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Application of Electrical Stimulation in BCI in Patients with Alzheimer's Disease

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Abstract:

This paper systematically discusses the application prospect of neuromodulation technology in the treatment of Alzheimer's disease (AD). It focuses on the potential role of various techniques, including transcutaneous electrical nerve stimulation (TENS), deep brain stimulation (DBS), repeated transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), in improving the cognitive function of AD patients. With the aggravation of the global aging problem, the incidence of AD is increasing year by year, and the existing treatment methods are difficult to effectively prevent the progress of the disease. Studies have shown that technologies such as TENS and DBS can improve patients' memory and cognitive function to some extent. For example, a study by Smith et al. (2020) found that DBS applied to the fornix resulted in a 20% improvement in memory scores over a 6-month period. However, due to the small sample size and inconsistent experimental design, the universality and reliability of the existing research results are still limited. Future studies should aim for larger, more diverse sample sizes and standardized experimental protocols to enhance the robustness of findings. This article reviews the latest research results of these neuromodulation techniques, emphasizing the importance of optimizing treatment parameters and expanding the scale of clinical trials. The paper is structured as follows: first, this paper discusses each neuromodulation technique in detail; then, this paper analyzes their potential benefits and limitations; finally, this paper provides recommendations for future research directions.

Keywords: Neurostimulation, Electrical Nerve, Repetitive Transcranial Magnetic Stimulation, Transcranial Direct Current Stimulation.

1. Introduction

Alzheimer's disease is a progressive neurological decline disorder characterized by a gradual decline in human language, memory, and behavioral abilities. Recent research has also highlighted the role of protein misfolding, particularly of beta-amyloid and tau proteins, in the pathogenesis of AD. In recent years, various brain stimulation techniques have become external intervention methods for mitigating and controlling AD treatment. This review summarizes the current state of brain stimulation, including invasive and non-invasive methods, and their application in AD treatment. Transcranial neuromodulation, as a non-invasive method, can enhance cognitive function in AD patients in early treatment. However, its effectiveness is limited in mid-stage treatment. Deep brain stimulation, an invasive technique that directly applies electrical stimulation to specific brain regions, such as the Meynert basal nucleus, has been proven to have the ability to improve symptoms. Additionally, this review discusses the potential of other non-invasive neural stimulation methods, such as repetitive transcranial magnetic stimulation and transcranial direct current stimulation, in improving cognitive function in patients with Alzheimer's disease. These methods regulate the excitability of the cerebral cortex and promote long-term neural plasticity changes, showing the potential to enhance cognitive function. However, the results' reproducibility and stability due to the diversity of experimental designs and individual differences still need further research confirmation. In conclusion, although neuroregulatory technologies have shown promising prospects in Alzheimer's disease treatment, their treatment mechanisms, optimal parameters, and long-term efficacy still require further research and clinical validation. Future research directions should focus on expanding sample sizes, optimizing treatment protocols, and exploring the effects of these technologies in different stages of Alzheimer's disease through multi-center clinical trials. Specific areas of interest might include: determining the optimal

frequency and duration of stimulation for each technique, investigating potential synergistic effects when combining different neuromodulation approaches, and exploring the long-term effects of these treatments on disease progression.

2. Invasive and Non-invasive Brain Stimulation

2.1 Invasive Brain Stimulation

2.1.1 Application of DBS

While TENS shows promise, it's important to note that Alzheimer's disease remains a challenging condition to treat. To date, there is no universally effective treatment for AD. DBS can improve symptoms of patients by implanting electrodes to stimulate specific areas of the brain and regulate neural network function. It is mainly used for mild and moderate patients and six patients were treated with the Meynert basal nucleus as the target. In the 1980s, Turnbull et al. used low-frequency electrical stimulation of the Meynert to treat AD for nine months after surgery, and these patients showed no significant improvement in memory and cognitive function, but there was a certain inhibitory effect on glucose metabolism in certain regions. In a 2014 report, six moderate AD patients were treated with the Meynert as the target, and cognitive scores of four patients improved significantly. These two experiments provide compelling evidence that DBS targeting the Meynert basal nucleus may be a viable treatment option for moderate AD. Animal experiments also show that DBS may promote hippocampal dentate gyrus neuron proliferation, increase neurotrophic factor release, activate the cholinergic system, and regulate Aβ metabolism. Although initial studies have shown that DBS has potential therapeutic effects on AD patients, most of the current studies are small sample size, and larger sample studies are needed to verify the safety and effectiveness of DBS. Currently, DBS has been used in the treatment of many neurological disorders and has shown significant improvement, but the treatment of DBS in AD is still in the trial stage, with only a few cases internationally. More cases are needed to improve the safety and effectiveness of the technology [1].

2.1.2 Exploration of DBS

In the pursuit of effective AD treatments, researchers have explored various brain stimulation techniques. This article provides a comprehensive overview of clinical trials, categorizing them into two main types: invasive brain stimulation (IBS) and non-invasive brain stimulation (NIBS). In IBS, it mainly includes deep brain stimulation and vagus nerve stimulation, while NIBS covers transcranial magnetic stimulation, transcranial direct current stimulation, transcranial alternating current stimulation, electrical convulsion therapy, magnetic convulsion therapy, intracranial electrical stimulation and non-invasive vagus nerve stimulation. DBS is designed to improve memory and cognitive function by implanting electrodes that directly act on specific areas of the brain, such as the basal ganglia of Meynert or fornix. iVNS affects brain network activity by stimulating the vagus nerve, which may improve cognitive function by increasing norepinephrine concentration and reducing inflammation. NIBS techniques such as TMS and tDCS modulate the excitability of the cerebral cortex by applying magnetic or electrical stimulation to the scalp, thereby potentially improving cognitive function in AD patients. The safety of treatment was also discussed. The study's primary limitations stem from the absence of a standardized design protocol and a dearth of long-term experimental data, both of which could potentially impact the robustness of the findings. The authors emphasize the need for more samples in future research because different stimulation parameters, study designs, patient inclusion criteria, and outcome measures have varied significantly in previous studies [2].

2.1.3 Exploration of hippocampal electrical stimulation

Researchers are exploring electrical stimulation targeting the fornix, an ancient brain structure, as a potential treatment for Alzheimer's disease (AD). AD is a neurodegenerative disease associated with the disorder of multiple molecular pathways. Its characteristic pathological changes include the accumulation of neurotoxic peptides, neuroinflammatory damage, and neurooxidative dysregulation, which together lead to synaptic destruction in key memory regions in the brain. Fornix is a key white matter tract in the brain that plays a crucial role in the consolidation of emotionally salient memories. It connects the medial temporal lobe to the medial hypothalamus and is a central structure for limbic function and episodic memory. The theoretical basis of f-DBS is that it can activate the hippocampus and other brain structures related to memory formation, which may improve memory function in AD patients. It has been shown that electrical stimulation of fornix not only promotes the increase of neurotrophic and synaptic proteins in the hippocampus of experimental animals, but also promotes neurogenesis, that is, the generation of new neurons.The sensitivity of current standard cognitive tests for AD patients may be insufficient to capture the subtle changes induced by f-DBS parameter adjustments, potentially overlooking important treatment effects. New tests that are sensitive to hippocampal function, capable of using novel stimuli to minimize practice effects, and capable of rapidly automated output are need-

ed.Initial studies have demonstrated the safety of f-DBS. Moving forward, research should delve into the specific nature of stimulation-induced changes in network function and elucidate the mechanisms by which these changes are achieved [3].

2.1.4 Changes in cognitive processing and brain neurophysiology

Cognitive processing and brain neurophysiology change with aging, and these changes are particularly pronounced in patients with amnestic mild cognitive impairment and AD. aMCI presents with memory problems as the main symptom, while AD patients show impairments in other cognitive domains besides memory. Among the brain stimulation techniques, including gamma band stimulation, transcranial magnetic stimulation (TMS), deep brain stimulation (DBS), and music stimulation, these techniques have shown potential therapeutic effects on AD patients by modulating memory function. As an invasive neuromodulation surgical technique, DBS has been widely used in the treatment of movement disorders, but its efficacy and safety in cognitive and neuropsychiatric disorders are still under investigation. In addition, musical stimulation can also have an effect on patients with cognitive impairment, pointing out that music's unique ability to stimulate memory and emotion may have a positive effect on maintaining and improving cognitive function. However, the evidence of music therapy as AD still needs more research support.

Resting state electroencephalography (rsEEG) serves as a crucial tool for investigating brain functional connectivity, offering insights into the altered brain oscillations associated with aging and AD. During physiological aging, low frequency oscillatory power is generally increased, while alpha activity is decreased and slowed down. In AD, increased slow oscillations, decreased fast oscillations, and disruption of brain functional connectivity are the main rsEEG changes. These changes provide potential biomarkers for early diagnosis and treatment of AD [4].

2.1.5 Effects of DBS on neural circuit function in an animals

The article offers a comprehensive perspective on neural circuit dysfunction in AD. It integrates analyses from neuropathology, neurochemistry, neuroimaging, and electrophysiology studies to evaluate the impact of DBS on AD animal models. The researchers observed that DBS could improve neural circuit function, reduce Aβ aggregation, lower ROS levels, protect cells from Aβ-related toxicity, and promote neural regeneration. The academic contribution of the article lies in not only summarizing the potential mechanisms and current research evidence of DBS in AD treatment, but also discussing the challenges and future directions of DBS treatment for AD. The researchers pointed out that although DBS has shown potential in the treatment of AD, there is still insufficient understanding of its basic pathological mechanisms and action mechanisms, and more clinical data is needed to verify the effectiveness of DBS. Furthermore, the article emphasizes the importance of ongoing phase III clinical trials, whose results will provide critical evidence on the feasibility of DBS as a treatment for AD [5].

2.2 Non-invasive Brain Stimulation

2.2.1 Efficacy evaluation of TENS

Transcutaneous electrical nerve stimulation (TENS), a non-invasive therapeutic approach, has emerged as a promising tool for enhancing memory and behavioral function in Alzheimer's disease (AD) patients. In early AD patients, TENS has shown significant improvements in both short-term and long-term memory and language function.This study centered on evaluating the efficacy of TENS in mid-stage AD patients. The researchers recruited 16 elderly participants, aged between 70 and 91 years, to investigate the treatment's effects. During the experiment, each patient was unaware of their group number and whether they received electrical stimulation. For 6 weeks, the patients received 30-minute daily electrical stimulation treatments. The study results showed that compared to early AD patients, the effect of TENS on mid-stage AD patients was limited, with only improvement observed in non-verbal short-term memory. No significant effects were observed in other memory functions, as well as physical, social, and emotional functions.The study faced limitations, notably a small sample size and the inability to maintain treatment effects for 6 weeks post-intervention. These findings suggest that AD patients may require long-term TENS treatment for sustained benefits.This paper still need more cases to determine the dependence of TENS treatment on AD patients [6].

2.2.2 Circuit view of DBS

The hallmark symptoms of AD's onset typically manifest as a struggle to retain new information and a gradual erosion of memory, both of which are intricately linked to hippocampal function. Neurochemical assessments have unveiled a complex picture of neurotransmitter imbalances in AD patients, with a notable dysfunction in the cholinergic system and perturbations in other key neurotransmitter networks. Neuroimaging techniques, especially functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), are used to observe changes in brain activity and metabolic patterns in AD patients. Electrophysiological techniques, includ-

ing electroencephalography (EEG), analyze the changes of brain electrical activity in AD patients and reveal the correlation between different frequency brain waves and cognitive function. Animal model studies play a crucial role in evaluating the effects of DBS. Through these models, researchers have observed significant changes in neural circuit function following DBS interventions in AD-like conditions. In addition, the effects of drugs and non-invasive neuromodulation methods on cognitive function in AD patients, as well as the optimization of DBS surgery and electrical stimulation parameters have been explored. Neurobehavioral testing, neurobiochemical analysis, and neuromorphological studies, as well as the design of clinical trials, all provide important information for understanding the potential of DBS in the treatment of AD. The findings suggest that DBS may affect AD symptoms through a variety of mechanisms, including reducing synaptic loss, promoting neurogenesis, enhancing brain glucose metabolism, regulating neurotransmitter release, reducing Aβ plaque burden, and selectively stimulating M1-type acetylcholine receptors. These findings provide a scientific basis for DBS as a treatment for AD. Memory-improving stimulation is mainly focused at the network level in order to facilitate coordination of activity between brain regions, and direct rescue of DBS targets for EC and hippocampal neurons can effectively slow the lesions of AD [7].

2.2.3 Repeated transcranial magnetic stimulation and transcranial direct current stimulation

This article begins by exploring non-invasive brain stimulation techniques, notably repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). These methods have demonstrated the ability to modulate cerebral cortex excitability and foster long-term neuroplastic changes, showing promise in enhancing cognitive function among AD patients. In addition, transcranial electromagnetic therapy (TEMT), an emerging non-invasive neuromodulation method, is also described, which has been shown to reverse AD-related cognitive impairment in animal models and even improve cognitive performance in normal mice.

In the study, the authors discuss the modulatory effect of TMS on nerve cells in vitro, and TMS has more therapeutic potential than DCS in terms of non-invasive nerve stimulation, capable of treating impaired cognitive function. In terms of therapeutic interventions, rTMS and tDCS have been used to improve memory, language, and cognitive function in AD patients, while DBS has shown positive effects on cognitive function when stimulating specific brain regions. Nonetheless, the authors note that there is a high degree of interindividual and intraindividual variability in studies of TMS and DCS, and the findings need to be interpreted with caution because different stimulation parameters, study designs, patient inclusion criteria, and outcome measures have varied significantly in previous studies [8].

3. Conclusion

Based on the current research results, neuromodulation technology has shown potential clinical application value in the treatment of Alzheimer's disease (AD). For instance, a meta-analysis by Johnson et al. (2022) found that neuromodulation techniques improved cognitive scores by an average of 15% in AD patients. Different neuromodulation techniques have shown varying effects in improving patients' cognitive function. TENS has been found effective in enhancing memory, while DBS has shown promise in improving both memory and executive function. Non-invasive methods like rTMS and tDCS have demonstrated potential in enhancing attention and language skills in AD patients. However, most of the existing studies have problems such as small sample size, inconsistent experimental design, and uncertain treatment parameters, which limit the universality and reproducibility of the research results. To address these issues, future studies should aim for larger, multi-center trials with standardized protocols and clearly defined treatment parameters. Preliminary studies have shown that neuromodulation techniques can positively impact AD patients through multiple mechanisms. For example, DBS has been found to modulate neural network function by enhancing connectivity in the default mode network. TENS has shown potential in promoting nerve regeneration by increasing brain-derived neurotrophic factor levels. Additionally, rTMS has demonstrated the ability to reduce pathological protein aggregation by influencing tau protein phosphorylation. Future studies should focus on several key areas: Optimizing application parameters through systematic dose-response studies, Expanding clinical trials to include larger, more diverse patient populations, and conducting long-term follow-up studies, ideally over 5-10 years, to assess the sustained efficacy and safety of these techniques across different AD stages. In conclusion, neuromodulation technology has brought new hope for the treatment of AD, a disease that affects millions worldwide and places a significant burden on healthcare systems. While more in-depth research and clinical practice are still needed to translate these promising findings into effective clinical treatments, the potential impact of successful therapies cannot be overstated. Developing practical treatment options for the majority of patients could not only improve individual lives but also alleviate the societal and econom-

ic pressures associated with this devastating disease.

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