Advances and Challenges in Neuromodulation Therapies for Post-Traumatic Stress Disorder: A Comparative Analysis of Direct Stimulation and Neurofeedback Approaches

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Abstract: The number of people with Post-Traumatic Stress Disorder (PTSD) has increased as a result of global wars and the instability of contemporary society, which affects daily life in minor cases and may even be life-threatening in serious cases. In this situation, it is urgent to research and improve the methods of treatment of PTSD. This paper explores the effects and limitations of two neuromodulation approaches: direct stimulation and non-invasive neurofeedback training. According to a review of several trails, core PTSD symptoms were successfully reduced by high frequency transcranial magnetic stimulations (TMS) directed at the right dorsolateral prefrontal cortex (DLPFC), although its effects are short-term and lack long-term data. Non-invasive neurofeedback training, by modulating brain regions such as the DLPFC and amygdala, enhances emotional regulation and mitigates PTSD symptoms, with decoded neurofeedback (DecNef) showing promising potential. However, most research faced challenges, including small sample sizes, heterogeneity in experimental parameters, and insufficient mechanistic exploration. Future research should focus on expanding sample sizes, standardizing treatment protocols, and investigating the mechanisms and long-term efficacy of these treatments.

1 INTRODUCTION

Post-Traumatic Stress Disorder (PTSD) is a normal psychiatric disorder that severely affects the mood and functioning of patients. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), PTSD is a trauma and stress-related disorder that is intimately linked to maladaptive fear of learning and aberrant stress reactions. The global prevalence of PTSD has increased in recent years, highlighting the urgent need for effective treatment strategies. Although pharmacologic and psychotherapeutic approaches have been widely adopted, they often fail to give good outcomes for all patients, problems like high cost, high recurrence rate, short duration of efficacy of medicine, and inability to solve the problem in the long term. In this case, alternative treatment approaches are needed.

Recent advances in neuromodulation techniques have shown promise for the treatment of PTSD. Direct stimulation techniques such as TMS and non-invasive neurofeedback training have been investigated for modulating brain activity in specific regions such as the DLPFC and amygdala. High-frequency TMS targeting the DLPFC has been shown to provide significant symptomatic relief, particularly for intrusive memories and excessive anxiety. Similarly, neurofeedback approaches provide a non-invasive means of modulating brain function that may improve mood regulation and symptom control. However, existing studies have limitations such as small sample sizes, inconsistent methods, and lack of long-term efficacy data.

The purpose of this paper is to compare and analyze the effectiveness of TMS and neurofeedback training in the treatment of PTSD by reviewing relevant studies. Key aspects such as treatment efficacy, side effects and current limitations are discussed in order to find a future direction of neuromodulation therapy for PTSD. Standardized treatment protocols and further mechanistic explorations are suggested as key steps in advancing this area of research.

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2 POST-TRAUMATIC STRESS DISORDER (PTSD) AND NEUROMODULATION

Some parts of the brain are abnormally active in patients with PTSD, especially at the onset of the disease. The author learned that specific areas such as the dorsolateral prefrontal cortex (DLPFC) experience unusual activity through research conducted by researchers such as Edinoff, A. N, Karsen, E. F. This paper has concluded that it is possible to relieve the symptoms of people with PTSD by modulating the activity in specific brain regions. An altered stress response and reinforced learnt fear behavior are linked to post-traumatic stress disorder (PTSD), a mental illness that significantly impairs functioning (Deinoff et al., 2022). According to the Diagnostic and Statistical Manual (DSM-5), it is categorized as a "trauma and stressor-related disorder." A great number of people are suffering from it. Neuromodulation is the alteration of a specific brain region's activity by something that makes the region more or less active. Neuromodulation can be achieved by direct stimulation and non-invasive interventions, and both methods have their own advantages and disadvantages in terms of efficiency and efficacy.

3 THERAPY EFFECT OF DIRECT STIMULATION ON THE SPECIFIC BRAIN REGION IN PTSD

Edinoff, Hegefeld and other researchers mentioned the therapy effects of transcranial magnetic stimulation (TMS) in PTSD patients (Deinoff et al., 2022). The participants in this experiment were mainly PTSD patients, mostly are adult population, with some patients with other co-morbidities such as depression. The experiment was designed as a randomized controlled trial, and the experimenters used high-frequency TMS and low-frequency TMS to stimulate the dorsolateral prefrontal cortex (DLPFC) region. The study applied repetitive transcranial magnetic stimulation (rTMS) to the DLPFC of participants. The specific parameters were a stimulation frequency of 10 Hz, intensity at 120% of the individual motor threshold, 3,000 pulses per session, with one session per day for 2 consecutive weeks, totalling 10 sessions. Testing the effects of TMS on functional brain networks, especially the interaction between the DLPFC and the limbic system by fMRI. In addition, the study used standardized scales such as the posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5), clinician-administered PTSD scale (CPAS) to assess patients' changes in PTSD symptoms and detect side effects of the treatment. The data analysis showed that high-frequency TMS was effective in relieving core PTSD symptoms like reappearance, flashbacks, and high arousal, and it was more effective in reducing symptoms compared to low-frequency TMS. The results of the experiment showed that TMS exerted a significant effect on DLPFC, as demonstrated by the fact that PTSD symptom improvement was associated with enhanced DLPFC function. The study reported significant symptom improvement after treatment, but the duration of effect may be short. In addition, most studies report the side effects of this therapy such as headache, nausea, and in rare cases, possible seizures. Studies have also found that TMS can improve emotion regulation in PTSD patients by enhancing the connection between prefrontal cortex and the limbic system. Researchers have concluded that TMS is an effective and relatively safe treatment for PTSD, especially for patients who did not get good feedback from medication or psychotherapy. TMS has received attention for its low side effects and potential neuromodulation abilities compared to established pharmacological treatments. However, Edinoff, A. N's study clearly points out some limitations. First, the sample sizes are generally small, which reduces the statistical efficacy and credibility of the results. Second, there is heterogeneity in the results of the studies, with some studies failing to provide a consistent assessment of efficacy, which may be related to differences in treatment parameters and study design. In addition, most of the available studies focused on short-term efficacy and lacked observations of the persistence of long-term effects. Finally, although some of the studies used brain imaging techniques, the current neural mechanism studies are insufficient to reveal the mechanism for the role of TMS in the treatment of PTSD. Mainly because of limitations in research methods, complexity of inter-brain interactions, individual response differences, lack of long-term data, and non-harmonization of TMS parameters.

Karsen, Watts & Holtzheimer also reviewed the effect of TMS on PTSD in their study (Karsen et al., 2014). The study includes 132 participants in total, ranging in age from 29 to 55.9, with an average gender distribution. The participants were mainly people with different types of PTSD. A variety of study designs were used, including randomized

controlled trials (RCTs), double-blind trials, and open-label trials. The studies used different TMS treatment parameters, such as different stimulation frequencies, stimulation region, and stimulation intensities. Some studies combined TMS with exposure therapy. Symptom assessment for PTSD relies on the standardized quantitative scales PCL and CAPS. Data analysis indicated that most of the treatment groups showed significant results on the PTSD scale, right-side high-frequency TMS was effective in relieving PTSD symptoms, but the effect of stimulation frequency on efficacy is unclear. The article states that TMS has been proved to be an effective and well-tolerated therapy for PTSD. Although there are variations in stimulation frequency and target regions, it significantly reduces key PTSD symptoms such as intrusive memories, avoidance behaviour, and heightened alertness. (Karsen et al., 2014) This also greatly supports the results of the first experiment. However, the experiment also has the same problem as Edinoff, A. N.'s experiment, which is small sample size and heterogeneity, and it varied widely in the choice of frequency, number of pulses and stimulation regions. Most of the studies only assessed short-term efficacy and lacked long-term research data. In addition, most studies reported inadequate monitoring of side effects like seizure risk, headache or scalp discomfort, hearing effects, and transient changes in cognitive function or mood. These potential side effects need to be further evaluated and reported in future studies.

In Che Jiang et al.'s study, they mentioned that only the high-frequency transcranial magnetic stimulation of DLPFC showed a significant advantage in improving PTSD (Jiang et al., 2024). This supports the results of Karsen's experiment that high-frequency stimulation of the right side is better than that of the left side and also reinforces the results of Edinoff's experiment. Philip, N. S. and Barredo, J. also stated in their research that the effective target of TMS is the right DLPFC, and more than five treatments are required to get a significant improvement (Gouveia et al., 2020). However, they also suggested limitations of this treatment, as PTSD is a highly heterogeneous condition that may be associated with different psychiatric disorders, and therefore identifying a specific treatment for this patient group may be quite challenging, and it's better for future studies to use standardized targeting and stimulation parameters. Philip, N. S. and other researchers conducted a trial of intermittent Theta Burst Stimulation (iTBS) in 2019, a new therapy with a similar mechanism to TMS. The experiments found that most of the improvement in clinical symptoms from iTBS stimulation occurred in early stage, suggesting that further research is needed on the best time and duration of iTBS. In addition, the stimulation method is consistent with the previous role of TMS in default mode network connectivity 9 (Philip et al., 2019). The efficacy of iTBS proves that the mechanism of TMS stimulation is unproblematic, but the disadvantages of both treatments are similar, which is they both lack long-term effects.

All five experimental papers mentioned above demonstrate the effectiveness of TMS for the treatment of PTSD, especially for high-frequency stimulation of the right DLPFC. Neural activity modulation through direct stimulation of specific brain regions can effectively suppress and relieve the symptoms of PTSD, which also build the basic for future treatments in this direction. However, this type of treatment exhibits the disadvantage of a short effective period, which needs to be further improved in future experiments. In addition, almost all experiments contain the limitations of small experimental sample size, high heterogeneity of experimental results, and large differences in experimental parameters. Increasing the sample size as much as possible, standardizing the experimental objectives and parameters (e.g. Recruit PTSD patients with the same comorbidity or no comorbidity, target a specific part of the brain with a particular frequency and numbers of stimulation) may help the experimental results a lot in future experiments.

4 THERAPY EFFECT OF NON-INVASION NEUROFEEDBACK TRAINING ON THE SPECIFIC BRAIN REGION IN PTSD

In addition to the direct stimulation therapies associated with TMS described above, non-invasive neuromodulation therapies also seem to have good results. Ros's study showed a kind of non-invasion treatment called neurofeedback training. Neurofeedback training is non-invasive, personalized, and helps individuals regulate their brain activity through real-time feedback, which has a lasting effect and is widely used to improve problems such as attention, anxiety, and depression. The experiment included 21 patients in the PTSD group and 40 healthy adults in the healthy control group. The PTSD patients were evaluated according to DSM criteria, and neurofeedback used EEG to

measure alpha wave amplitude. The study used fMRI techniques to measure participants' brain activity while viewing visual stimuli. The data was analyzed using functional connectivity analysis to assess synchronized activity between different areas of the visual cortex, and graph theory analysis is used to understand the topology of brain networks. The effects of real neurofeedback (NFB) were compared with sham neurofeedback (SHAM) in the healthy group, and only NFB treatment was used in the PTSD group. The results showed that single-session neurofeedback training has improved neurodynamic symptoms in PTSD patients by modulating alpha-wave long range time correlation (Ros et al., 2017). This study supports the theory that neurofeedback improves EEG dynamics and is consistent with other studies on NFB for ADHD and depression. The limitations of this trial are that there were only 21 PTSD patients, and no SHAM comparisons were made in the PTSD group, which may be biased. This study greatly proved that non-invasion neurofeedback treatment is effective in treating PTSD symptoms. However, the study had the limitation of not comparing the efficacy and persistence of effects with other therapies.

Kohl and Mehle's experiment also support the result from the last study. They experimented in a systematic review of fNIRS-based neurofeedback research. The experiment involved 441 individuals, 337 were healthy individuals and 104 were patients. This study focused on neurofeedback training using functional Near-Infrared Spectroscopy (fNIRS), a functional neuroimaging technique based on cerebral hemodynamics, which is non-invasive. Measurements were made using the fNIRS technique to measure prefrontal cortex, especially areas such as the DLPFC. The results show that multiple studies have demonstrated that individuals can modulate hemodynamic signaling in the cerebral cortex via fNIRS neurofeedback. In addition, in healthy participants, fNIRS neurofeedback helped to modulate motor control and prefrontal function, and in clinical participants, it helped to improve symptoms. Patients were observed to experience a reduction in impulsivity and anxiety-based symptoms, suggesting the potential of this approach for mood regulation and cognitive improvement (Kohl et al., 2020). The reduced symptoms are also components that need to be improved in patients with PTSD. However, the quality of the current study is considered moderate due to the lack of large randomized controlled trials, resulting in insufficient statistical efficacy. Compared to other neurofeedback studies, fNIRS neurofeedback research is still in its early stages and further studies are needed to validate its specificity and potential clinical utility.

Nicholson and Rabellin studied the neural activity of the amygdala during emotion regulation in patients with PTSD. The results showed that PTSD patients were able to effectively reduce the level of amygdala activation by rt-fMRI-nf training (Nicholson et al., 2017). In addition, the patients' symptoms improved and their emotion regulation ability was enhanced after the training. This study suggests that the rt-fMRI-nf technique can be used as an effective tool for emotion regulation training in patients with PTSD. However, this study does have certain drawbacks, though. First, the results' generalizability may be impacted by the limited sample size, there were only 20 participants. Second, personalized trauma-related words were utilized during neurofeedback training sessions, it may trigger strong emotional reactions and affect the training effect. This study modulated the activity of the amygdala through neurofeedback training, and although the modulation region was different from the previous two experiments, it also achieved the same effect of relieving the symptoms of PTSD, which also proved the feasibility of neurofeedback training treatment. Maculed-Franchi's article focuses on describing that EEG neurofeedback training can modulate DLPFC activity, which confirms the validity of the neurofeedback training from previous experiments (Micoulaud-Franchi et al., 2014). It also supports the importance of DLPFC region in PTSD treatment. The experiment's main limitations include the short number of investigations, the comparatively small number of participants in each study, and the varied methodology regarding to the EEG-NF protocols' features.

Chiba, T. and Kanazawa described a new type of neurofeedback therapy called decoded Neurofeedback (DecNef) in their research. Conventional neurofeedback is based on average neural signals in specific brain regions, which makes it difficult to induce neural representations associated with specific traumas, and DecNef may help to improve this. DecNef allows patients to implicitly modulate the multivariate somatostatin pattern of BOLD signalling associated with fearful stimuli, the effects of which may originate from exposure or counterconditioning, or a combination of both (Chiba et al., 2019). According to preliminary research, DecNef's three days of feedback training helped to reduce PTSD symptoms. This result was similar to both the neurofeedback technique and traditional exposure therapy, despite its uncertain nature. Although this is a new approach to neurofeedback, it

also gets similar results as conventional methods and has the potential to be able to induce neural representations associated with specific traumas based on this new approach, which has a good prospect for future research.

The above studies demonstrate that the neurofeedback approach to non-invasion is effective and promising. In addition, it has shown comparable results to direct stimulation of brain regions, and Chiba and Kanazawa's novel neurofeedback modality, DecNef, may help to improve the effectiveness of this kind of treatment and clarify the mechanism in the future. All the experiments had similar limitations to the experiments with direct stimulation and lacked a large experimental sample and insufficient statistical efficacy, resulting in experimental data that are not generalized. Secondly, many of the experiments demonstrated results that were effective in relieving patients' symptoms, but the underlying mechanisms need to be explored, and more in-depth researches are needed. For example, detecting the effect of neurological interventions by brain imaging techniques, or recording changes in the way neurons are connected in the brain by using human connectome projects (HCP). It is recommended that the sample size of the experiments should be increased and the new DecNef neurofeedback should be combined with conventional neurofeedback for testing and comparison.

5 CONCLUSION

This study reviewed two major neuromodulation therapies for the treatment of PTSD: direct brain stimulation therapies such as TMS and non-invasive neurofeedback training. The results indicate that while high-frequency transcranial magnetic stimulation that targets the DLPFC can effectively alleviate PTSD symptoms including intrusive memories and hyper anxiety, its effects are typically transient. Similarly, neurofeedback training, including new techniques such as decoded DecNef, has shown promising results in enhancing emotion regulation and relieving symptoms by modulating brain activity in areas such as the DLPFC and amygdala.

The main limitations identified include small sample sizes, high heterogeneity of study parameters, and insufficient exploration of underlying mechanisms, especially in terms of long-term efficacy. To solve these issues, future studies should focus on standardizing experiment approaches, increasing sample sizes, and combining new technologies such as DecNef with traditional approaches. In addition, exploring the neural mechanisms underlying these therapies is critical to refining and improving their clinical efficacy.

The significance of this study is to provide a comprehensive understanding of the current progress and challenges of neuromodulation therapies for PTSD. By identifying research gaps and making actionable recommendations, this paper will contribute to the advancement of targeted and effective therapies for patients with PTSD.

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