NONINVASIVE NEUROMODULATION (TMS AND TDCS) IN THE TREATMENT OF NEUROLOGICAL DISEASES: CLINICAL EVIDENCE, NEUROBIOLOGICAL MECHANISMS, AND PERSPECTIVES

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José Isaque do Nascimento Mangueira[1], Diogo Henrique Juliano Pinto de Moura[2], Jennifer Nascimento da Silva[3], Ronaldo Pereira da Silva[4], Bianca de Almeida Rocha de Souza[5], Weslei Talhaferro Batista[6], Yara Yanaê de Melo de Maria[7], Stefanie Silva Vieira[8], Thayssa Ferreira dos Santos[9] and Luély Vacari Ortiz[10]

[1] Undergraduate student in Medicine
Centro Universitário Maurício de Nassau - UNINASSAU, Campina Grande PB
E-mail: jose22isaque@gmail.com
Lattes: https://lattes.cnpq.br/6272108472528668
[2] Undergraduate student in Medicine
Faculdade Serra Dourada - SERRA DOURADA, Lorena SP
E-mail: diogohjmoura@gmail.com
Lattes: https://lattes.cnpq.br/6267523224276372
[3] Master's degree in Industrial Biotechnology
Universidade Tiradentes - UNIT, Aracaju SE
E-mail: enf.jennifernascimento@outlook.com
Lattes: http://lattes.cnpq.br/2471301220200705
[4] Graduated in Nursing
Centro Universitário Maurício de Nassau - UNINASSAU, Aracaju SE
E-mail: naldopsm@gmail.com
Lattes: https://lattes.cnpq.br/2924772288208724
[5] Undergraduate student in Physiotherapy
Faculdade Estácio - ESTÁCIO, Belém PA
E-mail: bianca Almeida.1401@gmail.com
Lattes: https://lattes.cnpq.br/5587005903102492
[6] Pharmacy undergraduate student
Universidade Federal de Pampa - UNIPAMPA, Uruguaiana RS
E-mail: wesleitalhaferro9@gmail.com
Lattes: https://lattes.cnpq.br/1428578093822445
https://orcid.org/0009-0009-7254-6479
[7] Graduated in Biomedicine
Universidade Federal de São Paulo - UNIFESP, Itapetininga SP
E-mail: yarayaneyah@gmail.com
Lattes: https://lattes.cnpq.br/8626698063315544
[8] Graduated in Psychology
Centro Universitário Poi Décimo - UNIPOI
E-mail: stefanie.vieira@hotmail.com
[9] PhD candidate in Neuroscience and Cell Biology
Universidade Federal do Pará - UFPA, Belém PA
E-mail: thayssafisio@hotmail.com
Lattes: http://lattes.cnpq.br/0799402170432303
ORCID: https://orcid.org/0009-0008-8699-585X
[10] Nursing graduate
Universidade Federal de Ciências da Saúde de Porto Alegre - UFCSPA, Porto Alegre RS
E-mail: lvaortiz@hcpa.edu.br
Lattes: https://lattes.cnpq.br/6201333964721384
ORCID: https://orcid.org/0000-0002-2522-1317

Abstract

Non-invasive neuromodulation, particularly through transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), has emerged as a promising therapeutic strategy for neurological and neuropsychiatric disorders between 2021 and 2025. This review analyzed recent clinical evidence, underlying neurobiological mechanisms, and advances related to personalized medicine. Findings indicate that therapeutic effects vary according to clinical condition, disease stage, and patients' neurobiological profiles, with more robust outcomes observed in early stages and when stimulation is combined with structured rehabilitation interventions. From a mechanistic perspective, neuromodulation regulates cortical excitability, promotes functional reorganization of neural networks, and modulates synaptic processes mediated by neurotrophic factors, thereby supporting adaptive neural plasticity. However, interindividual variability in treatment response remains a significant challenge, highlighting the need for individualized therapeutic strategies. In this context, neurophysiological, molecular, and neuroimaging biomarkers have emerged as relevant tools for predicting treatment response and optimizing stimulation parameters. Future perspectives include the implementation of neuroimaging-guided neuronavigation, adaptive stimulation protocols, and the integration of artificial intelligence to enhance therapeutic precision. Therefore, incorporating personalized medicine principles represents a critical step toward consolidating neuromodulation as an evidence-based, biomarker-informed intervention in contemporary clinical practice.

Keywords: Biomarkers, Neural plasticity, Neuromodulation, Personalized medicine, Transcranial magnetic stimulation.

INTRODUCTION

Non-invasive neuromodulation (NIBS; non-invasive brain stimulation) has emerged as a promising therapeutic strategy in the treatment of neurological and psychiatric diseases by modulating cortical excitability and synaptic plasticity through electrical or magnetic stimuli applied to the scalp.

Among the main techniques, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) stand out, both extensively investigated over recent decades regarding clinical efficacy, neurobiological mechanisms, and potential application across different pathological contexts (Desarkar, Vicario and Soltanlou, 2024; Camacho-Conde et al., 2021). These interventions have been considered alternatives or adjuncts to traditional pharmacological therapies, particularly in conditions characterized by neural network dysfunctions and therapeutic resistance (Hyde et al., 2022).

TMS uses pulsed magnetic fields to induce electrical currents in the cerebral cortex, promoting focal neuronal depolarization and modulating cortico-subcortical circuits (Somaa, De Graaf and Sack, 2022). In turn, tDCS applies low-intensity electrical current through electrodes positioned on the scalp, altering neuronal membrane potential and facilitating or inhibiting cortical excitability depending on the polarity used (Yamada and Sumiyoshi, 2021). Both techniques demonstrate the capacity to induce activity-dependent plasticity, influencing mechanisms such as long-term potentiation (LTP) and long-term depression (LTD), which are fundamental to processes of learning, memory, and functional reorganization after injury (Barbati, Podda and Grassi, 2022).

From a molecular perspective, recent evidence indicates that non-invasive neuromodulation promotes transcriptomic and neurochemical changes associated with the regulation of neurotrophic factors, glutamatergic and GABAergic modulation, as well as effects on inflammatory and cerebral metabolic pathways (Agrawal et al., 2025; Markowska and Tarnacka, 2024). Comparative studies show that the effects of tDCS may present long-term functional equivalence with TMS, suggesting convergence of underlying biological mechanisms despite physical differences between the stimuli (Agrawal et al., 2025). Complementarily, modulation of the prefrontal cortex by tDCS influences dopaminergic and reward circuits, indicating therapeutic implications in substance use disorders (Chmiel and Kurpas, 2025; Ramos et al., 2025).

In the field of neurodegenerative diseases, neuromodulation has been investigated in conditions such as Alzheimer’s disease, Parkinson’s disease, and amyotrophic lateral sclerosis (ALS). Systematic reviews indicate that both TMS and tDCS can improve cognitive and functional performance in patients with memory impairment associated with Alzheimer's disease (Fernandes et al., 2024; Wang et al., 2023).

In addition, stimulation of cortical networks involved in cognition and motor control can attenuate symptoms and contribute to functional stabilization in neurodegenerative diseases (Oyovwi et al., 2025). In the context of ALS, recent studies point to neuromodulation as a potential strategy to modulate cortical hyperexcitability, one of the pathophysiological markers of the disease (Della Toffola et al., 2025), and high-definition tDCS protocols are being investigated in multicenter clinical trials (Laurentino et al., 2025).

In cerebrovascular diseases, especially ischemic stroke, NIBS has been explored as a tool to promote cortical reorganization and motor recovery. Molecular changes in the ischemic brain may constitute therapeutic targets for TMS and tDCS, reinforcing the possibility of combined interventions with intensive rehabilitation and pharmacological therapies (Markowska and Tarnacka, 2024). Moreover, evidence indicates that tDCS provides benefits in balance rehabilitation across different neurological disorders, consolidating its role as an adjunct intervention in neurological physiotherapy (Beretta et al., 2022).

In the field of chronic neuropathic pain, non-invasive neuromodulation has shown consistent evidence of clinical efficacy. Evidence-based reviews demonstrate that both TMS and tDCS promote a significant reduction in pain intensity, especially when directed to the primary motor cortex (Duarte-Moreira et al., 2025). These findings support the hypothesis that modulation of cortico-thalamic networks and descending inhibitory pain systems constitutes one of the main mechanisms of action of these techniques (Camacho-Conde et al., 2021).

The application of neuromodulation also extends to psychiatric disorders, in which connectivity dysfunctions and neurochemical imbalances are central. Comprehensive meta-analyses have demonstrated the efficacy of neurostimulation in several mental disorders, including major depression, obsessive-compulsive disorder, and schizophrenia, with a favorable safety profile (Hyde et al., 2022; Sabé et al., 2024). In addition, the reorganization of dysfunctional neural networks, especially fronto-limbic circuits, constitutes one of the main therapeutic targets of neuromodulation in psychiatry (Michalopoulou et al., 2025).

In language and cognitive disorders, such as primary progressive aphasia, recent reviews identified improvement in linguistic functions with the use of TMS and tDCS, suggesting potential for modulation of perisylvian networks (Gobbi et al., 2025). Such findings broaden the perspective of using these techniques in structured cognitive rehabilitation programs (Fernandes et al., 2024).

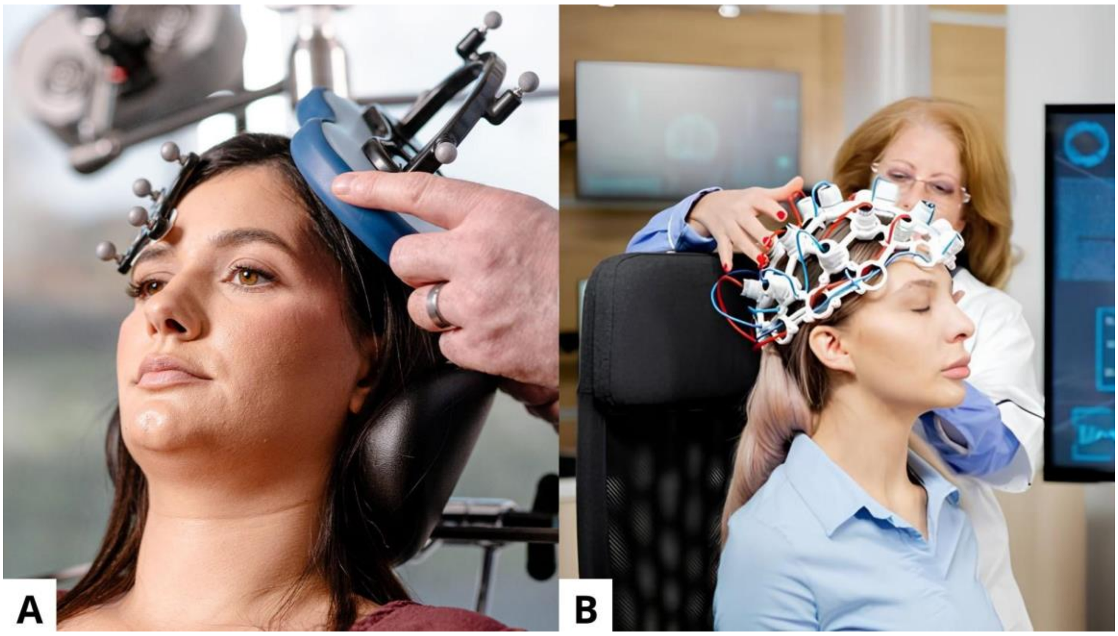
Technological advances have expanded the scope of neuromodulation, including non-invasive or minimally invasive deep brain stimulation approaches that seek to reach subcortical structures with greater precision (Liu et al., 2022).

In parallel, the importance of the perspectives of patients and professionals regarding acceptability, safety, and ethical aspects in the application of these techniques is emphasized, highlighting the need for standardized protocols and robust clinical guidelines (Maier et al., 2024).

Despite advances, challenges persist, including methodological heterogeneity across studies, interindividual variability of response, standardization of stimulation parameters, and definition of predictive biomarkers of efficacy. A deeper understanding of neurobiological mechanisms is essential to optimize therapeutic protocols and maximize clinical outcomes by integrating neuroimaging, neurophysiology, and molecular biology data (Camacho-Conde et al., 2021; Markowska and Tarnacka, 2024). Figure 1 presents a representation of TMS and tDCS, facilitating comparative understanding of the two techniques.

Figure 1

Representation of non-invasive neuromodulation: TMS and tDCS



Source:A) About TMS - Magstim (2024), B) Transcranial Direct Current Stimulation (tDCS) Therapy in Mumbai (2022)

In view of the increasing prevalence of neurological and psychiatric diseases, associated with high functional, social, and economic impact, it becomes imperative to explore safe, effective, evidence-based therapeutic interventions. Non-invasive neuromodulation presents a favorable safety profile, low risk of serious adverse events, and potential for outpatient application, constituting a strategic alternative especially in refractory cases or as an adjunct therapy (Hyde et al., 2022; Sabé et al., 2024). Thus, the consolidation of clinical evidence and elucidation of its neurobiological mechanisms justify the scientific and clinical relevance of deepening this topic, contributing to the expansion of innovative therapeutic approaches and to the strengthening of interdisciplinary clinical practice.

Accordingly, the present study aims to analyze clinical evidence, neurobiological mechanisms, and future perspectives of non-invasive neuromodulation—emphasizing TMS and tDCS—in the treatment of neurological diseases, discussing their pathophysiological foundations, therapeutic applications, and challenges for evidence-based clinical implementation.

METHODOLOGY

This is an integrative literature review with a qualitative approach and a descriptive-analytical character, conducted with the objective of synthesizing scientific evidence regarding non-invasive neuromodulation—with emphasis on transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS)—in the treatment of neurological diseases. This design was chosen because it enables the inclusion of different methodological designs, allowing a broad and systematized analysis of clinical evidence, neurobiological mechanisms, and therapeutic perspectives.

The bibliographic search was conducted from January 2021 to December 2025, including national and international publications available in the PubMed/MEDLINE, Scopus, Web of Science, Embase, and Virtual Health Library (BVS) databases. This temporal delimitation is justified by the need to gather updated evidence, considering recent technological and methodological advances in the field of brain neuromodulation.

Controlled and uncontrolled descriptors were used, combined with Boolean operators (AND, OR), according to the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH). The main descriptors employed were: “Transcranial Magnetic Stimulation”, “Repetitive Transcranial Magnetic Stimulation”, “Transcranial Direct Current Stimulation”, “Non-invasive Brain Stimulation”, “Neuromodulation”, “Neurological Disorders”, “Neurodegenerative Diseases”, “Chronic Pain”, “Stroke”, “Alzheimer Disease”, “Amyotrophic Lateral Sclerosis”, and “Neurobiological Mechanisms”. Search strategies were adapted according to the specificities of each database.

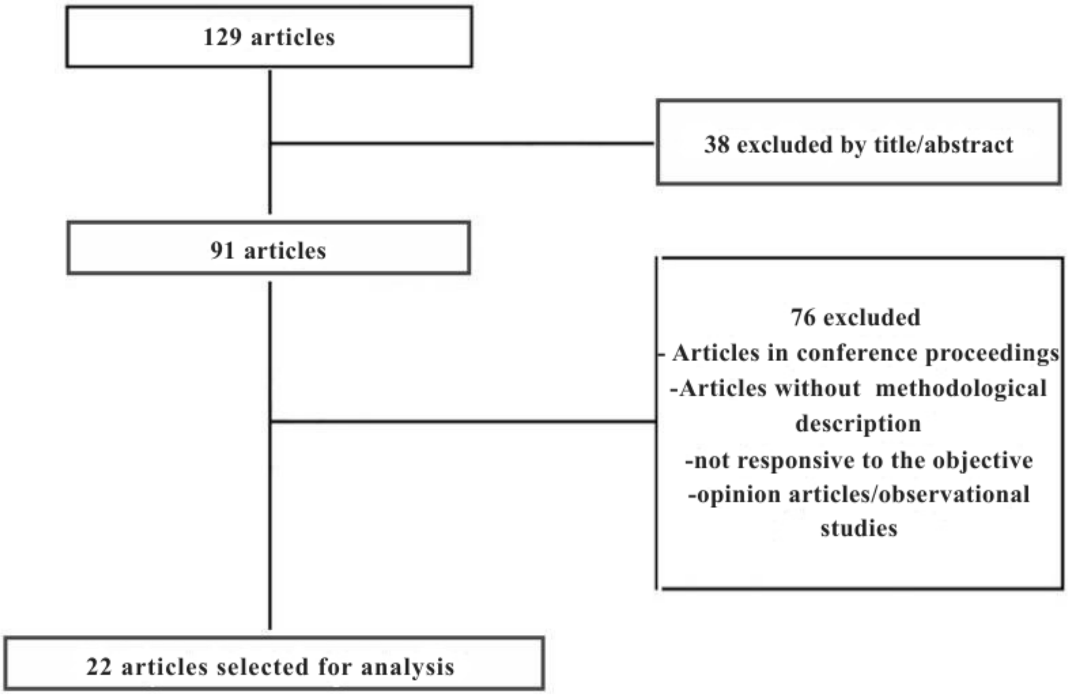
The inclusion criteria were: (1) original articles, systematic reviews, meta-analyses, narrative reviews, and randomized clinical trials; (2) studies published between 2021 and 2025; (3) publications in English, Portuguese, or Spanish; (4) research addressing TMS and/or tDCS applied to neurological or psychiatric diseases; (5) studies presenting clinical outcomes, neurobiological mechanisms, or therapeutic perspectives related to non-invasive neuromodulation; and (6) full-text availability.

The exclusion criteria were: (1) duplicate studies across databases; (2) isolated case reports, editorials, letters to the editor, and conference abstracts without full publication; (3) research involving exclusively invasive brain stimulation, such as conventional deep brain stimulation, without correlation with non-invasive methods; (4) studies with insufficiently described methodology; and (5) publications whose focus was not directly related to the therapeutic application or mechanisms of TMS and/or tDCS.

Figure 2 presents the flowchart of the process of identification, screening, eligibility, and inclusion of studies, according to the methodological stages adopted in this integrative review.

Figure 2

Flowchart of the study selection process



Source: Authors (2026)

For data analysis and synthesis, a qualitative approach was adopted, with thematic categorization into three main axes: (1) clinical evidence of TMS and tDCS in neurological diseases; (2) neurobiological mechanisms involved in cortical and synaptic modulation; and (3) future perspectives and challenges for clinical implementation. Results were organized in a descriptive and comparative manner, enabling the identification of convergences, divergences, and gaps in current scientific knowledge.

As this is a literature review study using exclusively secondary data in the public domain, submission to a Research Ethics Committee was not required, in accordance with current regulations for research that does not directly involve human beings.

Thus, the adopted methodology enabled the construction of a comprehensive, up-to-date analysis grounded in recent scientific evidence (2021–2025), ensuring rigor in study selection and consistency in interpreting findings regarding non-invasive neuromodulation in the treatment of neurological diseases.

RESULTS AND DISCUSSION

The studies included in the present review show that non-invasive neuromodulation—especially through TMS and tDCS—demonstrates variable yet clinically relevant efficacy in managing different neurological conditions, with impacts on motor, cognitive, and functional outcomes. It was observed that the magnitude of therapeutic effects is directly related to the underlying clinical condition, disease stage, the patient's neurophysiological profile, and the stimulation parameters employed, such as frequency, intensity, duration, and cortical target area. Moreover, the results indicate that clinical benefits appear to be supported by neurobiological mechanisms associated with modulation of cortical excitability, reorganization of neural networks, and induction of activity-dependent synaptic plasticity. However, substantial methodological heterogeneity persists among studies, particularly regarding protocol standardization and identification of predictors of therapeutic response. In this context, the findings reinforce the need for stratified analysis of the evidence, considering clinical and biological specificities, which underpins the organization of the discussion into the following thematic axes: Clinical Evidence Stratified by Neurological Condition and Patient Profile; Neurobiological Mechanisms and Modulation of Neural Plasticity; and Personalized Medicine, Biomarkers, and Future Perspectives.

CLINICAL EVIDENCE STRATIFIED BY NEUROLOGICAL CONDITION AND PATIENT PROFILE

Analysis of clinical evidence demonstrates that the efficacy of non-invasive neuromodulation through transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) varies according to the neurological condition treated, disease stage, clinical phenotype, and individual patient characteristics such as age, brain connectivity pattern, and baseline level of cortical excitability.

As highlighted by Desarkar, Vicario and Soltanlou (2024), therapeutic application of neuromodulation must consider the heterogeneity of neural networks involved in each pathology, since different cortico-subcortical circuits respond differently to stimulation protocols.

In the context of neurodegenerative diseases—especially Alzheimer's disease—evidence points to moderate cognitive benefits, particularly when stimulation is directed to the dorsolateral prefrontal cortex and temporoparietal regions. Fernandes et al. (2024), in a meta-analysis, identified significant improvements in episodic memory domains and executive functions after repeated cycles of TMS and tDCS, with a favorable safety profile. Complementarily, Wang et al. (2023) emphasize that tDCS shows promising results when compared to other non-invasive stimulation modalities, particularly in mild to moderate stages of the disease. Oyovwi et al. (2025) emphasize that patients in early stages tend to show greater therapeutic responsiveness, possibly due to partial preservation of synaptic networks and greater residual neural plasticity capacity.

In amyotrophic lateral sclerosis (ALS), neuromodulation has been investigated with a focus on modulating cortical hyperexcitability, considered one of the central pathophysiological markers of the disease. Della Toffola et al. (2025) report that repetitive TMS protocols may contribute to temporary stabilization of functional progression, although results remain heterogeneous. Laurentino et al. (2025), when describing a multicenter clinical trial protocol with high-definition tDCS, highlight the importance of stratifying patients according to clinical stage, bulbar impairment, and respiratory capacity—factors that can influence response to stimulation.

In patients with stroke sequelae, neuromodulation has been widely used as an adjunct to motor rehabilitation. Markowska and Tarnacka (2024) note that efficacy is related to interhemispheric balance and the degree of structural lesion, being more pronounced in individuals with subcortical lesions and partial preservation of the primary motor cortex. Beretta et al. (2022), in a systematic review with meta-analysis, demonstrated that tDCS combined with physiotherapy improves balance and reduces fall risk across different neurological disorders, reinforcing the role of combined intervention. Camacho-Conde et al. (2021) argue that integrating neuromodulation with conventional therapies enhances functional reorganization of motor networks.

In the management of chronic neuropathic pain, robust evidence indicates that stimulation of the primary motor cortex promotes a significant reduction in pain intensity. Duarte-Moreira et al. (2025), in an evidence-based umbrella review, observed consistency in the analgesic effects of TMS and tDCS, especially in patients with central post-stroke pain and peripheral neuropathy. However, the authors emphasize that variables such as pain duration, etiology, and psychiatric comorbidities influence clinical outcomes, indicating the need for therapeutic personalization.

In psychiatric disorders, although not strictly neurological, neuromodulation has been applied in common comorbidities among neurological patients, such as depression and anxiety disorders. Hyde et al. (2022), in a meta-analysis covering 208 randomized clinical trials, demonstrated significant efficacy of neurostimulation across multiple mental disorders. Sabé et al. (2024) reinforce that both TMS and tDCS provide clinical benefits with low risk of serious adverse events. Michalopoulou et al. (2025) highlight that therapeutic response is associated with prior functional connectivity patterns, suggesting that neuroimaging biomarkers may help select ideal candidates.

In language disorders such as primary progressive aphasia, Gobbi et al. (2025) identified improvement in naming tasks and verbal fluency after repeated TMS and tDCS protocols. The results suggest that patients with less extensive variants of perisylvian degeneration have greater response potential, reinforcing the importance of prior clinical and neuroanatomical characterization.

In substance use disorders, Chmiel and Kurpas (2025) and Ramos et al. (2025) highlight that stimulation of the dorsolateral prefrontal cortex can reduce craving and improve inhibitory control, especially in individuals with greater impairment of reward circuits. Yamada and Sumiyoshi (2021) emphasize that neurochemical factors such as baseline dopamine and glutamate levels may influence the magnitude of clinical response.

Additionally, Agrawal et al. (2025) demonstrate that the transcriptomic effects of tDCS may present long-term functional equivalence to TMS, suggesting that choice of technique may consider clinical profile, availability, and tolerability without significant loss of efficacy in certain conditions. Barbati, Podda and Grassi (2022) reinforce that modulation of structural plasticity is dependent on physiological context and the functional state of the stimulated neural network.

Stratification by patient profile also involves sociodemographic aspects and therapeutic acceptability. Maier et al. (2024) show that perceived safety, expectation of benefit, and understanding of the procedure influence adherence and treatment continuity. Liu et al. (2022) highlight that new approaches to deep non-invasive stimulation may expand the spectrum of eligible patients, especially in refractory cases.

In a synthetic manner, Table 1 presents the stratification of the main clinical evidence according to neurological condition and predominant response profile.

Table 1

Clinical evidence of non-invasive neuromodulation stratified by neurological condition and patient profile

Neurological Condition	Predominant Modality	Main Outcomes	Profile with Greater Response
Alzheimer's disease	TMS / tDCS	Improved memory and executive functions	Mild to moderate stages; greater cognitive reserve
ALS	TMS / tDCS-HD	Modulation of cortical hyperexcitability	Early stage; less bulbar impairment
Stroke	TMS / tDCS	Motor recovery and balance	Central post-stroke pain; fewer psychiatric comorbidities
Neuropathic pain	TMS / tDCS	Reduction of pain intensity	Subcortical lesions; partial cortical preservation
Progressive aphasia	TMS / tDCS	Improved naming and verbal fluency	Less extensive variants; less perisylvian atrophy
Substance use disorders	tDCS	Reduced craving and improved inhibitory control	Greater functional prefrontal impairment

Source: Authors (2026)

In summary, clinical evidence indicates that non-invasive neuromodulation has significant therapeutic potential when applied in a stratified and personalized manner. Response variability reinforces the need to integrate detailed clinical assessment, neurobiological characterization, and careful definition of stimulation protocols. Therefore, understanding the specificities of each neurological condition and the patient's individual profile constitutes a central element for maximizing efficacy and consolidating neuromodulation as an evidence-based therapeutic tool.

NEUROBIOLOGICAL MECHANISMS AND MODULATION OF NEURAL PLASTICITY

Understanding the neurobiological mechanisms underlying non-invasive neuromodulation is a central element for consolidating TMS and tDCS as evidence-based therapeutic interventions.

Although both techniques rely on distinct physical principles, they converge in their capacity to modulate cortical excitability, reorganize neural networks, and induce activity-dependent synaptic plasticity. As highlighted by Yamada and Sumiyoshi (2021), the effects of tDCS involve neurophysiological, chemical, and anatomical changes that go beyond immediate modulation of membrane potential, reverberating in enduring processes of functional reorganization.

At the neurophysiological level, TMS acts by inducing intracortical electrical currents capable of triggering action potentials and modifying neuronal firing patterns. High-frequency protocols tend to increase cortical excitability, whereas low frequencies produce inhibitory effects, modulating the excitatory–inhibitory balance of cortical networks (Somaa, De Graaf and Sack, 2022). In contrast, tDCS, by applying low-intensity direct current, alters neuronal firing threshold without necessarily generating direct action potentials, facilitating or reducing the probability of synaptic activation according to electrode polarity (Yamada and Sumiyoshi, 2021).

In terms of synaptic plasticity, both techniques influence mechanisms analogous to long-term potentiation (LTP) and long-term depression (LTD), processes fundamental to learning and memory. Barbati, Podda and Grassi (2022) emphasize that tDCS can promote structural remodeling, including changes in dendritic spine density and reorganization of synaptic connections, especially when combined with behavioral tasks or active rehabilitation. This interaction between electrical stimulation and behavioral activity enhances consolidation of adaptive functional networks.

At the molecular level, recent evidence expands understanding of the effects of neuromodulation on transcriptomic pathways and intracellular signaling. Agrawal et al. (2025), when comparing the temporal effects of tDCS and TMS, demonstrated that both can induce sustained changes in gene expression related to neurotrophic factors such as BDNF (brain-derived neurotrophic factor), synaptic proteins, and inflammatory mediators. The authors suggest that, although immediate effects may differ between techniques, there is convergence in terms of long-term molecular plasticity.

Moreover, Markowska and Tarnacka (2024) highlight that, in the context of ischemic brain injury, TMS and tDCS can modulate pathways associated with neuroinflammation, oxidative stress, and glutamatergic excitotoxicity. Reduction of cortical hyperexcitability and restoration of balance between excitatory and inhibitory neurotransmitters constitute relevant mechanisms in post-stroke functional recovery. This effect is particularly important in conditions characterized by dysregulation of the GABAergic and glutamatergic systems.

In the field of substance use disorders, Chmiel and Kurpas (2025) demonstrate that tDCS applied to the dorsolateral prefrontal cortex modulates mesocorticolimbic dopaminergic circuits, influencing nucleus accumbens activity and reducing craving. Ramos et al. (2025) reinforce that these effects are associated with restoration of executive control and functional reorganization of reward networks. These findings indicate that neuromodulation acts not only on superficial cortical areas but also indirectly on subcortical structures through connective networks.

Additionally, Michalopoulou et al. (2025) emphasize that neuromodulation promotes reconfiguration of large-scale neural networks, influencing functional connectivity among frontal, limbic, and parietal regions. This systemic reorganization may explain the clinical effects observed across different neurological and psychiatric disorders, indicating that therapeutic impact goes beyond the directly stimulated area.

Interindividual variability of response also has a neurobiological basis. According to Desarkar, Vicario and Soltanlou (2024), factors such as cortical thickness, white matter integrity, genetic polymorphisms related to BDNF, and baseline excitability state influence the magnitude and duration of stimulation effects. This reinforces the need to integrate neurophysiological biomarkers with personalized protocols.

Below, Table 2 synthesizes the main neurobiological mechanisms associated with TMS and tDCS, organized by level of analysis and clinical implications.

Table 2

Neurobiological mechanisms of non-invasive neuromodulation and implications for neural plasticity

Scientific Evidence	Level of Analysis	Main Mechanism	Clinical Implications
Somaa, De Graaf and Sack (2022); Yamada and Sumiyoshi (2021)	Neurophysiological	Modulation of cortical excitability (facilitation or inhibition)	Restoring excitatory–inhibitory balance; control of hyperexcitability
Barbati, Podda and Grassi (2022)	Synaptic	Induction of LTP/LTD and dendritic remodeling	Consolidation of learning and functional recovery
Agrawal et al. (2025)	Molecular	Changes in gene expression (BDNF, synaptic proteins)	Long-term plasticity and neuroprotection
Chmiel and Kurpas (2025); Markowska e Tarnacka (2024)	Neurochemical	Glutamatergic, GABAergic, and dopaminergic modulation	Reduction of craving, pain, and motor symptoms
Michalopoulou et al. (2025); Desarkar, Vicario e Soltanlou (2024)	Network Connectivity	Reorganization of cortico-subcortical networks	Cognitive, motor, and behavioral improvement

Source: Authors (2026)

In summary, the neurobiological mechanisms of non-invasive neuromodulation are multifactorial and interdependent, involving everything from immediate changes in neuronal excitability to sustained structural and transcriptomic changes. Convergence between TMS and tDCS in molecular and plasticity pathways suggests that both techniques share common neurobiological foundations, even though they differ in stimulus intensity and focality. An integrated understanding of these mechanisms provides a rational basis for developing more effective, targeted, and personalized protocols, consolidating neuromodulation as a strategic tool for the adaptive modulation of neural plasticity.

PERSONALIZED MEDICINE, BIOMARKERS, AND FUTURE PERSPECTIVES

The consolidation of non-invasive neuromodulation in contemporary clinical practice is directly related to the transition from standardized therapeutic models to approaches grounded in personalized medicine. The interindividual variability observed in response to TMS and tDCS shows that clinical, neuroanatomical, genetic, and functional factors significantly influence therapeutic outcomes. As highlighted by Desarkar, Vicario and Soltanlou (2024), the heterogeneity of clinical results reflects intrinsic differences in the organization of neural networks, requiring biomarker-based strategies that enable prediction of responsiveness and optimization of protocols.

Within neurophysiological biomarkers, measures such as motor evoked potentials, cortical motor threshold, functional connectivity assessed by functional magnetic resonance imaging (fMRI), and quantitative electroencephalography (qEEG) have been investigated as predictive tools. Yamada and Sumiyoshi (2021) emphasize that baseline cortical excitability state directly influences the magnitude of modulation induced by tDCS, suggesting that prior assessments may guide stimulation intensity and polarity. Complementarily, Michalopoulou et al. (2025) emphasize that fronto-limbic connectivity patterns can predict response in psychiatric disorders, broadening the scope of personalized neuromodulation.

In the molecular domain, Agrawal et al. (2025) demonstrate that neuromodulation can induce sustained transcriptomic changes, suggesting that gene expression markers related to BDNF and synaptic plasticity may serve as indicators of therapeutic response. Markowska and Tarnacka (2024) reinforce that, in ischemic conditions, inflammatory biomarkers and levels of oxidative mediators can help define the ideal moment for intervention, maximizing functional recovery.

Integration of clinical data and biomarkers is also relevant in neurodegenerative diseases. Fernandes et al. (2024) suggest that greater cognitive reserve and lower degree of cortical atrophy are associated with better responses to TMS and tDCS in patients with Alzheimer’s disease. Similarly, Della

Toffola et al. (2025) indicate that measurable cortical hyperexcitability assessed by TMS may serve as a marker of therapeutic eligibility in ALS.

The personalized medicine perspective also involves technological advances such as neuroimaging-based neuronavigation systems, enabling precise targeting of cortical areas. According to Liu et al. (2022), non-invasive deep brain stimulation approaches and improved focusing techniques expand the ability to reach specific circuits with greater anatomical precision. This technological evolution supports interventions adapted to individual connectivity profiles.

In addition, factors related to acceptability, safety, and therapeutic expectations also influence outcomes. Maier et al. (2024) note that psychosocial factors, perceived efficacy, and understanding of treatment affect adherence and continuity, constituting a relevant subjective dimension within therapeutic personalization.

Table 3 synthesizes the main biomarkers investigated in non-invasive neuromodulation and their potential clinical applications.

Table 3

Biomarkers associated with non-invasive neuromodulation and applications in personalized medicine

Biomarker Category	Examples	Scientific Evidence	Potential Clinical Application
Neurophysiological	Cortical motor threshold; evoked potentials; qEEG	Yamada e Sumiyoshi (2021)	Adjustment of stimulation intensity and polarity
Functional Neuroimaging	Fronto-limbic connectivity; motor networks	Michalopoulou *et al.* (2025)	Target-area selection and response prediction
Molecular/Genetic	BDNF expression; inflammatory markers	Agrawal et al. (2025); Markowska e Tarnacka (2024)	Monitoring plasticity and identifying the ideal time for intervention
Clinical-Structural	Degree of cortical atrophy; disease stage	Fernandes et al. (2024); Della Toffola et al. (2025)	Patient stratification and therapeutic prognosis

Source: Authors (2026)

With regard to future perspectives, there is a trend toward combining neuromodulation with behavioral, pharmacological, and rehabilitation interventions, enhancing synergistic effects. Barbati, Podda and Grassi (2022) note that associating stimulation with cognitive or motor training supports structural consolidation of stimulated neural networks. This integrated approach increases therapeutic potential and reduces response variability.

Another emerging perspective involves the use of artificial intelligence and machine learning for analyzing large volumes of clinical and neurobiological data. As argued by Desarkar, Vicario and Soltanlou (2024), predictive models based on multiple parameters may assist in automated definition of personalized protocols, integrating clinical, genetic, and neuroimaging information.

Table 4 presents the main future trends in the clinical application of non-invasive neuromodulation.

Table 4

Future perspectives in non-invasive neuromodulation

Innovation Axis	Description	Potential Clinical Impact
Individualized Neuronavigation	Neuroimaging-guided targeting based on structural and functional data	Greater anatomical precision and therapeutic efficacy
Adaptive Protocols	Dynamic adjustment of parameters according to clinical response	Reduction of adverse effects and higher response rates
Multimodal Integration	Combination with pharmacotherapy and intensive rehabilitation	Potentiation of neural plasticity
Artificial Intelligence	Response prediction models based on big data	Personalized stratification and therapeutic optimization
Advanced Focal Stimulation	High-definition techniques and non-invasive deep stimulation	Expansion of indications and greater network specificity

Source: Authors (2026)

In summary, incorporating biomarkers and personalized medicine strategies represents a crucial step for the scientific and clinical maturity of non-invasive neuromodulation. Integrating neurophysiological, molecular, structural, and behavioral data makes it possible to design interventions tailored to each patient's particularities, reducing response heterogeneity and increasing therapeutic efficacy. Thus, the future of TMS and tDCS lies in the convergence of technology, translational neuroscience, and individualized clinical practices, consolidating neuromodulation as a strategic component of contemporary neurology and psychiatry.

CONCLUSION

Non-invasive neuromodulation—especially through transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS)—is consolidating as a promising therapeutic strategy in managing neurological and neuropsychiatric conditions. Throughout this review, it was shown that these techniques promote modulation of cortical excitability and functional reorganization of neural networks, contributing to motor, cognitive, and behavioral recovery. The breadth of clinical applications observed between 2021 and 2025 reinforces the expansion of the field and the increasing methodological sophistication of clinical trials.

Clinical evidence stratified by neurological condition indicates that therapeutic effects depend both on clinical profile and disease stage. Patients in early phases, with greater cognitive reserve or a lower degree of structural impairment, tend to show more robust responses to intervention. In addition, integrating neuromodulation with intensive rehabilitation programs shows potential to enhance functional gains, suggesting that stimulation effects are amplified when paired with directed behavioral stimuli.

From a neurobiological standpoint, underlying mechanisms involve synaptic modulation, changes in functional connectivity, and regulation of molecular pathways associated with neural plasticity, such as those mediated by neurotrophic factors. The ability to induce activity-dependent plasticity positions neuromodulation as a relevant tool in adaptive reorganization of the central nervous system. However, interindividual variability remains one of the main clinical challenges, underscoring the need for more individualized approaches. In this context, incorporating neurophysiological, molecular, and neuroimaging biomarkers represents a strategic advance toward personalized medicine.

Using prior measures of cortical excitability, functional connectivity, and inflammatory or genetic markers can contribute to predicting therapeutic response and optimizing stimulation parameters. Integrating these data with artificial intelligence tools tends to improve patient stratification and selection of more effective protocols.

Despite advances, gaps remain regarding protocol standardization, definition of ideal doses, duration of effects, and long-term longitudinal follow-up. Multicenter studies with larger samples and robust methodological designs are needed to strengthen the level of evidence and allow greater generalization of results. Moreover, translational investigations connecting molecular and clinical findings may clarify mechanisms that are still poorly understood.

As a suggestion for future research, it is proposed to conduct a multicenter randomized clinical trial evaluating the efficacy of an adaptive neuromodulation protocol guided by functional connectivity and cortical excitability biomarkers in patients with mild cognitive impairment of neurodegenerative etiology. The study could integrate functional neuroimaging analysis, serum BDNF measurement, and longitudinal neuropsychological assessment, comparing a standard protocol versus a personalized protocol. Such a design would allow investigation of whether biomarker-based personalization results in greater magnitude and duration of therapeutic effects, contributing to consolidating neuromodulation as a precision intervention in contemporary clinical practice.

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