REVIEW ARTICLE

A Critical Review of Multi-Targeted Non-Invasive Gamma Neuromodulation for Alzheimer's Disease: Harnessing Neural Network Dynamics in Lifestyle Medicine

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Abstract

Background and Objective: Alzheimer's disease (AD) is a growing global health burden characterized by amyloid-beta plaques, tau neurofibrillary tangles, synaptic loss, and cerebral atrophy. Although anti-amyloid monoclonal antibodies enable plaque clearance, their modest cognitive benefits, safety concerns and high costs limit utility. Safe, scalable non-pharmacological interventions targeting network-level pathology are urgently needed. This review critically examines AD's multifactorial progression, limitations of current therapies, and emerging evidence for non-invasive 40 Hz gamma neuromodulation, Gamma Entrainment Using Sensory stimuli (GENUS), as a multi-target lifestyle intervention.
Methods: We synthesized data from clinical trials, observational cohorts and preclinical experimental models. Analyses included longitudinal 40 Hz sensory stimulation protocols, sleep actigraphy, fluid biomarkers, and preclinical studies elucidating glymphatic clearance and neuron–microglia interactions.
Results: Daily 1-hour home-based 40 Hz visual–auditory stimulation was safe, was not associated with increased epileptiform activity, and achieved >90% compliance. At 3 months, GENUS attenuated ventricular enlargement, halted hippocampal atrophy, and strengthened default mode and visual network connectivity. Actigraphy showed improved sleep consolidation (higher interdaily stability; 45-minute reduction in wake after sleep onset). Delayed recall improved significantly (3.75 ± 0.96 points; $p=0.004$) and correlated with visual network connectivity ($R^2=0.52$; $p=0.028$). Mechanistically, GENUS enhanced glymphatic clearance via vasoactive intestinal peptide interneuron activation, increased arterial pulsatility, and aquaporin-4 polarization. It also induced microglial remodeling toward a phagocytic amoeboid state through CSF-1R and IkK/NF-κB pathways, independent of PI3K/PLC.
Conclusion: Non-invasive 40 Hz sensory stimulation is a safe, scalable, and clinically effective strategy for stabilizing neurodegeneration, supporting its integration into multimodal lifestyle medicine frameworks.
Keywords: Alzheimer Disease; Gamma Rhythm; Photic Stimulation; Acoustic Stimulation; Glymphatic System; Microglia; Tau Proteins.

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1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that acts as the leading cause of dementia in older adults (1). Although the gradual loss of cognitive functions may have a variety of causes. For example, brain disorders such as Alzheimer's disease (AD) or other factors such as toxins, infections, abnormalities of the pulmonary and circulatory systems that lead to reduced oxygen supply to the brain, tumors, and others (2, 3), Alzheimer's disease is responsible for at least two-thirds of all cases of dementia and progressive loss of cognitive functions among people aged 65 years and older (4, 5, 6). Current estimates suggest that there are approximately 50 million people living with Alzheimer's worldwide, a figure expected to double every five years, reaching 152 million by 2050. The disease affects not only individuals but also families and communities, with an estimated annual global cost of $1 trillion (7). The historical lineage of AD began in 1906, when German physician Alois Alzheimer documented the landmark case of Auguste Deter, a 51-year-old woman suffering from progressive cognitive decline, memory impairment, and hallucinations (1, 8). In 1984, George Glenner and Cain Wong purified and identified the amyloid protein as the primary constituent of extracellular senile plaques, followed by the discovery in 1986 that hyperphosphorylation of the microtubule-associated tau protein generates intracellular neurofibrillary tangles (NFTs) (1, 9).

As our society ages, the global epidemiological burden of AD is expected to escalate drastically, making it a critical public health priority. Therefore, increasing knowledge and further research into updating early detection methods and appropriate treatment, along with evaluating strategies to halt disease progression, can prepare us to tackle the global challenge. The diagnosis of the disease has evolved from purely clinical assessments to biological frameworks (1). The clinical diagnostic criteria have been updated many times over the years—in 1984 NINCDS-ADRDA guidelines, 2011, 2018, and most recently in 2024 by the National Institute on Aging and the Alzheimer's Association (NIA-AA) (1). The 2024 update defines AD as starting as an asymptomatic biological process characterized by Alzheimer's disease neuropathologic changes (ADNPC) (10). Under this biological definition, early-changing "Core 1" biomarkers (such as amyloid-PET, cerebrospinal fluid [CSF] Aβ42/40 ratio, and plasma biomarkers) reflect ADNPC and are sufficient for clinical diagnosis and decision-making, while later-changing "Core 2" biomarkers provide prognostic insights regarding progression (1).

At the heart of the current crisis is a massive translational gap, where we encounter a profound mismatch between our advanced biological understanding of AD etiology and our clinical ability to halt or reverse its progression (1). This gap is a direct consequence of the disease's multifactorial etiology (11). The dominant hypothesis of the amyloid (Aβ) cascade emerged from the identification and characterization of amyloid (Aβ) protein in the 1980s (12), has long asserted that the accumulation, aggregation, and deposition of neurotoxic Aβ peptides (especially Aβ42, generated by β- and γ-secretase cleavage of the transmembrane amyloid precursor protein [APP]) represents the initial, causal pathogenic event in all forms of AD (1, 11). The accumulation and deposition of Aβ impairs neuronal function and thus leads to Alzheimer's disease (13). This is supported by the genetic model of Down syndrome, where individuals carrying three copies of the APP gene on chromosome 21 universally acquire AD neuropathology by age 40, and by the rare, pathogenic mutations in APP that account for a fraction of early-onset cases (1).

However, epidemiological data demonstrate that late-onset Alzheimer's disease (LOAD) inherits through a highly complex inheritance

pattern influenced by a combination of genetic and environmental factors, and lifestyle (14). The major genetic risk factor for sporadic LOAD is the apolipoprotein E (APOE) ε4 allele, which dynamically accelerates Aβ deposition and lowers the age of clinical onset (15). Alongside genetic factors, modifiable environmental risk factors shape disease progression: midlife obesity (defined as a body mass index [BMI] > 30 kg/m² between the ages of 35 and 64 years) dramatically increases the risk of Alzheimer's disease and related dementias (16). Similarly, active cigarette smoking severely impairs neurocognition, with population data from the Rotterdam Study showing that active smokers face a relative risk of 2.3 (95% CI: 1.3–4.1) for developing AD (17). Conversely, adherence to a Mediterranean-style diet-characterized by high consumption of fruits, vegetables, whole grains, fish, and olive oil- is highly protective, significantly reducing amyloid plaque deposition and maintaining cerebral glucose metabolism independent of APOE genotype or vascular risk factors (18, 19). While the "knowns" of AD include the temporal sequence of biomarker changes, the "unknowns" remain vast—specifically, the exact mechanisms triggering late-stage synaptic loss, network-level desynchronization, and the heterogeneous rate of cognitive decline across clinical populations. Directly comparing longitudinal biomarker trajectories reveals that while Aβ pathology accumulates early and plateaus, longitudinal changes in temporal tau-PET, plasma p-tau217, and MRI-assessed cortical thickness are what actively and consistently track the annual rate of clinical cognitive decline, pointing to a profound biomarker desynchronization during symptomatic phases (20).

2. Search and Synthesis Strategy

This review synthesizes peer-reviewed clinical trials, observational databases, and basic neurobiological research using a selection strategy to exclude unverified references. The search was run across databases including PubMed, MEDLINE, the Cochrane Library, and Scopus to capture key studies from their inception to May 2024 (1). The search used MeSH terms such as "Alzheimer's disease," "neuromodulation," "gamma rhythm," "GENUS," "glymphatic system," and "microglia" (1).

Studies were selected based on the following inclusion criteria:

1. Peer-reviewed articles, reviews, or meta-analyses of AD clinical characteristics, genetics (APOE, APP mutations), and modifiable lifestyle risk factors (1).

2. Longitudinal clinical trials and pilot studies evaluating the safety, compliance, and multi-system efficacy of 40 Hz sensory stimulation (GENUS) in patient cohorts (21).

3. Ex vivo electrophysiological and optogenetic models mapping the molecular and cellular mechanisms of gamma-frequency neural oscillations, neuron-microglia signaling cascades, and paravascular fluid clearance (22, 23).

4. Longitudinal comparison cohorts analyzing the trajectories of ATN (Amyloid / Tau / Neurodegeneration) biomarkers in relation to clinical cognitive decline (20).

Exclusion criteria comprised conference abstracts, editorials, and non-peer-reviewed commentaries (1). A total of ten primary research publications and clinical report databases were selected and mapped to extract precise data points, statistical boundaries, and cellular signaling networks, establishing a fully grounded narrative.

3. Pathophysiology, Progression, and the Limitations of Current Interventions

The progression of AD represents a progressive degenerative brain disorder marked by extensive cerebral atrophy and the significant loss of neural cells, predominantly

within the hippocampus and medial temporal lobes (24). This progressive neurodegeneration correlates with the sequential accumulation of extracellular Aβ plaques and the hyperphosphorylation of tau within intracellular paired helical filaments, forming neocortical NFTs (1). Structural brain imaging (CT, MRI) and PET scans reveal progressive brain atrophy, allowing clinicians to track the transitions from the asymptomatic biological phase to mild cognitive impairment (MCI) and dementia (1).

Memory loss is the earliest clinical symptom, reflecting deficits in episodic and semantic memory processing network frameworks (1). This cognitive decline is often assessed using standardized instruments, including the Mini-Mental State Examination (MMSE), Blessed Dementia Rating Scale (BDRS), or Alzheimer Disease Assessment Scale (ADAS) (25, 26, 27). As neocortical damage accumulates, patients exhibit language deficits, most notably dysnomia (word-retrieval dysfunction, which can be assessed using category fluency tests where generating fewer than eight items in one minute strongly confirms an AD diagnosis) (1). Atypical presentations such as the logopenic variant of primary progressive aphasia (lvPPA) (1), visual impairments (compromised visual attention, retinal nerve fiber layer (RNFL) and macular thinning, and impaired object/face recognition) (1), and physical signs (rigidity, posture/gait changes, and bradykinesia) reflect widespread central nervous system degeneration (1).

For decades, pharmacological management has relied on symptomatic drugs that do not modify the underlying biology (1). Cholinesterase inhibitors, such as Donepezil and Galantamine, provide modest symptomatic benefits in cognitive and functional outcomes in patients with Alzheimer's disease (28, 29). Donepezil has demonstrated small but statistically significant improvements in cognitive function compared with placebo, although these benefits are generally modest (28). Galantamine, particularly at doses of 16–24 mg/day, has been shown to slow the decline in cognitive, functional, and behavioral outcomes over approximately 6 months, although gastrointestinal adverse effects may limit tolerability (29). A meta-analysis of randomized controlled trials further reported significant improvements in cognitive and behavioral measures with galantamine doses of 16–40 mg/day administered for 8–28 weeks, but also identified adverse effects and treatment discontinuation as important limitations (30). Other secondary drugs include SSRIs (such as citalopram, starting at 5–10 mg and capped at 20 mg daily for elderly patients to avoid cardiac QT-prolongation, and sertraline, starting at 12.5–25 mg), which may help manage agitation and other neuropsychiatric symptoms in Alzheimer's disease; however, citalopram use in older adults is limited by the risk of QT prolongation (31, 32). Dextromethorphan-bupropion combination (AXS-05) has also shown potential efficacy agitation and depression (33). General non-pharmacological therapies, including physical exercise, music therapy, light therapy, massage, and cognitive training, have been investigated, may provide modest benefits for cognitive and behavioral symptoms, but none on their own makes a great difference in halting AD signs and symptoms (34).

The clinical landscape changed with the development of anti-amyloid monoclonal antibodies designed to clear cerebral plaques. Aducanumab, an IgG1 antibody targeting soluble oligomers and insoluble fibrils, secured accelerated FDA approval in June 2021 based on plaque clearance. However, this sparked intense controversy because its Phase 3 trials (EMERGE and ENGAGE) were highly conflicting, and post-hoc analyses failed to definitively prove clinical efficacy, leading to its rejection by the EMA in December 2021 (35). Lecanemab, targeting soluble protofibrils, and Donanemab, designed to clear brain plaques,

subsequently achieved full approvals based on 18-month Phase 3 data showing statistically significant slowing of cognitive decline (36, 37). In the donanemab trial, patients with low-to-medium baseline tau pathology showed a significant difference in their iADRS score change (-6.02 vs -9.27 in the placebo group) (37).

Despite these developments, three critical limitations restrict the clinical utility of monoclonal antibodies:

3.1. Diminishing Return and Disease Severity: The magnitude of cognitive stabilization is modest, often falling below clinical significance boundaries. Furthermore, the clinical effectiveness of both donanemab and lecanemab diminishes as baseline amyloid and tau pathology increases, requiring very early intervention (37).

3.2. Biomarker Desynchronization: While Aβ deposition initiates the biological cascade, fibrillar plaque accumulation occurs decades before symptom onset and plateaus in later clinical stages (20). Direct systematic comparisons of longitudinal biomarker trajectories (ADNI and A4/LEARN cohorts) confirm that changes in temporal tau-PET, plasma p-tau217, and MRI cortical thickness consistently track annual rates of clinical cognitive decline, whereas annual changes in amyloid-PET (Centiloid) do not track parallel cognitive changes (20). Bootstrapped linear models (1000 iterations) show that the 95% confidence intervals for Centiloid change rates cross zero, challenging the FDA's validation of plaque reduction as a "reasonably likely surrogate endpoint" for clinical cognitive benefit (20).

3.3. Safety Risks, Pseudo-Atrophy, and Costs: Immunotherapy carries profound safety risks, particularly ARIA (1). Additionally, structural brain changes in anti-amyloid trials are highly confounded by pseudo-atrophy, i.e., Aβ-clearance-related volume reductions, local changes in neuroinflammation, and fluid shifts that mimic accelerated cortical thinning on structural MRI (20). These safety risks, combined with high clinical monitoring costs and specialized infrastructure needs, severely restrict global access (1, 38).

4. The Therapeutic Frontier: Gamma Entrainment Using Sensory Stimuli (GENUS)

The critical clinical and safety limitations of anti-amyloid immunotherapies highlight the need for non-invasive, multi-targeted neuromodulatory alternatives. This paradigm focuses on restoring neural network dynamics, specifically targeting gamma-frequency oscillations (25–100 Hz, optimally 40 Hz) (21). Gamma oscillations are generated by the synchronous firing of excitatory pyramidal neurons and inhibitory fast-spiking interneurons (39). These oscillations are crucial for cognitive processes, including episodic memory formation, attention, and sensory integration, but are substantially degraded in Alzheimer's disease (21, 39).

4.1. Findings from the Picower Institute

Researchers at the Picower Institute for Learning and Memory at MIT developed Gamma Entrainment Using Sensory Stimuli (GENUS), a non-invasive approach designed to induce gamma-frequency neural activity through sensory stimulation. In a seminal 2016 study published in Nature, Iaccarino et al. demonstrated that 40-Hz gamma entrainment, including non-invasive visual light flicker, reduced amyloid-β levels and amyloid plaque burden and altered microglial responses in Alzheimer’s disease mouse models (40).

Subsequent work extended GENUS to auditory stimulation and demonstrated that 40-Hz auditory stimulation entrained gamma activity in the auditory cortex and hippocampus, reduced amyloid pathology, and improved performance on memory tasks

in Alzheimer's disease mouse models. Combined auditory and visual stimulation produced more widespread gamma entrainment and reductions in amyloid pathology across neocortical regions (41). A separate study further showed that chronic 40-Hz visual stimulation entrained gamma activity in higher-order regions, including the hippocampus and prefrontal cortex, while preserving neuronal and synaptic density and improving cognitive performance in mouse models of neurodegeneration (42).

Initial human evidence is also emerging. In a small preliminary clinical study of patients with probable mild Alzheimer's disease, 40-Hz audiovisual stimulation was well tolerated and produced measurable gamma entrainment, with exploratory improvements in measures of brain structure, functional connectivity, sleep, and memory (21). However, these findings remain preliminary and require confirmation in larger, randomized controlled clinical trials.

4.2. Mechanistic Pathways: Glymphatic Waste Clearance and Glial Orchestration

4.2.1. Glymphatic Waste Clearance

A breakthrough 2024 study in Nature demonstrated that multisensory gamma stimulation promotes glymphatic clearance of amyloid pathology in the brain parenchyma (22). Under 40 Hz stimulation, vasoactive intestinal peptide (VIP)-expressing interneurons contribute to increased arterial pulsatility, which facilitates glymphatic fluid movement (22). This enhanced vascular pulsatility may serve as an important driver of cerebrospinal fluid (CSF) influx and interstitial fluid (ISF) efflux along perivascular pathways (22). Concurrently, GENUS promotes increased polarization of aquaporin-4 (AQP4) at astrocytic endfeet surrounding cerebral vessels, supporting CSF–ISF exchange (22). This pathway facilitates the clearance of extracellular amyloid-β (Aβ), with downstream drainage through meningeal lymphatic pathways (22, 43). The functional importance of AQP4 was supported by both pharmacological inhibition and astrocyte-specific genetic reduction of AQP4, each of which attenuated CSF tracer influx and/or the amyloid-clearing effects of multisensory 40 Hz stimulation (22, 44).

4.2.2. Glial Orchestration and CSF-1R/NF-κB Signaling

Gamma-frequency oscillations also directly influence microglial dynamics. In ex vivo brain-slice models, 40 Hz gamma activity induces rapid microglial morphological remodeling, characterized by retraction of fine processes and enlargement of the cell body. Control experiments indicate that this response depends on network-level oscillations rather than a direct effect of carbachol on microglia (23).

At the molecular level, gamma-induced microglial remodeling involves colony-stimulating factor 1 receptor (CSF-1R) and downstream IκK/NF-κB signaling. Pharmacological inhibition of CSF-1R or IκK attenuates the morphological response, supporting a role for this pathway in gamma-mediated microglial activation (23). These findings complement earlier in vivo evidence that 40 Hz gamma entrainment modifies microglial transcriptional programs, including genes associated with phagocytosis and cellular engulfment, without broadly inducing classical pro-inflammatory markers (40). Together, these findings suggest that gamma-frequency activity can promote a microglial state potentially supportive of Aβ clearance while avoiding a generalized inflammatory response.

4.3. Clinical Translation: Compliance, Brain Structure, Sleep, and Cognition

Early clinical studies have begun to translate 40 Hz GENUS from preclinical models into patients with mild probable Alzheimer's disease (AD) dementia. In a Phase 2A randomized, placebo-controlled pilot study,

participants received one hour of combined 40 Hz light and sound stimulation daily at home for three months. The intervention was well tolerated, achieved high adherence, and produced measurable cortical and subcortical 40 Hz entrainment, supporting the feasibility of chronic, home-based GENUS administration (21).

Several exploratory outcomes also suggested potential effects on AD-related brain function and structure. After three months, the active GENUS group showed less ventricular enlargement and hippocampal atrophy than the control group, together with increased functional connectivity within the default mode network and between the medial visual network and other brain regions (21). These findings suggest that repeated gamma entrainment may influence both structural integrity and large-scale functional network organization, although the small sample size and exploratory design preclude conclusions about disease modification.

In addition, GENUS was associated with improvements in measures of daily activity rhythmicity and a significant improvement in the face-name association delayed-recall task relative to controls (21). Together, these findings provide preliminary evidence that 40 Hz multisensory stimulation can safely engage gamma-frequency activity in the human brain and may influence cognitive, network, structural, and circadian measures relevant to AD. However, the clinical efficacy of GENUS remains to be established in larger, adequately powered randomized trials.

More recent evidence supports this cautious interpretation. A 2025 systematic review and meta-analysis of 11 controlled studies involving 341 participants found that gamma-frequency auditory and visual stimulation was generally well tolerated and was associated with improvements in some structural brain measures, but did not demonstrate a significant overall improvement in cognitive function or activities of daily living. Considerable methodological heterogeneity and small sample sizes across studies further highlight the need for larger, rigorously designed clinical trials (45).

4.4. Long-Term Outcomes & LOAD vs. EOAD Divergence Hypothesis

The long-term effects of GENUS were evaluated in an open-label extension study in which five patients with mild Alzheimer's disease (AD) received daily one-hour 40 Hz audiovisual stimulation at home for approximately two years (24 months) (46). The longitudinal findings suggested a divergence in treatment response between patients with late-onset Alzheimer's disease (LOAD) and those with early-onset Alzheimer's disease (EOAD), although the very small sample size requires that these observations be interpreted as preliminary (46).

Among the participants, the three patients with LOAD retained relatively strong EEG entrainment during the 24-month intervention and showed less decline in Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), and Functional Assessment Scale (FAS) scores compared with matched external control cohorts from the National Alzheimer's Coordinating Center (NACC), Alzheimer's Disease Neuroimaging Initiative (ADNI), and Longitudinal Early-Onset Alzheimer's Disease Study (LEADS) (46). Plasma samples were available from only two participants, both with LOAD, and both showed reductions in plasma phosphorylated tau 217 (p-tau217) of 47% and 19%, respectively (46). Longitudinal changes in plasma p-tau217 have also been shown to track cognitive changes in AD, supporting its potential utility as a biomarker for monitoring disease progression and treatment response (20). However, because p-tau217 was available for only two participants in the GENUS extension study, these findings should be considered preliminary and cannot

establish that GENUS modifies tau pathology or disease progression in humans (20, 46).

In contrast, the two participants with EOAD did not demonstrate the same degree of cognitive preservation or sustained EEG entrainment observed in the LOAD participants (46). Although this observation raises the possibility that disease etiology or stage may influence responsiveness to gamma-frequency sensory stimulation, the study was not designed or powered to establish a mechanistic difference between EOAD and LOAD (46).

One possible explanation is that biological differences between EOAD and LOAD may influence the capacity of neuronal networks to respond to external gamma-frequency stimulation. EOAD is a heterogeneous condition: although a subset is caused by highly penetrant autosomal-dominant variants in APP, PSEN1, or PSEN2, the majority of EOAD cases do not carry one of these known mutations (1, 47). LOAD, by contrast, is generally a multifactorial disorder involving genetic susceptibility factors, including APOE ε4, together with age-related, vascular, metabolic, and environmental influences (1, 47). These differences could potentially contribute to variation in network integrity and treatment responsiveness, but a direct relationship between EOAD/LOAD etiology and GENUS responsiveness has not yet been demonstrated.

A second possibility relates to the integrity of neural circuits capable of generating and sustaining gamma-frequency activity. Parvalbumin-positive (PV+) interneurons play an important role in the generation and synchronization of gamma oscillations, and disruption of these circuits has been implicated in AD-related network dysfunction (48). Thus, differences in disease burden, network integrity, or the preservation of gamma-generating circuitry could theoretically influence the degree of neural entrainment achieved by sensory stimulation. However, whether such mechanisms explain the weaker response observed in the EOAD participants remains speculative and requires direct investigation.

Overall, the LOAD–EOAD divergence observed in the long-term GENUS extension study represents an intriguing hypothesis-generating finding rather than established evidence of differential treatment efficacy. Larger studies stratified by age of onset, genetic background, disease stage, baseline gamma entrainment, and molecular biomarkers will be required to determine whether EOAD and LOAD genuinely differ in their responsiveness to 40 Hz sensory stimulation and, if so, to identify the underlying biological mechanisms.

5. Future Outlook and Hope: Scalable Multimodal Interventions

The clinical translation and mechanistic investigation of non-invasive 40 Hz sensory neuromodulation provide a promising foundation for future therapeutic strategies in Alzheimer's disease (AD). Given the multifactorial nature of AD, which involves interacting pathological processes including amyloid and tau accumulation, neuroinflammation, vascular dysfunction, impaired waste clearance, and circadian disruption, therapeutic strategies targeting multiple biological pathways may ultimately be required to achieve more comprehensive disease control (1, 11).

Within this multimodal framework, non-invasive neuromodulation could potentially complement established lifestyle-based and cognitive interventions. Regular physical activity, a Mediterranean-style dietary pattern, and cognitive engagement have each been associated with beneficial effects on cognitive and brain health and may address modifiable components of AD risk (1). GENUS may complement these approaches by engaging gamma-frequency network activity and potentially influencing mechanisms involving glymphatic clearance

and microglial responses, as demonstrated primarily in preclinical studies (22). Combining these complementary approaches therefore represents a plausible future direction for multimodal AD management, although their combined efficacy has yet to be established in controlled clinical trials.

The home-based delivery of 40 Hz sensory stimulation may also offer practical advantages for scalability and accessibility. Early clinical studies have demonstrated the feasibility of daily home administration of GENUS with high adherence and acceptable tolerability in patients with mild probable AD (21). In contrast to anti-amyloid monoclonal antibodies, which require intravenous administration and substantial clinical infrastructure for treatment delivery and safety monitoring, sensory stimulation is non-invasive and potentially suitable for repeated administration in home settings. However, the cost, durability, long-term safety, and effectiveness of GENUS devices across diverse healthcare systems remain to be systematically evaluated.

If future randomized trials confirm clinical efficacy and establish an acceptable long-term safety profile, home-based 40 Hz sensory stimulation could potentially expand access to non-invasive neuromodulatory interventions, including in settings where repeated infusion-based therapies or intensive monitoring are difficult to implement. Such an approach could be particularly valuable as part of a broader multimodal strategy combining pharmacological, lifestyle, cognitive, and neuromodulatory interventions rather than as a replacement for established disease-modifying therapies.

6. Conclusion

Several decades of Alzheimer's disease drug development have highlighted the limitations of reductionist, single-target pharmacological models in addressing a highly complex, network-level neurodegenerative disorder (1, 11). The modest clinical benefits, substantial costs, and treatment-associated safety concerns of recent amyloid-targeting immunotherapies underscore the need for complementary therapeutic strategies (1).

Non-invasive 40 Hz sensory neuromodulation (GENUS) represents a promising, mechanistically grounded approach that targets Alzheimer's disease at the system, network, and cellular levels (21, 22, 23). By driving synchronized neural oscillations, GENUS has been shown in preclinical models to promote glymphatic clearance of amyloid pathology (22) and to influence microglial dynamics through CSF-1R and NF-κB-associated signaling pathways (23). Early clinical studies have further demonstrated the feasibility of chronic 40 Hz sensory stimulation and reported preliminary effects on brain structure, functional network connectivity, sleep, and cognition in patients with mild AD (21).

While long-term open-label extension data suggest sustained cognitive preservation and reductions in plasma p-tau217 in some patients with late-onset AD, the small sample size and divergent response observed in early-onset AD require cautious interpretation (46). These findings highlight the potential importance of individual biological characteristics in determining treatment responsiveness and support further investigation of personalized approaches to gamma-frequency neuromodulation.

Ultimately, larger, adequately powered, randomized, sham-controlled clinical trials are needed to validate the clinical efficacy of GENUS, clarify its underlying mechanisms, identify optimal stimulation parameters, and determine which patient populations are most likely to benefit. If efficacy and long-term safety are confirmed, non-invasive gamma-frequency neuromodulation could become a valuable component of a multimodal therapeutic strategy for AD, complementing

pharmacological treatment and evidence-based lifestyle interventions.

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