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Noninvasive Neuromodulation for Acute and Subacute Stroke management and Rehabilitation

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Abstract:

Stroke is a leading cause of death and disability worldwide, leaving many survivors with long-term motor, cognitive, and functional deficits. Conventional treatments like thrombolysis and antiplatelet therapy reduce immediate damage but do not repair neural tissue. Noninvasive neuromodulation (NN) offers a promising approach for early stroke rehabilitation by using electricity, magnetism, ultrasound, or vagal stimulation to enhance neuroplasticity and reorganize neural networks. Techniques using ultrasonic, electrical, magnetic waves and vagal nerve stimulation have shown benefits in improving motor control, posture, swallowing, cognition, mood, and pain. Combining NN with rehabilitation exercises appears to maximize recovery by modulating cortical excitability and connectivity. Despite promising results, current studies are small and protocols vary, highlighting the need for larger, standardized trials. Overall, NN is a safe, adaptable, and effective tool that can significantly improve outcomes in stroke rehabilitation.

Keywords: Acute stroke management, Ultrasound stimulation, Magnetic stimulation, Alternating current stimulation, direct current stimulation, Theta burst stimulation, Vagus nerve stimulation.

Abbreviations:

Noninvasive neuromodulation - NN

Transcranial ultrasonic wave stimulation - TUS

Low intensity focused ultrasound stimulation - LIFUS

Transcranial magnetic stimulation - TMS

Repetitive transcranial magnetic stimulation - RTMS

Theta burst stimulation - TBS

Transcutaneous electrical nerve stimulation - TENS

Transcranial direct current stimulation - TDCS

Post stroke Cognitive impairment - PSCI

Mini-Mental State Examination - MMSE

Montreal Cognitive Assessment - MOCA

Post-stroke depression - PSD

central post-stroke pain - CPSP

Introduction:

Stroke is a leading cause of global disability and mortality, resulting from acute cerebrovascular events that disrupt cerebral blood flow. It most commonly manifests as ischemic or hemorrhagic stroke, and despite advances in acute management, results in significant physical disability, cognitive impairment and long-term sensorimotor deficits [2,5].

The mainstay of stroke management is reperfusion using pharmacological or mechanical thrombolysis (with tissue plasminogen activator) and dual antiplatelet therapies. Though effective, these methods are limited by their narrow therapeutic windows, technical hurdles and high cost [5]. These modalities, though effective, are focused at reducing damage, and have no healing effect on neural tissue.

Early rehabilitation strategies aim at reducing disability and long-term deficits by employing various neuromodulatory systems, and have shown promise in acute stroke management [2,5]. Noninvasive

neuromodulation (NN) techniques involve the use of neuroexcitatory factors such as electricity, magnetism and ultrasonic waves to promote neuroplasticity and reorganization of neural networks [5,8]. Further, they allow focal targeted therapy and have shown adaptability very early post-stroke [2]. This review aims to compare and present the role of the various NN techniques in acute stroke management and how these neurophysiological interventions may impact cortical excitability, neural connectivity, and key biological processes.

Methodology:

Search strategy

A comprehensive search was conducted using multiple electronic journals accessed through PubMed. The search was conducted without language and year restrictions. The keywords used were as follows: “noninvasive neuromodulation”, “acute stroke management”, “ultrasound stimulation”, “magnetic stimulation”, “alternating current stimulation”, “direct current stimulation", "theta burst stimulation" and “vagus nerve stimulation”. No mesh or advanced search methods were applied.

Screening and Selection Process

Following the search, all identified articles from PubMed were screened and filtered. The titles and abstracts of the remaining articles were reviewed to identify those relevant to the topic. Inclusion was based on the relevance of information, full-text availability, and published language being English. Thus selected articles were then full-text reviewed. A total of 17 articles were included for manuscript writing.

Modalities of Noninvasive Neuromodulation:

In recent years, noninvasive neuromodulation techniques have gained attention in acute stroke recovery. They are used to noninvasively modulate brain activity and rehabilitate stroke patients reducing long term neurological deficits. Multiple methods have been shown to be effective, such as Ultrasonic, Magnetic, Electrical and Vagal stimulation.

Ultrasonic wave Stimulation

Transcranial ultrasonic wave stimulation (TUS) is a NN technique that modulates brain activity by using ultrasonic waves. It targets focal brain regions and alters neural activity and has proven effective in promoting recovery for acute post-stroke management. This technique modulates the excitability of neurons through acoustic pressure which affects ion channels, membrane permeability and synaptic

transmission. The stimulation is applied through the skull using transducers that release pulses or continuous ultrasound waves. The frequency, intensity and duration are carefully monitored to avoid thermal damage [8].

A more advanced version, known as low intensity focused ultrasound stimulation (LIFUS), is currently being developed. In a phase 1 trial, LIFUS was applied on the motor cortex of stroke patients while learning new motor sequences for using the affected hand. This study aimed to find the safest pulse intensity of LIFUS and found it to be from 0 to 8 W/cm². However, LIFUS has a higher risk of severe adverse effects such as second-degree scalp burns, new lesions, and seizures. The researchers have measured the response time of Motor Sequence Learning and the motor reaction potential before and after stimulation. LIFUS is a promising NN technology and current research is focused on optimisation and limiting its adverse effects [7,8].

Magnetic Stimulation

Magnetic stimulation is a widely used noninvasive brain stimulation technique, where transcranial magnetic stimulation (TMS) is used to generate local electrical signals, which excite the cortex and increase neuroplasticity in areas with stroke-related dysfunction [3,9,16]. Repetitive transcranial magnetic stimulation (RTMS) involves firing focal magnetic signals repeatedly and it has shown better regulation of the immune response, better neurogenesis, improved cortical excitability and neural remodeling [3,9,10,15,16]. It has also been shown to improve upper limb muscle weakness in post-stroke patients and helped reduce dysphagia scores and improve postural control [6,15,16].

RTMS has three main forms, Low-frequency, High-frequency, and Theta burst stimulation (TBS). TBS, in particular, has demonstrated efficacy in improving motor dysfunction post-stroke. It works by enhancing cortical excitability, facilitating neural network reorganization, and improving cerebral circulation and metabolism [16]. They have also demonstrated significant improvements in depression and headache scores when compared to sham stimulation (a placebo-like control method used in trials to test real effect) [10].

Vagus nerve stimulation

Vagus nerve stimulation (VNS) has become a crucial aspect in post stroke care. The primary mechanism of VNS begins with the concept that the vagus nerve is built with afferent fibers and they are connected to many other nuclei such as the solitary tract, locus coeruleus, and raphe nuclei and they are responsible to produce neuromodulatory chemicals such as acetylcholine, norepinephrine, and serotonin which are the main mode of connecting with the cortex [17]. Through monoaminergic neurotransmitters VNS could perform some simple tasks, increase serotonin and norepinephrine concentration in the cerebrospinal fluid and regulate mood by influencing prefrontal cortex and limbic system, it is also responsible for increasing the expression of a growth factor called the brain-derived

neurotrophic factor which is pivotal in the rehabilitation process of post stroke especially in learning, memory and improving depression [17].

Paired VNS showed excellent results in animal modules regarding plasticity and it also regulates the immune response which has improved outcomes in post stroke and PTSD therapy. Paired VNS is a concept involving neuromodulation using VNS with physical rehabilitation. Animal studies have shown that pairing a movement with VNS improves the plasticity of the motor and auditory cortex using neurotransmitters. As with any treatment or care the earlier we begin, the better the outcome for the patient [17]. The effectiveness of VNS increases proportionally to the strength of the stimulation, but this could be challenging to tolerate and this limits the potential efficacy of the treatment. A study concluded that the 20-30 Hz range would be the optimal range [17].

Methods of VNS neuromodulation are mainly divided into invasive and noninvasive. The invasive method is the standardised procedure performed on the neck's left side and an implantable pulse generator is positioned in the infraclavicular region, and the stimulation is activated 2 weeks post surgery. We could also adjust the parameters according to the desired outcome and the patent's comfort [17]. This is generally a safe procedure with minimal complications, the most common ones being postoperative hematoma, infection, vocal cord palsy, facial weakness, pain, and lead disconnections [17].

Noninvasive techniques include stimulating the vagus nerve trunk in the neck through transcutaneous stimulation or the auricular branch of the vagus nerve by placing electrodes on the earlobe (transcutaneous auricular VNS). This technique has shown positive results in improvement of upper extremity motor function and sensory loss in patients [17]. In one of the studies they revealed that stimulating the ear of the same side of the target brain region produced more pronounced motor movement compared to the contralateral side [17]. One of the pilot studies revealed that Motor activated auricular vagus nerve stimulation showed much more therapeutic effect on upper extremity motor function compared to the transcutaneous auricular approach [17]. Noninvasive methods are more patient friendly, affordable and avoid all the complications of invasive VNS, though the potency and the efficiency of invasive methods are higher.

Electrical stimulation

Electrical NN techniques, such as the Transcutaneous electrical nerve stimulation (TENS) and the Transcranial direct current stimulation (TDCS), have shown promise as treatment strategies addressing both motor and cognitive deficits in stroke survivors [11,12].

TENS is a NN technique that primarily stimulates nerves through skin to influence how the nervous system detects sensations and muscle function. A systematic review study on the effects of TENS in post stroke upper limb recovery revealed that TENS combined with physical rehabilitation showed marked improvement, while TENS alone did not show significant improvement [11]. This was further

supported by other studies to conclude that TENS neuromodulation must be carried out in combination with rehabilitation strategies to extract optimal benefits.

TDCS is another NN technique which involves stimulating the pre and postsynaptic membrane to give excitatory or inhibitory effects. This method is extensively used in neurorehabilitation and as with TENS, TDCS is more effective when combined with cognitive rehabilitation techniques [12,13]. The combination therapy consisting of TDCS and cognitive rehabilitation strategies proved that it could yield positive outcomes, with improved scores in cognitive functional tests such as the Montreal Cognitive Assessment (MOCA), Mini-Mental State Examination (MMSE), and the Modified Barthel Index [12,13].

When TENS and TDCS were combined with different rehabilitation strategies, it was found that TDCS combined with the brain computer interface therapy showed significant improvements in upper limb mobility and mirror therapy coupled with TDCS enhanced motor function in both upper and lower limb. Apart from muscle motor activity, balancing was also checked and the study proved that in order to improve balance it is crucial to pair TDCS with acupuncture and moxibustion [14].

Clinical Outcomes:

Swallowing Function and Quality of Life:

A common complication in stroke patients is dysphagia, which is defined as difficulty to swallow. Dysphagia affects a big percentage of stroke patients in the acute phase, ranging from 50-80%. It significantly impairs food intake and nutrition, which increases the patients' chances of developing more serious complications such as aspiration, pneumonia, bronchospasm and airway obstruction, making prevention an important goal in acute post-stroke management. Noninvasive stimulation is one of the safest and most effective modalities for dysphagia prevention and improvement of the swallowing function. Multiple stimulation methods were studied and compared and RTMS has shown to be the most effective method to improve the swallowing function in stroke patients, with a Standardized Mean Difference (SMD) of 5.10 compared to other methods. Its main function is remodeling of the motor cortex to improve the swallowing action. In addition to RTMS, both Pharyngeal Electrical Stimulation which works via direct stimulation of the pharyngeal nerve, and TDCS, contribute to improved swallowing function by increasing neural activity in swallowing-related brain regions [1].

Motor Control and Postural Stability:

Several persistent challenges with motor function and postural stability are frequently experienced by approximately two-thirds of stroke survivors [3,6]. Noninvasive brain stimulation techniques (TDCS, TMS and RTMS) demonstrate encouraging results for boosting neural plasticity and motor recovery in

stroke patients [3]. They simply regulate the cortical excitability to trigger neural circuitry in stroke-affected brain regions.

A marked overall influence (SMD = 0.79) of brain stimulation on postural control have been revealed via systematic reviews and a meta analysis of 15 studies, consisting of stroke patients exhibiting stronger responses with SMD of 0.95 when compared to intact healthy individuals with an SMD of 0.39. Out of all the mentioned techniques, TDCS demonstrated notable efficacy in rehabilitation for postural control (SMD = 1.79), while IBS showed moderate efficacy (SMD = 0.68) [3]. A large review of 12 studies found that NN methods noticeably boosted arm function for patients compared to when they started rehabilitation. Researchers also noticed that post-treatment, communication between the brain's two hemispheres improved significantly, and this directly resulted in better arm movement [6].

The most favorable outcomes were achieved by stimulating the primary motor cortex (SMD = 1.21), with the next best being cerebellar stimulation (SMD = 0.75) and lastly dorsolateral prefrontal cortex interventions (SMD = 0.35). Development of targeted neuromodulatory approaches were supported by the previous findings which proved that there is enhanced neuroplastic potential in stroke survivors using NN [3].

Cognitive impairment, mood and pain management in post stroke patients:

Mental imbalance and Post stroke Cognitive impairment (PSCI) is a very common and devastating complication of stroke leading to long-term misery. Multiple NN techniques, especially in association with other rehabilitation therapies have shown promise in metal rehabilitation [4]. A meta-analysis and a systematic review revealed that the effects of multi-site non-invasive brain stimulation were higher on MOCA compared to single site intervention [12]. Also, enhancements in visuospatial abilities and trail-making test abilities indicated that participants with this modality improved in overall executive skills [12].

A differential analysis explored the effect of combining TDCS with cognitive rehabilitation in PSCI patients; including 11 randomized controlled trials, to conclude that accrued therapy demonstrated a considerable improvement in terms of cognitive performance and activities of daily living [13]. These results were assessed using the MOCA, MMSE, and the Loewenstein Occupational Therapy Cognitive Assessment [13]. Other studies support that TDCS in combination with other rehabilitation techniques, significantly improve cognition [16].

Mood and Pain Management:

Mood disturbances and pain syndromes are common post-stroke and are significant comorbidities that adversely affect post-stroke motivation, interaction and recovery [9]. A systematic review and analysis of twelve studies showed that RTMS was linked to the reduction of depressive symptoms and

improvement in the activities of daily living in patients with post-stroke depression (PSD). Specifically, some treatment regimes including the Valentine combination, high frequency, low frequency TMS, and IBS were all better than sham treatments. The results indicate that a four-week bilateral RTMS treatment that involves stimulating the dorsolateral prefrontal cortex for twenty minutes each day can be especially effective [9].

Another obstacle in the development is central post-stroke pain (CPSP), which can lead to permanent pain, sleep problems and a low quality of life. Pharmacological treatment didn't show much improvement leading to exploration of alternative methods, among which RTMS has been found to be effective in treating CPSP noninvasively with analgesic effects [10]. The analysis of six trials proved that RTMS was effective in reducing the severity of pain as compared to sham controls. The mechanisms underpinning the effects of RTMS on CPSP are unknown, but hypothesised that RTMS alters the immune status, stimulating the generation of new neurons, increasing cortical excitability and deepening interneuronal connections. Such results reveal the multifaceted opportunities of NN in the management of stroke complications [10].

Limitations and future directions:

Despite the promising therapeutic potential of NN, a multitude of different limitations hinder advancement [2,5]. Primarily, preexisting studies are often limited to small sample sizes, which decreases the generalizability of findings and the ability to draw definitive conclusions. Furthermore the lack of standardized protocols make direct comparison difficult and optimal protocols unclear [5,8].

Building upon these findings, future research should endeavor to prioritize large-scale, multi-center, randomized controlled trials to provide robust evidence of clinical efficacy [5,8]. Furthermore, standardized treatment protocols should be implemented in these trials, aiming to explore and identify the most effective configuration for each subtype of stroke [5].

Conclusion:

The reviewed studies thoroughly emphasise the importance and growing promise of NN approaches for acute post-stroke therapy. In terms of improving the range of outcomes for stroke survivors, such as swallowing function, muscle tone, motor control, and postural stability, a number of modalities, including ultrasonic, magnetic, and electrical stimulation techniques like RTMS, IBS, TENS, and VNS have shown encouraging results. For instance, RTMS is specifically effective for improving swallowing function, while TDCS has demonstrated marked improvement in postural stability and control.

The encouraging results of noninvasive stimulation in the treatment of stroke patients highlight the importance of early-phase intervention for optimal rehabilitation outcomes. The time of the techniques' use significantly influences therapeutic success, with an increasing number of studies

documenting better outcomes with earlier interventions. By merging these techniques as an element of early stroke recovery, long term outcomes for stroke patients can be improved significantly.

In conclusion, NN strategies have proven to be an effective post-stroke management modality which significantly improves functional, cognitive and motor rehabilitation, which would benefit from further research and introduction into stroke protocols. Appropriate patient selection, standardised assessment modalities and higher clinical evidence is needed to enhance implementation and adoption into daily practice.

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