serious[d]	Not serious	Not serious	None	133	127	-	SMD 0.87	⊕⊕◯◯	IMPORTANT

	trials		SD (0.39 to higher)	higher higher 1.36 LOW

a. In general, the studies had poor methodological rigor, with few blinded studies. b. I-squared is equal to 61%. c. I-squared is equal to 66%. d. I-squared is equal to 74%. CI: Confidence interval; SMD: standardised mean difference; SD: standard deviation.

Additional Table 3 Pairwise meta-analysis results of Fugl-Meyer assessment.

Study	SMD (95%CI)
dTMS *vs*. Sham	
Chieffo et al. (2014)	0.01 (-0.91, 0.94)
HF *vs*. LF	
Du et al. (2016)	-0.03 (-0.60, 0.55)
Liu et al. (2019)	0.06 (-0.59, 0.71)
Summary	0.01 (-0.42, 0.45)
HF *vs*. Sham	τ^2=0.13, I^2=49%
Chang et al. (2010)	-0.05 (-0.82, 0.72)
Du et al. (2016)	0.34 (-0.25, 0.92)
Guan et al. (2017)	-0.48 (-1.09, 0.14)
Liu et al. (2019)	0.77 (0.09, 1.45)
Wang et al. (2019)	0.32 (-0.75, 1.38)
Summary	0.16 (-0.29, 0.61)
iTBS *vs*. Sham	τ^2=0.43, I^2=72%
Koch et al. (2019)	0.91 (0.20, 1.62)
Lin et al. (2019)	-0.18 (-1.06, 0.70)
Summary	0.40 (-0.67, 1.47)
LF *vs*. Sham	τ^2=0.07, I^2=46%
Chen (2018)	0.50 (0.26, 0.74)
Du et al. (2016)	0.34 (-0.25, 0.92)
Elkholy et al. (2014)	1.07 (0.41, 1.74)
Forogh et al. (2017)	-0.99 (-1.82, -0.17)
Huang et al. (2018)	-0.14 (-0.77, 0.50)
Lin et al. (2015)	0.13 (-0.56, 0.83)
Lin et al. (2019)	0.71 (0.03, 1.38)
Meng and Song (2017)	0.61 (-0.29, 1.51)
Rastgoo et al. (2016)	0.38 (-0.25, 1.00)
Wang et al. (2012)	0.16 (-0.64, 0.96)
Wang et al. (2016)	0.44 (-0.28, 1.17)
Zhao et al. (2018)	0.42 (-0.04, 0.88)
Summary	0.34 (0.11, 0.58)

Heterogeneity standard deviation (τ^2) has been estimated using the methods of moments and is reported only for comparisons for which is estimable and larger than 0. CI: Confidence interval; dTMS: deep transcranial magnetic stimulation; HF: high-frequency repetitive transcranial magnetic stimulation; iTBS: intermittent theta-burst stimulation; LF: low-frequency repetitive transcranial magnetic stimulation; SMD: standardized mean difference.

Additional Table 4 Pairwise meta-analysis results of speed.

Study	SMD (95%CI)
dTMS vs. Sham	
Chieffo et al. (2014)	0.15 (-0.77, 1.08)
HF vs. Sham	
Cha and Kim (2017)	0.95 (0.02, 1.89)
Cha and Kim (2015)	0.75 (0.01, 1.49)
Ji et al. (2014)	0.77 (0.01, 1.53)
Ji et al. (2015)	0.75 (0.10, 1.41)
Kakuda et al. (2013)	0.28 (-0.65, 1.21)
Wang et al. (2019)	0.57 (-0.52, 1.66)
Summary	0.70 (0.37, 1.03)
iTBS vs. Sham	
Lin et al. (2019)	-0.36 (-1.24, 0.53)
LF vs. Sham	τ^2=0.51, I^2=77%
Elkholy et al. (2014)	1.76 (1.03, 2.48)
Kim et al. (2014b)	0.74 (-0.09, 1.58)
Wang et al. (2012)	0.22 (-0.53, 0.97)
Summary	0.91 (-0.01, 1.83)

Heterogeneity standard deviation (τ^2) has been estimated using the methods of moments and is reported only for comparisons for which is estimable and larger than 0. CI: Confidence interval; dTMS: deep transcranial magnetic stimulation; HF: high-frequency repetitive transcranial magnetic stimulation; iTBS: intermittent theta-burst stimulation; LF: low-frequency repetitive transcranial magnetic stimulation; SMD: standardized mean difference.

Additional Table 5 Relative effects estimated from the network meta-analysis with respect to speed and motor evoked potential amplitude

HF	**-0.27 (-0.58, -0.04)**	**-0.19 (-0.47, 0.00)**		
-0.24 (-1.04, 0.54)	LF	0.07 (-0.15, 0.30)		
0.00 (-0.39, 0.41)	0.25 (-0.44, 0.93)	Sham		
-0.66 (-3.66, 2.66)	-0.42 (-3.43, 2.96)	-0.66 (-3.60, 2.69)	dTMS	
3.42 (-3.64, 13.88)	3.63 (-3.44, 14.13)	3.41 (-3.68, 13.89)	4.19 (-3.96, 15.49)	iTBS

Upper triangle: Network meta-analysis. Lower triangle: Sensitivity analysis. Heterogeneity standard deviation (τ^2) has been estimated using the methods of moments and is reported only for comparisons for which is estimable and larger than 0. dTMS: Deep transcranial magnetic stimulation; HF: high-frequency repetitive transcranial magnetic stimulation; iTBS: intermittent theta-burst stimulation; LF: low-frequency repetitive transcranial magnetic stimulation.

Additional Table 6 Pairwise meta-analysis results of balance

Study	SMD (95%CI)
LF vs. HF	
Cha et al. (2014)	1.23 (0.34, 2.12)
HF vs. Sham	
Choi et al. (2016)	0.14 (-0.58, 0.86)
iTBS vs. Sham	τ^2=1.05, I^2=85%
Koch et al. (2019)	1.73 (0.93, 2.54)
Lin et al. (2019)	-0.08 (-0.95, 0.80)
Lin et al. (2019)	-0.20 (-1.08, 0.68)
Summary	0.50 (-0.76, 1.76)
LF vs. Sham	τ^2=0.04, I^2=37%
Chen (2018)	0.01 (-0.22, 0.25)
Elkholy et al. (2014)	0.93 (0.28, 1.58)
Forogh et al. (2017)	0.38 (-0.39, 1.16)
Huang et al. (2018)	0.22 (-0.42, 0.86)
Kim et al. (2014b)	-0.11 (-0.86, 0.64)
Rastgoo et al. (2016)	0.04 (-0.58, 0.66)
Wang et al. (2016)	0.48 (-0.25, 1.21)
Zhao et al. (2018)	0.55 (0.09, 1.01)
Summary	0.28 (0.03, 0.52)

Heterogeneity standard deviation (τ^2) has been estimated using the methods of moments and is reported only for comparisons for which is estimable and larger than 0. CI: Confidence interval; dTMS: deep transcranial magnetic stimulation; HF: high-frequency repetitive transcranial magnetic stimulation; iTBS: intermittent theta-burst stimulation; LF: low-frequency repetitive transcranial magnetic stimulation; SMD: standardized mean difference.

Additional Table 7 Relative effects estimated from the network meta-analysis with respect to balance and Barthel Index

HF	6.32 (-8.39, 23.60)	-7.16 (-14.81, 0.55)	19.18 (-1.01, 38.45)
8.54 (0.72, 17.40)	LF	-3.55 (-12.76, 2.89)	13.22 (-2.78, 23.37)
3.31 (-3.41, 10.43)	2.07 (-0.75, 4.22)	Sham	16.77 (5.47, 25.33)
5.26 (-4.26, 15.63)	-3.62 (-8.62, 2.62)	-5.59 (-10.06, 0.58)	iTBS

Upper triangle: Network meta-analysis with respect to Barthel Index. Lower triangle: Network meta-analysis with respect to balance. Heterogeneity standard deviation (τ^2) has been estimated using the methods of moments and is reported only for comparisons for which is estimable and larger than 0. HF: High-frequency repetitive transcranial magnetic stimulation; iTBS: intermittent theta-burst stimulation; LF: low-frequency repetitive transcranial magnetic stimulation.

Additional Table 8 Node-splitting approach for balance

Name	Direct effect	Indirect effect	Overall	Median	*P*-value
HF, LF	-11.12 (-19.49, -2.10)	1.57 (-5.88, 7.77)	-3.47 (-10.89, 1.59)	1.24 (0.14, 5.07)	0.03
HF, Sham	-1.04 (-7.50, 5.00)	-14.40 (-23.10, -5.36)	-5.11 (-11.88, 0.15)	1.31 (0.11, 4.87)	0.03
LF, Sham	-2.22 (-4.31, 0.25)	10.78 (-0.26, 21.60)	-1.62 (-4.04, 1.35)	1.43 (0.24, 5.30)	0.03

HF: High-frequency repetitive transcranial magnetic stimulation; LF: low-frequency repetitive transcranial magnetic stimulation.

Additional Table 9 Pairwise meta-analysis results of motor evoked potential amplitude

Study	SMD (95%CI)
HF vs. LF	τ^2=0.17, I^2=59%
Cha et al. (2014)	1.45 (0.53, 2.37)
Du et al. (2016)	0.82 (0.21, 1.42)
Du et al. (2016)	0.27 (-0.31, 0.85)
Summary	0.77 (0.15, 1.38)
HF vs. Sham	τ^2=0.25, I^2=59%
Cha and Kim (2017)	1.72 (0.66, 2.78)
Du et al. (2016)	0.85 (0.25, 1.46)
Du et al. (2016)	0.22 (-0.36, 0.80)
Wang et al. (2019)	0.00 (-1.06, 1.06)
Wang et al. (2019)	-0.19 (-1.25, 0.87)
Summary	0.52 (-0.06, 1.10)
LF vs. Sham	τ^2=0.13, I^2=52%
Du et al. (2016)	0.19 (-0.39, 0.77)
Du et al. (2016)	-0.10 (-0.67, 0.48)
Huang et al. (2018)	0.56 (-0.26, 1.38)
Wang et al. (2012)	-1.02 (-1.88, -0.16)
Wang et al. (2012)	-0.32 (-0.96, 0.32)
Summary	-0.11 (-0.55, 0.33)

Heterogeneity standard deviation (τ^2) has been estimated using the methods of moments and is reported only for comparisons for which is estimable and larger than 0. CI: Confidence interval; HF: high-frequency repetitive transcranial magnetic stimulation; LF: low-frequency repetitive transcranial magnetic stimulation; SMD: standardized mean difference.

Additional Table 10 Pairwise meta-analysis results of Barthel Index

Study	SMD (95%CI)
HF vs. Sham	τ^2=0.29, I^2=70%
Chang et al. (2010)	1.56 (0.67, 2.45)
Du et al. (2016)	0.90 (0.29, 1.51)
Guan et al. (2017)	0.18 (-0.42, 0.79)
Summary	0.83 (0.09, 1.56)
iTBS vs. Sham	τ^2=4.17, I^2=95%
Koch et al. (2019)	3.05 (2.03, 4.07)
Lin et al. (2019)	0.08 (-0.80, 0.96)
Summary	1.55 (-1.36, 4.46)
LF vs. Sham	
Du et al. (2016)	0.90 (0.29, 1.51)
Huang et al. (2018)	0.31 (-0.33, 0.96)
Lin et al. (2015)	0.46 (-0.25, 1.16)
Meng and Song (2017)	0.95 (0.01, 1.88)
Summary	0.63 (0.28, 0.97)

Heterogeneity standard deviation (τ^2) has been estimated using the methods of moments and is reported only for comparisons for which is estimable and larger than 0. CI: Confidence interval; HF: high-frequency repetitive transcranial magnetic stimulation; iTBS: intermittent theta-burst stimulation; LF: low-frequency repetitive transcranial magnetic stimulation; SMD: standardized mean difference.