Neuroregulation Techniques in the Treatment of Depression

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Abstract. Depression, a pervasive mental disorder, profoundly diminishes patients' well-being, affecting millions globally. As the need for effective treatment strategies heightens, neuroregulation techniques are emerging as promising tools against this ailment. Techniques such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and deep brain stimulation (DBS) have gained significant traction in recent times. These methods, while rooted in different operational principles, aim to modulate neural activity, thereby influencing mood and depressive symptoms. Early clinical studies have demonstrated their potential in producing therapeutic benefits. Notably, patients who were previously resistant to conventional treatments have shown remarkable improvement with these neuroregulation approaches. Yet, challenges persist. The response to these treatments often varies across individuals, complicating standardized approaches. Additionally, the optimal parameters for applying these techniques remain elusive, often requiring trial-and-error to determine. Moving forward, the research landscape should pivot towards refining these parameters, unearthing reliable biomarkers that can predict treatment efficacy, and exploring synergistic applications combining multiple neuroregulation methods. By addressing these challenges, we can potentially unlock a new era of depression therapy, providing hope to those grappling with this debilitating condition.

Keywords: Depression; Neuroregulation; Transcranial Magnetic Stimulation; Transcranial Direct Current Stimulation.

1. Introduction

Depression, as a pervasive mental health issue globally, not only subjects affected individuals to immense emotional and psychological stress but also places a heavy burden on societies and families [1]. Although pharmacotherapy has achieved significant progress in this domain, there arises a therapeutic challenge for patients who are non-responsive to conventional medications. This challenge has prompted the exploration of neuromodulation techniques in the treatment of depression [2].

The evolution of neuromodulation can be traced back to foundational research from the last century, which predominantly focused on the relationship between brain structures and their functions. With a deepening understanding of neural networks, neurotransmitters, and intercellular signaling mechanisms, researchers began to experiment with external interventions to modulate these processes, hoping to achieve therapeutic outcomes [3]. Initial technical modalities included electrical and magnetic stimulation. In terms of the therapeutic principle, neuromodulation primarily functions by altering electrical activities in specific brain regions. For instance, transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) both apply external stimuli to the cerebral cortex to adjust neuronal activity patterns. Specifically, TMS induces short-lived magnetic fields to modulate neuronal excitability, while tDCS employs direct current to regulate the same [4].

Regarding clinical efficacy, neuromodulation has showcased promising results in the treatment of depression. Numerous clinical trials have indicated that both TMS and tDCS can provide significant relief for patients unresponsive to traditional drug therapies [5]. Even more crucially, compared to drug treatments, the side effects resulting from neuromodulation are considerably fewer. However, this does not imply that the technique is devoid of risks; prolonged or inappropriate use might potentially harm the brain.

In summary, neuromodulation offers new hope and possibilities for treating depression. Yet, concurrently, it serves as a reminder that in the pursuit of medical innovation, the safety and welfare

of patients should always remain paramount, ensuring the scientific validity, safety, and efficacy of therapeutic approaches [6].

2. Development of Neuroregulation Techniques

2.1. Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) emerged in the early 1990s, capturing the attention of the world and soon finding its place in the treatment of depression. Repetitive transcranial magnetic stimulation (rTMS), a subset of TMS, holds a significant position especially in neuropsychological therapy.

The working principle of rTMS primarily involves generating brief, focused magnetic fields to alter the membrane potential of neurons, thus modulating the excitability of the cerebral cortex. This mechanism plays a pivotal role in the synthesis and release of neurotransmitters, making it highly relevant for the treatment of depression. Specifically, in the anterior cingulate cortex - a brain region associated with emotional processing, rTMS can notably enhance its activity, leading to symptom improvement in depressed patients. Early research predominantly focused on high-frequency stimulation of the left dorsolateral prefrontal cortex, as this area exhibited decreased activity in those with depression. By employing high-frequency rTMS, the depolarization time of neurons can be increased, subsequently boosting its functional connectivity, which in turn augments the region's activity. However, the parameters chosen in these initial studies were not standardized, leading to inconsistent therapeutic outcomes.

To address these challenges, more recent research has delved into the optimization of parameter selection. Researchers recognized that the conditions of each patient are unique, hence personalized therapeutic strategies might be more effective. By adjusting the stimulation intensity, frequency, and treatment duration, the therapeutic efficacy of rTMS has indeed been markedly enhanced. Beyond the conventional high-frequency rTMS stimulation, some new strategies, such as low-frequency θ wave stimulation, have demonstrated potential benefits in clinical trials. Furthermore, stimulation of the right-associated brain areas, not just the left, has also exhibited therapeutic effects, broadening the scope of rTMS in the treatment of depression. In conclusion, rTMS offers a novel and promising direction for the treatment of depression. However, to ensure its optimal efficacy and safety, further in-depth research is required to refine and optimize treatment parameters.

2.2. Transcranial Direct Current Stimulation

Transcranial Direct Current Stimulation (tDCS) is a neurostimulation technique that was discovered in the early 1960s, and researchers found that it can transiently modulate the excitability of cortical neurons. By the early 21st century, this technique began to play a role in the treatment of depression.

The core mechanism of tDCS involves the transmission of weak direct current through bipolar electrodes, leading to alterations in cell membrane potentials and subsequently modulating cortical activity. In practice, reducing inhibitory control over the left dorsolateral prefrontal cortex or enhancing activity in the corresponding right hemisphere has been demonstrated to effectively improve the emotional states of individuals with depression. This discovery has provided crucial insights into the localized brain function and the neurobiological basis of depression.Despite offering new hope for depression treatment, tDCS faced several challenges in its early research, with parameter selection being the most prominent issue. Different studies used varying stimulation intensities, durations, and electrode placements, leading to inconsistent treatment outcomes.However, in recent years, research in this field has become more sophisticated and refined. Researchers have optimized stimulation parameters, explored different target regions, and delved into the long-term effects of repeated treatments. These advancements have not only provided us with more precise treatment approaches but have also shed light on potential benefits or risks associated with long-term tDCS application.

Most importantly, the optimized stimulation protocols have been proven to significantly enhance the antidepressant effects of tDCS. This is undoubtedly a boon for individuals who do not respond to traditional pharmacotherapy, offering them a novel treatment option. In conclusion, transcranial direct current stimulation technology has demonstrated tremendous potential in the treatment of refractory depression, indicating that it may become one of the mainstream therapeutic approaches in the future. However, caution is advised, and further in-depth research is warranted to ensure the safety and long-term efficacy of this technique.

2.3. Deep Brain Stimulation

Originally used for movement disorders, deep brain stimulation (DBS) has recently been applied to depression treatment. DBS involves the implantation of electrodes in specific brain regions, continuously providing electrical stimulation to modulate the activity of the target area and its associated neural circuits. Common target areas include the ventral striatum and hypothalamus, both closely associated with emotional regulation. However, the complexity of parameter selection and optimal individualized target localization limits its widespread use.

3. Therapeutic Principles

The therapeutic mechanisms behind these neuroregulation techniques are linked to the pathophysiology of depression. Core elements include abnormalities in the monoaminergic neurotransmitter system, dysregulation of the hypothalamo-cortical connection, and abnormal activation in the anterior cingulate cortex [7].

3.1. Monoaminergic System

Various neuroregulation techniques enhance the synthesis and release of monoamine neurotransmitters, particularly serotonin (5-HT). Reduced 5-HT is closely associated with depression. Animal studies have shown that these stimulation techniques promote central 5-HT system activity, increasing 5-HT release in key brain areas like the hippocampus and anterior cingulate cortex. Clinical research also shows that after neuroregulation, cerebrospinal fluid concentrations of 5-hydroxyindoleacetic acid and 5-HT significantly increase. Reactivation of the monoaminergic system, especially the 5-HT pathway, is considered one of the key mechanisms by which neuroregulation treats depression. Further research is required to understand the exact pathways and effects of different techniques.Below is a diagram of the fast-acting antidepressant 5-HT-Glu/GABA long feedback neural circuit as shown in Figure 1.

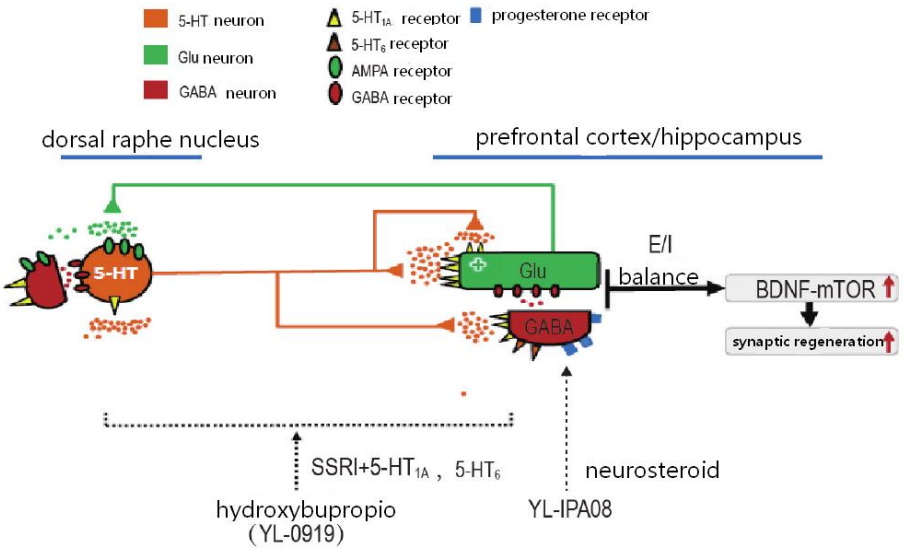


Fig. 1 Diagram of the fast-acting antidepressant 5-HT-Glu/GABA long feedback neural circuit [8]

In summary, by modulating the monoaminergic neural system, particularly promoting the synthesis and release of 5-HT, neuroregulatory technologies can effectively improve depressive symptoms. This might be one of the primary mechanisms underlying its antidepressant effects.

3.2. Cortico-Hypothalamic Circuit

Neuroregulatory techniques such as Deep Brain Stimulation (DBS) can modulate the activity of the hypothalamus, which in turn affects the functional activation of specific cortical areas. This ultimately improves the connectivity of key cortico-hypothalamic neural circuits in patients with depression. Research has found that DBS can act directly on the hypothalamus, increasing its electrophysiological activity. Transcranial magnetic stimulation can also have a distant effect on the hypothalamus. Changes in hypothalamic activity subsequently regulate the function of cortical areas connected to it, such as the anterior cingulate cortex, alleviating regional connection imbalances and restoring normal information transmission. Post-treatment, the connectivity of brain functional networks in patients with depression has been shown to enhance. Therefore, by modulating the hypothalamus and affecting cortical activation, neuroregulatory techniques can repair abnormalities in the cortico-hypothalamic circuit caused by depression. This might be another crucial mechanism underpinning their therapeutic effects as shown in Figure 2.

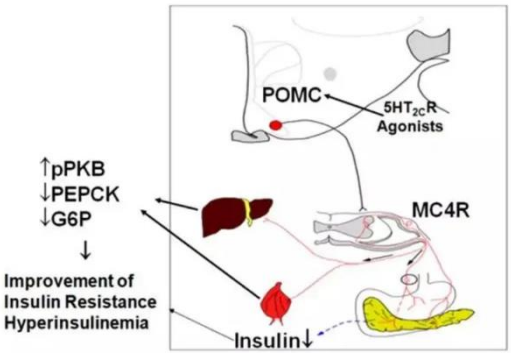


Fig. 2 Mechanism of Action of the Hypothalamus [9]

3.3. Overactivation of the Anterior Cingulate Cortex

Research has found that patients with depression exhibit pathological overactivation in the anterior cingulate cortex region, which is directly related to abnormal processing of negative emotions. Non-invasive neuroregulatory techniques, such as Repetitive Transcranial Magnetic Stimulation (rTMS) and Transcranial Direct Current Stimulation (tDCS), are capable of modulating the activity of the anterior cingulate cortex and alleviating its abnormally high activation state. For instance, rTMS uses inhibitory low-frequency stimulation on the anterior cingulate cortex or stimulates its mutually inhibitive right inferior frontal lobe, thereby directly reducing the pathological activation. On the other hand, tDCS modulates its excitability by altering the cell membrane potential, producing a similar effect. The reduction in the activity of the anterior cingulate cortex can restore its functional connectivity with deeper structures, enhance the balance of the brain network, and ultimately improve the emotional state of patients with depression. Therefore, alleviating the overactivation of the anterior cingulate cortex might be one of the key mechanisms in the neuroregulatory treatment of depression as shown in Figure 3, functional and structural imaging results in humans indicate that the cortico-basal ganglia neural circuit is at the core of the reward system. Key structures in this network include the anterior cingulate gyrus, orbitofrontal cortex, ventral striatum, ventral pallidum, and midbrain dopamine neurons. Additionally, the downstream nuclei of the ACC, including the ventral tegmental area (VTA), nucleus accumbens (NAc), and medial prefrontal cortex (mPFC), are also critical regions of the midbrain dopaminergic reward circuit [10].

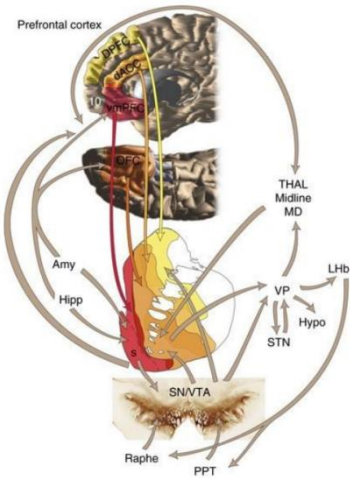


Fig. 3 Schematic diagram of the reward circuit [10]

4. Clinical Efficacy Evaluation

Large-scale randomized controlled studies have shown that, compared to the sham stimulation group or the conventional treatment group, the neuroregulation group has significantly improved symptoms of depression. However, individual variations exist, and recent studies have focused on factors influencing predictive efficacy.

4.1. Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (rTMS) is a non-invasive brain stimulation technique that has garnered substantial evidence supporting its clinical efficacy in the treatment of depression. A systematic review showed that, compared to the sham stimulation group, patients with depression who actually underwent rTMS treatment had an overall effectiveness rate of approximately 58%. Clinical response is clearly related to treatment parameters; protocols using high frequencies above 10Hz and more than 1,000 pulses per session achieve the best outcomes. Additionally, the course of depression and the responsiveness to drug treatments can also influence the efficacy of rTMS. Patients experiencing their first episode without prior medication use or those who have poor responsiveness to treatment exhibit a more pronounced therapeutic response. However, for chronic depression with multiple episodes, the effects of rTMS are relatively weaker. Therefore, while rTMS is an important non-pharmacological intervention for the treatment of depression, precise individual parameter optimization and combined drug therapy still require further research as shown in Table 1.

Table 1. Effects and Influencing Factors of Transcranial Magnetic Stimulation (rTMS) in the Treatment of Depression

Treatment Parameters for Depression	Overall Effectiveness Rate (%)	Optimal Treatment Protocol	Patient Population
High-frequency rTMS (>10Hz)	65%	Over 1,000 pulses per session	Patients experiencing their first episode without medication
Low-frequency rTMS (<10Hz)	45%	Fewer than 1,000 pulses per session	Patients with poor responsiveness to drug treatment
Chronic depression with multiple episodes	40%	High-frequency rTMS	Patients with multiple episodes of chronic depression
First-time patients using drug treatment	55%	Low-frequency rTMS	First-time patients concurrently using drug therapy
Chronic depression + drug therapy	50%	High-frequency rTMS	Chronic depression patients concurrently using drug therapy

4.2. Transcranial Direct Current Stimulation (tDCS)

Compared to the placebo treatment group, patients with depression treated with transcranial direct current stimulation (tDCS) achieved an overall effectiveness rate of around 40%. Clinical responses are associated with the strength and location of the stimulation parameters, type of disease, and duration of illness. Optimal results are achieved by anodal stimulation of the left dorsolateral prefrontal cortex and placing the cathode between the eyebrows on the right side. Moreover, due to electrophysiological changes in the brain, elderly patients with depression tend to have a better therapeutic response compared to younger patients; the effect of tDCS on bipolar depression is less significant than on unipolar depression because of the complexity of the brain functional network; the response is better in first-episode depression and poorer in recurrent chronic depression. In conclusion, tDCS represents a new avenue for the treatment of depression, but precise parameter selection and individualized treatment require ongoing optimization to achieve optimal therapeutic effects. The following details the effects and influencing factors of transcranial direct current stimulation (tDCS) in the treatment of depression as shown in Table 2.

Table 2: Effects and Influencing Factors of Transcranial Direct Current Stimulation (tDCS) in Depression Treatment

Depression Treatment Parameters	Overall Efficacy Rate (%)	Optimal Stimulation Parameters	Patient Group
Anodal stimulation of the left dorsolateral prefrontal cortex, cathode on the right eyebrow	50%	Intensity: 2mA, Unipolar depression	Patients with depression, older age
Anodal stimulation of other brain areas, cathode on the right eyebrow	35%	Intensity: 1mA, Bipolar depression	Patients with depression, younger age
Anodal stimulation of the left dorsolateral prefrontal cortex, cathode in other locations	45%	Intensity: 2mA, Unipolar depression	First-episode depression patients
Anodal stimulation of the left dorsolateral prefrontal cortex, cathode on the right eyebrow	30%	Intensity: 2mA, Recurrent chronic depression	Patients with recurrent chronic depression
Placebo treatment group	20%	No stimulation	Placebo group

4.3. Deep Brain Stimulation

Deep Brain Stimulation (DBS) is a technique that stimulates specific deep-brain regions directly by implanting electrodes. Early research indicates that the overall success rate of DBS for treating depression is around 42%. However, due to a small sample size, the level of evidence for these results is not high. Precise targeting and individualized treatment are key to enhancing the efficacy of DBS. Common stimulation targets include the ventral striatum, hypothalamus, and other areas closely related to emotion regulation. By precisely locating the electrode implantation point using high-resolution MRI and employing individualized stimulation parameters, treatment outcomes can be significantly improved. Moreover, there's complementary functionality between different target areas, and combined stimulation of various brain regions has also shown synergistic effects. In summary, DBS offers a new strategy for treatment-resistant depression, but the optimization of precise individualized treatment parameters still requires further research as shown in Table 3.

Table 3. Deep Brain Stimulation (DBS) in the Treatment of Depression: Efficacy and Influencing Factors

Stimulation Target	Overall Success Rate (%)	Individualized Treatment Parameters	Stimulation Combination
Ventral Striatum	50%	High-resolution MRI targeting, individualized intensity	Isolated stimulation of Ventral Striatum
Hypothalamus	45%	High-resolution MRI targeting, individualized intensity	Isolated stimulation of Hypothalamus
Ventral Striatum + Hypothalamus	60%	High-resolution MRI targeting, individualized intensity	Combined stimulation of Ventral Striatum and Hypothalamus
Control Group	20%	No stimulation	Non-stimulation control group

5. Prospects

Neuro-modulation technologies have paved new therapeutic pathways for treatment-resistant depression, yet the challenge of personalized precision treatment persists. Future research might focus on the following aspects in order to further enhance efficacy and expand clinical applications:

Optimizing stimulation parameters will be a key direction. Given the variability among individuals, establishing professional standards for parameter selection can help in achieving consistent therapeutic results.

Investigating factors and biomarkers that predict treatment efficacy is essential. Identifying clinical or biochemical indices that can accurately predict treatment outcomes can significantly increase the proportion of precision treatments.

As different brain targets complement one another, combining various neuro-modulation techniques for treating depression has shown synergistic effects. This strategy deserves thorough investigation and might emerge as a new method to optimize therapeutic outcomes.

Lastly, developing portable transcranial modulation devices, prolonging each treatment session, and enhancing patient compliance can further extend the clinical scope and beneficiary population of these technologies.

In summary, while the application of neuro-modulation technologies in depression treatment still demands continuous optimization and research, the future is promising. It could be a boon for patients suffering from treatment-resistant depression.

6. Conclusion

This article systematically reviews the application and progress of neuro-modulation technologies in the treatment of depression, focusing on its developmental history, therapeutic mechanisms, and clinical applications. Techniques like transcranial magnetic stimulation, transcranial direct current stimulation, and deep brain stimulation offer novel treatment approaches for treatment-resistant depression. Their mechanisms are associated with enhanced monoamine system activity, cortical-hypothalamic circuit reconstruction, and anterior cingulate inhibition. Clinical research supports the antidepressant effects of these techniques. However, challenges like significant individual differences and difficulty in precision parameter selection still limit their widespread application. Hence, future studies should continue to optimize parameters, identify factors or biomarkers that can predict clinical efficacy, and explore combined application strategies of different neuro-modulation techniques. Only through continuous in-depth research can we achieve precise application of these technologies, aiming to significantly improve treatment outcomes and quality of life for depression patients. This article intends to provide a reference for basic and clinical research in this field and contribute to the advancement of diagnostic and therapeutic standards for depression.

References

[1] Xie Huta, Zhang Jianguo. Past, present, and future of neuro-modulation technology [J]. Journal of Sichuan University (Medical Edition), 2022, 53(04): 559-563.

[2] Luo Yi, Sun Jifei, Ma Yue, et al. Clinical research progress of non-invasive neuro-modulation technology in the treatment of depression [J]. Journal of Psychiatry, 2022, 35(03): 319-323.

[3] Li Jie, Chen Xin, Yu Sixun, et al. Effects of neuro-modulation technology on neurogenesis in the dentate gyrus of the hippocampus [J]. Journal of Neuroanatomy, 2022, 38(01): 98-102.

[4] Xu Ke. The impact of auricular acupuncture (auricular vagus nerve stimulation) on the emotional cognitive brain functional network in treatment-resistant depression [D]. Chinese Academy of Traditional Chinese Medicine, 2020.

[5] Li Yingxuan, Peng Yan, Lin Hua. Current status and future of non-invasive neuro-modulation technology [J]. Journal of Brain and Neurological Disorders, 2019, 27(02): 114-116.

[6] Li Guofeng, Qiu Weibao, Qian Ming, et al. Ultrasonic neuro-modulation technology and scientific instruments [J]. Life Science Instruments, 2017, 15(01): 3-8.

[7] Wang Yehan, Ling Zhipei. Application of neuro-modulation technology in neurosurgery in China [J]. Journal of Military Medical Postgraduate College, 2012, 33(08): 806-808+841.

[8] Li Yunfeng. Development strategies for fast-acting antidepressants: Proposal of the monoamine (5-HT) - non-monoamine (Glu/GABA) long feedback neural circuit candidate hypothesis [J]. Chinese Journal of Pharmacology and Toxicology, 2019, 33(03): 161-173.

[9] Gao, M., Shan, A., Zhang, H., et al. (2023). Research Advances in Non-invasive Neurostimulation Techniques for the Treatment of Multiple System Atrophy. Chinese Clinical Neurosciences, 31(04), 469-475.

[10] Qi Zhongyang. Application of optical detection and manipulation methods in the study of the function of the anterior cingulate cortex in behavioral mice [D]. Huazhong University of Science and Technology, 2021.