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HOT TOPIC

Non-invasive Brain Stimulation in Physical Medicine and Rehabilitation

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Abstract The non-invasive brain stimulation techniques of transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have developed considerably over the last 25 years. Recent studies have used these techniques to enhance motor and cognitive function, modulate psychiatric symptoms, and reduce pain. Here, we briefly present TMS and tDCS techniques, discuss their safety, and provide examples of studies applying these interventions to enhance movement function following stroke. Though further studies are required, investigations so far provide important first steps in the use of non-invasive brain stimulation techniques to aid routine rehabilitation therapy. We discuss future directions for the field in terms of study development, choice of motor task, and target sites for stimulation.

Keywords Transcranial magnetic stimulation (TMS) · Transcranial direct current stimulation (tDCS) · Motor function · Upper limb rehabilitation · Lower limb rehabilitation · Speech rehabilitation

Introduction

Non-invasive brain stimulation techniques developed since the late 1980s have been used to modulate both brain function and behavior. Here we provide an overview of two of the most frequently used forms of non-invasive brain stimulation; transcranial magnetic stimulation (TMS); and transcranial direct current stimulation (tDCS). We review applications of these techniques in the context of physical medicine and rehabilitation, with particular emphasis on their use as an adjuvant strategy to enhance function in stroke patients. Finally, we consider future applications of these techniques informed by meta-analytical evidence and recent studies in healthy individuals.

Transcranial Magnetic Stimulation

Developed by Barker et al. [1], TMS uses the principle of electromagnetic induction to painlessly stimulate neural tissue [2, 3]. A TMS coil is positioned on a region of the head overlying the targeted brain area. A brief current is produced in the coil to generate a magnetic field, which in turn induces an electric field in the brain, activating neurons in the vicinity of the coil. The geometry of the coil used for TMS affects the focality and depth of the stimulation [4, 5]. The most frequently used coil design comprises two circular coils wound in a figure-of-eight pattern, allowing focal stimulation at their intersection. TMS applied over the primary motor cortex (M1) activates the corticospinal system (Fig. 1). TMS can activate pre-synaptic neurons to the pyramidal cells, allowing detection of plastic changes occurring at cortical level. If the intensity is large enough to activate the pyramidal cells, the corticospinal tract is engaged, resulting in muscle contractions. Thus, electromyography can be used to record the resulting compound action potentials, known as motor evoked potentials (MEPs). It is possible to measure the level of M1 excitability by studying the amplitude of the MEPs, for instance by calculating the 'resting motor threshold'—

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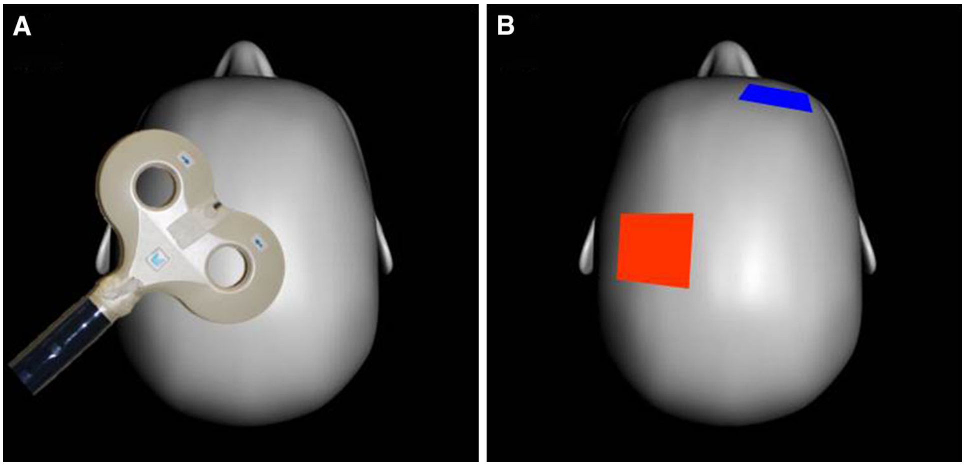

Fig. 1 Illustration of stimulation protocols to target the left primary motor cortex. **a** A standard 'figure of eight' TMS coil. **b** A tDCS electrode montage, with the excitatory anodal electrode (*red*) over the primary motor cortex, and the inhibitory cathodal electrode (*blue*) over the contralateral supraorbital region (Color figure online)

defined as the intensity of TMS stimulus required to elicit 5/10 MEPs of at least 50 µV in amplitude [6].

A single TMS pulse is brief in duration (lasting approximately 0.35 ms [7]) and elicits effects lasting in the order of milliseconds [1]. In comparison, repetitive TMS (rTMS) techniques, which involve stimulating at a fixed frequency for several minutes, can induce longer lasting excitability changes. Applied over the motor cortex, rTMS at a frequency of 1 Hz leads to reduced cortical excitability [8], while rTMS at frequencies in the range of 3–25 Hz increases it [9]. Such effects last for around 30–60 min, depending on the protocol. More recent studies have used patterned TMS protocols such as theta burst stimulation, in which high frequency (50 Hz), but short duration and low intensity trains of stimulation result in changes that last 30–60 min [10]. The finding that rTMS can change excitability for a prolonged time led to tests of its use to affect behavior in a therapeutic manner. However, it is important to keep in mind that there is considerable between-subject variability in responses to both repetitive and patterned TMS protocols [11, 12].

Studies using TMS as a therapeutic tool face the challenge of applying appropriate sham stimulation for placebo control interventions. TMS can cause tactile sensations under the coil that are difficult to replicate in sham conditions. Sham TMS coils are available, but generally only mimic the noise produced when the stimulator discharges. Because of this many studies apply sham stimulation by delivering TMS to an inert region. Thus, the potential to conduct effective double blind experiments using TMS is limited.

Transcranial Direct Current Stimulation

Animal studies have demonstrated that applying weak direct currents to the brain can induce long-lasting enhancements or reductions in cortical excitability [13, 14]. This occurs through modulation of neuronal activity rather than forcing direct neuronal depolarization as in the case of TMS. Recent studies in humans show that applying tDCS induces reliable and long-lasting (yet reversible) changes in cortical excitability [15]. These neuromodulatory effects are mediated by changes in TrkB and NMDA receptor activation [16] and GABA activity [17]. This ability to enhance cortical excitability for periods ranging from minutes to approximately an hour has led to tDCS being used to enhance behavioral processes such as those related to motor learning [18, 19, 20, 21•] and tests of its application as an adjuvant of rehabilitation training.

Typical tDCS protocols involve placing two saline-soaked sponge electrodes on the head and passing a small electric current (normally 1–2 mA) between then. The position, polarity, and intensity of stimulation are all important factors in tDCS. Positioning the positive (anodal) electrode over a target brain region typically leads to an excitatory effect, while positioning the negative (cathodal) electrode over the target leads to an inhibitory effect [15, 22]. Frequently utilized electrode montages involve placing one electrode over a targeted brain region, and another over an inert region for the task being studied (e.g., the cheek or supraorbital region).

tDCS is applied by gradually increasing the current in a ramp-like manner (typically over 10–30 s) until it reaches the desired intensity, leaving the stimulation at the desired level for several minutes, and then ramping the current down again. Applying current can lead to 'itchy, tingly' sensations under the electrodes. Although the perceived intensity of these sensations varies between individuals, participants typically habituate to them within a few minutes. Sham tDCS conditions are conducted by ramping the current up to the desired intensity and then by immediately ramping it down again. This procedure provides the same initial tactile sensations as real tDCS, yet the duration of stimulation is so short that substantial excitability changes cannot develop. Importantly, this short application is generally convincing, especially to participants who have not previously experienced tDCS. Notably, tDCS machines can perform this ramping procedure automatically, allowing researchers to conduct double blind experiments with a convincing sham condition.

Though modeling studies have begun to use MRI data and realistic head models to predict the distribution of currents produced by tDCS [23–26], our understanding of this process is still incomplete. Furthermore, safety considerations related to current density (discussed below) result in tDCS studies employing relatively large electrodes (typically 5 × 5 cm), limiting focality. However, recent studies have varied the size of the active and reference electrodes, delivering focal stimulation while maintaining safe current densities (see for example Vollmann et al. [27]).

Safety Considerations

Non-invasive brain stimulation techniques are generally considered safe, with low level of risk of adverse effects. The most serious adverse events are the occurrence of seizures in response to TMS. However, in the majority of these cases participants received rTMS procedures in excess of existing safety guidelines, and/or in patients receiving treatment with drugs that may lower the seizure threshold [28, 29]. Since the development of safety guidelines, TMS-induced seizures are considered to be extremely rare events, especially when considering the number of subjects who have undergone TMS procedures without complications [29].

In tDCS, the current density and total charge should be carefully monitored. Values too high can result in the electrode burning the skin. This can be minimized by carefully controlling the current and electrode sizes. Ideally, tDCS should be delivered using non-metallic electrodes completely covered by sponges soaked in saline solution. Only the sponges should be in direct contact with the skin, minimizing the chance of burns [30].

More mild reactions to non-invasive brain stimulation may include headaches, dizziness, nausea, and muscular discomfort [31]. Such effects are reported to occur in approximately 1/20 TMS sessions [31], and anticipation or anxiety related to perceived side effects of non-invasive brain stimulation may exacerbate these effects [29, 31]. Altogether, non-invasive brain stimulation procedures are considered to be safe and well tolerated [28, 29, 31].

Non-invasive Brain Stimulation in Physical Medicine and Rehabilitation

Non-invasive brain stimulation has been applied across a diverse range of populations in physical medicine and rehabilitation. This includes applications in patients with stroke, spinal cord and traumatic brain injuries [32–34], and enhancing recovery from behavioral disorders (e.g., hemispatial neglect [35], phantom limb pain, fibromyalgia, and treatment of chronic pain disorders [36–38]). For practical purposes, this review will focus on the large body of literature in which TMS and tDCS have been applied to enhance recovery of motor function following stroke. These techniques have primarily been used with the goal of augmenting cortical reorganization and restoring balance to a hypothetical abnormal interhemispheric balance.

Motor recovery following stroke is associated with cortical and subcortical reorganization, where different brain regions attempt to compensate for the loss of damaged tissue. This can occur at local, secondary motor, and bihemispheric levels (for a review see Hoyer and Celnik [39]. The level at which reorganization occurs is typically associated with both the phase of recovery and the overall severity of impairment. Neuroimaging studies indicate that contralesional activity may be important during early recovery, but typically activation returns to the ipsilesional hemisphere at later stages in those who recover well [40, 41]. Ipsilesional activity is typically associated with better motor recovery [42••], whereas patients with poorer recovery typically show continued contralesional or bihemispheric activation [40, 43, 44], but c.f [45, 46] Several TMS studies have also linked contralesional motor responses to poor recovery [47–50] illustrating the potential for TMS to be used in a diagnostic capacity to localize cortical activity and reorganization.

In the healthy brain, mutual interhemispheric inhibition exerted through transcallosal pathways can be measured via TMS of the primary motor cortex [51]. In the context of movements, chronic stroke patients experience abnormal interhemispheric inhibition. The contralesional hemisphere, the non-stroke side, exerts persistent inhibition of the lesioned hemisphere [52, 53]. When healthy controls perform movements, interhemispheric inhibition turns to excitation just prior to movement onset. By comparison, in chronic stroke patients it remains inhibitory right up until movement execution, a phenomenon associated with poor movement performance [52, 53]. These findings suggested that increasing excitability in the ipsilesional side should balance out the inhibitory tone, the healthy side exerts over the lesioned hemisphere. On the contrary, decreasing activity of the contralesional hemisphere should reduce the inhibitory influence it exerts on the ipsilesional hemisphere, allowing improved movement control.

This model of hand control following stroke [44] resulted in several studies testing the effects of non-invasive brain stimulation in the context of physical rehabilitation. Excitatory stimulation could be applied to the ipsilesional hemisphere to promote activity and reorganization at local and secondary motor levels. Alternatively, inhibitory stimulation could be applied to the contralesional hemisphere, reducing the likelihood of the contralesional or bihemispheric activity thought to be associated with poor recovery, and addressing the imbalance in interhemispheric inhibition brought about by stroke. Another alternative is the application of bilateral stimulation, combining the benefits of exciting the ipsilesional hemisphere and inhibiting the contralesional hemisphere.

As a systematic review is beyond the scope of the current article, here we discuss example studies that have tested these approaches, predominantly by stimulating the primary motor cortex (M1). We focus on representative studies using non-invasive brain stimulation to address upper and lower limb rehabilitation, as well as speech.

Upper Limb Rehabilitation

Tms

Khedr et al. [54] were the first to test the effects of rTMS over the ipsilesional hemisphere in acute stroke patients. Patients recruited 5–10 days after a stroke received 10 daily sessions of 3 Hz rTMS, just prior to daily inpatient rehabilitation therapy sessions. A matched control group of patients received sham TMS with the coil angled away from the head. A blinded rater found that reductions in motor impairment were greater in the real than the sham rTMS group, and were maintained at least 10 days after the final rTMS session. Although it is difficult to deliver a true sham rTMS condition (in this case, participant's previous experience of single pulse TMS may have allowed them to identify sham rTMS), this study illustrates the effectiveness of stimulating the ipsilesional hemisphere. A follow-up by the same group investigation indicated this protocol led to significant reductions in motor impairment that were still present a year later [55••]. These studies provide a strong case for using neurostimulation techniques early in recovery to enhance responses to traditional therapies.

Mansur et al. [56] used a blind crossover design to examine the effects of inhibitory rTMS over the contralesional motor cortex. The study also included TMS delivered with a sham coil in a control condition (which produces the same noises as real TMS, but not the stimulation or tactile sensations). Participant reaction times and motor performance improved significantly following real rTMS compared to sham stimulation. Although the effectiveness of the sham condition may be questionable (especially as participants experienced both real and sham rTMS), the significant improvements in motor performance by inhibiting the healthy hemisphere were promising and supportive of the hypothesized model of abnormal interhemispheric balance. A later study combined behavioral measures and neuroimaging to provide a comprehensive overview of the effects of contralesional rTMS in stroke [57]. Participants received either real rTMS of the primary motor cortex, or rTMS over the vertex in a sham condition. Real rTMS led to a small but significant improvement in motor performance (increased frequency of whole hand fist closures) in comparison to baseline and sham conditions. Dynamic causal modeling was used to assess the interactions between brain regions following stimulation. Real rTMS decreased the inhibitory influence of the contralesional hemisphere, and led to a significant increase in coupling between the ipsilesional supplementary motor area and primary motor cortex. The data supported the notion that rTMS of the contralesional motor cortex both reduces its inhibitory influence on the ipsilesional primary motor cortex, and enhances motor processing in the ipsilesional hemisphere.

tDCS

Two double blind crossover sham-controlled studies by Hummel et al. [58, 59] demonstrate for the first time the efficacy of applying excitatory (anodal) tDCS to the affected hemisphere. The first one [58] assessed manual control using the Jebsen-Taylor hand function test. Following baseline assessments, participants completed the task while receiving either excitatory or sham tDCS. Excitatory tDCS led to significant improvements in performance (reduced movement durations) that were not present in the sham condition. A later study [59] showed similar effects, with anodal tDCS reducing reaction times and showing trends for increased pinch forces. It should be considered that both papers examined patients with relatively low levels of impairment (reported average upper body Fugl-Meyer scores of 90–95 %), with primarily subcortical lesions that did not involve the primary motor cortex. Furthermore, the effects of tDCS appear to be transient; while motor performance was improved for at least 25 min following stimulation, testing on subsequent days showed that performance had returned to baseline levels.

A more recent study has shown that inhibitory (cathodal) tDCS over the contralesional motor cortex can enhance skill acquisition in the paretic hand [60•]. In a blind crossover design participants, practiced a finger movement task while receiving either cathodal or sham tDCS. Training led to an increase in the rate at which participants could accurately complete the sequence, and this was greater when participants received cathodal compared to sham stimulation. This illustrates that reducing excitability of the contralesional hemisphere can enhance motor performance in the ipsilesional hand.

The potential to apply tDCS using a bihemispheric montage (e.g., excitatory anodal stimulation of the ipsilesional hemisphere, and inhibitory cathodal stimulation of the contralesional hemisphere) has also been explored. In a study by Lindenberg et al. [61], patients received bihemispheric or sham tDCS in combination with their normal physical or outpatient therapy for five consecutive sessions. Patients receiving bihemispheric stimulation showed greater improvement in motor performance than those receiving sham stimulation. While this indicates that bihemispheric stimulation led to improved performance, it is difficult to ascertain whether similar results could have been found with unihemispheric stimulation [see 62].

Lower Limb Rehabilitation

Relatively few studies have used non-invasive brain stimulation to enhance lower limb function and/or gait. An early study combined TMS with peripheral nerve stimulation, adapting a ‘paired associative stimulation’ (PAS) paradigm. Uy et al., [63] used this approach to stimulate the affected leg of stroke patients. Having experienced PAS stimulation daily for four weeks, neurophysiological measures were variable, with five of the nine patients exhibiting increases in cortical excitability. However, while two separate baseline measures of performance did not differ, the group showed a significant improvement in several functional measures of walking following the intervention. These data indicate that such paired associative stimulation protocols may enhance walking function in stroke survivors. Though the consistency across the two baseline sessions indicates that placebo effects are unlikely, further evidence for the efficacy of this paradigm could be provided using a sham stimulation control group.

Later work compared the effects of rTMS, PAS, and tDCS in lower limb rehabilitation. Using a crossover design, Jayaram and Stinear [64] compared inhibitory rTMS of the contralesional motor cortex, inhibitory PAS of the contralesional hemisphere, and excitatory (anodal) tDCS of ipsilesional motor cortex during locomotion. All protocols increased excitability of the ipsilesional hemisphere and decreased excitability of the contralesional hemisphere, but none of the protocols were stronger than the other in causing these excitability effects. Thus, these protocols appear to have similar effects on the corticospinal system, and are all viable approaches to enhance rehabilitation training. Excitatory (anodal) tDCS has subsequently been applied to the motor cortex to improve fine motor control of the hemiparetic ankle [65]. Participants moved a cursor to track a sinusoidal wave by performing ankle flexion and extension movements. Performance was greater when they received anodal stimulation in comparison to sham. This provides evidence that tDCS can be used to enhance motor function in the lower limbs.

Compelling evidence that non-invasive brain stimulation can enhance motor function of the lower limbs comes from a clinical trial of the use of rTMS and task-orientated training [66]. Participant received either inhibitory rTMS of the contralesional motor cortex or sham stimulation (the coil was held perpendicular to the position used in real rTMS) prior to 10 sessions of physical training. Patients receiving real rTMS achieved a more symmetrical walking pattern than participants who received sham rTMS. This study provides further evidence that non-invasive brain stimulation can augment responses to training in the lower extremities (albeit with the caveat that it is difficult to provide a true sham condition using rTMS).

Speech Rehabilitation

Recent studies have used non-invasive brain stimulation to enhance speech production following stroke. Compelling evidence is provided by a randomized, double blind clinical trial of bihemispheric rTMS in post stroke aphasia [67••]. Participants in a real rTMS group received inhibitory stimulation over the right hemisphere counterpart of Broca’s area, followed by excitatory stimulation over Broca’s area. Sham rTMS was delivered with the coil held at 90 degrees to the target brain area. All participants completed a language-training program after receiving rTMS for 10 days. Training improved language skills in both groups, but improvement was greater in the bihemispheric rTMS group compared to the sham group. Importantly, this effect persisted at follow-up testing sessions 1 and 2 months after training, illustrating significant and lasting benefits of adjuvant therapy with non-invasive brain stimulation.

Studies using tDCS to facilitate recovery from aphasia have provided interesting, yet seemingly contradictory results. Monti et al. [68] applied tDCS over left frontotemporal regions, positioning the electrodes over Broca’s region based on the 10–20 EEG system. Participants performed a picture-naming task before and after receiving tDCS. They found a polarity-dependent effect where cathodal stimulation led to improved performance on a picture-naming task, while anodal and sham stimulation had no effect. The authors attributed this effect to decreased activity in cortical inhibitory circuits and argued that this lead to disinhibition of the impaired language areas. A later double blind, sham-controlled study by Baker et al. [69] provided contrasting results. Neuroimaging was used to identify the area of the left frontal cortex showing the greatest activation during correct naming of pictures. Anodal or sham tDCS was applied over this region for 20 min, while participants performed a word-naming task, and this procedure was repeated for five consecutive days. Results revealed that training-related improvements in picture naming were almost doubled when training was combined with excitatory tDCS, relative to the sham condition. While the contrary results of these studies can potentially be explained by incongruence in electrode placement and the timing of stimulation in relation to testing, they also point to disparity of the literature on tDCS effects in aphasia.

Alternate Targets for Stimulation

When discussing facilitation of recovery from brain lesions, one of the domains that has received most attention so far has been the motor system. Although a lot of work has been done in this area, many questions remain open. One fundamental issue is what particular component of the motor system should be targeted to facilitate recovery. Here we discuss this question in the context of the motor domain. However, similar considerations should be given in the future when addressing the use of non-invasive brain stimulation to facilitate recovery and/or function of other domains (i.e., cognition, language, and perception).

Motor learning is thought to be one of the important process that takes place during recovery of motor function following stroke [70, 71]. Recent meta-analytical evidence indicates brain areas crucial to motor learning show additional activation following stroke [42, 72]. Secondary motor regions (i.e., the premotor cortex and supplementary motor area) and the cerebellum present viable targets for enhancement with neurostimulation techniques. In particular, the premotor and supplementary motor cortices are frequently associated with cortical reorganization following stroke [39].

In healthy individuals, the dorsal premotor cortex is associated with movement preparation [73, 74] and has been identified as a key node for motor learning [72]. Stroke patients with more severe impairment are less likely to show dorsal premotor activity, suggesting that this area might play an important role in the recovery of motor function [42]. The ventral premotor cortex is essential for the visuospatial coordination underlying grasping actions [74–76], and stroke survivors typically show bilateral increases in ventral premotor activity following stroke [42]. The supplementary motor area is typically associated with the self initiation of voluntary movements [77, 78]. Evidence from neuroimaging indicates increasing the activity of the ipsilesional supplementary motor area may also benefit the ipsilesional primary motor cortex [79], and increases the coupling between these regions are associated with improved motor performance [57]. In primates, secondary motor regions have reciprocal connections with the primary motor cortex and contribute to the corticospinal tract, yet are typically thought to have limited ability to influence direct movement execution [80, 81]. However, these connections make secondary motor regions uniquely suited to play a key role in cortical reorganization following stroke [50]. The potential to enhance recovery by applying neurostimulation techniques to secondary motor regions is, therefore, gaining increased attention [82, 83].

The cerebellum is also a promising target for neurostimulation interventions in stroke. In healthy individuals, one cerebellar hemisphere interacts with the contralateral motor cortex [84, 85]. Cerebellar activity is greater in stroke survivors who show better recovery [42]. The cerebellum is also essential to the process of adaptive motor learning to account for changes in the environment [86], and recent neurostimulation studies in healthy individuals have suggested how this may be utilized in physical rehabilitation [87]. While stroke patients may show asymmetric gait patterns due to hemiparesis, their locomotor symmetry can be improved by walking on a split belt treadmill [88]. Participants adapt to the difference in speeds between the two belts using cerebellum dependent mechanisms [89], and anodal cerebellar tDCS can enhance the rate of acquisition of this new walking pattern [20]. Interestingly, research from other tasks using adaptation paradigms indicates that healthy participants who spend longer periods in an adapted state show increased retention of that state [90]. Applying anodal tDCS to expedite adaptation would, therefore, allow stroke patients the benefit of moving in more symmetrical walking patterns for longer periods of time. Importantly, most neurological patients suffering hemiparesis do not have cerebellar lesions. Thus, applying non-invasive brain stimulation to the cerebellum to facilitate recovery might be a more efficacious approach than directly stimulating the injured cortex.

Limitations and Future Directions

This review highlights evidence supporting the efficacy of applying non-invasive brain stimulation in the context of neuro-rehabilitation. However, it is important to consider that recent systematic reviews have identified a lack of ‘strong’ evidence for the application of non-invasive brain stimulation in motor and language rehabilitation [91–93]. Further randomized controlled trials with parallel group designs and larger sample sizes are required to clarify whether non-invasive brain stimulation is truly effective when treating larger populations that are not carefully selected to participate in lab-based research. In other words, large clinical trials are still needed to show the exact effectiveness of non-invasive brain stimulation in the field of physical medicine and rehabilitation.

A factor to consider of many studies testing brain stimulation in neurological patients is that the majority of the investigations to date have examined patients with relatively low levels of impairment. This is likely attributed to the general finding that neurostimulation techniques enhance behavioral performance in conjunction with performing a training task, and thus only participants who are able to perform a task to begin with are included in the studies. Future investigations combining the use of assistive devices with neurostimulation [e.g., 94] will address this limitation.

Another important consideration for studies testing the effects of brain stimulation in the treatment and management of neurological patients is that both the phase of recovery and degree of impairment affect cortical reorganization. Thus, studies need to consider assessing which brain areas are relevant during movement, language, or cognitive task performance to appropriately determine the ideal target for neurostimulation interventions. Similarly, it is assumed that non-invasive brain stimulation in stroke acts to rebalance interhemispheric interactions. However, relatively few studies have examined how the interventions affect interhemispheric activity at a physiological level [57, 64], and no studies have directly assessed whether non-invasive brain stimulation rebalances interhemispheric inhibition.

A further limitation of many studies assessing brain stimulation after stroke is that the large majority have tested patients with subcortical strokes, with little emphasis on patients with lesions to cortical regions, especially the primary motor cortex. There is also concern that applying neurostimulation techniques to brain regions with a chronic lesion filled with cerebrospinal fluid can lead to unpredictable spread of the current affecting other areas that were originally not targeted [95].

Despite all these limitations and concerns, several studies now indicate that non-invasive brain stimulation techniques have a positive adjuvant effect when combined with rehabilitation interventions. Thus, future studies will need to address the above-mentioned limitations to determine the true impact that these interventions can have in the clinical rehabilitation setting.

Conclusions

The studies outlined above describe the potential of using non-invasive brain stimulation in physical medicine and rehabilitation. Further randomized, double blind, sham-controlled clinical trials with large sample sizes are required to validate the use of non-invasive brain stimulation as an adjuvant of rehabilitation training. This is the case for studies addressing recovery of motor, language, and other cognitive functions.

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Compliance with Ethics Guidelines

Conflict of Interest RM Hardwick and PA Celnik both declare no conflicts of interest.

Human and Animal Rights and Informed Consent All studies by the authors involving animal and/or human subjects were performed after approval by the appropriate institutional review boards. When required, written informed consent was obtained from all participants.

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- • Of importance
- •• Of major importance

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