

# Overview of Non-Invasive Brain Stimulation for Motor Recovery After Stroke

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Stroke is the major cause of disability worldwide. A number of neurological functions are impaired by stroke; the most common impairment is motor disability contralateral to the stroke lesion side. Despite rehabilitation, the motor function outcome after stroke is often incomplete, and dexterity deficits are a considerable handicap to stroke survivors [1]. Motor recovery after stroke is related to neural plasticity, which refers to the ability of the brain to develop new neuronal interconnections, acquire new functions, and compensate for impairment [2,3]. Therefore, various strategies based on neural plasticity are developing that aim to enhance motor recovery [4,5].

In particular, many reports have shown that non-invasive brain stimulation (NIBS) techniques help improve the efficacy of rehabilitative strategies employed after stroke by using physiological peculiarity that can alter the cortical excitability. The idea is that modulation of cortical excitability may induce neural plasticity and/or interfere with maladaptive neural activation, which subsequently weakens motor function and limits motor recovery [3]. Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are NIBS techniques that can alter excitability of the human cortex [6]. rTMS is defined as repetition of TMS; high-frequency rTMS increases cortical excitability, whereas low-frequency rTMS suppresses cortical excitability [6]. Theta burst stimulation (TBS) has also been reported as an effective rTMS method. It uses repeating bursts of very low-intensity combined-frequency rTMS [7]. Each burst consists of 3 stimuli (delivered at 50 Hz) repeating at 5 Hz. TBS can be used in 2 ways: a continuous train is used to suppress cortical excitability and an intermittent pattern is used to enhance cortical excitability. tDCS is another commonly used NIBS technique. There are 2 types of tDCS: anodal tDCS increases the excitability of the stimulated cortex, whereas cathodal tDCS decreases the excitability of the stimulated cortex [8].

NIBS therapy for motor stroke aims to augment neural plasticity and improve motor function based on the interhemispheric competition model. The interhemispheric competition model proposes that motor deficits in stroke patients are due to reduced output from the affected hemisphere and excessive interhemispheric inhibition from the unaffected hemisphere to the affected hemisphere [9,10]. Therefore, using NIBS, improvement in motor deficits can be achieved by increasing the excitability of the affected hemisphere or decreasing the excitability of the unaffected hemisphere [11,12]. No relevant adverse effects of NIBS, such as epileptic seizure induction, have been reported to occur in stroke patients when current safety guidelines regarding the intensity, frequency, and time of stimulation are adhered to [13,14].

Inhibitory NIBS increases excitability in the ipsilesional motor cortex by reducing the excessive interhemispheric inhibition from the contralesional motor cortex [10,15]. Excitatory NIBS over the affected hemisphere directly increases the excitability of the ipsilesional motor cortex [16-18]. Excitability enhancement in the motor cortex appears to be required for motor learning [19]. It has been reported that use-dependent plasticity is impaired in the affected hemisphere [20,21]. Therefore, NIBS can ameliorate impaired experience-dependent plasticity in stroke patients and induce motor recovery by directly or indirectly increasing the excitability in the ipsilesional motor cortex.

As another mechanism, NIBS reduces hyperactivity in the primary and non-primary motor cortices in the unaffected hemisphere and neural coupling of both hemispheres [22,23]. Moreover, NIBS enhances neural coupling between the primary and non-primary motor cortices in the affected hemisphere [22]. In addition to facilitation of the ipsilesional primary motor cortex, excitability modulation in both hemispheres and reconstructed neural coupling between the primary and non-primary motor cortices in the affected hemisphere after NIBS contribute to motor recovery in stroke patients. These findings suggest that artificially modulating the cortical excitability by NIBS may induce a more suitable environment for neural plasticity. In fact, NIBS can be an important technique in the rehabilitation of stroke patients; providing motor training along with NIBS will help sustain the effect of NIBS and improve motor function [12,15]. Thus, it is important to impart additional motor training while NIBS modulates the neural network between both hemispheres and remodels the disturbed network in the affected hemisphere.

An advantage of inhibitory NIBS over the unaffected hemisphere is that its response is more uniform than of stimulation over the affected hemisphere, because the unaffected site is less likely to be affected by neuronal loss or tissue damage [24]. Moreover, inhibitory NIBS over the unaffected hemisphere is expected to be safer with respect to any potential seizure risk (particularly in case of rTMS) or tissue damage [14]. However, it was noted that inhibitory NIBS reduces the interhemispheric inhibition that controls bimanual movement [25,26]. In fact, a recent study reported that inhibitory rTMS over the unaffected hemisphere deteriorated the performance in the anti-phase bimanual tapping task in stroke patients [27]. Therefore, inhibitory NIBS may deteriorate bimanual movement by reducing the interhemispheric inhibition that controls bimanual movement.

Although excitatory NIBS over the affected hemisphere has the advantage that it does not inhibit the stimulation site, its effect is dependent on the anatomical changes in the affected hemisphere. Damaged brain tissue evolves into scar tissue and is replaced by cerebral spinal fluid (CSF) spaces (particularly in cortical damage); scar formation and large CSF spaces inhibit the effect of NIBS, because the conductance of the CSF is 4 to 10 times higher than that of normal brain tissue [28,29]. Therefore, careful modeling using a stereotactic system with integrated anatomical data is required to predict the effect of excitatory NIBS over the affected hemisphere [28,29].

A few studies have clarified which stroke patients are more

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responsive to NIBS therapy [30,31]. Therefore, we must estimate the effect of NIBS therapy for stroke patients from studies that revealed the mechanism of NIBS therapy. Age is an important factor for effect of NIBS therapy. It has been reported that NIBS could improve motor recovery in adults as well as children [32]. However, the corpus callosum is not formed until 6–8 years of age [33]. Therefore, it is unlikely that inhibitory NIBS over the unaffected hemisphere will improve the motor function of the paretic side in children younger than 6–8 years, because inhibitory NIBS improves motor recovery by reducing the excessive interhemispheric inhibition to the affected hemisphere [10]. In addition, NIBS therapy might be less effective for elderly stroke patients [31,34] because elderly patients have lower motor learning ability and neural plasticity induced by NIBS [34,35]. It is important to determine whether NIBS therapy is more effective in the acute or chronic stage after stroke. If NIBS therapy is more effective in acute stages, early modulation of cortical excitability may facilitate motor recovery and prevent development of maladaptive neural plasticity by rebalancing interhemispheric communication and normalizing neural activity within the motor areas of both hemispheres. Although it has been reported that both inhibitory and excitatory NIBS facilitates motor recovery in stroke patients at the acute stage [16,36,37], a recent study showed that inhibitory NIBS did not facilitate motor recovery in patients in acute stages of stroke [38]. Further investigations are required to determine whether NIBS in the acute stroke stage can promote the final motor function. The lesion site may also influence the effect of NIBS therapy. The common target of both inhibitory and excitatory NIBS is ipsilesional motor cortex activation. Therefore, NIBS therapy might be less effective for cortical stroke patients, particularly in the ipsilesional motor cortex. The evaluation of corticospinal tract integrity also may be useful to predict the benefits of NIBS. Thus, Clinicians must consider that clinical factors, including age, stroke duration, and lesion site, may influence the effects of NIBS therapy.

NIBS can modulate cortical excitability, so NIBS might be an adjuvant therapy for developed neurorehabilitation strategies. Several studies showed that the combination of NIBS with specific neurorehabilitation techniques improved motor recovery [39-41]. However, the number of these combination studies is still small, and they are preliminary and controversial. Although it is likely that NIBS promotes the effects of developed neurorehabilitation strategies for stroke patients, future studies are required to determine the appropriate combination of methods for motor recovery.

The common aim of inhibitory and excitatory NIBS is activation of the ipsilesional motor cortex and rebalancing both hemispheres. Therefore, considering the interhemispheric competitive model, it may be more suitable for motor recovery to stimulate both hemispheres using inhibitory and excitatory NIBS. Several recent studies have reported that compared to unilateral NIBS, simultaneous bilateral NIBS using rTMS and tDCS improves motor recovery more effectively in stroke patients [27,42]. Moreover, bilateral NIBS using rTMS induces disinhibition of ipsilesional motor cortex that contributes to neural plasticity by unmasking latent networks [12]. Therefore, bilateral NIBS may more effectively facilitate neural plasticity and induce motor recovery after stroke. In addition to motor recovery, bilateral NIBS can protect against the deterioration of bimanual movement caused by inhibitory NIBS over the unaffected hemisphere. Inhibitory NIBS might worsen the anti-phase bimanual movement by reducing the interhemispheric inhibition that controls bimanual movement [27]. However, a combination of inhibitory NIBS over the unaffected hemisphere and excitatory NIBS over the affected hemisphere could prevent this deterioration by decreasing the reduction of interhemispheric inhibition [27].

As mentioned above, recent studies have reported that bilateral NIBS can more effectively facilitate neural plasticity and induce motor recovery after stroke. However, the best NIBS pattern has not been established. Moreover, the frequency, intensity, and number of pulses are important factors for rTMS effects, and the amplitude and stimulation duration are important factors for tDCS effects. Although more researchers have begun to evaluate the effectiveness of different NIBS stimulation protocols for motor recovery after stroke, further well-designed studies in larger populations are required to identify the most effective types of NIBS from various protocols, including tDCS for stroke treatment. Therefore, at present, clinicians have to select the NIBS type by considering the advantages and disadvantages.

#### Disclosures

This editorial commentary summarizes previous review article [43].

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