Repetitive Transcranial Magnetic Stimulation of Primary Motor Cortex for stroke upper limb motor sequelae rehabilitation. A systematic review.

Abstract

Background: Repetitive Transcranial Magnetic Stimulation (rTMS) over the primary motor cortex (M1) has been used to treat stroke motor sequelae regulating cortical excitability. Early interventions are widely recommended, but there is also evidence showing interventions in subacute or chronic phases are still useful.

Objective: To synthetize the evidence of rTMS protocols to improve upper limb motor function in people with subacute and/or chronic stroke.

Methods: Four databases were searched in July 2022. Clinical trials investigating the effectiveness of different rTMS protocols on upper limb motor function in subacute or chronic phases post-stroke were included. PRISMA guidelines and PEDro scale were used.

Results: Thirty-two studies representing 1137 participants were included. Positive effects of all types of rTMS protocols on upper limb motor function were found. These effects were heterogeneous and not always clinically relevant or related to neurophysiological changes but produced evident changes if evaluated with functional tests.

Conclusions: rTMS interventions over M1 are effective for improving upper limb motor function in people with subacute and chronic stroke. When rTMS protocols were priming physical rehabilitation better effects were achieved. Studies considering minimal clinical differences and different dosing will help to generalize the use of these protocols in clinical practice.

Keywords: Repetitive Transcranial Magnetic Stimulation; Stroke; Upper limb motor function; Subacute; Chronic; Motor Cortex

Article type: Review.

1. Introduction

According to World Health Organization, 15 million people suffer from stroke each year, which is also the leading cause of adult disability worldwide (Katan & Luft, 2018). Stroke modifies the functioning of several neurological areas. The most common and the one that causes the main limitations in basic activities of daily life is the motor domain (Hankey et al., 2002). Total recovery of motor function occurs in less than 40% of survivors, despite rehabilitation programs (Hummel & Cohen, 2006).

Brain plasticity plays an important role in the recovery of lost functions in the brain and is achieved through the reorganization of networks (Carino-Escobar et al., 2019; Dromerick et al., 2021; Hordacre et al., 2021). Although there is evidence that brain plasticity still operates at 4 months from stroke (Cicinelli et al., 1997) more than 60% of subjects with hand function impairment will not reach sufficient functional levels to be independent in their Basic Activities of Daily Living after 6 months (Dobkin, 2004).

Cortical excitability diminishes after a stroke in the lesioned hemisphere (Pennisi et al., 1999), reflected by the decrease of motor-evoked potentials (MEPs) in response to transcranial magnetic stimulation (TMS). Additionally, decreased cortical excitability after stroke produces changes in movement kinematics (Ameli et al., 2009), which in turn alter upper limb motor function. Cortical excitability can be measured by determining the intensity required of a single TMS pulse applied to the primary motor cortex (M1) to evoke a motor response. This neurophysiological measure has been interpreted as a prognostic factor of upper limb functional recovery (Bembenek et al., 2012). Under normal conditions, both motor cortices are reciprocally inhibited via cortico-cortical interhemispheric connections in order to avoid mirror movements (Duque et al., 2005). Based on this mechanism, after stroke, the contralesional M1 becomes uninhibited and exerts an exaggerated inhibition on the M1 of the affected hemisphere (Nowak et al., 2009; Ward et al., 2004), impairing motor recovery of the injured cortex due to an interhemispheric communication breakdown (Assenza et al., 2013).

In recent years, several non-invasive neuromodulation techniques have been shown to be effective to enhance brain plasticity and stroke recovery. Among these interventions, repetitive TMS (rTMS) is a technique that involves repetitive pulses of magnetic stimulation applied focally in a particular brain area at a specific frequency (Kobayashi & Pascual-Leone, 2003). Frequencies of rTMS equal to or less than 1 Hz provoke an inhibitory effect, while higher frequencies can increase cortical excitability and cause facilitation (Rossi et al., 2009). Cortical excitability can be modulated through rTMS, inducing synaptic plasticity, decreasing maladaptive mechanisms and inducing normal physiological activity (Xiang et al., 2019), what might underly positive clinical effects according to recent evidence-based guideline (Lefaucheur et al., 2020). according to the interhemispheric competition model (Hendricks et al., 2002; Xiang et al., 2019).

Although promising results have been reported from the use of rTMS in upper limb motor rehabilitation after stroke, standardized protocols have not been widely validated, and most of the protocols are applied in early stages post stroke (<6 months) (G. Chen et al., 2022; Lefaucheur et al., 2020). In the last years, its interest has increased by combining it with conventional rehabilitation programs, mirror therapy (T. Kim et al., 2016) or motor training (Kwon et al., 2014). In fact, combining rTMS protocols with other neurorehabilitation therapies might target different mechanisms and might be desirable to potentiate homeostatic metaplasticity, creating a synergistic effect. The synergistic effects that occur might vary depending on the type of application and dose of rTMS, as well as rehabilitation dosage and content(Takeuchi & Izumi, 2015).

Early post stroke rehabilitation studies suggest the existence of a period of high plasticity in which the patient seems to be more responsive to treatment, nevertheless patients with persisting deficits in subacute (3-6 months) and chronic (>6 months) stages continue rehabilitation, and their therapists look for adjuvant therapies to optimize results. There is scarce information about the effects of rTMS neuromodulation on upper limb motor function during subacute and chronic stages.

The aim of this review is to synthetize the available evidence on the effects of rTMS on enhancing upper limb motor function in subacute and chronic stages after stroke. The updated information on the treatment strategies and results will provide an entry point for new studies that seek unified protocols that can be applied clinically to impact the recovery process of subacute and chronic stroke upper limb motor sequelae.

2. Methods

This review followed the PRISMA 2020 guidelines (Page et al., 2021) and was prospectively preregistered on the Open Science Framework (https://osf.io/bnqd7/).

2.1. Identification: Search Strategy and Sources

Four electronic databases were searched: Web of Science, PubMed, Scopus and PEDro. Citation tracking from eligible articles was carried out manually. The search was performed on July 13th, 2022.

Search terms were variations on three concepts: rTMS, upper limb motor function and stroke. Search strings varied slightly depending on the MeSH terms within each database. The following terms were selected: (rTMS OR "repetitive transcranial magnetic stimulation" OR “Theta Burst”) AND (stroke OR "cerebrovascular accident" OR CVA) AND “motor cortex” AND (upper limb or hand) with no time limits.

2.2. Eligibility criteria and Selection

The eligibility criteria were as follows. Inclusion criteria: (1) peer-reviewed article, (2) written in English, French or Spanish, (3) clinical trial design (including parallel and crossover trials), (4) intervention with rTMS on M1, of any type (unilateral/bilateral, high/low frequency, theta burst), (5) participants who had suffered an ischemic or hemorrhagic stroke and were in the subacute (3-6 months) or chronic (>6 months) recovery periods and (6) upper limb motor function outcomes provided. Exclusion criteria: (1) protocols for randomized trials, pilot, or observational studies, (2) other non-invasive (transcranial direct current stimulation) and invasive (epidural electrical stimulation) brain stimulation interventions, (3) studies investigating animal models of stroke or pediatric stroke, (4) upper limb outcome measure not provided.

After removing duplicates, search results were double screened on title and abstract by two authors (F.S.C and J.P.R). Proceedings, conference articles, book chapters, posters and editorials were excluded before full text screening. Any disagreement was resolved through consensus and if it was not reached, a third author (Y.G.Z) had the deciding vote.

2.3. Data Extraction and Analysis

Once the selection criteria were applied, full-text articles were screened to collect information for each study based on a data extraction table developed in Microsoft Excel. This table covered information about study characteristics (year of publication, design, purpose, presence of a control group), sample size, participant characteristics (age, gender, type of stroke (ischemic or hemorrhagic), lesion location (cortical or subcortical) and evolution phase (subacute or chronic)), intervention dosage (total number of sessions and frequency (sessions per week)), rTMS parameters (frequency (in Hz), intensity (percentage of the action/resting motor thresholds) and number of total pulses), outcome measures of upper limb motor function and main findings.

2.4 Methodological quality assessment

The PEDro scale was used (Maher et al., 2003; Sherrington et al., 2000). It comprises 11 items whose purpose is to quickly identify which clinical trials may have sufficient internal validity and enough statistical information to make their results interpretable. Each item is rated as 1 point (criterion fulfilled) or 0 points (criterion not fulfilled) and therefore higher scores imply greater methodological quality. The first item of the scale (source of participants and selection criteria) is not given a numeric value and thus the instrument provides scores between 0-10 points.

Each article was assessed by 2 independent evaluators (F.S.C. and Y.G.Z.). To measure the consensus between both raters the kappa value (k) was calculated, and interpreted as high, moderate and low level of agreement when k was >0.7, 0.5-0.7 and <0.5, respectively.

3. Results

3.1. Study selection

The PRISMA diagram (Figure 1) reflects the flow of information. Initially, the searches yielded 1164 results, 559 of which were duplicates, and thus, were eliminated. The remaining 605 records were screened on titles and abstracts. After this step, 504 records were removed, leaving a total of 101 full texts that were screened for eligibility. Of these, 69 articles were excluded (see Figure 1). A total of 32 articles met the selection criteria and were finally included.

3.2. Study characteristics

The review included 32 studies, 24 with parallel group design and 8 with crossover design. Thirty studies randomly allocated participants to interventions and 2 did not. Twenty-nine studies presented a control group and 3 did not (Table 1).

3.3. Participant characteristics

A total sample of 1137 participants (711 men, mean age = 59.5 ± 10.4 years) were included. They represent the reality of the sociodemographic characteristics of people with stroke. Twenty-three studies included participants with ischemic and hemorrhagic stroke, and 9 studies included only people with ischemic stroke. Twenty-seven studies enrolled participants who had suffered a cortical or subcortical lesion, and 5 studies included only people with subcortical lesions. Twenty-six studies enrolled participants in the chronic stage and 6 in the subacute phase.

3.4. rTMS and control interventions

3.4.1. rTMS interventions

In terms of stimulation frequency, 73% of the studies used low-frequency rTMS on the contralateral M1 compared to 16% of them, which used high-frequency rTMS applied to the ipsilateral M1(Cho et al., 2017; Haghighi et al., 2021; T. Kim et al., 2016; Kwon et al., 2014; Malcolm et al., 2007). Only 20% of the studies used intermittent TBS to stimulate the ipsilateral M1 (Ackerley et al., 2010; Y.-H. Chen et al., 2021; Sung et al., 2013; Talelli et al., 2012; Wang et al., 2014; J. J. Zhang et al., 2022) (Table 2). The most common frequencies used were 1 Hz for low frequency, inhibitory rTMS, and 10 Hz for high-frequency, facilitatory protocols. The number of total pulses varied between 160 and 2400. Fifteen studies used more than 1000 pulses. Regarding the stimulation threshold, just three studies used 100% of the resting motor threshold (Demirtas-Tatlidede et al., 2015; Fregni et al., 2006; Rose et al., 2014) and the rest used 90-80%.

3.4.2. Control interventions

Twenty-one studies used sham TMS as the control intervention. Five trials used conventional rehabilitation and one study used audiotape, a tape-guided relaxation program with soothing music. Two studies used rTMS as control intervention, when comparing to rTMS plus adjuvant therapy and one study utilized unilateral application with rTMS. Two studies did not present a control group.

3.5. Outcome measures

All the studies focused their evaluation on arm/hand motor function through scales or instrumental evaluation. Besides, spasticity, cognition, and/or neurophysiological variables were also assessed. Evaluation metrics were highly heterogeneous between studies. All studies performed assessments before and after treatment.

Motor function evaluation was carried out using diverse metrics. We categorized them according to the constructs they assess. General upper limb motor function was assessed with the Fugl-Meyer Assessment (FMA) in 15 studies, the Wolf Motor Function Test (WMFT) in 9 studies and the Motor Activity Log (MAL) in 5 studies. Two studies assessed upper limb strength with the Medical Research Council (MRC) scale. Gross manual dexterity was assessed by the Box and Blocks Test (BBT) in 7 studies. Fine manual dexterity was assessed by the Nine Hole Peg Test (NHPT) in 12 studies, by the Action Research Arm Test (ARAT) in 7 studies, by the Purdue Pegboard Test (PPT) in 3 studies and by the Jebsen Taylor Hand Function Test (JHFT) in 3 studies.

Regarding spasticity, its presence and intensity were assessed only in 9 studies and always using the Modified Ashworth Scale (MAS). Finally, instrumental measures were performed by 5 studies that assessed handgrip strength with dynamometry, and 7 studies that assessed pinch strength with a pinchmeter.

Regarding neurophysiological measures to detect changes in cortical excitability, TMS based measures using different stimulation models and coils were utilized in 16 studies. Among the metrics used were interhemispheric inhibition (IHI), intracortical inhibition (ICI), short interval intracortical inhibition (SICI), intracortical facilitation (ICF), ipsilateral silent period (ISP), cortical silence period (CSP) and motor evoked potential (MEP).

3.6. Effectiveness of rTMS on upper limb motor sequelae

Comparison 1: active rTMS vs sham rTMS. Active rTMS groups presented significant improvements in FMA-UE, ARAT, STEF, NHPT, WMFT, MAL, BBT, JHFT, movement accuracy, movement time, movement acceleration, pinch force, and hand grip. Only 5 studies did not find significant differences between groups (Harvey et al., 2018; Rose et al., 2014; Talelli et al., 2012; Tretriluxana et al., 2013).

Comparison 2: rTMS vs conventional rehabilitation. rTMS groups presented significant improvements in FMA-UE, FMA-TT, WMFT, MAS, MAL, SIS, BBT, grip and pinch strength, Modified Barthel Index (MBI), Functional Independence Measure (FIM), FAS, MMSE and reaction time. Only one study did not find significant differences with respect to the control intervention (Kwon et al., 2014). Regarding the rest of the control groups, those who used rTMS without any other adjuvant therapy or audiotape, a tape-guided relaxation program with soothing music, found significant improvement in the experimental group according to FMA, WMFT, BBT and MBI.

Comparison 3: high-frequency rTMS vs low-frequency rTMS. Significant improvements in favor of the contralateral application with low-frequency stimulation, compared to the ipsilateral application with high-frequency, was found for FMA-UE, grip strength, MAS, NHPT, BBT, WMFT, and SIS.

Comparison 4: unilateral rTMS vs bilateral rTMS. Experimental groups presented significant improvements in favor of bilateral protocols not only in acceleration and pinch force (Takeuchi et al., 2009) but also in MRC, FMA-UE, WMFT, and reaction times (Sung et al., 2013)

Comparison 5: active TBS vs sham TBS. Stimulation with active TBS was significantly more effective than sham TBS according to FMA-UE, MAS, MAL, ARAT and SIS, except in one study (Talelli et al., 2012).

3.7. Methodological quality

The included studies had a mean PEDro score of 7.09 ± 1.97 (F.S.C) and 7.22 ± 1.80 (Y.G.Z) points. Figure 2 represents the distribution of total scores of each article according to both reviewers. Moderate agreement was found between raters according to the kappa value (k = 0.61). The values show good general methodological quality of the sample of included studies. Inclusion of a control group as well as double-blind and/or randomized designs correlated with higher PEDro scores.

4. Discussion

This review systematically analyzed the evidence from clinical trials published to date to determine the effectiveness of rTMS on upper limb motor function in subacute and chronic stages after stroke. The findings indicate that there is evidence that supports its routine use in clinical practice. In the variables included in our review, regardless of the time of treatment initiation, rTMS seems to have a positive effect on the functionality of the upper limb when evaluated with functional tests. This is consistent with literature data showing beneficial effects of rTMS in the acute phase of evolution (G. Chen et al., 2022).

Recent systematic reviews with meta-analyses (G. Chen et al., 2022) have proven the effectiveness of rTMS on general upper limb motor function measured with the FMA-EU. However, its effects on other motor function domains such as strength, dexterity or muscle tone have been previously overlooked. In this review, we synthesize evidence that suggests that rTMS might be effective on these constructs, which contribute to the performance of activities of daily living. Furthermore, we also synthesize evidence on the neurophysiological correlates of these functional improvements through the collection of cortical excitability measures., which is one of the strengths of this review.

Thirty-two studies matching our inclusion criteria were included in this review, published between 2005 and 2022. Most of them (n=19) had good methodological quality according to PEDro score (≥7), which guarantees the validity of the conclusions extracted. However, there was large heterogeneity among the included studies regarding sample size, brain lesion topography and stroke type. Some studies had very limited sample sizes (n=3) and most of them did not include more than 50 patients. Only one study included 240 individuals. Furthermore, there was consistent underreporting of sample size calculations, which may have introduced statistical biases. Although cortical and subcortical topography of the lesions and their size might determine the effect of the stimulation (Ameli et al., 2009), most of the studies made no difference between patients with different etiologies or topography of stroke. Nine studies only included people with ischemic stroke, but their results were not significantly different from those including hemorrhagic stroke.

Our review identified a greater number of low-frequency protocols applied over the contralesional hemisphere compared to interventions with high-frequency stimulation over the affected hemisphere (21 vs. 5). Nonetheless, there is controversy on the relative effectiveness of these interventions and whether one is superior to the other in terms of their clinical effects on upper limb motor function. The present review is in accordance with previous meta-analyses suggesting more robust effects of low-frequency rTMS in comparison to high-frequency stimulation in chronic stroke (G. Chen et al., 2022), although these findings are far from definite. Moreover, there is emerging evidence that low-frequency stimulation over the unaffected hemisphere might concomitantly disrupt ipsilateral motor commands, and in consequence, might impair non-paretic upper limb function, deteriorating bimanual coordination and trunk control (Takeuchi & Izumi, 2012). Although these findings are preliminary and should be confirmed in large scale clinical trials, researchers and clinicians should be aware of the possible adverse effects of this type of rTMS. Much more high-quality research should be done to confirm these results and develop evidence-based recommendations which fairly consider the strengths and weaknesses of unilateral rTMS interventions.

There is currently contradictory evidence regarding the superiority of bilateral protocols combining low-frequency and high-frequency rTMS interventions in comparison to their isolated use. We found that bilateral stimulation was superior to unilateral rTMS, but recent meta-analyses did not. According to the studies included in our review, bilateral rTMS was more effective than unilateral stimulation in acceleration and pinch force, as well as MRC, FMA-UE, WMFT and reaction times. There is therefore incipient evidence that bilateral protocols are also effective in improving some upper limb motor sequelae in the chronic stage after stroke. However, due to the small number of trials that undertook bilateral application, more research should be done on the study of its effects in comparison with unilateral protocols.

Besides safety guidelines (W.-S. Kim & Paik, 2020), there are no consensus recommendations on the most effective dosing (intensity, number of pulses, or sessions) that should be used for stroke rehabilitation. This directly contrasts with rTMS applications for depression and chronic pain, which have recommendations based on a high level of evidence that inform about the site of stimulation and the type of frequency to use. However, it seems that the safety of rTMS interventions is consolidated, as none of the included studies (unilateral or bilateral) reported severe adverse effects like seizures, although it should be noted that safety assessment was not their primary aim.

With respect to the number of sessions, previous studies suggest that five sessions of rTMS have more beneficial effects on the function of the upper extremities compared to a single session or more than 10 sessions (L. Zhang et al., 2017). Our analysis showed that the most common protocol used 10 sessions (13 studies) distributed in two weeks. Notwithstanding, there is evidence suggesting that there are beneficial effects on functional and physiological outcome measures even when only one session was delivered (Ackerley et al., 2010; Bashir et al., 2016; Carey et al., 2014; Y.-H. Kim et al., 2006; Kwon et al., 2014; Mansur et al., 2005; Takeuchi et al., 2008; Tretriluxana et al., 2013). No security concerns were given to justify the low number of sessions. On the other hand, there is no certainty of the real duration of the effects of rTMS protocols in stroke as there is no long-term follow-up (>3 months) or the effect of repetition of the protocol was evaluated.

Most people with stroke receive physical therapy as the basis of their rehabilitation. Thirteen studies included muscle activation or physical therapy alongside rTMS treatment and showed that better outcomes were observed when physical activation was performed during (Etoh et al., 2013) or after (Aşkın et al., 2017; Avenanti et al., 2012; Barros Galvão et al., 2014; Harvey et al., 2018; Kuzu et al., 2021; Rose et al., 2014; Takeuchi et al., 2008, 2009; Vongvaivanichakul et al., 2014; Wang et al., 2014; Yamada et al., 2022; J. J. Zhang et al., 2022) rTMS with limited effects when performed before neuromodulation (Avenanti et al., 2012). Nonetheless, one study (J. J. Zhang et al., 2022) used robot-assisted rehabilitation with and without iTBS priming showing more efficacy of the primed protocol and two studies tested successfully the effect of 6 Hz priming before 1 Hz inhibition (Carey et al., 2014; Cassidy et al., 2015). All these priming approaches may cause better outcomes due to the combination of different complementary neurophysiological mechanisms. This has led to justifying different combinations of non-invasive brain stimulation techniques (Lang et al., 2004) or pairing cortical neuromodulation with subsequent motor learning (Jung & Ziemann, 2009). In the case of physical activity priming, fatigue may be a factor inhibiting cortical excitability (Sharples et al., 2016) and thus impairing the proper activation by subsequent rTMS with poor clinical results when compared to rTMS priming.

The lack of homogeneity regarding outcome measures of upper limb motor recovery makes difficult to comprehensively compare between different rTMS protocols. Aside from the effect on general upper limb motor function measured with the FMA, our review also found positive effects on other specific domains that contribute to the overall function. MAS was used to evaluate spasticity in nine studies, although only five showed a positive effect (Aşkın et al., 2017; Barros Galvão et al., 2014; Y.-H. Chen et al., 2021; Du et al., 2022; Kuzu et al., 2021).

In fact, this review found that rTMS not only improves functional measures related to the affected upper limb, but generalized improvements were also evidenced (Aşkın et al., 2017; Avenanti et al., 2012; Barros Galvão et al., 2014; Fregni et al., 2006; Hirakawa et al., 2018; Vongvaivanichakul et al., 2014; Wang et al., 2014), as handgrip strength (Demirtas-Tatlidede et al., 2015), as well as acceleration and pinch force improvements (Takeuchi et al., 2008, 2009). These might involve wider neural networks as cerebellar motor control and processing speed (Shaughnessy et al., 2020; Ward et al., 2007). Furthermore, some studies suggested that there may be an association between cortical neurophysiological variables (i.e. resting motor threshold reduction, changes in MEP amplitude) and improved function in the affected upper limb after stroke (Di Lazzaro et al., 2008; Yozbatiran et al., 2009). Nevertheless, The neurophysiologic evaluation of interhemispheric inhibition and cortical excitability measures (IHI, SICI, ICF, CSP, RMT and MEP) in most of the included studies, wereas not related to clinical effects in most of the included studies nor the other way around. Only three studies demonstrated significant changes in neurophysiological metrics and significant clinical and functional improvements. This is the case of group A of Cassidy et al., where significant differences were found in ipsilesional CSP duration (p=0.012) and SICI from baseline (p=0.047) (Cassidy et al., 2015), protocol C from Takeuchi et al., where there were significant changes in MEPs amplitude (contralesional p=0.018, ipsilesional p=0.015) and ICI (p=0.032) (Takeuchi et al., 2009) and finally Avenanti et al., who found that ISP and RMT changed significantly in both rTMS groups (Avenanti et al., 2012). Although cortical excitability measures have been correlated with motor performance after stroke (Huynh et al., 2016), it seems that clinical improvement is not always related to measurable neurophysiological changes with the selected metrics, preventing from identifying causal relationships between them. This highlights that, at present, the underlying neural mechanisms of stroke recovery are still poorly understood and multiple hypotheses might provide insight into the neuroplastic changes mediating behavioral improvements observed after traditional rehabilitation and non-invasive neuromodulation interventions.

Although cognitive effects were not the main objective of any of the included studies, cognitive variables were included in six studies, and three of them presented significant improvements according to the MiniMental State Examination (MMSE), Simple Reaction Time (sRT) and Choice Reaction Time (cRT) (Aşkın et al., 2017; Bashir et al., 2016; Mansur et al., 2005). The three other studies did not reveal cognitive improvements (Carey et al., 2014; Fregni et al., 2006; Sung et al., 2013).

Limitations

Due to the variation in rTMS procedures (duration, intensity.), outcome measures, control intervention protocols, and duration of follow-up, it was not possible to pool data for quantitative analyses, which is the most important limitation of this review. In addition, the associated costs and or economic benefit of rTMS were not reported in any study, as it was not their main aim. Therefore, there is currently a knowledge gap in terms of cost-effectiveness of rTMS interventions.

5. Conclusions

Based on the results of this systematic review, interventions using rTMS over M1 seem to be effective for improving upper limb motor function in people with subacute and chronic stroke. Different rTMS protocols, including inhibition of the contralesional hemisphere, facilitation of the lesioned hemisphere, and bilateral application through their combination, have proven to be effective to this purpose. This partially confirms the influence of interhemispheric inhibition mechanisms to play a key role in post-stroke functional recoveryProtocols combining conventional rehabilitation approaches with rTMS have been found to be more effective when the stimulation is delivered before motor training programs.

To capture meaningful information on the effectiveness of rTMS, the effects of neuromodulation treatments should be measured with combinations of both instrumental and clinical scales examining improvements on functional outcomes instead of tests measuring specific motor function constructs (e.g., muscle strength or acceleration). Neurophysiological measures are not always correlated with clinical effects. Studies considering minimal clinical differences and guidelines for maximum dosing should be elaborated to generalize the use of these protocols in clinical practice.

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FIGURE CAPTIONS

Figure 1. PRISMA flow diagram illustrating the selection process and flow of information.

Figure 2. Total PEDro score of the included studies assigned by each reviewer.