Unleashing the potential: 40 Hz multisensory stimulation therapy for cognitive impairment

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ABSTRACT

Cognitive impairment encompasses a spectrum of disorders marked by acquired deficits in cognitive function, potentially leading to diminished daily functioning and work capacity, often accompanied by psychiatric and behavioral disturbances. Alzheimer's disease (AD) and Post-stroke cognitive impairment (PSCI) are significant causes of cognitive decline. With the global population getting older, AD and PSCI are becoming major health concerns, underscoring the critical necessity for successful treatment options. In recent years, various non-invasive biophysical stimulation techniques, including ultrasound, light, electric, and magnetic stimulation, have been developed for the treatment of central nervous system diseases. Preliminary clinical studies have demonstrated the feasibility and safety of these techniques. This review discuss the impact of 40 Hz multisensory stimulation on cerebral function, behavioral outcomes, and disease progression in both animal models and individuals exhibiting cognitive deficits, such as AD and PSCI. Furthermore, it summarizes the potential neural pathways involved in this therapeutic modality by synthesizing evidence from a variety of studies within the field. Subsequently, it evaluates the existing constraints of this technique and underscores the potential advantages of 40 Hz multisensory stimulation therapy for individuals with cognitive deficits, with the goal of enhancing the management and care of AD and PSCI.

PLAIN LANGUAGE SUMMARY

As the world's population ages, Alzheimer's disease and post-stroke cognitive impairment are growing health issues, highlighting the need for effective treatments. This study explores the impact of a 40 Hz multisensory stimulation treatment on brain function, behavior, and disease progression in animal models and individuals with cognitive deficits like AD and PSCI.

KEYWORDS: Cognitive impairment, 40Hz multisensory stimulation therapy, post-stroke cognitive impairment, Alzheimer's disease, gamma oscillations

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Introduction

Gamma oscillations, characterized by a rapid neural oscillation, exhibit a broad frequency spectrum ranging from 25 to 100 Hz. These oscillations are induced by inhibitory postsynaptic potentials originating from inhibitory interneurons that are modulated by gamma-aminobutyric acid A (GABA) receptors. The presence of gamma oscillations enables excitatory signals within neural networks to momentarily surpass inhibitory signals, thereby augmenting the efficacy, accuracy, and specificity of information propagation across various brain regions. Several studies have demonstrated a strong correlation between gamma oscillations and cognitive function.[1-3] When the brain is engaged in tasks that necessitate high levels of cognitive control and information integration, there is an increase in both the intensity and synchrony of gamma oscillations. These oscillations are essential for various cognitive processes, including memory encoding, working memory, and memory retrieval, facilitating the execution of more intricate and sophisticated cognitive functions.[4-8]

Alzheimer's disease (AD) is defined by a complicated development that includes Aβ plaques, NFTs,[9,10] astrocytosis, microglial activation, and cerebral amyloid angiopathy.[11] These pathological changes disrupts the balance between excitatory and inhibitory signals,[3] leading to dysregulation in neuronal activity and dysfunction in neural network operation, ultimately impeding the production of Gamma oscillations in the brain.[12,13] Stroke can result in neuronal death and functional impairment, as well as impact the activity and connectivity of

interneurons and pyramidal cells, leading to abnormalities in the amplitude, frequency, synchronicity, and stability of Gamma oscillations.[14-16]

Over the past few decades, clinical interventions for the treatment of Alzheimer's disease (AD) and post-stroke cognitive impairment (PSCI) have primarily focused on maintaining neural network activity and cognitive function through molecular pathology approaches, aiming to regulate neural network activity via pharmacological means. However, the clinical efficacy of these treatments has generally been poor[17-19]. As a result, many researchers have shifted their attention to the impact of non-chemical therapies on patients with cognitive impairment, hoping to help these patients through alternative methods. 40 Hz multisensory stimulation therapy is one such approach, which involves applying specific frequencies and intensities of stimulation to different sensory regions of the brain (such as visual, auditory, and tactile regions) to regulate neural activity. This method improves the function of neurons and synapses and modulates the activity of interneurons, thereby influencing higher-order neural functions such as cognition and emotion. Early experimental studies have preliminarily demonstrated the positive effects of 40 Hz stimulation on cognitive function. For example, some animal model studies have shown that mice receiving regular 40 Hz multisensory stimulation performed better in cognitive tasks, exhibiting improved memory and learning abilities. Even more encouraging, in experiments on AD model mice, 40 Hz light and sound stimulation was found to significantly reduce the accumulation of β-amyloid plaques in the brain.[20] Building on these laboratory breakthroughs, an increasing number of clinical trials have confirmed that patients, after undergoing a period of 40 Hz multisensory stimulation therapy, experienced varying degrees of improvement in cognitive abilities, memory, and executive function.[21] Therefore, 40 Hz multisensory stimulation therapy may serve as an alternative approach for treating patients with cognitive impairment, offering a new option for treatment.

This analysis examines the potential therapeutic benefits of 40 Hz multisensory stimulation treatment for cases associated with AD and PSCI. It explores recent studies on how Gamma stimulation affects brain function, disease progression, and cognitive abilities in individuals with cognitive impairments. Furthermore, it explores preclinical studies conducted on AD and PSCI, shedding light on the underlying neural mechanisms of Gamma stimulation. Lastly, the review considers the future prospects of this therapeutic approach.

Examining the effects of 40 Hz audio-visual stimulation on an animal model of AD

Gamma oscillations within the cerebral cortex and hippocampus play crucial roles in facilitating the precise transmission of information during processes involving attention, cognition, and memory.[22,23] Moreover, studies have shown that sensory stimulation at a frequency of 40 Hz can improve cognitive functions by correcting dysfunctional brain structures in a preclinical AD model.[24-26] Table 1 provides an overview of the significance of Gamma oscillations in mouse models with cognitive deficits.

Several research studies have indicated that Gamma oscillations may serve as an early electrophysiological marker for the beginning of AD. In the hippocampal area of 5xFAD mice, a reduction in Gamma waves occurs before the development of amyloid-beta (Aβ) plaques and cognitive deficits, with irregularities in slow Gamma waves associated with sharp wave ripples (SWRs) also being detected.[27-29] In mouse models with a human ApoE4 gene knock-in, a significant reduction in slow Gamma waves associated with SWRs was observed. Correcting this deficit by selectively removing ApoE4 from forebrain GABAergic interneurons improves cognitive functions and memory deficits in these animals. These observations suggest that slow Gamma waves connected to SWRs play a vital role in the development of learning and memory issues related to ApoE4.[30-32]

Iaccarino et al utilized a light stimulation protocol to modulate neural oscillations in the 5XFAD mouse model, with specific frequency flashing. The study results showed that exposing the visual cortex to 40 Hz light flicker stimulation effectively increased 40 Hz neural oscillations, controlled peak potential firing rates, and decreased amyloid-beta (Aβ) plaque accumulation by around 50% in the hippocampal CA1 region. Conversely, light stimulation at frequencies of 20 Hz or 80 Hz did not yield comparable or superior outcomes.[27] Adaikkan and colleagues replicated these results in both Tau P301S AD and CK-p25 mouse models. Following prolonged exposure to 40 Hz light, researchers observed a decrease in neurodegeneration across various brain regions, including the visual cortex V1, hippocampal CA1, and medial prefrontal cortex (mPFC), compared to the control group. The light stimulation led to improved synaptic function, higher levels of factors that protect the brain, reduced DNA damage in neurons, and decreased inflammation in microglial cells.[33,34]

Martorell et al further investigated the effects of auditory stimulation on the auditory system by exposing 5XFAD mice to various frequencies of auditory stimuli for 1 h daily over the course of 1 week. Their findings revealed that only the 40 Hz auditory stimulation significantly reduced amyloid-beta deposits in the auditory cortex and hippocampal regions, along with a decrease in tau protein phosphorylation levels. During cognitive function tests, mice subjected to 40 Hz auditory stimulation demonstrated enhanced performance, as evidenced by higher scores in object recognition and spatial memory compared to mice exposed to different frequency stimulations. Furthermore, researchers observed a rise in the count of microglia and astrocytes in AD mice subjected to 40 Hz auditory stimulation. These cells exhibited improved capabilities in clearing amyloid-beta deposits, consequently mitigating Alzheimer's disease-associated vascular pathological alterations.[35] Expanding on their previous research, Martorell et al

Table 1. Summary of clinical studies on the sensory modulation of human neural oscillations and cognitive performance.

CITATION	STIMULATIONS	DURATION AND COURSE	PARTICIPANTS	KEY POINTS
PMID: 37007205	40 Hz auditory sound (sinusoidal or square wave)	2 min	N = 10 health participants	1. During closed-eye state, a 40 Hz sine wave sound caused the strongest neural response in the prefrontal region compared to other conditions. 2. A 40 Hz square wave sound suppresses the alpha rhythm in the EEG signal.
PMID: 34027028	40 Hz audiovisual stimulation	1-h daily for 4 or 8 weeks	N = 10 patients with MCI due to AD	1. Gamma flicker was found to be safe, well-tolerated, and easy to follow. 2. MRI and CSF proteomics suggest that prolonged flickering may impact neural networks and immune factors in the nervous system.
PMID: 34630050	40 Hz audiovisual stimulation	1 h daily for 6 months	N = 22 patients with mild to moderate AD	1. Gamma sensory stimulation reduced nighttime activity and improved sleep quality compared to the sham group. 2. Patients in the gamma sensory stimulation group maintained their functional abilities, while those in the sham group experienced a decline in ADCS-ADL scores.
PMID: 36454969	40 Hz audiovisual stimulation	Stimulation for 3 months every day	N = 25 cognitively normal volunteers N = 16 patients with mild AD	After 3 months of daily 40 Hz stimulation, the group showed reduced ventricular dilation and hippocampal atrophy, increased connectivity in certain brain networks, better memory performance, and improved daily activity rhythms compared to the control group.
PMID: 30155285	40 Hz light flicker	1 h twice daily for 10 days	N = 5 patients with AD N = 1 patients with MCI	There was no statistically significant reduction in PiB SUVR values observed across the various volumes of interest examined (including the primary visual cortex, visual association cortex, lateral parietal cortex, precuneus, and posterior cingulate), as well as in the total motor cortex.
PMID: 27031491	40 Hz vibrotactile stimulation	Twice a week over 6 weeks for a total of 6 times per treatment	N = 18 patients with AD (6 mild, 6 moderate, 6 severe)	Combining 40 Hz vibrotactile stimulation with low-frequency sound stimulation can lead to progressive improvement of cognitive ability (SLUMS) and enhance the behavioral ability of mild to moderate AD patients.
PMID: 36497624	40 Hz auditory sound Stimulation 40 Hz tactile stimulation (sine wave)	5 times per week for 30 min per day for 1 year	N = 2 patients with AD N = 1 patients with MCI	1. The 3 patients' MoCA scores improved after one year of treatment. 2. The 3 patients' GDS scores decreased, showing a reduction in depressive symptoms. 3. The 3 patients' QOL-AD scores increased, indicating an improvement in their quality of life.

incorporated 40 Hz audiovisual stimulation in their study by applying Gamma Entrainment using Sensory Stimulation (GENUS) to 5XFAD mice for one hour daily over the course of a week. The results showed that the simultaneous 40 Hz audiovisual stimulation had a greater effect on removing amyloid-beta (Aβ) proteins than either auditory or visual stimulation individually. Additionally, the 40 Hz audiovisual stimulation showed a notable impact on the abundance of microglia in the medial prefrontal cortex. These microglia cells clustered around protein plaques and contributed to their removal. After one week of simultaneous stimulation, a significant decrease of 37% in the overall size of plaques in the frontal lobe was observed, as well as a 34% reduction in plaque quantity compared to non-stimulated mice.[35] Studies on animals with AD indicate that 40 Hz audiovisual combined stimulation (GENUS) could be effective in enhancing key pathological features of the disease, such as the accumulation of amyloid-beta (Aβ) plaques, neurofibrillary tangles, and disrupted neuronal synaptic function. These results support the rationale for investigating the potential therapeutic benefits of 40 Hz multisensory stimulation in patients with AD.

In contrast, some research teams have reported findings contrary to these. In research led by Soula et al., the effects of 40 Hz stimulation were investigated in animal models, including those with acute and chronic conditions like APP/PS1 and 5xFAD. The study revealed that exposure of the neocortex

and hippocampus to 40 Hz flickering light did not lead to a significant decrease in Aβ protein levels. Alternatively, mice displayed avoidance behaviors in response to the stimulation, and only a limited number of neurons in the hippocampus and olfactory regions exhibited activity in reaction to light stimulation, without any discernible impact on gamma oscillations.[36] This research presents a challenge to established findings; nevertheless, it is imperative to account for individual variations in animal models, potential experimental inaccuracies, and other unidentified variables that could impact the outcomes. Given the insufficient confirmation of related study results, further research is necessary to determine and verify the exact therapeutic benefits of 40 Hz light stimulation for treating neurological disorders.

Examining the effects of audiovisual stimulation at 40 Hz on cognitive abilities in Alzheimer's patients

Preclinical investigations into the effects of multisensory stimulation in AD mouse models have demonstrated notable outcomes. Subsequent early-stage clinical trials have indicated promising therapeutic advantages of multisensory stimulation in AD patients, with established safety, feasibility, and optimal protocols for gamma sensory stimulation therapy. Table 1 provides a summary of clinical trials involving 40 Hz multisensory stimulation therapy in individuals with cognitive impairment. Subsequent sections will offer a comprehensive analysis of the advancements made in these studies.

Several clinical trial teams have demonstrated that exposing the brain to 40 Hz visual and/or auditory stimulation can lead to enhanced oscillatory activity, as well as significant enhancements in neural network connectivity and oscillatory activity across different areas of the brain.[37-39] Lee, Park, and colleagues conducted a study to explore the most effective parameters for inducing gamma oscillations in young adults through flickering light stimulation, varying colors, brightness levels, and frequencies. The findings indicated that flickering red light at a frequency of 34-38 Hz and a brightness of 700 cd/m^2 elicited more robust and widespread cortical gamma oscillations extending beyond the visual cortex. Furthermore, the research team also discovered that among the elderly demographic, irrespective of race, exposure to flickering light stimulation at 700 cd/m^2 at frequencies of 32 Hz or 34 Hz could elicit robust gamma oscillations across the entirety of the brain.[40,41] Previous research has examined the impact of inducing gamma oscillatory activity in the brain in various auditory contexts. Data obtained from continuous scalp EEG recordings suggest that exposure to 40 Hz binaural beats can trigger significant cortical activity and improve memory performance.[42,43] In their study, Han et al conducted an evaluation of the impact of gamma activity induction in the brain across various auditory conditions. Their findings revealed that 40 Hz sine wave auditory stimulation elicited the most robust neural oscillatory response in the frontal lobe region when compared to square waves. Additionally, the researchers observed that 40 Hz square wave stimulation suppressed alpha rhythm in the frontal lobe region, while 40 Hz auditory stimulation did not induce oscillatory activity in the temporal lobe.[44] Zhang and colleagues employed a 64-channel electroencephalography (EEG) system to investigate the neural responses to 40 Hz light stimulation in a cohort of healthy young individuals. Additionally, they performed microstate analysis to explore the impact of this stimulation. The findings of the study revealed a notable enhancement in the power of the 40 Hz frequency band within the visual cortex regions, particularly at electrodes O1, Oz, and O3.[45] Khachatryan and colleagues carried out a study with 15 participants undergoing scalp EEG recordings. Additionally, the study featured a person with epilepsy, who had 50 electrodes positioned on the temporo-parietal cortex's surface and 14 depth electrodes targeting the hippocampus and insula. The findings of the study demonstrated that augmenting the visual attention task during 40 Hz flickering light stimulation not only amplified the coherence and spatial distribution of gamma waves in the brain but also promoted gamma oscillatory activity within the hippocampus, a deep brain region. This discovery is of considerable significance as it sheds light on the impact of visual attention tasks on gamma oscillations and their influence on deep brain structures, notably the hippocampus.[46]

The research group led by Tsai Li-Huei has increasingly explored the application of GENUS, a type of 40 Hz audiovisual stimulation. Experiments involving human subjects have yielded varying degrees of success. In a preliminary investigation, Annabelle C. Singer's team employed GENUS with 10 patients exhibiting mild cognitive impairment due to AD, randomly assigning them to one of 2 groups. One group received daily 1-h sessions of 40 Hz audio-visual flicker stimulation for 8 weeks, while the other group underwent a 4-week delay before receiving a 4-week treatment in the experiment. The findings of the trial demonstrated that the 40 Hz audio-visual flicker stimulation was well-received and deemed safe, resulting in widespread brainwave entrainment among all patients. Following an 8-week treatment period, an improvement in brain network connectivity was observed. This finding aligns with studies on mice with AD, where the 40 Hz audio-visual flicker treatment also elicited an immune response in humans. After 8 weeks of audio-visual stimulation, there was a noticeable trend towards reduced cytokine and immune factor levels in the cerebrospinal fluid.[47] Cimenser and colleagues carried out research involving 22 patients with mild to moderate AD, randomly allocating them to either an active treatment group or a sham group. The active treatment group underwent 40 Hz visual and auditory stimulations with eyes closed for 1 h daily over 6 months to induce cortical 40 Hz oscillations. The sham group received similar sensory stimulation that did not induce these oscillations. The results of the study indicated that the active treatment group exhibited notable enhancements in nighttime sleep compared to the sham group, while their daily life functioning remained stable and did not deteriorate

further.[48] Chan and associates conducted a clinical trial to assess the effect of Gamma sensory stimulation on neurodegeneration imaging biomarkers in patients with mild AD. Fifteen individuals with a diagnosis of mild AD underwent treatment with the GENUS device, which entailed daily one-hour sessions of 40 Hz audiovisual stimulation over a period of 4 months. The results showed that using the GENUS device could safely and effectively induce neural oscillations in both cortical and subcortical regions, including areas previously found unresponsive to Gamma oscillations through auditory or visual stimuli in earlier studies. Conversely, the placebo intervention yielded no significant effects. The group receiving treatment showed several positive results after 3 months of GENUS stimulation therapy, in contrast to the control group that received a placebo. The outcomes revealed enhanced connectivity within the default mode network (DMN) and the medial visual network (MVN), maintained hippocampal volume, better circadian rhythm, and cognitive performance improvements, particularly evident in the face-name memory test. Furthermore, changes were noted in cytokine levels and immune factors in the cerebrospinal fluid.[49] The research conducted by Chan et al provides initial evidence suggesting that GENUS treatment may potentially slow the progression of neurodegenerative alterations in individuals diagnosed with AD. Further research has delved into the effects of 40 Hz sensory stimulation therapy on markers associated with AD. In a particular study, 10 individuals with mild cognitive impairment (MCI) underwent daily one-hour sessions of GENUS stimulation at home for either 4 weeks or 8 weeks. Post-treatment assessments showed no significant alterations in the cerebrospinal fluid levels of amyloid-beta 42 (Aβ42), phosphorylated tau (p-tau), total tau (t-tau), or the t-tau/Aβ42 ratio. Nevertheless, after 8 weeks of daily 40 Hz sensory stimulation, a reduction was noted in certain cytokines, including TWEAK, transforming growth factor alpha, macrophage inflammatory protein 1β, delta and notch-like epidermal growth factor receptor, and interleukin (IL)-5.[47] Recent research has expanded the understanding of brain plasticity to include changes in white matter structure and organization.[50,51] It suggests that restoring or preventing myelin loss could be a treatment strategy.[52] Since myelin is crucial for communication in the brain, its degeneration can disrupt function and connectivity. Monitoring white matter volume and myelin content changes could provide valuable insights into AD progression. A recent randomized controlled clinical trial examined the impact of non-invasive 40 Hz gamma sensory stimulation on the integrity of white matter and myelin in individuals diagnosed with AD. Over a 6-month period, participants with AD underwent 40 Hz visual and auditory gamma sensory stimulation. The study assessed white matter volume through T1-weighted MRI and evaluated myelin content using both T1-weighted and T2-weighted MRI techniques. The findings revealed a substantial decrease in white matter atrophy and an enhancement in myelin thickness within the treatment group. Furthermore, cognitive assessments indicated superior cognitive performance in the treatment group, particularly in spatial memory, learning capacity, and cognitive flexibility. Additionally, the treatment group showed a pronounced reduction in neuroinflammatory markers, accompanied by increased expression of neuroplasticity markers, including nerve growth factor (NGF) and synaptic proteins. These results suggest that gamma stimulation may confer neuroprotective effects.[53] Therefore, further validation is needed to determine whether GENUS treatment can reverse the pathology of AD.

The findings from studies utilizing multisensory stimulation in human subjects indicate that 40 Hz audiovisual stimulation therapy may augment Gamma oscillatory activity and cognitive processing efficiency in the brain. Yet, investigations into the potential benefits of 40 Hz multisensory stimulation for AD patients are still in the nascent stages. These investigations are typically constrained by limitations such as small study groups, brief treatment periods, and a lack of extended follow-up. Currently, most clinical trials on 40 Hz multisensory stimulation therapy are still in the feasibility study phase, with safety concerns under further evaluation. A recent study assessed the safety, tolerability, and efficacy of gamma oscillation induction therapy in patients with mild to moderate AD. The results indicated that the treatment was safe and well-tolerated in the majority of patients, with no serious adverse reactions. Mild side effects, such as headaches and a tingling sensation on the skin, were relatively common, but all were within tolerable limits.[54] However, some studies have found that prolonged exposure to 40 Hz flickering light stimulation may pose potential risks for patients with certain neurological conditions. For instance, studies conducted by researchers such as Hermes have demonstrated that neuronal oscillations generated within the visual cortex can potentially precipitate epileptic seizures or provoke pre-ictal epileptic events in individuals with photosensitive epilepsy.[55] Consequently, it's imperative to conduct comprehensive clinical studies to fully ascertain the treatment's efficacy and confirm the actual applicability of 40 Hz multisensory stimulation therapy in the treatment of AD.

The impact of 40 Hz vibratory tactile stimulation on animal models of AD and patients with AD

Various research teams have undertaken studies involving 40 Hz multisensory stimulation with light and/or sound on AD mice and human patients, leading to enhancements in cognitive abilities. This research has now progressed to include vibratory tactile stimulation. In a study by Ho-Jun Suk et al, tau-p301s mice and CK-p25 mice were exposed to vibratory stimulation, with the experimental group being exposed to 40 Hz sound vibrations generated by a speaker, while the control group remained in cages in the same room without any stimulation. The study was primarily directed at investigating the primary somatosensory cortex (SSp) and the primary motor cortex (MOp) within the brain. Following 3 weeks of vibratory stimulation, findings revealed a significant decrease in tau protein levels in the SSp region of tau-p301s mice belonging to the experimental

group, a trend that was similarly observed in the MOp area. For CK-p25 mice in the experimental group subjected to 6 weeks of vibratory stimulation, there was an increase in synaptic protein markers in both the SSp and MOp brain regions, accompanied by a diminished extent of DNA damage. Additionally, the mice models that received vibratory tactile stimulation showed an improvement in motor skills as indicated by increased time spent on the rotating rod.[56] Hence, the results indicate that vibratory tactile stimulation may have potential advantages in decreasing tau levels, enhancing synaptic protein markers, reducing DNA damage, and enhancing motor function in AD mouse models. Additional investigation is necessary to ascertain the applicability of these outcomes to individuals with AD.

In 2016, Clements-Cortés and colleagues conducted a study to investigate the effects of combining 40 Hz vibratory tactile stimulation with low-frequency sound stimulation (RSS) on 18 AD patients at different stages of the disease (6 mild, 6 moderate, and 6 severe). The experimental group was treated with 40 Hz RSS therapy, whereas the control group was given visual stimulation. Both interventions were administered twice weekly for a duration of 6 weeks. The findings suggest that exposure to 40 Hz RSS resulted in incremental enhancements in cognitive function, assessed through the Saint Louis University Mental Status Examination (SLUMS), and improved behavioral abilities in persons with mild to moderate AD.[57] In 2022, Clements-Cortés and team conducted a subsequent study, employing the Sound Oasis VTS 1000 multisensory stimulation device on 2 patients with AD and one with Mild Cognitive Impairment (MCI) over a year. The study's outcomes revealed that the cognitive functions of all 3 participants remained constant throughout the study, as assessed by the SLUMS.[58] Initial results indicate that 40 Hz audiovisual tactile stimulation might be effective in positively influencing the progression of AD in individuals. The studies referenced collectively provide evidence supporting the use of 40 Hz audiovisual tactile stimulation for decelerating disease progression, enhancing cognitive functions, and possibly improving mental well-being in individuals with AD.

The impact of 40 Hz light stimulation on post-stroke animal models

A stroke can lead to neuronal death and functional deficits, impacting the activity and connectivity of interneurons and pyramidal cells, which in turn can result in aberrations in the amplitude, frequency, synchrony, and stability of gamma oscillations.[59] Post-stroke, neuronal activity may persist in a depolarized state due to various factors such as diminished Na^+/K^+-ATPase activity, suppression of K^+ channels, and the entry of Na^+ through non-selective cation channels and other routes. This abnormal depolarization is compounded by disturbances in interneuronal function.[60-63] The excitability of neurons, a critical factor in neuronal communication and synaptic plasticity, is markedly diminished in the peri-infarct region. This diminution has been demonstrated to constrain functional recovery following a stroke.[64-66] However, gamma oscillations have the capacity to modulate the function of interneurons, thereby influencing the propagation of excitability and ultimately improving the synchronization and transmission of information within the neural circuitry.[67,68]

Recent studies have shown that there is a steady decline in the intensity of low gamma oscillations (30-50 Hz) within the peri-infarct area as the distance from the central lesion increases. Conversely, the power of delta and theta oscillations (1-12 Hz) remains stable. The reduction in low gamma oscillations is linked to neuronal damage and activation of glial cells.[67,69] In contrast, the contralateral homologous region of the infarct shows a notable rise in local field potential (LFP) power across all frequency ranges.[70,71] This increase in LFP is associated with heightened neuronal excitability and synaptic plasticity.[72,73] Matilde Balbi and her research team employed the transgenic VGAT-ChR2 mouse model to induce strokes in the somatosensory and motor cortex under awake conditions through photothrombosis. One hour post-stroke, they administered 40 Hz optogenetic stimulation to the peri-infarct region. Control groups were included, comprising those that received no stimulation and those subjected to 10 Hz low-frequency stimulation. The experiment's findings demonstrated that acute optogenetic stimulation at 40 Hz successfully reinstated neuronal activity in both the motor and associative regions, along with cerebral blood flow, 24 h after a stroke. This stimulation resulted in a significant decrease in both the size of the lesion and the occurrence of spreading depolarization waves (SDWs), providing nerve protection and enhancing motor function. Furthermore, the research team conducted an in-depth investigation into the subacute phase, specifically 3 to 7 days post-stroke. Their findings revealed that, in the group subjected to optogenetic stimulation, neuronal activity, synaptic plasticity, and both the amplitude and power of gamma oscillations in the peri-infarct region had nearly normalized by the seventh day following the stroke Figure 1.[74,75]

New studies suggest that exposing the brain to 40 Hz flickering light can trigger gamma oscillations by improving the flexibility of nerve cell connections, which may help maintain healthy brain function and safeguard neurons during oxygen deprivation. Zheng and colleagues carried out research utilizing a mouse model of cerebral ischemia, triggered by occlusion of the bilateral common carotid artery (2VO). They discovered that stimulation with 40 Hz light flicker efficiently reinstated slow gamma oscillations in the hippocampal CA1 area and reestablished the phase-amplitude coupling with theta oscillations. Nevertheless, it failed to reverse the decrease in high gamma oscillations. Exposing the ischemic CA1 area to light at frequencies of 30 Hz, 40 Hz, and 50 Hz demonstrated protective benefits for nerve cells and enhanced motor abilities, spatial learning, and memory in the 2VO mice. The study verified that exposing the brain to 40 Hz light flicker helps protect it by enhancing RGS12's regulation of

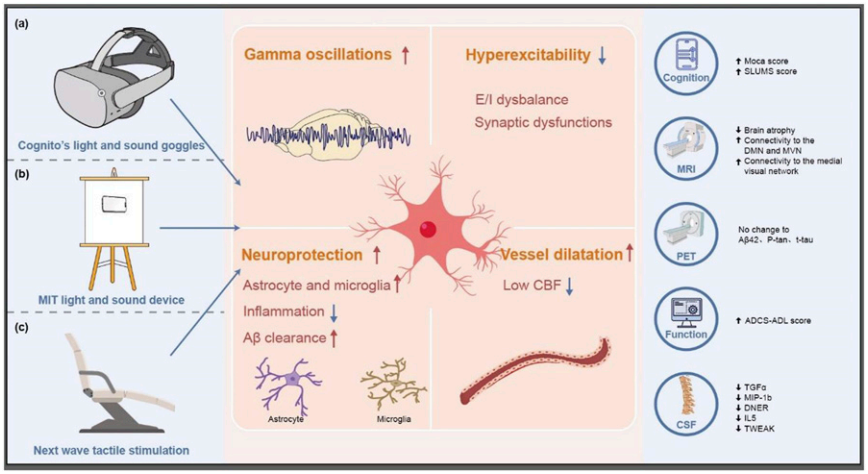

Figure 1. The mechanisms and effects of gamma oscillations in improving cognitive function. The most significant benefits are observed when visual and auditory stimuli are combined, rather than relying on a single mode of stimulation. (a) Cognito's light and sound goggles, (b) MIT light and sound device, and (c) NextWave tactile stimulation chair. 40 Hz multisensory stimulation therapy enhances cognitive function by targeting specific sensory areas of the brain with precise frequencies and intensities, improving neuron and synapse functionality, regulating interneuron activity, increasing cerebral blood flow, modulating immune responses, influencing gamma oscillations, and ultimately enhancing cognitive function. SLUMS: Saint Louis university mental status examination, MoCA: Montreal cognitive assessment, DMN: default mode network, MVN: medial visual network, ADCS-ADL: Alzheimer's disease cooperative study activities of daily living inventory, IL5: interleukin-5, MIP-1β: macrophage inflammatory protein 1β, TGF-α: transforming growth factor alpha, TWEAK: tumor necrosis factor-related weak inducer of apoptosis.

synaptic plasticity between CA3 and CA1, as well as long-term potentiation after 2VO, leading to the restoration of slow gamma oscillations.[76]

The study findings show that stimulating gamma oscillations provides significant protection for the nervous system, especially in mice with impaired brain function after a stroke. Through the modulation of distinct frequencies, not only are impaired neurons activated, but their synchronization is also improved, facilitating the recovery of motor skills and cognitive capabilities. Gamma oscillations have the potential to enhance the brain's milieu through the mitigation of inflammatory reactions and the reinforcement of neuronal connections, thereby offering considerable implications for the rehabilitation of individuals who have suffered a stroke. Additionally, this modality presents a promising therapeutic avenue that may aid in the non-invasive treatment of stroke patients, facilitating the restoration of neural functionality and enhancing their overall well-being Table 2.

Conclusions and future perspectives

Recent studies have elucidated a strong correlation between gamma oscillations and advanced cognitive processes.[59,77] The efficacy of 40 Hz multisensory stimulation therapy in eliciting gamma oscillations, modulating synaptic plasticity, and promoting neuronal synergy and connectivity has been empirically demonstrated, suggesting promising therapeutic applications for a range of neurodegenerative conditions, particularly those affecting cognitive function.[78-81] The non-invasive nature of this therapy positions it as a valuable modality in the realm of rehabilitative interventions for brain-related disorders. Its distinctive diffusive properties set it apart from conventional non-invasive brain stimulation methods like TMS and tDCS because it doesn't necessitate direct skull contact and impacts a wider array of important brain regions.[82-84]

In light of the safety and health considerations linked to 40 Hz multisensory stimulation therapy, it is imperative to formulate a comprehensive treatment plan or framework. Primarily, during the administration of 40 Hz multisensory stimulation, careful regulation of the frequency, intensity, and duration is essential to prevent overstimulation, which may adversely affect the nervous system. Research indicates that moderate stimulation may enhance cognitive function; however, excessive or prolonged stimulation may elicit adverse reactions, including headaches, seizures, visual fatigue, and mood swings. Consequently, the treatment protocol ought to adopt a personalized approach, tailoring the stimulation in accordance with variables such as the patient's age, disease progression, and nervous system sensitivity. Furthermore, the development of the 40 Hz multisensory stimulation therapy framework should incorporate comprehensive monitoring and feedback mechanisms. During the course of treatment, systematic evaluations of the patient's cognitive functions, emotional status, and neurological responses should be routinely performed to promptly assess therapeutic efficacy and identify any adverse reactions. Furthermore, it is imperative to establish a follow-up system, particularly for long-term treatments, to continuously monitor the patient's health status, ensure the stability of therapeutic outcomes, and promptly address any potential side effects. By integrating these safety considerations and health monitoring mechanisms, the therapy can be implemented more effectively in clinical settings.

Table 2. Summary of the effects of 40 Hz multisensory stimulation therapy on central nervous system gamma oscillations in animal research.

CITATION	SUBJECT	METHOD	AFFECTED BRAIN MAJOR FINDINGS AREA	KEY POINTS
PMID: 31757962	J20-APP mice	Optogenetic stimulation of MSPV neurons	Hippocampus	1. Hippocampal theta-low gamma phase-amplitude coupling↑ 2. Spatial memory ↑ 3. No significant change in Aβ amyloid plaque deposition
PMID: 27161522	ApoE4-KI mice ApoE3-KI mice	/	Hippocampus	1. The number of sharp-wave ripples (SWRs) ↓ 2. Slow gamma activity during SWRs in aged ApoE4-KI mice↓ 3. ApoE4-KI mice exhibit memory deficits and learning impairments. ↓
PMID: 31076275	P 301S mice CK-p25 mice	GENUS	V1, CA1,mPFC	1. Learning and spatial memory ↑ 2. Neuronal loss, microglial inflammatory response↓ 3. Neurons degenerative state,DNA damage in neurons ↓
PMID: 27929004	5XFAD mice	40 Hz visual stimulation	VC	1. Amyloid-β (Aβ)1-40and Aβ1-42 isoforms↓ 2. Increased microglia co-localization with Aβ↑
PMID: 27929004	5XFAD mice	40 Hz optogenetic stimulation of FSPV interneurons	CA1	1. Amyloid-β (Aβ)1-40and Aβ1-42 isoforms↓ 2、 Increased microglia co-localization with Aβ↑
PMID: 30879788	5XFAD mice P 301S mice	40 Hz auditory stimulation	AC,Hippocampus	1. Aβ amyloid plaque deposition and tau protein phosphorylation ↓ 2. Object recognition and spatial memory capabilities↑ 3. Reactive microglia and astrocytes has increased ↑
PMID: 30879788	5XFAD mice	GENUS	mPFC	1. Aβ amyloid plaque deposition↓ 2. Reactive microglia ↑
PMID: 37273653	Tau-p 301S mice CK-p25 mice	40 Hz vibrotactile stimulation	Primary somatosensory cortex (SSp) Primary motor cortex (MOp)	1. Brain pathology in SSp and MOp↓ 2. Neural activity ↑ 3. Motor performance ↑
PMID: 33727098	C57BL/6 J mice:a permanent cortical ischemia induced	/	Peri-infarct cortex	1. Delta and theta oscillations in the peri-infarct cortex were normal. 2. Low gamma oscillations decreased gradually near the lesion border.
PMID: 33535035	VGAT-ChR2 mice	40 Hz optogenetic stimulation	The area of forelimb sensory and motor cortex	1. Neuronal activity in motor and parietal association areas improves after stroke within 24 hours in the peri-infarct zone. 2. 40 Hz stimulation reduces lesion volume and enhances motor function.
PMID: 37979173	VGAT-ChR2 mice	40 Hz optogenetic stimulation	The area of forelimb sensory and motor cortex	1. 40 Hz stimulation after stroke improves synaptic plasticity within 24 hours. 2. Plasticity genes are increased and cell death genes are decreased.
	2VO mice	40 Hz light flicker	Hippocampal CA1	1. Lights at 30 Hz, 40 Hz, and 50 Hz protected CA1 neurons after 2VO. 2. 40 Hz light flicker improved motor skills, spatial learning, and memory in 2VO mice.

The innovative approach of 40 Hz multisensory stimulation therapy has attracted significant interest in scholarly circles due to its potential mechanisms and effectiveness in treating conditions such as AD and PSCI. However, research in this area remains in its nascent stages, with numerous uncertainties surrounding the precise underlying mechanisms. Current investigations into PSCI are predominantly confined to animal models, and there exists a paucity of data to substantiate its

translation to human applications. The current clinical trials in this field are at the forefront of implementing this therapy from theoretical to practical application. Nevertheless, the limited sample sizes hinder our capacity to thoroughly evaluate its clinical effectiveness and safety. To more precisely assess the true impact of 40 Hz multisensory stimulation therapy on enhancing the cognitive function of patients with impairments, further comprehensive experimental investigations are required to elucidate its specific effects on brain functionality. It is crucial to carry out extensive longitudinal clinical trials on a larger scale to evaluate the clinical effectiveness of this treatment method. These trials are essential for confirming the long-term durability and stability of treatment effects, as well as monitoring potential side effects that may arise in patients over extended periods of treatment. This comprehensive evaluation is necessary to fully understand the benefits and drawbacks of the treatment. Through thorough research, we can create customized and effective treatment strategies for patients, ultimately improving their quality of life and decreasing societal and economic burdens.

Author contributions

Xiao Chen: Conceptualization; Investigation; Supervision; Writing - original draft; Writing - review & editing.
Zhongyue Lv: Conceptualization; Writing - original draft; Writing - review & editing.
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Yan Zhou: Investigation: Writing - review & editing.
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Ethical statement

Consent for publication

Not applicable.

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