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Review Article

Neuromodulation techniques in poststroke motor impairment recovery: Efficacy, challenges, and future directions

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ABSTRACT

Cerebrovascular accidents, also known as strokes, represent a major global public health challenge and contribute to substantial mortality, disability, and socioeconomic burden. Multidisciplinary approaches for poststroke therapies are crucial for recovering lost functions and adapting to new limitations. This review discusses the potential of neuromodulation techniques, repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation, spinal cord stimulation (SCS), vagus nerve stimulation (VNS), and deep brain stimulation (DBS), as innovative strategies for facilitating poststroke recovery. Neuromodulation is an emerging adjunct to conventional therapies that target neural plasticity to restore lost function and compensate for damaged brain areas. The techniques discussed in this review have different efficacies in enhancing neural plasticity, optimizing motor recovery, and mitigating poststroke impairments. Specifically, rTMS has shown significant promise in enhancing motor function, whereas SCS has shown potential in improving limb movement and reducing disability. Similarly, VNS, typically used to treat epilepsy, has shown promise in enhancing poststroke motor recovery, while DBS may be used to improve poststroke motor recovery and symptom mitigation. Further studies with standardized protocols are warranted to elucidate the efficacy of these methods and integrate them into mainstream clinical practice to optimize poststroke care.

KEYWORDS: *Deep brain stimulation, Spinal cord stimulation, Stroke, Transcranial direct current stimulation, Transcranial magnetic stimulation*

INTRODUCTION

Cerebrovascular accidents, commonly known as strokes, pose significant public health challenges worldwide [1]. As leading causes of mortality and long-term disability, they impose substantial socioeconomic burdens owing to medical costs and loss of productivity [2]. Effective poststroke therapy is crucial, as it facilitates recovery, allows adaptation to limitations, and enhances quality of life [3]. This therapy typically employs a multidisciplinary approach, integrating physical, occupational, and speech–language therapies to tackle a wide array of stroke-induced impairments, ranging from motor and sensory deficits to communication and swallowing difficulties [4].

Neuromodulation represents an innovative therapeutic strategy in poststroke care. It involves applying electrical, magnetic, or other forms of energy to specific neural structures to modulate neuronal activity. The aim is to restore lost function and compensate for damaged brain areas [5]. Neuromodulation includes both noninvasive and invasive techniques, such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), spinal cord stimulation (SCS), vagus nerve stimulation (VNS), and deep brain stimulation (DBS). These techniques target specific brain regions linked to motor or cognitive functions, enhancing neural plasticity and aiding recovery [6-9]. They offer a customizable and adaptable complement to traditional rehabilitation, potentially accelerating recovery and improving functional outcomes for stroke survivors. Notably, the parameters of these neuromodulation techniques can be precisely adjusted to meet individual rehabilitation needs and goals [10]. Advances in neuromodulation are transforming poststroke care, offering novel recovery options

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for stroke survivors. This narrative review explores the role of neuromodulation in poststroke motor recovery.

TRANSCRANIAL MAGNETIC STIMULATION FOR STROKE

Noninvasive neuromodulation techniques, such as repetitive TMS (rTMS), are gaining recognition for their potential in enhancing neural plasticity, especially in poststroke rehabilitation. rTMS involves the external application of magnetic or electrical stimuli to the body, utilizing a magnetic coil to emit a brief, high-intensity magnetic field that targets specific brain areas [11]. This stimulation can either facilitate or inhibit cortical excitability, depending on its parameters.

Low-frequency rTMS, typically at or below 1 Hz, or continuous theta burst stimulation (cTBS), is known to induce inhibitory effects. This approach is often employed to mitigate imbalances in interhemispheric competition. Such imbalances can occur following a stroke, where one hemisphere of the brain may become more dominant, impeding recovery. By reducing the excitability of the overactive hemisphere, low-frequency rTMS or cTBS can help restore a more balanced neural activity across the hemispheres [12]. In contrast, high-frequency rTMS – generally at or above 5 Hz – or intermittent theta burst stimulation (iTBS) is used to increase cortical excitability. This mode of stimulation is particularly beneficial in stroke rehabilitation when applied to the hemisphere with the lesion. By enhancing the excitability of the affected areas, high-frequency rTMS or iTBS can facilitate neural plasticity and recovery of function [13]. These contrasting properties of rTMS are critically important for stroke survivors. Altering cortical excitability through rTMS can significantly impact the integrity of the corticospinal tract, which is vital for motor control and plays a key role in the recovery of limb functions poststroke [11]. By judiciously applying either low-frequency or high-frequency rTMS, depending on the specific needs of the patient, clinicians can significantly aid in the motor recovery process.

Two studies highlighted the efficacy of repetitive transcranial magnetic stimulation (rTMS) in poststroke recovery. The first study reviewed 34 randomized controlled trials involving 904 patients with stroke, focusing on upper limb recovery. It revealed significant short-term and long-term improvements in manual dexterity, particularly when rTMS was administered during the acute phase of stroke, especially for subcortical lesions, and through a five-session treatment protocol. Notably, iTBS proved more effective than cTBS [14]. The second study analyzed eight randomized controlled trials with 169 patients with stroke, examining the impact of rTMS on lower limb recovery. This study found that rTMS significantly enhances lower limb function, activity, and motor-evoked potentials. Importantly, the benefits of rTMS were observed regardless of the time elapsed poststroke or the specific mode of stimulation used, leading to improvements in walking speed and Fugl-Meyer Assessment scores for lower limbs. Although there was a potential risk of bias, the study concluded that rTMS is a safe and effective short-term intervention for lower limb recovery in patients with stroke, with minimal adverse effects reported [15].

In terms of safety, rTMS is generally considered safe with some mild side effects, such as headache and anxiety. Patients should be screened before undergoing the procedure according to safety guidelines [16]. Overall, rTMS presents as a promising method for poststroke rehabilitation, particularly for recovering upper limb motor functions. However, the diversity of current studies makes selecting specific rTMS protocols for different poststroke impairments challenging. Future research involving larger patient cohorts and standardized protocols is essential for integrating this technique more extensively into clinical practice.

TRANSCRANIAL DIRECT CURRENT STIMULATION FOR STROKE

tDCS is a noninvasive technique that modulates neuronal activity using a constant, low electrical current, typically between 1 and 2 mA, delivered through scalp electrodes [17]. In clinical settings, tDCS is being explored for treating depression, and chronic pain and aiding in stroke rehabilitation. The process involves placing the positive electrode (anode) over the target area for anodal stimulation, leading to neuronal depolarization, which increases excitability and firing likelihood. Conversely, the negative electrode (cathode) causes hyperpolarization, decreasing neuronal excitability. tDCS is believed to induce neuroplastic changes in the brain, potentially leading to long-term functional improvements with repeated sessions [18].

In Khedr *et al*.'s randomized control trial, patients with stroke with upper motor impairment were treated with tDCS, including anodal, cathodal, or no electrical treatment, alongside regular rehabilitation. The experimental group received 2 mA tDCS for 25 min daily for 6 days over the motor cortex hand area. Measurements of motor cortical excitability, muscle strength, and the Barthel Index at the 3-month follow-up showed a higher level of improvement in the experimental group than in the control group, demonstrating the efficacy of tDCS in enhancing rehabilitation outcomes [19].

Furthermore, a meta-analysis of eight trials involving 213 patients with stroke indicated that tDCS significantly enhances motor recovery, as measured by the Fugl-Meyer Assessment Upper Extremity (FMA-UE) scale. The effect was more pronounced in patients with chronic stroke and those receiving bihemispheric tDCS. The study also highlighted a dose-response relationship, with better outcomes linked to higher current, charge density, and the use of smaller electrodes [20].

Although tDCS is generally considered safe within recommended guidelines, it can cause mild side effects such as itching, tingling, or discomfort at electrode sites, with a low risk of severe effects such as skin burns or seizures. However, it is not extensively regulated or approved by major health authorities such as the FDA for most proposed uses and is often categorized as research or experimental therapy [21]. In future, it is recommended to conduct large-scale studies to further investigate the therapeutic effects of tCDS.

Spinal cord stimulation for stroke

SCS is a therapeutic approach primarily utilized for chronic pain management; however, there is increasing interest in its potential applications for motor improvement following central nervous system injuries, such as spinal cord injury (SCI) [22]. SCS involves the alteration of nerve activity through the targeted delivery of a stimulus to specific neurological sites in the body. This can affect muscle activity indirectly by modifying the neural signals that control muscle contraction and movement [23]. Several preliminary clinical studies have demonstrated that lumbar epidural stimulation can achieve temporal and spatial control of lower-limb movement in patients with SCI who have paraplegia [24]. In combination with regular rehabilitation, SCS can allow patients with chronic SCI to walk overground with minimal assistance. The underlying mechanisms of action may involve both distal muscular control from stimulation of specific contacts and reconnection with the cerebral cortex and corticospinal tract [25]. Given the similar anatomical composition to limb control, studies have been conducted on whether SCS can promote functional recovery in stroke survivors by modulating neural pathways and promoting neuroplasticity [26]. Early studies have suggested that electrical SCS may facilitate the reorganization of neural circuits, which may enhance motor function and reduce disability in stroke survivors.

Upper limb paresis, characterized by limited or no movement of the hands and arms, is a source of distress in patients with chronic stroke as it impedes the recovery of functional activity. Employing a mechanism similar to that of lumbar SCS, Greiner *et al*. initially performed computational analysis of SCS of the cervical spinal cord in monkeys [9]. They observed better muscular recruitment upon activation of laterally positioned, rather than medially positioned, electrode contacts. The recruitment of arm motor neurons facilitates upper arm movement involving segmental control of muscle groups. Furthermore, activity and movement patterns are modulated by the amplitude and frequency of the stimulation [9]. Among five patients, three with chronic neuropathic pain and surgically implanted paddle leads positioned over C6 to T1 showed similar activation patterns of muscular recruitment. These patterns were characterized by segmental rostral-caudal innervation and movement facilitation. However, compared to the primate studies, the human studies showed lower stimulation specificity with poor control of individual upper limb muscles.

In a recent proof-of-concept study, two patients with chronic poststroke upper limb weakness were implanted with an epidural stimulation electrode over the cervical spinal cord for 29 days [26]. In this study, continuous stimulation not only facilitated functional movement but also increased strength and kinematics through specific contact modulation. Furthermore, this improved movement remained after cessation of the SCS. The aforementioned findings suggest that cervical SCS may have both facilitative and restorative roles in stroke survivors who have upper-limb paresis. SCS may enhance neuroplasticity, i.e., the ability of the brain to reorganize and adapt, which could facilitate the rewiring of neural circuits damaged by a stroke, thereby improving motor function and recovery.

Unlike other experimental stroke treatments, SCS is minimally invasive and involves the placement of electrodes immediately beneath the skin and over the epidural space. This approach mitigates the risks linked to invasive surgical procedures and intracranial access; however, it still carries surgical risks, potential for dural tear, lead migration, battery-related issues, and changes in sensation as side effects [7]. Based on its use in the treatment of chronic neuropathic pain, SCS can be customized to each patient's needs to improve movement. Specifically, the stimulation parameters, intensity, and duration can be adjusted for each individual to optimize outcomes [9]. Nonetheless, SCS for stroke treatment is still in its experimental stages, and further studies are warranted to establish its safety and efficacy. Moreover, clinical trials are required to determine the optimal parameters, patient selection criteria, and long-term outcomes of SCS for stroke rehabilitation.

Vagus nerve stimulation for stroke

VNS involves the installation of a device capable of stimulating the vagus nerve, which is the tenth cranial nerve. The vagus nerve is integral in the regulation of various physiological processes, including heart rate, digestion, respiratory rate, and mood [27]. VNS is widely used to treat epilepsy, especially refractory seizures [28]. Typically, VNS devices are composed of a generator, which is analogous to a pacemaker and a lead wire. A tethering anchor is secured around the vagus nerve, with the positive and negative electrodes positioned appropriately before being connected to the generator through a lead wire threaded under the skin. The VNS device is usually implanted on the left side to avoid interaction with the sinoatrial node connected to the right vagus nerve, which is responsible for heart rate regulation. This placement prevents potential cardiac side effects such as bradycardia and asystole [27,29].

The primary mechanism through which VNS is thought to aid stroke recovery is by promoting neuroplasticity – the brain's ability to reorganize itself by forming new neural connections. Stimulation of the vagus nerve can release various neurotransmitters and neuromodulators, such as norepinephrine, serotonin, and GABA, which facilitate this process. These changes can have various effects, from mood regulation to potentially aiding in the recovery of neural function poststroke [8]. Studies have been conducted on the application of VNS as a therapeutic option for several neurological conditions, including poststroke complications, for example, motor deficits, cognitive impairments, and mood disturbances. Emerging evidence supports the efficacy of VNS in facilitating poststroke motor recovery [30].

Rat studies on subcortical ischemia have demonstrated the synergistic effects of VNS combined with rehabilitative training on enhancing forelimb function recovery. This therapeutic strategy demonstrates potential translational benefits in chronic ischemic stroke [31].

Dawson *et al*. assigned participants with ischemic stroke for >6 months to receive VNS and rehabilitation or rehabilitation alone. They observed a significant between-group difference in the change in FMA-UE scores, which indicated that VNS combined with rehabilitation is a viable and effective strategy for enhancing recovery in patients with chronic ischemic stroke [32].

Subsequently, Dawson *et al*. randomly assigned participants to receive rehabilitation paired with active VNS or sham stimulation. Participants who received active VNS showed a mean (± standard deviation) increase of 5.0 (±4.4) points in their FMA-UE scores on the 1st day after the completion of in-clinic therapy; after 90 days, 47% of these participants achieved a clinically meaningful improvement in their FMA-UE score [8]. This study demonstrated that VNS combined with rehabilitation substantially improved motor impairment and function. For the aforementioned studies, the utilized parameters for VNS were as follows: a current of 0.6–0.7 mA, pulse width of 100 μs, frequency of 30 Hz, and duration of 0.5 s [8,32].

VNS is a medical treatment that involves delivering electrical impulses to the vagus nerve. It has proven to be beneficial for various conditions; however, it can lead to side effects. These side effects can vary among individuals, but common ones include voice changes, coughing, effects on heart rhythm, swallowing difficulties, and device malfunction [33]. Despite these potential side effects, the combination of VNS with rehabilitation is a promising modality for optimizing recovery and augmenting motor function in patients with chronic ischemic stroke. Further studies on this innovative approach for poststroke therapeutic interventions are warranted to maximize patient recovery and improve quality of life.

Deep brain stimulation for stroke

DBS is used to treat various neurological and neuropsychiatric conditions, including Parkinson's disease, dystonia, depression, and obsessive–compulsive disorder [34]. It involves precise implantation of insulated electrodes into designated brain regions, including the subthalamic nucleus, globus pallidus internus, and thalamus, according to the specific condition being treated. These electrodes are connected to a pulse generator; moreover, insulated wires are tunneled under the skin, usually from the head to the chest area [35]. DBS is primarily used to treat specific movement disorders. However, some exploratory studies have investigated the utility of DBS for treating specific poststroke symptoms or complications. The cerebellum is crucially involved in coordinating and regulating skilled movements by establishing neural connections with the primary motor cortex. The central projection from the cerebellum to the primary motor cortex is a disynaptic excitatory pathway that relays through the ventral thalamus. Therefore, DBS may promote neuroplasticity, thereby aiding in the recovery of functions lost due to stroke [36]. Given the pivotal role of the cerebellum in orchestrating skilled movements through neural connections with the primary motor cortex, rat studies on cerebral ischemia have demonstrated that electrical stimulation of the contralesional lateral cerebellar nucleus can significantly augment motor function recovery [37].

This device has been used in stroke survivors since the year 2000. Phillips and Bhakta used DBS to treat chronic stroke in a patient who presented with pain and right-sided hemiparesis. Specifically, a DBS electrode was surgically implanted in the periventricular gray matter on the left lateral aspect of the third ventricle. During the stimulation sessions, the patient observed enhancements in voluntary movement of the paralyzed arm and leg as well as mild pain relief [38].

Baker *et al*. conducted a nonrandomized Phase I trial involving 12 participants with chronic stroke and significant upper extremity impairment. The participants underwent DBS of the cerebellar dentate nucleus combined with intensified physical rehabilitation. The parameter settings were as follows: a current of 4.4–9.0 mA for intensity, a pulse width of 90–200 μs, and a frequency of 30–185 Hz. Each rehabilitation session lasted between 1 and 1.5 h. This substantially improved the median FMA-UE scores, which was closely linked to cortical reorganization, as demonstrated by increased metabolic activity on the affected brain hemisphere [7].

Although the primary association between DBS and movement disorders remains unclear, its prospective applications in poststroke recovery are being increasingly recognized. Preliminary findings in both animal and human studies are promising, suggesting the potential of DBS in enhancing motor recovery and mitigating symptoms following stroke. Although DBS offers significant benefits, it is associated with the following potential side effects arising from both the surgery and the ongoing stimulation: surgical risks, infections, balance difficulties, and device-related problems. It is noteworthy that the likelihood and severity of the aforementioned side effects can differ greatly among individuals [39]. Nonetheless, further research and clinical studies to elucidate the therapeutic implications of DBS in poststroke rehabilitation are warranted, which may improve the quality of life of stroke survivors with persistent neurological impediments.

Table 1 includes a summary of original studies and review articles on neuromodulation techniques employed for the rehabilitation of patients poststroke.

Conclusion

Neuromodulation techniques, such as TMS, SCS, VNS, and DBS, are emerging as potential adjuncts in the comprehensive management of stroke-related impairments. TMS applies electromagnetic induction to stimulate neurons in specific brain regions, modulate cortical excitability, and promote neuroplasticity. SCS can potentially facilitate the reorganization of neural networks disrupted by stroke and improve motor function by modulating spinal neural circuits. The potential synergy between VNS and rehabilitative exercises may offer a novel approach for enhancing stroke recovery by optimizing neural plasticity and facilitating relearning. Preliminary studies have indicated that DBS may aid in mitigating stroke-induced motor and cognitive impairment by modulating dysfunctional neural circuits.

Table 1: A summary of studies on neuromodulation techniques for patients with chronic stroke, including devices, treatment methods, and outcomes

Author, year [reference number]	Participants	Device	Method	Outcome
Zhang *et al*., 2017 [14]	34 RCTs (*n*=904)	rTMS	Meta-analysis of randomized controlled trials	Significant short-term and long-term improvements in manual dexterity
Tung *et al*., 2019 [15]	Eight studies (*n*=169)	rTMS	Meta-analysis of randomized controlled trials	Significantly enhanced lower limb function, activity, and motor-evoked potential
Khedr *et al*., 2013 [19]	Eight studies (*n*=40) Subacute ischemic stroke	tDCS	tDCS at an intensity of 2 mA for 25 min daily for 6 consecutive days	Cortical excitability, muscle strength, and Barthel index were higher in tDCS group than in the sham group
Chhatbar *et al*., 2016 [20]	*n*=213	tDCS	Meta-analysis of randomized controlled trials and Quasi-experimental	tDCS significantly enhances motor recovery. Better outcomes were linked to higher current and charge density
Powell *et al*., 2023 [26]	Ischemic stroke >6 months (*n*=2)	SCS	Implanted for 29 days with two linear leads at C3–T1	Continuous stimulation through selected contacts improved strength and functional movements
Dawson *et al*., 2016 [32]	Ischemic stroke >6 months (*n*=21)	VNS	VNS plus rehabilitation or rehabilitation alone	FMA-UE score was significantly improved in the VNS group
Dawson *et al*., 2021 [8]	Ischemic stroke that occurred between 9 months and 10 years (*n*=108)	VNS	VNS plus rehabilitation or sham VNS stimulator rehabilitation 6 weeks of in-clinic therapy followed by a home exercise program	Both FMA-UE and WMFT scores were significantly increased in the VNS group
Phillips and Bhakta, 2000 [38]	Left-posterior cerebral-artery territory infarction 5 years (*n*=1)	DBS	Only surgery, no rehabilitation	Voluntary movement of the paralyzed arm and leg was noted Pain-relieving
Baker *et al*., 2023 [7]	Ischemic stroke 12–36 months (*n*=12)	DBS	DBS and rehabilitation phase, rehabilitation time minimum period of 4 months (maximum of 8 months)	Both the FMA-UE score and quality of movement were significantly improved in DBS + rehab phase

RCT: Randomized controlled trial, TMS: Transcranial magnetic stimulation, SCS: Spinal cord stimulation, VNS: Vagus nerve stimulation, DBS: Deep brain stimulation, FMA-UE: Fugl–Meyer assessment-upper extremity, WMFT: Wolf motor function test, tDCS: Transcranial direct current stimulation

These neuromodulation techniques offer new avenues for promoting neural plasticity, augmenting rehabilitation outcomes, and improving the quality of life of stroke survivors. However, the translation of these techniques from experimental to standard clinical practice requires further research on their long-term impacts, safety profiles, and effectiveness across diverse stroke conditions and patient groups. Their promise in stroke rehabilitation underscores the importance of sustained research efforts and clinical validation in this evolving field.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

There are no conflicts of interest.

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