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Non Invasive Neuromodulation in Motor Recovery after Stroke: State of the Art, Open Questions and Future Perspectives

Raffaella Chieffo MD*, Giancarlo Comi MD and Letizia Leocani MD, PhD*

Neurological Department, Scientific Institute Vita-Salute University San Raffaele, Institute of Experimental Neurology, Milan, Italy

Abstract

Stroke is the leading cause of adult disability. Unfortunately, less than 40% of stroke survivors completely recover, despite intensive acute care and rehabilitation training. Non invasive brain stimulation (NIBS) techniques have been recognized as a promising intervention to improve motor recovery after stroke. Repeated sessions of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) can, indeed, induce changes in cortical excitability and long term plasticity. Several protocols of stimulation have been already tested and proven efficient in modulating the lesioned as well as the unlesioned hemisphere after stroke. However, not all patients can be considered as responder to NIBS. We provide an overview of the rationale, open questions and future perspectives for NIBS after stroke.

Keywords: Neuromodulation; Stroke: Rehabilitation; Motor recovery

Introduction

Stroke is a leading cause of adult disability in the western world [1]. Sensorimotor and cognitive impairments often have a great impact on quality of life in post stroke survivors. It is well known that the human brain continues to adjust throughout life. After ischemic brain injury, neuroplasticity is particularly active in the first months [2]. However, it has been demonstrated that, even years after stroke, the human brain still retains the capacity to reorganize in response to interventions influencing motor recovery [3]. Several efforts have focused on the development of new restorative therapies. In particular, non invasive brain stimulation (NIBS) techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), constitute an extensive chapter on this topic. The rationale for the application of NIBS for rehabilitation of neurological deficits is its capacity of modulate cortical excitability and induce plasticity in humans. Repetitive TMS (rTMS) refers to regularly repeated single TMS pulses delivered in trains at specific frequencies. In general, low-frequency rTMS (≤ 1 Hz) usually results in cortical excitability reduction [4] in healthy subjects, whereas with higher frequencies (5 Hz or more) cortical excitability is usually increased [5]. Modulation by rTMS does not only depend on pulses frequency. Intensity of stimulation, trains duration and inter-train wait time can be all manipulated to influence neuroplasticity [6]. Theta-burst stimulation (TBS) is a relative more recent technique, consisting in brief bursts of theta frequency low intensity stimuli. TBS delivered in a continuous pattern (cTBS) produces a decrease in motor cortex excitability, while an intermitted paradigm (iTBS) produces an opposite effect [7]. The so called tDCS consists in the application of weak electrical currents through the scalp. This technique utilizes two surface electrodes (anode and cathode), which placement is fundamental for outcome, by determining the direction of the current flow. The montage with anode on the brain region of interest (anodal tDCS) has an excitatory effect (and cathodal tDCS the opposite), possibly through mechanisms involving neuronal membrane depolarization or hyperpolarization respectively [8,9].

In general, a single session of NIBS induces reversible effects that last from a few minutes up to about 1 h. To induce long lasting effects several stimulation sessions are often needed. The mechanisms underlying long-term effects of rTMS are not completely understood. It is likely that a number of interacting mechanisms are involved. There are several evidences that the effects of these NBS techniques are mainly due to long term potentiation (LTP)-like and long term depression (LTD)-like mechanisms [10-13]. Moreover, experiments performed in healthy rat brain shown that NIBS has the ability to mediate neural plasticity by enhancing the expressions of neurotransmitters and neurotrophins, such as glutamate, N-methyl-D-aspartate (NMDA), and brain-derived neurotrophic factor (BDNF) [14-16].

Considering safety, because of the facilitatory effect of high-frequency rTMS, the major concern with its use is the risk of inducing seizures. Luckily, this is a quite rare adverse effect (risk estimate of 1.4% in epileptic patients, less than 1% in healthy subjects) [17]. Seizures can be induced by rTMS when pulses are applied with relatively high frequencies and short interval periods between trains of stimulation that should be always set at more than 1 second [18]. For tDCS, the main problem reported is transient skin reactions below the stimulating electrodes. To effectively minimize risks, safety guidelines have been issued regarding stimulation parameters for both rTMS and tDCS [17,19,20].

NIBS and Upper Limb Motor Recovery

Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies show increase activation of homologous motor areas and secondary motor regions involving both hemispheres during movement of the paretic hand in the acute and postacute phases after stroke [21-23]. The degree of such motor overflow correlated with severity of motor deficit as well as with poor motor outcome suggesting a maladaptive plastic reorganization of the

***Corresponding author:** Letizia Leocani MD, PhD and Raffaella Chieffo MD, Neurological Department and Institute of Experimental Neurology - INSPE, Scientific Institute Hospital San Raffaele, Milan, Italy, Tel: +39-02-2643-3092; Fax: +39-02-2643-3085; E-mail: letizia.leocani@hsr.it

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unaffected hemisphere after stroke [24]. Also in neurophysiological studies an early disinhibition of the motor pathways has been demonstrated. Interhemispheric inhibitory circuits resulted, indeed, altered after monohemispheric stroke [25,26] as well as intracortical inhibition (ICI) over affected and unaffected hemisphere was found reduced in stroke studies [27-30]. Mapping the motor cortex with TMS offers the possibility to study acute and rapid plastic rearrangements of cortical motor output in physiological or pathological conditions [31]. An enlargement of the map of output from the unlesioned primary motor cortex to the contralateral hand has been documented in the subacute phases of cortical and subcortical stroke [32,33].

Although acute hyperexcitability of the unaffected hemisphere tends to recover over time, it has a negative prognostic value on motor recovery and it has been associated with a transitory motor impairment of the non paretic hand [32]. Overall, these observations suggest a diffuse and bilateral distress of the motor system occurring after acute stroke. As described by Ward and Cohen (2004) and more recently stated by Nowak et al (2009), the hypothesis of interhemispheric competition proposes that post stroke motor deficits are due to reduced output from the damaged hemisphere not only because of infarct itself but also because of excessive transcallosal inhibition from the intact hemisphere. Motor performance also depends on competitive inhibitory processes between both hemispheres [22,34]. According to the concept of interhemispheric competition, NIBS have been mostly finalized in acute as well as in chronic stroke patients to induced inhibition of M1 of the contralesional hemisphere (low frequency rTMS, cTBS, cathode tDCS) or facilitation of excitability of M1 of the ipsilesional hemisphere (hight frequency rTMS, iTBS, anodal tDCS) in order to normalize the interhemispheric balance through transcallosal connections and to promote output from the lesioned motor cortex [35]. It is necessary to specify that, in the chronic phases after stroke, interhemispheric competition would be less pronounced than in the earlier subacute period, as suggested by the finding that both transcallosal asymmetry [36] and hyperxcitability of the unlesioned hemisphere [32] slow down with time. Although the optimal recovery after stroke well correlates with the reacquisition of innervations from areas surrounding the lesion, in contrast to activation at more distant locations [24], it is possible that the reorganization of the non primary regions in the post-acute or chronic phases may play a constructive role via an interaction with surviving corticospinal tract from the affected hemisphere (AH). Consistently with this view, disruption of activity in contralesional M1 did not greatly impair hand function in patients with chronic subcortical stroke and good motor recovery [37]. For example temporary interference of ipsilesional dorsolateral premotor cortex (PMd) [38] and even more of contralesional PMd [39] using TMS appears to worsen performance of a simple hand motor task in chronic subcortical stroke patients but not in healthy controls.

Inhibition of the Unlesioned Hemisphere

The down-regulation of the unlesioned M1 seems to be effective in the subacute phases and in the chronic phases post stroke as well. Nowak and colleagues (2008) evaluated the effect on fMRI neural activation of a single session of 1 Hz rTMS over the unlesioned M1 in fifteen patients affected by subcortical stroke. They found that rTMS applied to the contralesional M1 improves the kinematics of finger and grasp movements in the affected hand and reduces the overactivity in the contralesional primary and non primary motor areas during a single motor task performed with the paretic hand [40]. Changes in cortical activity are likely related to modifications of intracortical excitably and interhemispheric connections. Indeed, it has been demonstrated that low frequency rTMS reduces the amplitude of motor evoked potentials (MEPs) in contralesional M1, increases excitability in the affected hemisphere and reduces transcallosal inhibition (TCI) from the unaffected toward the affected hemisphere [41,42]. Moreover, the improvement in motor function after 1 Hz rTMS seems to significantly correlate with a reduced TCI duration. The estimated effect size of a single session of low-frequency rTMS or cathodal tDCS on upper limb motor function ranges from 10% to 60% improvement [43]. This effect, in line with effects on cortical motor excitability in human [6,44-46] and animal models [47], is however transitory and outlasts the stimulation period from minutes to 1 – 2 hours. Multiple stimulation sessions and/or the association of a motor training are needed to induce longer lasting effects on cortical excitability and motor function (2-4 weeks) [42,48-50]. In particular, Avenanti et al. (2012) evaluated the effect of 10 daily sessions of 1 Hz rTMS administered either immediately before or after physiotherapy (PT), in 30 subjects affected by chronic subcortical stroke. Treatment induced cumulative rebalance of excitability between the two hemispheres and a reduction of interhemispheric inhibition in comparison PT alone. Moreover, greater and more stable behavioural and neurophysiologic outcomes were found in the group of patients receiving rTMS before PT, whereas the application of rTMS after PT showed a slight improvement that declined over time [51]. On the contrary, cTBS of the unlesioned hemisphere seems to be not effective. Tadelli et al. in 2007 found that cTBS suppressed the MEPs evoked in the healthy hands but did not change motor behaviour or the electrophysiology of the paretic hands in 6 chronic stroke patients [52]. In another study (10 chronic subcortical stroke) paretic upper limb motor function was even impaired by cTBS of the contralesional M1, and this was correlated with reduced ipsilesional corticomotor excitability [53].

Facilitation of the Lesioned Hemisphere

The facilitation of the affected hemisphere appears to be a useful approach to enhance motor function of the paretic limb after stroke and several NIBS protocols have been tested (3 Hz, 5Hz, 10 Hz, 20 Hz rTMS, iTBS, anodal tDCS). Increased of motor cortical excitability within the affected hemisphere, expressed as MEPs amplitude or recruitment curves increase and reduced short interval intracortical inhibition, has been observed after iTBS, anothal tDCS or high frequency rTMS [52,54,55]. The estimated effect size to improve paretic motor function ranges from 10% to 150% for all these methods [43]. Besides differences in the techniques and in the outcome measurements used in these studies, the large variability in results could be influenced by other factors. Amelie and collegues (2009) compared the effect of 10 Hz rTMS over ipsilesional M1 in cortical and subcortical stroke patients. Interestingly, they found that 10 Hz rTMS over the ipsilesional M1, but not over the vertex, improved movement kinematics in 14 of 16 patients with subcortical stroke [56]. On the contrary, rTMS slightly deteriorated dexterity of the affected hand in 7 of 13 cortical stroke patients. These two behavioural effects were associated with different fMRI neural activation patterns. In subcortical stroke, rTMS over ipsilesional M1 reduced neural activity of the contralesional M1, while in cortical stroke caused a widespread bilateral recruitment of primary and secondary motor areas [56]. Moreover, activity in ipsilesional M1 at baseline correlated with rTMS-induced improvement of finger tapping frequency, suggesting that the effectiveness of facilitatory rTMS applied over ipsilesional M1 depends on the functional integrity of the stimulation site and/or the extent of the brain area affected by the stroke [56]. Accordingly, a significant improvement of the paretic upper limb motor function was observed after subcortical stroke, by applying anodal tDCS over the M1 of the affected hemisphere in contrast with little effects in the presence of cortical lesions [57]. A recent meta-analysis showed that NIBS techniques have similar effect in improving recovery in the acute (<2 weeks, but often >1 week), subacute (2 weeks to 6 months) and chronic (> 6 months) phases after stroke [58]. However, a double blind, sham-controlled study on 25 patients after acute stroke undergoing anodal tDCS stimulation (vs 25 undergoing sham) on the affected hemisphere from the second day after acute stroke for five days, failed to demonstrate a significant advantage compared with the sham stimulation group on NIHSS and Fugl-Meyer motor scale [59].

As observed with inhibitory stimulation of the unlesioned hemisphere, also the facilitation of the affected hemisphere trough NIBS seems to be a therapeutic adjuvant to motor training techniques such as conventional physical and occupational therapy, reaching and grasping exercises, robot-assisted arm training [57,60-62]. On the contrary, no significant synergic effects of 20 Hz rTMS over the M1 of the lesioned hemisphere combined with constraint-induced therapy (CIMT) were found in comparison with CIMT alone [63]. Clinical effects of high-frequency rTMS in 17 patients with hemiparesis after stroke (onset > 5 months) have been investigated together with neural correlates [64]. Ten daily sessions of 1000 pulses of real or sham rTMS were applied at 10 Hz over the primary motor cortex of the affected hemisphere, each fifty-pulse train was followed by sequential finger motor training of the paretic hand. Movement accuracy of sequential motor tasks showed greater improvement in the real group than in the sham group, whereas fMRI acquisitions highlighted how patients in the real rTMS group significantly enhanced activation in the affected hemisphere compared to the sham rTMS group [64]. According to these results, high-frequency rTMS coupled with motor training improved motor performance through modulation of activities in the cortico-basal ganglia-thalamocortical circuits.

Bilateral Stimulation Protocol

Both anodal tDCS over the ipsilesional M1 and cathodal tDCS stimulation of the contralesional M1 have been shown to induce amelioration of motor performance of the paretic upper limb as well as changes in cortical excitability [35]. More recently, it has been hypothesized that an additive effect could be produced delivering anodal and cathodal tDCS simultaneously [65]. Positioning the anode over one motor cortex and the cathode over the contralateral motor cortex can induce an increase in cortical excitability on the anodal a decrease in the cathodal stimulated side [66]. Two sham-controlled studies showed a significant improvement of the paretic upper limb motor function in chronic stroke after 1 and 5 consecutive sessions of bihemispheric tDCS (anodal tDCS of the ipsilesional M1 and cathodal tDCS of the contralesional M1) combined with physical therapy [67,68]. A stronger fMRI activation of intact ipsilesional motor regions during movements of the affected limb has been found after 5 session of real treatment whereas no significant activation changes were seen in the control group [67]. These studies suggest that the bihemispheric tDCS application combined with physical therapy may be an ideal strategy to generate functional improvement in stroke patients. However, comparing the effect of the 3 different tDCS montages, more recently findings indicate the superiority of anodal tDCS or cathodal tDCS over bilater tDCS in improving upper limb motor function in chronic stroke patients [69,70]. Also in healthy subjects, anodal and cathodal tDCS induce greater changes in cortical excitability in comparison with bilateral tDCS [66,70].

Open Questions

Recent studies performed on a larger number of subjects failed to demonstrate the efficacy of NIBS techniques in post stroke motor recovery of the paretic upper limb [59,71,72]. These findings are indicative of the fact that not all the subjects may benefit from the application of the different NIBS techniques. Could be, therefore, useful to select patients best responder to NIBS. The identification of clinical, functional, neurophysiological and neurochemical markers of behavioural response to NIBS should help to predict patient outcome. As previously discussed stroke features are fundamental to predict response to NIBS. Effectiveness of facilitatory stimulation of the ipsilesional M1 depends on the functional integrity of the stimulation site and/or the extent of the brain area affected by stroke [56]. In general, a greater effectiveness of NIBS in subcortical stroke patients in comparison with patients with non specified lesion site has been confirmed in a recent meta-analysis [58]. Also baseline severity of the affected upper limb significantly influenced the treatment outcome, greatest results have been observed for less impaired patients [49]. The neurochemical predictors of behavioural response to tDCS after stroke have been searched using magnetic resonance spectroscopy [70]. Higher GABA levels in the ipsilesional M1 – and not in the occipital region – predicted subsequent behavioural gains by anodal tDCS, as measured using reaction time [70]. The authors argued that, as in healthy controls anodal tDCS induces a local reduction in M1 GABA levels [73], patients with high M1 GABA levels may have a higher potential dynamic range for GABA modification by Anodal tDCS [70]. The same authors did not find evidence of correlation between basal M1 GABA and its modification by anodal tDCS in health volunteers [74]. However, even in healthy subjects there is high variability in the neurophysiological and behavioural response to brain stimulation techniques. Many of the factors involved are still unknown, the identified factors have been, instead, summarized in a review by Ridding and Ziemann. Besides some non modifiable factors such as gender, age and genetic (BDNF polymorphism Val66Met), others can be manipulated such as time of the day of the stimulation session, concurrent aerobic exercise, pharmacological intake, attention. More recently, Humada and colleagues hypothesized that different responses to rTMS should be related to individual differences in recruitment of cortical neurons. They examined the effect of inhibitory and excitatory TBS in 56 healthy subject and they found that the effect of TBS was highly correlated with the efficiency of late I-wave recruitment. These results indicate that variation in response to rTMS is influenced by which interneuron networks are recluted by TMS pulse [75]. Further studies are needed to better understand the physiological mechanisms conditioning the response to NIBS techniques.

NIBS and Lower Limb Motor Recovery

Although the ability to walk is impaired in more than 80% of post-stroke patients [76], more efforts have focused on the recovery of the paretic upper extremity than on the recovery of lower limb function. This might be mainly due to functional and anatomical limitations. Concerning the latter, lower limb cortical motor areas are located close to the midline into the depth of the medial longitudinal fissure. These areas are less easily approached with NIBS techniques, especially when dealing with distal muscles. Pathophysiological reorganization of leg motor areas after stroke is still unclear. A study performed with near-infrared spectroscopic imaging system (NIRS) in stroke patients during walking showed that, similarly to upper limb, the cortical activation patterns of motor, premotor and supplementary lower limb motor cortex was greater for the unaffected rather than for the affected hemisphere [77]. Improvements of gait parameters of the paretic lower limb have been found associated with a reduction of the interhemispheric asymmetry of the primary sensorimotor cortical activations [78].

Inhibition of the Unlesioned Hemisphere

Based on the interhemispheric asymmetry between lesioned and unlesioned hemisphere observed after stroke, Jayaram and Stinear evaluated the effect of different NIBS protocols applied during walking on the lower limb motor cortex excitability. They tested the inhibitory paired associative stimulation (iPAS) and the inhibitory 1Hz rTMS applied to preferentially stimulate the unaffected lower limb, as well as the excitatory anodic tDCS applied with electrodes offset to preferentially stimulate the affected M1. They found that all NIBS protocols were effective in modulating excitability of both lower limb motor areas. The modulator effects consisted in the increase of MEPs amplitude over the paretic limb and in the decrease of MEP amplitude over the non paretic limb [79]. No behavioural effects were tested in this study. Wang and colleagues first evaluated, in chronic stroke patients, the clinical effect of task-oriented training associated with 1Hz repetitive transcranial magnetic stimulation (rTMS) performed to inhibit the unaffected lower limb motor cortex. The authors performed a sham controlled study, using a figure-of-eight coil tangentially positioned over the leg area at the optimal site for response from the rectus femoris muscle. They showed that 10 daily sessions of rTMS enhanced the effect of task-oriented training on walking performance and motor control ability thereby leading to a more symmetric gait pattern. Moreover, rTMS improved the symmetry of interhemispheric corticomotor excitability [80].

Facilitation of the Lesioned Hemisphere

The effect of facilitatory tDCS on fine motor control of the paretic foot was evaluated by applying anodal or sham tDCS in a random order over the lower limb primary motor cortex of the lesioned or non-lesioned hemisphere. In each session, tDCS was associated with a motor task consisting in tracking a sinusoidal waveform for 15 min using dorsiflexion–plantarflexion movements of their paretic ankle. Anodal tDCS over the affected hemisphere enhanced the task practice effect already revealed in the sham stimulation condition. tDCS applied over the unlesioned hemisphere eliminated, instead, the task-induced practice effect [81]. The facilitation of the unlesioned hemisphere alone seems to be, therefore, detrimental for the paretic lower limb performance. On the contrary, the simultaneous facilitation of both lower limb motor areas, performed with high frequency rTMS connected to a double cone coil, has been reported to significantly improve walking in chronic gait involvement following stroke [82,83]. To date, few studies evaluated the interhemispheric connections between the two lower limb motor areas. However, a bi-hemispheric control of foot movements have been hypothesized in healthy subjects [84]. During voluntary movement, a stronger lateralization of fMRI activation has been reported for finger movements in comparison with lower limb joints [85]. The latter finding suggests a different functional specialization and organization between brain circuits controlling hand and foot movement. Therefore, the hypothesis of inter-hemispheric competition in unilateral motor control, supported by converging evidence from studies on the upper limb, may not be transposed directly to the lower limb motor system.

Development of New Devices for NIBS

New devices for both rTMS and tDCS have been developed in the last years and may be further explored for their potential application in stroke research. In 2002, a new TMS coil, termed Hesed coil (H-coil), has been introduced [82] to effectively stimulate deep brain regions without increasing the electric field intensity in the superficial cortical regions [86]. The basic concept is to obtain summation of the electric field in depth, minimizing the current components that only cause accumulation of surface charge. Moreover, the drop of the induced field as a function of the distance is much slower compared to a double-cone coil. The H-coil efficacy in humans was tested by Zangen and colleagues on six healthy volunteers [83]. They evaluated the rate of decrease of the electric field by gradually increasing the coil distance from the skull and measuring the abductor pollicis brevis (APB) motor threshold at each distance. The motor cortex could be activated by a specific version of the H-coil at a distance of 5.5 cm vs 2 cm with the figure-of-eight coil [87]. Safety of H-coils has also been assessed by Levkovitz et al. at relatively high intensity (120% of motor threshold) [84]. Thirty-two healthy volunteers were tested in a pre–post design during three (single pulses, 10 Hz, and 20 Hz) stimulation sessions made with two H-coil designs (H1/H2), standard figure-of-8 coil, and sham-coil control. H-coils were well tolerated, with no adverse physical or neurological outcomes [88]. The H-coils designed have been preferentially tested to evaluate the efficacy in cognitive and mood alteration in psychiatric and neurological diseases [89-91]. Using a H-coil designed to target the lower limb motor cortex, analgesic effects have been obtained in patients with painful diabetic neuropathy [92]. Contrary to what observed with TMS, the standard tDCS electrode configurations deliver a wider and superficial electric filed. The so called high-definition (HD)-tDCS is a new approach finalized to improve spatial focality and to optimize intensity of stimulation at target [93,94]. It consists in 5 electrodes of smaller size displaced in a concentric-ring configuration with the polarity (anode or cathode) set by a centre electrode and the area of cortical modulation restricted by adjusting the radii of 4 return electrodes [93,94]. In particular, high-resolution MRI-based forward models have been used to probe the unidirectional and targeted stimulation of the 4x1-ring montage of HD-tDCS. Although data on the application of these techniques to improve stroke outcome are not available, further research may explore these new directions.

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