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NEUROMODULATION IN ANXIETY AND DEPRESSIVE DISORDERS: MECHANISMS OF ACTION, EFFICACY, AND DIRECTIONS FOR PERSONALIZED THERAPY

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ABSTRACT

The aim of this article is to present current research and conclusions regarding the effectiveness, mechanisms of action, and clinical applications of neuromodulation methods-such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS), and noisy galvanic vestibular stimulation (nGVS)-in the treatment of depressive and anxiety disorders, with particular emphasis on their neurobiological foundations.
Neuromodulation represents a novel, promising therapeutic strategy in the treatment of affective and anxiety disorders, especially in patients resistant to pharmacotherapy and psychotherapy. Techniques using electrical and electromagnetic modulation have demonstrated antidepressant effects that may constitute an important component of the therapeutic approach in these disorders. Transcranial magnetic stimulation and transcranial direct current stimulation influence prefrontal–limbic circuits, normalizing functional connectivity through the regulation of cortical excitability and activation of signaling pathways involving brain-derived neurotrophic factor (BDNF). More recent techniques such as tACS and tRNS enable frequency-specific modulation of neuronal oscillations, showing promising results in treatment-resistant depression. The routine use of neuromodulation in depressive and anxiety disorders-particularly when other treatments have proven ineffective-may become a new therapeutic paradigm in psychiatry. However, further clinical studies are required to standardize stimulation parameters and assess the long-term efficacy of these methods.

KEYWORDS

Neuromodulation; Depression; Anxiety Disorders; Transcranial Magnetic Stimulation (TMS); Transcranial Direct Current Stimulation (tDCS); Transcranial Alternating Current Stimulation (tACS); Transcranial Random Noise Stimulation (tRNS); Neuroplasticity; Neural Networks; Personalized Medicine

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Introduction

Mental disorders such as depression and anxiety remain a major clinical challenge in psychiatry, particularly in cases resistant to standard treatments including psychotherapy and pharmacotherapy, as well as due to the frequent recurrence of depressive and anxiety episodes. Consequently, alternative therapeutic strategies are being actively explored. In recent years, techniques enabling electrical and electromagnetic modulation of brain activity have attracted considerable interest as novel, non-invasive psychiatric treatments capable of influencing neural networks without the need for surgical intervention. Particular attention has been paid to repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and more advanced approaches such as transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS), and closed-loop adaptive systems.

Advances in neuroimaging and neuronavigation enable increasingly precise, targeted neuronal stimulation, which may become a key component of treatment personalization.

Current research indicates that rTMS is highly effective in the treatment of depression, including treatment-resistant cases. In generalized anxiety disorder (GAD), the method provides moderate therapeutic benefits. New neuromodulation techniques and adaptive closed-loop approaches represent a promising direction for the future of psychiatry. However, research limitations-including heterogeneous protocols, small sample sizes, short follow-up periods, and lack of standardized procedures-should be acknowledged.The aim of this article is to organize current knowledge regarding TMS, tDCS, and emerging neuromodulation techniques in the treatment of depressive and anxiety disorders, with particular emphasis on mechanisms of action, clinical efficacy, major research challenges, and future directions.

Methodology

This article is a narrative literature review incorporating elements of systematic data retrieval. Its purpose was to present the current state of knowledge concerning the efficacy, mechanisms of action, and personalization strategies of non-invasive neuromodulation methods. Searches were conducted in the following databases: PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. Data were analyzed descriptively and qualitatively.A quantitative meta-analysis was not performed, as the objective of this work was to synthesize recent trends and mechanistic insights in neuromodulation. The review included:

1. studies involving adult patients (≥18 years) diagnosed with major depression, treatment-resistant depression, or anxiety disorders;
2. interventions involving TMS, tDCS, tACS, tRNS, or other non-invasive neuromodulation techniques;
3. studies reporting at least one of the following outcomes:
– changes in clinical symptoms (HAM-D, MADRS, BDI, HAM-A, GAD-7),
– neurophysiological or neuroimaging indicators (EEG, fMRI, MRS),
– biomarkers or neurobiological variables;
4. original research articles, meta-analyses, or systematic reviews with full text available online.

Foundations of Neuromodulation

Neuromodulation refers to the use of external electromagnetic or electrical stimuli to modulate neuronal activity. Techniques are divided into invasive and non-invasive approaches. Invasive methods include deep brain stimulation (DBS) and vagus nerve stimulation (VNS). Non-invasive techniques include transcranial magnetic stimulation (TMS, including rTMS), transcranial direct current stimulation (tDCS), and newer approaches such as tACS, tRNS, and closed-loop systems.

The effectiveness of neuromodulation is primarily based on neuroplasticity-the ability of neurons to reorganize synaptic connections, modify excitability, and shift activity across neural networks. These mechanisms resemble long-term potentiation (LTP) and long-term depression (LTD). Studies show that TMS can produce rapid neuronal activation changes both locally and in distant brain regions [1]. In contrast, tDCS modulates neuronal membrane potentials by influencing ionic balance and the likelihood of generating action potentials.

Neuromodulation also modulates interregional communication. Key networks involved in mood regulation include the Default Mode Network (DMN), Central Executive Network (CEN), and Salience Network (SN). Depression is characterized by DMN hyperactivity and CEN hypoactivity, which may be modulated through stimulation of the dorsolateral prefrontal cortex (DLPFC), a region central to emotional regulation and cognitive control [2]. Additionally, neuromodulation affects neurotransmitter systems and molecular factors, including glutamate and GABA levels, monoaminergic activity (dopaminergic, serotonergic), and expression of neurotrophic factors such as BDNF [2]. Evidence also indicates effects on neuroinflammatory processes-neuromodulation may reduce the brain-wide inflammatory state associated with depression and anxiety [3].

Clinical outcomes depend on many factors, including individual brain anatomy (cortical thickness, gyral morphology), stimulation parameters (intensity, duration, target location), and the patient's ongoing neural activity. Combined use of neuromodulation with psychotherapy or pharmacotherapy can also influence its effectiveness. Placebo effects may also contribute-neuromodulation techniques generate somatosensory sensations such as tingling or pressure, which may increase expectations and subjective improvement [4].

Transcranial Magnetic Stimulation (TMS)

Numerous meta-analyses confirm the effectiveness of TMS in treatment-resistant depression and major depressive disorder. rTMS applied after the failure of at least two antidepressants resulted in significant reductions in symptom severity [5]. Accelerated protocols (aTMS), involving multiple daily sessions, may reduce the time required to achieve therapeutic effects, though they have not shown clear superiority over standard rTMS [6]. TMS is also effective in depression with a prominent anxiety component. Deep TMS provides moderate reductions in anxiety symptoms [7].

TMS generates brief magnetic field pulses that induce electrical currents in cortical tissue, leading to changes in cortical excitability and neuroplasticity resembling LTP and LTD. TMS influences glutamatergic and GABAergic transmission and increases the expression of neurotrophic factors such as BDNF [6]. The most common stimulation target is the DLPFC, a region crucial for emotion regulation and cognitive control.

The effectiveness of TMS depends on patient profile, treatment history, baseline neuroplasticity, and stimulation parameters (frequency, intensity, number of pulses, session duration, number of sessions). Concurrent psychotherapy or pharmacotherapy can enhance outcomes. Research limitations include high heterogeneity, poor reproducibility, and protocol variability. Future studies should focus on personalized stimulation parameters guided by MRI-based neuronavigation, predictive biomarkers, and long-term outcomes [8].

Transcranial Direct Current Stimulation (tDCS)

Transcranial direct current stimulation involves applying a weak current (typically 1–2 mA) between electrodes placed on the scalp. It modulates neuronal membrane potential-anodal tDCS increases cortical excitability, whereas cathodal stimulation decreases it [9]. This results in altered resting membrane potentials, ion channel activity [10], neurotransmission (glutamate, NMDA), BDNF levels, and functional network activity [11]. Its effectiveness depends on factors similar to TMS, including combination with other treatments. tDCS combined with cognitive-behavioral therapy or SSRIs yields better results than stimulation alone [12]. Electrode placement and polarity are essential (commonly: anode over left DLPFC, cathode over right DLPFC).

Randomized trials and meta-analyses confirm that anodal tDCS over the left DLPFC significantly improves depressive symptoms compared to sham stimulation [13]. Evidence for anxiety disorders such as GAD or panic disorder is more limited and less consistent [14]. Compared to rTMS, tDCS may be slightly less effective but is cheaper, easier to administer, and well-tolerated [15].

Efforts are increasingly directed toward individualized stimulation parameters based on neuroanatomy, treatment resistance, and functional network activity assessed with fMRI or EEG [16]. Research suggests that tDCS is moderately effective with variable individual responses. Key limitations include lack of standardized protocols, device variability, and individual differences in anatomy and neurophysiology. Personalized stimulation and integration with cognitive or pharmacological therapies may enhance clinical efficacy [14].

Emerging Neuromodulation Techniques for Depression and Anxiety

New approaches include tACS, tRNS, tPCS, nGVS, and hybrid protocols.tACS delivers alternating current at specific frequencies (1–100 Hz), modulating rhythmic neuronal activity by enhancing or disrupting oscillatory coherence [17].

EEG and fMRI studies show that alpha-frequency tACS over the prefrontal cortex improves functional synchronization between the DLPFC and cingulate cortex, correlating with reductions in depressive symptoms [18]. Meta-analyses demonstrate moderate antidepressant effects, particularly in treatment-resistant populations. In anxiety disorders, stimulation in the theta and alpha ranges may reduce amygdala hyperreactivity and anticipatory anxiety [19]. tRNS applies alternating current with randomly fluctuating frequencies, increasing neuronal excitability and synaptic plasticity [20]. tRNS may reduce depressive symptoms, especially when combined with cognitive-behavioral therapy [21], and shows comparable effectiveness to tDCS with better tolerability [22]. Evidence for anxiety disorders is limited but suggests potential benefits in emotional regulation and autonomic arousal reduction [23].

Novel techniques such as tPCS (pulsed current stimulation) and nGVS (noisy galvanic vestibular stimulation) modulate vestibular nuclei and their limbic connections, reducing somatic symptoms of anxiety and improving autonomic balance [24,25]. Hybrid approaches (e.g., tDCS + tACS, TMS + EEG-guided stimulation) are also under development [26]. Personalized neuromodulation guided by functional imaging (fMRI, EEG, MEG) enables adjustment of stimulation parameters to individual patterns of network dysfunction [27].

Personalization and the Future of Neuromodulation in Psychiatry

Despite clear evidence supporting neuromodulation, its effectiveness varies considerably. For TMS, therapeutic response rates range from 20% to 60%, depending on the patient population [28]. Individual differences in anatomy, functional connectivity, and baseline excitability contribute to this variability. Recent research focuses on personalization through neuroimaging (MRI, fMRI, EEG, MEG) to determine the optimal stimulation location, frequency, intensity, and phase [29]. Integrating EEG or fMRI with TMS and tES allows tailoring stimulation to current brain states-known as state-dependent stimulation—which enhances therapeutic effectiveness and durability of outcomes [30,31].Artificial intelligence (AI) and machine learning are increasingly used to predict which patients will respond best to specific TMS or tDCS protocols based on multimodal data (EEG, MRI, clinical variables) [32]. In the future, AI may autonomously adjust stimulation parameters in real time [33].Multimodal therapies combining neuromodulation with psychotherapy, cognitive training, mindfulness, or autonomic biofeedback represent another promising direction [34]. Ultimately, neuromodulation is likely to become a component of precision psychiatry based on neurophysiological and genetic biomarkers [35].

Conclusions and Future Directions

Neuromodulation may serve as an alternative to standard pharmacological and psychotherapeutic approaches, especially in treatment-resistant cases. TMS and tDCS are effective in reducing depressive symptoms, and growing evidence indicates their potential in anxiety disorders [35]. Novel techniques such as tACS, tRNS, and nGVS expand therapeutic possibilities by enabling more selective and precise modulation of neuronal activity [17,18]. A key determinant of neuromodulation efficacy is treatment personalization, achieved by tailoring stimulation parameters to a patient's neurobiological characteristics using neuroimaging, EEG, and genetic biomarkers [28]. Combining neuromodulation with cognitive-behavioral therapy, emotional training, or pharmacotherapy may yield synergistic therapeutic effects [33,34]. Further large-scale clinical studies with standardized protocols and long-term follow-up are necessary. In the future, neuromodulation may become a cornerstone of personalized biological psychiatry, enabling dynamic mapping and modulation of neural circuits.

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