SYSTEMATIC REVIEW OPEN

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The safety and efficacy of gamma frequency auditory and visual stimulation in the treatment of alzheimer's disease: a systematic review and meta-analysis

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BACKGROUND: Alzheimer's disease (AD) is a progressive neurodegenerative disorder associated with cognitive decline and significant global health burden. Current treatments offer limited benefits, highlighting the need for novel therapies. Gamma-frequency auditory and visual stimulation (GFAVS), utilizing 40 Hz neuromodulation, has gained attention as a non-invasive treatment for cognitive deficits and underlying pathophysiology in AD.
OBJECTIVE: This systematic review and meta-analysis aimed to assess the safety and efficacy of GFAVS in treating Alzheimer's disease (AD) and mild cognitive impairment (MCI).
METHODS: A comprehensive literature search across multiple databases (PubMed, Cochrane Library, MEDLINE, Web of Science, and Embase) was performed up to November 2025. Controlled trials involving adults (≥50 years) with AD or MCI, using GFAVS, were included. Meta-analyses assessed adverse events, cognitive function, and brain changes.
RESULTS: Eleven studies (341 participants) were included. GFAVS was safe, with no significant increase in overall adverse events ($RR = 0.99$, $P = 0.93$; $RD = -0.01$, $P = 0.93$). However, GFAVS significantly increased the risk of tinnitus (RR = 6.46, $P = 0.08$; RD = 0.16, $P = 0.01$). GFAVS significantly improved structural brain changes ($SMD = 1.74$, $P = 0.02$), especially in mixed AD and MCI populations ($SMD = 3.05$, $P < 0.00001$). Nevertheless, no significant improvements were observed in cognitive function ($SMD = 0.16$, *95% CI* [-0.36 to 0.68], $P = 0.55$) or activities of daily living ($SMD = 0.53$, *95% CI* [-1.26 to 2.33], $P = 0.56$), despite the observed structural brain changes. High heterogeneity was observed.
CONCLUSION: GFAVS appears to be well tolerated and may induce structural brain alterations in individuals with Alzheimer's disease or mild cognitive impairment; however, its impact on cognition or daily functioning remains to be established. Large-scale, rigorously designed trials are required to clarify optimal protocols and address the observed heterogeneity.

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INTRODUCTION

Alzheimer's disease (AD) represents a significant global health challenge, with no definitive cure currently available [1]. It is characterized by a gradual and irreversible cognitive decline, which typically begins with deficits in short-term memory formation. As the disease progresses, it inevitably impairs a wide range of intellectual functions, ultimately resulting in total dependence for basic daily activities and premature mortality [2]. According to the World Alzheimer Report 2024, approximately 6.9 million individuals aged 65 and older in the United States are living with Alzheimer's dementia. Projections suggest that by 2060, this figure could rise to 13.8 million, underscoring the growing public health burden of this condition [3]. Currently, the therapeutic landscape for Alzheimer's disease (AD) remains in an exploratory phase, with existing treatments primarily aimed at symptom management. These treatments predominantly include cholinesterase inhibitors, such as donepezil, galantamine, and rivastigmine, alongside NMDA receptor antagonists like memantine. While these pharmacological interventions can provide modest symptomatic relief, their efficacy is limited, and they are frequently associated with side effects that may detract from their overall benefit [4].

Research into more effective treatment modalities for Alzheimer's disease (AD) has been both arduous and protracted, with numerous obstacles hindering progress [5, 6]. Nevertheless, recent advancements offer hope for novel therapeutic strategies [7]. Among these, Gamma Frequency Auditory and Visual Stimulation (GFAVS) therapies have emerged as particularly promising,

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demonstrating potential to stimulate cognitive function and providing new avenues for intervention that may enhance patient outcomes.

GFAVS is a neuromodulation technique that combines visual and auditory stimuli using a specific gamma frequency (40 Hz) [8]. The method works by synchronizing the rhythms of visual and auditory signals to stimulate the corresponding neural activity in the brain, specifically the neural oscillations [9, 10].

GFAVS has emerged as a promising non-invasive therapeutic approach for Alzheimer's disease, supported by several putative molecular mechanisms [11]. Nevertheless, the translational value of these findings is limited, as most supporting evidence originates from preclinical models, and robust clinical validation is still warranted. One of the key mechanisms involves the modulation of gamma oscillations (30-100 Hz), which are closely linked to cognitive functions such as attention, sensory processing, and learning [12]. By enhancing these oscillations, GFAVS has been shown to influence synaptic plasticity, a crucial process for memory consolidation and cognitive flexibility, potentially ameliorating cognitive deficits associated with AD. Additionally, GFAVS appears to promote the clearance of amyloid-beta plaques, a hallmark of AD pathology. Research suggests that gamma stimulation activates microglial cells, enhancing their ability to clear these toxic aggregates, thereby reducing plaque accumulation and mitigating disease progression [13]. Beyond plaque clearance, GFAVS has also been shown to enhance neural connectivity and facilitate the synchronization of activity across brain regions involved in cognition, which could help restore disrupted communication networks in the AD brain [14]. Finally, GFAVS may exert neuroprotective effects by modulating neuroinflammation, a critical driver of neurodegenerative processes in AD [15]. By reducing the production of pro-inflammatory cytokines and modulating glial cell activity, GFAVS creates a more favorable neuroenvironment, supporting neuronal health and potentially slowing the progression of the disease. Together, these mechanisms highlight the multifaceted potential of GFAVS as a therapeutic intervention for Alzheimer's disease, warranting further investigation into its clinical efficacy [14].

Earlier studies using 40 Hz visual or auditory stimuli in animal models of Alzheimer's disease (AD) showed significant reduction in β-amyloid plaques and cognitive improvement [16]. While these findings are encouraging, it is important to recognize that they are primarily based on early-phase studies, and the clinical utility of GFAVS remains to be fully validated. Further research has explored various stimulation methods, with multisensory 40 Hz stimulation (visual and auditory) offering stronger neuroprotective effects by promoting gamma rhythm synchronization in the brain. Initial clinical trials and smaller studies in individuals with mild cognitive impairment (MCI) and early-stage AD have shown cognitive improvements, supported by EEG evidence of gamma rhythm synchronization. Although promising, these findings are preliminary and require further clinical validation to confirm therapeutic efficacy [17].

The treatment of AD continues to present substantial challenges, as current pharmacological therapies are insufficient in effectively decelerating disease progression or significantly alleviating symptoms [18]. In recent years, GFAVS has emerged as a promising non-pharmacological therapeutic modality, demonstrating potential in enhancing cognitive function, fostering neural regeneration, and facilitating the clearance of amyloid plaques. However, existing research has been hindered by issues such as methodological variations, small sample sizes, and other limitations, which undermine the robustness of the findings. By conducting a systematic review and meta-analysis, it is possible to synthesize the available evidence, providing a comprehensive assessment of the safety and efficacy of GFAVS in AD treatment. This approach would offer a solid scientific foundation for its clinical application and establish clear guidance for future research. This is the first meta-analysis to evaluate the safety and efficacy of Gamma Frequency Auditory and Visual Stimulation in the treatment of Alzheimer's Disease. The significance of this study lies in its potential to uncover novel and effective treatment avenues for Alzheimer's disease, carrying both substantial academic and clinical implications.

METHODS

Protocol and registration

This research protocol adheres to the guidelines specified in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [19]. It has been registered in the Prospective International Registry of Systematic Reviews (PROSPERO) database under the identifier CRD42024593490.

Search strategy

A comprehensive search strategy was employed to identify relevant literature, focusing on terms related to {["Alzheimer Disease (MeSH)" OR "Dementias (MeSH)"] AND ["Gamma frequency light and sound stimulation (free terms) "]}. The search was conducted across multiple databases, including PubMed, Cochrane Library, PsycINFO, MEDLINE, Web of Science Core Collection and Embase covering all articles from the inception of each database up to November 1, 2025. We further searched ClinicalTrials.gov as a source of grey literature to locate summary results of completed or terminated trials that may remain unpublished in peer-reviewed journals. The search was restricted to the databases listed above. Detailed information regarding the search methodology is available in eTable 1 in Supplement 1. After removing duplicates, two authors independently screened the titles, abstracts, and full-text articles. Any disagreements were resolved through discussion and consensus. A flow diagram of the study selection process is presented in Fig. 1.

Eligibility criteria

The inclusion criteria for the studies were: (1) participants were older adults aged 50 years or above; (2) participants had a diagnosis of Alzheimer's Disease (AD) or Mild Cognitive Impairment (MCI) confirmed by a medical specialist using standardized clinical criteria; (3) the study design was a controlled trial, with the experimental group receiving Gamma-frequency auditory and visual stimulation and the control group receiving sham stimulation; (4) the studies reported at least one of the following outcome measures: adverse events, Mini Mental State Examination (MMSE) scores, Neuropsychiatric Inventory (NPI), Montreal Cognitive Assessment (MoCA), Alzheimer's Disease Assessment Scale–Cognitive Subscale-14 (ADAS-Cog14), and Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) scores. The exclusion criteria included: (1) profound hearing or visual impairment; (2) a history of seizures; (3) ongoing antiepileptic treatment.

Data extraction and risk of bias assessment

Data extraction was performed using Microsoft Excel, capturing key information such as the first author's name, publication year, country of publication, sample size, gender distribution, type of light therapy, pre-intervention MMSE score, and outcome data. The Cochrane risk of bias tool was utilized to assess potential bias in randomized controlled trials (RCTs), categorizing findings as low, unclear, or high risk of bias. For observational studies, including cross-sectional, cohort, and case-control studies, the Newcastle-Ottawa Quality Assessment Scale was applied, with findings categorized as low, medium, or high bias. Two reviewers independently conducted data extraction and bias assessment. Among the included RCTs, seven were assessed as having a moderate risk of bias, primarily attributable to limitations in randomization and blinding procedures, while three were

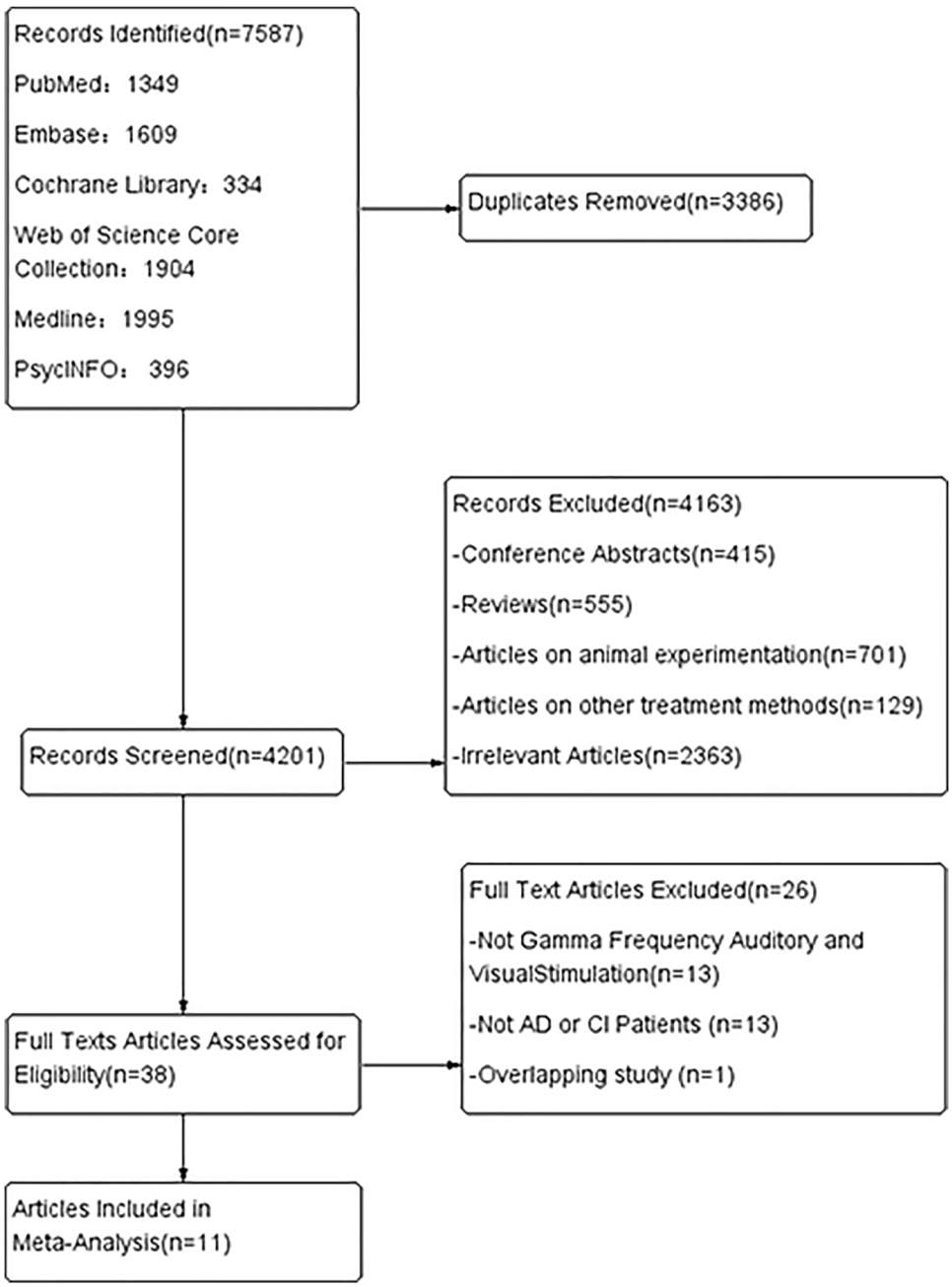

Fig. 1 Flow chart of literature search.

considered to have a high risk of bias. The single non-randomized case-control study was judged to carry a moderate risk of bias, mainly due to the absence of randomization.

Statistical analysis

Statistical analyses were conducted using RevMan statistical software (version 5.3; The Cochrane Collaboration) and STATA MP statistical software (version 14.0). Graphical editing and presentation were performed using Adobe Illustrator (version 27.8.1). For dichotomous outcomes, both the risk ratio (RR) and risk difference (RD) were calculated as summary effect measures to quantify the magnitude of intervention effects between treatment and control groups. Pooled RR estimates along with their 95% confidence intervals (CIs) were synthesized using a random-effects model (Der Simonian-Laird method), which incorporates between-study heterogeneity. In cases where statistical heterogeneity was low (I^2 < 50%), a fixed-effect model (Mantel-Haenszel method) was additionally employed as a sensitivity analysis to assess the robustness of the pooled RR estimates. Similarly, RD and its 95% CIs were computed and pooled using the same modeling strategy: random-effects model as the primary approach, with fixed-effect model applied under conditions of low heterogeneity (I^2 < 50%) for comparative validation. For continuous data, Mean Difference (*MD*) and Standardized Mean Difference (*SMD*) were employed as effect sizes. *MD* was used for absolute differences, while *SMD* was used for relative differences, especially when different measurement tools or scales were used across studies. Both *MD* and *SMD*, along with their *95% CIs*, were pooled using a random-effects model, with a fixed-effect model applied if heterogeneity was low (I^2 < 50%). Heterogeneity was assessed using the I^2 statistic, with values ranging from 0% to 100%, indicating the proportion of

variation due to heterogeneity rather than sampling error. $I^2 < 25\%$ was considered low heterogeneity, $25\% \leq I^2 < 50\%$ moderate, and $I^2 \geq 50\%$ high. Sensitivity analyses were conducted to test the robustness of results by recalculating pooled effect sizes on a study-by-study basis. Subgroup analyses were performed based on potential sources of heterogeneity, such as study design, participant characteristics, or type of intervention. Publication bias was assessed using funnel plots and Egger's tests, with asymmetrical funnel plots or significant Egger's test results indicating potential publication bias.

RESULTS

Study selection and characteristics

The study initially retrieved 7587 articles from six databases: 1609 from Embase, 1349 from PubMed, 334 from the Cochrane Library, 396 from PsycINFO, 1995 from Medline, and 1904 from the Web of Science Core Collection. After eliminating duplicates, 4201 studies remained. A preliminary screening based on titles and abstracts excluded 4163 articles that did not meet the study's criteria, leaving 38 articles for full-text review. Ultimately, 11 articles were included in the analysis (see Table 1 for details). The study population comprised patients diagnosed with Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI), totaling 415 participants. Detailed information regarding study design, diagnostic criteria, sex ratio, average age, intervention protocols, and outcome measures is provided in Table 1. The selected articles included 10 randomized controlled trials (RCTs) and one non-randomized case-control study. The risk of bias assessment for the RCTs, depicted in Fig. 2, indicated that 7 studies had a moderate risk of bias, while 3 had a high risk. The non-randomized case-control study was assessed to have a moderate risk of bias.

Safety

General safety. Safety was assessed based on the incidence of adverse events reported in five articles [20–24]. The experimental group experienced a 63.86% incidence of adverse events, compared to 62.07% in the control group. The heterogeneity test indicated no significant heterogeneity ($I^2 = 0\%$), allowing for data analysis using a fixed-effect model. The analysis revealed no statistically significant difference in the risk of adverse events between patients treated with 40 Hz light stimulation and those in the control group (RR = 0.99, 95% CI [0.78 to 1.26], $P = 0.93$; RD = -0.01, 95% CI [-0.16 to 0.14], $P = 0.93$). **(**Fig. 3A, eFigure 1A in Supplement 1**)**.

Specific adverse events. **Headache:** Three articles [20, 23, 24] reported headache occurrences during treatment, with an incidence of 13.79% in the experimental group and 6.85% in the control group. The heterogeneity test showed no significant heterogeneity ($I^2 = 0\%$), and a fixed-effect model was used for analysis. The results indicated no statistically significant difference in headache risk between the two groups (RR = 1.94, 95% CI [0.80 to 4.70], $P = 0.14$; RD = 0.11, 95% CI [-0.02 to 0.25], $P = 0.11$). **(**Fig. 3B, eFigure 1B in Supplement 1**)**.

Tinnitus: Tinnitus was reported in two articles [20, 24], with an incidence of 15.46% in the experimental group and 0.00% in the control group. The heterogeneity test showed no significant heterogeneity ($I^2 = 0\%$), and a fixed-effect model was applied. The analysis demonstrated a significantly higher risk of tinnitus in the experimental group compared to the control group (RR = 6.46, 95% CI [0.81 to 51.73], $P = 0.08$; RD = 0.16, 95% CI [0.04 to 0.28], $P = 0.01$). **(**Fig. 3C, eFigure 1C in Supplement 1**)**.

Dizziness: Three articles [20, 23, 24] reported dizziness, with an incidence of 4.29% in the experimental group and 8.89% in the control group. The heterogeneity test indicated no significant heterogeneity ($I^2 = 0\%$), and a fixed-effect model was used. The results showed no statistically significant difference in dizziness risk between the groups (*RR* = 0.53, *95% CI* [0.14 to 2.10], $P = 0.37$; RD = -0.04, 95% CI [-0.14 to 0.05], $P = 0.38$). **(**Fig. 3D, eFigure 1D in Supplement 1**)**.

Anxiety: Anxiety occurrences were reported in three articles [20, 22, 23], with an incidence of 4.11% in the experimental group and 10.64% in the control group. The heterogeneity test showed no significant heterogeneity ($I^2 = 0\%$), and a fixed-effect model was used. The analysis indicated no statistically significant difference in anxiety risk between the groups (*RR* = 0.46, *95% CI* [0.13 to 1.64], $P = 0.23$; RD = -0.06, 95% CI [-0.15 to 0.04], $P = 0.25$). **(**Fig. 3E, eFigure 1E in Supplement 1**)**.

Agitation: Two articles [20, 23] reported agitation, with an incidence of 3.08% in the experimental group and 7.50% in the control group. The heterogeneity test showed no significant heterogeneity ($I^2 = 0\%$), and a fixed-effect model was used. The results indicated no statistically significant difference in agitation risk between the groups (*RR* = 0.44, *95% CI* [0.09 to 2.16], $P = 0.31$; RD = -0.04, 95% CI [-0.14 to 0.05], $P = 0.38$). **(**Fig. 3F, eFigure 1F in Supplement 1**)**.

Disorientation: Disorientation was reported in two articles [20, 23], with an incidence of 0.00% in the experimental group and 7.50% in the control group. The heterogeneity test showed no significant heterogeneity ($I^2 = 0\%$), and a fixed-effect model was used. The analysis revealed no statistically significant difference in disorientation risk between the groups (*RR* = 0.16, *95% CI* [0.02 to 1.36], $P = 0.09$; RD = -0.07, 95% CI [-0.17 to 0.02], $P = 0.13$). **(**Fig. 3G, eFigure 1G in Supplement 1**)**.

Effectiveness

Structural changes in the brain. Six articles [20–22, 25–27] investigated structural changes in the brain during treatment. The heterogeneity test revealed significant heterogeneity ($I^2 = 91\%$), necessitating the use of a random-effects model for analysis. Substantial heterogeneity was observed ($I^2 = 91\%$) in the evaluation of brain structural changes, indicating variability among studies that should be considered when interpreting the meta-analytic findings. The results indicated significant differences in structural brain changes between patients receiving 40 Hz light stimulation and the control group (*SMD* = 1.74, *95% CI* [0.31, 3.18], $P = 0.02$). **(**Fig. 4**)**.

Cognitive function. Six articles [21, 22, 27–30] examined cognitive function during treatment. The heterogeneity test indicated moderate heterogeneity ($I^2 = 44\%$), and a random-effects model was used for analysis. The results showed no significant difference in cognitive function between patients treated with 40 Hz light stimulation and the control group (*SMD* = 0.16, *95% CI* [-0.36 to 0.68], $P = 0.55$). **(**Fig. 5**)**.

Ability of daily living activities. Four articles [22, 27–29] assessed the ability of daily living activities during treatment. The heterogeneity test revealed significant heterogeneity ($I^2 = 87\%$), requiring a random-effects model for analysis. The results indicated no significant difference in daily living activities between patients receiving 40 Hz light stimulation and the control group (*SMD* = 0.53, *95% CI* [-1.26, 2.33], $P = 0.56$). **(**Fig. 6**)**.

DISCUSSION

The potential of novel therapeutic interventions for Alzheimer's disease (AD) has garnered significant attention in recent years, particularly those that aim to enhance brain activity and mitigate the pathological features of the disease. One such approach is gamma-frequency stimulation, which has been investigated for its effects on the brain's neurophysiological processes. In earlier investigations, visual or auditory stimuli at a frequency of 40 Hz were employed to assess their effects on animal models of Alzheimer's disease (AD). These studies have demonstrated that γ-

Table 1. The characteristics of the participants.

	First author	year	country	illness	Study design	Sample size		Sex ratio (male/female)		Average age (year)		Therapeutic method	Stimulation duration	Outcome indicator
						active group	sham group	active group	sham group	active group	sham group			
01	Hyelim Chun, MD	2025	Korea	AD	RCT	13	13	3/10	4/9	69.31 ± 5.86	71.15 ± 8.09	Transcranial photobiomodulation(40 Hz light stimulation)	6 times per week for 12 weeks	K-MoCA,K-MMSE2, CERAD-K, GDepS
02	Xiao Da	2024	America	AD, MCI	RCT	33	17	10/23	10/7	69.21 ± 7.54	75.06 ± 11.26	40 Hz visual and auditory evoked gamma oscillations	1 h each day for 6 months	total corpus callosum, corpus callosum subregional areas, Annual atrophy rates in the corpus callosum
03	Kuan Ying Li	2024	China	AD	no RCT	35	43	12/23	15/28	80.8 ± 8.9	80.9 ± 7.0	40 Hz light stimulation	at least 5 h each day, 5 days each week, for a total of 12 weeks	Estimated MMSE, CASI score, CDR-SB, NPI-Q, ZBI
04	Mohammadreza Razzaghi	2024	Iran	AD, MCI	RCT	6	7	5/1	5/2	74.66 ± 14.40	75.85 ± 7.19	40 Hz light stimulation	lasting 20 min each day for 12 weeks	MoCA, HAM-A, HDRS, DAD
05	Mihály Hajós	2024	America	AD	RCT	42	28	19/23	15/13	69.8 ± 8.08	75.3 ± 9.95	40 Hz visual and auditory evoked gamma oscillations	1 h each day for 6 months	Safety and tolerability, MADCOMS, MMSE, ADCS-ADL, ADAS-Cog14, CDR-SB, ADCOMS, NPI, QoL, ZBI, iADRS, Amyloid PET imaging, Brain volumetric MRI, Correlations between brain volumetric MRI and clinical endpoints, Clinical outcomes stratified by baseline PET amyloid status
06	Xiao Da	2024	America	AD, MCI	RCT	25	13	7/18	8/5	68.36 ± 7.69	76.62 ± 9.97	40 Hz visual and auditory evoked gamma oscillations	1 h each day for 6 months	white matter structures, Myelin structures
07	Mikkel Pejstrup Agger	2023	Denmark	AD	RCT	5	6	2/3	1/5	72.2 ± 5.16	68.5 ± 9.77	40 Hz Invisible Spectral Flicker	12 weeks	Adverse events, feasibility, The Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-Cog) plus exec utive functioning (EF) and functional ability (FA), structural MRI
08	Diane Chan	2022	America	AD	RCT	8	7	3/5	2/5	77.6 ± 7.5	71.2 ± 8.2	40 Hz visual and auditory evoked gamma oscillations	1 h each day for 3 months	Safety and compliance of usage, Structural MRI, Functional MRI, Daily rhythmicity in activity, Cognitive function, Post-hoc testing for effect of years of education

Table 1. continued

	First author	year	country	illness	Study design	Sample size		Sex ratio (male/female)		Average age (year)		Therapeutic method	Stimulation duration	Outcome indicator
						active group	sham group	active group	sham group	active group	sham group			
09	Aylin Cimenser	2021	America	AD	RCT	14	8	4/10	3/5	66.5 ± 8.0	73.5 ± 6.6	40 Hz visual and auditory evoked gamma oscillations	1 h each day for 6 months	Safety, Adherence, Sleep Evaluated by Continuous Actigraphy Recordings, Effects of Gamma Sensory Stimulation on Sleep Quality Determined by Continuous Actigraphy Recordings, Functional Ability as Assessed by Alzheimer's Disease Cooperative Study Activities of Daily Living Was Maintained in Patients Treated With Gamma Sensory Stimulation
10	Qiliang He	2021	America	AD	RCT	5	5	3/2	2/3	72 ± 7.29	70.6 ± 5.85	40 Hz visual and auditory evoked gamma oscillations	1 h each day for 8 weeks	Tolerance, Adherence, Safety, EEG entrainment to flicker, Increased default mode network functional connectivity after 8 weeks of daily flicker, No significant changes in CSF Aβ and tau levels after 4 or 8 weeks of daily flicker, Altered levels of cytokines and immune factors in CSF after 8 weeks of daily flicker
11	Linda L. Chao	2019	America	dementia, AD	RCT	4	4	1/3	2/2	80.5 ± 6.5	79.0 ± 5.9	Photobiomodulation Treatments (40 Hz light stimulation)	3 times per week for 12 weeks	Behavioral outcomes: ADAS-Cog and NPI-FS, Imaging outcome: ASL perfusion, DMN activity

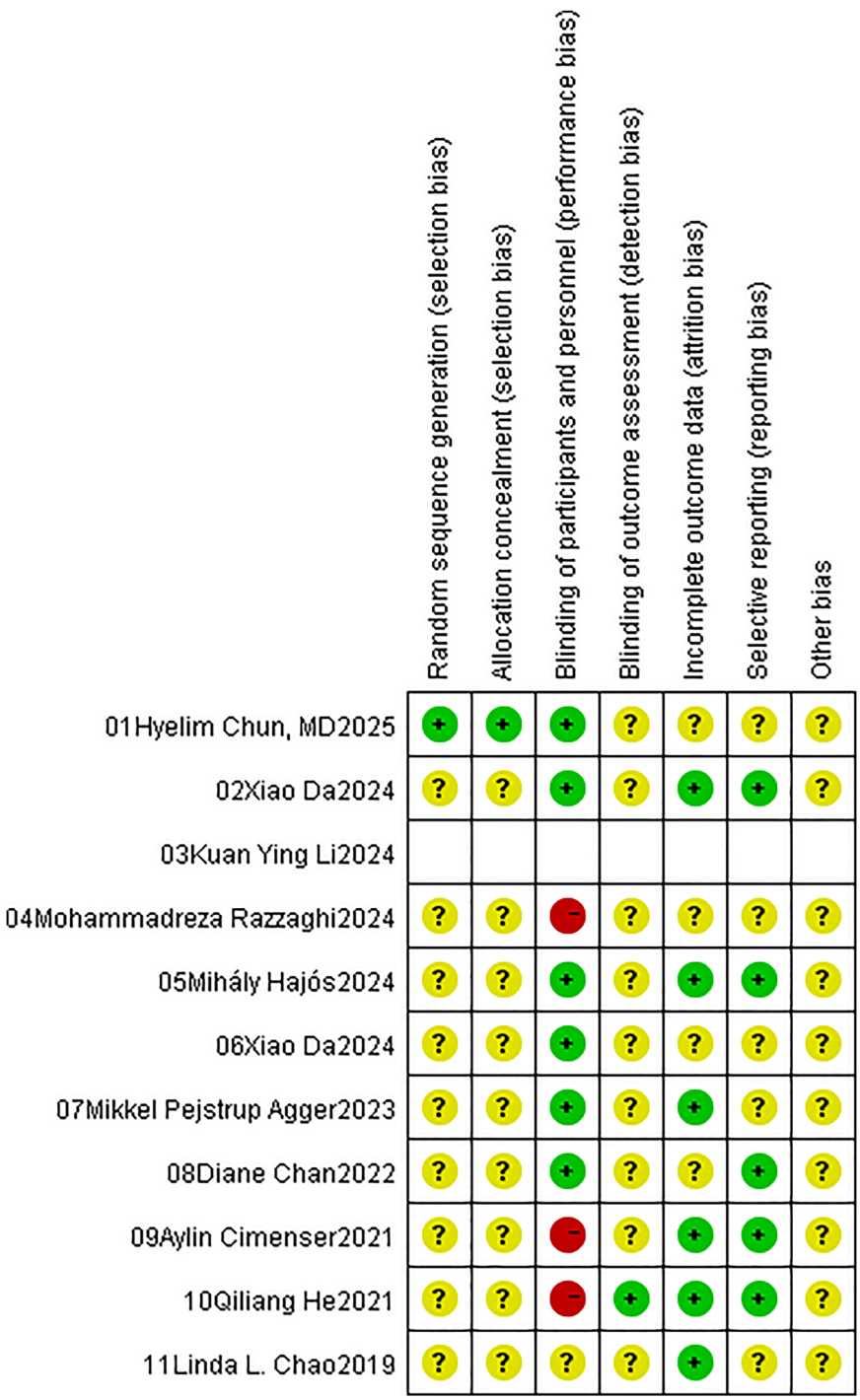

Fig. 2 Quality assessment of included studies.

frequency stimulation at 40 Hz significantly attenuates the accumulation of β-amyloid plaques and enhances cognitive performance in murine models. Further preclinical research has delved into the efficacy of various stimulation modalities in AD models, particularly in aging mice. Notably, multisensory stimulation at 40 Hz, incorporating both visual and auditory inputs, has been found to offer more robust neuroprotective effects. These findings suggest that such stimulation can foster synchronization of gamma rhythms in the brain, thereby improving neurological function [31]. Initial clinical trials and smaller-scale studies have indicated promising therapeutic effects of 40-Hz visual and auditory stimulation in individuals with mild cognitive impairment (MCI) and early-stage Alzheimer's disease. These investigations have reported improvements in cognitive function, with electroencephalographic (EEG) evidence supporting the synchronization of gamma rhythms in the brain. Several comprehensive reviews have synthesized the evolving body of research on gamma-frequency stimulation for AD, highlighting its potential in ameliorating cognitive decline, reducing neuroinflammation, and promoting brain plasticity. However, it is important to note that the majority of these findings are preliminary, and additional rigorous clinical validation is required to fully ascertain the therapeutic efficacy of this approach. Continued research in this field holds great promise for developing non-invasive treatments

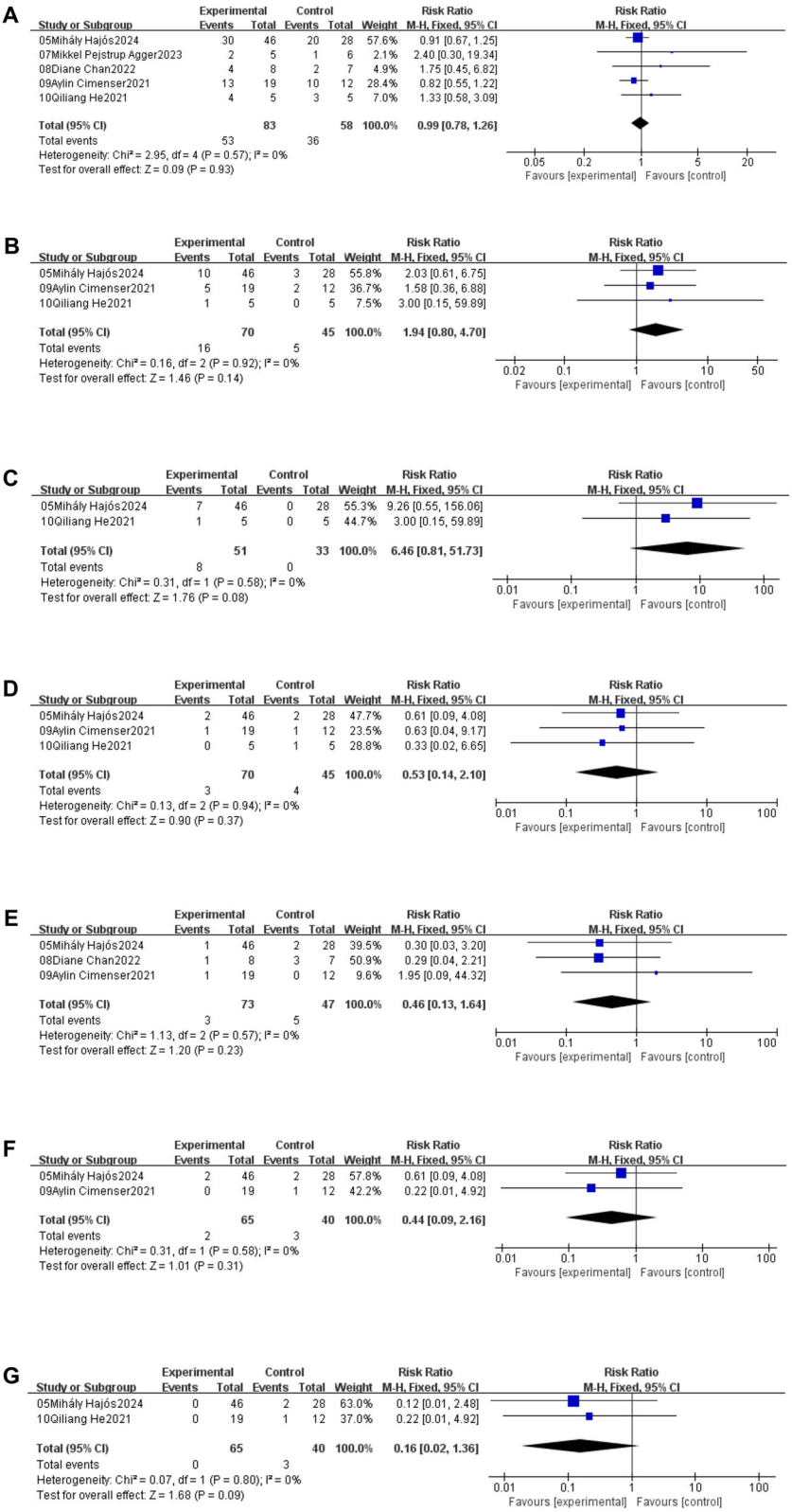

Fig. 3 **A** Forest plot of risk ratio (RR) for the incidence of adverse events. **B** Forest plot of risk ratio (RR) for the incidence of headache. **C** Forest plot of risk ratio (RR) for the incidence of tinnitus. **D** Forest plot of risk ratio (RR) for the incidence of dizziness. **E** Forest plot of risk ratio (RR) for the incidence of anxiety. **F** Forest plot of risk ratio (RR) for the incidence of agitation. **G** Forest plot of risk ratio (RR) for the incidence of disorientation.

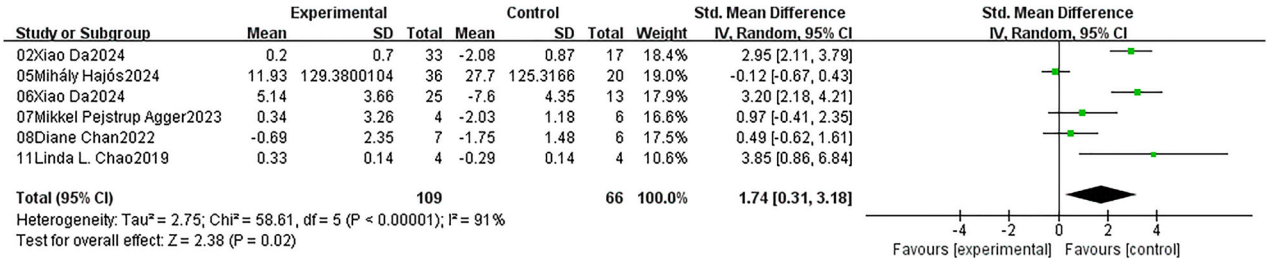

Fig. 4 Forest plot of structural changes in the brain.

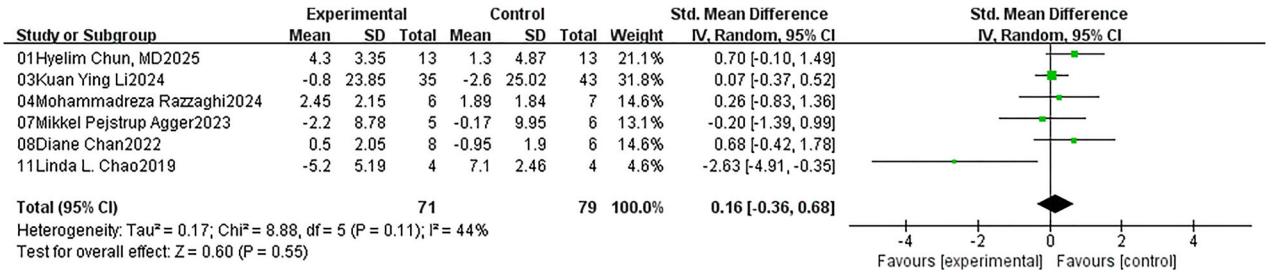

Fig. 5 Forest plot of cognitive function.

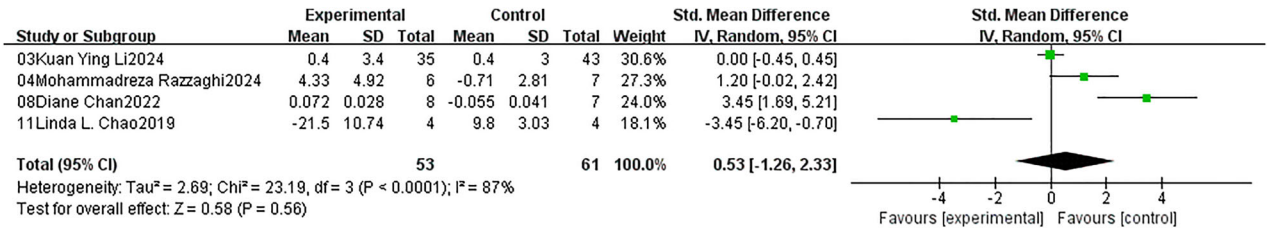

Fig. 6 Forest plot of ability of daily living activities.

that could offer a meaningful therapeutic option for individuals with Alzheimer's disease [32].

Overall effect and safety

The meta-analysis results indicate that 40 Hz light stimulation significantly improves brain structural changes in Alzheimer's Disease (AD) patients, with a standardized mean difference (SMD) of 1.74 (*95% CI* [0.31 to 3.18], $P = 0.02$). This effect is particularly pronounced in mixed populations of AD and mild cognitive impairment (MCI), where the SMD is 3.05 (*95% CI* [2.40 to 3.70], $P < 0.00001$). The observed changes can be attributed to several factors. Firstly, 40 Hz acousto-optic stimulation has been shown to induce vasoactive intestinal peptide (VIP)-expressing interneurons to release increased levels of VIP, which in turn enhances arterial pulsation. This process is significant because VIP plays a role in combating Alzheimer's disease and may facilitate the clearance of amyloid through the lymphatic system [31]. Secondly, GFAVS has been found to protect synaptic plasticity and mitochondrial function, both of which are potentially beneficial in the treatment of Alzheimer's disease [33]. While these mechanisms have been primarily demonstrated in preclinical studies, they offer promising avenues for future clinical research to establish their translational potential in human subjects. Regarding safety, the analysis reveals that 40 Hz light stimulation does not significantly increase the risk of total adverse events (*RR* = 0.99, *95% CI* [0.78 to 1.26], $P = 0.93$; *RD* = -0.01, *95% CI* [-0.16 to 0.14], $P = 0.93$). However, there is a notable increase in tinnitus incidence in the treatment group compared to the control group (*RR* = 6.46, *95% CI* [0.81 to 51.73], $P = 0.08$; *RD* = 0.16, *95% CI* [0.04 to 0.28], $P = 0.01$).

The potential causes of tinnitus induced by GFAVS can be attributed to several interconnected mechanisms. Firstly, GFAVS is known to induce neural oscillations, particularly in the gamma (γ) band, which may lead to synchronized neural activity affecting auditory system processing and the perception of tinnitus [8]. Secondly, this stimulation can selectively activate regions within the pontine cerebellum and auditory cortex, resulting in increased cerebral blood flow to the contralateral auditory cortex, superior temporal gyrus (STG), and ipsilateral posterior central gyrus. Such alterations in auditory cortex activity may contribute to the onset of tinnitus [8]. Additionally, GFAVS can alter the levels of certain neurotransmitters and metabolites, including adenosine, a neuromodulator involved in regulating sleep and wakefulness. Changes in adenosine levels may influence tinnitus perception in the auditory cortex [34]. Furthermore, the stimulation is implicated in intracellular energy metabolism pathways, affecting adenosine production, which may indirectly impact auditory system functioning and tinnitus development [35]. Moreover, GFAVS may influence auditory perception, including tinnitus, through transmodal interactions, such as those between auditory and visual systems [36].

Cognitive function and activities of daily living

Although 40 Hz light stimulation demonstrated beneficial effects on brain structure, it did not yield significant improvements in cognitive function (*SMD* = 0.16, *95% CI* [-0.36 to 0.68], $P = 0.55$) or activities of daily living (*SMD* = 0.53, *95% CI* [-1.26, 2.33], $P = 0.56$), underscoring the necessity for future studies to explore the underlying mechanisms linking structural and functional changes. The most critical finding of this study is that GFAVS demonstrates

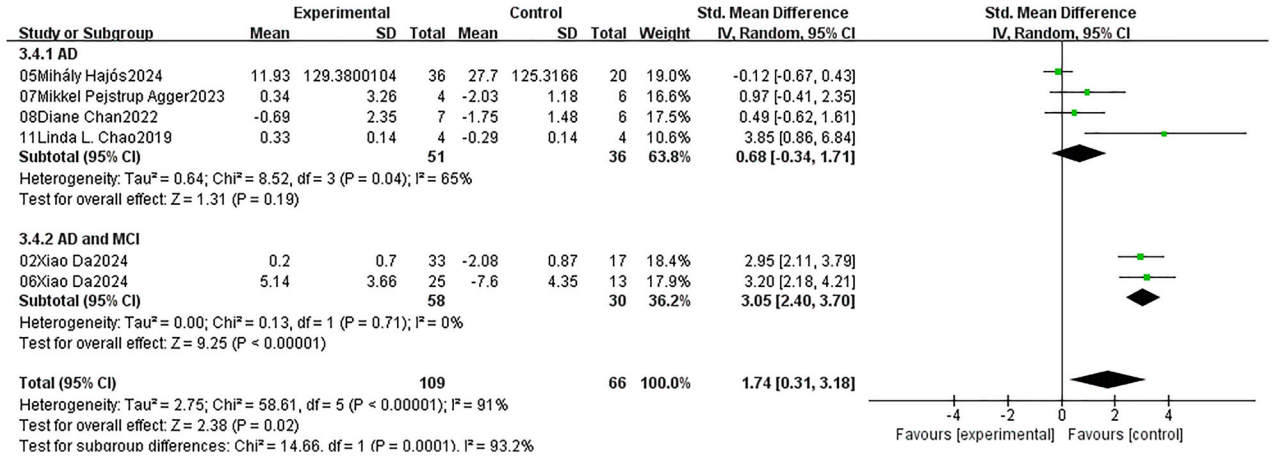

Fig. 7 Forest plot of the subgroup analysis for structural changes in the brain.

significant efficacy in inducing brain structural changes, yet this effect fails to translate into improvements in cognitive performance or activities of daily living. This dissociation between structural changes and functional benefits represents a central challenge in the field of neuromodulation and constitutes the primary focus of this discussion. To bridge this gap, future research should prioritize identifying intermediate biomarkers [37]—such as EEG synchronization patterns [38] or amyloid-beta (Aβ) clearance dynamics [39] — that can link structural alterations to functional gains and may thus serve as more proximal predictors of clinical efficacy. Additionally, further exploration of the mechanistic pathways linking GFAVS-induced structural changes (e.g., enhanced VIP-expressing interneuron populations [31] and improved glymphatic-mediated amyloid clearance) to measurable functional recovery is warranted.

The limited efficacy of GFAVS in improving cognitive and daily living skills in individuals with Alzheimer's disease may be attributed to several factors. First, insufficient treatment duration and frequency may play a crucial role. Studies suggest that effective therapeutic outcomes often require GFAVS to be administered consistently over a period of two weeks to two months or longer. In cases where the treatment duration is too short or the frequency of stimulation is inadequate, the intervention may fail to produce meaningful improvements in cognitive and functional abilities [34]. Second, individual differences and variations in treatment response further complicate outcomes. Factors such as genetic background, the stage of disease progression, and pathological characteristics can influence patients' responses to the intervention, leading to inconsistent efficacy across populations [40]. Third, the molecular mechanisms underlying the effects of GFAVS remain inadequately understood. While the technique has been shown to enhance synaptic plasticity and mitochondrial function, the precise molecular pathways that connect these changes to cognitive and functional improvements are yet to be fully elucidated [41]. Fourth, the specific and selective nature of the treatment may also contribute to its limited success. Evidence indicates that GFAVS may target specific brain regions or neural pathways, potentially leaving other regions critical for cognition and daily functioning relatively unaffected [42]. Additionally, the duration and sustainability of therapeutic effects present another challenge. Some studies suggest that the benefits of GFAVS may diminish once treatment is discontinued, indicating that ongoing intervention may be necessary to maintain therapeutic outcomes [34]. Fifth, the pathological complexity of Alzheimer's disease poses a significant hurdle. The disease involves multiple neurobiological processes, and it is unlikely that a single intervention, such as GFAVS, can address all associated cognitive and functional impairments [43]. Finally, limitations in clinical study design and results must be considered. Small sample sizes, inadequate study designs, and suboptimal evaluation tools may undermine the ability of clinical trials to fully capture the potential benefits of GFAVS [42].

In summary, the multifaceted reasons for the limited efficacy of GFAVS in Alzheimer's disease include factors such as insufficient treatment duration, individual variability, incomplete understanding of molecular mechanisms, the selective nature of the treatment, the complexity of Alzheimer's pathology, and methodological limitations in clinical studies. Future research should aim to address these challenges by refining therapeutic protocols, exploring the underlying mechanisms in greater depth, and improving clinical trial designs to optimize the potential of GFAVS as a treatment for Alzheimer's disease.

Heterogeneity and risk of bias

Substantial between-study heterogeneity was observed for brain-structural outcomes ($I^2 = 91\%$). This variability is attributable to differences in study design, participant characteristics and treatment parameters; however, the consistently limited sample sizes of the six included trials constitute the principal source of imprecision. Among the six studies that reported structural brain outcomes, all relied exclusively on magnetic resonance imaging (MRI). Five studies acquired high-resolution T1-weighted (T1w) anatomical sequences to quantify changes in brain structural volume [20–22, 26, 27], one study utilized T1-weighted (T1w) and T2-weighted (T2w) MRI acquisition sequences [25]. Despite this uniform reliance on MRI, heterogeneity remained pronounced ($I^2 = 91\%$) owing to differences in scanner manufacturers (Siemens or Philips) and slice thickness (1.2 mm or 0.9 mm). Consequently, although the pooled SMD suggested a positive structural effect, the wide confidence interval and high inconsistency limit the certainty of this conclusion. Subgroup analysis divided subjects into an AD group and an AD and MCI group. In the AD group, significant heterogeneity was observed ($I^2 = 65\%$), with no significant difference in structural changes between the treatment and control groups ($SMD = 0.68$, *95% CI* [-0.34, 1.71], $P = 0.19$). In contrast, the AD and MCI group showed no significant heterogeneity ($I^2 = 0\%$), with significant differences in structural changes between the treatment and control groups ($SMD = 3.05$, *95% CI* [2.40, 3.70], $P < 0.00001$). (Fig. 7) Of particular importance, the zero-heterogeneity ($I^2 = 0\%$) and large effect ($SMD = 3.05$) observed in the AD/MCI-mixed subgroup indicate that GFAVS may achieve its most consistent and potent structural benefits in broader, prodromal-stage populations. We therefore recommend that forthcoming efficacy trials prioritize the enrolment of such mixed cohorts; this strategy is expected to minimize between-study variance and provide the clearest demonstration of clinical benefit.

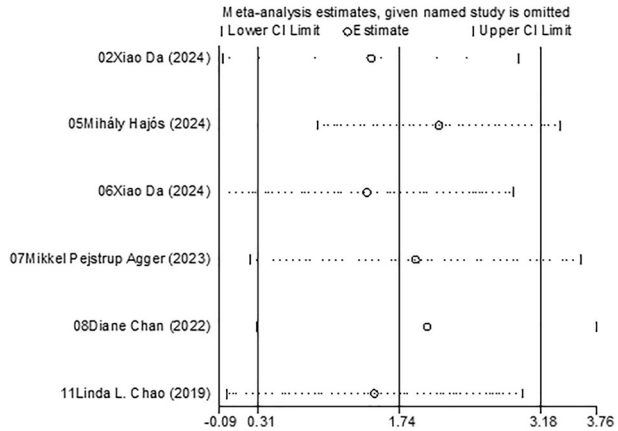

Fig. 8 Sensitivity analysis of structural changes in the brain.

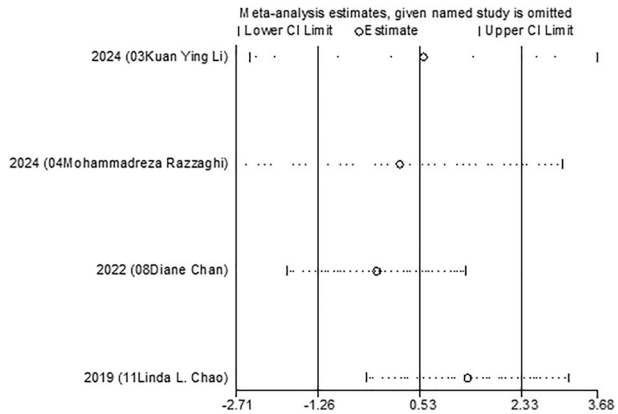

Fig. 9 Sensitivity analysis of ability of daily living activities.

The AD group also shows significant heterogeneity ($I^2 = 65\%$), potentially linked to individual differences in disease progression and treatment response. Conversely, no heterogeneity is observed in the mixed AD and MCI groups ($I^2 = 0\%$), suggesting a more uniform response to 40 Hz light stimulation in a broader patient population. Egger's regression test revealed no significant publication bias for Brain Structure ($t = 1.19$, $P = 0.300$) or Activities of Daily Living ($t = 0.37$, $P = 0.747$). Notwithstanding this reassuring finding, the included studies nevertheless carry a moderate-to-high risk of bias, stemming chiefly from inadequate randomisation and incomplete blinding. This methodological fragility, compounded by uniformly small sample sizes, yields imprecise effect estimates with correspondingly wide confidence intervals. Consequently, while the absence of publication bias strengthens the credibility of our summary effects, these limitations continue to constrain both the reliability and generalisability of the observed therapeutic benefits for GFAVS. We therefore underscore that large-scale, rigorously blinded trials with adequate statistical power remain essential to establish definitive evidence.

Sensitivity analysis

To assess the robustness of the pooled estimates we sequentially removed each individual study and recalculated the summary effect. The direction and magnitude of the combined estimates remained materially unchanged, indicating that no single trial dominated the results. (Figs. 8, 9).

Limitation

The included studies exhibited considerable variability in design, encompassing randomized controlled trials (RCTs), non-randomized controlled trials, and single-blind studies. This design heterogeneity may undermine the comparability of the results across studies. Several studies did not provide explicit details regarding the implementation of randomization and blinding procedures, which could introduce selection bias and placebo effects, thereby increasing the potential for confounding. Additionally, many studies were characterized by small sample sizes and insufficient statistical power, which may result in unstable findings and elevate the risk of false-negative results. The primary limitation of this meta-analysis lies in the limited number and small sample sizes of the included studies, which may constrain the robustness and generalizability of the findings. The observed heterogeneity (I^2 up to 91%) and the consistently small sample sizes jointly erode the reliability of the pooled estimates. High heterogeneity signals true diversity in treatment effects across studies, yet with limited participants per trial, random error predominates and can spuriously inflate or deflate effect sizes. Consequently, confidence intervals are wide, point estimates are unstable, and the generalizability of the results to broader AD and MCI populations remains uncertain. These limitations underscore that the current evidence is preliminary and should be interpreted cautiously until confirmed by adequately powered, harmonized RCTs.

There was also substantial variation in the diagnostic criteria and disease staging across studies, with some failing to report diagnostic criteria explicitly. This inconsistency may hinder accurate assessment of disease severity among study participants and, consequently, affect the ability to reliably compare treatment effects. Additionally, substantial heterogeneity in stimulation protocols and the relatively short follow-up durations across studies may limit the consistency and sustainability of the observed treatment effects. Moreover, substantial differences were observed in the parameters of gamma-frequency stimulation, such as stimulation frequency, duration, and treatment length, ranging from short-term (weeks) to long-term (months). These variations may affect the uniformity and comparability of the outcomes, thus limiting the ability to draw definitive conclusions regarding the optimal treatment protocols.

Moreover, the generalizability of the findings may be limited, as the majority of included studies were conducted in high-income countries, potentially restricting their applicability to more diverse populations. The majority of the included studies were conducted in a limited number of countries, with most focusing on patients with mild to moderate Alzheimer's disease (AD). This restricted study population may limit the generalizability of the findings, particularly in relation to patients from diverse ethnic, cultural, and disease severity backgrounds.

Despite these limitations, this review provides valuable insights into the potential efficacy of gamma-frequency auditory and visual stimulation in the treatment of AD. Future research should aim to further validate the safety and efficacy of gamma-frequency stimulation by utilizing larger sample sizes, employing more robust study designs, standardizing diagnostic criteria and outcome measures, and incorporating long-term follow-up.

Conclusion

This meta-analysis provides preliminary evidence for the safety of Gamma Frequency Auditory and Visual Stimulation (GFAVS) and its capacity to induce structural brain changes in individuals with Alzheimer's disease (AD) or mild cognitive impairment (MCI). However, its clinical efficacy in improving cognitive function and activities of daily living remains to be definitively established. A key insight emerging from this analysis is the observation of zero heterogeneity and a robust effect within the mixed AD/MCI subgroup, suggesting that GFAVS may be most effective in a broader, potentially earlier-stage population. Therefore, future research should prioritize large-scale, high-quality randomized controlled trials specifically designed to enrich for this mixed AD/

MCI population, thereby minimizing variability and conclusively determining efficacy. Such trials should also systematically investigate long-term treatment effects, individual response predictors, and optimal stimulation parameters to fully establish the clinical utility of gamma frequency stimulation.

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AUTHOR CONTRIBUTIONS

SJA: conceptualization, methodology, software, writing—original draft. XYZ: conceptualization, methodology, software, writing—original draft. JLH: methodology, software, validation. KYX: methodology, software, validation. XZD: software, supervision, validation. YG: methodology, visualization. XW: methodology, software. JHL: methodology, software, validation. XRL: visualization, review & editing. BC: visualization, review & editing. YL: visualization, review & editing. JHZ: conceptualization, supervision, writing—review & editing. SL: conceptualization, supervision, writing—review & editing.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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