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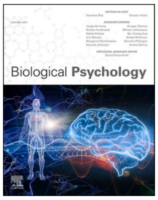

Review

Shaping gamma oscillations through sensory stimulation: A systematic review in healthy adults

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ABSTRACT

Gamma-band brain activity (30–80 Hz) plays a key role in sensory processing and cognitive functioning and is increasingly studied as a potential biomarker for neurological and psychiatric disorders. Recently, Gamma ENtrainment Using Sensory stimulation (GENUS) has emerged as a promising non-invasive approach to modulate this activity, with protocols targeting entrainment of intrinsic neural rhythms. However, substantial methodological variability persists across studies, limiting comparability and reproducibility. To better understand current practices and identify sources of heterogeneity, we reviewed 22 studies investigating gamma-band entrainment through visual, auditory, and multisensory stimulation in healthy adults. We summarized the main stimulation parameters and analytic methods used, discussed critical methodological challenges in evaluating entrainment efficacy, and proposed directions to improve standardization and interpretability. Our findings indicate that sensory modality, stimulus features (i.e., frequency, color), and individual differences shape gamma responses and must be carefully controlled in research and clinical settings. Although 40 Hz is the most frequently used frequency in entrainment studies, optimal effects vary across individuals and brain regions. Spatial patterns of activation also vary: visual stimulation primarily engages occipital-parietal regions, auditory protocols extend to fronto-temporal areas, and multisensory paradigms elicit broader and sometimes super-additive responses. Promising stimulation strategies for enhancing both response strength and participant comfort include invisible flicker, sinusoidal tones, and cross-sensory stimulation. This review highlights important implications for developing therapeutic GENUS protocols and provides guidelines for the stimulation and measurement of gamma responses in experimental and clinical settings.

1. Introduction

Neural oscillations are rhythmic patterns of activity, reflecting the coordinated firing of large populations of neurons. Gamma-band oscillations (30–80 Hz) are frequently associated with high-level cognitive functions such as attention, working memory, and sensory integration (Bosman et al., 2014; Cannon et al., 2014; Chan et al., 2022); they were initially proposed by Wolf Singer and colleagues as a mechanism for perceptual binding and large-scale neural coordination (Gray et al., 1989; Engel & Singer, 2001).

Gamma rhythms are generally thought to arise from the dynamic interplay between excitatory pyramidal neurons and inhibitory interneurons, supporting efficient communication across distributed brain networks (Antonoudiou et al., 2020). Although they share a common principle of rhythmic feedback, multiple circuit mechanisms are described to generate this activity. Early studies provided the first mechanistic insights into how gamma oscillations arise from local circuit interactions. Traub et al. (1996) first demonstrated that interconnected inhibitory interneurons networks can sustain coherent gamma activity across long distances, with spike doublets enabling synchronization despite conduction delays (Traub et al., 1996). Later, Börgers and Kopell (2003) showed that reciprocal interactions between excitatory and inhibitory neurons could robustly generate gamma rhythms in sparsely connected networks when inhibition is fast and strong, highlighting the

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critical role of excitation-inhibition balance.

Building on these foundational works, two principal frameworks have been established to explain gamma generation. In the interneuron gamma model, rhythmic activity emerges from mutual inhibition among GABAergic interneurons under tonic excitatory drive, whereas in the pyramidal–interneuron gamma model, oscillations result from alternating cycles of pyramidal-cell excitation and feedback inhibition from interneurons (Fernandez-Ruiz et al., 2023).

Because gamma oscillations are sensitive to the brain's excitatory-inhibitory balance, their disruption has been increasingly studied as a marker of neuropsychiatric dysfunction. Abnormal gamma band responsiveness, defined as the magnitude and reliability of gamma-band activity elicited by sensory stimulation, has been implicated in a variety of neurological and psychiatric conditions, including Alzheimer's (Yao et al., 2020) and Parkinson's (Guerra et al., 2022) diseases, schizophrenia (Gonzalez-Burgos et al., 2015) and autism spectrum disorder (Hashemi et al., 2017). In Alzheimer's disease, in particular, altered gamma rhythms have been identified as early electrophysiological markers that may precede clinical symptoms (Blanco-Duque et al., 2024). These findings have sparked interest in the therapeutic potential of modulating gamma activity, with the goal of restoring circuit integrity and enhancing cognitive functions in at-risk or symptomatic individuals (Adaikkan & Tsai, 2020).

Among the available strategies, neural entrainment appears to be one of the most promising. Various approaches have been proposed to modulate or entrain gamma oscillatory activity, including pharmacological interventions (Jankovic & Tan, 2020), invasive electrical stimulation (Ni et al., 2016), and non-invasive brain stimulation techniques such as transcranial alternating current (Liu et al., 2018; Benussi et al., 2021) or transcranial magnetic (Traikapi & Konstantinou, 2021) stimulations. While some of these methods have obtained encouraging results, they also present notable limitations, such as poor spatial specificity, limited tolerability, safety concerns, or inconsistent effects across individuals (for a review, see Adaikkan & Tsai, 2020). In light of these challenges, sensory rhythmic stimulation by means of auditory, visual, tactile or multisensory stimuli, also known as Gamma ENtrainment Using Sensory stimulation (GENUS), is emerging as an interesting, non-invasive and well-tolerated option for the neuromodulation of brain rhythms.

1.1. Conceptual foundations of GENUS

GENUS is a non-invasive method to influence brain activity by leveraging the brain's natural resonance to rhythmic sensory input (Park & Tsai, 2025). Delivered through visual, auditory, tactile stimulation, or combined, multisensory, modalities, this approach engages sensory pathways to induce oscillatory activity in targeted neural circuits. Compared to pharmacological or electrical stimulation, sensory-driven protocols are more physiologically grounded and better tolerated, offering greater translational potential (Martorell et al., 2019; Park & Tsai, 2025).

A particularly promising line of GENUS research focused on 40 Hz stimulation in Alzheimer's disease animal models, where rhythmic sensory input has shown to modulate gamma activity while reducing amyloid and tau accumulation, enhancing microglial function, and improve cognitive performance (Iaccarino et al., 2016; Adaikkan & Tsai, 2020). These findings have led to early-phase human trials showing that this kind of sensory stimulation is well tolerated and capable of modulating neural activity in cortical and subcortical regions (Chan et al., 2022). Furthermore, multisensory protocols, which synchronize visual and auditory stimuli while compensating for sensory processing delays, appear particularly effective, with evidence of robust entrainment in brain regions such as the hippocampus and amygdala (Martorell et al., 2019; Blanco-Duque et al., 2024).

However, across GENUS studies, there is substantial heterogeneity in experimental paradigms, including stimulation type and duration, as well as in the measures used to assess entrainment. To clarify the current state of the field, this review systematically examines existing evidence on sensory gamma entrainment in healthy adults. We focus on three interrelated domains. First, we address conceptual ambiguities in the definition of gamma responses. Second, we evaluate methodological considerations related to the detection and characterization of gamma activity using non-invasive electrophysiological techniques such as EEG and MEG. Third, we analyse empirical variability in stimulation protocols, sensory modalities, and outcome measures. By mapping current practices and identifying recurring limitations, this review aims to advance the development of more consistent, comparable, and effective approaches to gamma entrainment in both research and translational contexts.

1.2. Classifying gamma-band responses: conceptual models and terminology

A central question in GENUS literature concerns the absence of a unified framework for defining and classifying the resulting neural responses. Sensory stimulation in the gamma range can elicit a range of effects, some precisely phase-locked to the driving stimulus, others more diffuse and not phase-aligned, reflecting distinct underlying mechanisms.

From the perspective of dynamical systems theory, entrainment occurs when an oscillator's phase becomes synchronized with an external periodic drive, maintaining a stable phase relationship over time (Rosenblum et al., 2001; Tass et al., 1998). This mathematical formulation provides the conceptual basis for interpreting entrainment as a phase-alignment between intrinsic brain rhythms and extrinsic rhythmic sensory stimulation.

Building on this principle, Ichim et al. (2024) proposed a neuroscientific taxonomy for classifying gamma-band responses to rhythmic sensory input, distinguishing three major categories: (i) *Entrained gamma*, referring to phase-locked neural responses that synchronize with rhythmic stimuli; (ii) *Induced gamma*, reflecting increases in gamma power without consistent phase alignment; (iii) *Spontaneous gamma*, representing ongoing oscillatory activity in the absence of stimulation.

Although this taxonomy provides conceptual clarity, the operational definition of entrainment remains a subject of debate. Some authors adopt a narrow view, defining entrainment strictly as the phase alignment of ongoing endogenous oscillations to an external periodic input, characterized by features such as phase concentration and persistence after stimulus offset (Ng et al., 2013; Hanslmayr et al., 2019). Others favor a broader definition, suggesting that consistent phase-locking, even without evidence of intrinsic oscillators, is sufficient to define entrainment (Ichim et al., 2024). A third perspective emphasizes the need for resonance between the stimulation frequency and intrinsic neural dynamics (VanRullen & Macdonald, 2012).

These theoretical differences challenge cross-study comparisons and highlight the need for greater clarity in terminology and methodological consistency in assessing gamma-band responses.

1.3. Methodological considerations for measuring gamma-band activity

Detecting and quantifying gamma-band responses to sensory stimulation presents several methodological challenges. These include technical limitations of non-invasive recordings, inconsistencies in analytic approaches, and the frequent use of indirect or insufficient metrics (Griffiths et al., 2023; Wu et al., 2025; Hyafil et al., 2015).

An essential starting point is to clarify what is meant by 'gamma-band activity' from an electrophysiological perspective. While increases in gamma-band power are often interpreted as evidence of neural oscillations, this interpretation can be misleading.

Gamma power recorded with EEG or MEG sensors may reflect not only oscillations but also widespread, asynchronous spiking and synaptic activity, particularly at higher gamma frequencies (the so-called 'high-gamma' range; Ray & Maunsell, 2011). The observed signal thus represents a mixture of true periodic oscillations, transient bursts, and changes in the aperiodic (1/f) background spectrum (Donoghue et al., 2020). Consequently, an increase in gamma-band power alone does not necessarily indicate a genuine oscillatory process or enhanced rhythmic synchrony. In line with this, recent works argue that the superposition of broadband high-frequency activity (i.e., aperiodic increases in synaptic drive and firing) is often related to unpredictable inputs, while narrowband gamma oscillations emerge when inputs are highly regular and predictable (Vinck et al., 2025).

In the context of entrainment detection, EEG is limited by its low spatial resolution and high susceptibility to artifacts, which can obscure the distinction between different types of gamma responses (Zoefel & Heil, 2013). Furthermore, measuring gamma power, particularly in the high-gamma range, can be technically demanding with EEG. Standard preprocessing pipelines often apply low-pass filters around 40 Hz to suppress line noise and muscle artifacts, which may inadvertently attenuate or exclude higher-frequency components (Yuval-Greenberg et al., 2008). This filtering convention likely contributes to the underrepresentation of induced high-gamma effects in the broader EEG literature.

By contrast, MEG, with its higher spatial resolution, has successfully demonstrated the coexistence of broadband gamma activity and externally driven narrowband flicker responses, particularly in the visual cortex (Duecker et al., 2021; Erickson et al., 2022).

Although increases in spectral power remain the most common indicator of gamma responses (Schwarz & Taylor, 2005; Draganova et al., 2008; Karino et al., 2006; Sugiyama et al., 2022; Bayram et al., 2011; Henney et al., 2024), phase-based analyses provide complementary insights by quantifying the consistency of phase alignment across trials (Takai et al., 2025; Yoon et al., 2025). However, these approaches are also subject to limitations, as they can be confounded by trial variability and physiological artifacts such as micro-saccades or muscle activity (Yuval-Greenberg et al., 2008).

To improve entrainment detection in the gamma range, recent studies have employed single-trial analyses and high-resolution signal decomposition methods such as superlets, which enhance both temporal and spectral resolution (Ichim et al., 2024). These methods help disentangle overlapping signal components and better characterize the dynamics of gamma responses.

Another issue is the substantial variability in stimulation protocols and outcome measures of studies using sensory stimulation to elicit gamma-band activity report. Such variability reflects the complex interplay between different factors such as the adopted sensory modality, type and frequency of the sensory stimulation, along with other methodological choices (Park & Tsai, 2025). While the 40 Hz stimulation is often used as a reference in GENUS protocols, particularly in those inspired by animal models (Iaccarino et al., 2016; Chan et al., 2022), its effectiveness is far from universal. Moreover, studies employing other gamma-range frequencies have demonstrated that neural responsiveness varies across individuals and brain regions, suggesting that no single frequency is optimal for all contexts (Manippa et al., 2024).

Variability is also modality-dependent. Visual, auditory, and multisensory protocols differ not only in terms of perceptual qualities, but also in the spatial and temporal characteristics of the elicited neural responses (Martorell et al., 2019; Borges et al., 2023). These differences complicate cross-study comparisons and raise questions about how modality-specific dynamics influence the likelihood or detectability of gamma responses.

Finally, inter-individual factors further contribute to the heterogeneity of findings. Age, baseline EEG characteristics, and individual differences in sensory processing can all modulate the strength, spatial distribution, and stability of stimulation-evoked gamma responses (Duecker et al., 2021; Michael et al., 2023; Yoon et al., 2025). As highlighted by Ingendoh et al. (2023), even under standardized conditions, individual traits can substantially influence outcomes, underscoring the need for personalized or adaptive approaches to protocol design.

1.4. *Aim of the present study*

Building on recent theoretical advances (e.g., Ichim et al., 2024; Duecker et al., 2024), the present review systematically examines studies employing GENUS in healthy adults. We critically analyse how gamma-band responses are defined, operationalized, and measured across sensory modalities, and map entrainment protocols efficacy in terms of elicited neural outcomes. Specifically, we categorize studies by their stimulation parameters, methodological approaches, and key neural measures - namely, amplitude changes, phase alignment, and spatial propagation of gamma activity.

2. Materials and methods

2.1. *Search strategy*

We conducted a systematic search in April 2025 using PubMed and Scopus databases to identify relevant studies investigating gamma-band neural activity entrained by sensory stimulation in healthy humans. The search was limited to English-language original research articles, with no restrictions on publication date.

Separate search strategies were developed for each sensory modality (visual, auditory, tactile, and multisensory) to ensure comprehensive coverage of gamma-range sensory stimulation. Search terms targeted sensory stimulation of gamma band activity and were applied to titles, abstracts, and keywords where applicable. The full search syntaxes and retrieval count for each modality and database are provided in Supplementary Table 1.

For visual stimulation, terms included photic stimulation, visual flicker, and light stimulation, combined with gamma-related keywords and filters for healthy populations. Auditory queries focused on auditory click, binaural beats, and Auditory Steady-State Responses (ASSR) in the gamma range. Multisensory searches combined visual and auditory terms such as audiovisual and bimodal stimulation, while tactile queries included vibrotactile and somatosensory stimulation, all linked to gamma activity and excluding clinical populations.

Duplicates were removed manually prior to screening. To include additional relevant studies, citation tracking of included articles and hand-searching of recent reviews were also performed to mitigate indexing gaps or terminological inconsistencies.

2.2. *Eligibility criteria*

Studies were eligible for inclusion if they met the following criteria: (1) employed gamma rhythmic sensory stimulation - specifically visual, auditory, tactile, or multisensory; (2) involved healthy human participants, regardless of age; and (3) reported neural measures of entrainment gamma activity obtained through EEG or MEG.

Studies employing cognitive paradigms, such as tasks assessing memory, decision-making, or problem-solving abilities, were excluded to minimize confounding influences related to endogenous neural activity. These tasks are known to independently modulate gamma oscillations, making it difficult to isolate the effects of sensory stimulation. In contrast, studies that employed simple vigilance or detection tasks were retained, as these allow for sustained attention without introducing significant task-related modulation of oscillatory activity.

Additional exclusion criteria included studies using pharmacological interventions, non-human models, or non-sensory stimulation methods (such as transcranial alternating current stimulation) and studies lacking direct neural measurements of gamma activity. No exclusions were made based on whether the study explicitly pursued entrainment: given that the characterization of neural rhythmic responses is itself a central object of evaluation of entrainment efficacy in this review, all studies employing rhythmic sensory stimulation and EEG/MEG phase-locking analyses were considered eligible.

2.3. Study selection

The initial database search yielded 99 records: 69 from Scopus and 30 from PubMed. After removing 22 duplicate entries, 77 records remained for full-text consideration and underwent a more detailed eligibility assessment. Seventy-two studies were excluded at this stage because they did not meet the aforementioned inclusion criteria (n = 61), or used cognitive tasks (n = 4**)**, pharmacological interventions (n = 2), or applied non-sensory stimulation methods (transcranial Alternating Current Stimulation, tACS; n = 5).

Additional 17 records were identified through citation searching of included articles and relevant literature reviews, in light of the relatively scarce and fragmented nature of research on sensory-driven gamma-band entrainment in healthy populations.

At the end, 22 studies met the inclusion criteria and were incorporated into the final synthesis. All the included studies applying visual (n = 12), or auditory (n = 6), or multisensory (audiovisual and/or cross-modal; n = 4) stimulations. While no studies employed tactile stimulation as the sole modality, one multisensory study included a tactile component alongside other sensory inputs.

The complete study selection process is summarized in the PRISMA 2020 flow diagram (Fig. 1).

2.4. Quality assessment

The methodological quality of the included studies was assessed using the "Quality Assessment Tool for Before–After (Pre–Post) Studies With No Control Group" developed by the U.S. National Heart, Lung, and Blood Institute (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). This tool was selected because most included studies employed within-subject designs without independent control groups. It comprises 12 criteria covering participant selection, intervention fidelity, outcome measurement, and statistical analysis.

It is worth noting that, since the primary objective of these studies was to assess the effects of acute GENUS (i.e. effects of single stimulation session), outcome measures were predominantly collected during stimulation and rarely immediately after. Accordingly, the tool was pragmatically applied to all studies to allow consistent quality assessment. For question 10 ("Were statistical methods used to examine pre-to-post changes, with p-values reported?"), studies that compared baseline to during-stimulation data using appropriate statistical analyses were rated as "Yes." In contrast, for question 11 ("Were outcome measures taken multiple times before and after the intervention?"), only studies that included any post-stimulation assessments, typically limited to a single time point, were rated as "Yes."

Two reviewers independently assessed each study (A.R.L., L.Z.), with disagreements resolved by consensus. Ratings informed the narrative synthesis but were not used as inclusion/exclusion criteria.

2.5. Data extraction and outcome measures

Full-text articles meeting the eligibility criteria were reviewed in detail, and relevant information was inserted into a structured spreadsheet. This information included publication year, sample size, participant demographics, manipulated stimulation parameters (e.g., luminance, frequency, duration, modality), recording technique (EEG or MEG), and outcome measures related to gamma-band activity and entrainment.

The primary outcome was neural activity in the gamma range (30–80 Hz) elicited by rhythmic sensory stimulation, assessed through

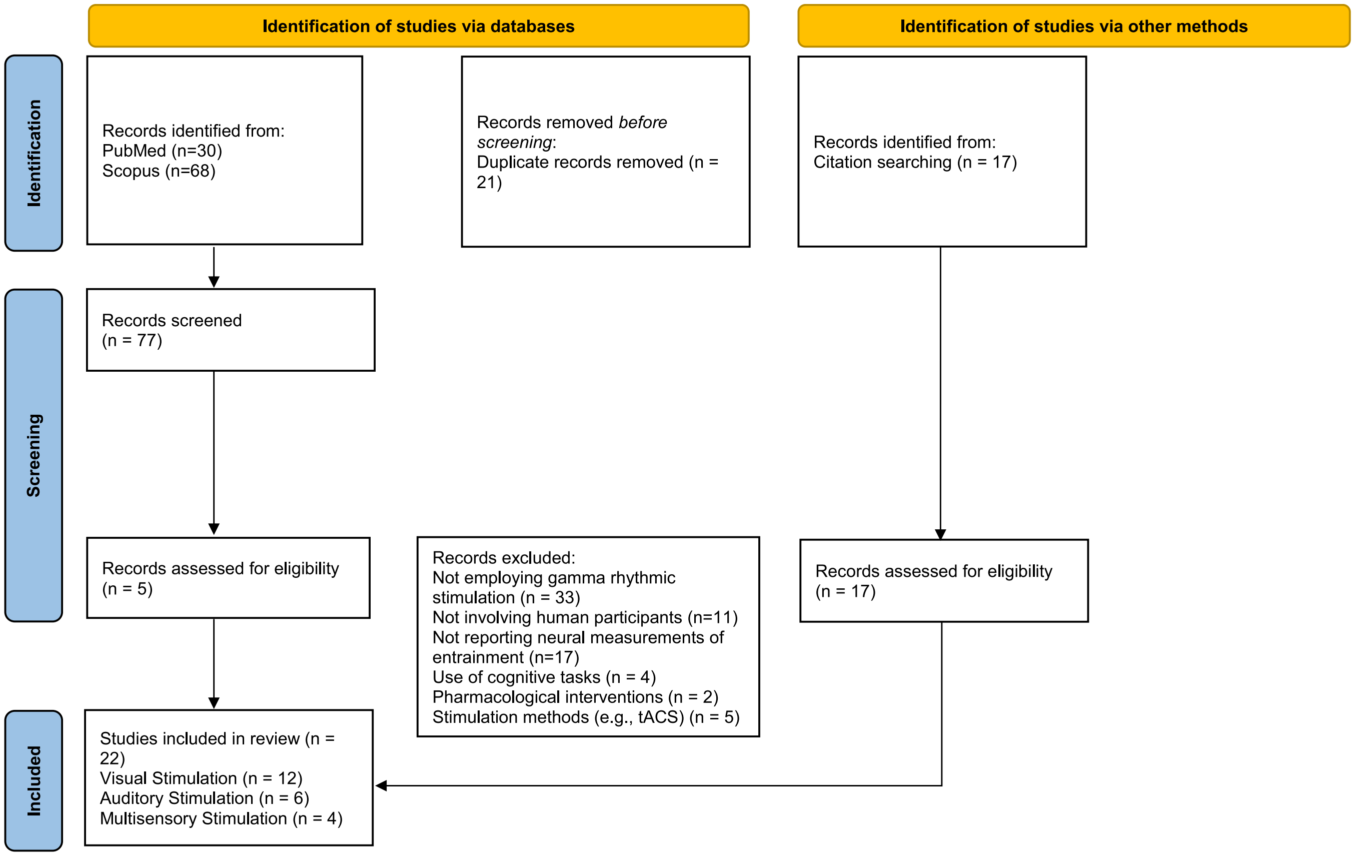

Fig. 1. PRISMA 2020 flow diagram for the present systematic review which included searches of databases, registers and other sources.

metrics such as spectral power, phase synchrony, and coherence. Phase-locking indices and time–frequency analyses were also reviewed to evaluate the temporal alignment between the stimulus and the neural response, and therefore the efficacy of entrainment.

To structure comparisons across studies, we grouped outcomes into three analytical dimensions: (1) Amplitude: changes in gamma power relative to baseline, (2) Phase-locking: consistency of neural phase relative to the stimulus rhythm, and (3) Spatial propagation: extent and distribution of gamma activity across cortical areas. These dimensions allowed for a systematic evaluation of how different stimulation protocols, modalities, and inviduals' characteristics influenced gamma entrainment.

3. Results

3.1. *Quality assessment of included studies*

Methodological quality across the 22 included studies varied across specific domains rather than following consistent patterns. Most studies clearly reported participant eligibility criteria, described the stimulation procedures, and used established EEG or MEG methods to assess gamma-band activity. However, several key methodological elements were inconsistently reported.

Only a minority of studies (n = 5; 22.7 %) included post-stimulation measurements, limiting the possibility to assess whether modulation effects persisted beyond the stimulation window (e.g., Lee et al., 2021; Han et al., 2023; Wu et al., 2025; Jirakittayakorn & Wongsawat, 2017). The remaining studies exclusively focused on online responses (e.g., Agger et al., 2022; Chan et al., 2022; Duecker et al., 2021). Statistical analyses were generally appropriate: 90.9 % of studies (n = 20) reported formal comparisons between baseline and stimulation periods with associated p-values (e.g., Noda et al., 2021; Yi & Wang, 2022).

Sample size justification was reported in only 4.5 % of studies (n = 1). Several studies lacked detailed descriptions of outcome timing or stimulation fidelity (e.g., Bayram et al., 2011; Jones et al., 2019), potentially limiting replicability.

Overall, while most studies met basic methodological standards and reported neural outcomes using appropriate tools, heterogeneity in reporting, outcome timing, and statistical transparency suggests a need for more standardized practices. Detailed item-level responses for each study are provided in Supplementary Table 2.

4. Visual stimulation studies

4.1. *Sample characteristics*

The 12 studies (14 experiments) employing visual stimulation collectively included 1756 healthy participants, with a mean age of approximately 28 years. Most studies recruited young adults (age: 20–35 years), though some targeted older adults (e.g., Yoon et al., 2025, age: 65–70 years). Gender distribution was nearly balanced in the majority of studies (50.7 % male, 49.3 % female). Sample sizes ranged from case studies (Jones et al., 2019) to large retrospective cohorts (Zibrandtsen et al., 2020, n = 1464), with most studies enrolling 13–44 participants (see Supplementary Table 3).

4.2. *Definitions and measures of gamma responses*

Gamma responses were mainly assessed reporting power increase phase-locked to rhythmic stimulation. Entrained responses were typically assessed using Steady-State Visual Evoked Potentials (SSVEPs) or phase-locking metrics (e.g., Bayram et al., 2011; Henney et al., 2024). See Table 1 for further details on analytic methods and response type categorization.

Table 1
Gamma entrainment metrics and definitions across visual studies.

	First author	Year	Measure(s) used	Operational definition
1	Agger et al.	2022	Power Spectral Density analysis using Welch method; Signal-to-Noise Ratio (SNR); EEG and fMRI to assess cortical and subcortical responses.	Entrainment defined as a significant increase in 40 Hz SNR during exposure visual stimulation.
2	Bayram et al.	2011	Steady-State Visual Evoked Potentials (SSVEPs) measured via EEG; Amplitude of Fundamental and Harmonic Peaks	Entrainment defined as stable SSVEP peaks at stimulation frequency and harmonics (e.g., 40 Hz) during visual flicker stimulation. Confirmed by reproducible amplitude increases at resonant frequencies (10, 20, 40 Hz), and corresponding EEG-fMRI coupling.
3	Duecker et al.	2021	Time-Frequency Representations; Phase-Locking Value between MEG and photodiode signal to assess synchronization; Phase Plateau Analysis; Relative Power Change	Entrainment defined by phase-locking and/or a frequency shift of endogenous gamma oscillations toward the driving flicker frequency (phase entrainment or frequency entrainment).
4	Hansen et al.	2024	Signal to noise ratio (SNR)	Entrainment is operationalized as a significant increase in SNR at 40 Hz in the EEG power spectrum. The SNR is calculated using the Welch method and reflects how prominent the 40 Hz peak is compared to surrounding frequencies. Entrainment is interpreted as successful when SNR at 40 Hz is significantly higher for flickering stimuli than for control (non-flickering) light.
5	Henney et al.	2024	Steady-State Visually Evoked Potentials (SSVEPs); Signal-to-Noise Ratio (SNR); Power Spectral Density	Entrainment was defined as an increase in 40 Hz SSVEP response (measured by SNR) during 40 Hz heterochromatic flicker stimulation, compared to baseline.
6	Jones et al.	2019	Power Spectral Density (PSD)	Entrainment Exceeding Threshold metric: Entrainment was defined as a peak at 40 Hz that exceeded the baseline PSD by a threshold of 1 unit in power; widespread electrode activation indicated stronger entrainment.
7	Lee et al.	2021	Event-Related Spectral Perturbation; Steady-State Visually Evoked Potentials (SSVEPs); Spectral Granger Causality (sGC)	Entrainment defined as an increase in SSVEP power at the stimulus frequency (32–50 Hz) during flickering light stimulation compared

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Table 1 (*continued*)

	First author	Year	Measure(s) used	Operational definition
				to baseline. Propagation: evidence of gamma activity spreading from visual cortex to other brain regions via sGC analysis.
8	Noda et al.	2021	Power Spectral Density; Steady-State Visual-Evoked Potentials; Phase-Amplitude Coupling	Entrainment defined as increased EEG power around 40 Hz during 40 Hz violet light or white light stimulation compared to baseline. Additional evidence through enhanced alpha-gamma phase-amplitude coupling.
9	Petro et al.	2024	Time-Frequency Analysis of MEG; Baseline-normalized Gamma Power; Virtual Sensor Extraction; Functional Connectivity analysis (DICS beamforming based on coherence)	Entrainment defined as sustained increases in gamma-band power at the stimulus frequency (32, 40, or 48 Hz) compared to baseline. Stronger entrainment was indicated by larger amplitude changes and wider brain connectivity patterns centered around the visual cortex.
10	Yoon et al.	2025	Event-Related Spectral Perturbation (ERSP) to identify the individual centre frequency; Phase-Locking Value (PLV); Spread, Strength, Stability metrics based on PLV	Entrainment defined as increased gamma-band power (ERSP) at individual central frequencies during visual flicker stimulation compared to baseline, and propagation evidenced by stronger, broader, and more stable gamma connectivity (higher PLV) from visual to non-visual regions.
11	Zhang et al.	2021	Power Spectral Density; EEG Microstate Analysis	Entrainment defined as an increase in 40 Hz EEG power during 40 Hz light flicker stimulation compared to baseline and random flicker control. Further supported by alterations in EEG microstate parameters (coverage, transition, complexity) specifically during 40 Hz stimulation.
12	Zibrandtsen et al.	2020	Complex Morlet Wavelet Transform; Automatic Peak Detection; Signal-to-Noise Ratio	Entrainment defined as the presence of a distinct peak at 40 Hz during 40 Hz intermittent photic stimulation, exceeding amplitude threshold and surpassing background noise.

4.3. *Visual stimulation protocols*

The included visual stimulation studies employed a variety of experimental designs, primarily using rhythmic visual inputs to engage gamma-band oscillatory activity. Most studies delivered rhythmic visual flicker at gamma-band frequencies (typically 40 Hz) to entrain gamma activity (e.g., Bayram et al., 2011; Yoon et al., 2025), while others introduced variations in stimulus parameters, including flicker color, luminance, temporal frequency within the gamma band, and the extent of the visual field stimulated. (Agger et al., 2022; Hansen et al., 2024; Henney et al., 2024; Lee et al., 2021; Noda et al., 2021). Trial durations ranged from 2 to 45 s (Duecker et al., 2021) to repeated 30-second blocks (Agger et al., 2022).

To facilitate comparison across studies, we classified the manipulated experimental variables using common labels. Because many studies manipulated more than one parameter, percentages below refer to the proportion of studies addressing each variable and may sum to more than 100 %.

The most varied parameters were (see also Fig. 2):

- **Stimulation frequency**: 57.1 % of studies varied flicker frequency within the gamma band, most commonly centered around 40 Hz (e.g., Petro et al., 2024).
- **Stimulus type**: 28.6 % of studies employed structured patterns, such as gratings, with full-field flicker stimuli (e.g., Duecker et al., 2021). Other contrasted visible (overt) flicker with invisible (imperceptible but still rhythmic) flicker (e.g., Agger et al., 2022).
- **Color**: 28.6 % of studies manipulated the chromatic properties of the flicker, using red, white, or heterochromatic combinations (e.g., Lee et al., 2021; Henney et al., 2025).
- **Luminance intensity**: 14.3 % of studies varied the luminance of the visual stimulus to examine its effect on gamma responses (e.g., Jones et al., 2019).
- **Stimulated visual field**: 7.1 % of studies presented stimuli at different positions within the visual field to assess spatial effects (e.g., Hansen et al., 2024, Exp 2).

One study (Zibrandtsen et al., 2020) used a single fixed stimulation paradigm of visual parameters.

Supplementary Table 3 summarizes the specific parameters tested and the corresponding results.

4.4. *Overall entrainment rate*

Of the 14 visual experiments identified as assessing neural entrainment (see Supplementary Table 3), 13 reported phase-locked responses to rhythmic flicker, corresponding to a 92.9 % rate of observed entrainment. The one exception was Duecker et al. (2021), which applied more stringent criteria requiring not only narrowband stimulus-driven activity, but also evidence of interaction with endogenous gamma rhythms. In their analysis, flicker-evoked and intrinsic gamma oscillations were interpreted as coexisting but independent: the former elicited by rhythmic stimulation, the latter induced by moving gratings, existed in different areas of the visual cortex without evidence of mutual modulation.

4.5. *Stimulation frequency*

Across studies, 40 Hz white flicker reliably elicited phase-locked gamma-band activity in occipital and parietal cortices (Zhang et al., 2021; Jones et al., 2019; Petro et al., 2024). However, some evidence suggests that lower frequencies (32–38 Hz) may enhance responses in specific brain regions: Bayram et al. (2011) and Lee et al. (2021) found that parietal entrainment peaked at 36–38 Hz, while frontal areas were more sensitive to 32–36 Hz.

Individualized frequency tuning (i.e., identifying gamma oscillations responsiveness prior to GENUS) further challenged the universality of 40 Hz stimulation. In the MEG study by Duecker et al. (2021), the stimulation frequency was matched to each participant’s endogenous gamma peak, previously elicited by moving gratings, with the aim of maximizing resonance, but no evidence of entrainment was found. In contrast, Yoon et al. (2025) identified individualized central frequencies

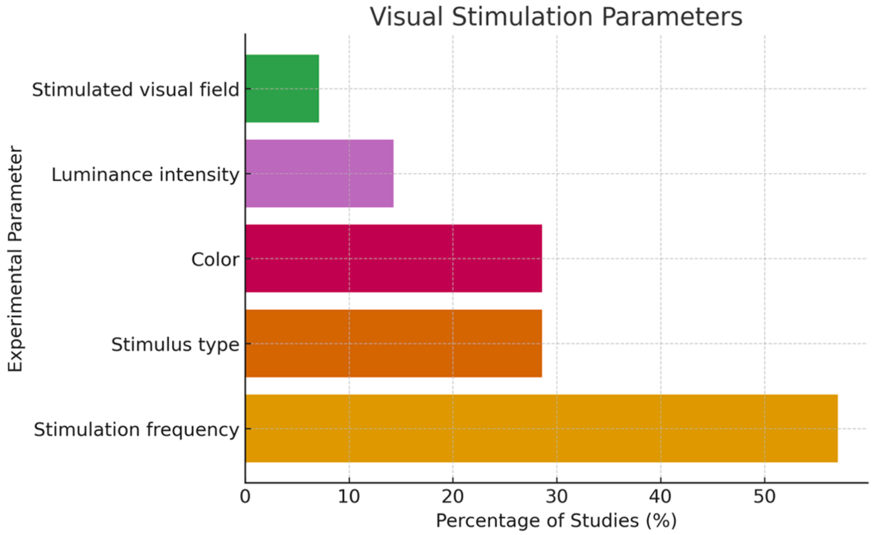

Fig. 2. Percentage of studies varying specific visual stimulation parameters to elicit gamma-band responses.

based on the flicker frequency that elicited the strongest event-related spectral perturbation response in older adults (32–40 Hz) and showed that personalized stimulation enhanced entrainment.

4.6. *Stimulus type*

Four experiments compared different types of 40 Hz visual flicker. Agger et al. (2022) found that stroboscopic light produced the strongest phase-locked gamma responses, whereas invisible spectral flicker was better tolerated despite weaker responses. Hansen et al. (2024, Exp 1) similarly reported that white luminance flicker elicited more robust occipito-parietal entrainment compared to red/green chromatic or invisible flicker, though invisible flicker was rated as more comfortable. In Exp 2, Hansen et al. (2024) showed that invisible flicker induced significant entrainment regardless of its location in the visual field. Among the studies manipulating stimulus type, Duecker et al. (2021) tested flicker superimposed on moving gratings; however, consistent with their frequency-testing results, this combined stimulation did not elicit entrainment. These findings demonstrate that visible, high-contrast flicker maximized entrainment strength, while invisible flicker improved tolerability.

4.7. *Color and luminance intensity*

Four studies explored the influence of chromatic content. Lee et al. (2021, Exp 1) and Henney et al. (2025) demonstrated that rhythmic red flicker elicited stronger phase-locked responses than white, particularly over parietal and frontal regions.

Henney et al. (2025) further showed that heterochromatic combinations (e.g., amber–red, blue–red) produced the strongest responses and were better tolerated. Noda et al. (2021) compared white and violet flicker, finding that white elicited typical parieto-occipital gamma suppression, while violet increased gamma–alpha coupling post-stimulation, suggesting distinct mechanisms. Luminance was examined by Lee et al. (2021, Exp 2), who reported that 700 cd/m^2 produced maximal gamma entrainment but greater discomfort, whereas 400 cd/m^2 achieved strong responses with better comfort and fronto-temporal propagation of entrainment. Similarly, Jones et al. (2019) reported that 40-Hz high-intensity light produced the strongest and most widespread gamma responses across occipital–parietal regions, with reduced efficacy at higher frequencies, lower intensities, or with eyes closed.

4.8. *Additional results*

Zibrandtsen et al. (2020) examined age differences in a large retrospective sample (n = 1464, aged 18–88) and reported reliable 40 Hz entrainment across ages, though response amplitude decreased with age. Yoon et al. (2025) showed that individualized frequency tuning enhanced functional connectivity in older adults. These findings underscore the importance of accounting for age-dependent variability in gamma responsiveness when designing entrainment protocols.

5. Auditory stimulation studies

5.1. *Overall characteristics of the sample*

The six auditory stimulation studies included 101 healthy adults, with a mean age of 32.2 years (range: 22.4–38.8). Gender was reported in all six studies, averaging 40.6 % male and 59.4 % female. Across the included studies, sample sizes ranged from 7 to 23 participants. Although some studies originally included clinical populations, only data from healthy controls were considered for this review (see Supplementary Table 4).

5.2. *Definitions and measures of gamma responses*

All auditory stimulation studies met the criteria for neural entrainment. Notably, although Sugiyama et al., (2022, 2023) and Choi et al. (2023) did not explicitly aim to assess entrainment, they analysed different properties of gamma Auditory Steady-State Responses (ASSRs) manipulating rhythmic stimulation protocols in healthy and clinical populations, using spectral amplitude and phase-locking values, widely accepted indicators of entrainment. See Table 2 for further details on analytic methods and response type categorization.

5.3. *Auditory stimulation protocols*

Auditory stimulation studies employed a variety of experimental designs, primarily using rhythmic auditory inputs designed to engage gamma-band oscillatory activity. Most commonly, studies delivered 40 Hz click trains or amplitude-modulated tones through headphones during resting-state conditions with eyes open (e.g., Han et al., 2023; McFadden et al., 2014). Stimulation durations and session structures varied across studies.

To ensure clarity and consistency in summarizing experimental protocols across studies, we grouped the manipulated experimental

Table 2
Gamma entrainment metrics and definitions across auditory studies.

	First author	Year	Measure(s) Used	Outcome operational definition
1	Choi et al.	2023	Total Power (ERSP); Inter-Trial Coherence (ITC); ISI-dependent ITC; ITC onset slope; ITC centroid latency	Auditory steady-state response (ASSR) measured by an increase in 40-Hz spectral power and phase-locking (ITC) specifically within the stimulation period at the stimulus frequency (40 Hz).
2	Han et al.	2022	Normalized spectral power (Multi-taper method); Time-frequency power spectra	Neural entrainment explicitly defined as the synchronization of EEG activity to repetitive auditory stimulation at 40 Hz, observed as an increase in EEG power specifically at the driving frequency compared to baseline.
3	Jirattayakorn & Wongsawat	2017	Absolute power of gamma (30–100 Hz) and beta oscillations (12–30 Hz); Fast Fourier Transform	Neural entrainment defined explicitly as frequency-following response, characterized by enhanced oscillatory activity at the beat frequency (40 Hz) generated by binaural beats, compared to baseline EEG.
4	McFadden et al.	2014	Evoked power; Inter-Trial Phase Coherence (ITPC); phase-locking factor, PLF)	ASSR defined as an increase in 40-Hz spectral power and inter-trial phase coherence specifically in the post-stimulus interval (200–500 ms) compared to pre-stimulus baseline, signifying consistent neural phase-locking at the stimulus frequency.
5	Sugiyama et al.	2022	Source strength waveforms (dipole analysis); Time-frequency analysis (amplitude and inter-trial coherence)	ASSR explicitly defined as intrinsic oscillatory processes in auditory pathways, represented by enhanced spectral power specifically at the driving frequency (40 Hz), distinct from other gamma-band oscillations, and modulation or suppression of ongoing neural activity at adjacent gamma frequencies.
6	Sugiyama et al.	2023	Source strength waveforms (dipole analysis); Time-frequency analysis (Morlet wavelet transform); Inter-Trial Phase Coherence (ITPC)	ASSR at 40 Hz, specifically represented by enhanced spectral amplitude and increased phase coherence (ITPC) at 40 Hz or its harmonic frequencies, induced by auditory stimuli at various subharmonic frequencies, indicative of a specialized neural circuit tuned to 40 Hz oscillations.

variables into standardized categories. Because some studies manipulated more than one parameter, the percentages below refer to the proportion of studies addressing each variable and may sum to more than 100 % (see Fig. 3).

The most frequently manipulated parameters were:

- **Stimulus type:** 33.3 % of studies compared click trains, pure tones, and white noise (e.g., McFadden et al., 2014; Han et al., 2023).
- **Stimulation frequency:** 33.3 % of studies varied auditory stimulation frequency within the gamma band, testing frequencies between 13.3 and 54 Hz (e.g., Sugiyama et al., 2022, 2023).
- **Inter-stimulus interval:** 16.7 % of studies varied the time interval between successive auditory stimuli, testing intervals ranging from 500 ms to 3500 ms (e.g., Choi et al., 2023).
- **Eye state:** 16.7 % of studies compared open- and closed-eye conditions during auditory stimulation (e.g., Han et al., 2023).

One study (Jirakittayakorn & Wongsawat, 2017) did not manipulate any experimental parameters and applied a fixed 40 Hz binaural beat protocol.

Supplementary Table 4 provides a detailed breakdown of which studies manipulated each parameter and the associated findings.

5.4. *Overall entrainment rate*

Gamma-band entrainment was only explicitly reported in two of the included studies (McFadden et al., 2014; Han et al.,2023). Although the remaining four studies did not explicitly refer to entrainment, based on our operational definition and the measures they employed (see Table 2), we consider the auditory protocols used in those studies to be adequate for inducing neural gamma entrainment.

5.5. *Stimulus type*

Two studies systematically compared different auditory waveforms at a fixed frequency of 40 Hz. Han et al. (2023) reported that sinusoidal tones delivered with eyes closed elicited the strongest gamma responses, particularly in frontal regions, while square waves induced greater alpha suppression, interpreted as a marker of attentional modulation. Similarly, McFadden et al. (2014) found that click trains produced more consistent ASSR responses than white noise, likely due to their sharper temporal structure. Entrainment was strongest in the left hemisphere and included both the 40 Hz fundamental and its 80 Hz harmonic component.

5.6. *Stimulation frequency*

Two studies by Sugiyama et al. (2022, 2023) systematically examined the effect of auditory stimulation frequency on gamma-band responses. Both studies used rhythmic pure tones at 70 dB and recorded MEG responses.

In Sugiyama et al. (2022), tones ranging from 20 to 54 Hz were delivered in brief bursts, and the strongest gamma activity was consistently observed at 40 Hz, particularly in the right auditory cortex. Notably, 30 Hz power was suppressed during both 30 Hz and 40 Hz stimulation, which the authors interpreted as reflecting inhibitory interactions between oscillatory populations.

In Sugiyama et al. (2023), the authors included additional lower-frequency conditions (13.3 Hz and 20 Hz) and again observed the strongest gamma response at 40 Hz. Interestingly, even sub-gamma inputs (13.3 Hz and 20 Hz) entrained gamma activity peaking at 40 Hz, suggesting a resonance effect in the auditory system.

5.7. *Inter-stimulus interval*

Choi et al. (2023) examined the effect of varying the inter-stimulus interval on auditory gamma ASSRs. Using 40 Hz click trains with inter-stimulus intervals of 500, 2000, and 3500 ms, they assessed phase-locked responses using total power and inter-trial coherence. Results showed that shorter intervals, particularly 500 ms, elicited

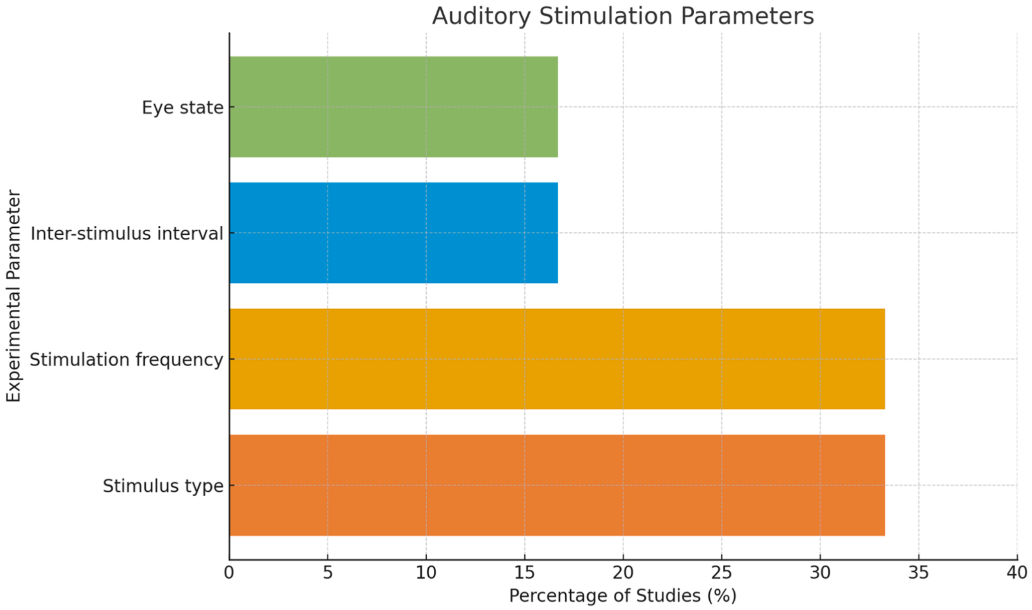

Fig. 3. Percentage of studies varying specific auditory stimulation parameters to elicit gamma-band responses.

stronger gamma entrainment, whereas longer intervals resulted in progressively weaker responses.

These findings suggest that shorter inter-stimulus intervals enhance the efficacy of auditory gamma entrainment, likely by maintaining temporal synchrony and neural engagement. Optimizing temporal structure (not just stimulation frequency) appears to be critical for maximizing entrainment strength.

5.8. *Additional results*

One study (Jirakittayakorn & Wongsawat, 2017) tested the effect of a fixed 40 Hz binaural beat protocol without manipulating any other experimental parameters. EEG recordings revealed strong narrowband gamma responses, primarily over right frontal-temporal and central regions. The strongest gamma response was observed within the first 15 min of the 30-minute stimulation session, after which the response declined, with no further enhancement after 20 min. The authors interpreted these findings as evidence of a time-limited entrainment window, suggesting that overstimulation may reduce neural responsiveness or induce fatigue.

6. Multisensory stimulation studies

6.1. *Overall characteristics of the sample*

The four multisensory stimulation studies included a total of 58 healthy adults, with a mean age of approximately 32.8 years (range: 21–64). Sample sizes ranged from single case studies (Yi & Wang, 2022) to 20 participants (Wu et al., 2025). Gender was reported in all studies, with an average distribution of 60.3 % female and 39.7 % male. Although the studies varied in methodological approach and age groups targeted, all focused on healthy participants exposed to single-session multisensory stimulation (see Supplementary Table 5).

6.2. *Definitions and measures of gamma responses*

Multisensory studies varied in how gamma-band responses were defined and measured, reflecting differences in theoretical assumptions and methodological choices (Table 3).

A variety of neurophysiological metrics were employed to assess gamma entrainment, including EEG power spectral density, coherence measures, signal-to-noise ratio, and latency or amplitude peaks in MEG recordings. Notably, Yi and Wang (2022) calculated the Gamma Entrainment Index, defined as the ratio of post- to pre-stimulation gamma power, as a composite measure of response strength.

Table 3
Gamma entrainment metrics and definitions across multisensory studies.

	First Author	Year	Measure(s) Used	Operational Definition
1	Chan et al.	2022	EEG power spectral density; Coherence across electrode sites; Structural and functional MRI; Actigraphy	Entrainment defined as increased 40 Hz power spectral density and coherence in EEG.
2	Sugiyama et al.	2019	MEG ; Peak latency of 40-Hz Auditory Steady-State Response (ASSR)	Not a direct definition of entrainment per se. However, the latency of the 40-Hz ASSR was used as an indicator of cross-modal influence on ongoing oscillations, interpreted as evidence of phase-resetting and accelerated processing.
3	Wu et al.	2025	EEG signal-to-noise ratio (SNR); Power spectral density	Entrainment defined and measured as a significant increase in 40 Hz EEG amplitude (SNR) compared to surrounding frequencies (38–42 Hz).
4	Yi & Wang.	2022	EEG gamma power; Gamma Entrainment Index (GEI)	Entrainment defined as an increase in gamma-band EEG activity, quantified through the GEI: ratio of gamma power post- vs. pre-stimulation

6.3. *Multisensory stimulation protocols*

Multisensory stimulation protocols involved combinations of auditory, visual, or tactile stimulations, delivered in single-session designs (Supplementary Table 5). The most common paradigms tested the effects of fixed audio-visual or audio-tactile stimulation to entrain gamma-band activity. Despite protocols' variability, all the included studies reported that rhythmic multisensory stimulation entrained gamma activity in cortical, and sometimes subcortical, regions.

More specifically, Yi and Wang (2022) tested auditory, visual, and audiovisual stimulation in a single-subject EEG study. Audio-visual stimuli (40 Hz auditory + 20 Hz visual) produced the strongest gamma response, exceeding the sum of unimodal effects and demonstrating a superadditive effect of multisensory input. Sugiyama et al. (2019) examined auditory–tactile stimulation with MEG, pairing 40 Hz auditory stimulation with either ipsilateral or contralateral tactile pulses. Contralateral tactile input significantly reduced ASSR latency (~0.4 ms), suggesting that tactile input can enhance the temporal precision of auditory gamma responses.

Three studies assessed the efficacy of a fixed multisensory protocol, defined as a predetermined combination of auditory and visual stimuli with constant parameters (e.g., 40 Hz frequency, fixed duration and intensity) applied uniformly across sessions. Chan et al. (2022) exposed young and older adults to 3-minute sessions of synchronized 40 Hz white light flicker and binaural clicks. EEG and fMRI analysis revealed robust gamma activity at 40 Hz and its harmonics (20 Hz, 80 Hz) across cortical and subcortical regions, with stronger frontal responses in younger adults. Wu et al. (2025) exposed young adults to 30 min of 40 Hz audiovisual stimulation, showing strong occipital and frontal gamma activity during stimulation, but no sustained effect post-stimulation.

Together, these studies confirm that fixed audiovisual protocols reliably entrain gamma-band activity, though the effects tend to dissipate once stimulation stops.

7. Discussion

This systematic review analysed 22 studies (24 experiments) investigating GENUS in healthy individuals. This approach has been inspired by evidence that rhythmic sensory stimulation at gamma frequency can modulate neural activity and produce widespread neurophysiological effects (Iaccarino et al., 2016). To provide guidelines for designing efficient GENUS protocols aimed at reliably entraining the human brain, this review sought to summarize entrainment efficacy across existing GENUS studies, with particular attention to stimulation parameters and sensory modality.

7.1. Recommended guidelines for GENUS protocol design across sensory modalities

7.1.1. Visual stimulation

Current evidence indicates that visual GENUS protocols should prioritize parameters that maximize both local entrainment and large-scale network recruitment. Frequencies in the low-gamma range remain a reliable starting point, but 40 Hz might not represent a universal standard. Instead, frequency selection should reflect the targeted cortical area and individual responsiveness, with slightly lower frequencies (32–38 Hz), potentially more effective for parietal and frontal propagation (Lee et al., 2021) and for older adults (Yoon et al., 2025).

Stimulus design should incorporate heterochromatic or chromatically enriched flicker, specifically involving red, as it engages broader neural populations (Lee et al., 2021; Henney et al., 2024). This pattern aligns with basic visual physiology and findings from brain-computer interface (BCI) research. Indeed, longer wavelengths (white and red) preferentially activate L-cones, which are substantially more numerous in the human retina than M- and S-cones (Goldstein, 2009; Strettoi et al., 2010) and may engage the visual cortex more efficiently. BCI studies taking advantage of SSVEPs also show that luminance strongly influences information-transfer rate, underscoring the importance of tuning chromatic luminance for efficient neural tracking (Bieger et al., 2010).

For longer or repeated sessions, 'invisible' flicker or moderate luminance levels preserve entrainment while improving comfort (Hansen et al., 2024).

Overall, frequency and chromaticity should be treated as active components of visual entrainment design.

7.1.2. Auditory stimulation

Within the auditory domain, sinusoidal tones (Han et al., 2023) or click trains yield more consistent entrainment than broadband noise (McFadden et al., 2014), provided that onset jitter and inter-stimulus intervals are tightly controlled (Choi et al., 2023).

Interestingly, frequency-testing studies consistently reveal a marked preference of the auditory cortex for stimulation around ~40 Hz (Sugiyama et al., 2022; 2023). This finding is in agreement with extensive evidence showing that endogenous 40-Hz oscillations represent an intrinsic and transient operating mode of the auditory system, supporting rapid synchronization across sensory and higher-order cortical regions (Ward et al., 2010). Such responses are elicited at stimulus onset and index the formation of a perceptual network. In line with the idea that entrainment efficacy may depend on the resonance properties of a pre-existing oscillator (Duecker et al., 2024; see also the paragraph *Challenges in operationalizing and measuring gamma responses*), calibrating auditory stimulation around 40 Hz may be a good strategy for GENUS protocols.

Although conducted outside the GENUS research, Ward et al. (2010) additionally demonstrated that adding low-level noise facilitates 40-Hz synchronization through stochastic resonance (i.e., introduction of a weak level of noise enhances the detection of a signal), amplifying coordinated neural activity rather than degrading it. Consistently, Duchet et al. (2023) reached a similar conclusion showing that adding broadband noise (i.e., 'dithering') suppresses spurious harmonics while selectively strengthening entrainment at the target frequency. These complementary findings suggest that incorporating controlled noise into auditory GENUS protocols may enhance entrainment, an approach that, to our knowledge, has not yet been explored in this field.

7.1.3. Multisensory stimulation

Early evidence suggests that combining modalities can amplify entrainment or stabilize it over sustained stimulation, likely by engaging complementary neural circuits (Chan et al., 2022). In terms of spatial propagation or stronger synchrony, pairing visual flicker with temporally precise auditory cues appears to be the most advantageous strategy.

Multisensory GENUS protocols should therefore be developed with explicit attention to cross-modal timing, ensuring that auditory and visual (or tactile) cues reinforce rather than compete with one another (Sugiyama et al., 2019). Tactile inputs may further enhance temporal precision or reduce habituation by distributing sensory load across channels (Jirakittayakorn & Wongsawat, 2017; Sugiyama et al., 2019).

7.1.4. Cross-modal comparisons

Across sensory systems, entrainment efficacy depends not only on frequency and stimulus properties but also on a wider set of protocol dynamics. Overall, current evidence suggests that visual GENUS protocols reliably elicit strong gamma responses, yet their spatial reach is comparatively constrained. Visual flicker rarely drives entrainment far beyond occipital, and occasionally parietal, regions (Lee et al., 2021; Hansen et al., 2024). In contrast, auditory stimulation engages broader areas, often extending into frontotemporal regions and occasionally exhibiting hemispheric differences (Jirakittayakorn & Wongsawat, 2017; Sugiyama et al., 2022). Finally, combining audio-visual rhythmic stimulation appears to amplify these effects, engaging wider and more distributed networks, also showing super additive responses (Yi & Wang, 2022). These patterns are consistent with findings from both human and animal research (e.g., Martorell et al., 2019) and may reflect distinct neural pathways and processing architectures underlying sensory-driven gamma activity. This modality-specific distinction has potential clinical implications: selecting the sensory modality that most effectively engages broader cortical networks may be particularly advantageous for conditions involving frontal and prefrontal dysfunctions, such as Alzheimer's disease, schizophrenia, and traumatic brain injury, where broader cortical engagement may enhance therapeutic effects.

Additionally, future protocols should carefully consider stimulation duration, as neural adaptation and reduced physiological responsiveness can emerge after approximately 15 min of continuous stimulation (Jirakittayakorn & Wongsawat, 2017). Shorter, repeated blocks, or multisensory combinations with distributed load, may offer more stable entrainment over time. Adopting such personalized, parameter-driven approaches will be essential for translating GENUS from proof-of-concept paradigms into therapeutic tools.

7.2. *Translating acute entrainment into lasting effects*

Most studies in this review examined acute neural responses during or immediately after stimulation, and only a few assessed whether entrainment effects persist beyond the stimulation window. Although limited evidence (e.g., Noda et al., 2021) suggests the possibility of short-lived post-stimulation changes, sustained or cumulative effects remain largely undocumented within the GENUS literature. Notably, Chan et al. (2022) extended their acute auditory–visual 40-Hz protocol into a 3-month trial in patients with Alzheimer's disease. Despite the small sample, the authors reported reduced brain atrophy, preserved functional connectivity, improvements in sleep-related markers, and better performance in an associative memory task . These preliminary results indicate that 40-Hz GENUS may have clinically meaningful effects and underscore the importance of conducting randomized clinical trials to evaluate its potential as a disease-modifying intervention.

In the context of prolonged stimulation, however, maintaining stimulus salience may be essential for sustaining entrainment over time. For example, a major barrier may be habituation: repetitive auditory stimulation has been shown to reduce steady-state response amplitude over time (~15 min) (Jirakittayakorn & Wongsawat, 2017), raising concerns that prolonged exposure to identical rhythmic input may diminish efficacy. To address this, future studies should explore how parameters optimized, such as specific frequencies or modality pairings, can be adapted for repeated or prolonged use.

In this context, several useful strategies can be drawn from the broader neuroscience literature, particularly those grounded in earlier work on neural synchronization. Even though they have not yet been applied within the entrainment field, they may be fruitfully adapted to GENUS protocols. Among these, techniques that introduce controlled variability, such as jittering of timing or intensity (Ross et al., 2005), can help preserve neural responsiveness and counteract adaptation. Additionally, the evidence from the works by Ward et al. (2010) and Duchet et al. (2023) suggest that adding low-level or broadband noise can enhance rhythmic-stimulus detection and suppress spurious harmonics (see also the *paragraph Recommended guidelines for GENUS protocol design across sensory modalities*).

Together, the current literature suggests that incorporating carefully calibrated fluctuations into stimulation protocols may help stabilize gamma-band engagement during prolonged GENUS sessions.

7.3. *Challenges in operationalizing and measuring gamma entrainment*

A persistent obstacle across studies is the lack of standardized criteria for identifying genuine gamma entrainment. A key methodological challenge concerns the widespread reliance on steady-state neural responses (i.e., ASSRs or SSVEPs) to infer effective gamma entrainment. Although these measures are commonly used to quantify neural synchronization to rhythmic sensory input, they can be misleading when applied to GENUS protocols as entrainment measure. There is a fundamental distinction between true phase-locking of endogenous oscillations and the neural response evoked by each cycle of the stimulus. Both ASSRs and SSVEPs may simply capture rhythmic brain responses to periodic input, often reflecting a mixture of endogenous oscillatory dynamics and evoked responses, and interval-prediction processes, which are inherently produced by each sensory event (Wilson et al., 2022; Zoefel et al., 2018). However, current steady-state methodologies cannot reliably dissociate these mechanisms, underscoring the need for refined approaches capable of distinguishing evoked responses from genuine modulation of intrinsic gamma dynamics.

Built on the premise that gamma response may also arise as interval-based temporal prediction of periodic stimuli, it has been suggested that patients with cerebellar dysfunction, impaired in timing and temporal prediction (Breska & Ivry, 2018), may help dissociate interval-based mechanisms from neural synchrony reflecting entrainment. Applying this rationale, Breska and Ivry (2020) showed that although individuals with cerebellar degeneration have deficits in interval-based prediction, their phase alignment during periodic stimulation is comparable to that of neurological healthy controls. This finding supports the view that phase alignment in rhythmic stimulation paradigms reflects rhythm-specific oscillatory entrainment rather than interval-prediction processes.

As Zoefel et al. (2018) also emphasize, there is the possibility of relying on specific paradigms to provide compelling evidence that rhythmic stimulation has aligned ongoing brain activity, rather than merely eliciting time-locked responses. Accordingly, a useful approach is the assessment of aftereffects following stimulus offset, referred to as 'entrainment echoes' (Duecker et al., 2024), which are based on the principle that endogenous oscillations, once entrained, should exhibit a degree of persistence beyond the physical stimulation period (Farahbod et al., 2020; L'Hermite and Zoefel, 2023). Because these echoes are measured once external input has ceased, they are less confounded by overlapping evoked responses. Evidence for echoes has been found in the auditory domain at both low frequencies (e.g., ~2–8 Hz) and higher frequencies (~40 Hz) in the frequency-following response, where the response relaxes gradually back to a preferred intrinsic frequency (Coffey et al., 2021; Lerousseau et al., 2021). The presence of post-stimulation rhythmicity therefore can provide stronger evidence for endogenous alignment also in the gamma-band activity.

Another strategy focuses on how neural responses evolve over time. Evoked responses typically peak immediately and then habituate, whereas entrainment of an endogenous oscillator often requires multiple cycles to develop and shows a gradual increase in phase synchrony. In the rodent prefrontal cortex, for instance, 40 Hz stimulation elicits a strong onset response followed by a slower emergence of phase-locked gamma synchronization, consistent with the time course expected from coupled oscillatory circuits (Ummear Raza et al., 2023; Gautam et al., 2024).

A key consideration is that rhythmic sensory stimulation interacts with oscillatory activity that is already present before stimulus onset, and the nature of this interaction depends on the intrinsic properties of the underlying circuits (Pikovsky & Rosenblum, 2003). Individuals and neural systems themselves show stable resonance tendencies, which can be characterized through oscillator-model predictions such as Arnold tongues. Arnold tongues describe the frequency-amplitude window within which an external rhythm can successfully capture an intrinsic oscillator. Demonstrating such selective, intensity-dependent, phase--locking provides stronger evidence for entrainment than spectral amplitude alone, as it shows that stimulation interacts with a pre-existing oscillatory circuit rather than merely generating repeated evoked responses (Zoefel et al., 2018). This framework is also useful for interpreting harmonics and subharmonics often reported in unisensory and multisensory GENUS studies, which may reflect nonlinear neural dynamics but can equally result from artefacts or suboptimal stimulation choices (Notbohm et al., 2016). To mitigate these interpretive ambiguities, tuning stimulation parameters explicitly within an oscillator's Arnold tongue is suggested. However, even when preferred frequencies exist, and have been more extensively characterized in the alpha band

(Corcoran et al., 2018), characterizing the presence of pre-existing oscillations in the gamma band presents several challenges.

7.4. Sources of variability in gamma responsiveness

Gamma activity exhibits substantial intra- and inter-individual variability, suggesting that future work should clarify how endogenous gamma responsiveness is shaped by both biological factors and methodological choices (Yoon et al., 2025; Duecker et al., 2021). The influence of individual differences is supported by the evidence from the study on a large sample by Zibrandtsen et al. (2020), showing that older adults exhibit reduced responsiveness to rhythmic stimulation compared to younger adults, likely reflecting age-related declines in plasticity and sensory processing (Freitas et al., 2011; Bashir et al., 2014; Opie et al., 2017). To address this issue, authors draw on methodological strategies that may help move the gamma entrainment literature forward, based in part on knowledge derived from research on alpha-entrainment, which is currently more established. However, these approaches should be applied and validated with caution in the gamma band, as gamma dynamics present different and greater complexities (see: *Methodological considerations for measuring gamma-band activity*), and this is likely the very reason why alpha research has advanced more rapidly. For instance, gamma-band activity is much more heterogeneous: scalp-level gamma reflects a mixture of true oscillations, transient bursts, aperiodic high-frequency broadband activity, and asynchronous spiking (Hyafil et al., 2015; Ray & Maunsell, 2011; Donoghue et al., 2020).

Two studies included in this review, Yoon et al. (2025) and Duecker et al. (2021), applied individual gamma frequency (IGF) approaches, measuring endogenous gamma activity prior to GENUS stimulation. As previously discussed, such paradigms are particularly valuable for GENUS research because they assess endogenous oscillators, directly capturing inter-individual variability that may meaningfully shape entrainment efficacy. To illustrate how methodological choices shape the characterization of endogenous gamma dynamics, we describe the two contrasting approaches used in Yoon et al. (2025) and Duecker et al. (2021). Yoon and colleagues defined Central Frequencies as the flicker frequency eliciting the strongest event-related spectral perturbation response, in a predominantly older sample (~69 years old), clustered around 32–34 Hz; critically, stimulation at these participant-specific frequencies produced stronger gamma responses than the conventional 40-Hz protocol. By contrast, Duecker et al. (2021) estimated IGFs from endogenous oscillations evoked by moving gratings, yielding much higher intrinsic frequencies (mean ≈ 68 Hz). When these individualized high-frequency IGFs were later applied as flicker stimulation (52–90 Hz), entrainment did not improve: both power and phase-locking declined as flicker frequency increased. Moreover, grating-induced oscillations coexisted alongside, but did not interact with, flicker-driven responses even when the stimuli were superimposed, suggesting that the two stimulus types engage distinct neural populations.

Such discrepancy in methodologies and findings raises a methodological question: whether non-periodic stimuli are optimal for capturing the true resonance properties relevant for periodic stimulation, and whether different stimulation tap into distinct neural generators of gamma activity in the visual cortex. For instance, the use of gratings to probe gamma activity should be interpreted in light of extensive evidence showing that visual gamma responses are strongly shaped by the properties of the stimulus. Motion, velocity, and contrast all modulate the magnitude and frequency of gamma responses, and studies consistently report that moving gratings evoke robust gamma peaks around ~65–70 Hz in occipito-parietal regions (Muthukumaraswamy and Singh, 2013; Orekhova et al., 2020). However, faster motion tends to shift gamma to higher peak frequencies while simultaneously reducing power, an effect that may parallel the decline in power and phase-locking observed by Duecker et al. (2021) when flicker frequency increases.

These converging findings indicate that grating-induced gamma reflects stimulus-dependent visual processing and may not always provide a stable or direct estimate of the resonance properties of the visual cortex relevant for periodic entrainment. Accordingly, we argue that such individualized-frequency approaches should be considered more cautiously in the gamma frequencies, particularly in the visual cortex where global resonance properties of gamma responses are less evident than in the auditory domain. By contrast, individual alpha frequencies are relatively easy to characterize; when measured using resting-state EEG, they show high reliability and stability within participants (Ronconi et al., 2018; Corcoran et al., 2018).

Overall, current evidence argues against a one-size-fits-all approach and underscore the value of personalizing stimulation parameters. Tailoring frequency, modality, or timing to individual neurophysiological profiles may enhance both the reliability and the functional impact of gamma-band activation and GENUS. This is particularly relevant for future applications in elderly or clinical populations, where gamma oscillations are known to be altered.

7.5. Limitations and future directions

Several methodological limitations emerged from the current literature on gamma-band responses to sensory stimulation. Most studies relied on small, homogeneous samples and single-session protocols, limiting both statistical power and insights into the persistence or cumulative effects of gamma responses. Individual variability in response susceptibility is likely underestimated.

Another gap is the underrepresentation of certain sensory modalities: while visual and auditory stimulation dominate, tactile and multimodal approaches have been scarcely explored, despite their potential to entrain gamma-activity. Moreover, the lack of homogeneous definitions and outcome measures for entrained neural responses (particularly phase-locking) hampers comparability across studies and precludes meta-analytic synthesis.

To advance the field, future research should prioritize the development and adoption of standardized protocols for stimulus delivery and response measurements. Multi-session and longitudinal designs are needed to explore the cumulative effects of stimulation and assess their potential neuroplastic outcomes. Investigating individual factors, such as age, cognitive state, or baseline oscillatory profiles, may help identify subgroups with distinct gamma response sensitivity to inform tailored stimulation strategies.

Finally, systematic testing of refined sensory stimulation with paradigms capable of isolating endogenous oscillatory dynamics, leveraging resonance properties, and minimizing confounds such as transient responses or harmonic artefacts, will be crucial for advancing the development of reliable and mechanistically grounded gamma-entrainment protocols, as well as essential for the understanding of gamma-band activity and its role in the human brain.

CRediT authorship contribution statement

Arianna Rebecca Longo: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Laura Zapparoli:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization. **Nadia Bolognini:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT (developed by OpenAI) in order to improve the readability and language of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopsycho.2026.109211.

Data availability

No data was used for the research described in the article.

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