

Systematic Review and Meta-Analysis

Clinical Efficacy of Repetitive Transcranial Magnetic Stimulation in Recovery of Hand Function Among Stroke Patients: A Scoping Review

Gurav Pooja Ramesh^{ID}, Manju Devi^{ID}, Suresh Mani^{*ID}

Department of Physiotherapy, School of Allied and Healthcare Sciences, Lovely Professional University, Punjab, 144401, India

*Corresponding Author: vemsuresh@gmail.com

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ABSTRACT

Background: Delayed hand function recovery is common after stroke. Repetitive transcranial magnetic stimulation (rTMS) is an emerging non-invasive brain stimulation technique with potential for post-stroke recovery, particularly for hand function, an area with limited research. **Objective:** Therefore, the aim of this scoping review was to ascertain the clinical efficacy of rTMS in the recovery of hand function among stroke patients. **Methods:** A systematic search of PubMed, Cochrane, and ScienceDirect from 2005 to 2023 identified original research on rTMS, stroke, and hand function. The reviewers independently screened articles for eligibility, and data were extracted on rTMS intervention protocols and outcomes. Methodological quality was assessed using PEDro analysis. **Results:** Of 5423 titles screened, 13 studies met the inclusion criteria and were of excellent quality according to PEDro analysis. The studies used varied rTMS intervention parameters, such as frequencies (1 Hz to 20 Hz), stimulus duration (2 sec to 55 sec), numbers of stimuli (10-1000), and variable rest intervals. **Conclusion:** Overall, rTMS has a positive and clinically significant effect on hand function recovery, but its intervention parameters vary widely. Therefore, further research is needed to establish standardized treatment guidelines to determine the long-term effects of rTMS on motor hand function recovery.

Keywords: hand function, hand recovery, non-invasive brain stimulation, post-stroke recovery, repetitive transcranial magnetic stimulation

1. Introduction

Stroke is identified as a major global health concern due to its widespread occurrence and significant impact on disability [1]. Current statistics show that the elderly population aged 60 or above is around 650 million people worldwide; thus, the projections suggest a higher risk of experiencing a stroke [2]. Estimates show that 75% of post-stroke patients suffer from upper limb (UL) functional impairments [3]. This particular problem of UL functional impairment cumulates in causing restrictions while performing functional tasks, daily activities, and causes decreased health-related quality of life [4]. A study thereof reported 50–60% of patients exhibiting a differing amount of motor function limitation, even though traditional physiotherapy rehabilitation programs were undertaken by the patients [5].

Recent advances in the medical management of cases of stroke have improved and increased survival rates substantially [6], and this shines a light on the need for optimal, comprehensive acute and longer-term rehabilitation management for motor and non-motor impairments that contribute to disability directly. Even though spontaneous motor recovery occurs post-stroke at 3 months, approximately 70% of stroke survivors are reported to have restrictions in functional tasks and activities of daily living (ADLs), which is due to motor/sensory deficits, incoordination, and spasticity in chronic stroke cases. During the recovery phase after

stroke, there tends to be an abnormal neuronal activity that causes disruption and disturbances in regular interhemispheric communication, targeting the motor system [7].

In recent years, a vast array of interventions has been introduced for the recovery of post-stroke patients. A wide range of novice alternatives and adjuncts to physiotherapy techniques have also been introduced, such as mental practice and robotics [8]. These newly found intervention strategies aim to manipulate or induce brain plasticity. However, this is a similar aim of repetitive transcranial magnetic stimulation (rTMS), which is a newly emerging non-invasive, neuro-modulatory therapeutic intervention to enhance the functional recovery by modulating neuroplastic processes, restoring the disrupted equilibrium and inter-hemispheric communication [9, 10]. It administers electrical current to modulate cortical neuronal excitability at the stimulation site by applying a series of magnetic stimuli to target specific brain areas. It induces an inhibitory effect on motor excitability within the cortex via low-frequency (LF) stimulation (≤ 1 Hz) and an excitatory effect via high-frequency (HF) stimulation (≥ 5 Hz) on the targeted brain areas [11]. Due to such defining features and qualities, the use of rTMS has increased exponentially as it is seen as one of the potential rehabilitation tools. Clinicians have increasingly turned to repetitive transcranial magnetic stimulation (rTMS) as a rehabilitation option for post-stroke conditions. However, the existing literature on the superiority of combining rTMS with upper limb (UL) training compared to conventional physiotherapy is limited [12]. As hand function recovery poses a significant challenge in neuro-rehabilitation, Intermittent Theta Burst Stimulation (iTBS), a type of rTMS, holds promise for UL function recovery, but conclusive evidence is lacking. The research question of this scoping review is twofold. First, what is the extent of original research reporting evidence of rTMS efficacy on hand function recovery in post-stroke patients? Second, how are these outcomes reported and measured in clinical practice along with quality evidence? Therefore, the aim of this scoping review was to ascertain the clinical efficacy of rTMS in the recovery of hand function among stroke patients.

2. Methods

The scoping review followed the methodological framework outlined by Arksey and O'Malley [13,14], as well as Levac et al., 2010 [15], and its findings were presented in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Review (PRISMA-SCR) guidelines to retain methodological quality of the review [16]. To ensure studies were a true representation of current application of rTMS among post-stroke survivors, we searched the following databases from 2005 to 2023: US National Library of Medicine Database (PubMed), Medical Literature Analysis and Retrieval System Online (MEDLINE), Cochrane Database of Systematic Reviews, and Science Direct database. The reviewer conducted a literature search using relevant keywords and their combinations, such as “(repetitive transcranial magnetic stimulation) OR (rTMS) AND (hand function) AND (rehabilitation)) AND (stroke); (repetitive transcranial magnetic stimulation) OR (rTMS) AND (hand function) AND (rehabilitation)) AND (hemiplegia); (repetitive transcranial magnetic stimulation) OR (rTMS) AND (hand function) AND (rehabilitation)) AND (hemiparesis); (repetitive transcranial magnetic stimulation) OR (rTMS) AND (hand function) OR (spastic hand) AND (rehabilitation)) AND (stroke); (repetitive transcranial magnetic stimulation) OR (rTMS) AND (spastic hand) AND (rehabilitation)) AND (stroke); (non-invasive brain stimulation) AND (rTMS) AND (hand function) AND (rehabilitation) AND (stroke) OR (hemiparesis); (repetitive transcranial magnetic stimulation) OR (rTMS) AND (hand function) AND (rehabilitation) OR (recovery)) AND (stroke)”. Subsequently, articles not containing these keywords were reviewed for their abstracts during the screening process and eliminated if deemed irrelevant.

2.1. Inclusion/exclusion criteria

We included: Population-adult stroke survivors regardless of age and gender. Concept- outcome measures assessing upper limb and hand functions with repetitive transcranial magnetic stimulation (rTMS) (example- Fugl-Meyer Assessment, Box and Block test (BBT), Wolf Motor Function Test (WMFT), Modified Ashworth Scale (MAS), Motor Activity Log (MAL), Nine Hole Pegboard Test, and Range of motion (ROM)). Articles where comparison groups received standard interventions as opposed to rTMS alone or a combination of interventions were also included. Context: original research articles from randomized controlled trials (RCTs) were sought.

Aligned with our research question, we excluded studies that reported lower limb impairments, aphasia, or trunk impairment using rTMS. Case studies, case series, and abstracts from conference proceedings were also excluded. Non-English language studies were not included for pragmatic reasons. One reviewer (GP) screened all titles and abstracts, eliminating obvious exclusions. Full-text citations selected for potential inclusion underwent independent assessment by two reviewers (MD, SM), with a third reviewer (GP)

available to resolve any disagreements.

2.2. Data collection and analysis

Initially, one reviewer (GP) examined all publications and extracted data from the electronic databases. The titles and abstracts of all identified articles were then independently screened by two reviewers (MD and GP) to assess their relevance to the research questions. Any discrepancies between the reviewers were resolved through discussion or by consulting a third reviewer (SM). Data were collected on various study characteristics, including study design, sample size, parameters such as frequency, intensity, and duration, coil type, stimulation site, outcome measures, and their main findings. A narrative synthesis was then undertaken to describe the characteristics and results of the included studies. The overall quality of study reporting was independently assessed by two reviewers (SM, MD) using the PEDro scale.

3. Results and Discussion

We initially identified 5423 potentially eligible citations during screening, of which 13 studies met the inclusion criteria, as outlined in our PRISMA study flow diagram (Figure 1). After meticulously scrutinizing the abstracts and full texts of the studies, 13 articles met the inclusion criteria for this review. The primary reasons for exclusion at the full-text stage were failure to include hand and exclusive focus on other interventions. Moreover, lower limb impairments, aphasia, or trunk impairment using rTMS were also excluded. Table 1 provides an overview of the study characteristics, encompassing ten randomized controlled trials (RCTs) conducted using either parallel or crossover designs. It also includes outcome measures employed and their respective findings. Among them, six studies included rTMS versus sham therapy, and four studies included rTMS versus other conventional therapies. At the same time, the majority of studies encompassed chronic post-stroke patients, with targeted specific hand impairments such as abnormal muscle tone, muscle weakness, muscle atrophy, and motor inabilities. Nearly all studies were published from 2005 ($n=13$), with considerable variation in stimulation sites and sample size (median 22, IQR 15). Most studies were conducted in the United States ($n=3$), Japan ($n=2$), Brazil ($n=2$), China ($n=2$), Korea ($n=2$), Canada ($n=1$), and Switzerland ($n=1$). The majority of the studies ($n=13$) assessed aspects of hand impairments. Additionally, evaluations were made on upper extremity movement ability, upper limb functional performance, unilateral gross manual dexterity, voluntary muscle activation, and precision grip. A wide array of outcome measures was employed, with the Medical Research Council Sum Score (MRC SS) being the most common (0-60).

3.1. Methodological Quality Assessment

The quality assessment of the studies included was assessed by Pedro, who is a valid and reliable tool for rating the quality of clinical trials and randomized clinical trials. Each article was critically appraised using standardized critical appraisal tools, including the PEDro scale, to ascertain adequate quality and appropriateness of the evidence to be used in the review (Table 2). The PEDro scale scores and evaluates 11 items: random allocation, concealed allocation, similarity at baseline, subject blinding, therapist blinding, assessor blinding, >85% follow-up for at least one key outcome, intention-to-treat analysis, between-group statistical comparison for at least one key outcome, and assignment of a point and score as either present or absent, with a total score out of 11 obtained through summation. The scale includes an additional item (eligibility criteria) to evaluate external validity. Studies with a PEDro score ≥ 5 will be considered at low risk of bias and of high methodological quality. A study with a PEDro score of ≥ 6 is considered to have level 1 evidence. Studies with scores 6-8 are considered good, while studies scoring 9-11 are excellent. Also, studies with a score of ≤ 5 are considered to have level 2 evidence, while studies that score 4-5 are considered acceptable, and those that score less than 4 are deemed poor [17].

In the studies we examined, we found a range of good to excellent quality research. Specifically, one study scored 11, six studies achieved a perfect PEDro score of 10, four studies received a score of 9, and two studies scored an 8 on the PEDro quality assessment scale, as shown in Table 2. Collectively, these studies average a PEDro score of 9.46, indicating excellent quality in randomized clinical trials. This assessment underscores the high quality of evidence available for evaluating the effectiveness of rTMS in post-stroke hand function rehabilitation. Thus, this review presents the most robust evidence to elucidate the effects and clinical applications of rTMS in post-stroke hand function recovery.

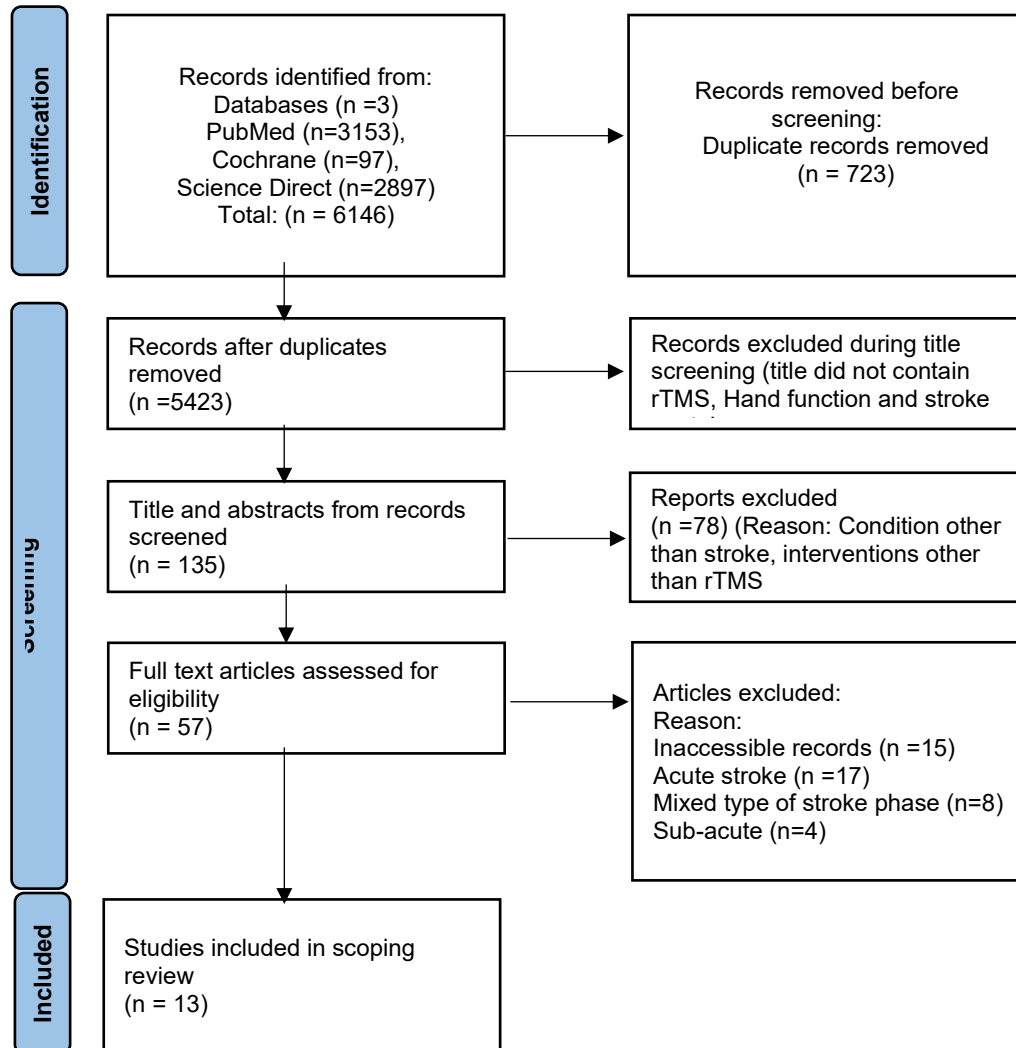


Figure 1. PRISMA Flow chart on selection and inclusion of studies

3.2. Outcome Measures

Articles reporting the outcome measures, inclusive of hand gross motor or fine motor components, are considered in this review. Common outcome measures for arm and hand functions across these studies include the Brunnstrom Recovery Stages, Fugl-Meyer Assessment, Box and Block Test, Functional Independence Measurement (FIM), Wolf Motor Function Test (WMFT), Modified Ashworth Scale (MAS), Motor Activity Log (MAL), Nine-Hole Peg Test, range of motion (ROM), Action Research Arm Test (ARAT), acceleration, and pinch force. Some studies also assessed and compared motor evoked potentials (MEP) following rTMS sessions, accurately reflecting changes in muscle activity and signal transmission. Statistically significant changes were observed in these outcomes post-rTMS treatment, including within-treatment differences from baseline in ipsilesional cortical silent period (CSP) duration, short-interval intracortical inhibition, reduced amplitude of motor-evoked potentials, and significant improvements in upper extremity behavioural measures.

3.3. rTMS Intervention Protocols

The intervention protocols in all 13 studies have distinct characteristics. While there are commonalities, such as using a figure-of-eight rTMS coil and preferring to stimulate the contralesional M1, other parameters vary. Most studies opted for an intensity of 90% RMT, but three studies used intensities of 80%, 100%, and 30% of 2RT, respectively. Although a frequency of 1Hz was commonly preferred, variations included frequencies of 5Hz, 10Hz, and 20Hz. Additionally, the rTMS pulse trains and the number of intervention sessions varied across studies. In essence, each study's rTMS protocols are unique.

Table 1. Study characteristics, rTMS protocol, and Outcomes

Author, year, country	Study Design	Sample size (E/C)	Frequency, intensity, duration per session, area of evaluation	Coil Type	Stimulation Site	Treatment duration	Outcome Measures	Results
Takeuchi et al 2005 Japan [18]	Double blind RCT	n=20	1Hz; 90% RMT; 25min; First dorsal interosseous (FDI) muscle (Hand function)	Figure 8	Contralesional M1	1 rTMS session	Acceleration and pinch force	rTMS reduced the amplitude of motor-evoked potentials in contralesional M1 and transcallosal inhibition (TCI) duration, and rTMS immediately induced an improvement in pinch acceleration and force of the affected hand.
Malcolm et al 2007 United States [19]	Prospective randomized, double-blind, parallel group study	n=19	20Hz; 90% MT; 2000 Pulses, 50 trains of 40 stimuli, train duration= 2 secs, inter train interval (ITI)= 28 secs; over-damaged hemisphere homologous to the hand area of the motor cortex	Figure 8	Ipsilesional M1	Ten consecutive weekdays for rTMS and Constraint-Induced Therapy (CIT) each	Wolf Motor Function Test (WMFT), Motor Activity Log (MAL), Box and Block Test (BBT), and MAL-How Well	The mean of the WMFT scores for the rTMS group was 20.0 points lower than the sham group at the baseline (P = 0.09). There was no significant difference between the two groups for the MAL-Amount at the baseline (p = 0.54). There was no significant difference between the two groups

Author, year, country	Study Design	Sample size (E/C)	Frequency, intensity, duration per session, area of evaluation	Coil Type	Stimulation Site	Treatment duration	Outcome Measures	Results
								for the Box and Block test at baseline (P = 0.95). There was no significant difference in motor threshold between the two groups at baseline (P = 0.96).
Takeuchi et al 2009 Japan [20]	Double-blind study	n=30	Bilateral (B/L) rTMS group, 1Hz 90% RMT; unaffected hemisphere = 50 sec train duration (50 stimuli) alternating 90% RMT, 10 Hz; affected hemisphere =5 sec train duration (50 stimuli), 5 sec interval for 20 times, 1000 stimuli for each hemisphere	Figure 8	Bilateral, affected, and unaffected hemispheres	20 rTMS sessions	Acceleration and pinch force	Bilateral repetitive transcranial magnetic stimulation (rTMS) and 1 Hz rTMS immediately improved the acceleration in the paretic hand. Compared to 1 Hz rTMS, bilateral rTMS reduced the inhibitory function of the affected motor cortex and amplified the impact of motor training on pinch force. Furthermore, the beneficial effect of motor training persisted for a week. Conversely,

Author, year, country	Study Design	Sample size (E/C)	Frequency, intensity, duration per session, area of evaluation	Coil Type	Stimulation Site	Treatment duration	Outcome Measures	Results
								10 Hz rTMS did not affect motor function.
Barros Galvão et al. 2014 Brazil [21]	Randomized sham-controlled trial	n=20	1Hz; 90% RMT; 1500 pulses, 10min	Figure 8	Contralesional M1	10 rTMS sessions	Modified Ashworth scale (MAS), upper-extremity Fugl-Meyer assessment (FMA), Functional Independence Measure (FIM), range of motion (ROM), and stroke-specific quality-of-life scale (SSQOL)	The Friedman test revealed that physical therapy (PT) significantly reduces upper limb spasticity when combined with rTMS. In the experimental group, 90% of patients showed a 1-point decrease in MAS score post-intervention, with 55.5% maintaining this improvement at follow-up. In the control group, 30% of patients showed similar changes post-intervention, with 22.2% maintaining these

Author, year, country	Study Design	Sample size (E/C)	Frequency, intensity, duration per session, area of evaluation	Coil Type	Stimulation Site	Treatment duration	Outcome Measures	Results
								changes at follow-up. No differences were observed between groups for other outcome measures, indicating similar behaviours over time for all variables.
Rose et al 2014 United States [22]	Double blind randomized sham-controlled	n=22	1Hz;100% RMT;1200 pulses, single train;	Figure 8	Contralesional M1	16 rTMS sessions	Wolf Motor Function Test (WMFT), Grip, Lateral Pinch (LP), Palmar Pinch (PP), and 3-Jaw Chuck (3JC) force, UEFM-M, Action Research Arm Test (ARAT), Semmes-Weinstein Monofilaments	No changes observed in outcome measure initially, on secondary analysis, statistically significant improvements in UE behavioural measures
Kwon et al 2014 Korea [23]	Single-blinded, randomized, crossover design	n=14	Interleaved combination method (ICM): 10Hz; 90% RMT, 5 sec; 20 times, 55 sec inter-train interval, 1000 pulses. 20-minute	Figure 8	Ipsilesional M1	2 rTMS sessions	Purdue pegboard test & nine-hole peg test	There were significant improvements in performance after both ICM ($p = 0.035$ for the Purdue Pegboard Test and $P = 0.039$ for the Nine-Hole

Author, year, country	Study Design	Sample size (E/C)	Frequency, intensity, duration per session, area of evaluation	Coil Type	Stimulation Site	Treatment duration	Outcome Measures	Results
			session Preconditioning combination method (PCM): 10 Hz, 90% RMT, 100 trains, 10 times repeated, 50-second inter-train interval, 1,000 pulses, 10 minutes.					Peg test) and PCM interventions (P = 0.013 for the Purdue Pegboard Test and P = 0.002 for the Nine-Hole Peg Test). However, there was no significant interaction between time (pre- vs post-intervention) and conditions (ICM vs PCM) for the Purdue Pegboard Test ($\chi^2 = 0.5$, P = 0.48) and the Nine-Hole Peg Test ($\chi^2 = 0.0$, P = 1.0)
Cassidy et al 2015 United States [24]	Repeated-measures cross-over design	n=11	1 Hz and 6 Hz, 90% RMT; 10-min session of active 1 Hz rTMS (600 pulses, 90% RMT). pre priming session: 10 min of active intermittent 6 Hz rTMS (5-s train, 2 trains/minute, 25-s intertrain interval;	70 mm air film coil	Contralesional M1	3 rTMS sessions. One per week, followed by a one-week washout period	Box and block test	6 Hz primed 1 Hz rTMS resulted in significant changes from baseline in ipsilesional cortical silent period (CSP) duration and short-interval intracortical inhibition within the treatment. Compared to

Author, year, country	Study Design	Sample size (E/C)	Frequency, intensity, duration per session, area of evaluation	Coil Type	Stimulation Site	Treatment duration	Outcome Measures	Results
			600 total pulses, 90% RMT), 10 min of active 1 Hz rTMS (600 pulses, 90% RMT), or 10 min of sham intermittent 6 Hz rTMS (5-s train, 2 trains/minute, 25-s intertrain interval; 600 pulses)					1 Hz priming and sham 6 Hz priming of 1 Hz rTMS, active 6 Hz priming led to significantly greater decreases in ipsilesional CSP duration. These enhanced effects were not observed in measures of intracortical facilitation or interhemispheric inhibition excitability.
Noh et al. 2019 Korea [25]	Prospective, randomized controlled trial	n=22	1Hz; 120% MT; 5 MEPs of >50 V in 10 consecutive trials	Figure 8	Contralesional M1	10 sessions	Brunnstrom stage, Fugl-Meyer assessment (FMA) score of the upper extremity, Manual Function Test (MFT), and grip power	After a 2-week trial, both groups showed significant improvements in total FMA and MFT scores. Notably, the MFT subscores for hand motor function and grip power improved significantly only in the combination therapy group. However, the effect

Author, year, country	Study Design	Sample size (E/C)	Frequency, intensity, duration per session, area of evaluation	Coil Type	Stimulation Site	Treatment duration	Outcome Measures	Results
								size of post-therapy changes did not significantly differ between the two groups.
Miller et al. 2019 Canada [26]	Cross-over Design	n=13	5Hz; 80% RMT; Thirty trains of rTMS + RW (or Sham rTMS + RW) were applied over the 120-150 min training session with rest breaks	Figure 8	Ipsilesional M1	2 rTMS + robotic exoskeleton (RW) session	Voluntary muscle activation: Fugl-Meyer Upper Extremity Motor Assessment (UE-FMA), Wolf Motor Function Test (WMFT)	For motor units (MUs) active both before and after training, significantly greater reductions in recruitment thresholds were observed post rTMS + RW training (p=0.0001) compared to Sham rTMS + RW (p=0.16). MU firing rate modulation increased following both training conditions (p=0.001). Ipsilesional MEPs were elicited before and after in only 5 out of 13 participants. No significant changes were observed in ipsilesional

Author, year, country	Study Design	Sample size (E/C)	Frequency, intensity, duration per session, area of evaluation	Coil Type	Stimulation Site	Treatment duration	Outcome Measures	Results
Kátia Monte-Silva et al 2019 Brazil [27]	Double blind Randomised control trial	n= 20	1 Hz rTMS	Figure 8		Three times per week for a total of ten sessions	Modified Ashworth scale	corticospinal excitability and transcallosal inhibition measures ($p > 0.05$) By the end of the treatment, the experimental group showed increased cortical excitability (lower MSO values) compared to the control group ($p = 0.044$) and baseline ($p = 0.028$). At the 4-week follow-up, spinal cord excitability was reduced ($p = 0.021$), and ULS decreased by the sixth session ($p < 0.05$). In conclusion, 1-Hz rTMS combined with PT improved unaffected hemisphere excitability, decreased spinal excitability, and reduced post-stroke ULS.

Author, year, country	Study Design	Sample size (E/C)	Frequency, intensity, duration per session, area of evaluation	Coil Type	Stimulation Site	Treatment duration	Outcome Measures	Results
Jixian Wang et al. 2021 China[28]	Randomized Trial	n=39	5-Hz stimulation over the affected hemisphere with 750 pulses	Figure 8	Ipsilesional	10 consecutive sessions	Jebsen–Taylor Hand Function Test (JTHFT), Fugl-Meyer assessment of upper extremity (FMA-UE), grip strength, modified Barthel index (mBI), and ipsilesional motor evoked potential (iMEP) latency	rTMS, along with hand grip training group all improved in JTHFT, FMA-UE, grip strength, and mBI ($p \leq 0.01$) compared with the baseline among the three groups
Hong Xing Wang et al. 2023 China[29]	Randomized control trial	n=36	TMS1 group: 1 Hz magnetic stimulation in the M1 region of the contralesional hemisphere +10 Hz magnetic stimulation in the tM1 region of the affected hemisphere; TMS2 group: 10 Hz magnetic stimulation in the M1 region of the affected hemisphere.	Figure 8	Contralesional hemisphere	5 days a week for 4 weeks	Fugl-Meyer Assessment for upper extremity (FMA-UE)	The rTMS treatment is beneficial to the recovery of upper limb motor function in stroke patients, and can significantly improve the intensity of brain network connections and reduce the island area. When the node degree of M1_Healthy region is less than 0.52, it is suggested to perform promotion therapy only

Author, year, country	Study Design	Sample size (E/C)	Frequency, intensity, duration per session, area of evaluation	Coil Type	Stimulation Site	Treatment duration	Outcome Measures	Results
								in the affected hemisphere. While the degree is greater than 0.52, and much larger than that in the M1_affected region.
Shim, J. Lee, S. et al 2023 Switzerland and	Randomized, sham-controlled, double-blind trial	n=33	high-frequency repetitive transcranial magnetic stimulation combined with the motor learning group (HF-rTMS + ML group) and a sham repetitive transcranial magnetic stimulation combined with the motor learning group (sham rTMS + ML group)	8 shaped coils	-	Three times a week for 4 weeks	Fugl-Meyer Assessment of the Upper Limbs, box and block tests, hand grip dynamometer) Korean version of the modified Barthel index	Regarding grip force, the high-frequency repetitive transcranial magnetic stimulation combined with the motor learning group improved significantly compared to the sham repetitive transcranial magnetic stimulation combined with the motor learning group (p < 0.05)

Table 2. Methodological quality assessment of the studies using PEDro

Study author	1	2	3	4	5	6	7	8	9	10	11	SCORE
(Takeuchi et al., 2005) [18]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	10
(Malcolm et al., 2007)[19]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	10
(Takeuchi et al., 2009)[20]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	10
(Rose et al., 2014)[22]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	10
(Kwon et al., 2014)[30]	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	9
(Cassidy et al., 2015) [24]	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	9
(Tosun et al., 2017)[31]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	9
(Noh et al., 2019)[25]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	9
(Miller et al., 2019)[26]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	8
(Dos Santos et al., 2019)[27]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	10
(Jixian Wang et al 2021)[28]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	8
(Hong Xing Wang et al., 2023)[29]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	10
(Shim, J. Lee, S. et al., 2023)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11

1. Were the eligibility criteria specified?
2. Subjects were randomly allocated to groups. (In a crossover study, subjects were randomly allocated an order in which treatments were received.)
3. Allocation was concealed?
4. The groups were similar at baseline regarding the most important prognostic indicators.
5. There was blinding of all subjects blinded?
6. Were all therapists who administered the therapy?
7. Were all assessors blinded who measured at least one key outcome?
8. Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups?
9. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome were analysed by “intention to treat”?
10. The results of between-group statistical comparisons are reported for at least one key outcome?
11. The study provides both point measures and measures of variability for at least one key outcome?

The included RCTs investigating the impact of rTMS on hand function recovery in chronic stroke patients have utilized a range of dosages and frequencies to achieve positive outcomes. Several key findings have emerged from the review. Firstly, the studies have brought to light the diverse rTMS protocols utilized in stroke recovery. These protocols vary from low-frequency rTMS ($\leq 1\text{Hz}$), targeting the unaffected hemisphere, to high-frequency rTMS ($\geq 5\text{Hz}$), targeting the affected or both hemispheres [22,29]. Therefore, it is essential to understand the underlying mechanisms of rTMS and their potential impact on activities involving the upper extremities.

Numerous studies have explored the mechanisms underlying the observed improvements in hand function post-stroke following rTMS interventions [24–26,32]. Specifically, a high-frequency rTMS in combination

with robot-assisted training modulates neurons in the spinal cord level, thereby enhancing the somatosensory afferent input from wrist movements [26], which is evidenced by a reduction in motor unit (MU) recruitment thresholds and an increase in MU firing rate modulation [26]. A recent study has proposed that the enhancement of hand function after receiving rTMS is attributed to the modulation of GABAergic inhibitory circuits. This theory is reinforced by the findings of a reduction in cortical silent period (CSP) duration and short-interval intracortical inhibition (SICI) following 6 Hz frequency stimulation [32]. Specifically, the changes in intracortical inhibition observed during 6 Hz rTMS suggest the presence of a form of homeostatic-like metaplasticity in the brain affected by stroke. This aligns with the previous work by Cassidy et al. (2015, which observed shifts in intracortical inhibition after transcranial direct current stimulation (TDCS) combined with 1 Hz rTMS [24]. Nonetheless, all these mechanisms involve changes in cortical excitability, modulation of interhemispheric inhibition, restoration of motor cortex balance, and facilitation of motor learning processes [21,31]. These findings underscored the complex interplay between neural plasticity, motor recovery, and rTMS-induced neurophysiological changes. In contrast, another study investigated the effects of rTMS, revealing that the motor evoked potential (MEP) amplitude in the stimulated primary motor cortex (M1) was reduced by 20% immediately after rTMS, returning to baseline 30 minutes later [33]. This underscores the importance of considering additional parameters when devising rTMS protocols.

A scarcity of literature that addresses stroke-related factors, such as lesion size, preservation of white matter tracts, and current medication use, which may impact individual responsiveness to rTMS and complicate the identification and differentiation of priming responses. Furthermore, earlier studies have not addressed inter-individual variability. Therefore, it is recommended that protocols be designed taking into account the duration of stroke and individual variabilities.

Moreover, among the outcome measures used across studies, the Medical Research Council Sum Score (MRC SS) was the most common, followed by assessments through Fugl-Meyer Assessment, Jebsen–Taylor Hand Function Test, Wolf Motor Function Test (WMFT), Box and Block Test, Functional Independence Measurement (FIM), Modified Ashworth Scale, Motor Activity Log (MAL), Manual Function Test (MFT) and Hand grip Dynamometer. These measures provided valuable insights into changes in motor function, muscle tone, and overall upper extremity function following rTMS interventions [22,24,25]. However, two studies noted limitations, such as the lack of long-term assessments and inconsistent translation of changes in cortical excitability to clinical effects [26,27]. Therefore, it is essential to incorporate new outcome measures with strong reliability and validity to comprehensively assess hand function recovery during long-term assessments.

Several outcome measures that can be utilized to assess manual ability and perceived difficulty in daily tasks include the Manual Ability Measure (MAM-36), the Chedoke Arm and Hand Activity Inventory (CAHAI) [34], and the ABILHAND Questionnaire [35]. These measures evaluate the ease or difficulty in various hand tasks, bilateral activities, and perceived difficulty in daily manual tasks, respectively. By incorporating these measures into the evaluation process before and after interventions, the assessment process can be significantly enhanced.

Despite the variations in rTMS protocol parameters, clinical effects, and outcome measures among the reviewed studies, they provide valuable insights into rTMS in hand function recovery. However, this also highlights the need for further research to determine the most effective rTMS protocols, specific outcome measures, and the impact of lesion severity. Specifically, there is a critical need for standardized rTMS protocols tailored to hand function recovery in post-stroke, along with guidelines to ensure safety and tolerance. Long-term follow-up studies are also essential to assess the sustainability of rTMS-induced improvements and to refine intervention strategies.

4. Conclusion

rTMS intervention combined with physiotherapy showed improvement in hand function among stroke patients. However, the rTMS intervention parameters vary widely, with frequencies (1 Hz to 20 Hz), stimulus durations (2 seconds to 55 seconds), numbers of stimuli (10-1000), and variable rest intervals. Additionally, the number of treatment sessions varies, with some studies administering only a few sessions and others up to 20, leaving the optimal treatment duration unclear. The intensity used also ranges from 80%, 90%, 100%, to 120% of the resting motor threshold. Therefore, further studies with longer treatment durations and larger patient populations are needed to establish the long-term effects of spasticity reduction on motor hand function recovery. Furthermore, this review strongly advocates for further research to comprehend the clinical effects of rTMS and establish appropriate safety and tolerance guidelines. While safety guidelines for rTMS usage exist, there's a necessity for guidelines specific to spastic hand

rehabilitation.

5. Data Availability Statement

The original contributions presented in the study are included in the article/supplementary material; further inquiries can be directed to the corresponding author.

6. Ethical Statement

Sumatera Medical Journal (SUMEJ) is a peer-reviewed international electronic journal. The following statement clarifies the ethical behavior expected from all parties involved in the publication process of articles in Sumatera Medical Journal (SUMEJ), including authors, the Editor-in-Chief, the Editorial Board, peer reviewers, and the publisher, TALENTA Publisher Universitas Sumatera Utara. This statement is based on the Best Practice Guidelines for Journal Editors developed by Committee on Publication Ethics (COPE).

7. Author Contributions

All authors contributed to conceptualization, manuscript drafting, writing, and finalizing the manuscript.

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10. Conflict of Interest

Authors have no conflicts of interest to disclose.

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