

A Review of Emerging Neuromodulation Therapies for Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is the most common form of dementia, primarily affecting the elderly. It is currently understood to be driven by the accumulation of β -amyloid ($A\beta$) plaques and tau protein tangles in the brain, leading to neuronal death. Currently, the most common and well-established treatment remains pharmacotherapy, years of clinical trials have demonstrated its efficacy, yet its high cost cannot be overlooked. Nowadays, with the advancement of physical modulation technologies, an increasing array of emerging techniques are steadily expanding their applications into the field of neuromodulation, including transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS), optical neuromodulation technologies, transcranial focused ultrasound (tFUS), gamma band oscillation stimulation technology. This review discusses development status and application fields of different techniques, containing clarifying the working principles, comparing advantages and disadvantages and provide an outlook on the treatment of Alzheimer's disease.

Keywords: Alzheimer's Disease; Neuromodulation Therapies; Noninvasive Physical Stimulation; Gamma Band Oscillation.

1. Introduction

Currently, there are approximately 50 million Alzheimer's disease (AD) patients globally, with this number expected to double every 5 years and reach 152 million by 2050. Additionally, the global annual cost of AD is estimated at US\$1 trillion [1]. To date, the recognized core pathology of AD is the deposition of $A\beta$ in the brain, which triggers hyperphosphorylation of tau and formation of neurofibrillary tangles, leading to synaptic dysfunction and neuronal death [2,3.] According to the Figure 1, it is clear to detect the difference between normal brain and AD disease brain [4].

In terms of treatment, pharmacological approaches have long been the mainstay. Pharmacological treatments approved by the FDA for AD's cognitive symptoms include acetylcholinesterase (AChE) inhibitors and the noncompetitive *N*-methyl-d-aspartate (NMDA) antagonist memantine, which only alleviate symptoms [5]. Recent research focuses on altering the progression of AD by targeting $A\beta$ and tau pathologies [6]. Beyond pharmacology, neuromodulation has emerged as a promising area. Numerous neuromodulation techniques based on neuroplasticity exist: invasive ones like transcranial magnetic stimulation (TMS), transcranial direct/alternating current stimulation (tDCS/tACS). These deliver electricity, sound, light, or magnetism to restore brain functions. Nowadays, the neuromodulation techniques combine with artificial-intelligence (AI) computing for further development. Neuromodulation is evolving from open-loop to closed-loop, with brain-machine interactive strategies enabling real-time sensing, processing, and stimulation, which demonstrates the boundless prospects of technology in the field of brain science research [7]. This review discusses the different treatments of AD and mainly summarizes the development of neuromodulation techniques, particularly the gamma band oscillation stimulation technology, including biological mechanisms and modulation techniques.

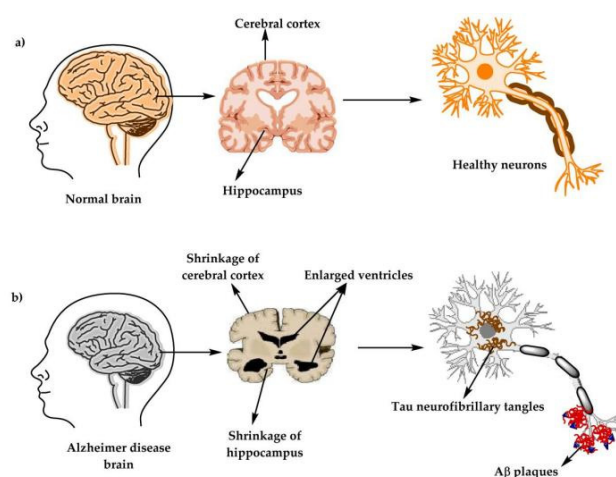


Figure 1. The image contrasts a normal brain, with a healthy cerebral cortex, hippocampus, and neurons, and an AD brain, which shows shrinkage of the cerebral cortex and hippocampus, enlarged ventricles, and neurons affected by tau neurofibrillary tangles and $A\beta$ plaques.

2. The Historical Development of Neuromodulation Technologies

At present, most neurological disorders are still managed with long-term, non-curative pharmacologic or biologic agents, or by creating focal lesions to relieve symptoms. Neuromodulation, however, can precisely target dysfunctional brain regions or networks and restore function through targeted stimulation [8]. In essence, neuromodulation uses physical (electricity, light, magnetism, etc.) or chemical stimulus means to alter nervous system signaling, modulate neurons or neural networks, and change brain functions. Notably, it induces both rapid local changes and sustained effects like synaptic plasticity [9]. Thus, it is key for studying neural circuits and treating neurological disorders.

2.1. Chemical Modulation Techniques

In AD therapy, chemical neuromodulation presents both advantages and drawbacks. Currently approved

cholinesterase inhibitors curb AChE-mediated ACh breakdown, raising ACh levels and enhancing cholinergic transmission, while NMDA receptor antagonists block excessive NMDA activation, curbing glutamate-mediated excitotoxicity and thereby protecting neurons and improving cognition and behavioral symptoms [10]. Yet these agents only alleviate symptoms and cannot cure the disease. More troubling, most AD drug trials launched in the past decade have failed, driving research toward new mechanisms such as aberrant tau metabolism and A β accumulation [4]. Over the past decade, immunotherapy has advanced rapidly, these agents, including monoclonal antibodies and molecules, stimulate the patient's own immune system, which are designed to reduce A β levels in the brain [12]. Aducanumab, a human IgG1 antibody, binds aggregated β -amyloid (oligomers/fibrils) via amino acids 3–7, reducing brain amyloid plaques and, in some, hyperphosphorylated tau. However, not all such antibodies succeed: bapineuzumab's clinical program was terminated for lacking effect [13]. Thus, immunotherapy shows promise for AD but faces lingering challenges.

2.2. Physical Modulation Techniques

Looking back at history, the development of neuromodulation technology is closely related to electricity. Its earliest origin can be traced back to 15 A.D., when the ancient Romans used the electric discharge of electric rays to treat chronic pain [14]. However, due to insufficient understanding of electricity, this primitive therapy persisted for over a thousand years [15]. From the late 18th century to the early 19th century, the "mystery veil" of electricity was lifted, and scholars began to attempt electrical stimulation of the nervous systems of animals and humans [16]. In 1884, Victor Horsley, the "father of functional neurosurgery," conducted the first intraoperative cortical electrical stimulation research [17]. In the first half of the 20th century, scholars such as Cushing and Penfield applied intraoperative electrical stimulation to locate cortical functional areas [18,19]. In 1947, Spiegel and Wycis invented the stereotactic head frame for the human brain, which greatly improved the safety and accuracy of deep brain surgery [20]. In 1967, spinal cord stimulation (SCS) based on the "pain gate theory" came into being, marking the birth of modern neuromodulation technology [21]. In addition to electrical stimulation, optical therapy is also an important branch. It relieves or treats diseases through light irradiation and is a non-invasive or minimally invasive method.

In 1903, Danish scientist Niels Finsen won the Nobel Prize for treating lupus erythematosus with red light, opening the chapter of optical therapy. In 1967, Hungarian scientist Endre Mester discovered the biological stimulation effect of 694 nm ruby laser, promoting the development of "low-dose laser therapy" [22]. Nowadays, optical therapy has formed three major technical systems. Recent studies have shown that it can regulate the activity of neurons and microglia and slow down the progression of neurodegenerative diseases [23].

Neuromodulation in the electromagnetic field is also based on classical theories. In 1831, Faraday put forward the principle of electromagnetic induction and conversion, laying the foundation for TMS. The TMS device generates a magnetic field through the transient current in the stimulation coil, which penetrates the skull and is converted into an induced current to change the activity of neurons [24]. In 1985, Barker et al. reported the first case of myoelectric

signals induced by TMS stimulation of the motor cortex [25]. Over the next 30 years, TMS developed into a mature technology and was widely used in disease diagnosis and treatment.

2.3. Emerging Neuromodulation Technologies

A frontier direction in closed-loop neuromodulation is developing lightweight, battery-free wireless devices for recording and modulating neural activity [25]. Pre-clinical evidence, such as closed-loop optogenetics with real-time signal processing, has shown potential in interrupting seizures in freely moving animals, with such conditional operation enabling precise, patient-specific treatments [26]. The closed-loop system can analyze neurobiological markers (such as local field potentials in the subthalamic nucleus) and predict behaviors or symptoms based on recorded brain activity, and these predictions can be used to control devices or deepen the understanding of the relationship between the brain and diseases [27]. These closed-loop systems allow for real-time, context-specific stimulation adjustments to reduce symptom burden. Meanwhile, Machine learning (ML) has become an important component in the design of these closed-loop systems, as ML models can predict or identify the presence of disease symptoms based on neural activity and adaptively learn to regulate stimulation [28]. Figure 2 mentioned as follow illustrates the working principle and technical framework of the closed-loop neuromodulation system [7]

3. Traditional Physical Neuromodulation Technologies

3.1. TMS

TMS is a non-invasive technology based on Faraday's law of electromagnetic induction: strong magnetic field pulses generated by a metal coil penetrate the skull, induce electric currents in the cortex, alter the membrane potential of neurons, generate action potentials, and thereby affect central nervous system functions [29]. Its biological effects are frequency-dependent—high-frequency (>1Hz) stimulation enhances cortical excitability, while low-frequency ($\leq$ 1Hz) stimulation reduces it, which may be related to synaptic long-term potentiation or long-term depression. Additionally, it influences neurotransmitter release, as well as receptor and gene expression [30]. In terms of applications, in scientific research, TMS can be used to detect nerve conduction function (e.g., obtaining physiological parameters through motor evoked potentials), localize cortical functions, or be combined with **functional magnetic resonance imaging (fMRI)** to study brain networks [31]. In clinical practice, repetitive transcranial magnetic stimulation (rTMS) has significant efficacy in treating depression and migraine, can improve motor dysfunction after stroke, and shows potential in fields such as Parkinson's disease [32–34]. Its advantages include non-invasiveness, simple operation, and high safety [35,36], but it has limitations such as limited stimulation depth, insufficient spatial resolution, large individual differences in efficacy, and an incompletely clarified mechanism of action [37]. The development context and related equipment of TMS technology from its biological origins to practical applications are illustrated in Figure 3 [38].

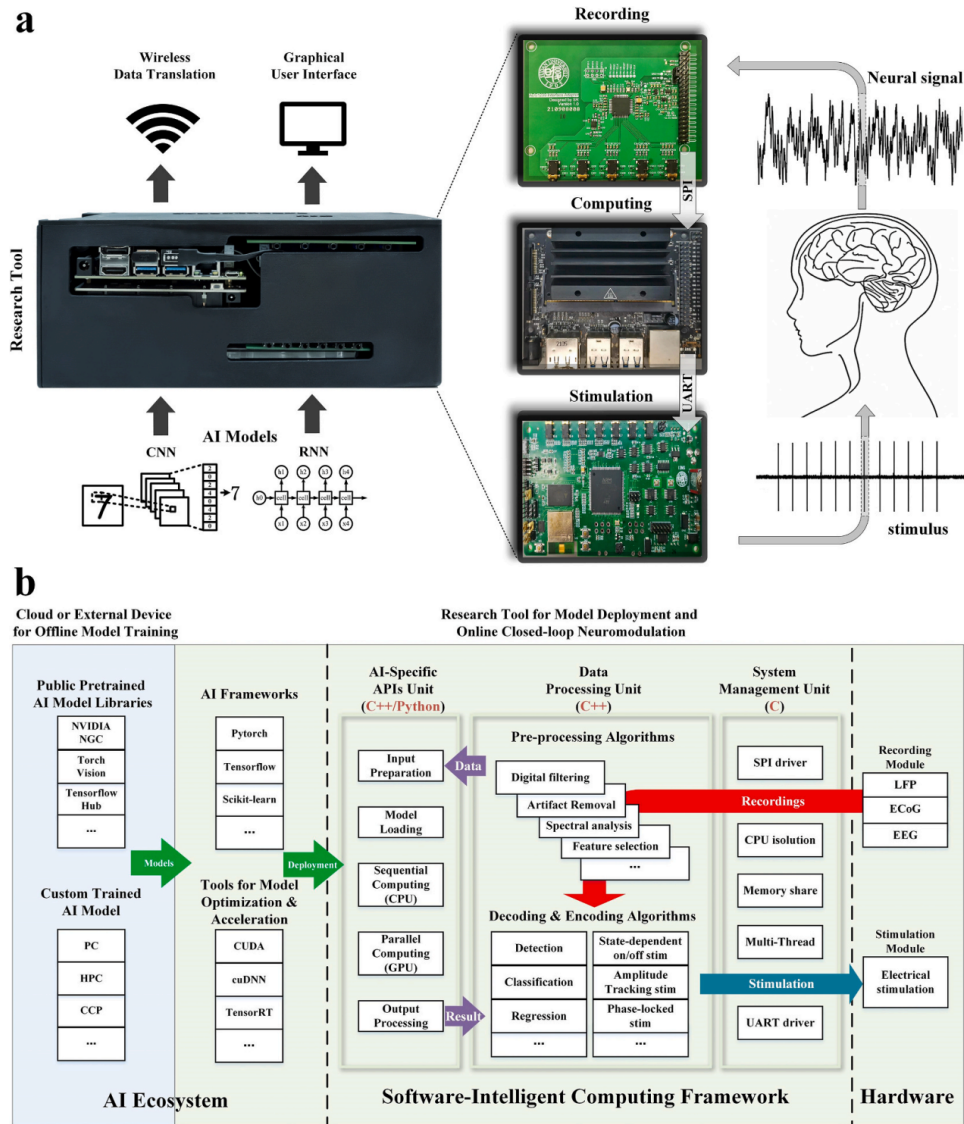


Figure 2. The image illustrates a comprehensive system for neural modulation, encompassing hardware for recording neural signals and delivering stimuli, along with a software - intelligent computing framework that integrates AI models and algorithms for data processing, all enabling closed - loop neuromodulation

3.2. tDCS / tACS

tDCS and tACS are both non-invasive brain stimulation technologies. tDCS applies a constant low-intensity direct current (0.5-2.0mA) through anode and cathode placed on the scalp. Anodal stimulation depolarizes neurons and increases cortical excitability, while cathodal stimulation hyperpolarizes neurons and reduces cortical excitability [39]. Its effects are related to current intensity, stimulation duration, as well as electrode size and placement. tACS, on the other hand, applies alternating current to the scalp, generating oscillating electric fields in the brain, which affects the timing of neuronal firing and further alters the power of local neural oscillations and coherence across frequencies and regions [40]. As illustrated in Figure 4 [41], The biological effects and mechanisms of tDCS and tACS are mainly reflected in the regulation of neuronal excitability, changes in neurotransmitter release, and influences on neural plasticity. For example, the long-term effects of tDCS may involve synaptic pathways similar to long-term potentiation and long-term depression through glutamatergic synapses [42], while tACS affects cognitive performance by regulating single or nested brain rhythms, local or long-distance synchronization, and metabolic activities [43]. In terms of scientific research

and clinical applications, both tDCS and tACS show broad application prospects. tDCS can be used to improve cognitive functions in healthy people, such as attention and working memory [44]. In patients with attention deficit hyperactivity disorder (ADHD), tDCS has a certain improvement effect on symptoms of inhibitory control and inattention [45]. In addition, tDCS also shows potential in the rehabilitation treatment of stroke patients, such as improving post-stroke motor dysfunction, cognitive impairment, pain, and depression [46,47]. tACS has potential in regulating neural activity and behavior, and customized stimulation targeting abnormal neural oscillations has shown positive results in alleviating psychiatric and neurological symptoms [48]. tDCS and tACS technologies have advantages such as non-invasiveness, simple operation, and high safety, but they have certain limitations in terms of stimulation depth and spatial resolution [49]. Nevertheless, with the continuous improvement and optimization of technologies, such as the development of new stimulation electrodes and the improvement of electrode configurations [50], the application prospects of tDCS and tACS in neuroscience research and clinical treatment remain broad.

3.3. Optical Neuromodulation Technologies

Optical neuromodulation technologies mainly include optogenetics and brain function imaging and neuromodulation technologies based on near-infrared light [51]. The former involves introducing photosensitive protein genes into nerve cells through viral vectors, and then using light of a specific wavelength to stimulate them to achieve precise regulation—neurons expressing cation channel proteins are excited after stimulation, while those expressing anion channel proteins are inhibited, and the co-expression of the two types of proteins enables bidirectional regulation [52]. The latter uses near-infrared light to penetrate brain structures, act on mitochondrial cytochrome oxidase, promote metabolism, and increase Adenosine Triphosphate (ATP) production [50]. In terms of applications, optogenetics can activate specific neurons to study neural circuits (such as improving memory in AD mice), and light stimulation of specific brain regions can also clarify the causal relationship

between neural activities and behaviors. It has entered clinical trials for retinal diseases and other conditions, while near-infrared light technology is used in the treatment of mental illnesses and the rehabilitation of neurological diseases (Figure 5) [54-56]. The advantages of these technologies lie in the high spatiotemporal resolution of optogenetics and the non-invasiveness of near-infrared light. However, optogenetics has issues with the safety of viral transfection, and near-infrared light is affected by penetration depth as well as the scalp and skull [57,58]. In the future, the optimization of photosensitive proteins and the advancement of gene editing technologies will enhance the effectiveness of optogenetics; the development of optical imaging and light source technologies will improve the resolution and penetration depth of near-infrared technologies [59], providing more powerful tools for brain science research and clinical practice.

3.4. Transcranial Focused Ultrasound (tFUS)

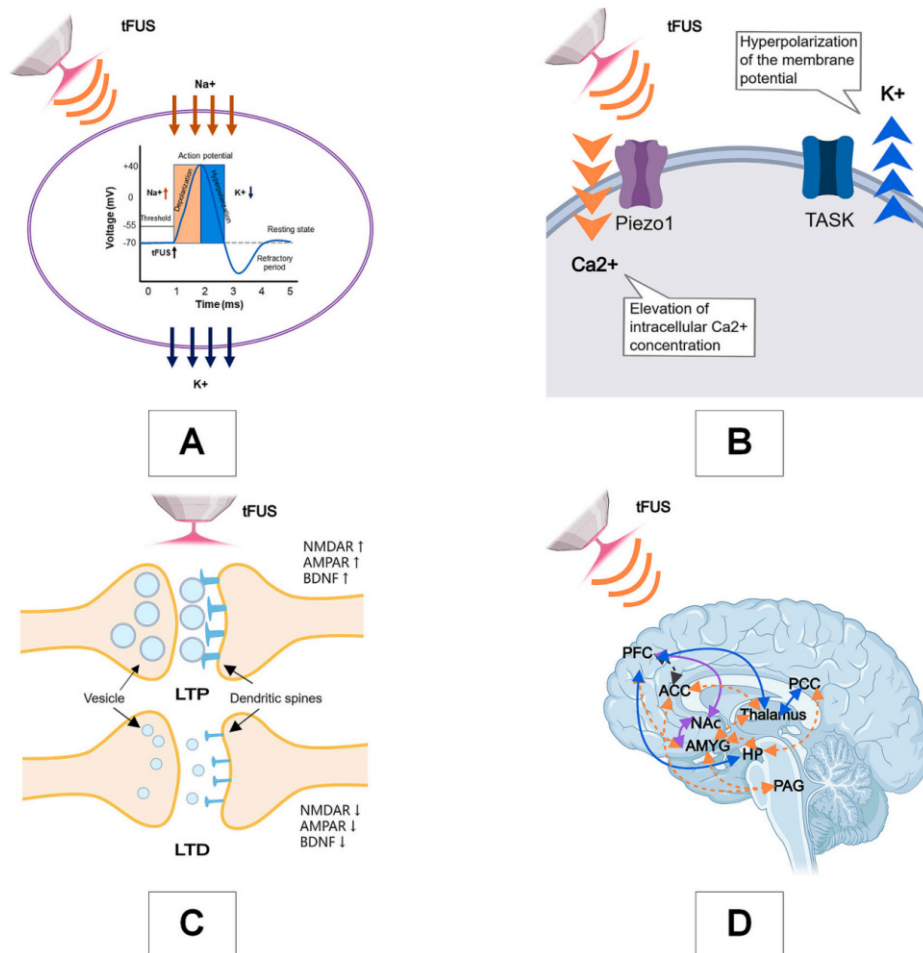


Figure 3. Multi-level mechanisms of tFUS neuromodulation and brain function regulation. A: The modulatory influence of tFUS on neuronal action potentials; B: The regulatory impact of tFUS on ion channels; C: The regulatory role of tFUS in synaptic plasticity and neurotransmitters; D: The modulation of tFUS on brain networks associated with psychiatric disorders. Abbreviation: ACC: Anterior cingulate cortex; AMPAR: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; AMYG: Amygdala; BDNF: Brain-derived neurotrophic factor; HP: Hippocampus; LTD: Long-term depression; LTP: Long-term potentiation; NAc: Nucleus accumbens; NMDAR: N-methyl-D aspartate receptor; PAG: Periaqueductal gray; PCC: Posterior cingulate cortex; PFC: Prefrontal cortex; tFUS: Transcranial focused ultrasound

tFUS is a new type of non-invasive neuromodulation technology. Its physical principle is to use the mechanical pressure waves of focused ultrasound to focus low-intensity ultrasound on specific deep regions of the brain, achieving precise regulation by adjusting stimulation parameters (such as duty cycle and amplitude) [60-62]. This technology is

divided into two categories: high-intensity focused ultrasound (HIFU) which ablates tissues through thermal effects, and low-intensity focused ultrasound (LIFU) which regulates neural activity through non-thermal effects (such as mechanical actions) without damaging tissues [63]. In terms of biological effects, LIFU can regulate neural activity by

stimulating mechanically sensitive ion channels through mechanical effects, promoting vasodilation, etc. It can also non-invasively open the blood-brain barrier to assist drug delivery [64]. In research, tFUS with an intensity of 80-400 mW/cm² can enhance neural oscillations in the motor cortex of animals [65]; in clinical practice, magnetic resonance-guided focused ultrasound for the treatment of refractory tremor-dominant Parkinson's disease (PD) can significantly improve patients' tremors, and also shows potential in the treatment of essential tremor, brain tumors and other diseases [66]. tFUS has advantages such as non-invasiveness, precise focusing (at the millimeter level), and deep penetration. However, its application is still in the early stage, its mechanism has not been fully clarified, and the equipment cost and operation requirements are relatively high [67,68]. In the future, after optimizing parameters and combining with other technologies, it is expected to play a greater role in neural research and clinical treatment.

4. Gamma Band Oscillatory Stimulation Regulation Technology

Brain oscillations refer to rhythmic brain activity [69]. Endogenous brain oscillations occur at different frequencies, including delta (δ , 1–4 Hz), theta (θ , 4–12 Hz), beta (β , 15–30), and gamma (γ , 30–80 Hz) bands [70, 71]. (Figure 4 [72]). Among them, Gamma oscillations are associated with cognition and memory, and can promote synaptic plasticity and communication between brain regions [73]. In 2016, Iaccarino et al. focused on early changes in gamma oscillations in their study on AD mouse models, which promoted the exploration of this technology as a therapeutic approach [74]. This technology has potential in disease treatment, such as AD research and improvement on relevant indicators and cognition [74]; in schizophrenia research, 40Hz-tACS combined with medication can alleviate symptoms[75].

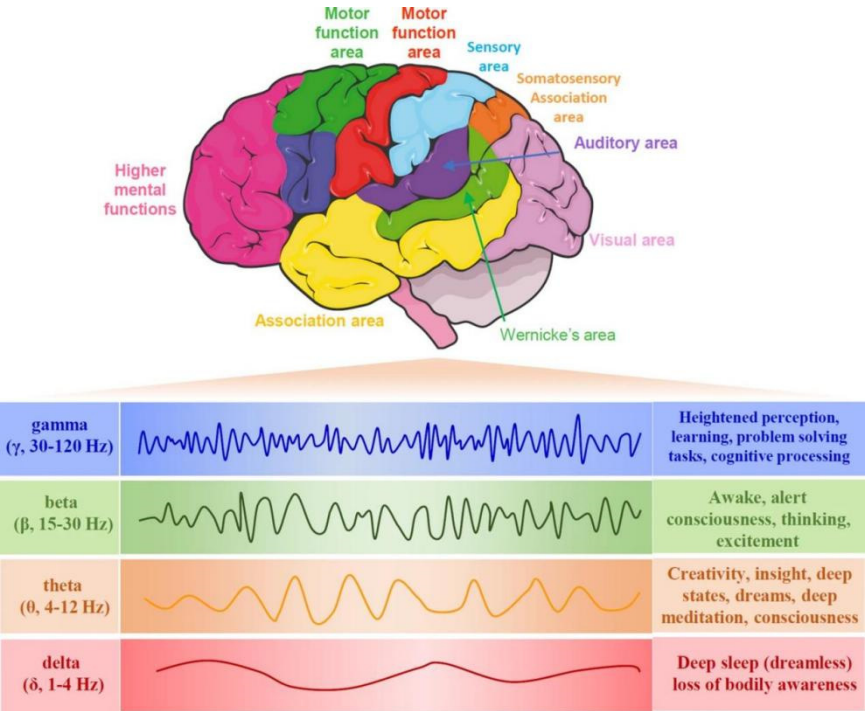


Figure 4. Diagram illustrates brain oscillation at different frequencies, including delta (δ , 1–4 Hz), theta (θ , 4–12 Hz), beta (β , 15–30), and gamma (γ , 30–80 Hz) oscillations

4.1. Biological Mechanism

Gamma oscillations, with frequencies ranging from 30 to 100Hz, arise from the coordinated operation of excitatory and inhibitory signals [76]. At the cellular level, the timing of synaptic interactions between pyramidal cells and interneurons matches the frequency of gamma oscillations. This matching relationship creates a favorable environment for synaptic plasticity and effectively promotes information exchange between brain regions. When external stimulation at a specific frequency is applied, such as 40Hz light flickering, it can significantly increase adenosine levels in the primary visual cortex and superior colliculus. As a key signaling molecule induced by increased energy consumption, elevated adenosine levels are closely associated with gamma oscillations [77]. Further studies have found that changes in extracellular adenosine levels induced by 40Hz light flickering depend on glutamatergic and GABAergic neurons, and the increase in extracellular adenosine is mediated by the ENT2 transporter. This process implies that stimulation

promotes an increase in the energy metabolism level of neurons, thereby producing more adenosine, which is secreted into the extracellular space through specific transporters, thus influencing neural activity [78]. In terms of regulating the synchrony of neural circuits, gamma oscillations are important carriers of information exchange between brain regions [79]. Relevant experiments have shown that external stimulation can optimize the connectivity of neural circuits and signal transmission efficiency [80]. In hippocampal slice experiments, researchers regulated the excitability of principal cells using closed-loop optogenetics, and found that this regulation can bidirectionally adjust the frequency and amplitude of gamma oscillations, thereby altering the synchrony of action potentials. This phenomenon indicates that external oscillatory stimulation can regulate brain function by affecting the synchronization state of neural circuits [81]. In addition, gamma oscillatory stimulation can also regulate the expression of synapse-related proteins, thereby enhancing synaptic plasticity [82]. Meanwhile,

stimulation may activate the expression of related genes, strengthen DNA repair mechanisms, and reduce DNA damage. This process protects neurons and reduces the risk of neurodegeneration [83].

4.2. Regulation Technology

Gamma band oscillation stimulation technology uses various physical methods to regulate the brain's endogenous gamma oscillations (30-100Hz), thereby affecting nervous system functions [84]. Technically, optogenetics involves implanting viruses carrying photosensitive channel protein genes into specific brain regions, then irradiating with blue light at specific frequencies to precisely activate target neurons and induce gamma oscillations [85]. TMS uses time-varying magnetic fields to penetrate the skull, induce currents in the cerebral cortex, regulate the excitability of glutamatergic and GABAergic neurons, and trigger local field potential oscillations in the gamma band [86]. Sensory entrainment, such as 40Hz light flickers or tones, activates gamma oscillations in the primary sensory cortex via visual or auditory pathways, which then spread across the brain through cortico-cortical projections [87]. Physical gamma stimulation enters the brain mainly through two pathways: sensory organs and transcranial routes. Via sensory organs, 40Hz light flickers are converted into electrical signals by retinal photoreceptors, transmitted through the optic nerve to the lateral geniculate nucleus of the thalamus, and then projected to the primary visual cortex [88] (Figure 5 [88]). For 40Hz tones, cochlear hair cells in the inner ear convert mechanical vibrations into electrical signals, which travel through the auditory nerve to the brainstem and finally to the primary auditory cortex [89]. Transcranially, TMS's time-varying magnetic fields directly penetrate tissues to induce currents in the cortex [86]; in optogenetics, specific-frequency blue light reaches target neurons via implanted devices, triggering gamma oscillations [90]. At the molecular and cellular levels, 40Hz light flickers increase adenosine levels in the primary visual cortex and superior colliculus. This depends on coordinated activity of glutamatergic and γ -Aminobutyric Acid-ergic (GABAergic) neurons, with release mediated by the **Equilibrative Nucleoside Transporter 2** (ENT2) transporter. Adenosine inhibits neuronal excitability via **Adenosine A1 Receptor** (A1 receptors) and regulates microglial phagocytosis via **Adenosine A2A Receptor** (A2A receptors), aiding amyloid plaque clearance and maintaining neural microenvironment stability [91]. Gamma oscillations rely on **Gamma-Gminobutyric Acid Type A Receptor**

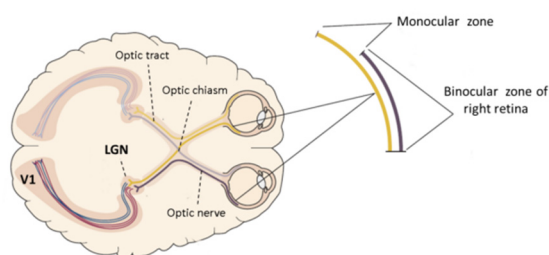


Figure 5. This diagram shows the visual system's neural pathway. Visual information travels from the eyeball via the optic nerve, partially crosses at the optic chiasm, goes through the optic tract to the **Lateral Geniculate Nucleus (LGN)** for initial processing, then to **Primary Visual Cortex (V1)**. The right side labels the right retina's monocular (visible to one eye) and binocular (visible to both, aiding depth/stereoscopic vision) zones.

(GABA_A) receptor-mediated inhibitory postsynaptic currents (matching gamma cycles to form "inhibitory gating"). External stimulation enhances inhibitory neuron firing synchronization, locking pyramidal cell action potentials to specific gamma phases. NMDA receptor activation regulates gamma frequency—higher α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid (AMPA)/NMDA ratios correlate with higher gamma frequencies. External gamma stimulation may adjust this ratio, affecting synaptic plasticity and signal transmission between neurons [92].

4.3. Current Application

In terms of disease treatment applications, Gamma band oscillation stimulation has demonstrated unique value through various physical modalities. Taking the exploration of Alzheimer's disease (AD) treatment as an example, the team led by Professor Li-Huei Tsai from the Massachusetts Institute of Technology pioneered relevant research in 2016. In the experimental design, they selected AD mouse models that had not yet formed obvious amyloid plaques but already had disordered gamma rhythms. Using optogenetic technology, they stimulated key interneurons in the mice's brains at a frequency of 40Hz. The results showed that the pathogenic amyloid protein A β in the mice's brains was significantly reduced. In-depth analysis revealed that 40Hz stimulation improved AD pathology through a two-pronged approach: inhibiting A β production and promoting the phagocytosis and clearance of A β by microglia. Later, the team further explored by externally irradiating AD mice with 40Hz flickering light, which reduced A β levels in the mice's brains by nearly 60% in just 1 hour. After 1 hour of daily irradiation for 7 consecutive days, the amyloid plaques in the brains were significantly reduced [90]. In 2019, the research team investigated the efficacy of auditory stimulation and found that 40Hz sound stimulation not only reduced A β deposition in the auditory cortex of AD mice but also synchronized the neuronal activities in brain regions such as the hippocampus and medial prefrontal cortex with 40Hz, improving the mice's performance in cognitive tasks. When combining sound and light to form a multi-sensory stimulation scheme, it not only triggered a stronger immune response but also significantly reduced A β in the medial prefrontal cortex and cortical plaques throughout the brain, decreased the level of hyperphosphorylated tau protein, and improved the cognitive function of AD mice behaviorally [93]. (Figure 6 [93]) In terms of human clinical trials, Cognito Therapeutics conducted relevant studies. In April 2018, it launched a Phase 1 trial called Overture to evaluate the effect of the Cognito Therapeutics Evoked Gamma Therapy System CO GTX-001 (CO GTX-001) Gamma Sense stimulation device on 60 patients with AD or mild cognitive impairment caused by AD. In the study design, the device was calibrated for each participant, and the induction of 40Hz steady-state gamma oscillations was verified by electroencephalography. Participants received 1 hour of daily 40Hz combined auditory and visual stimulation at home or a sham treatment for 6 months, with a follow-up assessment of safety after 1 month. The primary outcome measures were Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog), Clinical Dementia Rating–Sum of Boxes (CDR-sb), and Mild and Moderate Alzheimer's Disease Composite (MADCOMS) scores, and the secondary measures included Alzheimer's Disease Cooperative Study Activities of Daily Living scale (ADCS-ADL), Mini-Mental State Examination (MMSE), and

amyloid imaging. The trial was conducted at 5 sites in the United States and lasted until August 2021. The results showed that there were no serious adverse events in 46 participants who received active stimulation compared with 28 who received sham treatment, but more participants in the active stimulation group complained of tinnitus, and 28% of participants in each group dropped out midway. The trial did not meet all three primary endpoints, but among the 53 participants who completed the 6-month course, 44 continued to participate in a 1-year open-label extension study. Results from the initial 22 participants showed that the active treatment group had reduced nighttime activity and tended to stabilize in ADAS-ADL scores, while the sham treatment group showed a downward trend. The complete trial results indicated that there were no statistically significant changes in the primary and secondary endpoints, and Positron Emission Tomography (PET) scans did not find changes in amyloid levels. However, additional analysis of Magnetic Resonance Imaging (MRI) data showed that the active treatment group had less white matter atrophy and myelin content loss, especially in the entorhinal cortex[94]. Explorations have also been conducted in the field of Parkinson's disease treatment. A study recorded cortical field potentials for over 2000 hours in 23 brain hemispheres of 13 patients with idiopathic Parkinson's disease who had implanted Medtronic Olympus Research System (RC + S) or Percept devices. The study design was as follows: for 10

patients with endogenous cortical gamma oscillations (60-90Hz), the induction of gamma oscillations and clinical effects were quantified by gradually titrating the stimulation frequency and amplitude in clinical practice. Movement disorders neurologists and patients' self-reports were used to evaluate motor symptoms such as bradykinesia, rigidity, and tremor. The induction was calculated by the maximum power in the power spectrum at half the stimulation frequency under each set of stimulation parameters, and the induction score was correlated with the overall symptom/motor sign score to determine the clinical significance of induction. The results found that 70% of the patients' brain hemispheres had cortical gamma oscillations before the start of deep brain stimulation, and 94% of the hemispheres with endogenous cortical gamma oscillations showed induction during clinical stimulation. The study identified the induction range as a function of stimulation frequency and amplitude and found a significant negative correlation between symptom severity and induction, suggesting that gamma oscillation induction may reflect effective stimulation parameters in Parkinson's disease treatment [95]. Overall, Gamma band oscillation stimulation has shown initial positive results in animal experiments and some human clinical trials in the treatment of neurological diseases. However, more large-scale and rigorously designed studies are still needed to further clarify its therapeutic effects and mechanisms, so as to promote the transition from basic research to wider clinical applications.

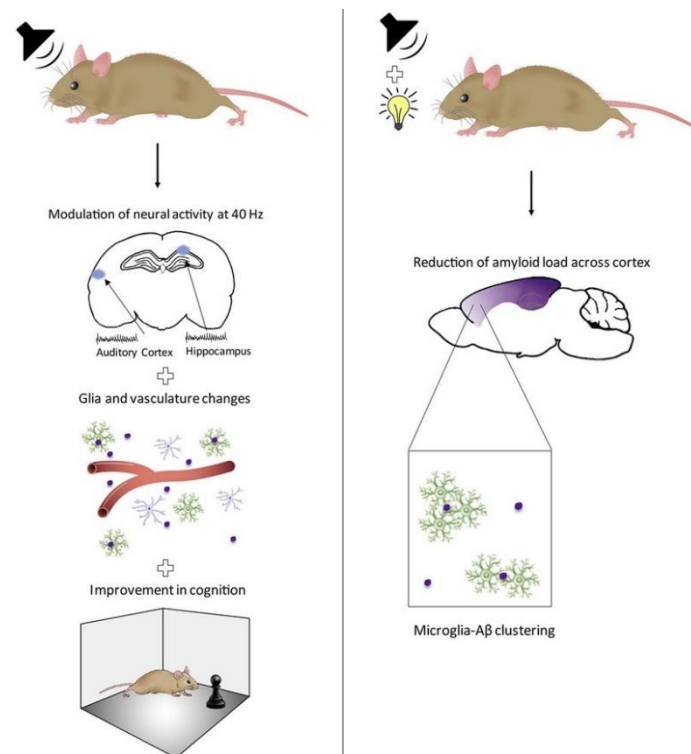


Figure 6. This figure illustrates the effects of two different stimuli on the mouse brain and cognition. On the left, auditory stimulation modulates neural activity in the mouse auditory cortex and hippocampus at 40 Hz, triggering changes in glial cells and blood vessels, and ultimately improving mouse cognition. On the right, combined audio - visual stimulation can reduce amyloid protein deposition in the mouse cerebral cortex, which is related to the aggregation of A β by microglia

4.4. Future Application

The clinical application prospects of Gamma band oscillation stimulation are promising. Cognito Therapeutics' Gamma Sense device synchronizes gamma oscillations through combined photoacoustic stimulation. In its Overture trial targeting Alzheimer's disease, patients who completed

the 6-month treatment course showed positive changes in indicators such as white matter atrophy. If parameters like stimulation frequency and duration are optimized in the future, it may further enhance the improvement effect on cognitive function[96]. In the field of mental illnesses, it is expected to improve the emotional state of patients with depression and anxiety through stimulation with specific parameters by

regulating gamma oscillations in brain regions such as the prefrontal cortex[97]. Meanwhile, since gamma oscillations are related to sleep cycles, this technology may optimize the quality of healthy sleep and stabilize daily emotions by synchronizing the activities of relevant brain regions[98]. AI can help realize personalized treatment. It can screen populations that may benefit by analyzing data such as patients' electroencephalographic signals and symptoms, and dynamically adjust stimulation parameters by real-time monitoring of oscillation changes[99]. In the future, it may be applied in more neurological diseases such as Parkinson's disease, promoting neuromodulation to enter a new stage of precision medicine [100].

5. Summary

The treatment of Alzheimer's disease has shifted from chemical drugs to physical regulation. Chemical drugs delay the progression of the disease by intervening in neurotransmitters, yet they have limited efficacy and significant side effects. In recent years, physical regulation technologies (such as TMS and tDCS) have emerged; however, due to their exogenous nature, they struggle to accurately align with endogenous neural activities. The gamma oscillation technology marks a breakthrough. Based on endogenous neural rhythms, it activates neural networks through stimulation at specific frequencies, promotes neuroplasticity, and improves cognition. Its advantage lies in precisely synchronizing with endogenous activities, holding promise for repairing damaged neural circuits. In the future, it may combine with gene therapy and stem cell therapy to form multimodal regimens. With technological optimization, it will open up new paths for overcoming AD.

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