

NEUROPLASTICITY AND NON-INVASIVE INTERVENTIONS: EVIDENCE OF BRAIN STIMULATION, COGNITIVE TRAINING, AND SENSORY MODULATION IN NEURAL REHABILITATION

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Date of publication: March 3, 2026

DOI: doi.org/10.55703/27644006060111

ABSTRACT

Objective: To critically analyze the scientific evidence on the impact of non-invasive interventions, including brain stimulation, cognitive training, and sensory modulation, on promoting neuroplasticity and neural rehabilitation. **Methods:** An integrative literature review was conducted based on PRISMA guidelines. The search was carried out in the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases, covering the period from 2000 to 2025. Randomized clinical trials, controlled studies, and meta-analyses involving adults subjected to non-invasive interventions with outcomes related to neural plasticity, cognitive function, or functional recovery were included. **Results:** A total of 20 studies were included, predominantly randomized clinical trials. Non-invasive brain stimulation, especially tDCS and rTMS, showed significant improvement in episodic memory, working memory, and executive function, with greater consistency in multi-session protocols. Combined interventions with cognitive training exhibited a synergistic effect superior to isolated interventions. Neurophysiological evidence indicated modulation of cortical excitability and neurochemical changes consistent with mechanisms of synaptic plasticity. Sensory modulation through virtual reality showed moderate benefit in post-stroke functional rehabilitation. **Conclusion:** Non-invasive interventions have a consistent neurobiological basis and promising clinical evidence in the modulation of neuroplasticity and neural rehabilitation. However, methodological heterogeneity still limits the standardization of protocols and definitive clinical recommendations, and multicenter studies with greater methodological robustness are needed.

Keywords: Neuroplasticity; Brain Stimulation; Neurological Rehabilitation; Cognitive Training; Transcranial Magnetic Stimulation.

INTRODUCTION

Neurological diseases represent one of the main causes of functional disability in the contemporary world, with an increasing impact on health systems. Conditions such as Alzheimer's disease (AD), mild cognitive impairment (MCI), stroke (CVA), and Parkinson's disease are associated with progressive decline in cognitive and motor functions, generating a high socioeconomic burden and reduction in quality of life. Epidemiological evidence indicates a significant increase in the prevalence of these conditions in recent decades, especially in aging populations elderly (5).

From a pathophysiological point of view, such conditions share structural and functional alterations in neural circuits, including synaptic loss, dysfunction of functional connectivity, and impairment of cortical plasticity. Neuroplasticity is defined as the adaptive capacity of the nervous system to reorganize its structure and function in response to internal or external stimuli, constituting the main biological mechanism underlying functional recovery after injuries or neurodegenerative processes (6).

Studies experimental They demonstrated that transcranial direct current stimulation (tDCS) is capable of modulating cortical excitability in a polarity-dependent manner, producing effects similar to the mechanisms of long-term potentiation (LTP) and long-term depression (LTD), central phenomena of synaptic plasticity (6). Neurochemical changes associated with tDCS were evidenced by magnetic resonance spectroscopy, with modulation of glutamate and GABA levels, reinforcing the mechanistic basis of this intervention (11).

In the clinical context, non-invasive brain stimulation interventions, such as tDCS and repetitive transcranial magnetic stimulation (rTMS), have been investigated as adjunctive therapeutic strategies in cognitive and functional rehabilitation. Randomized clinical trials have shown significant improvement in recognition memory in patients with Alzheimer's disease subjected to tDCS (1,3). Recent meta-analyses corroborate the favorable effect of multi-session protocols on global cognition in individuals with dementia or mild cognitive impairment (10).

Furthermore, studies combining brain stimulation with cognitive training demonstrate synergistic effects on cortical function modulation and cognitive performance, particularly in populations with Alzheimer's and post-stroke (7,14,16). Evidence also suggests that virtual reality-based interventions may enhance functional reorganization processes and motor recovery in neurological rehabilitation (20).

These findings support the hypothesis that non-invasive interventions can act as modulators of neural plasticity, promoting adaptive functional reorganization. However, despite

the growing body of evidence, there are still methodological heterogeneities related to stimulation protocols, technical parameters, studied populations, and outcome measures, which justifies the need for a structured integrative synthesis of the scientific literature.

In light of this scenario, the present study aims to critically analyze the available evidence on neuroplasticity and non-invasive interventions, focusing on brain stimulation, cognitive training, and sensory modulation in rehabilitation neural.

METHODOLOGY

This is an integrative literature review conducted based on the methodological recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), adapted to the integrative design. The objective was to identify, analyze, and synthesize scientific evidence on the effects of non-invasive interventions, including brain stimulation, cognitive training, and sensory modulation in promoting neuroplasticity and neural rehabilitation.

The search strategy was conducted in the databases PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library, considered international references in biomedical indexing. The search included studies published between January 2000 and March 2025, a period selected for encompassing the advancement of modern techniques of non-invasive brain stimulation.

Descriptors were used controlled (MeSH – Medical Subject

Headings) and free terms combined by boolean operators. The main strategy employed was: (“neuroplasticity” OR “neural plasticity”) AND (“noninvasive brain stimulation” OR “transcranial direct current stimulation” OR “tDCS” OR “repetitive transcranial magnetic stimulation” OR “rTMS” OR “transcranial alternating current stimulation” OR “tACS”) AND (“cognitive training” OR “cognitive rehabilitation”) AND (“sensory stimulation” OR “virtual reality” OR “sensory modulation”) AND (“rehabilitation” OR “recovery”). Additional filters were applied to restrict studies to humans, adults (≥ 18 years), and publications in English or Portuguese.

Inclusion criteria were established as: randomized clinical trials, controlled studies, quasi-experimental studies, and meta-analyses investigating non-invasive interventions with outcomes related to neuroplasticity, cognitive function, or functional recovery in neurological or elderly populations. Studies should present objective outcome measures, such as standardized cognitive performance, functional scales, neurophysiological measures (EEG, fMRI, motor evoked potentials) or neurochemical biomarkers.

Studies conducted exclusively on animal models, isolated case reports, narrative reviews without systematic analysis, studies without a comparator group, and articles with samples of fewer than 10 participants per group were excluded. Studies whose intervention was not clearly related to non-invasive neural modulation were also excluded.

The selection process followed four stages: identification, screening, eligibility, and inclusion. Initially, duplicate records were removed. Then, titles and abstracts were analyzed for thematic relevance. Potentially eligible studies were evaluated in full to verify inclusion and exclusion criteria. The selection flow was structured according to the PRISMA model, with a record of the number of studies identified, excluded, and included in the final synthesis.

The methodological quality of randomized clinical trials was assessed based on the criteria of the Cochrane Risk of Bias tool, considering random sequence generation, allocation concealment, blinding, incomplete data, and selective reporting. Intervention studies

non-randomized studies were analyzed for methodological clarity, bias control, and statistical robustness.

The extracted data included: author and year of publication, type of study, sample characteristics, technology used (tDCS, rTMS, tACS, cognitive training, or virtual reality), intervention parameters (intensity, frequency, number of sessions), primary and secondary outcomes, measures of

neuroplasticity and main clinical results.

The synthesis of the data was carried out descriptively and comparatively, considering methodological heterogeneities among protocols, studied populations, and assessment instruments. A quantitative meta-analysis was not performed due to the diversity of outcomes and variability of the technical parameters of the interventions.

RESULTS

The structured search resulted in the inclusion of 20 studies, predominantly randomized clinical trials, covering populations with Alzheimer's disease, mild cognitive impairment (MCI), stroke, Parkinson's disease, and healthy elderly individuals. The interventions analyzed included non-invasive brain stimulation (tDCS, rTMS, tACS), protocols combined with cognitive training, and sensory modulation strategies through virtual reality.

For analytical purposes, the results were organized according to the main outcome domains identified.

1. Effects on Episodic Memory and Working Memory

The majority of studies involving patients with Alzheimer's and MCI demonstrated significant improvement in episodic memory and working memory tasks after the application of tDCS or rTMS (1,3,7,8, 18). Protocols applied to the dorsolateral prefrontal cortex (DLPFC) and temporal regions showed greater consistency of effect.

Interventions combined with cognitive training showed a greater magnitude of response when compared to isolated stimulation (7,14,16). Included meta-analyses corroborate a small to moderate effect

in global cognition, especially when multi-session protocols were employed (10,18).

2. Executive Function and Global Cognition

Studies with rTMS and tACS applied to individuals with MCI and healthy adults demonstrated acute and sustained improvement in executive function tasks (14,18). Stimulation of the DLPFC was associated with gains in attentional control, cognitive flexibility, and processing speed.

Post-stroke clinical trials also demonstrated accelerated recovery of executive functions when rTMS was associated with conventional cognitive rehabilitation (10,16). Aggregate evidence indicates that protocols with a greater number of sessions tend to produce more lasting effects (5,10).

3. Cortical Excitability and Neurobiological Evidence

Studies experimental demonstrated that tDCS induces polarity-dependent modulation in cortical excitability, producing effects similar to long-term potentiation (LTP-like plasticity) (6). Changes

involving glutamatergic and GABAergic systems were observed by magnetic resonance spectroscopy after prefrontal stimulation (11).

Furthermore, studies with functional neuroimaging have shown increased cortical connectivity and prefrontal activation after structured cognitive training (13). These findings support the biological plausibility of the observed clinical effects.

4. Functional Rehabilitation and Sensory Modulation

Virtual reality-based interventions have demonstrated significant functional improvement in post-stroke patients, particularly in motor recovery and coordination (17,20). Virtual reality also showed a positive impact on executive function in the elderly (16).

The combination of brain stimulation with cognitive training or conventional rehabilitation was associated with greater functional gain compared to isolated protocols, suggesting a synergistic mechanism between cortical excitability modulation and directed behavioral activation (7,14,16).

Table 1 - Analytical Synthesis by Outcome Domain

Evaluated Domain	N of Studies	Predominant Evidence	Level of Consistency
Episodic memory / work	8	Significant improvement with tDCS/rTMS; greater effect with combination	Moderate to high
Executive function	6	Gains with rTMS/tACS in the DLPFC	Moderate
Excitability / Neurochemistry	3	Glutamate/GABA modulation; LTP-like effect	High (base mechanism)
Motor rehabilitation (CVA)	3	VR and rTMS associated with functional improvement	Moderate
Global cognition (meta-analyses)	3	Small to moderate effect; greater with multi-session	Moderate

Interpretative Synthesis

The results indicate that non-invasive interventions promote consistent improvement in specific cognitive domains, particularly memory and executive function. The robustness of the effects appears to depend on intensity, cortical location, and number of sessions.

Interventions combined demonstrated greater magnitude of benefit, suggesting that activity-dependent plasticity may be

enhanced when cortical stimulation is associated with structured cognitive demands.

From a neurobiological perspective, studies provide solid mechanistic support, evidencing modulation of cortical excitability and neurochemical changes compatible with synaptic reorganization processes.

However, methodological heterogeneity remains a limiting factor, especially regarding the standardization of technical parameters and assessment instruments.

DISCUSSION

The findings of this integrative review indicate that non-invasive interventions, particularly brain stimulation (tDCS, rTMS, tACS), whether alone or combined with cognitive training, have consistent potential in modulating neuroplasticity and improving cognitive and functional outcomes. The evidence suggests that such interventions work by modulating cortical excitability and facilitating activity-dependent synaptic mechanisms.

From a mechanistic perspective, transcranial direct current stimulation induces changes in cortical excitability in a polarity-dependent manner, promoting effects similar to long-term potentiation (LTP-like) or long-term depression (LTD-like), central phenomena of synaptic plasticity (6). Studies using magnetic resonance spectroscopy have demonstrated changes in glutamate and GABA levels following tDCS application, reinforcing the hypothesis of modulation of excitatory and inhibitory cortical circuits (11). These neurochemical changes support the biological plausibility of the cognitive gains

observed in populations with Alzheimer's, MCI, and post-stroke (1,3,7).

Repetitive transcranial magnetic stimulation has also demonstrated the ability for functional reorganization, especially when applied over the dorsolateral prefrontal cortex (DLPFC), a central region for executive functions and working memory (18). The repetitive activation of this region may favor frontoparietal cortical networks involved in cognitive control, resulting in measurable improvement in executive tasks (14,18). Meta-analyses included in this review indicate a small to moderate effect on global cognition, with greater robustness in multi-session protocols (10, 19).

A relevant aspect identified was the synergistic effect between brain stimulation and structured cognitive training. Combined interventions showed a magnitude of benefit greater than isolated stimulation (7, 14, 16). This phenomenon can be explained by the principle of activity-dependent plasticity, according to which modulation of cortical excitability creates a "facilitating state" that enhances the effects of targeted behavioral training. In other words, stimulation prepares the

The neural substrate, while training directs functional reorganization.

Sensory modulation based on virtual reality has also shown promising results, especially in post-stroke rehabilitation (17,20). Virtual reality provides an immersive multisensory environment that can increase engagement, practice intensity, and simultaneous activation of multiple neural networks, favoring functional cortical reorganization. However, the evidence is still moderate and lacks greater methodological standardization.

Despite the encouraging results, critical analysis reveals important limitations. Firstly, there is significant heterogeneity in the technical parameters of the interventions, including current intensity, stimulation frequency, session duration, and total number of applications. This variability makes direct comparisons difficult and prevents the clear definition of ideal protocols. Furthermore, many studies... present samples relatively small, which reduces the statistical power and generalizability of the findings.

Another relevant point is the variability in the outcomes used.

While some studies employed

Objective neurophysiological measures, such as cortical excitability and spectroscopy (6,11), have been used, while others have focused exclusively on clinical scales. The integration between biological and functional measures is still limited in the literature, representing an important gap for future research.

In a translational context, the results suggest that non-invasive interventions may represent a promising adjuvant strategy in neural rehabilitation, especially when integrated into structured protocols for cognitive training or motor rehabilitation. Clinical application, however, requires standardization of parameters, definition of responsive patient profiles, and longitudinal follow-up to assess the sustainability of the effects.

Overall, the findings support the idea that modulating neuroplasticity through non-invasive interventions is biologically plausible, clinically relevant, and potentially integrable into contemporary neurological rehabilitation programs.

However, the field still requires multicenter studies with larger samples and standardized protocols to...

consolidation definitive of the
clinical recommendations.

CONCLUSION

This integrative review evidences that non-invasive interventions, particularly transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), and alternating current stimulation (tACS), show potential significant in modulating neuroplasticity and improving cognitive and functional outcomes in different neurological conditions. The findings indicate consistent effects on episodic memory, working memory, and executive function, especially when multi-session protocols are employed.

The combination of brain stimulation with structured cognitive training demonstrated a magnitude of benefit superior to isolated interventions, suggesting a synergistic mechanism based on the principle of activity-dependent plasticity. Neurophysiological evidence supports the biological plausibility of these effects, with modulation of cortical excitability and neurochemical changes compatible with synaptic reorganization processes.

Interventions based on sensory modulation, such as virtual reality, also demonstrate relevant functional impact in post-stroke rehabilitation, although methodological robustness still varies among the available studies.

Despite the promising results, limitations related to the heterogeneity of protocols, variability in technical parameters, and the absence of standardization of the evaluated outcomes persist. Such factors restrict direct comparisons and hinder the definition of universally applicable clinical guidelines.

From a translational perspective, non-invasive interventions represent promising adjunctive therapeutic strategies in neural rehabilitation, especially when integrated into structured cognitive training and functional rehabilitation programs. However, multicenter clinical trials with expanded samples and standardized protocols are needed for consolidation definitive of clinical recommendations based on evidence.

In summary, modulating neuroplasticity through non-invasive interventions represents an expanding field with solid neurobiological foundations and significant relevance.

This clinical field is growing, establishing an important therapeutic frontier in contemporary neurology and rehabilitation.

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