Research progress on Transcranial Magneto-Acoustic Coupling for Improving Cognitive Function in Prodromal AD

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Abstract

Alzheimer's disease (AD) incidence rises with aging. Early intervention in prodromal AD (proAD) is critical. Traditional cholinesterase inhibitors may accelerate cognitive decline in proAD, and novel anti-Aβ drugs show limited efficacy, highlighting the need for non-pharmacological strategies. Transcranial magneto-acoustic stimulation (TMAS) is an emerging non-invasive technique that uses focused ultrasound and a static magnetic field to deliver precise deep-brain electrical stimulation, overcoming depth-focus limitations of conventional transcranial magnetic stimulation (TMS) and transcranial ultrasound stimulation (TUS). Basic research shows that TMAS improves synaptic plasticity in AD mice by activating Piezo1 channels and regulating hippocampal neural oscillations, with synergistic effects superior to ultrasound alone. Simulations and animal studies demonstrate

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that TMAS has the potential to modulate key AD-associated brain regions, including the hippocampus and prefrontal cortex, by regulating local field potentials and restoring dysfunctional neural circuits. Multimodal imaging and neural dynamics further reveal that default mode and central executive network abnormalities in AD are closely linked to disrupted hippocampal θ oscillations, providing a mechanistic basis for target selection. Future studies should integrate multimodal neuroimaging and machine learning to elucidate TMAS-induced neural plasticity and develop individualized protocols, thereby establishing a solid theoretical foundation for clinical translation of TMAS in proAD.

Keywords: Alzheimer's disease, neuromodulation, magneto-acoustic coupling, non-pharmaceutical interventions

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder causing dementia in the elderly. According to the *China Alzheimer Report 2024*, with the accelerating aging of the population in China, the incidence and prevalence of AD have been steadily increasing, imposing a heavy economic burden and immense psychological stress on patients, families, and society[1]. The situation is extremely serious, and experts worldwide have reached a consensus that the key to AD prevention and treatment lies in early detection, early diagnosis, and early intervention[2].

Prodromal AD (proAD), as defined in the Revised Criteria for Diagnosis and Staging of Alzheimer's Disease (2024) published by the Alzheimer's Association Workgroup[3], corresponds to stage 3 of symptomatic AD. At this stage, cognitive abnormalities can already be detected through a comprehensive neuropsychological test battery, and affected individuals meet the diagnostic criteria for mild cognitive impairment (MCI). Nevertheless, they remain capable of independent living, experiencing only subtle difficulties with complex tasks, such as managing finances. Once basic daily activities become impaired, the condition advances to the dementia stage, which is further subdivided according to symptom severity into stage 4 (mild dementia), stage 5 (moderate dementia), and stage 6 (severe dementia). Importantly, the prodromal stage represents a critical therapeutic window because neuronal loss and network dysfunction have not yet reached an irreversible state. During this stage, residual synaptic plasticity and compensatory capacity remain partially preserved, providing opportunities for circuit-level intervention. Moreover, functional abnormalities, including disrupted hippocampal θ oscillations and impaired large-scale network connectivity within the default mode network (DMN), may represent reversible targets rather than permanent structural damage. Therefore, interventions capable of restoring neural dynamics and promoting synaptic remodeling may achieve greater therapeutic benefits when applied during proAD rather than later dementia stages.

Recent findings on proAD treatment indicate that patients receiving cholinesterase inhibitors experience a faster rate of cognitive decline and a 77% higher risk of progressing to AD dementia compared with non-users[4], suggesting that this classic pharmacotherapy is unsuitable for proAD. Novel anti-amyloid beta (Aβ) disease-modifying treatments (DMTs) have brought hope for early-stage AD; however, clinical observations show that although DMTs can reduce Aβ deposition in patients with stage 3 and 4 AD, the improvement in clinical symptoms remains limited. Studies have shown that in proAD, even when only MCI is detectable, up to 48% of brain cells may already be lost by the time clinical symptoms manifest[5], devastating the brain's compensatory capacity and underscoring the imperative for intervention at this prodromal stage. Beyond pharmacological therapy, novel non-pharmacological interventions for proAD are urgently required.

Transcranial magneto-acoustic stimulation (TMAS) has shown unique potential in the treatment of proAD, offering promise in overcoming the limitations of pharmacotherapy and enabling precise intervention. It is hoped that this review will facilitate the clinical translation of TMAS and lay a solid foundation for the development of neuromodulation-based non-pharmacological strategies.

Current status of neuromodulation interventions in AD

Neuromodulation is a non-pharmacological therapeutic strategy that treats disease by directly modulating aberrant neural activity. Its core principle involves applying external stimuli—such as electrical, magnetic, optical, or acoustic energy—to specific targets, thereby promoting neuroplasticity and improving brain function[6], while simultaneously probing the causal relationships between particular brain regions and relevant cognitive functions or behaviors[7]. Neuromodulation techniques can be broadly classified according to invasiveness into two categories: invasive neuromodulation, including deep brain stimulation (DBS) and epidural cortical stimulation (ECS); and noninvasive neuromodulation, such as TMAS, transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and transcranial ultrasound stimulation (TUS)[8]. In addition, these techniques can be further divided by the type of energy employed into electrical, magnetic, optical, and acoustic stimulation.

Currently, the most extensively applied modalities in AD are repetitive transcranial magnetic stimulation (rTMS), tDCS, and low-intensity transcranial electrical stimulation (tES), while newer approaches such as transcranial alternating current stimulation (tACS) and temporal interference stimulation (TIS) are emerging[9]. Among these, rTMS primarily elicits action potentials in cortical regions near the scalp and can influence connected areas; it has shown some efficacy for mild cognitive impairment (MCI) (Level B evidence, with effects lasting at least one month), yet its therapeutic effect is markedly attenuated in patients with more advanced disease stage[9,10]. tES techniques, including tDCS and tACS, are characterized by low current intensity and high portability, and have demonstrated favorable outcomes in improving cognitive function and enhancing brain network connectivity in individuals with AD and MCI[11]. For example, a double-blind, sham-controlled randomized clinical trial showed that, following 4 weeks of treatment, patients with AD-induced MCI who received 40 Hz high-definition (HD) tACS exhibited significantly greater improvements in sleep quality and cognitive function during a 2-month follow-up period compared to those who received HD-tDCS or sham stimulation[12].

In recent years, TUS has garnered considerable attention for the treatment of neuropsychiatric disorders[13–15]. Studies investigating TUS-mediated reductions of Aβ deposition and memory enhancement in animal models of AD[16], along with safety and feasibility studies in healthy participants[17], have demonstrated the technique's safety for the human brain and its potential to improve treatment efficacy in cognitive disorders such as AD. This technology employs low-intensity ultrasound energy that penetrates the skull and, through non-thermal mechanisms, reversibly stimulates and modulates nuclei in deep brain regions, thereby regulating neural activity. Owing to these properties, TUS has been proposed as a potential alternative strategy for neurodegenerative diseases, and preliminary clinical trials targeting deep brain structures have been initiated[18]. Existing animal experiments and a limited number of clinical studies suggest that TUS has potential therapeutic efficacy in AD. For instance, TUS applied to the dorsolateral prefrontal cortex, temporal cortex, subcallosal cingulate gyrus, hippocampus, and amygdala has been shown to alleviate certain AD symptoms.

Conventional noninvasive electromagnetic brain stimulation techniques are fundamentally limited by the trade-off between penetration depth and spatial focality, making it challenging to selectively modulate deep brain structures without inadvertently affecting overlying cortical regions. Direct stimulation of deep brain regions is often accompanied by strong activation of superficial cortical areas, which can lead to unintended side effects[19]. Although DBS can circumvent this issue, its applicability is limited by its high invasiveness, substantial cost, and efficacy in only a subset of patients. The neuromodulatory mechanisms of TUS have not yet been fully elucidated; existing evidence suggests the possible involvement of multiple mechanisms, including mechanical, thermal, and cavitation effects. At the clinical application level, the combined influence of these mechanisms likely underpins the neuromodulatory effects of TUS[20,21]. Therefore, the development of safer and more effective noninvasive technologies capable of precise deep brain stimulation has become an urgent priority. In this context, TMAS, as an emerging

technology, shows unique advantages in overcoming the depth-focus limitation by providing synergistic focused stimulation through both acoustic and electric fields, thus offering a promising new avenue for achieving noninvasive, precise deep brain stimulation.

Principles of TMAS and research progress in prodromal AD animal models

TMAS technology employs a focused ultrasound beam transmitted into tissue placed within a static magnetic field. The acoustic beam induces vibration of conductive particles inside the tissue; these vibrating particles experience a Lorentz force within the magnetic field, generating a focused electric field in the ultrasound focal region along the direction of the cross product of the static magnetic field and the acoustic field propagation vector (as illustrated in Figure 1). Thus, TMAS exploits the high focusability and deep penetration of ultrasound to achieve noninvasive, high-spatial-resolution, precise electrical stimulation of deep brain regions. Compared with TMS, TMAS has the potential to provide millimeter-scale (< 4 mm) precision stimulation of deep brain targets (4–10 cm), overcoming the limitation of conventional electromagnetic stimulation in accessing deep structures. Compared with TUS, which primarily induces neuromodulatory effects through mechanical interactions between ultrasound waves and biological tissues, TMAS introduces an additional electrically mediated modulation component, providing a complementary pathway for regulating neuronal excitability. Compared with tACS, which mainly produces weak and distributed electric fields that are predominantly limited to superficial cortical regions, TMAS combines ultrasound-guided focusing with electrically mediated neuronal modulation, potentially enabling more localized stimulation of deep brain structures. Compared with TUS, whose biological effects rely primarily on mechanical mechanisms with incompletely defined electrophysiological pathways, TMAS introduces a controllable electric component that may provide a more direct link to neuronal excitability regulation.Therefore, TMAS integrates the spatial precision and deep penetration capability of focused ultrasound with the electrophysiological modulation properties of electrical stimulation, providing a promising strategy for precise noninvasive neuromodulation. Table 1 compares the features of different neuromodulation techniques. TMAS can provide a powerful noninvasive tool for whole-brain precise neuromodulation in brain science and neuroscience, advancing research on brain networks[22], cognitive neuroscience, and the modulation and rehabilitation of major neuropsychiatric disorders.

The principle of TMAS is based on the magneto-acoustic coupling effect, which has been investigated for over two decades in the context of magneto-acoustic conductivity functional imaging[23–26]. This has led to the rapid development of imaging modalities such as

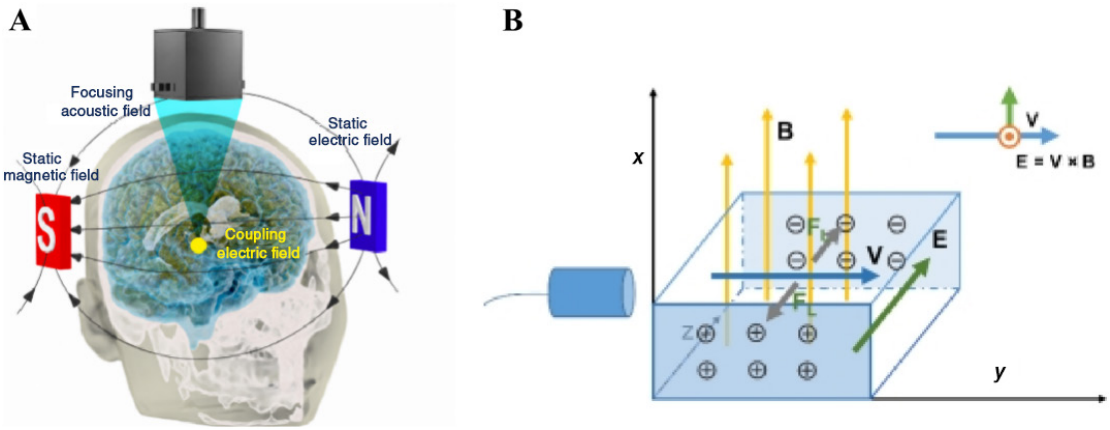


Figure 1: Schematic illustration of the principle of transcranial magneto-acoustic stimulation.

(A). Schematic representation of the TMAS system, showing focused ultrasound transmission within a static magnetic field and generation of a localized induced electric field through magneto-acoustic coupling. (B) Schematic illustration of the magneto-acoustic coupling mechanism. The static magnetic field B, ultrasound propagation vector V, and induced electric field E are indicated. The Lorentz force generates an electric field perpendicular to both B and V (please confirm).

Table 1: Comparison of different neural regulation technologies.

Technical metric	TMS	tACS/tDCS	TUS	TMAS
Physical principle	Magnetically induced electric field	Direct current-based electrical stimulation	Acoustic pressure waves	Magneto-acoustic coupling-induced electric field
Effective penetration depth	Superficial (mainly cortical regions)	Superficial	Deep (subject to skull attenuation)	Deep brain regions (focusable)
Spatial resolution	Centimeter-scale	Low, diffuse distribution	Millimeter-scale	Millimeter-scale
Key advantages	Well-established for various neuropsychiatric disorders	Portable, inexpensive, and easy to implement	High spatial precision and deep-brain targeting capability	Integrates the mechanistic advantages of electrical stimulation with the spatial precision of focused ultrasound

Note:TMS, transcranial magnetic stimulation; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; TUS, transcranial ultrasound stimulation; TMAS, transcranial magneto-acoustic stimulatio.

magnetoacoustic tomography (MAT)[23] and magneto-acousto-electrical tomography (MAET)[24], which are currently advancing[25,26]. Compared with imaging, the application of this effect for neural stimulation started relatively late and has only grown substantially over the past decade.

Although recent TMAS neuromodulation studies have been mainly conducted by Chinese research groups, the development of this technology is rooted in broader international advances in magneto-acoustic physics and focused ultrasound neuromodulation. Norton's pioneering theoretical work established the feasibility of combining focused ultrasound with electromagnetic fields for deep-brain modulation. Meanwhile, international studies on focused ultrasound neuromodulation have provided important foundations in ultrasound focusing, transcranial modeling, and safety evaluation, facilitating the further development and translation of TMAS. In 2003, Norton first proposed the idea of utilizing the magneto-acoustic coupling principle to apply the advantages of focused ultrasound to transcranial electrical stimulation and conducted basic theoretical derivations[22]. In 2006, Yang Shaohua at Zhejiang University performed spectral analyses on the electrical signals induced by ultrasound in charged gels placed in a static magnetic field, as well as on the ultrasound echo signals, providing preliminary validation of the feasibility of the ultrasonic electrical stimulation approach[27]. In 2015, Liu Zhipeng's group at the Institute of Biomedical Engineering, Chinese Academy of Medical Sciences, tested the intensity distribution and vector characteristics of ultrasonic electrical stimulation signals using copper wire samples, confirming that an induced electric field orthogonal to both the acoustic field and static magnetic field is generated in the stimulated sample and that the induced electric field distribution matches the acoustic field distribution of the ultrasound transducer[28]. In 2016 and 2017, Li Xiaoli and Yuan Yi's group performed simulation calculations of TMAS based on the Hodgkin–Huxley (H–H) and Hindmarsh–Rose neuron models, deriving stimulation parameters and providing a theoretical foundation for TMAS technology[29,30]. In 2018, Zhang Shuai's group at Hebei University of Technology improved the theoretical model of TMAS by incorporating the Izhikevich neuron model and accounting for the effect of acoustic radiation force on cell membrane capacitance, and conducted simulation calculations[31]. In 2024, Jian Xiqi's group at Tianjin Medical University extended this work by adopting the H–H model combined with cell membrane capacitance theory, using computed tomography (CT) image data to simulate the electrophysiological signals of basal ganglia neural networks stimulated by phased-array TMAS, aiming to ameliorate pathological β oscillations in Parkinson's disease[32]. Also in 2024, Zhang Liyuan's group at Beijing University of Technology constructed a biophysically based hippocampal network model and, through simulations, designed an effective TMAS parameter modulation strategy for hypersynchronous seizures, providing a theoretical basis for TMAS application in specific types of epilepsy[33]. Beyond AD, TMAS has also been investigated theoretically or experimentally in other neurological disorders, including Parkinson's disease and epilepsy,

where abnormal neural oscillations and network hyperexcitability represent major pathological features. These studies suggest that TMAS may provide a general framework for rhythm-based circuit modulation rather than being restricted to cognitive disorders. Moreover, insights from these disease models may help elucidate how TMAS regulates pathological neural synchronization and guide the development of stimulation strategies for AD-related network dysfunction. Studies in Parkinson's disease and epilepsy highlight the potential of TMAS to regulate pathological oscillations and network excitability, providing mechanistic insights that may also apply to AD, where abnormal θ and γ synchronization contributes to cognitive impairment. Moreover, these findings support the possibility that TMAS could modulate disease-related neural dynamics across different neurological conditions. In 2024, Ma Qingyu's group at Nanjing Normal University established a new magneto-acoustic coupled electric field model on the helical wavefront of a Bessel beam in a coaxial magnetic field. They performed simulations and experimental studies on the acoustic field and magneto-acoustic electric field generated by a sector-shaped planar transducer positioned in a coaxial annular magnet, utilizing a quasi-Bessel beam constructed by sawtooth phase modulation; this strategy can improve TMAS stimulation accuracy and reduce ultrasound energy[34].

In terms of stimulation technology applications, in 2016, Li Xiaoli and Yuan Yi's group found that TMAS could increase the amplitude of local field potentials in rats[35]. In 2023, Liu Zhipeng's group, based on the property that Piezo1 channels are controlled by both mechanical force and voltage, explored the effect of TMAS on synaptic plasticity in AD mice. They discovered that TMAS improved cognitive function in AD mice through the mechanosensitive Piezo1 channel, and that the improvement was superior to that achieved with TUS, thus verifying at the biological mechanism level that TMAS is a combined stimulation integrating the magneto-acoustic coupled electric field with the ultrasound field, and that this synergistic effect surpasses that of ultrasound stimulation alone[36–38]. From 2021 to 2024, Xu Guizhi and Zhang Shuai's group at Hebei University of Technology collected local field potential signals (LFPs) from the prefrontal cortex of rats during a T-maze working memory task after stimulation, investigating the influence of TMAS on γ rhythm in working memory[39]. Moreover, this group employed fiber photometry to monitor calcium ion concentrations in the mouse prefrontal cortex in real time. Results indicated that TMAS can alter calcium homeostasis in prefrontal cortical neuronal clusters, regulate their firing activity, and promote cognitive function[40]. They further found that TMAS may positively affect spatial memory in AD mice by modulating neural oscillations[41]. Notably, although TMAS has demonstrated good safety (no observed tissue damage or inflammation) and efficacy in rodent models, its translation to human applications still faces challenges including cross-species parameter calibration and the cranial bone barrier. To address this, researchers have begun developing high-performance hardware, such as a linear phased-array ultrasound excitation system reported in 2024[42], aiming to solve the problem of precise focusing beneath the primate and human skull through superior focusing capabilities and personalized simulation systems, thereby establishing the engineering foundation for the transition of TMAS from the laboratory to clinical applications[42].

Potential neural mechanisms by which TMAS improves cognitive function in proAD

TMAS, as a novel neuromodulation approach that integrates the mechanical effects of ultrasound with electrophysiological stimulation, exerts its cognitive-enhancing effects in prodromal AD through mechanisms spanning molecular, synaptic, and systems-circuit levels.

Activation of mechanosensitive ion channels and calcium signal transduction

The physical basis of TMAS lies in the micro-mechanical pressure field induced by ultrasound within brain tissue and the induced current generated in the magnetic field[43,44]. These two effects synergize to produce precise, gentle mechano-electrical stimulation in the target region. Studies indicate that mechanosensitive ion channels on the neuronal membrane, such as Piezo1, TRPV4, and TRPM7, play a key "transduction" role in this process[38,45]. The mechanical stress generated by TMAS can specifically activate Piezo1 channels, promoting the influx of extracellular calcium ions (Ca^{2+}).

Furthermore, the accompanying induced electric field can lower the activation threshold of voltage-gated calcium channels, further enhancing the intensity and duration of local calcium signals[46]. This elevation in local calcium concentration triggers downstream signaling cascades: on the one hand, calcium binds to calmodulin and activates Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), which promotes the phosphorylation and postsynaptic trafficking of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor GluA1 subunits, rapidly increasing synaptic response strength; on the other hand, calcium signals can activate the cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB)-dependent transcriptional pathway, initiating the expression of genes related to neuronal survival and synaptic remodeling[47,48]. Spanning from transient electrical activity to persistent functional modifications, this provides a complete molecular foundation for sustained neuronal excitability enhancement and altered synaptic plasticity.

Enhancement of synaptic plasticity and neurotrophin expression

Synaptic dysfunction is a direct cause of memory decline in proAD patients, typically manifested by impaired long-term potentiation (LTP) at glutamatergic synapses and abnormal dendritic spine loss[49]. TMAS stimulation can significantly upregulate the expression of brain-derived neurotrophic factor (BDNF) and its high-affinity receptor tropomyosin receptor kinase B (TrkB) in hippocampal neurons, while also enhancing the activity of downstream extracellular signal-regulated kinase (ERK)/CREB and phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathways[50]. BDNF release promotes the regeneration and maturation of dendritic spines, re-stabilizing spines originally atrophied due to Aβ toxicity, and inducing LTP. Concomitantly, the expression levels of postsynaptic density scaffold proteins (e.g., postsynaptic density protein (PSD)-95) and presynaptic vesicle proteins (e.g., synaptophysin) are notably restored, indicating improved structural integrity of excitatory synapses. By enhancing synaptic transmission efficacy at glutamatergic neurons and partially reversing the Aβ oligomer-induced suppression of N-methyl-D-aspartate receptor (NMDAR) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) function, TMAS may partially restore impaired neural connectivity in preclinical models, structurally safeguarding the recovery of cognitive function[51]. This process likely involves not only LTP enhancement but also the suppression of pathological long-term depression (LTD), driving synaptic weights back toward a physiological balance.

Neuroinflammation suppression and microenvironment modulation

Additionally, TMAS may improve the brain microenvironment by modulating the state of microglia and astrocytes. Preliminary studies have found that magnetoacoustic stimulation of appropriate intensity can induce a phenotypic shift of microglia from the pro-inflammatory M1 type to the anti-inflammatory M2 type[52,53]. This phenotypic switch is often accompanied by downregulation of the nuclear factor κB (NF-κB) signaling pathway and attenuation of NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome assembly, thereby reducing the release of pro-inflammatory cytokines (e.g., interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α)) and reactive oxygen species, while enhancing their phagocytic capacity and clearance of Aβ oligomers[54]. Meanwhile, TMAS can inhibit reactive astrocyte hyperplasia, reduce the expression of glial scar-related molecules, and render the perineuronal matrix environment more conducive to the maintenance of synaptic plasticity[55]. At the microcirculation level, the gentle mechanical effect of low-frequency ultrasound may promote the release of nitric oxide from cerebrovascular endothelium, improve local microcirculation, and accelerate glymphatic drainage, facilitating the clearance of toxic metabolites such as Aβ and tau from the brain parenchyma[56,57]. This multi-target regulatory effect, encompassing immune cell phenotype modulation, glial homeostasis restoration, and enhanced metabolic clearance, suggests the potential role of TMAS in slowing disease progression from proAD to the dementia stage of AD.

Abnormal neural mechanisms of AD revealed by multimodal imaging and neural dynamics

AD is not a homogeneous, diffuse decline in brain function; rather, it exhibits structural–functional

selective vulnerability, with specific brain regions and frequency-band-specific neurodynamic abnormalities emerging from the early disease stages. Multimodal imaging and neural dynamics studies indicate that the core structures affected earliest in the prodromal AD stage are the hippocampus and its associated network systems, including the default mode network (DMN), central executive network (CEN), and salience network (SN). Meanwhile, impaired hippocampal θ oscillation rhythmicity and reduced network synchronization efficiency are considered important neurophysiological substrates of episodic memory deficits.

By integrating structural magnetic resonance imaging, functional magnetic resonance imaging, diffusion tensor imaging (DTI), and positron emission tomography, multimodal imaging characterizes the pathological progression of AD at the structural, functional, and connectivity levels[58,59]. Existing evidence has identified the hippocampus as an early and critical region for AD pathology[60], playing a vital role in spatial navigation and memory functions. Structural magnetic resonance imaging (MRI) typically reveals cortical atrophy in the hippocampus of AD patients, which is closely correlated with individual cognitive dysfunction. Functional MRI has revealed abnormal activity patterns in the DMN, CEN, and SN in AD patients[61,62]. Among these, the hippocampus serves as a fundamental structure for encoding, storing, and retrieving information during memory processes, is closely functionally connected with the DMN, CEN, and SN, and participates in cognitive and working memory processing in AD. DTI can assess the integrity of white matter fibers. By measuring the direction of water molecule diffusion, DTI infers the orientation of white matter tracts; commonly used DTI metrics include fractional anisotropy (FA) and mean diffusivity (MD). AD patients typically exhibit reduced FA and increased MD in white matter fibers, indicating disruption of white matter structural integrity.

Neural dynamics investigates the temporal changes in nervous system activity, offering a theoretical framework for understanding the altered brain activity in AD patients. Neural dynamics models can simulate the activity of neuronal populations, explain the potential mechanisms underlying altered brain activity, and evaluate the functional connectivity strength and synchronization efficiency of brain networks. Common neural dynamics models include the neural mass model (NMM), spiking neuron model, and Kuramoto model. Abundant evidence suggests that the formation of episodic memory involves hippocampal θ oscillations[63]; θ oscillations coordinate periodic changes in excitability, thereby synchronizing spike activity across the hippocampal network without affecting the mean spike rate[64]. This synchronization of spike activity greatly amplifies information transmission above background activity and facilitates sustained access through spike-timing-dependent synaptic plasticity. In addition to the hippocampus, other brain regions closely linked to hippocampal function, such as the entorhinal cortex[65], precuneus[66], and posterior cingulate cortex (PCC)[67], are also significantly affected during the course of AD. The structural and functional abnormalities in these regions collectively contribute to the typical memory and spatial cognitive impairments in AD patients, thereby underscoring the evidence for the hippocampus and its tightly associated brain regions as powerful targets for early AD diagnosis and therapeutic intervention.

In addition to alterations in θ oscillatory activity, impaired θ–γ phase-amplitude coupling (PAC) has been increasingly recognized as an important electrophysiological hallmark of early AD. θ–γ coupling reflects the coordination between large-scale slow oscillations and local high-frequency neuronal synchronization, providing a temporal framework for organizing neuronal ensemble activity during memory encoding and retrieval. Disruption of θ–γ PAC may indicate impaired communication and coordination within hippocampal-related circuits, thereby contributing to cognitive decline in AD. Therefore, abnormalities in cross-frequency coupling provide an additional temporal dimension for understanding early AD network dysfunction and may represent a potential target for rhythm-based neuromodulation.

Thus, the structural and functional abnormalities revealed by multimodal imaging not only have diagnostic value but also provide explicit “spatial targets” for neuromodulation; the characterization of abnormal oscillatory patterns by neural dynamics, in turn, furnishes the “temporal target” basis for the design of stimulation frequency and rhythm parameters. Within this

framework, a theoretical correspondence is established between TMAS's capability for deep focused electrical stimulation and the early network abnormalities of AD.

Multimodal imaging and neural dynamics studies illuminate, from the structural, functional, and dynamical perspectives, the central role of hippocampus-related networks in prodromal AD animal models. The abnormal functional connectivity between the hippocampus and the DMN/CEN, together with disrupted θ oscillations, collectively constitute the most representative neural circuit pathological hallmark at this stage.

Perspectives

TMAS, as an emerging neuromodulation technology that integrates the high spatial resolution of ultrasound with the biological effects of electrical stimulation, has demonstrated unique physical advantages and clinical potential for improving cognitive function in AD. It can break through the depth-focus trade-off bottleneck inherent to conventional electromagnetic stimulation, precisely target deep brain regions such as the hippocampus, and achieve neuroplasticity repair by modulating neural circuit oscillations and potential molecular targets like Piezo1.

Compared with existing interventions for proAD, TMAS may provide complementary advantages by integrating deep-brain targeting capability, electrically mediated neuromodulation, and individualized parameter optimization. Unlike pharmacological approaches that primarily target molecular pathology, TMAS has the potential to modulate dysfunctional neural circuits and abnormal network activity, which may complement disease-modifying therapies by addressing circuit-level dysfunction. However, the clinical efficacy and therapeutic positioning of TMAS remain to be established through well-controlled clinical trials.

Nevertheless, TMAS remains at a critical juncture in the transition from preclinical validation to clinical translation, and future research should focus on conquering the following directions:

(1) Mechanism validation and causal verification. Current studies on Piezo1 channel-mediated neuroplasticity are largely hypothesis-driven. Future research should employ gene knockout or pharmacological blockade techniques to confirm the direct causal relationship between this mechanism and cognitive improvement, and further explore its deeper roles in Aβ clearance and immunomodulation.

(2) Safety evaluation and parameter standardization. Current research parameters (e.g., static magnetic field 0.1–1.0 T) are highly heterogeneous. To address this issue, standardized dosimetry frameworks should be established, integrating acoustic intensity, magnetic field strength, induced electric field intensity, and exposure duration to enable quantitative comparison across studies. Meanwhile, the thermal index (TI), mechanical index (MI), and potential cavitation risks under acousto-magnetic coupling should be rigorously evaluated. In addition, skull-induced acoustic aberration represents a critical challenge for the clinical translation of TMAS. Patient-specific acoustic modeling based on individual CT-derived skull morphology and acoustic properties will be essential to compensate for phase distortion, optimize phased-array stimulation parameters, and achieve reliable intracranial focusing. Furthermore, systematic assessment of thermal accumulation, mechanical effects, and long-term safety should be conducted in large-animal models before clinical translation. Establishing standardized safety guidelines will be essential for future clinical applications of TMAS.

(3) Paradigm innovation. The translational process must address the acoustic field distortion caused by the thick human skull. Given the inherent differences in hippocampal θ oscillation frequency between humans and rodents (1–8 Hz vs. 4–12 Hz), stimulation parameters should be recalibrated based on human electrophysiological characteristics rather than directly translated from animal models. Furthermore, non-human primate models should be introduced, and complex cognitive assessment paradigms covering executive function and verbal memory should be developed to bridge the gap between animal models and clinical efficacy.

(4) Standardization and multicenter validation. Establishing standardized stimulation protocols, including

acoustic intensity, magnetic field strength, induced electric field dosage, target selection, and treatment schedules, will be essential for reproducible clinical translation. Moreover, well-designed multicenter randomized controlled trials (RCTs) with standardized outcome measurements, consistent stimulation protocols, and long-term follow-up are required to establish clinical evidence and determine the therapeutic efficacy of TMAS across heterogeneous patient populations.

In summary, TMAS holds the promise of achieving the deep integration of "spatial precision" and "temporal precision" through imaging guidance, providing a novel noninvasive precise neuromodulation strategy for early intervention in AD.

Author contributions

Zhu Kai and Li Ruixian reviewed the literature and drafted the manuscript. Zhang Wei, Tao Fengli, Yang Jie, Guo Yuyan, Liu Xu, Chu Fangxuan, Liu Ruixu, Zhou Xiaoqing, Ma Ren, Wang Hao, Zhang Shunqi, Zhang Xiyang, and Yin Tao contributed to literature collection and manuscript revision. Liu Zhipeng and Han Ying provided critical comments, supervised the work, and revised and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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Ethics statement

Not applicable.

Data availability statement

No datasets were generated or analyzed for this work.

AI statement

The authors declare that no generative artificial intelligence (AI) or AI-assisted technologies were used in the preparation, analysis, writing, image generation, or image processing of this manuscript.

Conflicts of interest

Author Zhipeng Liu serves as a member of the Editorial Board of this journal. They were not involved in the editorial review or decision-making process for this manuscript. All editorial decisions were made independently by other members of the Editorial Board who have no conflicts of interest.

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