Review

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How does combining physical therapy with transcranial direct stimulation improve upper-limb motor functions in patients with stroke? A theory perspective

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Abstract

More than half of stroke survivors suffer from upper-limb dysfunction that persists years after stroke, negatively impacting patients' independence and, therefore, affecting their quality of life. Intense motor rehabilitation is required after a stroke to facilitate motor recovery. More importantly, finding new ways to maximize patients' motor recovery is a core goal of stroke rehabilitation. Thus, researchers have explored the potential benefits of combining the effects of non-invasive brain stimulation with physical therapy rehabilitation. Specifically, combining transcranial direct stimulation (tDCS) with neurorehabilitation interventions can boost the brain's responses to interventions and maximize the effects of rehabilitation to improve upper-limb recovery post-stroke. However, it is still unclear which modes of tDCS are optimal for upper-limb motor recovery in patients with stroke when combined with physical therapy interventions. Here, the authors review the existing literature suggesting combining physical therapy rehabilitation with tDCS can maximize patients' motor recovery using the Interhemispheric Competition Model in Stroke. The authors focus on two main rehabilitation paradigms, which are constraint-induced movement therapy (CIMT) and Mirror therapy with and without tDCS. The authors also discuss potential studies to elucidate further the benefit of using tDCS adjunct with these upper-limb rehabilitation paradigms and its effectiveness in patients with stroke, with the ultimate goal of maximizing patients' motor recovery.

Keywords: combined therapy, constraint-induced movement therapy (CIMT), mirror therapy, motor function, neuromodulation, Post-stroke, transcranial direct stimulation (tDCS), and upper limb

Introduction

Stroke is one of the leading causes of death and disability worldwide[1]. Stroke cases are expected to increase by 57–67% over the next 10 years[2]. Hemiparesis or paralysis of the upper-limb contralateral to the affected side is a typical stroke consequence[3]. Upper-limb dysfunction can be sustained years after stroke[4], negatively affecting patients' functional independence and quality of life[5,6]. After a stroke, intense motor rehabilitation is required to facilitate motor recovery and promote brain plasticity for upper-limb function[7–10]. Different physical therapy rehabilitation paradigms, namely constraint-induced movement therapy (CIMT)[11] and Mirror therapy[12], have been developed to target upper-limb motor recovery in patients with stroke. However, the progress of upper limb and dexterity function is still slow or even limited in severe cases[4,13,14]. Therefore, researchers have explored other techniques to enhance upper-limb motor functions for patients with stroke.

One of these techniques is transcranial direct current stimulation (tDCS), which is a non-invasive brain stimulation (NIBS) technique that can manipulate neural activities within the brain and subsequently induce functional changes[15,16]. Owing to its non-invasive nature and minimal side effects reported in previous studies[17,18], researchers have started investigating its benefits for upper motor recovery in patients with stroke[15–18]. Specifically, research has investigated the use of tDCS as a potential technical adjuvant to neurorehabilitative interventions to optimize brain plasticity by stimulating the human primary motor cortex (M1) with low-intensity electric fields delivered to the scalp, which modulates M1 cortical excitability[15,16]. The rationale for using tDCS for motor recovery after stroke is based on the interhemispheric competition model. The following sections will discuss the interhemispheric competition model and how physical therapy rehabilitation paradigms and tDCS can be applied to this model for upper-limb motor recovery post-stroke.

Interhemispheric competition model in stroke

The mechanism of controlling motor overflow, is interrupted in patients with stroke, resulting in a sequence of events referred to as interhemispheric compensatory communication[19–21]. Researchers have used the interhemispheric competition model to interpret this

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compensatory communication. In healthy subjects, the interhemispheric interaction changes from an inhibitory to an excitatory to facilitate the active motor cortex around movement onset (Fig. 1A). In contrast, patients with stroke who have motor deficits do not show this switch in the interhemispheric inhibition to facilitate the movement of the paretic hand; instead, they exhibit a persistent inhibitory influence on the ipsilesional motor cortex[22] (Fig. 1B). Thus, in this model, the excitability of the ipsilesional hemisphere is decreased, and its inhibitory effect on the contralesional hemisphere is weakened. In contrast, the excitability of the contralesional hemisphere is sustained, while its inhibition of the lesioned hemisphere is increased[22]. In other words, the model suggests that the contralesional (unaffected) motor region exerts an excessive inhibitory influence on the ipsilesional (affected) motor cortex. Therefore, it leads to maladaptive neural activation patterns, mainly caused by an imbalance in interhemispheric inhibition, which might limit post-stroke motor recovery[22]. Researchers have shown that the reactivation or overactivation of specific brain regions after a stroke is due to the imbalance of interhemispheric inhibition (IHI) caused by contralesional hemisphere inhibition of the lesioned hemisphere[23]. Furthermore, the contralesional hemisphere demonstrated activation with the movement of the affected limb[20]. The extent of this activity is related to the degree of functional impairment, which is highest in patients with high impairment[20]. This process has been shown to interfere with the patient's motor recovery and contribute to the reduced activity of the paretic hand[24]. Meanwhile, effective rehabilitation paradigms such as CIMT and Mirror therapy have shown evidence of modulating this interhemispheric imbalance by inducing brain reorganization and increasing the cortical excitability of the ipsilesional motor cortex, which in turn adjusts the IHI in patients post-stroke[19–23]. The following section will discuss different physical therapy interventions utilizing evidence of the interhemispheric competition model.

Physical therapy interventions for upper-limb post-stroke

Constraint-induced movement therapy

Evidence supporting the interhemispheric competition model stems from studies showing that patients with stroke attempting to move with the paretic hand fail because the unaffected hemisphere inhibits the affected hand and does not switch to the facilitation mode at the time of movement onset[24]. This impairment of upper-limb function can result in the non-use of the affected limb, which becomes learned over time and leads to the progressive decline of the affected limb function[11]. As a result, patients with stroke rely mainly on their non-affected upper limbs for most of their daily activities and avoid using their affected arm. This learning non-use phenomenon has been widely documented among patients post-stroke[9,11,25]. Meanwhile, most rehabilitation intervention practices focus on facilitating the patient's overall movements and functional independence, regardless of maximizing movement gain in the affected arm, leading to many compensatory mechanisms associated with maladaptive neuroplasticity[25,26]. In this view, functional independence does not mean promoting adaptive neuroplasticity with an emphasis on increasing functional gain in the affected hand; it simply means allowing the patients to use what is available for them, that is the non-affected hand, to get the job done. Thus, rehabilitation paradigms that targeted the affected limb based on neuroplasticity principles, such as CIMT, were developed[11].

The CIMT is based on the "learning non-use" theory and has been used in clinical and research neurorehabilitation settings to reverse learned non-use[11]. The CIMT or modified CIMT (m-CIMT) is a multifaceted neurorehabilitation intervention used in stroke patients to improve upper-limb motor function[9,26]. The basic principle of CIMT depends on facilitating the use of the affected limb to complete task-oriented repetitive training while restricting the movement of the unaffected limb and transferring the affected upper-limb use into the daily activities of stroke patients[27]. Thus, it indirectly reverses the interhemispheric imbalance communication that occurs post-stroke. Evidence supporting CIMT utilizing the interhemispheric competition model comes from neuroimaging and brain stimulation studies using transcranial magnetic stimulation (TMS) and functional magnetic resonance imaging (fMRI), showing that CIMT increased recruitment in the ipsilesional somatosensory cortex (SMC) and adjusting the IHI, which was accompanied by improvements in hand function as measured by the Wolf motor function test (WMFT) and Fugl Meyer assessment (FMA), as well as increased map expansion of paretic hand muscles in the ipsilesional motor cortex[26,28,29]. However, research has shown that CIMT is effective for patients with mild to moderate stroke and less effective for those who suffer from severe stroke.

Furthermore, CIMT requires the patient's unaffected hand to be constrained for ~90% of the waking hours with a minimum of

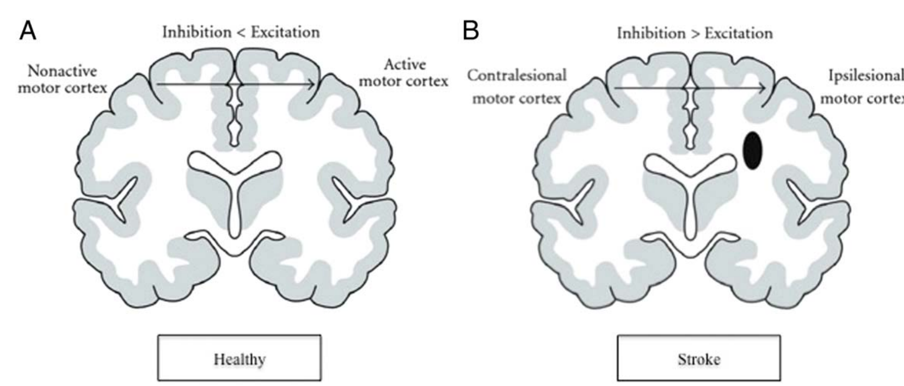

Figure 1. Interhemispheric interaction in healthy (A) and stroke (B) subjects (adapted and modified from Takeuchi *et al.*, 2012)

three hours of daily practice for the affected limb[28–30]. Thus, it's time-consuming for the patients and the therapists. Given the limited duration of the physical therapy sessions and the variety of stroke patients' severity, CIMT applicability is limited in clinical sitting.

Mirror therapy

Another way to target the lesional hemisphere and minimize inhibition from the contralesional hemisphere is to maximize the excitatory signal coming to the ipsilesional hemisphere, as neuroplasticity also occurs by involving brain regions distant from the affected site[29]. This neuroplasticity reveals bihemispheric changes in brain activity during movement of the affected limb, indicating brain reorganization, as evidenced by fMRI imaging studies[29]. An example of this form of neuroplasticity has been seen in Mirror therapy, which is a cognitive intervention technique that creates a visual illusion of movement in stroke patients utilizing the unaffected arm to activate the ipsilesional hemisphere by activating the mirror neuron system[30,31]. Thus improving motor performance on the affected side. Mirror therapy indirectly activates the ipsilesional primary motor area (M1) by activating mirror neurons in the pre-motor cortex, supplementary motor region, primary somatosensory cortex, and inferior parietal cortex[32]. A study by Rossite and colleagues investigated the cortical mechanism of Mirror therapy after stroke and found an activation of the ipsilesional M1 following Mirror therapy[33]. The duration of Mirror therapy ranges in the literature from 30 min to an hour, which seems reasonable to fit within the physical therapy sessions[34,35]. Interestingly, studies have shown that Mirror therapy can induce activation patterns similar to the action execution of the affected arm[36]. Although the neurological mechanism of CIMT is different than Mirror therapy (as presented in Fig. 2), both interventions activate the ipsilesional M1.

Mirror therapy helps patients with stroke experience sensory, perceptual, and motor deficits[12,37,38]. When comparing Mirror therapy with conventional physical therapy interventions, Mirror therapy showed superior upper-limb recovery in both acute and chronic patients with stroke[38]. The advantage of using Mirror therapy is that it uses different sensory feedback to help patients with even severe upper-limb movement limitations[39]. Utilizing Mirror therapy showed significant improvements in upper-limb functions as measured by the box and block test[40] and motor wolf tests[41,42]. Mirror therapy has been utilized in actual and virtual reality settings[43]. Combining Mirror therapy with virtual reality offers various plans and settings for Mirror therapy. Mirror therapy in virtual reality transforms simple movements into practical activities, providing a more enjoyable and effective treatment[43]. This method offers more cognitive and perceptual training opportunities that can be easily applied in real-life situations[43]. This combination of Mirror therapy and virtual reality showed improvements in the upper extremities' motor function in patients with stroke more than traditional Mirror therapy, as evidenced by an increase in the FMA hand subgroup and total FMA scores[39,43]. These findings suggested the benefit of implementing technologies such as virtual reality in rehabilitation for patients with stroke. Interestingly, combining Mirror therapy with CIMT is superior to CIMT or conventional physical therapy alone[44]. Other studies have shown that the CIMT could improve upper-limb functions more than Mirror therapy[45,46]. However, these studies did not implement Mirror therapy in virtual reality settings or use a combination of assistive technologies with rehabilitation, which reflects a long-standing belief among rehabilitation specialists that the duration and intensity of rehabilitation interventions are more important factors dictating patients' motor recovery.

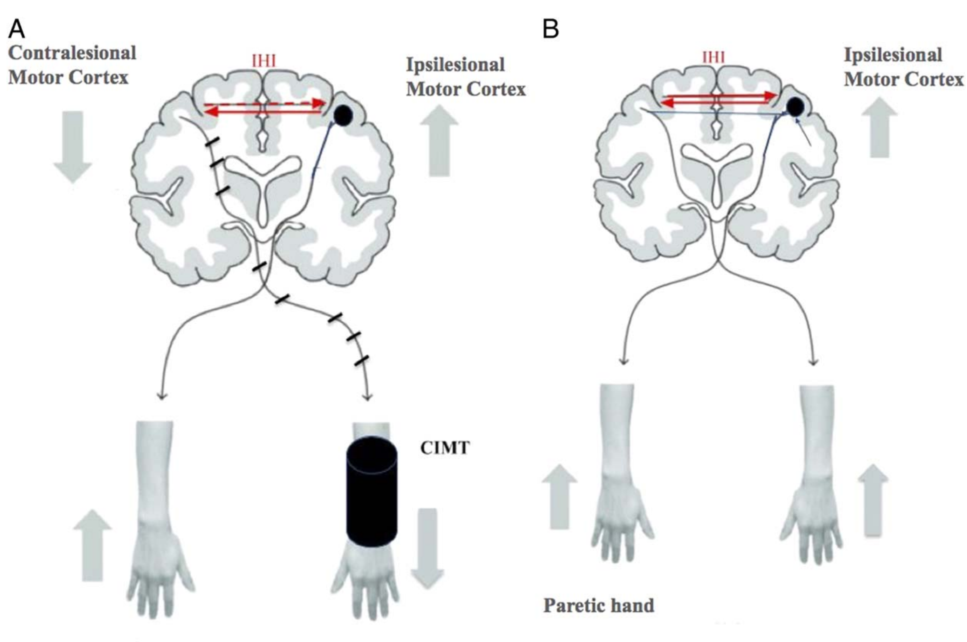

Figure 2. Hypothetical neural mechanism of constrained induced movement therapy (A). Mirror therapy (B). IHI: Interhemispheric Inhibition, CIMT, constrained induced movement therapy.

More research is needed to determine whether intensive rehabilitation training such as CIMT is superior to using a combination of technologies with rehabilitation, such as Mirror therapy in virtual reality, to improve upper-limb function for patients with stroke. In addition, further research is needed to determine the neurophysiological and functional changes associated with combining rehabilitation with advanced technologies compared with highly intensive repetitive training such as CIMT.

tDCS enhances upper motor recovery for patients with stroke

Rehabilitation is essential for upper-limb motor recovery after stroke, aiming to improve motor function and reinforce independence by limiting the severity of the initial injury, reducing functional loss, and improving overall motor performance[47]. Several neurorehabilitation treatments, such as CIMT and Mirror therapy, can indirectly modulate the motor cortex, resulting in greater upper-limb motor function[11,12]. Meanwhile, non-invasive brain stimulation (NBS), such as tDCS, can directly stimulate the targeted brain areas and modify the IHI in patients with stroke[48]. With tDCS, a low level of constant electric current can be delivered over the scalp to induce changes in brain activity, thus modulating cortical excitability and promoting the efficacy of the motor output[48,49]. tDCS can be used as a potential technical adjuvant to neurorehabilitative interventions to optimize brain plasticity by stimulating the primary motor cortex (M1)[15,16].

Different tDCS montages may induce different effects on neuronal networks, which depend on electrode placement and its polarity[49–52]. For instance, anodal (a-tDCS) stimulation led to an increase in the excitability of the ipsilesional hemisphere and was correlated with improved upper-limb functional outcome measure scores and patients' performance in activities of daily living post-stroke while the cathodal electrode over the contralateral induced subthreshold depolarization, promoting cortical excitation M1[4,22,23]. This tDCS technique can be easily applied to other rehabilitation interventions[42,49–60]. The use of tDCS for motor recovery after stroke is based on the interhemispheric competition model, which aims to adjust the abnormal interactions between the two hemispheres by inducing changes in the resting membrane potential of the neurons, leading to depolarization (excitation) of the lesioned hemisphere through anodal tDCS (a-tDCS), or hyper-polarization (inhibition) of the contralesional hemisphere through cathodal tDCS (C-tDCS), or combining a-tDCS (lesioned hemisphere) and C-tDCS (contralesional hemisphere)[49].

A combination of CIMT and tDCS has demonstrated interhemispheric modulation between the ipsilesional and contralesional hemispheres when motor-evoked potential amplitudes were compared pre- and post-intervention[46,60]. Furthermore, previous studies have demonstrated that combining tDCS with physical therapy might improve upper-limb motor recovery more than using physical therapy intervention or tDCS separately[42,56]. CIMT and bihemispheric tDCS have shown similar neural mechanisms of decreasing neural activity in the contralesional hemisphere and increasing neural activity in the ipsilesional hemisphere (Fig. 3A and B)[61–63]. Mirror therapy and anodal tDCS applied on the ipsilesional M1 can both increase the

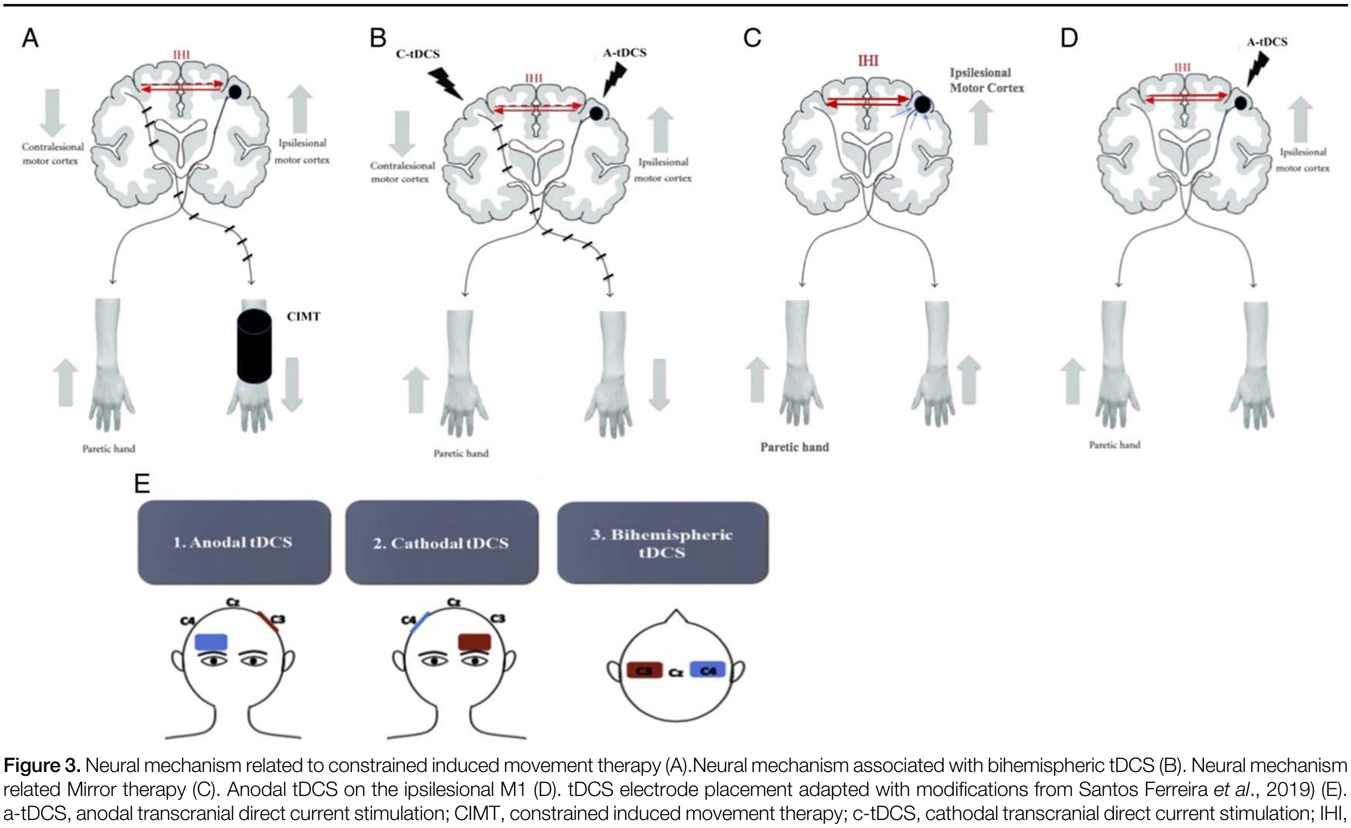

Figure 3. Neural mechanism related to constrained induced movement therapy (A).Neural mechanism associated with bihemispheric tDCS (B). Neural mechanism related Mirror therapy (C). Anodal tDCS on the ipsilesional M1 (D). tDCS electrode placement adapted with modifications from Santos Ferreira *et al*., 2019) (E). a-tDCS, anodal transcranial direct current stimulation; CIMT, constrained induced movement therapy; c-tDCS, cathodal transcranial direct current stimulation; IHI, interhemispheric inhibition; tDCS, transcranial direct current stimulation.

ipsilesional M1 cortical excitability, which in turn increases the inhibition from ipsilateral to contralateral M1 (Fig. 3C and D)[64].

Many studies have investigated the effect of combining tDCS stimulation with CIMT or Mirror therapy in patients with stroke to improve upper-limb recovery and promote adaptive brain plasticity. Specifically, Kim[56] assessed bihemispheric tDCS compared with sham stimulation combined with CIMT in patients with chronic stroke and concluded that tDCS enhanced the effects of CIMT. Participants who received tDCS with CIMT showed improved upper-limb function and increased use of the affected upper limb in daily activities[56]. While Rocha[65] examined anodal tDCS and cathodal tDCS compared to sham tDCS stimulation in chronic stroke patients, the group that received anodal tDCS appears to have a greater impact on improving the effects of CIMT on motor recovery than cathodal tDCS. In contrast, Garrido, 2022, investigated CIMT with bihemispheric tDCS compared to sham stimulation in patients with acute and subacute stroke and found significant improvements in the FMA and WMFT scores in the active tDCS + CIMT group[66].

On the other hand, the effect of pairing tDCS with Mirror therapy has been demonstrated in previous studies, which showed that these combinations were effective in helping chronic stroke patients regain motor function in their paralyzed upper limbs[67–69]. For example, Cho and colleagues investigated the effects of combining anodal tDCS with Mirror therapy on patients with chronic stroke[42]. The study showed that this combination significantly improved patient motor outcome measures such as the FMA, Box and Block Test (BBT), and grip strength. However, this study used traditional Mirror therapy and did not use Mirror therapy in virtual reality. On the other hand, a study by Chen, 2017, examined the concurrent effects of combining mirror visual feedback (MVF) and anodal tDCS on ipsilesional M1 excitability among healthy individuals compared to using tDCS alone[69]. Motor-evoked potential amplitude (MEPs) was greater compared to utilizing tDCS alone. To date, no study has been conducted to investigate the effects of combining Mirror therapy in virtual reality settings and different tDCS montages among patients with stroke.

The findings from the above-mentioned studies suggested that combining tDCS with CIMT and Mirror therapy significantly improves upper-limb function in patients with stroke. However, it is still unclear which modes of tDCS would be optimal for upper-limb motor recovery in patients with stroke. Therefore, future work is needed to determine the different effects of tDCS modes adjunct to CIMT and Mirror therapy on upper-limb motor recovery in patients with stroke. Further work is needed to determine the neurophysiological and functional changes of different montages of tDCS on upper-limb motor recovery in patients with stroke when combined with physical therapy rehabilitation. The hypothetical mechanism of CIMT, Mirror therapy, and tDCS are presented in Fig. 3.

Predictions and future experiments

A review of the literature leads us to conclude that (1) CIMT and Mirror therapy rehabilitation can indirectly modify the brain cortical excitability of the lesional M1 through different mechanisms; (2) tDCS can directly modulate neural activity and adjust the interhemispheric imbalance in patients with stroke;(3) combining CIMT with tDCS can increase cortical excitability (upregulating) of ipsilesional M1 using similar mechanism; and 4) Mirror therapy uses a different mechanism than CIMT to upregulate M1, by activating mirror neurons that connect to the lesional M1. Therefore, we predict that combining CIMT and Mirror therapy with tDCS would maximize the cortical excitability of ipsilesional M1 by recruiting M1 (affected) and the circuits connected to it via mirror neurons and minimizing the inhibition of contralesional M1. With this combination, we can magnify the effect of these interventions, which may lead to greater improvements in upper-limb functions in patients post-stroke. However, rehabilitation specialists would need to investigate the required dose, intensity, and duration of these combinations to be applied within the rehabilitation sessions. This may lead to new experiments that challenge traditional rehabilitation procedures or unimodal approaches utilized in current rehabilitation settings for the upper limbs in patients post-stroke.

Ethical approval

This paper is a review paper; there was no ethical approval required.

Consent

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Author contribution

The study concept, design, data analysis or interpretation, writing the paper all was conducted by A.A.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

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