Zhang *et al.*
*European Journal of Medical Research* (2025) 30:233
https://doi.org/10.1186/s40001-025-02493-8

European Journal
of Medical Research

REVIEW

Open Access

# Therapeutic potential and mechanisms of repetitive transcranial magnetic stimulation in Alzheimer's disease: a literature review

Xinlei Zhang[1†], Lingling Zhu[2†], Yuan Li[3], Hongna Yu[3], Tao Wang[4*] and Xiuli Chu[5*]

## Abstract

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder, affecting tens of millions worldwide with projections indicating increasing prevalence in coming decades. Characterized by progressive cognitive decline, AD manifests with varying degrees of executive, language, and visuospatial impairments that worsen over time, eventually leading to severe psychiatric symptoms, mobility difficulties, sleep disturbances, and incontinence. While pharmacological treatments remain the primary intervention approach, their efficacy often diminishes over time and may produce significant adverse effects. Repetitive transcranial magnetic stimulation (rTMS), as a non-invasive neuromodulation technique, has emerged as a promising alternative or complementary therapy. This literature review examines the therapeutic potential and mechanisms of rTMS in Alzheimer's disease. Through electromagnetic induction, rTMS can selectively modulate cortical excitability, with high-frequency stimulation (≥ 5 Hz) enhancing neural excitability and low-frequency stimulation (≤ 1 Hz) producing inhibitory effects. Recent clinical evidence demonstrates that rTMS can significantly improve cognitive function, memory, language abilities, and motor performance in AD patients, particularly when administered with optimized parameters targeting key brain regions, such as the dorsolateral prefrontal cortex. The neurobiological mechanisms underlying these effects include enhanced synaptic plasticity, increased expression of neurotrophic factors, modulation of neurotransmitter systems, and reduction of pathological protein aggregation. Meta-analyses indicate that high-frequency protocols (particularly 20 Hz) delivered over at least 3 weeks with a minimum of 20 sessions produce the most significant cognitive improvements, with effects potentially persisting for months post-treatment. Combined approaches integrating rTMS with cognitive training show particular promise through synergistic enhancement of neuroplasticity. Despite encouraging results, standardization of treatment protocols and larger clinical trials are needed to establish definitive guidelines and determine long-term efficacy. This review synthesizes current evidence supporting rTMS as an effective intervention for alleviating clinical symptoms of Alzheimer's disease while highlighting opportunities for advancing its therapeutic application.

**Keywords** Alzheimer's, Transcranial magnetic stimulation, Cognitive decline, Mechanism, Memory impairment

†Xinlei Zhang and Lingling Zhu have contributed equally to this work.

*Correspondence:
Tao Wang
immunology@163.com
Xiuli Chu
chuxiuli@sina.cn
Full list of author information is available at the end of the article

## Introduction

Alzheimer's disease is the most common neurodegenerative disorder, characterized by slow progression, neuritic plaques, and neurofibrillary tangles. Tens of millions of people worldwide currently suffer from Alzheimer's disease, with projections indicating increasing prevalence in the future, and no definitive cure exists [1]. The condition is defined by progressive cognitive decline and represents one of the most common causes of dementia. During early stages, patients typically experience varying degrees of impairment in executive function, language processing, and visuospatial skills. As the disease progresses, psychiatric symptoms gradually worsen, manifesting as apathy, social withdrawal, and other behavioral disorders. Advanced stages are marked by further deterioration, including mobility difficulties, sleep disturbances, and eventually incontinence. The late-stage progression necessitates full-time care, substantially increasing caregiving costs and creating significant challenges for patients' families and communities [2]. Clinical detection of core Alzheimer's disease biomarkers—including $\beta$-amyloid deposition, tau pathology, and neurodegeneration markers—has enabled improved classification and diagnosis of patients [3]. Pharmacological interventions remain the predominant treatment approach, with medications targeting neurometabolic function improvement, synaptic dysregulation prevention, and neuronal cell death inhibition. While these treatments can ameliorate cognitive impairment, reduce behavioral symptoms, and delay disease progression, research indicates that long-term pharmacological therapy often experiences diminishing efficacy. Moreover, complications ranging from headaches and cerebral edema to severe manifestations such as cerebral hemorrhage may occur in some cases [4]. Beyond pharmacological approaches, alternative interventions including dietary therapy, complementary medicine, and physical modalities—specifically transcranial magnetic stimulation and transcranial direct current stimulation—have demonstrated efficacy in improving Alzheimer's disease symptoms in several clinical studies [5].

Combining repetitive transcranial magnetic stimulation (rTMS) with pharmacological interventions for Alzheimer's disease demonstrates multiple advantages, including cognitive enhancement, safety and tolerability [6, 7], sustained long-term effects [8], and neuroprotective potential [9]. However, clinical implementation requires careful consideration of several factors, including variability in stimulation parameters [9, 10], disease stage-dependent efficacy [8], individualized treatment requirements, and integration with cognitive training protocols [7, 11]. Future large-scale trials are necessary to validate these preliminary findings and establish comprehensive clinical guidelines [6, 11] while also addressing potential placebo effects observed in current studies [8].

Repetitive Transcranial Magnetic Stimulation (rTMS) represents a non-invasive treatment modality that operates by generating a strong magnetic field through brief, high-intensity electric currents within a coil. This magnetic field penetrates the scalp and skull without attenuation, producing localized induced electric fields in targeted brain regions [12]. Extensive research has established the capacity of transcranial magnetic stimulation to effectively modulate cortical excitability. High-frequency transcranial magnetic stimulation (HF-rTMS, $\geq 5$ Hz) enhances local neural excitability, whereas low-frequency transcranial magnetic stimulation (LF-rTMS, $\leq 1$ Hz) produces inhibitory effects on neural activity [13]. These excitatory and inhibitory effects leverage the brain's inherent plasticity, enabling therapeutic applications across various neuropsychiatric conditions including depression, dementia, and cognitive dysfunction [14]. The clinical efficacy of transcranial magnetic stimulation has received regulatory recognition, with the FDA approving its use for treating depression, obsessive–compulsive disorder (OCD), and migraines, among other conditions. The versatility of this intervention extends to smoking cessation as well. Furthermore, individual transcranial magnetic stimulation devices can address a broad spectrum of disorders—including anxiety, emergencies, and sleep disturbances—through selective modifications of stimulation parameters and targeted anatomical sites [15].

Research indicates that rTMS serves as an effective non-invasive technique for treating Alzheimer's disease. The optimal parameters include high-frequency stimulation at 20 Hz, with stimulation durations of 1–2 s and intervals of 20–30 s between stimulations [9, 10]. Treatment protocols typically deliver a total of over 20,000 pulses across a minimum of 20 sessions conducted over at least 3 weeks [10]. The primary targets include the dorsolateral prefrontal cortex, with additional research exploring the anterior thalamus and cerebellum as potential sites [9, 16]. Regarding efficacy, rTMS has demonstrated significant improvements in cognitive and memory functions, with meta-analyses indicating moderate effectiveness [10]. These cognitive enhancements can persist for up to 2 months, although placebo effects may be present [8]. Some studies suggest that maintenance sessions conducted weekly following the initial treatment phase can further enhance symptom improvement [17].

In this paper, we reviewed the progress of research on the effectiveness of repetitive transcranial magnetic stimulation therapy for Alzheimer's disease. This comprehensive review examined several key aspects of rTMS

application in AD, beginning with the mechanism of action of transcranial magnetic stimulation therapy, including its neurophysiological effects, impact on cerebral metabolic functions, and modulatory effects on neurons. We then explored the pathophysiological dysfunctions in Alzheimer's disease and how rTMS specifically addressed these deficits. The review analyzed predictions regarding the effectiveness of rTMS therapy based on current evidence, with particular focus on optimal stimulation parameters and patient-specific factors. Safety considerations and potential adverse reactions associated with rTMS in the AD population were thoroughly discussed, followed by an examination of the synergistic potential of combining rTMS with other treatment modalities. Finally, we addressed current limitations in clinical application and explored future perspectives for advancing this promising therapeutic approach. Through this structured analysis, we aimed to provide researchers and clinicians with a comprehensive overview of the current state of knowledge and highlighted promising directions for future research and clinical implementation.

## Mechanism of action of transcranial magnetic stimulation therapy

The first transcranial magnetic stimulator capable of human application was proposed by Barker et al. in 1985. As the technology evolved, numerous transcranial magnetic stimulation devices became available for various routine diagnostic and therapeutic applications. When transcranial magnetic stimulation coils are applied to a patient's head, the generated magnetic field penetrates extracerebral tissues without attenuation, directly inducing an electric field sufficient to activate cortical nerves. This produces biological effects that are not only localized but also capable of propagating through the nervous system to generate therapeutic outcomes in regions distant from the stimulation site. The specific effects—whether excitatory or inhibitory—depend on coil type, proximity to the brain, pulse waveform, stimulation intensity, pattern, and frequency, which collectively determine the current density applied to neural tissues [18]. When a transcranial magnetic coil is positioned near the scalp, the time-varying magnetic field within the coil induces a current flowing in the opposite direction to the coil current at the brain stimulation site. This leads to neuronal depolarization, and when the intensity reaches a sufficient threshold, corresponding brain tissue stimulation occurs, generally without causing pain [19].

Currently, transcranial magnetic stimulation is employed for both studying and treating brain activity and function through two primary modalities: single-pulse transcranial magnetic stimulation (spTMS) and repetitive transcranial magnetic stimulation (rTMS). The former is predominantly utilized for investigating brain function, while rTMS induces sustained changes in brain activity. Since optical signals do not interact with magnetic effects, functional near-infrared spectroscopy (fNIRS) can be effectively utilized to measure local intravascular blood volume (BV), oxygenated hemoglobin ($HbO_2$), and deoxyhemoglobin (HHb), providing quantitative assessment of transcranial magnetic therapy effects [20]. During transcranial magnetic stimulation of the brain, the magnetic field generates electrical stimulation in the cerebral cortex, initiating neural activity that propagates through synapses to corticospinal neurons and subsequently to alpha-motor neurons. This cascade ultimately triggers motor-evoked potentials (MEPs) in target muscles, which can be measured as a direct reflection of corticospinal tract excitability [21].

Transcranial magnetic stimulation treatments are primarily categorized as excitatory or inhibitory. Excitatory effects are typically induced by high-frequency stimulation ($\geq 5$ Hz) or intermittent theta burst stimulation, while inhibitory effects result from low-frequency stimulation (1 Hz) or continuous theta burst stimulation [22]. Stimulus intensity is commonly expressed as a percentage of either resting motor threshold (rMT) or active motor threshold (AMT). The rMT represents the lowest intensity capable of inducing motor-evoked potentials exceeding a defined amplitude in half of the trials when applied to the motor cortex. Conversely, AMT refers to the lowest intensity capable of generating MEPs with amplitude at least five times greater than baseline during maintained voluntary muscle contraction. These thresholds can be assessed through visual observation of muscle twitches in either relaxed or tensed muscles (Fig. 1) [23].

### Excitatory or inhibitory stimulation of the brain by transcranial magnetic stimulation

Transcranial magnetic stimulation is classified into low-frequency stimulation ($\leq 1$ Hz) and high-frequency stimulation ($\geq 5$ Hz) based on stimulation intensity parameters. Low-frequency stimulation induces mechanisms similar to long-term depression in the brain, effectively reducing cerebral cortical excitability. This neurophysiological principle underlies the demonstrated efficacy of low-frequency transcranial magnetic stimulation in reducing seizure frequency, enhancing epilepsy treatment outcomes, and improving patients' cognitive function [24]. Conversely, high-frequency transcranial magnetic stimulation operates through long-term potentiation-like mechanisms triggered in specific brain regions. This modality stimulates the ipsilateral cerebral cortex, modulates neural circuit

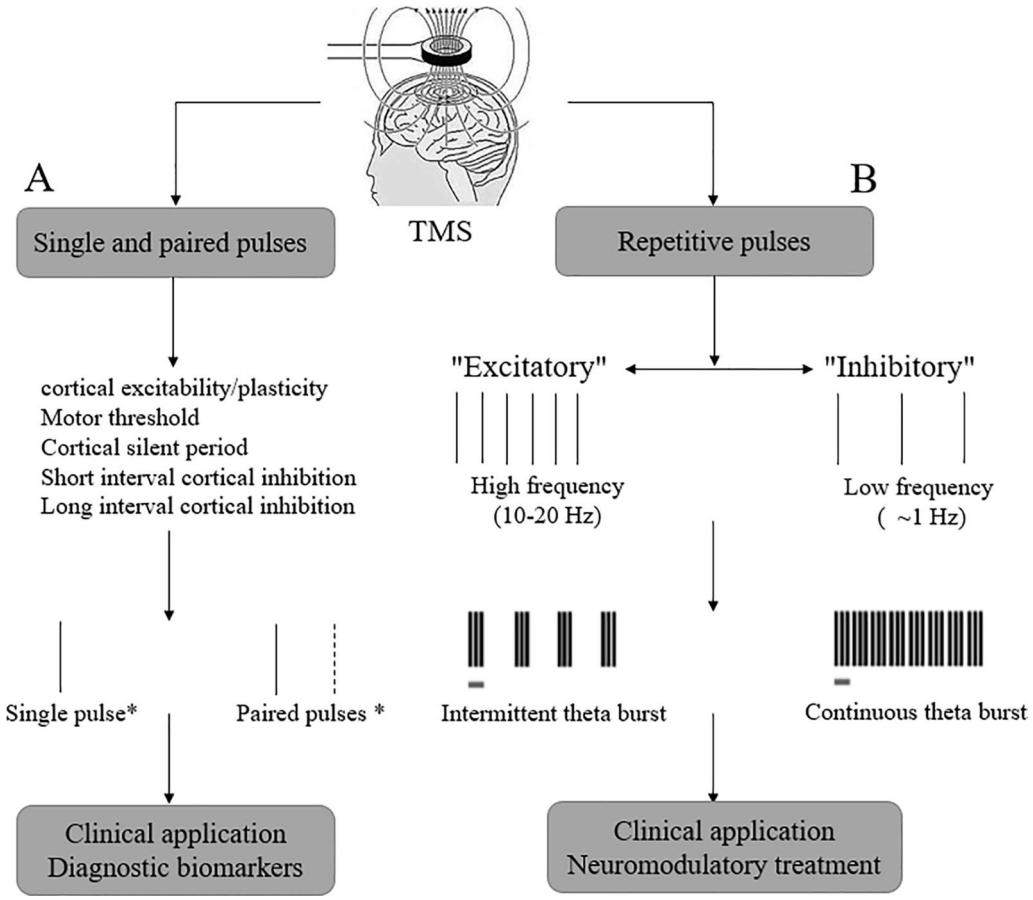


**Fig. 1** Mechanism of transcranial magnetic stimulation. **a** Paired pulse paradigm: dotted line, conditioned stimulus; Black line, test stimulus. **b** Time between gray underscores indicates the burst of three pulses at 50 Hz, and the interval between bursts is 250 ms The time between gray underscores indicates the burst of three pulses at 50 Hz, and the interval between bursts is 250 ms. The common scheme of intermittent θ burst is 2 s burst, 8 s off, and repeated in turn

excitability and connectivity, reduces blood–brain barrier permeability, promotes cerebrovascular function, inhibits neuronal apoptosis, and enhances cerebral neural activity. These neurophysiological effects render high-frequency stimulation effective in treating various conditions, including major depressive disorders, pain syndromes, cognitive impairments, and schizophrenia. Although transcranial magnetic stimulation may induce side effects, such as headache, neck pain, and sensory abnormalities, these adverse effects are typically mild and transient, establishing the overall safety profile of this intervention [25]. Within the high-frequency transcranial magnetic stimulation spectrum, frequencies between 5 and 20 Hz constitute the most extensively studied range. Excessive stimulation frequencies potentially induce seizures; therefore, 10 Hz has emerged as the most commonly employed frequency in clinical practice to ensure treatment safety and efficacy [26].

### Effects of transcranial magnetic stimulation on cerebral metabolic functions

When transcranial magnetic stimulation is applied to our head, the electric current delivered by its internal electromagnetic coil will form a strong magnetic field, which can pass through our skull without any obstruction, and induce tiny electric currents directly in the cerebral cortex, which will have a stimulating effect on the brain cells. After half an hour of transcranial magnetic stimulation treatment with 1.5 T, it can be observed that the phosphorylation level of the brain cells is significantly increased, which plays an important role in mediating the function of brain cells, affecting cell proliferation, growth, survival, and apoptosis, and also regulating neural signaling and transcription. This plays an important role in the mediation of brain cell function, affecting cell proliferation, growth, survival, and apoptosis, as well as regulating neural signaling and transcription [27].

Transcranial magnetic stimulation also detects, modulates, or restores brain activity in other forms, including specific intensities, frequencies, and modes of stimulation (paired pulses or repetitive magnetic stimulation) [28]. It is important to note that if there are metal objects near the stimulation site, such as aneurysm clips, intraocular fillings, orthopedic implants, shrapnel, etc., they may be displaced or heated during transcranial magnetic stimulation, inducing deeper stimulation that can lead to damage elsewhere, which can be borrowed from magnetic resonance imaging (MRI), and that those who meet the criteria for undergoing an MRI are generally considered safe to undergo transcranial magnetic stimulation. Those who meet the criteria for undergoing MRI are generally considered safe to undergo transcranial magnetic stimulation, and those with trauma, tumors, or infections in the brain may induce epilepsy when transcranial magnetic stimulation is performed, and these require special attention [29]. Intermittent theta Burst stimulation (ITBS) can improve depressive symptoms in patients with refractory menopause depression by administering rTMS stimulation to the left-sided DLPFC at 120% of motor threshold, 10 Hz×4 S, train intervals of 26 S, and 75 trains (37.5 min/trip), 5 times per week, for a total of 3000 pulses, for a total of 30 treatments (or up to the criterion of remission) [30].

When transcranial magnetic stimulation is applied to the head, the electric current flowing through its internal electromagnetic coil generates a strong magnetic field that penetrates the skull without obstruction, inducing localized electric currents directly in the cerebral cortex. These induced currents produce stimulatory effects on brain cells. Research has demonstrated that following 30 min of transcranial magnetic stimulation treatment at 1.5 T intensity, brain cells exhibit significantly increased phosphorylation levels. This biochemical change plays a crucial role in mediating neuronal function by influencing cell proliferation, growth, survival, and apoptosis, while simultaneously regulating neural signaling and transcriptional processes [27]. Transcranial magnetic stimulation can additionally detect, modulate, or restore brain activity through various parameters, including specific intensities, frequencies, and stimulation modes, such as paired pulses or repetitive magnetic stimulation protocols [28]. Safety considerations are paramount when administering transcranial magnetic stimulation. The presence of metallic objects near the stimulation site—including aneurysm clips, intraocular fillings, orthopedic implants, or shrapnel—presents a significant risk, as these materials may become displaced or heated during stimulation. This displacement can potentially induce unintended deeper stimulation and result in collateral tissue damage. Therefore, safety criteria similar to those employed for magnetic resonance imaging (MRI) are generally applied; patients who meet MRI safety criteria are typically considered appropriate candidates for transcranial magnetic stimulation. However, patients with brain trauma, tumors, or active infections require special consideration due to increased seizure risk during transcranial magnetic stimulation procedures [29]. Specific protocols such as intermittent theta burst stimulation (iTBS) have demonstrated efficacy in treating refractory menopausal depression. The therapeutic regimen involves administering rTMS to the left dorsolateral prefrontal cortex (DLPFC) at 120% of motor threshold, using 10 Hz frequency for 4-s durations, with 26-s intervals between train deliveries, totaling 75 trains (37.5 min per session). This protocol is typically administered five times weekly, delivering 3000 pulses per session for a total of 30 treatments, or until remission criteria are achieved [30].

### Modulatory effects of transcranial magnetic stimulation on neurons

Transcranial magnetic stimulation operates on Faraday's law of electromagnetic induction, whereby a rapidly changing magnetic field generates an induced current within adjacent conductive media. When applied to the brain—which functions as the conductive medium—this induced current stimulates neuronal cells to generate action potentials. These action potentials propagate through neural pathways, ultimately inducing movement in distal musculature [31]. Research has demonstrated that transcranial magnetic stimulation exerts multiple neuroprotective effects, including preservation of dopaminergic neuron function, reduction of glutamate-mediated excitotoxicity, and prevention of motor neuron death in amyotrophic lateral sclerosis. In addition, this intervention provides neuroprotection for pallidal GABAergic neurons, mitigates motor dysfunction, upregulates neurotrophic factors, reduces oxidative stress and neuroinflammation, and inhibits astrocytic proliferation—collectively contributing to its neuroprotective efficacy [32]. In rat models of cerebral ischemia, transcranial magnetic stimulation, particularly high-frequency protocols, activates calcium influx mediated by the *p*-Akt/GSK3β/β-catenin signaling pathway. This activation promotes neurotrophic factor release from peripheral nerve stem cells in the affected region and enhances neural stem cell proliferation, thereby reducing cerebral infarct volume [33].

### Adverse reactions and effects of transcranial magnetic stimulation therapy

Existing studies have confirmed that transcranial magnetic therapy is both safe and effective, demonstrating significant improvement in cognitive function.

However, several areas of disagreement persist in the literature. These include questions regarding the ethical implications of employing transcranial magnetic stimulation as a cognitive enhancer for healthy individuals or those with specialized needs. In addition, the long-term safety profile and sustained efficacy of transcranial magnetic stimulation require continued observation and documentation [34]. As a non-invasive neurostimulation modality, transcranial magnetic stimulation may induce certain adverse reactions. The most frequently reported adverse effect is localized discomfort at the stimulation site. This discomfort, resulting from the activation of superficial nerves and anterior muscle groups, may radiate ipsilaterally to the eyes, ears, nose, and other facial structures. These sensations are predominantly transient and typically resolve without intervention. More serious complications, though rare, include: seizures with convulsions, syncope, pain, transient psychiatric symptoms, and hearing impairment or tinnitus. To ensure patient safety during treatment administration, operators should maintain continuous observation throughout the procedure and immediately terminate stimulation upon detection of serious adverse reactions. Table 1 provides comprehensive management protocols for these potential complications [35].

## Dysfunction in Alzheimer's disease

Alzheimer's disease is a polygenic neurodegenerative disorder characterized by a progressive disease course. In early stages, behavioral and cognitive deficits manifest mildly; however, as the disease advances, central nervous system damage intensifies, precipitating the gradual emergence of diverse symptoms. Cognitive and behavioral impairments worsen progressively, with later stages marked by psychiatric manifestations and extrapyramidal symptoms. Throughout the disease trajectory, motor deficits intensify, accompanied by progressive loss of bowel control, ultimately necessitating continuous caregiving support [36]. Pathophysiological investigations have revealed that aggregation of oligomers formed by $\beta$-amyloid (Aβ) peptides triggers microglial and astrocytic hyperactivation, abnormal cerebrovascular development, cerebral hypoperfusion and hypometabolism, glial cell activation in the Alzheimer's disease brain, chronic neuroinflammation, and subsequent neuronal synaptic deterioration [37]. Despite extensive research efforts, clinically approved therapeutic interventions for Alzheimer's disease over the past three decades have been limited to cholinesterase inhibitors and NMDA receptor antagonists, both demonstrating modest efficacy. Although the US Food and Drug Administration granted conditional approval for aducanumab in 2021 for

**Table 1** Management of adverse effects associated with transcranial magnetic stimulation therapy

| Adverse reaction | Management protocol |
|---|---|
| Convulsion | ①Immediately terminate treatment. Ensure patient physical safety<br>②Assess need for first aid. Maintain open airway. Monitor vital signs<br>③Administer first aid if necessary. Transfer patient to safe position<br>④Maintain lateral position<br>⑤Document seizure start and end times<br>⑥Once patient regains consciousness, provide explanation and psychological support to patient and family |
| Fainting | ①Immediately terminate treatment. Position patient supine<br>②Monitor vital signs<br>③Assess syncope severity<br>④Document syncope duration<br>⑤Administer first aid if necessary<br>⑥Inform family that syncope is a potential complication without lasting consequences<br>⑥Advise patient on pre-treatment hydration<br>⑦Monitor blood pressure, pulse, and other physiological parameters |
| Transient Psychotic Symptoms | ①Recognize that transcranial magnetic stimulation may induce insomnia, anxiety, and agitation<br>②Employ standardized mania assessment scales for susceptible individuals<br>③Evaluate medication effects<br>④Determine whether transcranial magnetic stimulation discontinuation is warranted |
| Hearing Loss or Tinnitus | ①Assess hearing loss severity or tinnitus duration and extent<br>②Analyze potential relationship to transcranial magnetic therapy<br>③Verify integrity of hearing protection<br>④Monitor hearing loss and tinnitus progression<br>⑤Consult otolaryngologist if necessary |

Alzheimer's disease treatment, substantial controversy persists regarding its safety profile and therapeutic efficacy [38].

### Pathologic mechanisms of transcranial magnetic stimulation for Alzheimer's disease

Research has demonstrated that low-intensity pulsed magnetic field stimulation influences cytoskeletal architecture, intracellular calcium dynamics, and neural homeostasis. Repetitive transcranial magnetic stimulation (rTMS) activates regulatory mechanisms governing 5-hydroxytryptaminergic, adrenergic, and dopaminergic neurotransmitter concentrations, which collectively modulate synaptic plasticity and enhance memory function [39]. The progression and severity of Alzheimer's disease can be characterized along a biological and clinical continuum, extending from early manifestations of nominal memory deficits to advanced dementia development. Mechanistically, rTMS generates transient magnetic pulses that depolarize neurons and induce sustained alterations in cortical excitability, producing effects analogous to long-term potentiation or inhibition. Synaptic dysfunction represents a principal pathophysiological factor underlying cognitive deterioration in Alzheimer's disease. High-frequency rTMS administration induces enduring potentiation-like synaptic modifications that improve cognitive function. Furthermore, evidence indicates that rTMS enhances associative memory training efficacy and facilitates spatial reasoning generalization [40].

### Mechanism of action of transcranial magnetic stimulation in improving Alzheimer's disease

Research has established a correlation between cognitive ability and neuroplasticity in the dorsolateral prefrontal cortex (DLPFC) of Alzheimer's disease patients. Transcranial magnetic stimulation targeting this region directly excites neurons, reduces synaptic conduction thresholds, enhances synaptic activity, and increases synaptic connectivity. These mechanisms collectively improve frontal cortex transmission efficiency through enhanced synaptic plasticity. Clinical evidence indicates that 20 Hz transcranial magnetic stimulation applied to the left DLPFC significantly improves both cognitive and psychiatric symptoms in Alzheimer's patients [41]. Transcranial magnetic stimulation of the left DLPFC induces not only localized neurobiological changes but also remote effects on limbic structures, including the anterior cingulate cortex (ACC) and hippocampus. In addition, basal ganglia components such as the striatum, caudate nucleus, and nucleus accumbens are affected, resulting in dopamine release and enhanced functional neural connectivity [42].

The precuneus (PC), a critical component of the default mode network (DMN), represents another significant target for intervention. Altered DMN connectivity strongly correlates with Alzheimer's disease progression. Resting-state functional magnetic resonance imaging (fMRI) has demonstrated that the precuneus shows changes preceding cerebral atrophy, including tau pathology deposits and neuroinflammation. Repetitive transcranial magnetic stimulation (rTMS) of the precuneus strengthens connectivity between this structure and the temporal lobe cortex. Furthermore, 20 Hz rTMS increases brain-derived neurotrophic factor expression and dopamine DR4 receptors in both cerebral cortex and hippocampus, enhancing neural activity, improving memory function, and decelerating cognitive decline in Alzheimer's patients [43]. The reduction of neurotrophic factors and neurotransmitter imbalances significantly contribute to progressive cognitive deterioration in Alzheimer's disease. Animal studies have demonstrated that repetitive transcranial magnetic stimulation reverses hippocampal depletion of nerve growth factor and brain-derived neurotrophic factor (BDNF), enhances hippocampal long-term potentiation (LTP), and reduces $\beta$-amyloid (Aβ) aggregation—mechanisms that collectively improve cognitive function. Experimental evidence has confirmed these beneficial effects of transcranial magnetic stimulation on cognitive performance [44].

Additional research has demonstrated that transcranial magnetic stimulation exerts restorative effects on synaptic structure and density. Specifically, 1 Hz repetitive transcranial magnetic stimulation effectively ameliorates spatial learning and memory deficits induced by chronic rapid eye movement sleep deprivation (CRSD). The underlying mechanism appears to involve inhibition of kynurenine 3-monooxygenase (KMO), with a clear relationship established between KMO expression modulation and restoration of ultrastructural integrity in hippocampal synapses [45]. The *N*-methyl-*D*-aspartate receptor (NMDAR), a glutamate receptor crucial for synaptic transmission, synaptic plasticity, hippocampal long-term potentiation, learning, and memory, exhibits reduced expression in Alzheimer's patients. Experimental findings demonstrate that transcranial magnetic stimulation not only increases NMDAR expression but also elevates hippocampal dopamine levels and receptor concentrations while promoting vascular endothelial growth factor (VEGF) expression. These mechanisms collectively contribute to memory deficit repair [46]. Hypometabolism in the posterior medial parietal cortex serves as a validated biomarker for mild cognitive impairment (MCI). Studies demonstrate that 24 weeks of rTMS stimulation maintains cortical excitability, whereas

non-stimulated subjects exhibit significant decreases in cortical excitability as measured by TMS-evoked potentials. This research confirms rTMS's capacity to modulate mesolimbic dopaminergic circuits, thereby slowing cognitive decline progression in Alzheimer's disease [47].

#### The role of transcranial magnetic stimulation in improving motor dysfunction in Alzheimer's disease

Transcranial magnetic stimulation generates induced electric fields in the cerebral cortex that, depending on their strength, produce either excitatory or inhibitory effects. The resulting action potentials propagate through corticospinal tracts to the anterior horns of the spinal cord, subsequently activating lower motor neurons. This activation generates motor-evoked potentials and induces corresponding skeletal muscle responses or movements [48]. Upper limb motor dysfunction frequently results from imbalanced excitability between bilateral primary motor cortical hemispheres. Low-frequency transcranial magnetic stimulation effectively inhibits contralateral cerebral hemisphere cortical excitability, while high-frequency stimulation reverses ipsilateral cerebral hemisphere hyperexcitability. These modulatory effects influence corticospinal tract excitability and facilitate cerebral network remodeling, ultimately improving upper limb muscle strength and tone while promoting motor function restoration [49]. Through electrophysiological excitability regulation and enhanced cortical plasticity, high-frequency transcranial magnetic stimulation increases neural efficiency and improves motor function [50]. The resting motor threshold (RMT) serves as a comprehensive indicator of cortical, corticospinal, and spinal motor neuron excitability. Experimental investigations have demonstrated significant RMT reduction in Alzheimer's disease patients following transcranial magnetic stimulation, providing evidence of its efficacy in improving motor function [51].

#### The role of transcranial magnetic stimulation in improving speech and swallowing dysfunction in Alzheimer's disease

Verbal communication skills are fundamental to social interaction, and language impairment represents one of the most prevalent dysfunctions in Alzheimer's disease patients, emerging early in the pathological progression. Primary areas of language deterioration include fluency, naming abilities, speech component processing, and semantic knowledge comprehension. Research has demonstrated that targeted stimulation of the left dorsolateral prefrontal cortex (*L*-DLPFC) significantly enhances auditory sentence comprehension accuracy [52]. Dysphagia and swallowing weakness substantially compromise patient quality of life when they emerge. Transcranial magnetic stimulation induces cortical synaptic plasticity and increases swallowing center activation, thereby facilitating swallowing function recovery. Studies have identified 3 Hz as the optimal stimulation frequency for achieving maximal therapeutic benefit in addressing swallowing disorders [53]. Speech function progressively deteriorates as Alzheimer's disease advances. For aphasia patients, the implementation of transcranial magnetic stimulation as an adjunctive treatment modality improves and stabilizes speech function while concurrently enhancing listening comprehension capabilities to a measurable degree [54].

#### The role of transcranial magnetic stimulation in improving memory and attention deficits in Alzheimer's disease

Memory impairment constitutes one of the earliest manifestations of Alzheimer's disease. During early and intermediate disease stages, transcranial magnetic stimulation treatment enhances neural network plasticity and effectively improves patients' cognitive functions, including memory and language abilities [55]. Lesions affecting the parahippocampal gyrus, internal olfactory cortex, or portions of the perioral olfactory cortex frequently result in severe memory impairment. Transcranial magnetic stimulation targeting the hippocampal region increases synaptic excitability and consequently enhances memory capacity [56]. The dorsolateral prefrontal cortex (DLPFC) serves crucial functions in memory processing, attentional control, and problem-solving abilities. Experimental studies in rats have demonstrated that high-frequency transcranial magnetic stimulation applied to the DLPFC significantly increases brain-derived neurotrophic factor protein expression in prefrontal, hippocampal, and primary motor (M1) regions, resulting in measurable cognitive function improvement [57].

### Prediction of the effectiveness of transcranial magnetic stimulation therapy for the treatment of Alzheimer's disease

#### General efficacy and mechanisms

Transcranial magnetic stimulation, as a non-invasive extracorporeal stimulation therapy, can play a protective role for damaged cerebral blood vessels, help to improve the oxygenation of local tissues and inhibit the apoptosis of vascular endothelial cells while promoting the regeneration of nerves, helping patients to improve movement disorders, alleviate swallowing and speech disorders, and reduce anxiety, depression, and other mental symptoms [58]. In animal models of Alzheimer's disease, it was found that both low-frequency and high-frequency transcranial magnetic stimulation could help improve learning and memory depending on the frequency, with higher frequencies showing a more

pronounced improvement [59]. Studies have shown that both short-term and long-term high-frequency transcranial magnetic stimulation can help patients with Alzheimer's disease improve cognitive dysfunction, while some studies have found that low-frequency stimulation may impair cognitive function [60]. Recent meta-analyses have demonstrated that active rTMS significantly improved Mini-Mental State Examination (MMSE) scores compared to sham TMS, although the effect was not statistically significant for the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) [61]. High-frequency rTMS regimens, particularly those targeting specific brain regions, may be most effective, but the lack of standardized therapeutic protocols including stimulus frequency, intensity, and coil configuration poses a challenge to widespread clinical implementation [9]. Stimulation at 10 Hz induces inhibitory synaptic remodeling, which has a significant impact on the homeostatic structure of the entire brain. Such stimulation may initiate dynamically balanced synaptic remodeling, resulting in a loss of neuronal connectivity, which needs to be explored in further research [62].

The effectiveness of rTMS is influenced by multiple factors including patient characteristics and treatment protocols. For patients with very severe symptoms, the effect of using transcranial magnetic therapy may not be very good or even have no effect, but for patients with mild symptoms, a significant increase in the patient's neural sensitivity can be detected after treatment [63]. This is consistent with emerging evidence suggesting rTMS may be more effective in earlier stages of Alzheimer's disease. The functional connectivity of brain networks also affects treatment outcomes, with studies finding that connectivity within the executive control network (ECN) could predict cognitive improvements post-rTMS, indicating that individual brain network characteristics might determine who responds best to treatment [64]. Combining rTMS with cognitive training (rTMS–COG) has shown synergistic effects, enhancing cognitive outcomes more than cognitive training alone; this combination improved ADAS-cog scores significantly in patients with mild AD, suggesting a multimodal approach may be more effective [65]. The non-invasive nature of rTMS is associated with minimal side effects, making it a safer alternative to invasive methods like deep brain stimulation (DBS), which supports its applicability in a broader range of patients [66]. While short-term benefits are increasingly documented, the long-term effects remain less clear, with ongoing studies exploring the durability of cognitive improvements and the potential for home-based applications that could offer more accessible treatment options [67]. A significant challenge in evaluating rTMS efficacy is the methodological quality of existing systematic reviews and meta-analyses, which is often low and affects the reliability of conclusions; future studies should aim to provide more robust and scientifically rigorous data to support evidence-based clinical guidelines [11].

#### Optimal protocols and evidence from clinical studies

For stimulation frequency and intensity, high-frequency repetitive TMS (rTMS), particularly at 20 Hz, has shown efficacy in enhancing cognitive abilities in AD patients, with improvements observed in global cognitive function and memory [10, 68]. Moderate frequencies, such as 5 Hz and 10 Hz, have also demonstrated effectiveness, particularly when targeting specific brain regions, such as the left dorsolateral prefrontal cortex and bilateral cerebellums [68]. Regarding optimal treatment duration, studies suggest a minimum of 3 weeks, with sessions conducted 5 days per week, to achieve significant cognitive improvements. Some protocols extend treatment to 4 weeks, showing sustained benefits [8, 10]. At least 20 sessions are recommended to produce noticeable cognitive benefits, with improvements potentially lasting for at least 6-week post-treatment [52]. Concerning stimulation sites, the dorsolateral prefrontal cortex is a primary target for TMS in AD treatment, with evidence supporting its effectiveness in improving cognitive and behavioral symptoms [69]. Recent research also indicates that targeting the precuneus may help slow cognitive decline, suggesting stimulation of the default mode network could be beneficial [70]. Personalization of treatment protocols based on individual patient characteristics, such as disease stage and genetic traits, is increasingly recognized as important for optimizing outcomes [66].

A substantial body of clinical trial evidence now supports the efficacy of repetitive transcranial magnetic stimulation (rTMS) for improving cognitive function in Alzheimer's disease. Recent meta-analyses have provided valuable insights into the overall effectiveness of this intervention across studies with varying methodologies and patient populations. A comprehensive meta-analysis by Malo et al. found that rTMS significantly improved Mini-Mental State Examination (MMSE) scores in patients with mild cognitive impairment (MCI) and early AD, although it did not show a significant effect on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) scores, suggesting domain-specific effects of the intervention [61]. These findings align with a meta-analysis by Li et al., which reported that rTMS significantly enhances global cognitive ability and memory, with specific protocols showing particular efficacy—notably 20 Hz frequency stimulation,

multiple target sites, and a minimum of 20 sessions conducted over 3 weeks [10]. When examining combined approaches, Georgopoulou et al. systematically reviewed studies combining rTMS with cognitive and language training, finding improvements in global cognitive function and quality of life, though the authors noted that variability in rTMS parameters and cognitive training protocols necessitates cautious interpretation of results [6]. Despite the growing body of positive evidence, Hou et al. highlighted concerns regarding the methodological quality of some systematic reviews and meta-analyses, cautioning that limitations in study design and reporting could affect the reliability of conclusions about rTMS efficacy [11]].

The optimal rTMS protocol for Alzheimer's disease remains an area of active investigation, though emerging patterns from clinical trials provide some guidance. Multiple studies suggest that high-frequency stimulation, particularly at 20 Hz, demonstrates superior efficacy compared to lower frequencies, with treatment duration of at least 3 weeks and a minimum of 20 sessions showing the most consistent cognitive benefits [10]. Target selection also appears crucial, with protocols stimulating multiple brain regions, including the dorsolateral prefrontal cortex and precuneus, showing enhanced outcomes compared to single-site approaches. A large randomized controlled trial conducted by Moussavi et al. demonstrated significant cognitive improvement with active rTMS treatment, though interestingly, similar benefits were observed with sham treatment, raising important questions about potential placebo effects or the possibility that even sham stimulation may produce neurophysiological changes [8]. From a safety perspective, rTMS has consistently demonstrated favorable tolerability across clinical trials, with minimal serious adverse events reported. A systematic assessment by Andrade et al. confirmed that rTMS is generally well-tolerated with transient mild side effects, making it a viable option for patients who may not tolerate pharmacological treatments or who have shown incomplete response to standard therapies [71]. While the overall evidence supports rTMS as a promising intervention for cognitive enhancement in Alzheimer's disease, the heterogeneity in study designs, stimulation parameters, and outcome measures highlights the need for larger multi-center trials with standardized protocols to establish definitive clinical guidelines and optimize treatment approaches for different patient subgroups and disease stages.

Long-term follow-up data demonstrate that repetitive transcranial magnetic stimulation (rTMS) can sustainably enhance cognitive function in patients with Alzheimer's disease, with multiple meta-analyses confirming efficacy persistence for at least 6 weeks [10]. However, 2-month follow-up investigations have revealed cognitive improvements in both active and sham stimulation cohorts, suggesting potential placebo effects [8]. Regarding optimal therapeutic protocols, high-frequency (20 Hz) stimulation maintained for over 3 weeks, delivering a cumulative pulse count exceeding 20,000 [10], with primary targeting of the dorsolateral prefrontal cortex [9], has demonstrated superior outcomes. From a mechanistic perspective, rTMS may exert therapeutic effects through modulation of neural network dynamics [72] and neuroprotective mechanisms [9]. Despite these promising preliminary findings, methodological inconsistencies across existing studies [6, 10, 11] underscore the necessity for more rigorous, larger-scale clinical trials to definitively establish the long-term efficacy of rTMS in Alzheimer's disease treatment and to determine optimal parameter configurations for clinical implementation.

## Safety and adverse reactions of transcranial magnetic stimulation in Alzheimer's disease

### Safety profile of rTMS in Alzheimer's disease

Repetitive transcranial magnetic stimulation (rTMS) demonstrates a favorable safety profile in Alzheimer's disease treatment, with multiple studies reporting minimal serious adverse events. In a comprehensive meta-analysis of 143 studies, only four seizure-related adverse events were documented, with three deemed unrelated to rTMS and one resolved by simple coil repositioning [73]. Another systematic review confirmed almost no serious events in AD populations receiving rTMS treatment [74]. The common side effects are generally mild and transient, primarily consisting of headaches and scalp discomfort at the stimulation site, which are characteristic of rTMS procedures across all applications [73, 74]. This favorable safety profile makes rTMS particularly valuable for AD patients who may be vulnerable to side effects from pharmacological interventions.

The safety of rTMS is further supported by its demonstrated efficacy in improving cognitive functions without compromising patient well-being. Studies have shown significant improvements in memory and global cognition following treatment, with beneficial effects lasting up to 2 months [8]. The neuroprotective mechanisms of rTMS, including modulation of brain networks and cellular processes, such as synaptic plasticity and gene transcription pathways, contribute to cognitive enhancement through non-invasive means [9, 75]. When compared to traditional pharmacological treatments for AD, such as acetylcholinesterase inhibitors and NMDA receptor antagonists, rTMS has demonstrated fewer adverse events, positioning it as a potentially safer alternative for some patients [76]. Interestingly, some studies have reported similar cognitive improvements in both active

and sham rTMS groups, suggesting that placebo effects or low-level brain stimulation from sham coils might also contribute to perceived benefits, which complicates the assessment of treatment-specific effects [8].

#### Adverse reactions and risk factors

Despite its generally favorable safety profile, several adverse reactions associated with rTMS in Alzheimer's disease treatment require careful consideration. Seizures represent one of the most significant risks, particularly with high-frequency stimulation protocols. In one documented case, a patient experienced epilepsy following a 10 Hz rTMS session, which was subsequently managed by switching to a lower 0.8 Hz frequency [5]. Additional reported adverse effects include temporary cognitive changes, with some patients experiencing transient cognitive decline if stimulation parameters are not optimally suited to their individual characteristics [5]. Sleep disturbances have also been observed, with some patients reporting prolonged sleep duration following treatment, though these can often be managed by adjusting stimulation parameters [5]. The most common side effects remain transient scalp discomfort and headaches, which typically resolve quickly without specific intervention.

The likelihood and severity of adverse reactions are influenced by several key factors. Stimulation parameters, particularly frequency and intensity, play a critical role in determining safety outcomes. High-frequency stimulation ($\geq 5$ Hz) carries a greater risk of inducing seizures compared to low-frequency protocols ($\leq 1$ Hz), which may offer a safer profile but potentially different efficacy characteristics [5, 77]. Patient-specific factors significantly impact safety, including disease stage, comorbidities, age, and the presence of other neurological conditions [5]. For optimal safety in clinical implementation, standardized protocols regarding stimulation parameters, treatment duration, and maintenance schedules are needed, as the methodological quality of existing studies varies considerably [9, 10]. Regular monitoring before, during, and after treatment courses is essential for early detection and management of adverse effects, while careful screening for contraindications—such as metallic implants, history of seizures, or medications that lower seizure threshold—can help identify appropriate candidates for this intervention [9, 10].

#### Factors influencing safety and adverse reactions

The safety profile and likelihood of adverse reactions during rTMS treatment for Alzheimer's disease are influenced by multiple factors that require careful consideration in clinical practice. Stimulation parameters represent a primary determinant of both efficacy and safety outcomes. High-frequency stimulation protocols ($\geq 5$ Hz) are associated with greater seizure risk but may offer enhanced cognitive benefits, while low-frequency stimulation ($\leq 1$ Hz) typically presents a more favorable safety profile but potentially different therapeutic effects [5, 77]. The intensity of stimulation, measured as a percentage of motor threshold, also impacts safety, with higher intensities potentially increasing discomfort and risk while possibly enhancing therapeutic effects. The pattern of stimulation delivery—including continuous versus intermittent protocols and the specific brain regions targeted—further modifies both the therapeutic and adverse effect profiles of rTMS treatment in Alzheimer's patients [9, 10].

Individual patient characteristics significantly modify treatment safety profiles and must be carefully evaluated before initiating rTMS therapy. The stage of Alzheimer's disease appears particularly relevant, as patients with very severe symptoms may experience limited benefits or increased sensitivity to adverse effects, while those with mild symptoms often show more favorable responses and better tolerance [5]. Comorbidities, especially other neurological conditions, can increase vulnerability to adverse reactions, such as seizures and cognitive fluctuations. Age-related factors, including changes in cortical excitability and brain volume, may necessitate adjustments to standard protocols to maintain safety in older adults with Alzheimer's disease. Medication interactions represent another important consideration, as certain drugs commonly prescribed in this population may lower seizure threshold or otherwise interact with the neuromodulatory effects of rTMS [73, 74]. Comprehensive pre-treatment assessment addressing these factors can help optimize the safety and effectiveness of rTMS interventions for individual Alzheimer's patients.

#### Safety considerations for clinical implementation

For optimal safety in clinical implementation of rTMS for Alzheimer's disease, several key considerations must be addressed systematically. The development and adherence to standardized protocols represents a fundamental safety requirement, yet the field currently lacks consensus guidelines specific to Alzheimer's treatment. Future research should prioritize establishing clear parameters regarding optimal stimulation frequency, intensity, duration, and maintenance schedules to maximize efficacy while ensuring patient safety [9, 10]. The methodological quality of existing studies varies considerably, which affects the reliability of safety conclusions and highlights the need for more robust and scientifically rigorous data to support evidence-based clinical guidelines [11]. Comprehensive pre-treatment screening should include thorough evaluation for contraindications such as seizure history, metal implants, certain medications, and other

risk factors that might predispose patients to adverse events. Regular monitoring during treatment courses with standardized assessment tools for cognitive function, mood, and physical symptoms enables early detection and management of any emerging issues [73, 74].

The integration of rTMS into multimodal treatment approaches requires careful consideration of interaction effects with concurrent therapies. When combined with cognitive training, rTMS has shown synergistic benefits that may enhance overall outcomes while maintaining the favorable safety profile [8]. For patients receiving pharmacological interventions, potential interactions between medication effects and rTMS-induced neuromodulation should be evaluated, though current evidence suggests rTMS may offer a safer alternative with fewer adverse events compared to some medications [76]. Long-term safety monitoring remains an important area for further investigation, as the durability of both therapeutic effects and potential delayed adverse reactions requires clarification through extended follow-up studies. Patient and caregiver education regarding realistic expectations, potential side effects, and appropriate reporting procedures represents another essential component of safe clinical implementation. Through addressing these considerations systematically, clinicians can optimize the safety and therapeutic potential of rTMS in Alzheimer's disease management while minimizing the risk of adverse events [5, 8].

## Combination of TMS with other treatment modalities

The combination of transcranial magnetic stimulation (TMS) with other therapeutic approaches has emerged as a promising strategy to enhance treatment outcomes for Alzheimer's disease patients beyond what can be achieved with TMS alone. The integration of repetitive TMS (rTMS) with cognitive training has shown particularly encouraging results, with a systematic review by Georgopoulou et al. documenting improvements in global cognitive function, neurocognitive outcomes, neuropsychiatric symptoms, and quality of life in patients receiving combined intervention compared to controls, although the number of high-quality studies remains limited [6]. These findings are reinforced by a randomized, double-blind, placebo-controlled study conducted by Lee et al., which demonstrated significant cognitive enhancement in patients receiving rTMS combined with cognitive training (rTMS–COG) compared to those receiving cognitive training alone, reporting a notable 2.6-point improvement in ADAS-cog scores in the treatment group over a 24-week period [65]. A comprehensive meta-analysis by Liu et al. further confirmed that rTMS combined with cognitive training significantly improved overall cognition in AD patients compared to cognitive intervention alone, with the cognitive benefits persisting for weeks after treatment completion, suggesting durable neuroplastic changes [7]. The mechanism underlying this synergistic effect likely involves rTMS-induced enhancement of cortical excitability and neuroplasticity, creating a temporary window of enhanced learning capacity during which cognitive training can achieve more substantial and lasting effects. For optimal implementation of this combined approach, evidence suggests high-frequency rTMS should be administered immediately before cognitive training sessions, with treatment protocols typically spanning 3–4 weeks and sessions conducted 5 days per week to achieve significant cognitive improvements [8]. The dorsolateral prefrontal cortex represents a primary target for the rTMS component of combination therapy, with stimulation frequencies of 20 Hz showing particular efficacy for cognitive enhancement, although moderate frequencies (5–10 Hz) have also demonstrated effectiveness when targeting specific brain regions [10, 17].

While research on combining rTMS with pharmacological interventions for Alzheimer's disease is less extensive, there is growing interest in exploring potential synergistic effects between these treatment modalities. Benussi and Borroni have suggested that non-invasive brain stimulation techniques, including rTMS, could effectively complement pharmacological treatments by enhancing cognitive performance and potentially delaying disease progression through complementary mechanisms of action [66]. The theoretical basis for this approach involves medications increasing neurotransmitter availability or modulating specific receptor systems, while rTMS simultaneously enhances neuronal excitability and network connectivity, potentially creating synergistic effects that address multiple pathophysiological aspects of Alzheimer's disease. Despite these promising theoretical foundations, several important methodological considerations must be addressed in future research, as highlighted by Hou et al., who noted significant variability in the methodological quality across systematic reviews and meta-analyses of rTMS interventions, indicating a critical need for more rigorous studies to confirm the efficacy of rTMS in combination with other treatments [11]. An important consideration when evaluating combination therapy outcomes is the potential contribution of placebo effects, as Moussavi et al. reported cognitive improvements in both active and sham rTMS treatment groups, suggesting either a genuine placebo effect or the possibility that low-level current induction by sham coils may have neurophysiological effects that complicate the interpretation of results [8]. Patient selection represents another critical factor for combined interventions, with

evidence suggesting individuals with mild to moderate AD may derive the greatest benefit, while those with more advanced disease or a history of seizures require careful monitoring due to potentially increased risks [17]. Looking toward future directions, optimizing treatment parameters including stimulation frequency, intensity, duration, and maintenance protocols will be essential for maximizing the therapeutic potential of combined approaches, with Li et al. emphasizing the importance of clearly distinguishing the specific contributions of rTMS from those of concurrent cognitive interventions in future clinical trials [9, 10].

## Current limitations of TMS application in Alzheimer's disease

Despite the promising results, several significant limitations hinder the widespread clinical application of transcranial magnetic stimulation for Alzheimer's disease. A major challenge is the considerable variability in treatment protocols, with inconsistent parameters across studies regarding stimulus frequency, intensity, and stimulation sites, making it difficult to establish standardized treatment guidelines [9, 10]. The efficacy of TMS also shows inconsistency across clinical trials, with some studies reporting significant cognitive improvements, while others demonstrate no substantial difference compared to placebo treatments. This inconsistency is exemplified by a large multisite trial that found similar cognitive improvements in both active and sham rTMS groups, suggesting a potential placebo effect that complicates efficacy assessment [8]. The methodological quality of systematic reviews and meta-analyses on rTMS for AD is often suboptimal, reducing the reliability of conclusions drawn from these studies [11]. From a mechanistic perspective, the precise cellular and molecular pathways through which rTMS exerts its effects on the Alzheimer's brain remain incompletely understood, despite theories involving modulation of brain networks and promotion of neuroplasticity [75, 77]. Patient-specific factors further complicate clinical implementation, as treatment response may vary based on individual characteristics, such as disease stage and genetic factors, necessitating personalized approaches that are not yet well-defined [66]. In addition, while combining rTMS with cognitive training or other interventions shows promise, results remain mixed and protocols unstandardized [6]. Addressing these limitations through rigorous, well-designed clinical trials with standardized protocols and extended follow-up periods will be essential for establishing the role of TMS in routine clinical care for Alzheimer's disease.

## Future perspectives

Despite encouraging results, several important aspects of TMS therapy for Alzheimer's disease require further investigation to maximize its therapeutic potential and establish standardized clinical protocols. Future research should focus on establishing optimized stimulation parameters, including precise frequency ranges, intensity calibration methods, treatment duration, and maintenance schedules tailored to different disease stages and symptom profiles. Recent meta-analyses have identified effective protocols, including targeting single or multiple brain sites, using a frequency of 20 Hz, and conducting sessions over at least 3 weeks to significantly enhance global cognitive ability and memory [10]. Long-term efficacy and durability of TMS effects warrant extensive longitudinal studies, as current data are insufficient to determine whether benefits persist after treatment cessation, though some studies have shown cognitive improvements lasting up to 2-month post-treatment [8]. The development of personalized treatment approaches represents another critical research direction, with AI-driven personalized treatment protocols being developed to optimize patient-specific stimulation parameters, enhancing both the safety and efficacy of rTMS [78]. More sophisticated TMS devices with improved targeting precision, potentially incorporating real-time neuronavigation and multimodal neuroimaging guidance, would advance the field by ensuring accurate stimulation of intended brain regions while minimizing off-target effects. Technological advancements in rTMS devices have focused on improving coil designs and integrating brain–computer interfaces for more precise neuromodulation, which could significantly enhance therapeutic outcomes [78]. Integration of advanced neuroimaging and electrophysiological methods into routine TMS protocols has shown promise, with recent research demonstrating that rTMS can modulate neural oscillations, reducing delta and increasing theta oscillations associated with improved cognitive function in AD patients [72].

The synergistic effects of combining TMS with other treatment modalities deserve systematic investigation through well-designed factorial trials. Studies examining the combination of rTMS with cognitive training (rTMS–COG) have already shown synergistic effects, significantly improving cognitive outcomes compared to cognitive training alone [65]. Further research on interactions between TMS and various classes of cognitive-enhancing medications, specific cognitive training paradigms, lifestyle interventions, and other neuromodulation techniques could lead to more comprehensive treatment strategies that address multiple aspects of Alzheimer's pathophysiology. Large-scale, multicenter randomized controlled trials with extended follow-up periods

are urgently needed to confirm efficacy findings from smaller studies and establish TMS as a standard treatment option with clear clinical guidelines [66]. While the evidence supporting rTMS's efficacy is promising, the overall quality of systematic reviews and meta-analyses remains low, necessitating more reliable data to contribute to evidence-based medicine [11]. Economic analyses will be essential to determine the cost-effectiveness of TMS interventions compared to conventional treatments, particularly considering potential reductions in medication use and caregiver burden. A significant technological advancement with promising implications is the development of portable rTMS devices, which has expanded access to treatment by allowing for more flexible and convenient therapy options [78]. These portable technologies could dramatically increase treatment accessibility, potentially allowing for more frequent stimulation sessions without the logistical barriers of clinic visits, though substantial engineering and safety validation would be required before widespread implementation. Despite these technological advancements, challenges remain in standardizing rTMS protocols and addressing ethical considerations related to device complexity and equitable access [78]. Interdisciplinary collaboration incorporating expertise from neurology, psychiatry, biomedical engineering, and computational neuroscience will be crucial for addressing these complex research questions and translating findings into practical clinical applications that can meaningfully impact the lives of patients with Alzheimer's disease.

## Conclusion

Transcranial magnetic stimulation has emerged as a promising non-invasive therapeutic approach for Alzheimer's disease, with extensive research confirming its ability to improve cerebral vascular blood supply, promote neuronal proliferation, and reduce ongoing damage to brain tissue. The mechanisms of TMS involve direct modulation of neuronal excitability and indirect effects on neurotransmitter systems, with particular efficacy demonstrated through high-frequency stimulation of regions, such as the dorsolateral prefrontal cortex and precuneus. Multiple meta-analyses have confirmed significant improvements in cognitive measures following TMS treatment, although responses vary depending on disease stage, stimulation parameters, and individual patient characteristics. For Alzheimer's disease patients, TMS has shown efficacy in alleviating multiple symptoms, including cognitive decline, memory loss, attention deficits, speech impairments, and motor dysfunction, particularly when applied with appropriate frequency and duration protocols. The safety profile of TMS is notably favorable, with most adverse effects being mild and transient, making it suitable for patients who may not tolerate pharmacological interventions or who show incomplete response to conventional treatments. Combining TMS with other therapeutic approaches, including cognitive training and medication, has demonstrated enhanced efficacy through synergistic effects that address the complex pathophysiology of Alzheimer's disease more comprehensively. Recent clinical trials have provided stronger evidence for TMS efficacy, showing improvements in standardized cognitive assessments and functional outcomes across various stages of disease progression. The current body of evidence supports TMS as an effective treatment for alleviating clinical symptoms of Alzheimer's disease, particularly in early to moderate stages, though response patterns differ across cognitive domains and functional areas. As a safe and non-invasive treatment modality that can be precisely targeted to affected brain regions, TMS holds considerable promise for widespread clinical implementation in the multidisciplinary management of Alzheimer's disease.

**Acknowledgements**
The authors declare no competing interests.

**Author contributions**
Xinlei Zhang, Lingling Zhu, Yuan Li and Hongna Yu wrote the draft. Tao Wang and Xiuli Chu revised it.

**Funding**
The present study was funded by the Shandong Medical and Health Technology Development Fund (202,103,070,325) and the Shandong Province Traditional Chinese Medicine Science and Technology Project (M-2, 022,216).

**Availability of data and materials**
No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Competing interests**
The authors declare no competing interests.

**Author details**
[1]Department of Rehabilitation, The Second Affiliated Hospital of Shandong First Medical University, Taian 271000, Shandong, China. [2]Department of Pain Management, The Affiliated Taian City Central Hospital of Qingdao University, Taian 271000, Shandong, China. [3]Department of Rehabilitation, Taian Maternal and Child Health Hospital, Taian 271000, Shandong, China. [4]Department of Neurology, The Second Affiliated Hospital of Shandong First Medical University, Taian 271000, China. [5]Department of Neurology, Shanghai Sixth People'S Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China.

Received: 17 January 2025 Accepted: 22 March 2025
Published online: 04 April 2025

**References**

1. Zeinab B, Rafik K. Comprehensive review on Alzheimer's disease: causes and treatment. Molecules (Basel, Switzerland). 2020;25(24):5789.

2. Xiu H, Liu F, Hou Y, Chen X, Tu S. High-frequency repetitive transcranial magnetic stimulation (HF-rTMS) on global cognitive function of elderly in mild to moderate Alzheimer's disease: a systematic review and meta-analysis. Neurol Sci Off J Italian Neurol Soc Italian Soc Clin Neurophysiol. 2023;45:13–25.
3. Qiang Q, Skudder-Hill L, Toyota T, Huang Z, Wei W, Adachi H. CSF 14–3–3β is associated with progressive cognitive decline in Alzheimer's disease. Brain Commun. 2023;5(6):fcad312.
4. Sheikh M, Khan SJ, Butt HAT, Zaidi SAT, Na V. From symptomatic treatment to disease modification: a turning point in Alzheimer's disease management. Cureus. 2023;15(10): e47251.
5. Yang Z, Zhou Y. The repetitive transcranial magnetic stimulation in Alzheimer's disease patients with behavioral and psychological symptoms of dementia: a case report. BMC Psychiatry. 2023;23(1):354.
6. Georgopoulou E-N, Nousia A, Martzoukou M, Dimitriou NK, Liampas I, Messinis L, et al. Efficacy of rTMS combined with cognitive and language training in people living with Alzheimer's disease: a systematic review. Brain Sci. 2024;14(9):891.
7. Liu G, Xue B, Guan Y, Luo X. Effects of repetitive transcranial magnetic stimulation combined with cognitive training on cognitive function in patients with Alzheimer's disease: a systematic review and meta-analysis. Front Aging Neurosci. 2024;15:1254523.
8. Moussavi Z, Uehara M, Rutherford G, Lithgow B, Millikin C, Wang X, et al. Repetitive transcranial magnetic stimulation as a treatment for Alzheimer's disease: a randomized placebo-controlled double-blind clinical trial. Neurotherapeutics. 2024;21(3): e00331.
9. Zhu Y, Liao L, Gao S, Tao Y, Huang H, Fang X, et al. Neuroprotective effects of repetitive transcranial magnetic stimulation on Alzheimer's disease: undetermined therapeutic protocols and mechanisms. Neuroprotection. 2024;2(01):16–32.
10. Li S, Lan X, Liu Y, Zhou J, Pei Z, Su X, et al. Unlocking the potential of repetitive transcranial magnetic stimulation in Alzheimer's disease: a meta-analysis of randomized clinical trials to optimize intervention strategies. J Alzheimer's Dis. 2024;98(2):481–503.
11. Xue H, Li Y-X, Xiao Y-S, Fan W-H, He H-X. Repetitive transcranial magnetic stimulation for Alzheimer's disease: an overview of systematic reviews and meta-analysis. Front Aging Neurosci. 2024;16:1383278.
12. Vucic S, Stanley Chen KH, Kiernan MC, Hallett M, Benninger DH, Di Lazzaro V, et al. Clinical diagnostic utility of transcranial magnetic stimulation in neurological disorders. Updated report of an IFCN committee. Clin Neurophysiol Off J Int Fed Clin Neurophysiol. 2023;150:131–75.
13. Komatsu T, Hada T, Sasaki N, Kida H, Maku T, Nakada R, et al. Effects and safety of high-frequency rTMS in subacute ischemic stroke patients. J Neurol Sci. 2024;462: 123069.
14. Friedrich L, Simon G, Daniela E, Kostja S, Katharina K, Dietmar F. High frequency repetitive transcranial magnetic stimulation improves cognitive performance parameters in patients with Alzheimer's disease—an exploratory pilot study. Curr Alzheimer Res. 2022;9(9):681–8.
15. Faerman A, Buchanan DM, Williams NR. Transcranial magnetic stimulation as a countermeasure for behavioral and neuropsychological risks of long-duration and deep-space missions. NPJ Microgravity. 2024;10(1):58.
16. Millet B, Mouchabac S, Robert G, Maatoug R, Dondaine T, Ferreri F, et al. Transcranial magnetic stimulation (rTMS) on the precuneus in Alzheimer's disease: a literature review. Brain Sci. 2023;13(9):1332.
17. Shanok NA, Muzac S, Derbin B, Cabeza E, Rodriguez R. The effects of deep transcranial magnetic stimulation on Alzheimer's disease: a case report examining cognitive functioning, memory, and QEEG. Neurocase. 2023;29(3):81–6.
18. Lefaucheur JP, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol Off J Int Fed Clin Neurophysiol. 2014;125(11):2150–206.
19. Uzair M, Abualait T, Arshad M, Yoo WK, Mir A, Bunyan RF, et al. Transcranial magnetic stimulation in animal models of neurodegeneration. Neural Regen Res. 2022;17(2):251–65.
20. Gorban C, Zhang Z, Mensen A, Khatami R. The comparison of early hemodynamic response to single-pulse transcranial magnetic stimulation following inhibitory or excitatory theta burst stimulation on motor cortex. Brain Sci. 2023;13(11):1609.
21. Emanuele M, D'Ausilio A, Koch G, Fadiga L, Tomassini A. Scale-invariant changes in corticospinal excitability reflect multiplexed oscillations in the motor output. J Physiol. 2024;602(1):205–22.
22. Eldaief MC, McMains S, Izquierdo-Garcia D, Daneshzand M, Nummenmaa A, Braga RM. Network-specific metabolic and haemodynamic effects elicited by non-invasive brain stimulation. Nature mental health. 2023;1(5):346–60.
23. Garcia-Sanz S, Ghotme KA, Hedmont D, Arévalo-Jaimes MY, Cohen Kadosh R, Serra-Grabulosa JM, et al. Use of transcranial magnetic stimulation for studying the neural basis of numerical cognition: a systematic review. J Neurosci Methods. 2022;369: 109485.
24. Wang Z, Zhang X, Meiduo G, Song M, Wang S. Time-effectiveness of low-frequency rTMS for epilepsy and improvement in cognitive function in patients: a systematic review and meta-analysis. Epilepsy Res. 2023;199: 107277.
25. Cai M, Zhang JL, Wang XJ, Cai KR, Li SY, Du XL, et al. Clinical application of repetitive transcranial magnetic stimulation in improving functional impairments post-stroke: review of the current evidence and potential challenges. Neurol Sci Off J Italian Neurol Soc Italian Soc Clin Neurophysiol. 2023;45(4):1419–28.
26. Zhang Y, Zhang Y, Chen Z, Ren P, Fu Y. Continuous high-frequency repetitive transcranial magnetic stimulation at extremely low intensity affects exploratory behavior and spatial cognition in mice. Behav Brain Res. 2024;458: 114739.
27. Kim SK, Lee GY, Kim SK, Kwon YJ, Seo EB, Lee H, et al. Protective effects of repetitive transcranial magnetic stimulation against streptozotocin-induced Alzheimer's disease. Mol Neurobiol. 2023;61(3):1687–703.
28. Jannati A, Oberman LM, Rotenberg A, Pascual-Leone A. Assessing the mechanisms of brain plasticity by transcranial magnetic stimulation. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 2023;48(1):191–208.
29. Antczak JM, Dębowska W, Poleszczyk A, Kaźmierski J, Rymaszewska J, Waszkiewicz N, et al. Principles of patients selection and safety of repetitive transcranial magnetic stimulation-position statement of the Section of Biological Psychiatry of the Polish Psychiatric Association. Psychiatr Pol. 2022;56(6):1165–84.
30. Ikawa H, Osawa R, Takeda Y, Sato A, Mizuno H, Noda Y. Real-world retrospective study of repetitive transcranial magnetic stimulation (TMS) treatment for bipolar and unipolar depression using TMS registry data in Tokyo. Heliyon. 2024;10(5): e27288.
31. Chou YH, Sundman M, Ton That V, Green J, Trapani C. Cortical excitability and plasticity in Alzheimer's disease and mild cognitive impairment: a systematic review and meta-analysis of transcranial magnetic stimulation studies. Ageing Res Rev. 2022;79: 101660.
32. Wang N, Jia Y, Zhou X, Wang X, Zhou H, Xiao N. Effects of repetitive transcranial magnetic stimulation on pallidum GABAergic neurons and motor function in rat models of kernicterus. Brain Sci. 2023;13(9):1252.
33. Luo J, Feng Y, Hong Z, Yin M, Zheng H, Zhang L, et al. High-frequency repetitive transcranial magnetic stimulation promotes neural stem cell proliferation after ischemic stroke. Neural Regen Res. 2024;19(8):1772–80.
34. Asgarinejad M, Saviz M, Sadjadi SM, Saliminia S, Kakaei A, Esmaeili P, et al. Repetitive transcranial magnetic stimulation (rTMS) as a tool for cognitive enhancement in healthy adults: a review study. Med Biol Eng Compu. 2023;62(3):653–73.
35. McClintock SM, Reti IM, Carpenter LL, McDonald WM, Dubin M, Taylor SF, et al. Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. J Clin Psychiatry. 2018;79(1):3651.
36. Olczak A, Truszczyńska-Baszak A, Stępień A, Górecki K. Functional therapeutic strategies used in different stages of Alzheimer's disease—a systematic review. Int J Environ Res Public Health. 2022;19(18):11769.
37. Lin Y, Jin J, Lv R, Luo Y, Dai W, Li W, et al. Repetitive transcranial magnetic stimulation increases the brain's drainage efficiency in a mouse model of Alzheimer's disease. Acta Neuropathol Commun. 2021;9(1):102.
38. Yao Q, Tang F, Wang Y, Yan Y, Dong L, Wang T, et al. Effect of cerebellum stimulation on cognitive recovery in patients with Alzheimer disease: a randomized clinical trial. Brain Stimul. 2022;15(4):910–20.

39. Nouhaud C, Sherrard RM, Belmin J. Repetitive transcranial magnetic stimulation: a potential therapy for cognitive disorders? La Revue de Medecine Interne. 2017;38(3):188–94.
40. Bagattini C, Zanni M, Barocco F, Caffarra P, Brignani D, Miniussi C, et al. Enhancing cognitive training effects in Alzheimer's disease: rTMS as an add-on treatment. Brain Stimul. 2020;13(6):1655–64.
41. Li X, Qi G, Yu C, Lian G, Zheng H, Wu S, et al. Cortical plasticity is correlated with cognitive improvement in Alzheimer's disease patients after rTMS treatment. Brain Stimul. 2021;14(3):503–10.
42. Iimori T, Nakajima S, Miyazaki T, Tarumi R, Ogyu K, Wada M, et al. Effectiveness of the prefrontal repetitive transcranial magnetic stimulation on cognitive profiles in depression, schizophrenia, and Alzheimer's disease: a systematic review. Prog Neuropsychopharmacol Biol Psychiatry. 2019;88:31–40.
43. Koch G, Casula EP, Bonnì S, Borghi I, Assogna M, Minei M, et al. Precuneus magnetic stimulation for Alzheimer's disease: a randomized, sham-controlled trial. Brain A J Neurol. 2022;145(11):3776–86.
44. Choung JS, Kim JM, Ko MH, Cho DS, Kim M. Therapeutic efficacy of repetitive transcranial magnetic stimulation in an animal model of Alzheimer's disease. Sci Rep. 2021;11(1):437.
45. Zheng X, Wang R, Ma B, Zhang J, Qian X, Fang Q, et al. rTMS reduces spatial learning and memory deficits induced by sleep deprivation possibly via suppressing the expression of kynurenine 3-monooxygenase in rats. Behav Brain Res. 2024;456: 114704.
46. Bashir S, Uzair M, Abualait T, Arshad M, Khallaf RA, Niaz A, et al. Effects of transcranial magnetic stimulation on neurobiological changes in Alzheimer's disease (Review). Mol Med Rep. 2022;25(4):109.
47. D'Amelio M, Di Lazzaro V. Can transcranial magnetic stimulation rescue dopaminergic signalling in Alzheimer's disease? Brain A J Neurol. 2023;146(6):e43–5.
48. Ortega-Robles E, Cantillo-Negrete J, Carino-Escobar RI, Arias-Carrión O. Methodological approach for assessing motor cortical excitability changes with single-pulse transcranial magnetic stimulation. MethodsX. 2023;11: 102451.
49. Lv Y, Zhang JJ, Wang K, Ju L, Zhang H, Zhao Y, et al. Determining the optimal stimulation sessions for TMS-induced recovery of upper extremity motor function post stroke: a randomized controlled trial. Brain Sci. 2023;13(12):1662.
50. Zhang S, Liu L, Zhang L, Ma L, Wu H, He X, et al. Evaluating the treatment outcomes of repetitive transcranial magnetic stimulation in patients with moderate-to-severe Alzheimer's disease. Front Aging Neurosci. 2022;14:1070535.
51. Olğun Y, Aksoy Poyraz C, Bozluolçay M, Gündüz A, Poyraz B. A comparative transcranial magnetic stimulation study: assessing cortical excitability and plasticity in Alzheimer's disease, dementia with Lewy bodies and Frontotemporal dementia. Psychogeriatr Off J Jpn Psychogeriatr Soc. 2023;24:272–80.
52. Wei Z, Fu J, Liang H, Liu M, Ye X, Zhong P. The therapeutic efficacy of transcranial magnetic stimulation in managing Alzheimer's disease: a systemic review and meta-analysis. Front Aging Neurosci. 2022;14: 980998.
53. Sun M, Chen K, He Y, Zhang Y, Zhuo Y, Zhuang H. Effect of repetition of rTMS at different frequencies on the efficacy of swallowing disorders after stroke: a systematic review and meta-analysis. Medicine. 2023;102(43): e35504.
54. Sakurai Y, Abo M, Terajima S, Ikeda S, Ohara K, Hada T. Improved language function for post-stroke aphasia in the long term following repeated repetitive transcranial magnetic stimulation and intensive speech-language-hearing therapy: a case report. J Med Case Reports. 2023;17(1):285.
55. Budak M, Bayraktaroglu Z, Hanoglu L. The effects of repetitive transcranial magnetic stimulation and aerobic exercise on cognition, balance and functional brain networks in patients with Alzheimer's disease. Cogn Neurodyn. 2023;17(1):39–61.
56. San Agustín A, Crevillén D, Soto-León V, Moreno JC, Oliviero A, Pons JL. Transcranial magnetic stimulation combined with endogenous human hippocampal and motor cortical activity enhances memory. PLoS ONE. 2023;18(12): e0295413.
57. Wu Q, Xu X, Zhai C, Zhao Z, Dai W, Wang T, et al. High-frequency repetitive transcranial magnetic stimulation improves spatial episodic learning and memory performance by regulating brain plasticity in healthy rats. Front Neurosci. 2022;16: 974940.
58. Xing Y, Zhang Y, Li C, Luo L, Hua Y, Hu J, et al. Repetitive transcranial magnetic stimulation of the brain after ischemic stroke: mechanisms from animal models. Cell Mol Neurobiol. 2023;43(4):1487–97.
59. Pang Y, Shi M. Repetitive transcranial magnetic stimulation improves mild cognitive impairment associated with Alzheimer's disease in mice by modulating the miR-567/NEUROD2/PSD95 axis. Neuropsychiatr Dis Treat. 2021;17:2151–61.
60. Gu L, Xu H, Qian F. Effects of non-invasive brain stimulation on Alzheimer's disease. J Prev Alzheimer's Dis. 2022;9(3):410–24.
61. Malo PK, Ghosh A, Menon AJ, Sandhya G, Roy D, Issac TG. Effectiveness of repetitive transcranial magnetic stimulation in mild cognitive impairment and early Alzheimer's disease: a systematic review and meta-analysis. J Psychiatry Spectr. 2025;4(1):91–9.
62. Anil S, Lu H, Rotter S, Vlachos A. Repetitive transcranial magnetic stimulation (rTMS) triggers dose-dependent homeostatic rewiring in recurrent neuronal networks. PLoS Comput Biol. 2023;19(11): e1011027.
63. Anninos P, Adamopoulos A, Anninou N, Tsagas N. Analyzing the effect of weak external transcranial magnetic stimulation on the primary dominant frequencies of Alzheimer patients brain by using MEG recordings. Medicina (Kaunas). 2021;57(11):1164.
64. Geng Z, Wu Y, Liu J, Zhan Y, Yan Y, Yang C, et al. A study on the effect of executive control network functional connection on the therapeutic efficacy of repetitive transcranial magnetic stimulation in Alzheimer's disease. J Alzheimer's Dis. 2024;99(4):1349–59.
65. Lee J, Park KW, Park KW, Lee AY. Synergistic cognitive enhancement of repetitive transcranial magnetic stimulation with cognitive training in mild Alzheimer's disease: preliminary results. Alzheimers Dement. 2024;20: e086785.
66. Benussi A, Borroni B. Brain stimulation in Alzheimer's disease trials. J Alzheimer's Dis. 2024;101(s1):S545–65.
67. Vanzyl J, Zhen I, Ha K, Flores I, Taranto M, Melecio-Vazquez M, et al. The potential of non-invasive neurostimulation, tDCS for cognitive decline in Alzheimer's disease: through the lens of an ongoing clinical trial. Alzheimers Dement. 2024;20: e087482.
68. Yan Y, Tian M, Wang T, Wang X, Wang Y, Shi J. Transcranial magnetic stimulation effects on cognitive enhancement in mild cognitive impairment and Alzheimer's disease: a systematic review and meta-analysis. Front Neurol. 2023;14:1209205.
69. Yue W, Wenwei X, Xiaowei L, Qing X, Li T, Shuyan W. Adjunctive treatment with high frequency repetitive transcranial magnetic stimulation for the behavioral and psychological symptoms of patients with Alzheimer's disease: a randomized, double-blind, sham-controlled study. Shanghai Arch Psychiatry. 2015;27(5):280.
70. Koch G, Casula EP, Bonnì S, Borghi I, Assogna M, Minei M, et al. Precuneus magnetic stimulation for Alzheimer's disease: a randomized, sham-controlled trial. Brain. 2022;145(11):3776–86.
71. Andrade SM, de Oliveira Marques CC, de Lucena LC, Vieira da Costa K, de Souza IC, da Silva Machado CB, et al. Effect of transcranial direct current stimulation and transcranial magnetic stimulation on the cognitive function of individuals with Alzheimer's disease: a systematic review with meta-analysis and meta-regression. Neurol Res. 2024;46(5):453–65.
72. Velioglu HA, Dudukcu EZ, Hanoglu L, Guntekin B, Akturk T, Yulug B. rTMS reduces delta and increases theta oscillations in Alzheimer's disease: a visual-evoked and event-related potentials study. CNS Neurosci Ther. 2024;30(1): e14564.
73. Pagali SR, Kumar R, LeMahieu AM, Basso MR, Boeve BF, Croarkin PE, et al. Efficacy and safety of transcranial magnetic stimulation on cognition in mild cognitive impairment, Alzheimer's disease, Alzheimer's disease-related dementias, and other cognitive disorders: a systematic review and meta-analysis. Int Psychogeriatr. 2024;36(10):880–928.
74. Fernandes SM, Mendes AJ, Rodrigues PF, Conde A, Rocha M, Leite J. Efficacy and safety of repetitive transcranial magnetic stimulation and transcranial direct current stimulation in memory deficits in patients with Alzheimer's disease: Meta-analysis and systematic review. Int J Clin Health Psychol. 2024;24(2): 100452.

75. Ji Y, Yang C, Pang X, Yan Y, Wu Y, Geng Z, et al. Repetitive transcranial magnetic stimulation in Alzheimer's disease: effects on neural and synaptic rehabilitation. Neural Regen Res. 2025;20(2):326–42.
76. Wei N, Liu H, Ye W, Xu S, Lu C, Dai A, et al. Repetitive transcranial magnetic stimulation may be superior to drug therapy in the treatment of Alzheimer's disease: a systematic review and Bayesian network meta-analysis. CNS Neurosci Ther. 2023;29(10):2912–24.
77. Zhang S, Liu L, Zhang L, Ma L, Wu H, He X, et al. Evaluating the treatment outcomes of repetitive transcranial magnetic stimulation in patients with moderate-to-severe Alzheimer's disease. Front Aging Neurosci. 2023;14:1070535.
78. Tubbs A, Vazquez EA. Engineering and technological advancements in repetitive transcranial magnetic stimulation (rTMS): a five-year review. Brain Sci. 2024;14(11):1092.

## Publisher's Note