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NON- INVASIVE NEUROMODULATION APPROACHES: ADVANCED TECHNIQUES TO MANAGE POST STROKE COGNITIVE IMPAIRMENTS

Physiotherapy

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ABSTRACT

Stroke is the second greatest cause of death and the third leading cause of disability worldwide, affecting 15 million people each year. Long-term cognitive deficits continue to exist despite improvements in acute care. 30–70% of survivors, which hinders recovery and increases reliance. The limited effectiveness of the current therapies for post-stroke cognitive impairment (PSCI) emphasizes the need for more all-encompassing strategies. This review aims to cover various non-invasive neuromodulation approaches for PSCI. The databases Google Scholar, PubMed, and Web of Science were searched for relevant studies. Only experimental studies with results from 2020 to the present were considered. There were less experimental data specifically for PSCI on non-invasive neuromodulation techniques. Some experimental studies provided combined effects of neuromodulation techniques and cognitive training. This review revealed that the effectiveness of these techniques needs further examination. Techniques such as tDCS, rTMS, and tACS have been proven to be beneficial in improving cognitive functions. These methods can be utilized in clinical settings for patients with PSCI. However, it is important to conduct a thorough assessment of the specific cognitive domains before implementing any intervention.

KEYWORDS

Cognition, Cognitive Dysfunction, Cognitive Training, Transcranial Direct Current Stimulation

INTRODUCTION

Stroke represents the second leading cause of global mortality and a major contributor to disability worldwide. In 2019, stroke accounted for approximately 6.55 million deaths and 143 million disability-adjusted life-years globally Post-stroke cognitive impairment (PSCI) is referred as the manifestation of cognitive deterioration after any episode of stroke. It affects up to 1/3 of the patients with stroke and also impairs their capabilities to participate socially and in daily activities. Although frontal-subcortical functional impairment is common in PSCI, stroke-related cognitive impairment also affects sensorimotor-related brain areas. Research has demonstrated that these patients had reduced brain activity in the frontoparietal network (FPN), indicating that patients with stroke may have some cognitive impairment (Xu et al., 2024). Cognitive deficits can impact patients' communication and everyday activities, posing a burden on families and society. Researching intervention approaches for cognitive impairment is crucial and clinically significant (You et al., 2024).

As the fundamental building block of integrated cognition, executive functioning is a crucial and intricate aspect of neurocognitive processing. A common clinical manifestation of PSCI is impairment of executive functions which significantly lowers patients' quality of life. It is characterized by poor planning/organizational capacities, impaired task execution, and attentional deficiencies. Importantly, it shows a close relationship with everyday activities and quality of life metrics, making its improvement a key treatment goal in PSCI.

Diamond made significant contributions to literature by defining and explaining executive functions (Diamond, 2013). Author stated that these functions, also known as executive control or cognitive control, refer to a family of top- down mental processes. Executive functions include three core functions: inhibition (including self-control, behavioural inhibition, and interference control, selective attention and cognitive inhibition), cognitive flexibility and working memory.

Countries are competing fiercely to advance in the field of cognitive development and its management. In the 1980s, both invasive and non-invasive stimulation techniques were created. Recent research has validated their effectiveness in improving cognitive performance (Kar et al., 2020).

There are cognitive deficits such as executive dysfunction that are often not addressed in clinical settings after a stroke and managed using advanced techniques. Current research focuses on non-invasive transcranial stimulation, which can be integrated with neuroimaging methods. This study reviews the advancements in cognitive function treatment, with a focus on the implementation of neuromodulation.

Literature review strategy

This study specifically focused on the population with post- stroke cognitive impairments. We searched the databases Google Scholar, PubMed, and Web of Science, only experimental studies with results from 2020 to the present were considered. The keywords used for the search: post stroke cognitive impairment and neuromodulation; post stroke cognitive impairment and tDCS, tACS, rTMS; cognitive deficits and stroke; executive dysfunction and stroke.

Non- invasive neuromodulation techniques

Neuromodulation is a biomedical engineering technique that involves the use of invasive or non-invasive devices to target specific brain regions or nuclei. The main objective of this technique is to modulate neural pathways by either strengthening or inhibiting them, permitting the brain to relearn positive pathways and improve mental and cognitive functions (Clark & Parasuraman, 2014). One of the key benefits of non-invasive procedures is their ability to interact with appropriate neural signal in any region of the brain without causing harm to the skull. Existing advanced non-invasive methods of neuromodulation for cognitive functions are mentioned in Figure 1.

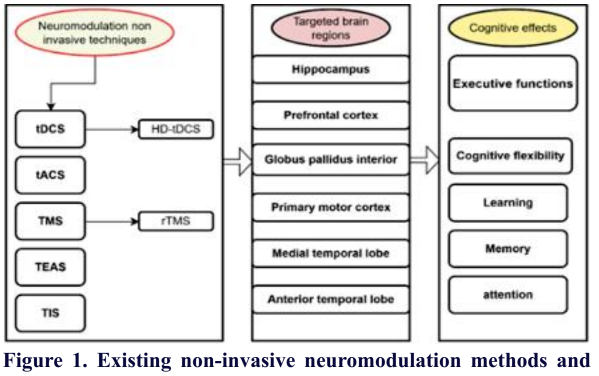

Figure 1. Existing non-invasive neuromodulation methods and their objectives.

Abbreviations: tDCS: transcranial direct current stimulation; HD-tDCS: high-definition transcranial direct current stimulation; tACS: transcranial alternating current stimulation; TMS: transcranial magnetic stimulation; rTMS: repetitive transcranial magnetic stimulation; TEAS: transcutaneous electrical acupoint stimulation; TIS: time interference stimulation;

Transcranial direct current stimulation (tDCS)

tDCS modifies cortical neuronal activity by applying a steady, low-intensity direct current (1-2 mA) to the scalp, which affects cognitive functions and the functioning condition of the brain. While cathodal stimulation raises the threshold and lowers the discharge rate, anodal stimulation lowers the activation threshold of neurons and enhances their spontaneous discharge rate. Furthermore, it is thought that tDCS affects how brain chemicals like neurotransmitters are released and reabsorbed, which affects nerve signal transmission (Zhao et al., 2020). It is very critical to carefully consider the targeted brain regions, when applying tDCS. As the effects of stimulation parameters and protocols can vary substantially. Targeting particular brain areas essential to the cognitive network is possible using tDCS, a non-invasive type of brain stimulation. It modifies neuronal transmembrane electrical potentials and, consequently, the excitability and firing rate of neurons by applying a steady, low direct current through external electrodes that pierce the skin, skull, and meninges (Thair et al., 2017).

Among the many benefits of tDCS are its low cost, ease of use, painlessness, and safety tDCS is frequently utilized in neuroscience studies and has been demonstrated to enhance cognition.

An experimental study found that the combination of tDCS application and aerobic exercises in patients with PSCI can improve working memory through neuroelectrophysiological mechanisms (Zhou et al., 2025). Another study found that tDCS enhanced cognitive function in PSCI after examining its effects on brain functional connectivity and network structure using resting-state functional magnetic resonance imaging (rs-fMRI) (Zhong et al., 2025).

Another study concluded that combined anodal stimulation of TDCS and cognitive training improved working memory in PSCI (Kazinczi et al., 2025). Here, we can see that previous literature evident that if tDCS combined with other therapeutics techniques improve cognitive functions, solely tDCS mechanisms can be explored in future studies.

Transcranial magnetic stimulation (TMS)

This non-invasive technique is painless and uses pulsed magnetic fields to enhance brain metabolism and nerve activity. It works by altering the action potential in the cortex through the induction of currents. Low frequency TMS, with a frequency of less than 5 Hz, inhibits excitability in the cortex, while high frequency TMS, with a frequency of 5-20Hz, enhances this excitability (Gorelick et al., 2014). These effects have led to effective clinical applications for treating neurological diseases and improving learning and memory. Adjustable repeated TMS (rTMS), which is now widely acknowledged for its efficacy in neurological disorder treatment and rehabilitation, was made possible by technological advancements (Šimko et al., 2022).

Protocols are categorized as either maintenance rTMS (mrTMS) or accelerated rTMS (arTMS) based on stimulation circumstances. By increasing the number of daily treatment sessions, arTMS builds on rTMS and can reduce the entire treatment duration, thereby addressing the problem of lengthy treatment periods and restricted availability (Fitzgerald et al., 2013). In order to maximize clinical responses, mrTMS refers to the extension of treatment cycles based on favorable patient outcomes following the achievement of initial therapeutic benefits. Clinically, both arTMS and mrTMS have been demonstrated to successfully improve long-term memory, speed up reaction times, and lessen neuropsychological deficiencies, providing fresh perspectives for further studies on the application of magnetic stimulation to promote cognitive function. Xu et al., (2024) reported that a dual-target rTMS is effective in improving cognitive impairments in patients with PSCI. The stimulation showed significant efficacy, indicating that dual-target stimulation (Left Dorsolateral prefrontal cortex (DLPFC)+M1) has potential as a target for TMS in treating PSCI. A study found that high frequency rTMS targeting the ipsilesional DLPFC can improve cognitive functioning in PSCI (Kim et al., 2022). Specifically, stimulation of the DLPFC with 10-Hz rTMS was found to have a significant therapeutic effect. Also, frequency of 10 Hz, 700 pulses of TMS improved the attention function (Liu et al., 2020). Another study utilized intermittent theta-burst stimulation (iTBS), a patterned form of TMS (Li et al., 2025). The study suggests that iTBS may endorse recovery of cognitive processes by regulating brain derived neurotrophic factor (BDNF) and attenuating neuroinflammatory processes. The researchers also concluded that iTBS enhanced the cognition of patients with subacute stroke. Han and colleagues utilized a high dose iTBS of 3600 pulses per day, aiming the individualized frontoparietal cognitive network. The results of this study were found to be significant for PSCI (Han et al., 2025). On the other hand, Wang and colleagues utilized two blocks of iTBS therapy, with 600 pulses in each block and a 50-minute interval between them. Their study showed positive therapeutic outcomes for PSCI (Wang et al., 2025). A study targeting left DLPFC and utilizing iTBS (1200 pulses per session) for patients with PSCI. The results showed a significant improvement in both global cognition and executive function (Xia et al., 2025).

Transcranial alternating current stimulation (tACS)

Because of its distinct operating principle and mechanism of action (as shown in figure 2.), tACS has garnered significant interest in the field of neuroscience. This form of brain stimulation is non-invasive, portable, safe, manageable, and well-tolerated (Wischnewski et al., 2023). Weak oscillating electric currents, usually ranging from 1 to 4 mA in humans, are applied to the scalp during tACS. Because of the restricted conductivity of the skull, the currents largely shunt via the tissues around the brain, including the skin and CSF, before arriving at the brain. The acting force of AC stimulation, the electric field generated in the brain, is measured in voltage per meter, or millivolt per millimeter, or mV/mm, and varies from 0.1 to 1 mV/mm (Opitz et al., 2016). These externally produced fluctuating electric fields fall within the range of intrinsic local field potentials (LFPs), which are measured at 1-4 mV/mm, but they are not strong enough to produce an action potential in a steady-state neuron. Accordingly, in-vitro and in-vivo investigations (De Jongh et al., 2011) have shown that tACS can bias spike timing and produce rhythmic variations in the neuron's membrane potential instead of action potentials.

In order to investigate the effects of tACS, a study used the EEG approach (Jaušovec & Jaušovec, 2014). Authors investigated at how various targets and intensities affected working memory and tried to ascertain the causal linkages between changes in working memory and neuromodulation parameters. Additionally, experimental studies (Li et al., 2017) conducted on healthy individuals and patients with chronic fatigue syndrome have demonstrated that tACS considerably enhances patients' working memory, emotional processing, and sleep quality when focusing on areas like the prefrontal cortex and the left DLPFC. As far as we know, there is a lack of evidence of experimental data on tACS for PSCI.

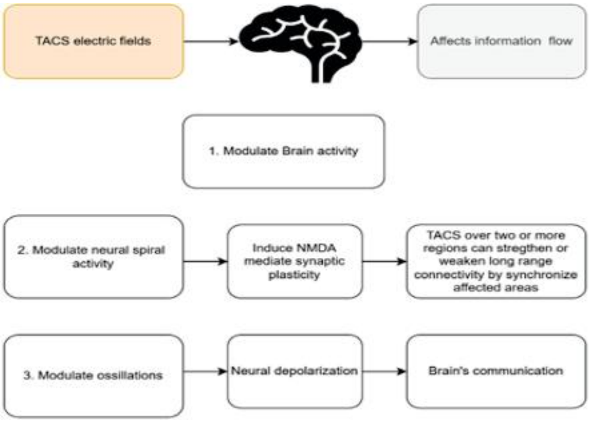

Figure 2. tACS: mechanism of action (physiological role)

Transcutaneous electrical acupoint stimulation (TEAS)

Combining a transcutaneous nerve electrical stimulation technology with traditional Chinese meridian and acupoint theories, TEAS is a significant complementary and alternative medicine approach. It reduces the discomfort of acupuncture, lowers labor expenses, and minimizes dangers like electrode displacement or needle breakage by providing non-invasive, gentle electrical stimulation that is customized to patients' clinical symptoms. It stimulates acupoints by using low-frequency pulse currents via electrodes affixed to the skin, protecting perioperative patients via preventing oxidative stress reactions in cognitive processes. By controlling the synchronization of brain networks and neuronal activity, TEAS improves cognitive performance.

A novel form of transcutaneous electrical stimulation (tES) called temporal interference stimulation is thought to be able to excite brain regions more deeply than regular TES (Lee et al., 2022). By combining two sets of sinusoidal currents with slightly varying frequencies within the high-frequency range, it modulates brain activity using high frequency (≥1000 Hz) oscillating electric fields. A low-frequency signal produced by an interference pattern can efficiently pass through the surface of the brain and deep into brain tissue, stimulating neuronal cells and causing reactions.

As far as we know, there is a lack of evidence in PSCI the use of TEAS. It has been proved beneficial to reduce cognitive impairments in postoperative patient with lumbar spine injury(Wang et al., 2022).

Time Interference Stimulation (TIS)

A kilohertz electric field is applied outside the skull using TIS, a non-invasive neuromodulation approach, usually with a small frequency differential between 10 and 200 Hz. This stimulates deep brain areas like the hippocampus and basal ganglia by causing emissions at a different frequency. TIS has a lot of promise for a variety of uses. The majority of this technique's study is still in the simulation stage and hasn't been used on humans yet.

Conclusion and Perspectives

This study provides experimental data on the impact of neuromodulation treatment approaches for PSCI. The review focuses on the strengths of various non-invasive techniques, specifically stimulation targets and their effectiveness. The novelty of this review lies in its provision of data highlighting the feasibility of using tDCS, rTMS, and tACS in various clinical settings. Despite this there were less experimental data specifically for PSCI on non-invasive neuromodulation techniques. Some experimental studies provided combined effects of neuromodulation techniques and cognitive training. The effectiveness of these techniques needs further examination.

Cognitive function encompasses various domains, including memory, attention, executive functions (working memory, inhibitory control, cognitive flexibility), language, processing speed, and calculation which often interact with one another. In order to thoroughly evaluate the impact of non-invasive techniques, multidimensional neuropsychological tests will be utilized. This approach will allow for a comprehensive assessment and minimize the risk of overlooking any specific cognitive impairments in patients with PSCI. After thoroughly reviewing the literature, it is also evident that no studies have conducted a pre-assessment of executive functions in patients with post-stroke cognitive impairments to determine which specific domains are impaired or spared. To accurately assess executive functions, it is recommended to use standardized tools such as computerised batteries.

Future studies could explore non-invasive neuromodulation techniques, utilizing neuroimaging methods to provide more precise guidance for their use in treating cognitive deficits. Clinically, the integration of neuromodulation treatment approaches and neuroimaging methods is crucial for accurately diagnosing and effectively treating executive function deficits. This integration is a vital area of research that will greatly advance our understanding and treatment of executive functions.

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