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Neuromodulator approaches to depression: The potential of transcranial electric stimulation

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Abstract. Depression, a widespread mental health disorder, presents significant challenges in diagnosis and treatment. Amidst the myriad treatments, non-invasive Transcranial Electric Stimulation (tES), encompassing Transcranial Alternating Current Stimulation (tACS) and Transcranial Direct Current Stimulation (tDCS), has emerged as a promising intervention for Major Depressive Disorder (MDD). This review delineates the mechanisms of these modalities, their distinctions, and their potential to modulate neural oscillations and influence cognitive functions. Studies showcased the efficacy of these techniques in ameliorating depressive symptoms, with EEG and fNIRS employed to gauge their neurological impact. Observations suggest the potential in modulating for specific brain rhythms to enhance memory functions in older adults and influence working memory processes. The dynamic interplay between tDCS and tACS in altering cortical activities and their interaction with neurotransmitters like GABA further underscores their potential. However, the need for extensive research, particularly double-blind randomized control trials, remains paramount to ascertain their safety and efficacy. This review provides a comprehensive insight into the prospective role of tES in the clinical landscape of MDD treatment.

Keywords: Transcranial Electric Stimulation, Major Depressive Disorder, neural oscillations, memory functions, neurotransmitters.

1. Introduction

1-3% of people in the US suffer from MDD and are resistant to different treatment trials. Major depression causes the disability of millions of people as well as brings an enormous financial loss to society. One of the treatment solutions for treatment-resistant depression is neuromodulation, which offers hope to people for recovery [1]. Being depressed and having a risk of depression are caused by negative biases, lack of positive biases, self-referential processing, interpretation, attention, and memory, as well as the use of maladaptive cognitive emotion regulation. According to recent studies, limitation in cognitive regulations of mood-related content is the base of these cognitive functions. Abnormalities of memory, sensation, behavior, and personality are syndromes that often are results of brain disorders [2]. According to the World Health Organization, death from suicide each year reaches around 800,000 due to mental health issues [3]. There were developed criteria for diagnosing brain disorders and their pharmacological and psychological treatment. Unfortunately, understanding the neural foundation of the brain and the processes involved in these diseases is limited. The low efficiency of pharmacological treatment of certain brain disorders made scientists look for alternatives. The brain stimulation of

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neuropsychiatric patients to modulate plasticity of their brain by different means of invasive and non-invasive methods [4-6]. Invasive neuromodulation using pharmacological interventions targeted microsimulation, optogenetics, etc., were employed to target brain function with spatial precision [5]. On the other hand, the way to modulate the brain without opening its skull is non-invasive brain neuromodulation (NIBS). Transcranial magnetic stimulation(TMS) and transcranial electric stimulation(tES) are the main methods of NIBS, which treat brain disorders [3].

What is: The foundation concepts of TMS and tES involve producing a potent current that activates neurons, affecting ion pathways and concentration differences to adjust the neuron's electrical balance. Three tES methods include transcranial direct stimulation(tDCS), transcranial alternating current(tACS), and transcranial random noise stimulation(tRNS) [8, 9]. The difference between them is the method of delivery of electric current.

Mechanisms: Transcranial alternating current stimulation(tACS) is a form of non-invasive deep brain stimulation with minimal side effects. Using an electric present influence on the brain's cortex enters brain oscillations and induces long-term synaptic plasticity to treat various psychiatric disorders. Cognitive neuroscientists have studied and examined tACS; however, its application of method was only recently used in psychiatry clinical trials [2]. tACS delivered low-amplitude electric current and was used for investigating the causal role of neural oscillations in cognition. Another neuromodulator approach that can influence neural systems function, cognition, and behavior is transcranial direct current stimulation(tDCS). Evidence shows that tDCS could impact various psychiatric symptoms, particularly depression and schizophrenia. Electrodes connected to the scalp delivered homogenous electric current in the range of 1-2mA, representing tDCS [10-12].

Interestingly, the current delivered as oscillations with specific frequency and stimulation amplitude is defined as tACS. tRNS is different from the other two methods by using random current amplitude. Modulation of ongoing neural oscillations and neuroplastic effect is a principle of tACS. On the other hand, membrane polarization-influenced neuronal excitability is the central concept for tDCS. There is a need to formulate definitive guidelines for tES, specifying the duration of modulation, intensity, and location of electrodes.

Transcranial direct current stimulation(tDCS) could also change neural system functions, cognition, and behavior. Evidence shows that tDCS could impact various psychiatric symptoms, particularly depression and schizophrenia. Nevertheless, research faces different challenges regarding how the method influences the effects, with no clear understanding of its effect on neural activity, functioning, and cognition of human beings. The essential points of the review are identifying future research priorities into MDD, such as mechanisms of action of tDCS and the potential of its clinical efficacy are the essential points the review. Constant monitoring of the progress of the crucial areas that containing data about advantages of using tDCS and its effectiveness during task training on prefrontal cortex could enhance behavioral performance. In the end, effective treatment of psychiatric disorders depends on an empirical study explaining the impact of tDCS on the CNS and its behavior [8].

It is essential to accurately assess neural activity in the brain, especially when using EEG for brain-computer interface objects. EEG is the oldest noninvasive neuroimaging modality, which is portable and has a higher temporal resolution as well as transcranial near-infrared stimulation(tNIRS) that measures oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HbR) [9].

2. Perspective of Clinical Research

Outcomes (clinic/research): Symptoms of depression were improved using tES, an electrical stimulation therapy modality. EEG and fNIRS evaluated neurological effects and assessed therapeutic performance from hemodynamic changes. The power spectrum of the alpha band was used to evaluate the differences before and after stimulation. There were alpha bands with different ranges of 8 to 12 Hz, 8 and 13Hz, or 7.5 and 12Hz. Delta, theta, and gamma frequency bands of event-related potential (ERP) were also analyzed as components of the EEG-derived characteristics. Further data was gathered on the placement of anode stimulations for both tACS and tDCS, specifically in the left dorsolateral prefrontal cortex (DLPFC), and features were extracted from the alpha frequency range . These data suggested that the

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left DLPFC is associated with right prefrontal hyperfunction and dysfunction of brain plasticity of depression.

A study using fNIRS revealed enhanced working memory performance and HbO in 26 patients with post-stroke depression after undergoing a 20-minute tDCS treatment with a 2-mA current on the left DLPFC, with the return electrode positioned on the right DLPFC. Another study was applied tACS at 10 and 40Hz in the DLPFC to examine the potential and effectiveness of altering alpha oscillations [10]. After 2 weeks of application, the 10-Hz tACS protocol was observed to decrease the intensity in the alpha frequency. Simultaneously, the current of 2 mA for 40 min was applied in one tDCS study, which was received thrice weekly for 6 weeks. There was an improvement in behavioral performance (emotional state and cognitive processing); however, brain activity assessments (frequency of distribution and ERP) had limited impact following the intervention. The exciting aspect of the studies was the different duration protocols and their effect on depression treatment. Short-term tDCS treatment protocols (5 sessions) positively affected the depression score and the power spectrum, but the improvement was sustained for a limited time of 4 weeks. Long-term tDCS treatment protocols (15 sessions) suggested improved mood and cognition in 50-60% of people with depression [11]. In addition, there were demonstrated that reduced ERP and frequency distribution (e.g., delta, theta, and alpha wave ranges) [12] by following tDCS protocols with lower intensity (1 and 5 mA) [13]. Specifically, combining positive psychotherapy with tDCS treatment protocols significantly influenced depression. Also, three months of follow-up exhibited a noticeable impact of combined therapy over tDCS alone [9] [12]. Non-invasive neuromodulation, tACS, developed guidelines can improve long-term and auditory-verbal working memory. Applying synchronous low-frequency neuromodulation to the parietal cortex showed enhanced working memory on days 3,4, and 1 month post-intervention. Similarly, synchronous high-frequency neuromodulation in the prefrontal cortex led to improved long-term memory on 2-4 and again after 1 month of the intervention. Based on memory-focused circuits' specific spatial and spectral characteristics, neuromodulation can effectively and continuously tackle the brain's adaptability.

Exploring distinctive rhythmic patterns in specific brain areas and exploiting these mechanisms by non-invasive methods such as tACS are essential tools to selective improve memory function in older adults. Working memory, long-term memory and free recall are considered to be influenced by oscillatory patterns in the theta and gamma frequency bands.

The scientists tested the hypothesis of improvement of auditory-verbal working memory function by modulation of theta rhythms in the inferior partial lobule (IPL) and improvement of auditory-verbal long-term memory function by modulation of gamma rhythms in the dorsolateral prefrontal cortex (DLPFC). A set of experiments was conducted, which showed that memory could be improved through neuromodulation of functionally specific brain rhythms [14].

Paring tACS and electroencephalographic (EEG) to measure the functional connectivity of neural networks has great neuromodulation potential and lasting behavioral effects. Also, focusing on the brain areas with tACS at the theta wave range influences working memory processing and capacity [15].

3. Discussion

Resetting brain oscillations by the electrical current emphasizes its safety and efficiency and enhances behavior outcomes, according to findings of the clinical studies. Researchers are utilizing the brain circuit's responsiveness to tACS as a valuable instrument for the diagnosing, clarificatying, and prognosis psychiatric disorders. Nevertheless, there are unresolved questions that future double-blind, randomized controlled trials could address by identifying response markers and adjusting for various complicating elements [16]. Customization of tES treatment protocols for patients with neurological and mental disorders offered the future direction by employing an integrated brain stimulation approach to maximize effectiveness and precision. Usually, there are extraordinary abilities of tDCS to induce excitability/inhibition and alter certain regions' cortical activity but limited to no abilities to modulate the specific oscillation frequencies. It has been reported that psychological mechanisms of tDCS have decreased gamma-aminobutyric acid(GABA) and elevated levels of glutamate/glutamine [17].

Decreased GABA levels have been associated with alterations in resting state connectivity. These findings have shown changes in functional connectivity after applying tDCS treatment.

On the other hand, tACS has the potential to generate a large number of neuronal firing events with externally introduced oscillations[18]. The most effective entrainment of tACS has been introduced when endogenous oscillation matches the stimulation frequency. The observed reliance of tACS on neural conditions might have been explained by this observation. In addition, tACS intervention suggested changes in GABA levels [19]. As a result, changes in functional synchronization of the brain would lead to alter following stimulation. The idea of using functional connectivity as a biomarker to monitor the tES effects might have been for future studies.

Most of the tES are not approved by the FDA for treating psychiatric disorders, which require authorization from licensed healthcare professionals. Also, instructions and guidelines on properly using these devices must be clarified and often confused. According to supervised and published research, there are no safety issues while using tES devices; however, they are not confirmed to have similar results if used individually and unsupervised. Unsupervised application of tES might cause potential injury, unforeseen cognitive impacts, and interference with other treatments. In addition, commercial and do-it-to-yourself (DIY) construction kits for tES must meet some electronic safety standards[20].

4. Conclusion

Depression, notably Major Depressive Disorder (MDD), continues to be a global health concern with enduring ramifications for affected individuals. The quest for effective interventions has directed attention to non-invasive neuromodulatory techniques, specifically Transcranial Electric Stimulation (tES). Within this spectrum, transcranial alternating current stimulation (tACS) and transcranial direct current stimulation (tDCS) stand out for their potential to offer symptom relief. Underscored by thir capacity to modulate brain oscillations, these modalities are redefining therapeutic approaches. Preliminary research and clinical trials have showcased their ability to address cognitive dysfunctions, neural connectivity issues, and related symptoms of MDD. This review underscores their mechanistic insights, potential advantages, and clinical applications. However, like any burgeoning field, there is an urgent need for more exhaustive, rigorous research. It involves understanding long-term effects, establishing standard treatment protocols, and ensuring safety and efficacy for diverse patient profiles. As the medical community gravitates towards these innovative techniques, the overarching goal remains clear: to provide reliable, effective, and patient-centric solutions for MDD, thus enhancing the quality of life for millions grappling with this disorder.

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