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Role of Non-Invasive Brain Stimulation Techniques in Peripheral Neuropathy: A Systematic Review

Anshika Singh[1]*, Suresh Mani[1], Sumit Raghav[2], Arvind Krishna[3]

[1]Department of Physiotherapy, Lovely Professional University, Jalandhar, Punjab, India, [2]Department of Physiotherapy, IIMT University, Meerut, Uttar Pradesh, India, [3]Swami Vivekanand Subharti University, Meerut, Uttar Pradesh, India. *Corresponding Author's Email: dranshikasingh.subharti@gmail.com

Abstract

Peripheral neuropathy (PN), a prevalent ailment frequently linked to elevated morbidity, can arise from both traumatic and non-traumatic origins. Along with motor, sensory, and autonomic alterations in the afflicted limb, it can also cause neuroplastic changes in the cerebral cortex. Researchers advise controlling the peripheral effects while maintaining the damaged nerve's cerebral plasticity. In most cases, this increases the motor activity in PN patients. One method for causing neuroplasticity in the cerebral cortex is non-invasive brain stimulation (NIBS). On the motor cortex, this has either excitatory or inhibitory effects. This systematic review was conducted by three independent reviewers. A thorough search was conducted using various electronic databases; Pub Med, Science Direct, Scopus, EMBASE and screened the eligibility of titles and abstracts by two reviewers 'SR' and 'AS', both physiotherapists. Studies involving use of NIBS techniques in human participants of any age having peripheral neuropathy was eligible. Through systematic search from different electronic databases, total 107 studies were identified in this systematic review. Only 7 studies were included. All included studies were written and categorized in tabular form. A thorough search shows that non-invasive brain stimulation (NIBS) methods, which include transcranial magnetic stimulation (TMS) and transcranial electric stimulation (tES), were used in cognitive neuroscience to induce transient changes in brain activity and thereby alter the physiological changes of the subject.

Keywords: Motor Cortex, Neuroplasticity, Non-Invasive Brain Stimulation, Peripheral Neuropathy, Rehabilitation.

Introduction

Peripheral neuropathy (PN) is a prevalent illness with a high morbidity rate, and it can be caused by both traumatic and non-traumatic factors (1). In addition to the motor, sensory, and autonomic abnormalities in the afflicted limb, PN can cause neuroplastic changes in the cerebral cortex (2). According to studies, the damaged nerve's cortical plasticity should be preserved while the peripheral effects are managed. In most people with PN, this enhances their motor activity. Neuroplasticity in the cerebral cortex is induced by non-invasive brain stimulation (NIBS) (3). Peripheral neuropathy can result from a variety of traumatic and non-traumatic clinical disorders. Non-traumatic causes include metabolic problems, systemic disorders, infections, and exposure to hazardous chemicals, poisons, and medicines. Traumatic causes include direct physical injury to peripheral nerves (4). Peripheral neuropathies can cause entire or partial loss of feeling, tingling in the limbs, neuropathic pain in the periphery, peripheral muscular weakness, or complete or partial paralysis, depending on the cause (5).

Peripheral neuropathies are prevalent and difficult to study, diagnose, and effectively manage due to the wide range of causes (6). The current pharmacological and non-pharmacological care of peripheral neuropathy focuses on treating the underlying cause as well as managing symptoms with the use of steroids, immune-modulator medications, NSAIDs, and anti-inflammatory ointments (7). Stress management, exercise, acupuncture, food management, and lifestyle alterations are some of the non-pharmacological alternatives mentioned in the literature. This also showed that progress toward alleviating neuropathic symptoms had been made (8). Non-invasive brain stimulation techniques (NIBS) can help people with peripheral neuropathy feel better (9). NIBS are a fascinating neuromodulatory

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technique that is used to help people develop neuroplasticity (10). The motor cortex is affected by NIBS, which produces inhibitory or excitatory effects (11). Transcranial Magnetic Stimulation (TMS), transcranial Direct Current Stimulation (tDCS), Cranial Electrotherapy Stimulation (CES), Reduced Impedance Noninvasive Cortical Electrostimulation (RINCE), and transcranial Random Noise Stimulation are the five types of NIBS treatments (tRNS). TMS and tDCS, however, are the most extensively used NIBS methods.

There are some guidelines for utilization of non-invasive brain stimulation such as, firstly, specification of the type of participants to be recruited (i.e., healthy adult participants - category A, non-patient special populations – category B, or patient populations – category C). Secondly, enhanced pre-participation screening of all potential participants using the Brain Stimulation Study Suitability Questionnaire (BSSSQ), consideration of potential interacting drugs, and consultation with a medical doctor if deemed a category B or C participant. After that, explicit statement of the relevant stimulation parameters of the protocol (i.e., paradigm, duration, frequency, intensity). Next, clear description of additional measures being taken that may interact with the protocol and elicit additive effects (for example, additional environmental stimuli, prior fatigue, nutritional interventions). In the last, clear statement that general and procedure-specific guidelines will be adhered to (including identification of the names of qualified users on the application and details regarding the management of adverse events) (12).

Since TMS and tDCS are safe, non-invasive ways to efficiently affect sensory processing in the cortex, they seem like appealing tools for studying multisensory interactions in the human brain. The mechanism of transcranial magnetic stimulation is based on electromagnetic induction; a coil receives a high voltage current that causes a rapidly fluctuating magnetic field. When this coil is placed near any electrically conducting material, like the brain, its magnetic field generates an electric current that disrupts regular neural activity. By using paired pulse TMS; it is feasible to expose the functional connectivity between various cortical areas in addition to changing the neuronal activity at the location of stimulation (13). Two different coils are used to deliver two TMS pulses in this paradigm. A test stimulus is then provided to a separate site in the same or opposing hemisphere of the brain after a conditioning stimulus at one location in the brain (14). The second primary technique for NIBS is called transcranial direct current stimulation (tDCS), which polarizes the brain by delivering a sustained electric current with low intensity (1-2 mA) to the scalp via 2 sizable electrodes (15).

People have been using tDCS for a very long time, however around the year 2000, this technique was reevaluated due to assertions of clinical importance and behavioral impacts (16). To provide better well-being to patients, availability of non-invasive brain stimulation is necessary at clinical set-up to provide the stimulation for diagnosed patients for better health as soon as possible which may also help in reducing economic burden of the patient. To enhance learning new skills and the brain's neural plasticity, tDCS modifies cortical excitability. As of right now, cognitive neuroscientists are finding this to be a valuable technique (17). Transcranial direct current stimulation has the ability to increase or decrease neuronal activity in the areas that are stimulated. Anodal stimulation causes the underlying neurons to become more excitable, whereas cathodal stimulation causes the opposite effect. Effects on neuronal excitability can extend up to 90 minutes after just 13 minutes of tDCS treatment (18). Unlike TMS, which directly stimulates neurons to increase activity, tDCS does not. Moreover, TMS can be used in conjunction with other methods for assessing brain activity, such as Electroencephalogram (EEG), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI), to investigate the functional interactions between heteromodal and modality-specific brain regions (19). Last but not least, despite the fact that TMS cannot directly strike the outer area of cortex, a new study has demonstrated that stimulation of the parietal cortex can modify activity in the thalamus, thus opening up new avenues for research on various sensory approach subcortical areas (20). To our knowledge, no systematic review has been conducted to date on the role of NIBS approaches in peripheral neuropathy. This will be the first evaluation of experimental evidence on the role of NIBS procedures in patients with PN of any age, delivered in any context, anywhere. This review

will address the question of whether NIBS procedures are effective in patients with PN.

Adopted Strategy for Searching

Only randomized control trials (RCTs) that investigate the effect of NIBS techniques in patients with peripheral neuropathy were considered for the review. Only human subjects of any age with peripheral neuropathy were eligible, and there were no limits on the number of limbs afflicted or the length of treatment. The review took into account both genders, males and females. This review has not included studies in which animals were used as participants. Only RCT-based studies were taken into account. Validated outcome measures were utilized at least twice: once at the start of the programme and again at the end. The intervention can be supervised or unsupervised, patient-specific with or without standard care, and initiated at any time, in a hospital or outpatient context. Standard exercise protocols including usual routine exercises among patients with peripheral neuropathy were included. The outcomes might include muscle strength testing (manual muscle testing, dynamometry, 3 repetitions maximum), electromyography (EMG) studies, nerve conduction velocity (NCV) studies, validated scales for functional assessment of peripheral neuropathy.

Additionally, according to the PICOS strategy the guiding question was elaborated: 'what is the role of non-invasive brain stimulation techniques in peripheral neuropathy?' All bibliographic databases of published research papers which were easily accessible had been assessed. All databases included were searched for papers published before 2023. The electronic database will include EBSCO (https://www.ebsco.com/), PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), Embase (https://www.embase.com/), Science Direct (https://www.sciencedirect.com/) and Scopus (https://www.scopus.com/). The search strategy combining MeSH terms and free-text words such as- 'Non-Invasive Brain Stimulation' or 'NIBS' or 'Transcranial Magnetic Stimulation' or 'TMS' or 'transcranial Direct Current Stimulation' or 'tDCS' or 'Cranial Electrotherapy Stimulation' or 'CES' or 'Reduced Impedance Non-invasive Cortical Electrostimulation' or 'RINCE' or 'transcranial Random Noise Stimulation' or 'tRNS' and 'peripheral neuropathy' or 'diabetic neuropathy' or 'leprosy neuropathy' or 'neuritis' were used.

The search results were saved to the researcher's account on PUBMED and references were also saved separately on 'Mendeley'. References of all the selected articles were reviewed for relevant studies. A citation search of the selected articles was also carried out for the identification of potentially relevant articles. We tried to balance the sensitivity and specificity of the search by putting search filters according to the inclusion criteria so that the potentially relevant articles were not get ignored. The search filters were include- type of article/publication, date of publication, species, gender, age, subject and language. Physiotherapists AS and SR, the two reviewers, conducted separate database searches and looked over the abstracts and titles to determine which ones qualified. We carefully reviewed the titles and abstracts of the searches and looked through reports that weren't relevant. The complete text of a few chosen, potentially pertinent publications was acquired; to reduce duplication, papers from the same study that were found in separate databases were connected. "Mendeley" (https://www.mendeley.com/) was used to combine search results. Additionally, the researcher's PubMed account (https://www.ncbi.nlm.nih.gov/pubmed/)retained the electronic searches. To encourage and facilitate collaboration among reviewers, the principal investigator/researcher will create a shared folder on "Google Drive" (https://www.google.com/drive/) that is open to the entire team and has secured access. The printed copies of summaries of each screened article were kept as a physical backup. The full-text papers were carefully evaluated by both reviewers (AS and SR) to ensure that they met the inclusion and exclusion criteria. In order to clear up any confusion, the writers' correspondence was conducted. The third reviewer's (SM) decision was deemed final in the event that the researchers disagreed. The first reviewer (AS) had completed the data analysis and synthesis of the publications that met the eligibility criteria. In order to manually add the references for the articles in the data extraction, the reviewer also looked them up. The first and second reviewers assessed the strengths and weaknesses of each study. The risk of bias was assessed using the Cochrane

collaboration tool. Based on results of the risk of bias assessments, no study was excluded. However, if substantial variations found in the results of the risk of bias of the included articles then on the basis of low risk and high risk of bias, results were synthesized separately. Subgroup analyses were conducted if there was availability of sufficient data. Papers were investigated for precautions to be taken before and during the administration of NIBS techniques and reporting of any adverse effects during and after the treatment. Also, articles related to financial/economic, psycho-social challenges faced before, during and /or after the administration of NIBS technique were shortlisted.

Seven of the 107 papers that the systematic review found were included by means of citation scanning of previously published works. After 31 publications were kept for full-text screening, 7 studies in Table 1 were found to satisfy the inclusion criteria specified by the systematic review. The full screening process is shown in Figure 1. Thirty percent of the publications that were eliminated had the study population as their primary reason. A thorough and organized summary of utilizing NIBS, including the sections of the body used, the target population, the technologies employed, and an assessment of the neuropathy-related end measure. Previous studies provided good opportunities to enhance the motor, sensory and cognitive skills using NIBS technologies among the patients with neuropathy. rTMS, TDCs, tRNS and other electronic stimulator improves the physical responses in addition to motor and behavioral changes.

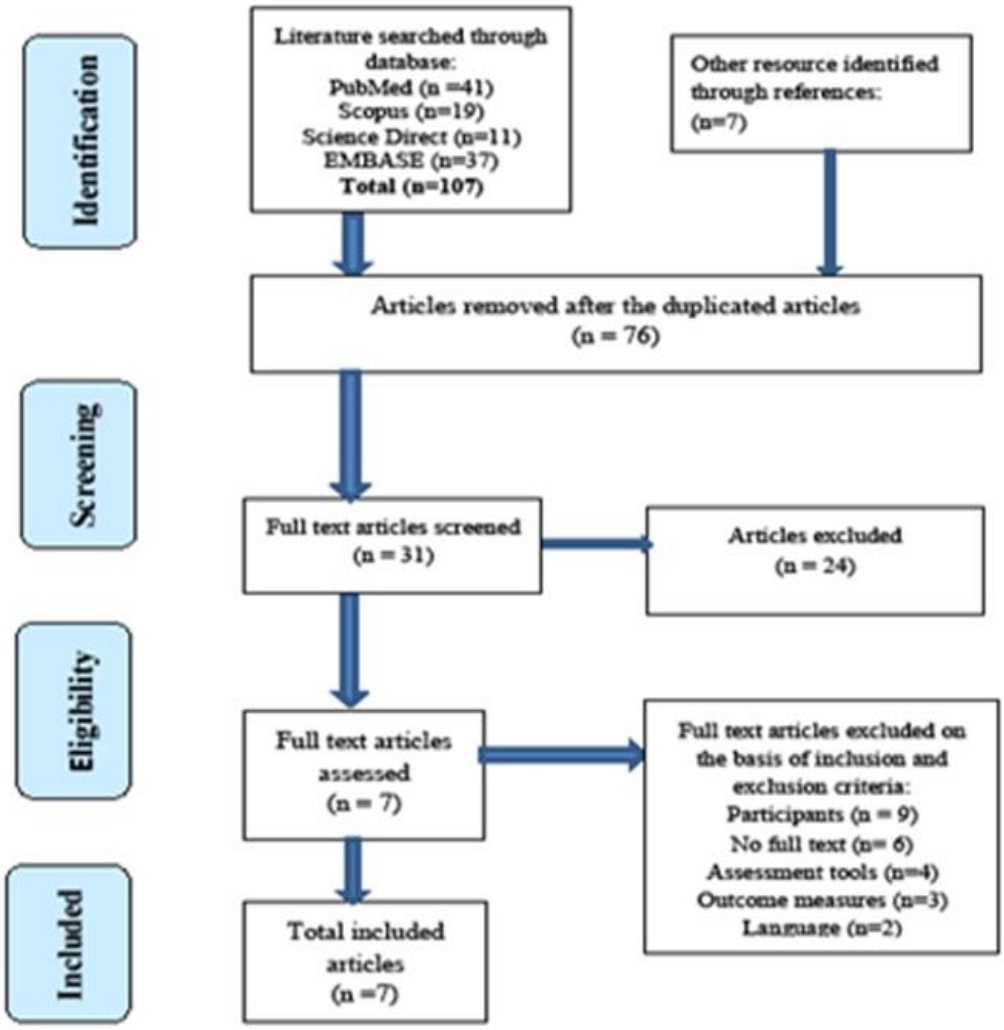

Figure 1: Strategy Adopted for Searching the Articles

Table 1: Included Studies in this Review

Title	Outcome Measures & Methods	Main findings relevant to proposed research work
Peripheral Neuropathy: Differential Diagnosis and Management (21)	Complete blood count; comprehensive metabolic profile; fasting blood glucose, vitamin B12, and thyroid-stimulating hormone level, nerve biopsy and electrodiagnostic studies	Electrodiagnostic studies, including nerve conduction studies and electromyography, can help in the differentiation of axonal versus demyelinating or mixed neuropathy.
Peripheral Neuropathy: Evaluation and Differential Diagnosis (22)	Complete blood count; comprehensive metabolic profile; fasting blood glucose, vitamin B12, and thyroid-stimulating hormone levels; and serum protein electrophoresis with immunofixation	Early peripheral neuropathy may present as sensory alterations that are often progressive, including sensory loss, numbness, pain, or burning sensations in a "stocking and glove" distribution of the extremities. Later stages may involve proximal numbness, distal weakness, or atrophy. Physical examination should include a comprehensive neurologic and musculoskeletal evaluation.
Modulation of untruthful response with non-invasive brain stimulation (23)	Investigated whether non-invasive brain stimulation over the dorsolateral prefrontal cortex (DLPFC) could modulate generation of untruthful responses about subject's personal life across contexts	findings add up to previous stud-ies demonstrating that it is possible to modulate some processes involved in generation of untruthful answers by applying non-invasive brain stimulation over the DLPFC and extend these findings by showing a differential hemispheric contribution of DLPFCs according to contexts.
Transcutaneous Magnetic Stimulation (tMS) in Alleviating Post-Traumatic Peripheral Neuropathic Pain States: A Case Series (24)	Low frequency (0.5 Hz) was developed over the affected area. 400 pulses of stimulation were given per protocol session. 3 to 4 sessions of protocol received by each patient for 2 months. Numeric pain rating scale was used for measuring the level of pain Between-subjects design.	The analgesic effect of low frequency tMS shows the potential impact with repeated protocol given to 6 to 8 week. Before intervention, higher level of pain diminished after 2 months of protocol session. tMS offers a no-invasive therapeutic approach for neuropathology induced pain conditions.
Investigate the interaction of rTMS and expectations on pain perception (25)	Analgesia-expectation group (TMS as a painkiller) and control group (no effect of TMS on pain). Of these, half assigned to active TMS and half to sham TMS. Heat-pain paradigm, low-frequency rTMS or sham TMS before expectation-induced placebo analgesia.	Placebo significantly increased pain threshold and pain tolerance. rTMS treatment did not affect pain perception but the disruption of DLPFC activity with TMS completely blocked expectation-induced placebo analgesia. Analgesia-expectation group reported more effective pain reduction than the control group.

		Participants in the active-TMS group perceived less analgesic effect than those in the sham group.
Repetitive transcranial magnetic stimulation in patients with chemotherapy-induced peripheral neuropathy (26)	rTMS was delivered at (5Hz) frequency on primary motor cortex targeting affected extremity. 500 pulses of rTMS stimulation were delivered per session. Visual analog scale and Japanese version of McGill questionnaire was used to measure the pain and dysesthesia.	rTMS decreased the intensity of pain by stimulating the primary motor cortex targeting the extremity. This is the first report on demonstration of the effect of rTMS in chemotherapy-induced peripheral neuropathy. They suggest rTMS could be good option for treating pain among the patients with chemotherapy-induced peripheral neuropathy.
Repetitive TMS in treatment of resistant diabetic neuropathic pain (27)	The application of high frequency (10Hz) of rTMS was delivered to 20 insulin-dependent (10) and non- insulin dependent (10) patients. The stimulation was given over the lower limb motor cortex. The treatment was given for 5 days. Pain and nerve conduction was measured by visual analog scale and electromyography with surface electrodes to compare the pre and post results of rTMS sessions.	rTMS appeared to be potential therapeutic approach for improving the pain and nerve conduction following rTMS protocol sessions. It produces the analgesics effects and promoting plasticity of the motor cortex and also activating the pain inhibitory response.

Searching Outcome

According to our knowledge, this will be the first review on experimental evidence related to the role of NIBS techniques, delivered in any setting, any place, for patients of any age suffering from PN. The included studies reveal that NIBS has a potential impact on the brain for changing the external factors associated with pathology. NIBS affect the neural connectivity of efferent and afferent communication which helps in progression of the condition via motor and sensory regeneration of the part of the body. Various studies advocated that NIBS improves the plasticity in brain and motor learning adjunct with therapeutic modulation. Plastic changes include learning new memories or motor skills. Synaptic alterations, alterations in neuronal excitability, emergence and integration of new neurons, and development and dissolution of new synaptic connections are all sources of plastic changes (28). Non-invasive brain stimulation can alter a brain region's physical makeup and state, affecting the success or failure of following processes like further stimulation or organic learning. Synaptic strength changes can result from pre- or postsynaptic alterations, and there are frequently concurrent changes in the excitability of the cell membrane (29).

Modifications post-synaptically occur in the quantity or subunits of the receptors, whereas changes in the neuron are brought on by changes in ion channels. A number of synaptic plastic alterations caused by the rate of synaptic activity have been uncovered by basic science research of synaptic plasticity (30). In the simplest trials, rapid rates, such as more than 10 Hz, result in long-term potentiation (LTP), and slow rates, such as 1 Hz, result in long-term depression (LTD). De-potentiation and de-depression are two terms for the reversal of LTP and LTD, respectively (31). Similar increases in excitability can be produced using NIBS, which imitates these procedures. The amplitude of the motor evoked potential makes it simple to assess the motor system's excitability (32). It is unclear whether fast and slow effects as found in the motor system always translate to other regions of the cortex (33). An identical intervention later on can have a different outcome if the brain's excitability is altered. Plasticity has

changed in the situation. Metaplasticity is the term for plasticity inside plasticity. Some types of metaplasticity are not homeostatic (34). Thankfully, a counter-process known as homeostatic metaplasticity steps in when excitability changes become excessive. With homeostatic metaplasticity, treatments have a tendency to either increase or decrease excitability depending on the level of activity (35).

The motor cortex's excitability steadily rose during early learning, but it then decreased once the sequence was understood (36). Any assessment of the clinical use of this strategy is conjectural due to the less account of clinical trials that evaluated the effectiveness of integrating no-invasive brain stimulation with physiotherapy (37). Although more research is required before any therapeutic implications can be considered, some considerations can be made now that will help this strategy be used most effectively in the future. We still don't know the best way to combine NIBS and motor therapy to maximize the effects, but it probably depends on a lot of factors, like baseline cortical activity, the kind of motor training, the stimulation site, when to stimulate in relation to physical intervention, and the illness stage (acute versus chronic). To maintain normal brain function, compensating regulatory systems, for instance, may be triggered by NIBS. On the other hand, activity-dependent forms of plasticity, such as those involving LTP and LTD pathways, become inherently unstable due to positive feedback. Therefore, a strong foundation in the comprehension of the fundamental plastic mechanisms and how they interact with activity-induced plasticity should be required before NIBS may be effectively implemented as an adjunctive physical therapy technique.

For instance, the timing of the NIBS treatment in relation to the motor task is a difficult problem. In contrast, functional therapies might theoretically be used in various stages of an NIBS intervention (38). Prior to the motor training, NIBS may be able to prepare the functional networks for the physical intervention. Alternatively, NIBS that is used concurrently with a behavioral intervention may interact preferentially with the networks that the active task has chosen to engage (39). This strategy's fundamental assumption is that, after the motor therapy-induced modulation, additional cortical excitability modulation may specifically increase a network's activity-dependent activation and assist its functional stabilization (40).

In the past two decades, a remarkably large number of studies have been published discussing the possible therapeutic effects of NIBS in a variety of disorders, including neuromuscular, musculoskeletal, and other systemic ailments (41). When combined with traditional medicines or training, NIBS may be a viable supplemental therapy that helps brain damage patients recover more quickly (42). Using NIBS with therapy raises the likelihood of creating a beneficial synergistic impact, according to the rehabilitation idea that aims to improve neuroplasticity (43). Additionally, it is believed that this causes both functional re-learning and modification of neuronal connections. The mechanisms of action for rTMS and tDCS are different when it comes to how NIBS affects neuronal networks, and the NIBS mechanism of action itself is still a hot topic of discussion (44). Yet, there is a consistent possibility for NIBS to have a beneficial effect on abnormal rhythms caused by disease or injury in the network (45). Previous neuroimaging research indicates that NIBS affects the cerebral cortex directly beneath the stimulation point or its functionally linked brain regions based on neural networks (46).

The commonality among them all is that the stimulation location was linked to a shift in activity in the relevant brain area. It is essential to acknowledge that every patient has a unique site of brain injury in order to facilitate the practical application of NIBS for cognitive impairment. As previously mentioned, NIBS impacts not just the cerebral cortex directly below the stimulation point, but also neural network-based brain regions associated with certain tasks. (47). For instance, the impact of the stimulation site and parameter on language function restoration of the damaged language areas and homologous language-related regions should be taken into consideration in a recent study on NIBS for aphasia (48). The onset period and the results of alterations in brain activity brought on by language workouts are taken into consideration while making these decisions. Cognitive and neuroimaging assessments will provide more evidence for the efficacy and accuracy of NIBS treatment (49). It is important to take into account the considerable limitations of this review. This systematic review first included papers that evaluated the effects of

NIBS using multiple neuropsychological tests. There were several overlapping portions in some of the neuropsychological tests used in our symptom-based classification of peripheral neuropathy.

Since TMS and tDCS are safe, non-invasive ways to efficiently affect sensory processing in the cortex, they seem like appealing tools for studying multisensory interactions in the human brain. But, previous research findings advocated that rTMS shows better improvement in terms of changes in the symptoms of peripheral neuropathy by delivering the same session of different techniques of non-invasive brain stimulation. Furthermore, the limited number of collected publications and the documented variability in cognitive symptoms, stimulation location, and parameters precluded us from doing sub-analyses in this review to clarify distinct neuropsychological symptoms, stimulation parameters, and stimulation site.

The drawback was that the target patients were chosen for the extraction trials based on reported symptoms of peripheral neuropathy rather than being categorized according to brain imaging that determined the exact brain lesion. However, from the standpoint of neuro-rehabilitation, the functional implications of the cognitive symptoms are thought to be more significant. Neurophysiological indicators of cognitive and functional rehabilitation, as well as functional neuroimaging, are likely needed to enable more accurate application of NIBS in neuro-rehabilitation of cognitive impairment following neuropathies. Lastly, a more significant consideration in peripheral neuropathy rehabilitation, in addition to managing symptoms, is assessing the influence of NIBS on the restoration of everyday functioning skills.

Future research must assess how modifications in everyday activities can support the effectiveness of NIBS when used in conjunction with general rehabilitation. The comprehensive analysis of reported information related to the intervention will provide the information related to evidence of significant benefits and whether the best practice can be maintained during one delivery of the NIBS techniques. The information provided by this review will be useful in planning of rehabilitation services for patients with peripheral neuropathy in future.

Conclusion

This review found evidence for the efficacy of non-invasive brain stimulation on neuropathy but larger randomized-controlled trials are needed to better understand its effect on the acute stage of peripheral neuropathy. Many may wonder if non-invasive brain stimulation is ready to be used clinically. While this is not the question addressed by the present review, the authors believe the answer is no for two reasons. One, while the results of this review are generally in favor of non-invasive brain stimulation, specific and definitive conclusions cannot be made from only low number and clinically heterogeneous trials.

Abbreviations

Nil.

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Nil.

Author Contributions

Anshika Singh conducted this study and contributed in study design, conceptualization and final draft of the study. Suresh Mani reviewed the study and suggested modifications. Sumit Raghav contributed in writing and editing the methodology and discussion of this study. Arvind Krishna reviewed the study and suggested modifications.

Conflict of Interest

Nil.

Ethics Approval

Not applicable.

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