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Short- and Long-term Effects of Repetitive Transcranial Magnetic Stimulation on Upper Limb Motor Function after Stroke: a Systematic Review and Meta-Analysis

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Abstract

Objective: The aim of this study was to evaluate the short- and long-term effects as well as other parameters of repetitive transcranial magnetic stimulation (rTMS) on upper limb motor functional recovery after stroke.

Data sources: The databases of PubMed, Medline, Science Direct, Cochrane, and Embase were searched for randomized controlled studies reporting effects of rTMS on upper limb motor recovery published before October 30, 2016.

Review methods: The short- and long-term mean effect sizes as well as the effect size of rTMS frequency of pulse, post-stroke onset, and theta burst stimulation patterns were summarized by calculating the standardized mean difference (SMD) and the 95% confidence interval using fixed/random effect models as appropriate.

Results: Thirty-four studies with 904 participants were included in this systematic review. Pooled estimates show that rTMS significantly improved short-term (SMD, 0.43; $P < 0.001$) and long-term (SMD, 0.49; $P < 0.001$) manual dexterity. More pronounced effects were found for rTMS administered in the acute phase of stroke (SMD, 0.69), subcortical stroke (SMD, 0.66), 5-session rTMS treatment (SMD, 0.67) and intermittent theta burst stimulation (SMD, 0.60). Only three studies reported mild adverse events such as headache and increased anxiety .

Conclusions: Five-session rTMS treatment could best improve stroke-induced upper limb dyskinesia acutely and in a long-lasting manner. Intermittent theta burst stimulation is more beneficial than continuous theta burst stimulation. rTMS applied in the acute phase of stroke is more effective than rTMS applied in the chronic phase. Subcortical lesion benefit more from rTMS than other lesion site.

Keywords

Systematic review, repetitive transcranial magnetic stimulation, stroke, motor function recovery, meta-analysis, arm

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Introduction

In a series of sequelae after stroke, deficit in manual dexterity would occur in two-thirds of the patients,[1] that have caused significant disability for stroke survivors who require partial or full dependence/assistance on others for activities of their daily living. Although neural reorganization occurs soon after stroke, the natural rehabilitation of functional recovery of upper limbs has often been limited. To overcome these limits, novel strategies to enhance neural regeneration, brain structural and functional recovery are needed. Recently, repetitive transcranial magnetic stimulation (rTMS) has been recommended as add-on methods to improve motor function recovery after stroke.[2]

Based on the theory of interhemispheric competition, normal healthy people have a balanced cortical excitability between the two hemispheres that are altered after stroke.[3] Often, the cortical excitability and the corresponding muscles' excitability controlled by the injured area in the affected hemisphere decrease, whereas the excitability in the unaffected hemisphere increases.[4] rTMS is a painless non-invasive stimulation method to modulate the equilibrium of interhemispheric cortical excitability.[5] Cortical excitability can be enhanced by high-frequency rTMS (> 1.0 Hz)[6] whereas low-frequency rTMS (⩽ 1.0 Hz) induces the depression of cortical activity.[7] Theta burst stimulation, as another form of rTMS generates bursts of low-intensity stimulation to harmonize cortical excitability. Intermittent theta burst stimulation enhances cortical excitability, whereas continuous theta burst stimulation suppresses cortical excitability.[8] Therefore, rTMS has been applied over motor cortical areas to treat motor dysfunction in post-stroke patients and many studies have been undertaken to investigate its efficacy.

Several previous reviews have suggested that rTMS can improve the motor functional recovery of paretic hands acutely in the short-term,[4,9,10] however, these reviews have not explore long-lasting beneficial effects of rTMS on upper limb motor function, which are the necessary indications for a truly successful intervention. Although one review[11] has reviewed the studies that investigated the long-term effect of rTMS on motor recovery after stroke, it has not obtained adequate data to evaluate the long-term efficacy of rTMS. To our best knowledge, so far no meta-analysis has been reported to compare the short- and long-term effects of rTMS on upper limb physical function after stroke. In addition, apart from two reviews published four years ago, there is no recent systematic reviews on the efficacy of rTMS treatment and different treatment parameters involved such as stimulus frequency, stroke duration and short- and long-term efficacy of rTMS treatment and so on. An understanding the potential effects of these different factors would be critical for improving rTMS-induced upper limb motor recovery.

The main purpose of this systematic review is to summarize and evaluate the short- and long-term efficacy of rTMS for the recovery of upper limb motor function following stroke. The second aim is to determine if factors such as frequency of pulse, stroke duration and adverse effect that may influence the motor outcomes.

Methods

Search strategy

The databases of PubMed, Medline, Cochrane Library, Embase, and ScienceDirect, published before October 30, 2016, were searched. The reports were limited to human studies. The search index terms were cerebrovascular accident/stroke and repetitive transcranial magnetic stimulation/rTMS and motor/movement/motion. Manual search of the reference lists of the retrieved articles and pertinent reviews were also conducted.[9–11] This systematic reviews adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

Study selection

The inclusion criteria for this systematic review were as follows: (1) all the participants were adult (⩾18 years); (2) patients were diagnosed with a stroke; (3) focused on rTMS effects on upper limb motor function in post-stroke patients; (4) the design of the studies was randomized controlled; (5) ⩾ 5 patients were included; (6) the studies were

published in peer-reviewed English journals; and (7) the outcome measures included continuous scales that assessed the motor function of the affected upper limb. Two reviewers evaluated and identified the assessment separately.

Study quality estimate

The methodological quality of the included studies were evaluated by two reviewers independently by using an modify checklist derived from a revised Consort Statement by Moher et al.[12] The assessment criteria are as follows: (1) allocated randomization; (2) blind process; (3) description of baseline data; (4) dropout; (5) control design; and (6) adverse effects. Random allocation was assigned as 1 if patients were allotted randomly. Blind process rating ranged from 0 to 2, in which 0 stood for non-mentioned or non-blind, 1 and 2 represented single-blind and double-blind respectively. Description of baseline data was recorded as 1 if presented. Control design was recorded as 1 if the experiment was designed with healthy controls, 2 with patient controls, and 3 with both controls; otherwise, recorded as 0. The dropout and adverse effect were denoted as a number of events.

Data extraction and analyses

The related data were collected by two reviewers independently and described by: study design, number of subject (experiment group and control group), stroke duration, treatment parameters, and outcome measurements and the duration of follow-up. If the mean and standard deviation (SD) of the change scores were not clearly defined in article, the post-treatment mean and SD were used in case that there were no statistical differences ($P > 0.05$) of the baseline mean and SD between the experimental and control groups. If graphs were reported instead of the original data in the articles, data were extracted with the assistance of GetData Graph Digitizer 2.25 (http://getdata-graph-digitizer.com/) based on the Cochrane Handbook for Systematic Reviews of Interventions.[13]

To investigate the short- and long-term effects of rTMS on upper limb motor function recovery, independent analyses were conducted based on the data collected immediately after the last session of rTMS (often within 24 hours of the last rTMS session that was considered as short-term outcome) and follow-up data (i.e. assessment made at or after one month from the last rTMS session that was considered as long-term outcome).[14] To determine potential influencing factors on motor recovery, subgroup analyses were also performed based on rTMS frequency (high versus low), pattern of theta burst stimulation (intermittent theta burst stimulation versus continuous theta burst stimulation), post-stroke duration (acute [$\leqslant$ 2 weeks] versus subacute [2 weeks to 6 months] versus chronic [> 6 months]),[4] lesion location (subcortical versus non-specified) and treatment sessions.

Studies were pooled for meta-analyses using STATA/SE version 11.0 (STATA Corporation, Texas, USA). The standardized mean difference (SMD) and the 95 % confidence interval (CI) were calculated for the different studies by using Hedges' g which is a variation of Cohen's d that corrects for biases due to small sample sizes.[15] The heterogeneity of outcomes in each study was evaluated by using an I^2 test. If $I^2 \geqslant 50$ %, the random-effect models were used for data analysis. Otherwise ($I^2 <$ 50%) the fixed effect model was performed. The Egger's test[16] were used to determine the publication bias. Sensitivity analysis was conducted to explore the impact on the effect size when low-quality studies and studies with cross-over design were omitted. The statistical significance level was set at $P = 0.05$. Finally, effect sizes were classified as small (<0.2), medium (0.2-0.8), or large (>0.8).[17]

Result

Study selection

The initial database search yielded a total of 2,376 relevant studies. Only 34 studies were identified ($N = 904$) by two independent reviewers based on the inclusion criteria. The flow diagram of the selection process is shown in Figure 1.

Study characteristics

The quality assessment of the selected studies is shown in Table S1 in the supplementary data. All

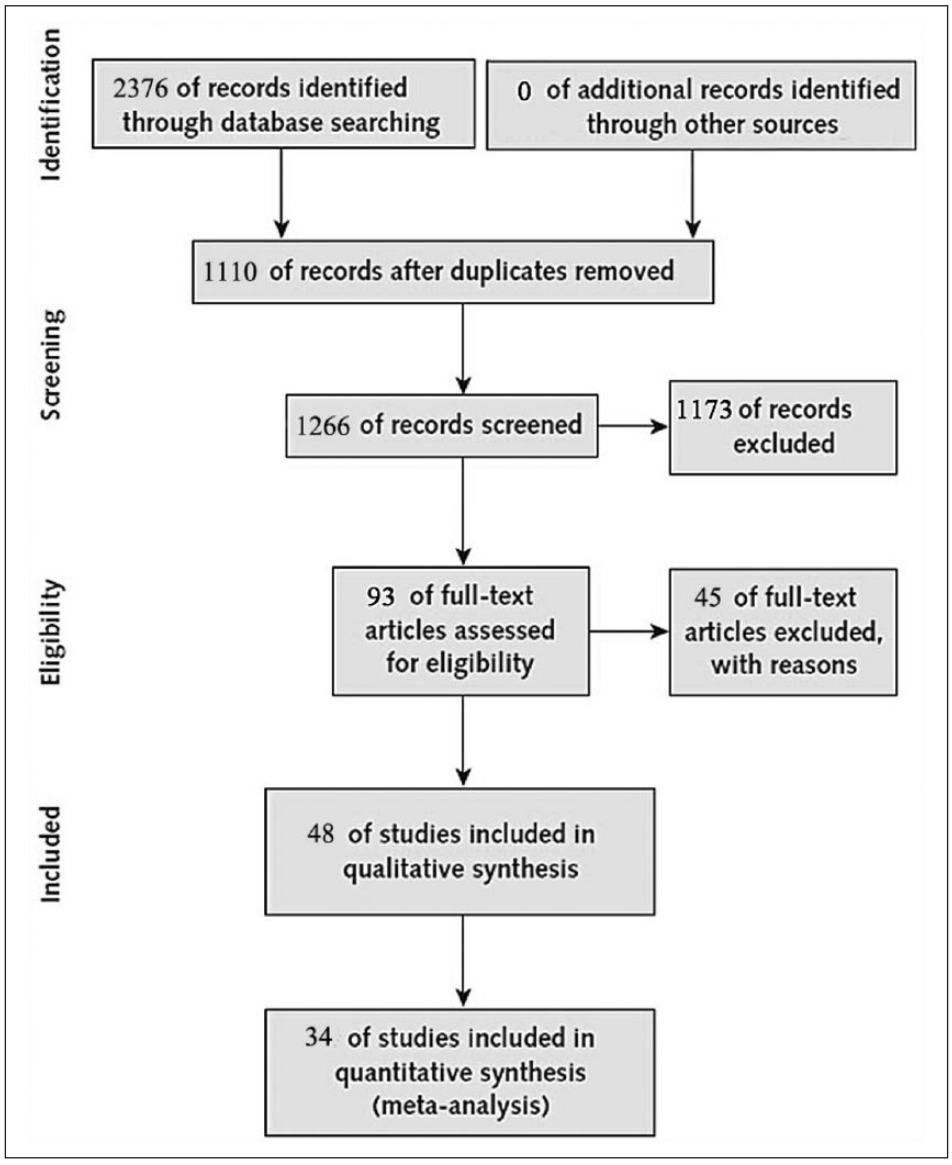

Figure 1. The flow diagram of the selection process.

studies applied rTMS over ipsilesional/contralesional M1 and used random allocation. Of these studies, 23 of them used double-blind procedure,[18–40] five used single-blind procedure,[41–45] and the other studies did not report blind procedure.[46–51] Only one study did not describe the baseline demographic data of patients.[21] Eight studies reported dropouts due to various reasons. [28,30,35,38,40–42,45]

Table S2 in the supplementary data summarizes the main characteristics of the studies included in the meta-analysis of this systematic review. Eight studies used crossover-sham control design [19,21,25,29,41,47–49] and the order of rTMS or sham stimulation was randomized and counterbalanced across the participants. The included studies used different protocols of intervention. The patterns of

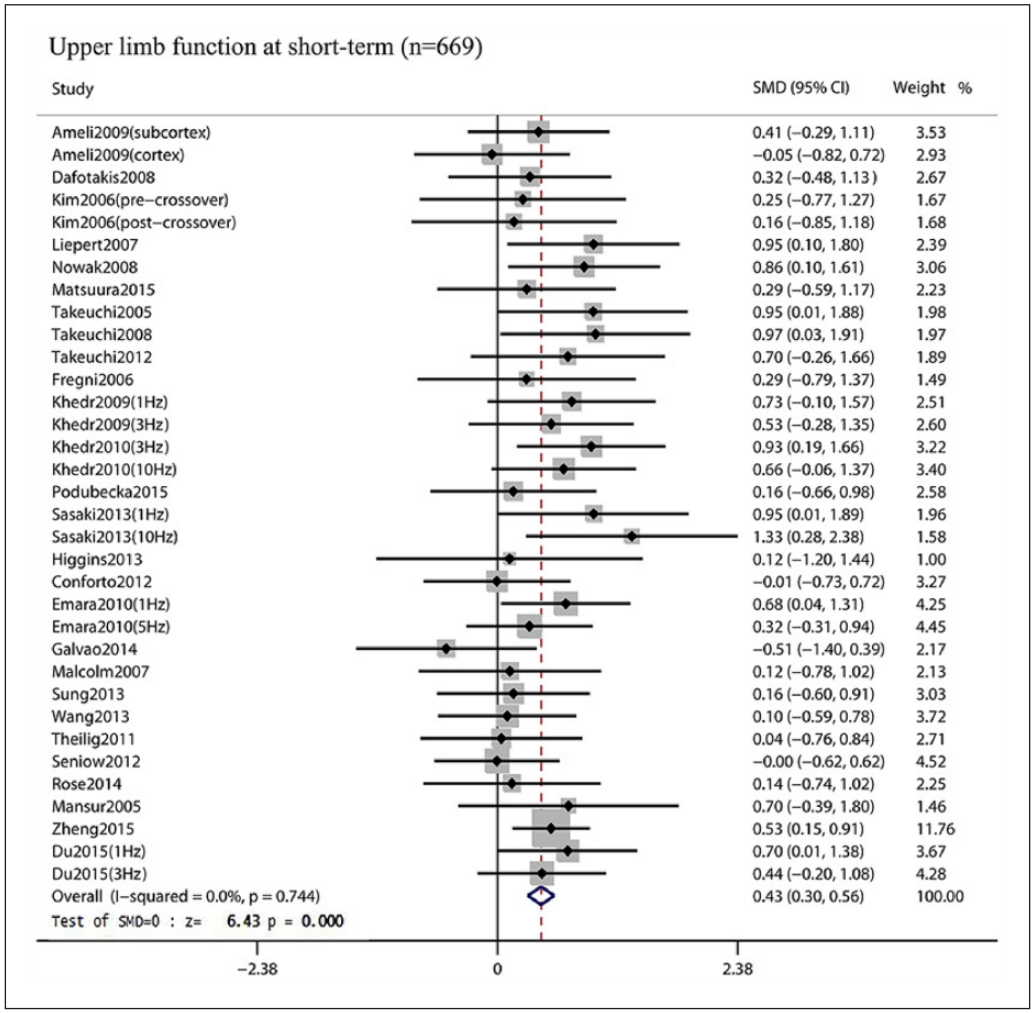

Figure 2. Forest plot from the meta-analysis of rTMS on upper limb function at short-term showing estimates of effect size (Hedges' g) with 95% confidence intervals. Relative weight for each trial is indicated by the size of the corresponding square.

the selected rTMS studies were: low-frequency rTMS, high-frequency rTMS, intermittent theta burst stimulation, and continuous theta burst stimulation. The frequency of rTMS ranged from 1.0 Hz to 50.0 Hz.[25,29,31,33] The start time of rTMS treatment varied from five days[42] to 10 years after stroke onset[45] The intervention period varied from 1 day[18,19,21,23,41,44,47-49] to 24 days.[38] There were studies[52-65] that explored the efficacy of rTMS on upper limb function recovery but did not met the eligibility of this meta-analysis, (Table S3 in the supplementary data).

Adverse effects

Twenty-eight of the included 34 studies monitored adverse effects, and 25 studies showed no adverse effects of rTMS. Fregni et al.[20] reported a mild headache in one patient and increased anxiety in another patient after rTMS treatment; Zheng et al.[38]

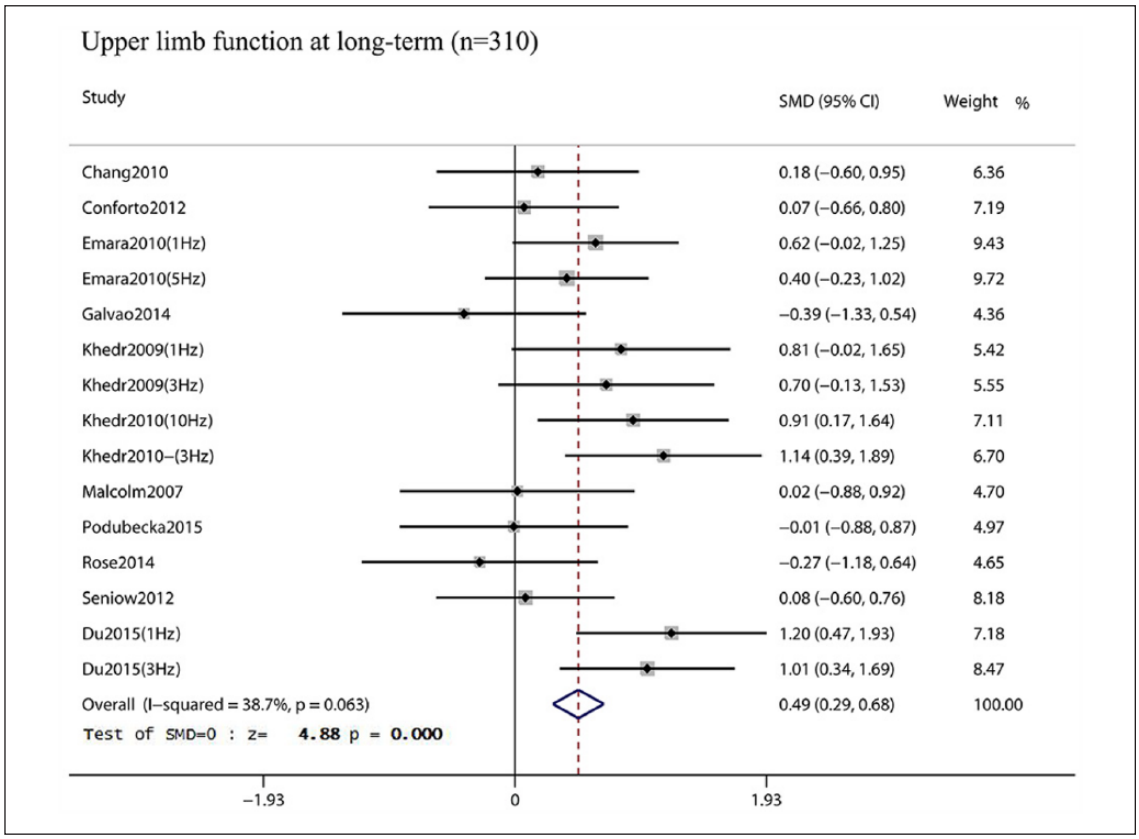

Figure 3. Forest plot from the meta-analysis of rTMS on upper limb function at long-term showing estimates of effect size (Hedges' g) with 95% confidence intervals. Relative weight for each trial is indicated by the size of the corresponding square.

reported a case of abnormal sleep, nausea, nonspecific neck pain, and two cases of dizziness; Du et al.[40] reported 3 cases of transient headache and 1 case of tingling sensation.

Synthesis of results

Short-term effect of motor outcome. The effect of rTMS on manual dexterity was evaluated by pooling post-intervention data from 27 studies involving 669 participants. Upper limb function was measured by the grip force[39,43] movement accuracy[18,23,41,44] keyboard tapping[24,26,48,49,51] pinch and lift force[45,47] and complex hand movements.[19-22,27,28,31,32,34-38,40] The results of pooled data showed a medium significant improvements (SMD, 0.43; 95% CI, 0.30 - 0.56, $P < 0.001$; Figure 2). The Egger's test (P=0.92) showed no significant publication bias and no evidence of heterogeneity in the estimates ($I^2 = 0.0\%$). Sensitivity analysis showed a minimal impact on the results after the removal of the cross-over studies [19,21,41,47–49] and the study with a high risk of bias[51] (Figure S1 in the supplementary data).

Long-term effect of motor outcome. The pooled estimate of the long-term effect size of rTMS on manual dexterity (11 studies and a total of 310 participants) showed medium significant benefit effect of rTMS (SMD, 0.49; 95% CI, 0.29 - 0.68, $P < 0.001$; Figure 3) with a non-significant heterogeneity ($I^2 = 38.7\%$) and low evidence of publication bias (Egger's test, P=0.11).

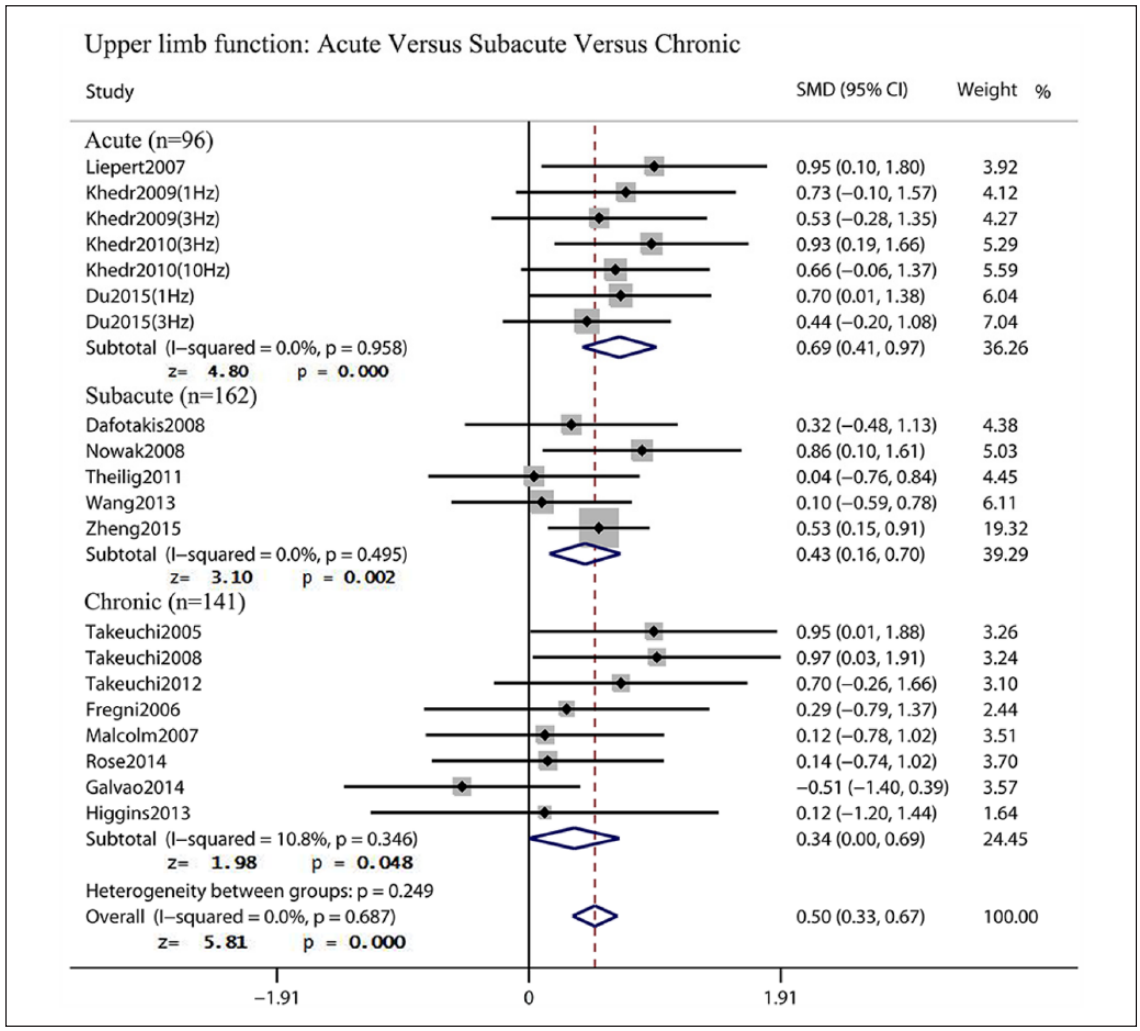

Figure 4. Forest plot from the meta-analysis of rTMS on upper limb function for studies comparing acute phase, subacute phase and chronic phase showing estimates of effect sizes (Hedges' g) with 95% confidence intervals. Relative weight for each trial is indicated by the size of the corresponding square.

Other parameters of motor outcomes. The mean effect size for the acute subgroup was 0.69 (95 % CI, 0.41 - 0.97; $P < 0.001$) and without heterogeneity ($I^2 = 0.0\%$). The mean effect size for subacute stroke was 0.43 (95% CI, 0.16 - 0.70; $P = 0.002$) without evidence of heterogeneity ($I^2 = 0.0$ %). The mean effect size for chronic stroke was 0.34 (95% CI, 0.00 - 0.69; $P = 0.048$) and without significant heterogeneity ($I^2 = 10.8\%$) (Figure 4). In the sensitivity analysis, the acute subgroup maintained the maximal effect of rTMS and the chronic subgroup had a minimal effect of rTMS after the removal of the cross-over studies[21,47,48] (Figure S2 in the supplementary data).

The stimulus frequency subgroup analysis used only the data of the high-frequency rTMS and low-frequency rTMS protocols. Eight studies were pooled for the effect of high-frequency rTMS on manual dexterity, and 23 studies were pooled for the low-frequency rTMS. The high-frequency

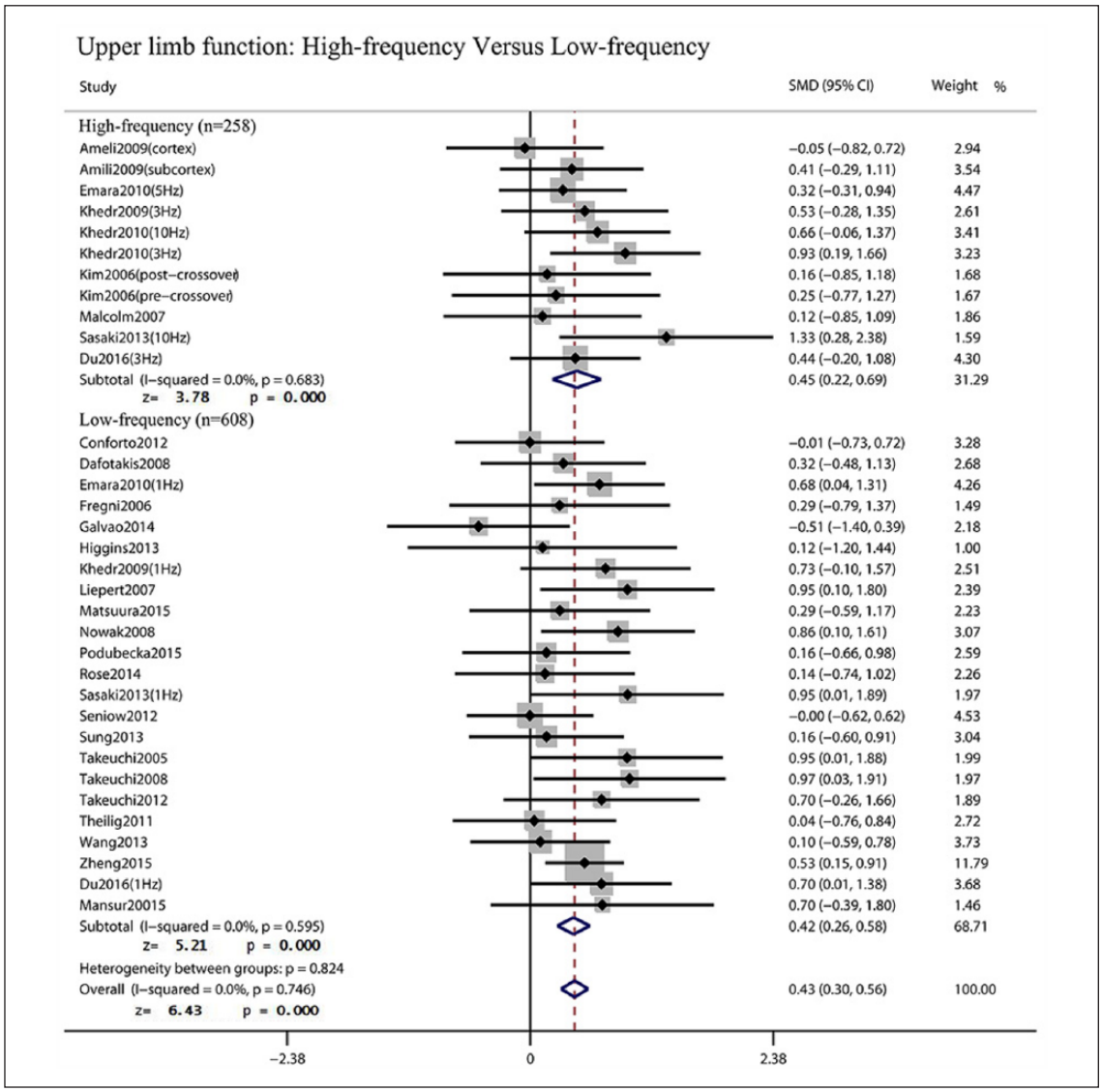

Figure 5. Forest plot from the meta-analysis of rTMS on upper limb function for studies comparing high-frequency and low-frequency rTMS protocol showing estimates of effect sizes (Hedges' g) with 95% confidence intervals. Relative weight for each trial is indicated by the size of the corresponding square.

rTMS subgroup showed the mean effect size of 0.45 (95 % CI, 0.22 - 0.69; $P < 0.001$; $I^2 = 0.0$ %) versus as the 0.42 (95 % CI, 0.26 - 0.58; $P < 0.001$; $I^2 = 0.0$ %) of the low-frequency rTMS subgroup (Figure 5). The sensitivity analysis showed little impact on the results after the removal of the cross-over studies [19,21,41,47-49] and the study with high risk of bias [51] (Figure S3 in the supplementary data).

Similarly, the mean effect size was significant for intermittent theta burst stimulation subgroup at 0.60 (95 % CI, 0.10 - 1.10; $P = 0.018$; $I^2 = 23.8$ %,), but was only at a trend level for continuous theta burst stimulation at 0.35 (95 % CI, -0.11 to 0.81; $P = 0.138$; $I^2 = 0.0$ %). The overall Egger's test (P=0.014) showed a significant publication bias (Figure 6).

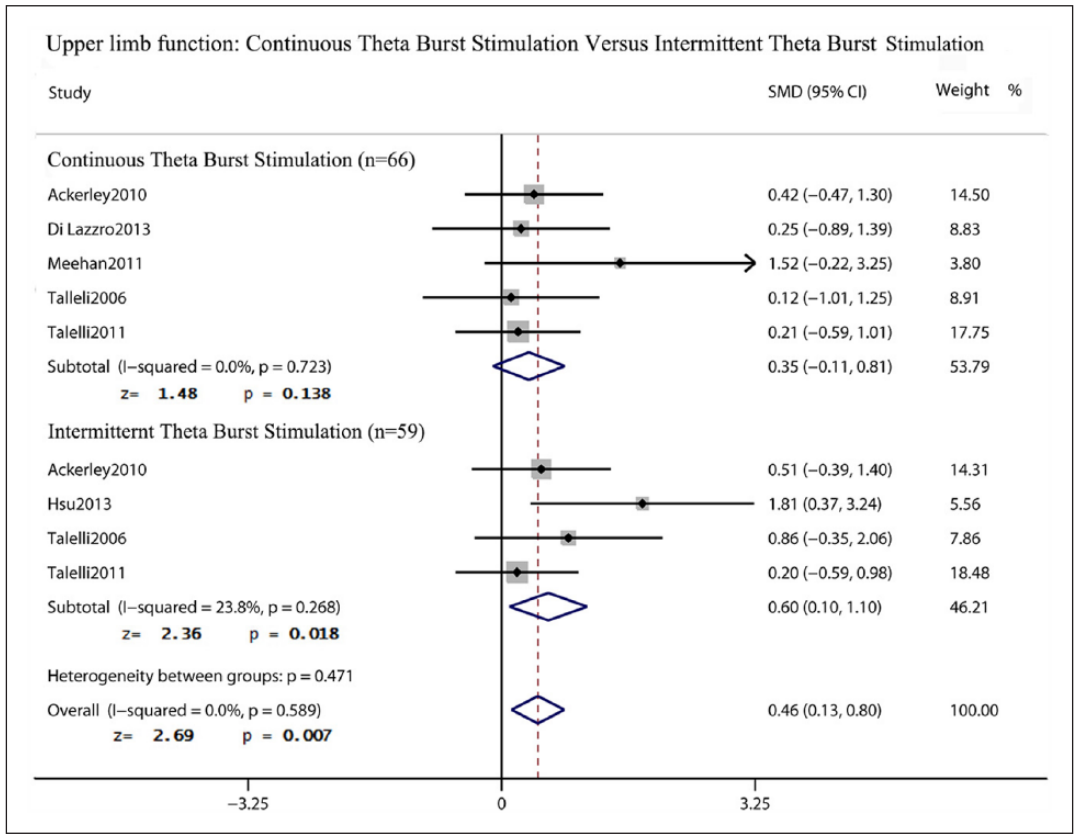

Figure 6. Forest plot from the meta-analysis of rTMS on upper limb function for studies comparing intermittent theta burst stimulation and continuous theta burst stimulation rTMS protocol showing estimates of effect sizes (Hedges' g) with 95% confidence intervals. Relative weight for each trial is indicated by the size of the corresponding square. intermittent theta burst stimulation, intermittent theta burst stimulation; continuous theta burst stimulation, continuous theta burst stimulation.

The pooled effect size for the subcortical subgroup was 0.66 (95 % CI, 0.36 - 0.95; $P < 0.001$) and without heterogeneity ($I^2 = 0.0\%$). The mean effect size for nonspecified subgroup was 0.39 (95% CI, 0.24 - 0.54; $P < 0.001$) without heterogeneity ($I^2 = 0.0\%$) (Figure 7). Sensitivity analysis showed minimal impact on the results after the removal of the cross-over studies [19,21,41,47-49] and the study with high risk of bias[51] (Figure S4 in the supplementary data).

Twenty-five studies were divided into four subgroups based on the numbers of session of the treatment: 1 session, 5 sessions, 10 sessions, and 15 - 16 sessions, with the mean effect sizes as follows: 0.55 (95 % CI, 0.29 - 0.81; $P < 0.001$; $I^2 = 0.0$ %) for 1 session; 0.67 (95 % CI, 0.41 - 0.92; $P < 0.001$; $I^2 = 0.0$ %) for 5 sessions; 0.20 (95 % CI, -0.06 - 0.41; $P = 0.13$; $I^2 = 0.0$ %) for 10 sessions; and 0.08 (95 % CI, -0.36 - 0.51; $P = 0.73$; $I^2 = 0.0$ %) for 15-16 sessions. (Figure 8), respectively.

Discussion

Enhancing stroke recovery by facilitating brain plasticity with the direct application of rTMS to the cerebral cortex is a relatively new area of investigation in rehabilitation and neuroscience. Some previous studies showed that rTMS could enhance upper limb function.[4,10,11] However, most of them had focused on the short-term beneficial effects of

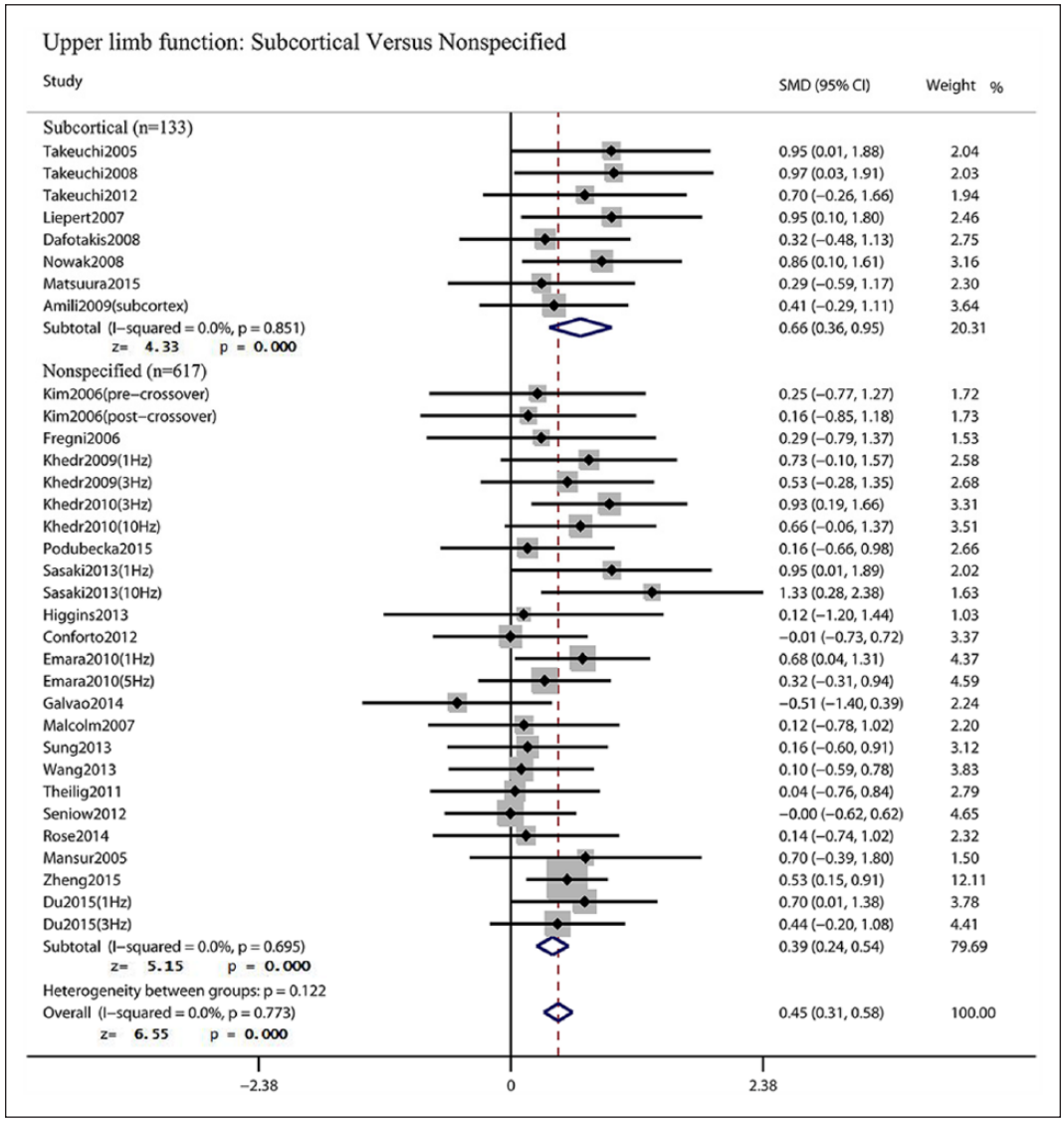

Figure 7. Forest plot from the meta-analysis of rTMS on upper limb function for studies comparing subcortical and nonspecified stroke showing estimates of effect sizes (Hedges' g) with 95% confidence intervals. Relative weight for each trial is indicated by the size of the corresponding square.

rTMS on motor function after stroke or on the mixed confounding effects of immediate and follow-up data collected after rTMS therapy.

To our knowledge, the ability of rTMS to increase the excitability of the affected hemisphere after stroke is based on the fundamental law of electromagnetic physics.[66,67] So far it is not clearly if rTMS can induce a long lasting improvement of motor function after such a short treatment duration or if the effects will disappear along with the end of the intervention course. The previous reviews have not estimated the long-lasting beneficial effects of rTMS on motor function, an essential measurement for a successful treatment. Until now

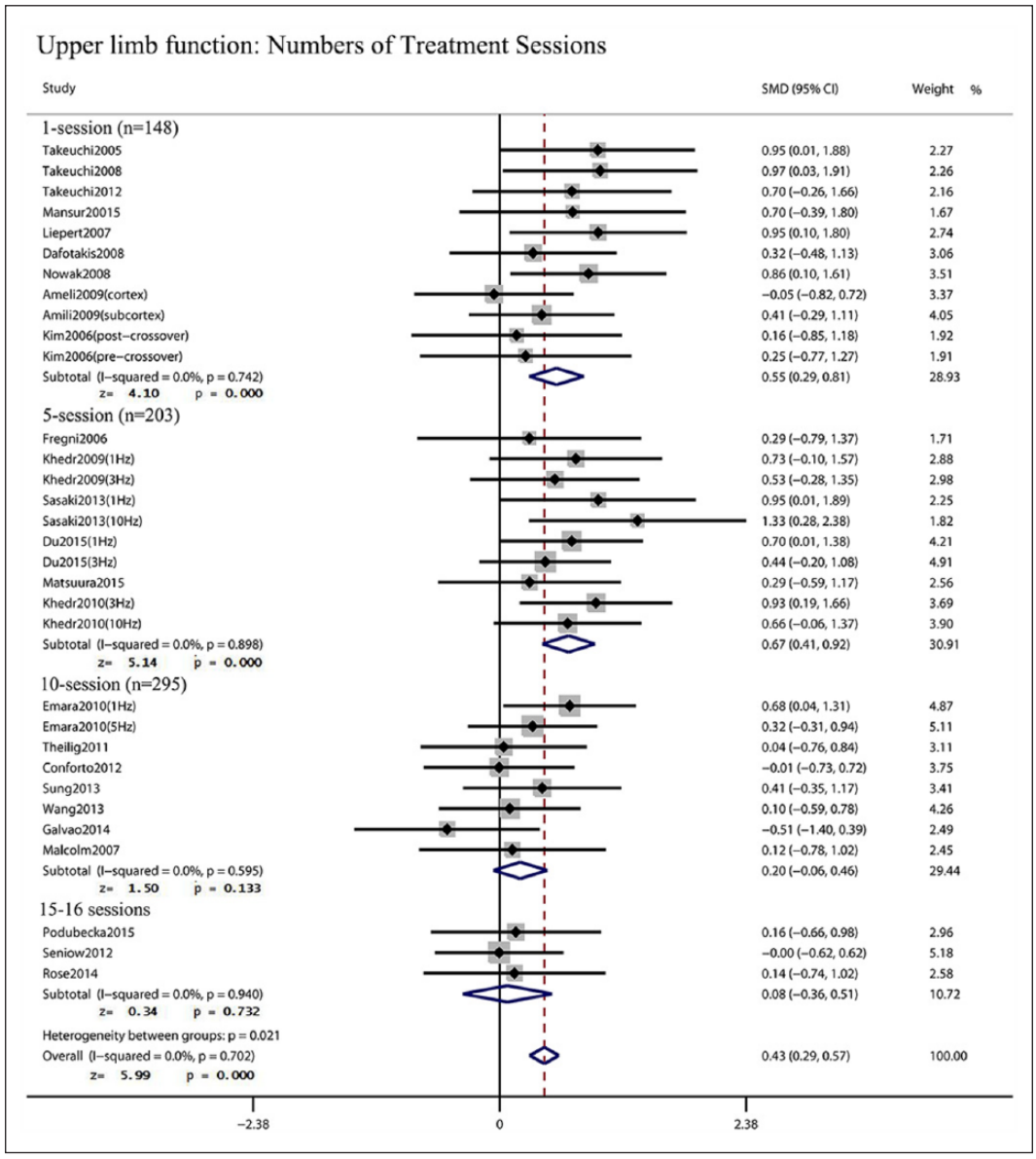

Figure 8. Forest plot from the meta-analysis of rTMS on upper limb function for studies comparing different sessions of rTMS protocol showing estimates of effect sizes (Hedges' g) with 95% confidence intervals. Relative weight for each trial is indicated by the size of the corresponding square.

the long-term effects of rTMS remain unknown. The long-term effects of rTMS were estimated by a previous study when the follow-up was conducted at or after one month from the last session of rTMS.[14] This current analysis gained similar results of short- and long-terms effect, that support a long-time-lasting effect of rTMS on the upper limb function recovery of stroke patients. Evidence from animal studies suggested that cortical stimulation can alter intracortical inhibitory circuits and

facilitate long-lasting potentiation and cortical remodeling.[68] This finding is agreement with our analysis of human stroke.

It is noted that the duration of rTMS application often varied from one day to more than ten days and the frequency of rTMS varied from 1 Hz to 10 Hz (detailed in Table S2 in the supplementary data) that could have potentially influenced the outcomes. As all long-term outcome data were extracted from the same studies that also examined the short-term outcomes, the protocol parameters used for both the long- and sort-term outcomes were the same, and the differences in the results would be due to the different treatment parameters rather than experimental errors.

Wahl et al[69] suggested the presence of critical time windows during which the brain was most responsive to the application of training-dependent plasticity. Nishibe et al.[70] suggested that motor training in the early phase of stroke can help shape the evolving neural network. For rTMS, there may be an optimal time windows for motor recovery too. To investigate this, a subgroup analysis for the effects of rTMS on different phase of stroke was performed by one previous study[4] published four years ago. Combined with the previously published studies, we now show a more robust result.

According to our analysis, the timing-dependent effectiveness of rTMS applied after stroke appeared to show the following descending order: the acute phase > the subacute phase and > the chronic phase. Hara et al.[68] reported that although stroke patients could benefit from rTMS administered in each phase of stroke, patients at acute phase obtained more beneficial effects. This is probably due in part to a temporal dynamics of corticomuscular interactions in post-stroke recovery. i.e. the changes of corticomuscular interaction were more obvious in the acute than in the chronic stage of stroke.[68] It was also considered that no matter how significant improvement was gained in the amplitudes of movements or the rebalance of neural activity during the first three months, stable states were often reached in the chronic stage of stroke recovery (six months after stroke).[4,71–73] Thus, the efficacy of rTMS-modulated rebalance of the neural excitability between the affected and unaffected hemispheres declines as the post-stroke time interval increases. To maximize the potential of rTMS-activated neural plasticity, and structural organization, our results and others [43] suggest that stroke patients would benefit more if rTMS is administered as early as phase practically possible during stroke recovery.

The frequency of pulses is an important factor influencing the effect of rTMS. One previous meta-analysis [4] showed that the motor improvement was more pronounced in studies that applied low-frequency rTMS to the unaffected hemisphere. Another study demonstrated a stronger beneficial effect of low-frequency rTMS on upper limb motor recovery than high-frequency rTMS.[24] Our subgroup analyses of this systematic review showed similar results: low-frequency rTMS to the unaffected hemisphere induced more functional recovery than high-frequency rTMS to the affected hemisphere. It is noted however, that one study[51] reported that high-frequency rTMS to the affected hemisphere was more effective for upper limb hemiparesis in the early phase of stroke, but not in the late phase of stroke. Nevertheless, we could not perform the subgroup analyses of the effects of high- versus low-frequency rTMS based on different stroke phases because the current data are very limited. Future studies should compare the effects of high- and low-frequency rTMS on motor recovery under different phases of stroke recovery when data are available.

Talelli et al.[46] reported that continuous theta burst stimulation suppressed excitability in the unaffected hemisphere but did not improve paretic hand motor function whereas intermittent theta burst stimulation enhanced motor behavior. Ackerley et al.[25] reported enhanced excitability of the ipsilesional hemisphere induced by intermittent theta burst stimulation but decreased excitability and deteriorated motor function induced by continuous theta burst stimulation. Our analysis of the intermittent theta burst stimulation versus continuous theta burst stimulation subgroups showed a significant difference between the two forms of rTMS but a significant publication bias in Egger's test. The publication bias may be due to the limited theta burst stimulation data which convinced Hsu et al.[4] not to perform the theta burst stimulation subgroup analysis. Nevertheless, the

results of Hsu et al.[4] and ours both suggested a beneficial effect of intermittent theta burst stimulation for motor recovery rather than continuous theta burst stimulation.

Improved manual dexterity after rTMS treatment has been frequently reported in stroke patients. However, it is not clear if rTMS stimulates cortical excitability in course-dependent manner or patients will gain greater functional recovery following more treatment sessions. Our subgroup analysis suggests a session number-dependent effect of rTMS on the manual dexterity recovery after stroke. While a single session rTMS was beneficial and effective in promoting the motor functional recovery, increasing the session number to 5 produced the most beneficial effects. More than 5 sessions of rTMS, however, did not produce additional improvements in motor function recovery. In fact, the therapeutic effect of rTMS treatment fell rapidly after more than 10 sessions (15 to 16 sessions). This phenomenon is thought to be related to the time adherence of rTMS.[44] Similar observations have been reported in a rTMS study of pain,[74] and in a study of tDCS modulated cortical excitability and plasticity and motor functional recovery after stroke.[75] Lindenberg et al.[75] also reported that after the initial 5 days of tDCS intervention of chronic stroke patients, the more sessions of tDCS, the less effective over the time. The underlying mechanism remains unclear.

To our knowledge, there was only one previous study[49] examined the different effects of rTMS on subcortical and cortical lesions of stroke. Ameli et al.[49] found that rTMS significantly improved motor recovery in stroke patients with subcortical lesions but not in patients with cortical lesions. The subgroup analysis of the lesion site of this systematic review also showed that patients with subcortical stroke benefit more from rTMS than patients with lesions of other sites.

Safety is an important consideration for any clinical intervention. One previous study[76] reported that intermittent theta burst stimulation at a stimulus frequency range of 20.0 Hz to 25.0 Hz with 120 % to 130 % motor threshold (MT) protocol increased the risk of seizure substantially. However, in the included studies of this systematic review, no adverse events of rTMS occurred at 20.0 Hz or 50.0 Hz with 80 % - 90 % MT.[22,50] Moreover, only three of the included studies of this review showed mild adverse events. Although rTMS is generally safe for stroke patients, it should follow the safety guidelines[77] to prevent or minimize the potential risk of side effects.

There are still limitations of the present study. First, six of the included studies were single blind, and six other studies did not report the blind process that could have caused potential bias. Second, the stimulation parameters and outcome measures varied between the selected studies. Third, the selected participants varied in age and other biological characteristics that may have been caused outcome variation. Last, because non-English studies were not included in this systematic review, relevant studies published in other languages may have been missed.

Clinical Messages

- rTMS may induce short-term and long-term therapeutic effect on motor functional recovery in the injured upper limb of stroke patients.
- Both low- or high-frequency rTMS can be safe and effective therapy for stroke.
- Stroke patients may benefit more from intermittent theta burst stimulation than from continuous theta burst stimulation. Compared with cortical stroke, rTMS is more effective for stroke patients with subcortical lesion than patients with lesions of other sites. rTMS administered during early phase could produce better outcome.
- The effect size of rTMS treatment is session number dependent, with the maximal therapeutic effect found after 5 sessions of rTMS treatment.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

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