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Review

Update on Non-invasive Brain Stimulation on Stroke Motor Impairment: A Narrative Review

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HIGHLIGHTS

- Non-invasive brain simulation has shown promising results in stroke motor recovery.
- Future studies on better optimization of neuromodulation are warranted.

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Update on Non-invasive Brain Stimulation on Stroke Motor Impairment: A Narrative Review

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ABSTRACT

Stroke is a leading global cause of death and disability, with motor impairment being one of the common post-stroke complications. Rehabilitation is crucial for functional recovery. Recently, non-invasive brain stimulation (NIBS) has emerged as a promising intervention that allows neuromodulation by activating or inhibiting neural activity in specific brain regions. This narrative review aims to examine current research on the effects of various NIBS techniques, including repetitive transcranial magnetic stimulation, transcranial direct current stimulation, vagus nerve stimulation, and transcranial focused ultrasound on post-stroke motor function.

Keywords: Stroke; Transcranial Magnetic Stimulation; Transcranial Direct Current Stimulation; Vagus Nerve Stimulation

INTRODUCTION

Stroke is one of the leading causes of death and disability worldwide, and recent data suggests that one in 4 individuals over age 25 is expected to experience stroke in their lifetime [1]. Motor impairment is one of the most prevalent post-stroke complications [2]. Approximately 80% of affected patients experience hemiplegia, with over 40% being chronic [3]. Poststroke motor complications are associated with a myriad of challenges, notably impairing the capacity of patients to perform essential activities of daily living (ADL). These complications not only affect the quality of life [4] but also pose a significant socio-economic burden [5].

The clinical importance of rehabilitation for the functional motor recovery of stroke patients is well established. Among the various rehabilitation therapies, non-invasive brain stimulation (NIBS) is a relatively recent technology that is based on the concept of interhemispheric imbalance following a stroke [6]. In patients affected by stroke, the functional balance between 2 hemispheres is affected under normal circumstances, and NIBS can be used to inhibit or enhance cortical excitability, thereby modulating neuroplasticity to improve motor function after stroke.

This literature review endeavors to explore and present recent findings of NIBS techniques on poststroke motor impairment, including repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), vagus nerve stimulation (VNS), and transcranial focused ultrasound (tFUS). The purpose is to provide a comprehensive overview of the current state of NIBS research on poststroke motor function, encompassing both upper and lower extremities.

rTMS

First introduced in the late 20th century [7], rTMS has been widely used in stroke rehabilitation. rTMS uses an electromagnetic coil to generate electrical current in the brain, modulating cortical excitability via various protocols. Low-frequency rTMS (LF-rTMS) decreases cortical excitability and is clinically administered to the unaffected hemisphere, whereas high-frequency rTMS (HF-rTMS) increases cortical excitability and is applied to the affected hemisphere. The application of rTMS is grounded in the interhemispheric competition model, which posits that stroke can disrupt the balance of transcallosal inhibitory circuits between the motor areas of both hemispheres. This imbalance leads to increased inhibition from the unaffected hemisphere to the affected one, potentially impeding motor recovery. By modulating cortical excitability, rTMS aims to restore this balance, thereby facilitating motor recovery [6]. Various clinical trials have been conducted to support the evidence of rTMS on motor recovery after stroke, but due to the variabilities between the studies, a conclusive consensus has not been established yet.

Effects of rTMS on upper extremity impairment after stroke

A recent systematic review covering 32 studies with 1,137 participants demonstrated that rTMS over the M1 cortex showed positive functional improvements in upper limb motor function in patients with subacute and chronic stroke patients [8]. Studies examining the application of LF-rTMS on the unaffected hemisphere, HF-rTMS on the affected hemisphere, and bilateral stimulation were included in the review. Most of the included studies have shown the effectiveness of LF-rTMS in the functional improvement of the upper extremity. However, the relative effectiveness of LF-rTMS over HF-rTMS had not been proven in this study.

A 2022 meta-analysis has also reported a positive effect on fine motor recovery in stroke survivors [9]. Specifically, this review highlighted the efficacy of different rTMS protocols based on stroke phases. In the acute phase of stroke (< 1 month), bilateral hemisphere stimulation was more effective than unilateral stimulation, and a regimen of 20 rTMS sessions produced greater improvement than < 20 sessions. In the subacute phase (1–6 months), affected hemispheric stimulation with a 40-session rTMS regimen was superior. Lastly, unaffected hemispheric stimulation with a 10-session rTMS regimen was the most effective in the chronic phase (> 6 months). This comprehensive review provided strong evidence of rTMS in enhancing the upper extremity function during different phases of stroke. However, a large randomized controlled trial found that administering 1 Hz rTMS to the unaffected motor cortex in patients with chronic stroke 3 to 12 months after onset did not show improvement in upper extremity function compared to sham stimulation [10]. This underscores the necessity of continued research to refine rTMS protocols and tailor them to specific stages of stroke recovery and the unique characteristics of each patient.

In a 2023 systematic review that classified the outcome measures according to the International Classification of Functioning, Disability, and Health, rTMS was associated with improved upper extremity muscle synergies within and beyond 3 months after stroke at the level of body function, and with improved upper extremity capacity within 3 months after stroke at the level of activities [11]. Additionally, according to the 2022 Clinical Practice Guideline for Stroke Rehabilitation in Korea, the incorporation of rTMS into rehabilitation therapy has shown promising effects on enhancing upper limb motor function, grip strength, and hand function. Even though the evidence is rated as low, it seems to be particularly beneficial depending on the condition of the patient, leading to a conditional recommendation for its use [12].

Effects of rTMS on lower extremity impairment after stroke

A network meta-analysis conducted with 18 randomized controlled trials found that LF-rTMS outperformed sham stimulation in improving lower extremity motor function after stroke. In contrast, HF-rTMS was shown to increase the amplitudes of motor-evoked potentials more than either LF-rTMS or sham stimulation [13]. In a 2022 meta-analysis, 9 studies investigated the role of rTMS in improving gait, balance, and lower limb function among 212 patients with stroke. Post-intervention results indicated that rTMS had a modest impact with HF-rTMS over the affected hemisphere, producing the most substantial effect. Conversely, LF-rTMS over the unaffected hemisphere demonstrated no significant effect. Follow-up data revealed that bilateral stimulation resulted in a potent effect, and LF-rTMS showed no significant improvement [14].

Furthermore, a recent systematic review showed that one study showed a significant effect of intermittent theta burst stimulation on standing maintenance and transfer within 3 months after stroke (standardized mean difference [SMD], 1.03, 95% confidence interval [CI], 0.26 to 1.79), whereas no significant effectiveness was found in lower limb muscle synergies [11]. Due to the lack of evidence from previous clinical studies, the effect of rTMS on lower limb function remains inconclusive [12].

tDCS

First proposed in 1998 [15], tDCS has been recognized for its potential in stroke rehabilitation, particularly in modulating neuronal activity by applying a 1–2 mA current to the brain through scalp electrodes. tDCS can either enhance or suppress cortical excitability through anodal or cathodal stimulation, respectively. tDCS is notable for its portability, cost-effectiveness, and patient comfort, positioning itself as a practical adjunct therapy in stroke rehabilitation [16]. Various studies and systematic reviews have explored the effects of tDCS on activities of motor function in patients with stroke, yet highlighting the need for further research to establish standardized protocols.

Effects of tDCS on upper extremity impairment after stroke

A recent overview of 6 systematic reviews and meta-analyses indicated that tDCS demonstrates superior effects in enhancing upper limb functions and ADL in patients with stroke compared to control interventions [17]. Despite variabilities in stimulation parameters and outcomes, this study concluded that cathodal stimulation targeting the non-affected brain region was identified as more potent than both anodal and dual tDCS stimulation. The studies predominantly utilized an intensity of 2 mA and typically administered sessions lasting 20 minutes. The most common treatment regimen entailed 5 sessions per week, with the overall treatment duration extending anywhere from a single day to 8 weeks. A 2022 network meta-analysis [18], in contrast, revealed that anodal tDCS and transcutaneous VNS were effective in upper limb motor function after stroke (VNS: mean difference [MD], 5.50, 95% CI, 0.67 to 11.67; anodal tDCS: MD, 5.23, 95% CI, 2.45 to 8.01). In improving ADL performance after stroke, transcutaneous VNS and tDCS (anondal and cathodal) were effective (VNS: SMD, 0.96, 95% CI, 0.15 to 2.06; anodal tDCS: SMD, 3.78, 95% CI, 0.0 to 7.56; cathodal tDCS: SMD, 5.38, 95% CI, 0.22 to 10.54).

The 2022 Clinical Practice Guideline for Stroke Rehabilitation in Korea recommended that tDCS can be effectively utilized to enhance the recovery of upper extremity motor and functional deficits in patients with stroke considering individual conditions, resulting in a conditional recommendation for its use [12].

Effects of tDCS on lower extremity impairment after stroke

A recent systematic review encompassing 19 studies revealed that active tDCS in isolation, regardless of the stimulation mode, did not significantly enhance lower extremity motor function in patients with stroke when compared with sham tDCS [19]. However, subgroup analysis showed a notable difference in favor of tDCS during the acute and subacute phases with a low quality of evidence.

A separate meta-analysis of 10 randomized controlled trials investigated the effects of tDCS on balance and gait [20]. Most of the included studies implemented anodal tDCS, targeting either the lower-extremity motor area or the supplementary motor area on the affected side. This systematic review also disclosed no significant changes in outcomes, including the Fugl-Meyer Assessment-Lower Extremity (FMA-L), Berg Balance Scale, 10-Meter Walk Test, and 6-Minute Walk Test. However, the effectiveness of anodal tDCS was noted in the Functional Ambulation Category (MD, −2.54, 95% CI, −3.93 to −1.15) and Timed Up and Go Test (MD, 0.35, 95% CI, 0.11 to 0.58), suggesting that tDCS might have some positive effects on poststroke walking independence, gait, and ambulation.

Another systematic review also indicated that tDCS with the use of 2 mA for at least 10 minutes, with either anodic or bihemispheric stimulation, may enhance gait parameters, balance, and lower limb function in patients with stroke [21]. However, long-term effects have not yet been demonstrated.

VNS

The use of VNS in stroke is based on the principle of modulating neurons in the motor cortex via the activation of noradrenergic, cholinergic, and serotonergic systems, influencing the release of various neurotransmitters [22,23]. VNS can be used both invasively and noninvasively, with invasive VNS having received approval from the US Food and Drug Administration to treat moderate to severe upper extremity motor deficits associated with chronic ischemic stroke [22]. However, due to the potential side effects related to device implantation surgery, such as vocal cord palsy [24], clinical trials of non-invasive VNS have been proposed.

Transauricular VNS (taVNS) is a non-invasive VNS technique that stimulates the afferent auricular branch of the vagus nerve located at the tragus in the external ear [19]. Recent studies have reported the modulatory effects of taVNS on motor cortex excitability, which is thought to be linked to GABAergic intracortical inhibition [25,26].

Building on this understanding, one randomized controlled trial focused on patients who had experienced a stroke within one month. This trial compared the effectiveness of taVNS with sham stimulation [27]. Motor impairment assessed with the Fugl-Meyer Assessment-Upper Extremity (FMA-U), FMA-L, and Wolf Motor Function Test (WMFT) showed significant improvement for at least a year after the intervention. In another study focusing on the subacute phase of stroke, the taVNS group showed significant improvements in FMA-U, WMFT, and Functional Independence Measurement scores compared to sham stimulation [28]. Furthermore, taVNS administered during robotic training in a chronic stroke population has shown increased upper limb motor control [29,30].

Recent research suggests that non-invasive VNS may have potentially beneficial effects on neuroplasticity after stroke, especially in upper limb function. However, further studies are warranted to fully understand its therapeutic potential and incorporate it into clinical practice.

tFUS

tFUS is a technique that uses ultrasonic waves to target specific regions of the brain. By adjusting the frequency of these waves (i.e., low-frequency range of 200–700 kHz), tFUS can penetrate deeper and with greater spatial specificity [31]. Although some animal studies have been conducted supporting the effectiveness of tFUS on neuromodulation [32-34], studies on motor impairment after stroke in patients are yet scarce.

One study evaluated the excitatory and inhibitory effects of tFUS on the human motor cortex (M1) using GABA and glutamate neurometabolic concentration. Excitatory tFUS involving parameters of pulse width = 200 µs, pulse repetition frequency (PRF) = 2,000 Hz, duty cycle (DC) = 40%, and stimulation period = 2 seconds significantly increased M1 excitability, whereas inhibitory tFUS with mode of pulse width = 400 µs, PRF = 50 Hz, DC = 2%, and stimulation period = 2 seconds significantly suppressed M1 excitability [35]. Although this study revealed the neurophysiologic basis of the tFUS on cortical excitability, more studies are needed to support the clinical use of tFUS after stroke in participants.

CONCLUSION

The use of NIBS for poststroke motor recovery has garnered significant interest. A growing number of studies suggest that NIBS is a promising therapeutic intervention to improve motor function after stroke. However, due to the heterogeneity in study designs and stimulation parameters, drawing a definitive conclusion about the best NIBS technique remains unclear. Future studies focusing on better optimization of neural plasticity and neuromodulation are warranted.

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