

Repetitive Transcranial Magnetic Stimulation Combined with Mirror Therapy for Post-Stroke Upper Limb Motor Dysfunction: A Narrative Review of Recent Developments

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Abstract: More than half of stroke survivors have upper-limb motor impairment, and it is one of the main reasons for difficulties in daily life. Repeated Transcranial Magnetic Stimulation (rTMS) and Mirror Therapy (MT) are both non-invasive methods; however, they work differently by affecting cortical excitability and interhemispheric balance, respectively, and MT is achieved through visual feedback and the mirror neuron system to induce sensorimotor reorganization. It has not been found that the combined state is better than either separately. According to Hebbian plasticity and homeostatic metaplasia, this narrative review will explore how to design trials for and apply them in practice. Meta-analytic evidence is favorable. In a synthesis of 12 randomised trials (628 patients), combined non-invasive brain stimulation and MT improved upper limb function compared with either intervention alone (FMA-UE mean difference 5.97, 95% CI 5.01–6.93), and a smaller pooled effect on activity (SMD 0.82, 95% CI 0.61–1.02). Results of hand strength and dexterity also support combined therapy, but the FMA-UE outcome has not been consistently reproduced. Most trials are small, have different protocols, have a short follow-up period, and few are properly sham-controlled. These deficiencies lead to early-stage recommendations. We have set the following objectives: determine a suitable time and dose for rTMS; correlate treatment results with the integrity of the corticospinal tract and other biomarkers; conduct multi-centre sham-controlled trials of combined therapy; and investigate whether closed-loop stimulation can improve precision without increasing the volume of treatment.

Keywords: Repetitive Transcranial Magnetic Stimulation; Mirror Therapy; Stroke Survivors; Upper-limb Motor Impairment; Non-invasive Brain Stimulation.

1. Introduction

Stroke is the second leading cause of death globally and the third cause of death and disability combined. The world's share has increased over the past 30 years [1]. Upper-limb motor dysfunction is frequent in the acute stage, affecting around 80% of patients, and in over half of survivors, it continues for several months or years [2]. It is inconvenient for dressing, eating and writing, so it is a primary target of rehabilitation [3, 4].

Two ways have drawn continuous attention to upper-limb recovery. Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive method of brain stimulation that alters cortical excitability via electromagnetic induction. High-frequency rTMS (≥ 5 Hz) is typically applied to the ipsilesional motor cortex to increase its activity; low-frequency rTMS (≤ 1 Hz) is used on the contralesional hemisphere to reduce excessive inhibition of the damaged side [5-6]. Mirror Therapy (MT) is easier. A mirror conceals the paretic side and shows the motion of the non-paretic side, thereby giving the appearance of symmetrical bilateral movement. Feedback is believed to activate the mirror neuron system, help with motor imagery, and cause sensorimotor rearrangement [7,8].

The combination of these treatments is promising, and their effects may be synergistic; rTMS offers top-down modulation of cortical circuits to prepare the motor system for training-induced plasticity. MT provides bottom-up sensory information linked to a purpose-driven motor activity. Together, they may create conditions conducive to Hebbian

plasticity [9]. Some randomised controlled trials (RCTs) and systematic reviews have compared the combination with either therapy alone [10-13].

Assess the Strength of Persuasion for that Evidence. It presents the mechanism and theoretical basis of combining rTMS and MT, clinical evidence from RCTs and meta-analyses, factors that affect the response to treatment, and outstanding problems for research and application. We will focus only on rTMS for this study and not use other types of non-invasive brain stimulation, such as tDCS, to make the stimulation protocols and results more consistent.

2. Mechanisms and Rationale for Combination Therapy

2.1. rTMS: Cortical Excitability and Interhemispheric Balance

The reason for using rTMS in stroke rehabilitation is generally based on the interhemispheric competition model. After unilateral stroke, excitability decreases in the damaged hemisphere, and the contralesional hemisphere is disinhibited to exert excessive transcallosal inhibition on the ipsilesional motor cortex [5,14]. Prolonged Motor Deficits have been associated with this imbalance. The two are strategies for correction. High-frequency rTMS (10-20 Hz) applied to the ipsilesional primary motor cortex (M1) enhances cortical excitability. Low-frequency rTMS (1Hz) is used to inhibit hyperactivity in the contralesional M1, reduce interhemispheric inhibition, and potentially disinhibit the

ipsilesional hemisphere [5, 15].

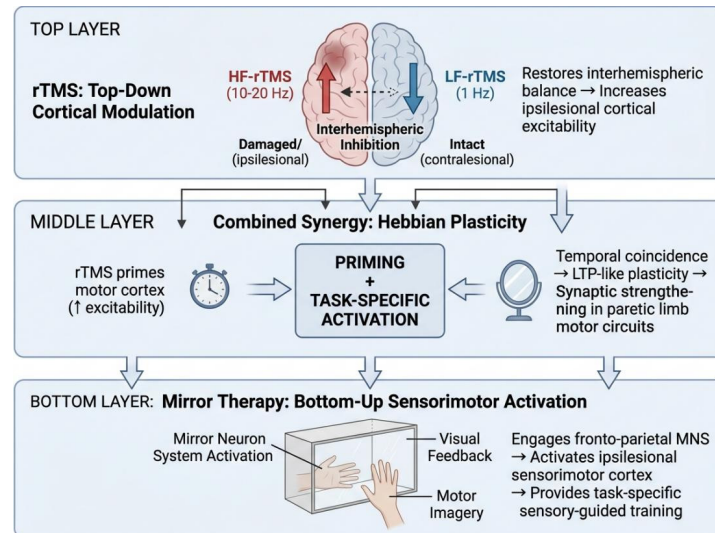


Figure 1. Proposed Synergy of rTMS and Mirror Therapy After Stroke. The three levels of the figure are: first, rTMS causes top-down cortical modulation and corrects interhemispheric imbalance; second, a temporal window for Hebbian plasticity is created; and third, mirror therapy provides bottom-up sensorimotor input via visual feedback and the mirror neuron system

Randomised Trials support both directions. Du et al. (2019) found that in early stroke patients, 10 Hz rTMS over the ipsilesional M1 and 1 Hz rTMS over the contralateral M1 improved upper limb Fugl-Meyer Assessment (FMA-UE) scores, and changes in ipsilesional motor cortex activity were associated with motor gains [15]. Safdar and others (2023) drew a similar overall conclusion but indicated that the optimal goal may be altered by the damage to the corticospinal tract [16].

At the level of cells, rTMS can induce long-term potentiation (LTP)-like or long-term depression (LTD)-like plasticity based on the frequency. It also promotes release of neurotrophic factors, including brain-derived neurotrophic factor (BDNF), which supports synaptic remodeling [14,17]. As a result, the environment for motor learning is more permissive, and residual circuits are more responsive to subsequent behavioural training [9].

2.2. Mirror Therapy: Mirror Neuron System and Sensorimotor Integration

First, Altschuler and others reported mirror therapy for upper-limb impairment after stroke, and later trials and meta-analyses expanded the evidence base [8, 18]. The main theory of the mirror-neuron system (MNS) is that both action execution and action observation engage the same fronto-parietal network [7,19]. When patients observe the reflection of their moving non-paretic hand, it appears to them that their paretic hand is also moving. This illusion is thought to activate the MNS and increase activity in the ipsilesional sensorimotor cortex [20].

Deconinck et al. (2015) have reviewed the brain effects of mirror visual feedback and found activation in the primary motor cortex, premotor cortex, primary somatosensory cortex, and cerebellum [7]. Zhang et al. (2018) reported that action observation with mirror feedback recruits ipsilesional motor pathways in stroke patients, a pattern consistent with functional reorganization [21], and fMRI and functional near-infrared spectroscopy (fNIRS) studies have also shown increased sensorimotor activation and bilateral cortical engagement during mirror feedback [22,23].

MT is not only visual. It also includes motor imagery and

the integration of visual and proprioceptive information, which may strengthen the disrupted sensorimotor loop after a stroke [24]. The multimodal nature of quality in MT refers to the combination of sensation and movement, and this may be why MT is effective with neuromodulation.

2.3. Theoretical Rationale for Combining rTMS and MT

Takeuchi and Izumi (2015) associated the combination with Hebbian plasticity and homeostatic metaplasticity [9]. Hebbian plasticity strengthens synapses due to co-occurrence of presynaptic and postsynaptic activity. rTMS can increase the excitability of the ipsilesional motor cortex and create a brief window during which behavioural training is more likely to strengthen task-relevant circuits [9,25].

Homeostatic metaplasticity is temporally disordered. Plasticity thresholds of neurons vary according to recent activity. If rTMS is used for an extended period before MT, the stimulating effect may be diminished by homeostatic mechanisms; therefore, the outcome of combining the two depends on whether convergent or divergent pathways are employed [9]. The Bienenstock-Cooper-Munro (BCM) model shows that excitatory priming can raise the threshold for the induction of LTP, and a period of low activity lowers it [26]. Therefore, one must plan the order and time intervals of therapy reasonably.

The system has a top-down cortical modulation and bottom-up sensorimotor excitation, generally increases cortical excitability via rTMS, and provides task-specific sensory input to guide plasticity in the relevant motor circuit [10, 27]. This logic is in line with the general bimodal stimulation system, and it is expected to induce more significant or prolonged neuroplastic changes through the combination of central neuromodulation and peripheral exercise [28].

3. Clinical Evidence

3.1. Evidence From Systematic Reviews and Meta-Analyses

The two most recent meta-analyses have supported the

addition of combination therapy. Zhao et al. (2022) pooled 12 RCTs involving 628 patients to compare combined non-invasive brain stimulation (NIBS) and MT with NIBS or MT alone [10]. The combined group had a better body structure and function (FMA-UE mean difference 5.97; 95% CI 5.01–6.93; $P < 0.05$) and activity scores (standardised mean difference [SMD] 0.82; 95% CI 0.61–1.02; $P < 0.05$). Motor evoked potential cortical latency (SMD -1.05; 95% CI -1.57 to -0.52; $P < 0.05$) and central motor conduction time (SMD -1.31; 95% CI -2.02 to -0.61; $P < 0.05$) also increased; however, MEP amplitude did not (SMD 0.47; 95% CI -0.29 to 1.23; $P = 0.23$). Subgroup analysis shows that the treatment effects of different stimulation sequences vary, so the order is important [10].

Abdelhaleem et al. (2024) pooled the results of eight RCTs on NIBS+MT and reported significant improvements in hand grip strength ($P = 0.001$) and gross manual dexterity ($P = 0.0002$) [11]. Their pooled estimate of sensorimotor function (FMA-UE) was not significant, which is different from Zhao et al. (2022) [10]. The reason for this difference may be the inclusion criteria; Abdelhaleem and others included more modalities of NIBS, such as tDCS, had higher-quality requirements and thus analysed a smaller sample size. The timing-dependent effect of tDCS + MT on sensorimotor function was also not significant, and therefore, the type of NIBS may affect outcomes [11].

Lin et al. (2025) employed network meta-analysis to compare the effects of rTMS combined with four rehabilitation methods on upper-limb function and daily living. Mirror therapy is one of the more effective adjunct behavioural treatments [29]. The directions of the benefits in these analyses are generally the same, but their sizes differ, and there is some heterogeneity.

3.2. Evidence from Individual Randomized Controlled Trials

Kim and Yim (2018) randomised 20 acute stroke patients

(<3 months after stroke) to either high-frequency rTMS alone (20 Hz over the ipsilesional hand M1) or the same stimulation plus task-oriented mirror therapy (TOMT) [30]. Both groups showed improvement in motor evoked potential and hand function ($P < 0.05$). Together, they achieved better improvements in pinch grip strength and Box-and-Block Test performance ($P < 0.05$) for fine hand-motor control tasks. Treatment lasted two weeks (10 sessions). Four patients dropped out due to scalp pain or other reasons, and no serious adverse events occurred [30].

Yang and others (2018) investigated the order of treatment for 44 chronic stroke patients [31]. One group received 10 Hz ipsilesional rTMS before MT; another received MT before rTMS; and the third received only MT. All were treated five times a week for four weeks, and rTMS before MT had better FMA-UE and Motricity Index scores than MT before rTMS. Therefore, according to the priming hypothesis, rTMS first increases cortical excitability and then causes use-dependent plasticity in the window of heightened responsiveness [31].

Chen et al. (2023) combined 1 Hz low-frequency rTMS over the contralesional hemisphere with MT in patients with hemiplegia [32]. Combination of rTMS and FMA improved FMA-UE scores and reduced cortical latency and central motor conduction time. Based on the results, the inhibitory contralesional strategy is effective when used with MT.

Some early pilot studies employed the same but different NIBS methods, mainly tDCS, and the results of cortical excitability were not consistent. Ji et al. (2014) found that 10 Hz rTMS + MT increased cortical excitability and motor recovery in chronic stroke patients [33], but tDCS + MT had more variable effects on MEP amplitude [10]. They can be used at any time, rTMS generates action potentials by electromagnetic induction, and tDCS modifies the resting membrane potential. Spatial Focality and Temporal Dynamics Also Differ [14].

Table 1. Randomized Controlled Trials and Meta-analyses of rTMS Combined with Mirror Therapy for Post-stroke Upper Limb Motor Rehabilitation.

Study	Design / N	rTMS Protocol	MT Protocol	Key Findings
Kim & Yim (2018) [30]	RCT, single-blind; N=20; acute (<3 mo)	20 Hz ipsilesional M1; 15 min/session; 10 sessions / 2 wk	Task-oriented MT; 30 min/session; 10 sessions	Significantly greater pinch grip ($P < 0.05$) and BBT ($P < 0.05$) vs. rTMS alone; both groups improved MEP
Yang et al. (2018) [31]	3-arm RCT; N=44; chronic	10 Hz ipsilesional M1; 10 min/session; 20 sessions / 4 wk	MT; 50 min/session; 20 sessions	rTMS-before-MT > MT-before-rTMS in FMA-UE and Motricity Index
Chen et al. (2023) [32]	RCT; subacute	1 Hz contralesional M1; combined with MT	MT; duration NR	Combined improved FMA-UE and shortened MEP-CL and CMCT vs. rTMS alone
Ji et al. (2014) [33]	RCT; N=35; chronic	10 Hz ipsilesional M1	MT; 15 min; 5x/wk / 6 wk	rTMS+MT improved FMA-UE, BBT, and MEP-CL vs. MT alone
Zhao et al. (2022) [10]	Meta-analysis; 12 RCTs; N=628	HF (10–20 Hz) ipsilesional or LF (1 Hz) contralesional	Varied MT; 20–50 min; 3–6x/wk, 2–6 wk	FMA-UE MD=5.97 (95% CI 5.01–6.93); activity SMD=0.82 (95% CI 0.61–1.02)
Abdelhaleem et al. (2024) [11]	Meta-analysis; 8 RCTs	Mixed NIBS (rTMS + tDCS)	Varied MT protocols	Significant for grip strength ($P=0.001$) and dexterity ($P=0.0002$)

Abbreviations: BBT = Box and Block Test; CI = confidence interval; CMCT = central motor conduction time; FMA-UE = Fugl-Meyer Assessment Upper Extremity; HF = high-frequency; LF = low-frequency; MD = mean difference; MEP = motor evoked potential; MEP-CL = MEP cortical latency; M1 = primary motor cortex; MT = mirror therapy; NIBS = non-invasive brain stimulation; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SMD = standardized mean difference.

3.3. Cortical Excitability as a Mechanistic Marker

Across trials, combined rTMS and MT has been associated with greater cortical excitability in the ipsilesional motor cortex, indicated by lower resting motor threshold (RMT), shorter MEP cortical latency, and shorter central motor conduction time (CMCT) [10,30,31]. These modifications are often considered to be the restoration of corticospinal pathway integrity and reduced interhemispheric inhibition. Enhancement of cortical excitability is associated with improvements in motor function, providing a mechanism for rTMS-induced plasticity-driven behavioural recovery [10,15].

MEP amplitude has not been stable, and several trials have failed to find a difference in the groups [10-11]. Another reason for measurement variation is that the amplitude changes based on coil position, stimulation intensity, state of the target muscle, and individual anatomy. A small sample size, generally 15-40 per group, has reduced the detection ability of amplitude changes.

4. Factors that Modify Treatment Response

4.1. rTMS Parameters: Frequency, Site, and Dose

The effect of treatment depends on the rTMS protocol. The two main types of rTMS+MT studies are: High-frequency stimulation (10-20 Hz) of the ipsilesional M1 aims to excite the damaged hemisphere [30, 31]. Low-frequency stimulation (1 Hz) of the contralesional M1 aims to inhibit transcallosal inhibition from the intact hemisphere [32, 34]. Both are suitable for use with MT, but there has been no direct comparison.

Frequency and Site May Relate to Patient Characteristics. Tang and others (2022) conducted a meta-analysis and found that excitatory rTMS applied to the ipsilesional M1 improved upper limb motor function, with a greater effect in patients with intact corticospinal tract [35]. Kim and others (2020) found that low-frequency rTMS over the contralesional M1 is more effective for severe damage with reduced ipsilesional excitability [34]. Based on the above results, personalised targeting will be carried out.

The Dosage is not uniform. All the studies have conducted 10-30 rounds of rTMS over 2-6 weeks and used 600-1,500 pulses per round. Lv et al. (2023) compared different numbers of sessions and found that more improvement occurred after 15-20 sessions than after 10 [36]. MT protocols were also irregular; the sessions lasted 20-50 minutes and were held 3-6 times a week [10, 30].

4.2. Stimulation Sequence and Timing

Order is probably required. Yang and others (2018) found better motor outcomes following rTMS prior to MT [31], and

Zhao et al. (2022) reported a significant interaction between sequence and treatment effect in a subgroup analysis [10]. First of all, rTMS priming increases the excitability of the ipsilesional M1 area and provides a suitable condition for MT-induced use-dependent plasticity. If MT occurs first, training-related fatigue may reduce the ability of the following rTMS to induce LTP-like plasticity, as expected under homeostatic metaplasticity [9].

The best interval for the treatment is unknown. Most studies of MT immediately followed the rTMS, within about 5 minutes; a few employed a longer delay. No studies have systematically changed the time period to find a suitable time.

4.3. Stroke Phase

Stroke Phase May Also Affect Response. Most RCTs in the Zhao et al. (2022) meta-analysis enrolled patients in the subacute to chronic stage, from more than 2 weeks to several years after stroke [10,11]. Kim and Yim (2018) found a benefit in acute patients (<3 months) and proposed that early combined treatment may be feasible during the period of enhanced neuroplasticity [30].

No direct comparisons of the stages. Fisicaro and others (2019) pointed out that the evidence from rTMS in stroke rehabilitation is mainly for chronic cases, and acute-subacute studies are still needed to determine whether earlier treatment yields greater or more lasting benefits [14]. Early intervention must also be balanced with the risk of seizures, which are increased after an acute stroke and are rare but serious side effects of rTMS [37].

4.4. Patient Characteristics and Biomarkers

The responses of rTMS in different patients vary, and some neurophysiological or imaging markers can predict these differences. Hildesheim et al. (2022) identified corticospinal tract (CST) integrity in a CanStim consensus review, as well as the presence of motor evoked potentials in the paretic limb and interhemispheric asymmetry in resting-state functional connectivity, as potential predictors [38].

Wang et al. (2022) found that the integrity of CST, expressed as fractional anisotropy, correlated with upper-limb motor recovery after rTMS; patients with higher CST integrity showed better improvement [39]. Thus, a bimodal balancing model is used. Patients with some preservation of the CST may respond better to facilitatory ipsilesional rTMS, and those with severe CST damage will need to rely more on compensatory contralesional mechanisms [16].

Barreto et al. (2025) suggested that some markers may enhance the predictive capability of RMT, MEP status, baseline FMA-UE and time since stroke [40]. If validated, this model can be used for triage to identify potential rTMS responders and provide combined therapy; non-responders will be offered other options.

4.5. Safety Considerations

rTMS has a good safety record in stroke. Kim and Paik (2021) have reviewed clinical rTMS studies and found that among the three trials of upper limb motor recovery that reported adverse events, most were mild and transient, such as headache [37]. Among all of the treated patients, only one had a seizure, and the estimated risk was less than 1% [37]. Zhang et al. (2026) also determined that serious adverse events are infrequent given the standard screening of epilepsy history, intracranial metal and pacemakers [41].

MT is behavioural and does not directly stimulate the brain; therefore, the risk is low. Dizziness, confusion and other emotional changes have been reported rarely in the mirror visual feedback [18]. Combining rTMS with MT has not added to the safety risks of rTMS alone.

5. Limitations and Research Priorities

Several deficiencies restrict the general clinical application of combined rTMS and MT.

Existing RCTs are small, usually 15–45 participants per group [10,11,30,31]. Therefore, no small but clinically significant associations between stimulation parameters and patient characteristics have been found. Blinding is also irregular. Raters are frequently blinded, but participant blinding with sham coils is relatively rare; thus, the effects may be biased by expectations and placebo effects [10,14]. Follow-up is infrequent, generally occurring soon after treatment, and little data are available beyond 1–3 months. The Longevity of the Benefit is Unknown. Finally, the parameters of rTMS, MT protocols and outcome measures in the studies are too different to be directly compared, and meta-analysis has had limited generalizability [10–11].

Mechanistic Evidence Remains Indirect. Hebbian plasticity and homeostatic metaplasticity provide a possible explanation for the co-occurrence [9], but few studies have examined these processes in stroke patients treated with both. Most inferences are based on healthy volunteer or single-modality stroke research. Trials of TMS-evoked potentials, electroencephalography, or fMRI before, during and after combined treatment are required to test the proposed mechanisms directly.

Cost and feasibility have not been widely studied; rTMS is relatively expensive in terms of equipment and personnel, while mT is relatively low-cost. It is unknown whether adding rTMS to standard MT-based rehabilitation is cost-effective.

Several Research Priorities Follow. First, tailor the therapy to the multimodal biomarker. Barreto et al. (2026) put forward the PRESp-rTMS framework to guide the decision of ipsilesional-versus contralesional stimulation, dose and timing relative to MT, based on CST integrity, cortical excitability and functional connectivity [42]. Machine-learning models can be trained with clinical, neurophysiological and imaging data to identify potential responders [38–40].

Second, real-time monitoring can support closed-loop delivery. Electroencephalography or fNIRS can track cortical activation during movement and trigger rTMS at the location of peak sensorimotor engagement to increase Hebbian coincidence and reduce homeostatic interference [9, 28].

Third, multi-center RCTs are required. Provide adequate power, include sham controls, use standardised protocols, and follow up with the patient for at least six months. FMA-UE is a popular and highly recommended main outcome. Mechanistic substudies should be built in advance rather than added later.

Technological adaptations of MT also need testing. Virtual reality mirror therapy, robot-assisted mirror training and digital telerehabilitation can improve engagement or increase the treatment dose, and in combination with rTMS priming, further benefits may be achieved [43]. At present, it is only a hypothesis and has not been verified.

6. Conclusion

rTMS + MT is biologically plausible and clinically effective for upper limb recovery after stroke. Meta-analyses and randomised controlled trials have indicated improvements in motor function, activity and cortical excitability compared with no intervention. The reasons are as follows: rTMS modulates cortical excitability and interhemispheric inhibition; MT exploits the mirror-neuron system to present task-specific sensorimotor information. Both may lead to Hebbian plasticity in the ipsilesional motor network.

At present, there is no sufficient evidence to support a general recommendation. There are many protocols, few small samples, no follow-up, and personalised treatment algorithms are generally not available. Optimal rTMS parameters, the best sequence and interval, and the most responsive patients have not been determined. The next experiments need to be sufficiently powered, sham-controlled, protocol-standardised and long-term to assess durability. Translational research will also be carried out to verify the mechanism of combined-treatment therapy.

Precision Rehabilitation is the future direction. Neurophysiological and neuroimaging markers can be used to guide treatment decisions, so combined rTMS and MT may be given only to patients who are likely to respond, thus achieving better functional outcomes and reducing wasted treatment. This aims to help many stroke survivors who have suffered upper-limb injuries live better after a stroke.

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