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Review Article

Non-invasive neuromodulation techniques for cognitive impairment intervention

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Abstract: Cognitive impairment involves sustained deficits across several key domains: memory, executive function, attention, and behavioral regulation. The condition encompasses cognitive dysfunction linked to Alzheimer's disease, mild cognitive impairment, vascular cognitive impairment, and other forms of neurodegeneration. Existing pharmacotherapies frequently yield inconsistent clinical benefits, are often accompanied by side effects, and generally lack disease-modifying properties. These limitations have spurred increasing attention toward safe, repeatable non-pharmacological strategies. Non-invasive brain stimulation, a central non-pharmacological tool, can regulate excitability in targeted brain regions, shape network-level connectivity, and facilitate activity-dependent neuroplasticity. Evidence from multiple clinical settings supports its potential to improve cognitive outcomes. This review centers on major NIBS techniques: repetitive transcranial magnetic stimulation, transcranial electrical stimulation, gamma-frequency sensory stimulation, photobiomodulation, and transcranial ultrasound stimulation. We synthesize their underlying mechanisms, clinical applications, and supporting evidence, aiming to provide an evidence-based framework to guide standardized clinical implementation and future research design in this area.

Keywords: Cognitive impairment, non-invasive brain stimulation, Alzheimer's disease, mild cognitive impairment

Introduction

Cognitive impairment (CI) is a clinical syndrome characterized by deficits in multiple cognitive domains, including memory, attention, executive function, and language. It covers a spectrum of conditions such as subjective cognitive decline (SCD), mild cognitive impairment (MCI), Alzheimer's disease (AD), and vascular cognitive impairment (VCI). According to a report from the World Health Organization, there are approximately 55 million people living with dementia worldwide, and this number is projected to increase to 82 million by 2030, with 60%-70% of cases caused by AD [1]. With the accelerating process of population aging, the incidence and prevalence of CI have been rising continuously, which has become a major public health challenge [2, 3]. In China, the number of patients with AD and related dementias ranks among the highest in the world [4], and its disease burden and socioeconomic impact have become increasingly prominent [5]. Although certain progress has been achieved in novel strategies such as disease-modifying therapeutic drugs and immunotherapy in recent years [6, 7], the efficacy of existing medications in improving cognitive function and delaying disease progression remains relatively limited. In addition, many restrictions still exist regarding their long-term safety, applicable populations, and clinical accessibility [8]. Therefore, exploring safe, repeatable, and well-tolerated non-pharmacological interventi-

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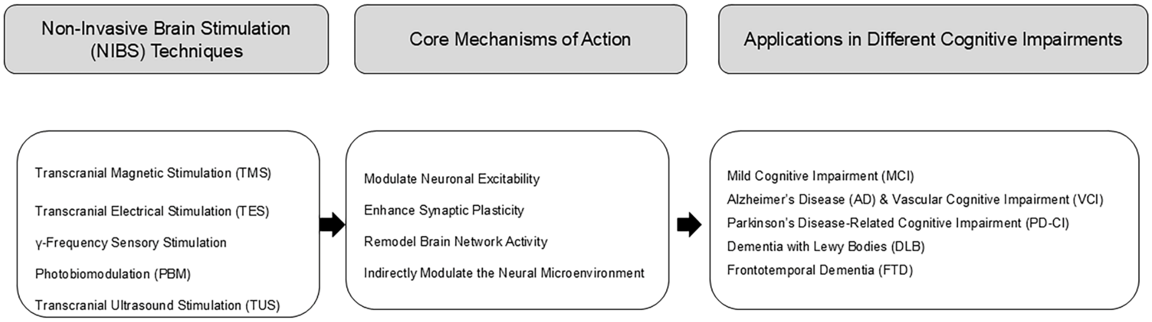

Figure 1. Mechanisms of action and clinical applications of non-invasive brain stimulation (NIBS) techniques in the intervention of cognitive impairment.

ons has become an important direction in the research on the prevention and treatment of CI [9, 10].

Non-invasive brain stimulation (NIBS) is a category of techniques that regulate brain activity in a non-invasive manner, mainly including transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (TES). It has received extensive attention in intervention research on CI in recent years [11, 12]. Evidence suggests these techniques can improve cognitive function by modulating neuronal excitability, synaptic plasticity, and brain network activity patterns [13-16]. Advances in multimodal neuroimaging have enabled the development of more precise stimulation strategies tailored to individual brain network characteristics. Such approaches may help enhance intervention efficacy and reduce variability in treatment outcomes. In this review, we summarize recent progress in non-invasive brain stimulation for cognitive impairment, with a focus on underlying mechanisms and clinical applications, to provide a practical reference for both clinical practice and future research (**Figure 1**).

Different NIBS techniques and their mechanisms of action

Transcranial magnetic stimulation

TMS operates on the principle of Faraday's law of electromagnetic induction. A coil positioned over the scalp delivers a rapidly changing magnetic field, which in turn induces electrical currents within the underlying cerebral cortex, modulating neuronal excitability and synaptic activity [17]. TMS is non-invasive and repeatable, with a strong overall safety profile. These characteristics have led to its widespread adoption in both basic neuroscience research and clinical interventions for a range of neuropsychiatric conditions [18, 19].

TMS can be classified by stimulation pattern into single-pulse, paired-pulse, and repetitive TMS (rTMS). Of these, rTMS delivers pulse trains continuously at a specific frequency, producing cumulative modulatory effects on cortical activity. Low-frequency stimulation (≤1 Hz) tends to inhibit cortical excitability, while high-frequency stimulation (≥5 Hz) typically enhances it [20]. TBS, an efficient variant of TMS, can induce long-lasting plastic changes within a relatively short time [21].

Regarding its mechanisms of action, TMS can directly regulate local neural activity by evoking neuronal depolarization and triggering action potentials. It can also induce synaptic plasticity changes similar to long-term potentiation or long-term depression, allowing the stimulatory effects to persist after the end of stimulation [22]. Relevant studies suggest that TMS may improve the excitation-inhibition balance by modulating glutamatergic and γ-aminobutyric acidergic (GABAergic) neurotransmitter systems, accompanied by altered expression of brain-derived neurotrophic factor (BDNF) and synapse-related proteins, while exerting certain regulatory effects on neuroinflammation [23, 24].

Furthermore, the modulatory effects of TMS are not restricted to the local stimulation target; its influence can propagate to distant brain regions along functional connectivity networks, achieving regulation at the brain network level [25]. On this basis, research paradigms are gradually shifting from a "region-symptom" correspondence toward network-oriented intervention strategies. In recent years, individualized navigation techniques combined with structural and functional magnetic resonance imaging have been widely used in TMS, helping to optimize the selection of stimulation targets and improve the consistency of interventions [26, 27].

Transcranial electrical stimulation

TES is a NIBS technique that modulates neural activity by delivering low-intensity electrical currents to the brain through scalp electrodes. It mainly includes transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and temporal interference (TI) stimulation.

tDCS generates a stable electric field in the cortex by delivering a constant weak direct current (usually 1-2 mA) between scalp electrodes, thereby regulating neuronal membrane potential and excitability. Generally, anodal stimulation tends to increase local excitability, whereas cathodal stimulation often exerts an inhibitory effect. However, the actual effects are influenced by factors such as stimulation intensity, duration, electrode montage, and individual baseline brain state [26, 28]. At the neuronal level, tDCS does not directly trigger action potentials. Instead, it modulates the firing probability of neurons through subthreshold effects, influencing neural information processing [29]. Repeated or prolonged stimulation can induce synaptic plasticity changes resembling long-term potentiation or long-term depression, likely via regulation of NMDA receptors, Ca^{2+} influx, and the GABAergic system [30]. The technique offers several advantages: high safety, few adverse reactions, and good repeatability. However, its limitations include weak electric field strength, poor spatial focality, and substantial interindividual variability in treatment response. Optimizing stimulation parameters and targeting strategies remains an important priority [31, 32]. tACS delivers weak alternating currents at specific frequencies to targeted brain regions. This modulation of intrinsic brain rhythmic activity alters processes linked to neuroplasticity, ultimately shaping cognitive and behavioral functions [33]. Its core mechanism involves entraining endogenous neural oscillations through an external alternating electric field, which improves information integration and network communication across brain regions [34, 35].

The physiological effects of tACS are driven by oscillating electric fields that are generated within targeted brain regions when alternating currents are delivered across the scalp. Acting at a subthreshold level, this form of stimulation elicits periodic modulation of neuronal membrane potentials. Its primary effect is on the temporal patterning of action potentials, rather than on gross firing rates [36-38]. Ultimately, the resulting neuromodulatory effects depend not only on stimulation amplitude and frequency, but also on the anatomical orientation of underlying neurons and the variability of current conduction through neural tissue. Current studies suggest that tACS effects mainly include two categories: one is the online modulatory effect achieved through rhythmic entrainment during stimulation; the other is the sustained offline effect that may be induced after stimulation via mechanisms such as spike-timing-dependent plasticity (S-TDP) [39, 40]. tACS has attracted growing interest in research on CI, particularly for AD. Studies have indicated that gamma-band (especially 40 Hz) neural oscillations are closely related to cognitive processes such as memory and information integration, and t-ACS targeting this frequency band may exert beneficial effects on related brain network functions by regulating abnormal rhythmic activities [33].

TI stimulation is an emerging transcranial electrical stimulation technique developed in recent years. Its basic principle is to simultaneously apply two or more high-frequency alternating currents with slightly different frequencies on the scalp, so that they superimpose in the target brain region to generate a low-frequency envelope signal, thereby achieving selective modulation of deep brain regions. Since the high-frequency carriers themselves exert weak direct activation on superficial cortical neurons, while the superimposed low-frequency envelope can produce effective modulation in deep areas, this technique theoretically overcomes the limitation of traditional transcranial electrical stimulation in stimulation depth [41].

Mechanistically, the low-frequency envelope signal generated by TI mainly regulates the rhythmic activity and excitability of neurons in the target brain region. The modulatory effects of TI are thought to involve phase synchronization of neural oscillations and subthreshold changes in neuronal membrane potential. Early evidence suggests that TI can target neural activity in deep brain structures such as the hippocampus and striatum, while producing minimal scalp side effects [42]. At present, TI remains largely limited to experimental investigation and early-stage clinical study. However, additional systematic work is needed to define optimized stimulation parameters, confirm long-term safety, and establish clinical effectiveness [43].

Gamma-frequency sensory stimulation (GSS)

GSS modulates neural oscillations in specific frequency bands through periodic visual or auditory input. Stimulation frequencies typically range from 30 to 100 Hz, with 40 Hz being the most commonly used [44]. Unlike techniques that deliver electromagnetic stimulation directly, this approach acts indirectly through sensory pathways. It is simple to administer and generally well tolerated [45]. The mechanisms behind its effects appear to involve enhancing or synchronizing gamma oscillations, which in turn influence cognitive processes such as attention, working memory, and information integration [46]. There is also evidence that this technique may modulate neuron-glia interactions and cerebral metabolic clearance, though the underlying details remain to be clarified [47].

This technique has drawn growing interest in cognitive impairment research, in part because it lends itself to home-based use. Standardized stimulation parameters and treatment protocols, however, are still lacking, and its clinical efficacy and long-term effects need to be assessed in well-designed randomized controlled trials [48].

Photobiomodulation (PBM)

PBM uses red or near-infrared light at specific wavelengths to modulate cellular function. In neuroscience research, it is commonly delivered through scalp irradiation or nasal light application to influence central nervous system activity [49]. The underlying mechanisms center on mitochondrial function: improving cellular energy metabolism, boosting adenosine triphosphate production, and reducing oxidative stress [50]. Meanwhile, it may indirectly affect cognitive function by regulating neuroinflammation, improving cerebral blood flow, and modulating neurovascular coupling [51]. These mechanisms suggest that PBM exerts its effects primarily by improving the neural microenvironment rather than directly regulating neuronal firing.

Current studies have demonstrated favorable safety and tolerability of PBM in individuals with CI, and some studies have observed improvement trends in memory, executive function, and other cognitive domains [52]. In 2022, Naval Medical University, relying on the First and only full-scale submarine environment simulation chamber in China (to date) at its Characteristic Medical Center, conducted a large-scale human trial on the regulation and intervention of circadian rhythm disorders in crew members within the submarine environment simulation chamber, filling the gap in nautical human factors engineering research in China. The results showed that light intervention significantly improved sleep quality and work efficiency in participants [53]. In addition, the research team established the only biobank and human performance database for crew members during long-duration open-sea voyages on real submarines in China.

Transcranial ultrasound stimulation (TUS)

TUS is a non-invasive neuromodulation technique that uses low-intensity focused ultrasound to penetrate the skull and target specific brain regions [54, 55]. Compared with electrical and magnetic stimulation, TUS exhibits superior spatial focality and penetration depth, enabling modulation of neural activity in the cortex and some deep brain structures without implanting electrodes.

Its mechanisms of action are mainly based on the mechanical effects generated by ultrasound, which regulate neuronal excitability and firing patterns by affecting mechanosensitive ion channels and other structures [56]. Current studies suggest that this neuromodulatory effect is not primarily attributed to thermal effects, but may also involve changes in regional cerebral blood flow and modulation of neurovascular coupling [57].

At present, research on TUS in the field of CI remains in the stage of basic experiments and early clinical exploration. Optimal stimulation parameters, safety ranges, and long-term efficacy remain unclear, and further systematic studies are needed to establish how best to apply these techniques in clinical settings [58].

Non-invasive neuromodulation methods span a range of technical modalities and differ substantially in their depth of brain penetration. Despite these differences, most modulate cognitive function through overlapping mechanisms, namely the regulation of neuronal excitability, neural oscillatory activity, and synaptic plasticity. They also diverge in their spatial focality, the range of adjustable parameters, and their applicability to particular patient populations. The strength of supporting clinical evidence and data on long-term efficacy also varies considerably across techniques, warranting further investigation. Here, we systematically summarize current advances in non-invasive neuromodulation applied to different subtypes of cognitive impairment. Despite differences in upstream regulatory pathways, these NIBS modalities share several core downstream mechanisms. They can modulate neural oscillations underlying cognitive processing, enhance synaptic plasticity, including BDNF-related signaling, and strengthen functional connectivity within cognitive networks. Collectively, these changes help explain the cognitive benefits seen across multiple techniques. The approaches differ, however, in spatial focality, parameter flexibility, and the patient populations for which they are most appropriate. Key hurdles to clinical translation persist: high-quality clinical evidence remains limited, and the long-term durability of treatment effects has yet to be firmly established. In this review, we synthesize current evidence for NIBS across a range of cognitive impairment subtypes.

Applications of NIBS in different types of CI

Applications of NIBS in MCI

TMS has been widely used in patients with mild cognitive impairment, though stimulation protocols vary considerably across studies-in frequency, intensity, treatment duration, and target selection. Commonly used stimulation frequencies range from 5 to 20 Hz, with major targets including the left or bilateral dorsolateral prefrontal cortex (DLPFC); some studies also selected the precuneus or right DLPFC as stimulation targets [25, 59-63]. The recently introduced accelerated intermittent theta-burst stimulation (aiTBS) protocol has further improved intervention efficiency by increasing pulse density and shortening treatment duration [64]. Most studies have demonstrated that rTMS exerts beneficial effects on cognitive function in patients with MCI, especially memory and global cognitive performance, although some inconsistencies remain across findings.

Relevant functional neuroimaging mechanistic studies have shown that the therapeutic effects of rTMS are associated with its modulation of specific brain networks. Stimulation of bilateral DLPFC dynamically enhances connectivity within the ventral attention network and the left frontoparietal control network, whereas stimulation of the right DLPFC dynamically attenuates abnormal connectivity within the default mode network (DMN) [62]. Studies targeting the precuneus further revealed that rTMS can enhance neural activity in the precuneus and alter effective connectivity between the precuneus and medial prefrontal regions, accompanied by modulation of β-band neural oscillations [25]. These changes correlate with cognitive improvement, suggesting that rTMS may act by reducing excessive functional compensation and improving network efficiency. Accordingly, individualized brain network navigation strategies based on resting-state functional magnetic resonance imaging (rs-fMRI) have been proposed to enhance intervention precision by selecting targets according to individual functional connectivity patterns, which may also help explain the heterogeneity observed in previous study results.

Numerous studies have been conducted on tDCS in MCI. Compared with rTMS, tDCS shows relatively high consistency in key parameters such as anodal stimulation and targeting of the left DLPFC, with a stimulation intensity of mostly 2 mA, whereas treatment duration and single-session duration vary considerably. Available evidence suggests that tDCS may improve global cognition and specific domains such as memory and attention in patients with MCI [65-68]. Some studies have attempted to combine it with cognitive training; although synergistic trends have been observed in certain tasks, some randomized controlled trials have shown that the combined regimen is not significantly superior to training alone, indicating that efficacy is influenced by task type and individual differences [69]. tACS has also been gradually applied to MCI intervention in recent years [70]. Most studies adopted single-session γ-frequency stimulation (2-3 mA, 30-60 minutes), targeting mainly the DLPFC or precuneus. Results indicate that γ-tACS exerts modulatory effects on cognitive function: stimulation of the DLPFC is mostly associated with improved executive function, whereas stimulation of the precuneus tends to enhance episodic memory. Neurophysiological studies further suggest that its effects may be related to the modulation of brain rhythmic activity and cholinergic transmission [71, 72].

Studies on emerging non-invasive neuromodulation approaches - such as sensory stimulation, PBM, and focused ultrasound stimulation (FUS) - in MCI are still few. A few feasibility studies suggest that γ-frequency sensory stimulation can enhance functional connectivity within the DMN [73], while PBM may improve task-related memory performance and increase neural recruitment efficiency [74]. A recent open-label study applied navigated transcranial pulse stimulation (TPS) in patients with MCI and reported statistically significant improvements in global cognition and executive function [75]. However, most of the above studies lack controlled designs, and their efficacy and safety still require further validation in more rigorous randomized controlled trials.

Applications of NIBS in AD

TMS is the most widely used non-invasive neuromodulation technique in clinical research on AD. Multiple reviews and meta-analyses indicate that rTMS can improve global cognition and several specific cognitive functions in patients with mild-to-moderate AD, and it has a favorable safety profile [14, 76-80]. Common stimulation targets include the DLPFC, precuneus, and temporal lobe. Most protocols employ conventional high-frequency stimulation (10-20 Hz), while some studies have also used TBS paradigms. Findings vary across studies, in terms of targets, parameters, and treatment courses, suggesting that efficacy may depend heavily on individualized protocols [81].

Intermittent theta-burst stimulation (iTBS), as a more efficient form of rTMS, has shown promising potential in AD intervention. Randomized double-blind placebo-controlled trials have confirmed that accelerated iTBS targeting the left DLPFC significantly improves associative memory and multiple cognitive functions in patients, with some effects persisting into the follow-up period, accompanied by enhanced cortical excitability, β-band oscillatory activity, and frontal-hippocampal network connectivity [82].

With deeper understanding of network pathology in AD, rTMS research has gradually shifted toward individualized strategies targeting brain network hubs. Key nodes of the DMN, such as the precuneus, have become major intervention targets. Long-term stimulation can delay cognitive and functional decline and enhance local γ oscillations [83]. Furthermore, approaches based on individual functional connectivity navigation, selecting cortical nodes with the strongest connectivity to the hippocampus as targets, have shown trends toward superior efficacy compared with traditional anatomical localization [84], further supporting the clinical feasibility of network-guided individualized intervention.

In addition to TMS, TES has also been investigated for the intervention of AD. Among these techniques, tDCS has shown mild beneficial effects on global cognition and memory in multiple meta-analyses [14]. Common targets include the DLPFC and temporal lobe, and stimulation of the temporal lobe may be more effective than that of the prefrontal cortex [85]. However, the clinical effects of tDCS are generally weaker than those of rTMS [86], which may be related to its limited spatial focality and relatively nonspecific neuromodulatory mechanisms [78, 87].

tACS, especially 40 Hz stimulation protocols targeting abnormal γ-band neural oscillations in patients with AD, has gained increasing attention in recent years [33]. Systematic reviews have indicated that γ-tACS can exert an ‘entrainment’ effect on intrinsic electroencephalographic activity via exogenous rhythms, thereby regulating the functional state of related networks [88]. Randomized controlled trials have shown that although γ-tACS has limited effects on improvements in major clinical cognitive scales, it significantly enhances γ oscillations, theta-gamma coupling, and related network activity in the hippocampus, and these changes in neurophysiological markers are associated with memory and global cognitive performance. This suggests that γ-tACS exhibits clear biological signals in modulating rhythmic and network activity, whereas the stability and long-term significance of its clinical effects still require further investigation [89].

Beyond TMS and TES, other non-invasive techniques, including sensory stimulation, PBM, and TUS, have also been preliminarily explored in patients with AD. GSS may improve cognition, memory, sleep, and daily functioning in AD patients, alongside enhanced connectivity of related brain networks and reduced brain atrophy; however, its effects on amyloid-beta load have not yet been confirmed [48, 90-92]. Research into PBM remains relatively scarce. While preliminary studies have shown trends toward improvements in memory and executive function, the small sample sizes and heterogeneous protocols call for further validation in standardized trials [93, 94]. Preclinical studies of TUS have suggested that it may improve cognition by opening the blood-brain barrier and reducing amyloid-beta deposition. Although a small-sample clinical study did not detect clear transient blood-brain barrier opening on imaging, it observed improvements in immediate and recognition memory, as well as enhanced metabolic activity in the right hippocampus [95]. In addition, TPS based on ultrashort pulses has shown potential in modulating memory network connectivity and improving global cognition in an uncontrolled study [96].

Applications of NIBS in vascular cognitive impairment

In patients with VCI and post-stroke cognitive impairment (PSCI), TMS has been widely used to assess and modulate cortical excitability and related brain network functions. Previous studies have suggested that such patients commonly exhibit impaired function in the prefrontal-subcortical pathways and frontoparietal networks, reflecting compensatory adaptation of the brain to disrupted network connectivity following vascular injury [97]. Several small-sample studies have demonstrated that high-frequency rTMS targeting the DLPFC may help improve executive function, attention, and information processing speed, and its mechanisms may be related to the modulation of prefrontal-subcortical circuits and related network functions [98]. However, considerable heterogeneity exists across existing studies in stimulation parameters, target selection, and protocol design, and sufficient high-level evidence is still lacking to support the stability of efficacy and long-term benefits.

Of note, one randomized double-blind sham-controlled trial employed individualized functional magnetic resonance imaging navigation to target the frontoparietal cognitive network and applied high-dose iTBS. The results showed that high-dose iTMS was significantly superior to the standard-dose group and the sham stimulation group in improving global cognition and multiple cognitive domains including memory, attention, and executive function, with a dose-dependent effect and favorable safety [99]. This study suggests that strategies based on individualized brain network targeting combined with sufficient stimulation doses may represent an effective approach to enhance intervention outcomes in post-stroke cognitive impairment.

In addition to rTMS, tDCS has been gradually applied in rehabilitation research on PSCI. One meta-analysis found that tDCS, which is generally well tolerated, appears to support cognitive recovery after stroke by enhancing neuroplasticity [100]. Most relevant studies have combined it with cognitive training [101]. Findings suggest potential benefits for attention, memory, and executive function, though responses vary considerably across individuals, and the optimal stimulation protocol has yet to be established.

Studies of tACS in VCI/PSCI are much fewer. The evidence so far comes mainly from small-sample exploratory trials. Current research has largely focused on γ-frequency stimulation, often combined with rehabilitation training [102]. These studies suggest the approach is feasible for modulating abnormal neural rhythms and network synchronization, but its clinical efficacy still needs confirmation.

PBM has also emerged as a potential intervention. Recent evidence suggests it may promote metabolic waste clearance by improving cerebral blood flow and glymphatic function [103]. This mechanism finds support in some animal models, though clinical research in VCI/PSCI remains at an early stage.

TUS has gained increasing attention in post-stroke cognitive rehabilitation, owing to its excellent tissue penetration and precise targeting [104]. Data from existing studies indicate that low-intensity focused or pulsed ultrasound can modulate neuronal activity through mechanical effects, upregulate neurotrophic factors, and promote neuroplasticity, angiogenesis, and functional network reorganization. Animal studies and a small number of clinical trials suggest that TUS may enhance learning, memory, and executive function. However, there is still no consensus on optimal parameters and target sites, and the clinical evidence supporting its efficacy remains insufficient.

Applications of non-invasive neuromodulation in other types of cognitive impairment

Research in PD-CI has mainly focused on two techniques: rTMS and tDCS. Numerous randomized controlled studies and meta-analyses have demonstrated that TMS exerts relatively consistent beneficial effects on non-motor symptoms of Parkinson's disease, especially cognitive function [105]. Among existing intervention protocols, high-frequency TMS targeting the DLPFC shows stable efficacy for cognitive outcomes, suggesting that targeting key nodes of the central executive network may be an effective strategy for PD-CI [106]. In contrast, findings from tDCS studies are highly heterogeneous. Although early studies indicated certain improvement potential [107, 108], recent analyses suggest that its efficacy may be limited to the early stage of the disease or specific patient subgroups [109].

Studies on NIBS in DLB remain at the preliminary exploratory stage. Current evidence is mostly derived from small-sample studies involving tDCS, TMS, light therapy, and other methods. A recent systematic review indicated that these interventions may produce modest improvements in attention, several cognitive measures, and neuropsychiatric symptoms. However, the overall evidence is insufficient to support firm clinical conclusions due to widespread issues such as suboptimal methodological quality and high heterogeneity across results [110, 111].

DLB is distinguished by unique neural oscillatory abnormalities: reduced α-rhythm and increased θ/δ activity, which are closely tied to fluctuations in cognitive function. Drawing on this finding, a randomized controlled crossover trial explored rhythm-targeted intervention and found that single-session occipital α-frequency tACS enhanced visuospatial and executive function in patients, alongside physiological changes including elevated α power and diminished δ power [112]. These results suggest that such intervention may indirectly affect cholinergic system function by modulating abnormal oscillations.

In FTD, a few open-label or small-sample studies suggest TMS may improve cognitive and behavioral symptoms, but the overall evidence is limited and lacks rigorous controls [113, 114].

Evidence for tDCS in FTD is relatively stronger. Several randomized, double-blind, controlled trials have shown that tDCS targeting the prefrontal or temporal cortex can improve language ability, executive function, and behavioral symptoms, with some benefits persisting into the follow-up period [115, 116]. The underlying mechanisms may involve modulation of frontotemporal network connectivity, cortical excitation-inhibition balance, and abnormal EEG rhythms [114, 115]. Different FTD subtypes, however, appear to respond differently to neuromodulation techniques, suggesting that efficacy depends on the specific disease phenotype and the brain networks targeted.

Emerging non-invasive neuromodulation techniques-including photobiomodulation, sensory stimulation, and transcranial ultrasound-are also being explored in patient studies or clinical trials for non-AD cognitive disorders such as PD-CI, DLB, and FTD [117-120]. The field is still in its early stages, however. Most available evidence comes from feasibility studies or small-scale trials. Whether these techniques produce meaningful cognitive benefits, how they work, and whether they are safe over the long term remain open questions. Large-sample randomized controlled trials with cognitive function as a primary endpoint are needed to address these issues.

Conclusion

NIBS is non-invasive, easily repeatable, and has a strong safety profile, making it a promising intervention for research into various forms of cognitive impairment. By modulating abnormal brain network activity and enhancing neuroplasticity, it can improve performance across multiple cognitive domains, highlighting its clinical potential. However, its efficacy varies with disease subtype, stimulation target, and parameter selection, which largely explain the substantial heterogeneity in current research outcomes.

Future studies should employ well-designed, multicenter, large-sample randomized controlled trials. Such trials need to take into account disease staging and the profiles of impaired brain networks - and systematically evaluate efficacy, safety, and optimal stimulation regimens for non-invasive neuromodulation in cognitive impairment. Ultimately, the goal is to build a solid evidence foundation that can facilitate the standardized, precise clinical translation of these approaches.

Disclosure of conflict of interest

None.

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