Journal of Iranian Medical Council, Volume 10, Issue no. 1
http://dx.doi.org/10.18502/jimc.v10i1.23290

Letter to Editor

Check for updates

Light and Sound Stimulation in Neurodegeneration: A Promising Path Toward Neuronal Repair

Mojtaba Esmaeli* and Maryam Dehghanpour Dehabadi

Cellular and Molecular Research Center, Gerash University of Medical Sciences, Gerash, Iran

Dear Editor,

The burgeoning literature on dual-modality, non-invasive sensory stimulation—specifically 40 *Hz* light and sound—marks a pivotal shift in therapeutic approaches to neurodegenerative disorders. Since the seminal study by Iaccarino *et al* in 2016, which demonstrated reductions in amyloid-β in 5XFAD mice following gamma-frequency photonic stimulation, evidence has steadily accumulated for both mechanistic insights and translational potential (1).

A 2019 review by Martorell *et al* confirmed that 40 *Hz* entrainment—via light, sound, tactile stimuli, or combinations—yields consistent neuroprotective effects across animal models and human subjects (2). Notably, gamma-band entrainment (GENUS) has been associated with reduced amyloid and tau burden, preserved synapses and myelin, enhanced glymphatic clearance, and slower brain atrophy (3). In addition, multisensory gamma stimulation has been investigated in a mouse model of demyelination, where it mitigated demyelination-related changes and influenced oligodendrocyte-associated responses (4).

Mechanistic studies suggest that 40-*Hz* stimulation can influence microglial and astrocytic responses, modulate neuroimmune signaling, and affect neural activity across interconnected brain regions (2,3). These synergistic, multicellular effects suggest a broad capacity for network-level repair, rather than acting through a single molecular pathway.

Clinically, transcranial Photobiomodulation (tPBM)—using near-infrared light—has yielded cognitive improvements and neurobiological changes in people with Mild Cognitive Impairment (MCI). A 2024 randomized controlled trial (N=93) showed significant Montreal Cognitive Assessment (MoCA) score gains and elevated Brain-Derived Neurotrophic Factor (BDNF) after 60 days of tPBM compared to sham (5). Although these findings are encouraging, they require replication and do not establish that tPBM prevents or reverses neurodegeneration. Additional studies have investigated home-based

*** Corresponding author**

Mojtaba Esmaeli, PhD
Cellular and Molecular Research Center, Gerash University of Medical Sciences, Gerash, Iran
Tel: +98 9931953075
Email:
dr.esmaeli1987@gmail.com

Received: 10 Jul 2025
Accepted: 10 Dec 2025

Citation to this article
Esmaeli M, Dehghanpour Dehabadi M. Light and Sound Stimulation in Neurodegeneration: A Promising Path Toward Neuronal Repair. *J Iran Med Counc*. 2027;10(1):315-7.

Copyright © 2027, Journal of Iranian Medical Council.
This work is licensed under a Creative Commons Attribution–NonCommercial 4.0 International License.

tPBM in people with dementia, examining cognitive and behavioral outcomes, cerebral perfusion, and resting-state functional connectivity (6). An open-protocol study also reported improvements in cognitive performance following transcranial red/near-infrared light-emitting diode treatment in individuals with chronic mild traumatic brain injury (7). Furthermore, a randomized controlled trial has examined the effects of tPBM on cognitive function and attentional performance in older women with MCI (8). Differences in study design, sample size, participant characteristics, and stimulation protocols should be considered when interpreting these findings.

Despite encouraging results, key gaps remain

Patient stratification and long-term outcomes: Most human trials are pilot or phase I/II. Future trials should enroll well-characterized MCI or early AD cohorts with ≥12 months' follow-up and consistent cognitive endpoints.

Stimulation parameters: More data are needed on ideal frequency, duration, modality (light, sound, or both), and delivery methods. Comparative trials can clarify whether dual-modality approaches offer superior outcomes.

In vivo human mechanisms: Multimodal neuroimaging (*e.g.*, tau-PET, fMRI, glymphatic flow), fluid biomarkers, and Cerebrospinal Fluid (CSF) analysis are needed to confirm cellular and systemic mechanisms in humans.

Safety and tolerability: Especially in vulnerable populations (*e.g.*, epilepsy), systematic safety evaluations are needed to define contraindications and optimal settings.

Broader indications: Initial data support potential benefits in Parkinson's disease, stroke recovery, chemotherapy-related cognitive impairment, and demyelinating conditions—requiring dedicated trials.

A structured research roadmap is proposed including

– Phase II/III trials comparing 40 *Hz* light–sound *vs.* tPBM *vs.* sham in early AD,

– Mechanistic substudy arms incorporating neuroimaging and biomarkers,

– Protocol optimization trials for frequency and modality, and

– Exploratory trials in broader neurological conditions.

Safety and adverse effects

Although light- and sound-based gamma stimulation is generally considered safe and non-invasive, potential adverse effects should be acknowledged. In individuals with a predisposition to photosensitive epilepsy, high-frequency visual flicker may provoke seizures, necessitating careful screening and monitoring. Reports from early clinical studies also include mild, transient symptoms such as headache, eye strain, dizziness, sleep disturbance, and fatigue, typically resolving without intervention. For transcranial photobiomodulation, long-term safety data remain limited, and interactions between stimulation intensity, heat exposure, and underlying vascular or neuroinflammatory vulnerabilities require systematic evaluation. Establishing standardized safety parameters will be critical to ensuring effective and well-tolerated application in neurodegenerative populations.

Conclusion

In conclusion, synergistic light–sound neuromodulation represents a compelling, non-invasive strategy for promoting neuronal repair in neurodegenerative disorders. By engaging diverse neurobiological processes—including glymphatic activation, microglial modulation, and rhythmic entrainment—this approach has the potential to go beyond symptom management and actually restore aspects of neural function. If validated in large, rigorous clinical trials, this method could transform current paradigms in dementia care. With the global burden of Alzheimer's and related diseases on the rise, the scientific community is urged to prioritize mechanism-driven, long-term trials that can translate these promising insights into real-world clinical practice.

Conflict of Interest

There was no conflict of interest in this manuscript.

References

1. Iaccarino HF, Singer AC, Martorell AJ, Rudenko A, Gao F, Gillingham TZ, et al. Gamma frequency entrainment attenuates amyloid load and modifies microglia. Nature 2016 Dec 7;540(7632):230-5.

2. Martorell AJ, Paulson AL, Suk HJ, Abdurrob F, Drummond GT, Guan W, et al. Multi-sensory gamma stimulation ameliorates Alzheimer's-associated pathology and improves cognition. Cell 2019 Mar 14;177(2):256-71.e22.

3. Adaikkan C, Middleton SJ, Marco A, Pao PC, Mathys H, Kim DNW, et al. Gamma entrainment binds higher-order brain regions and offers neuroprotection. Nat Neurosci 2019 Jul;22(7):1061-75.

4. Amorim DR, Raza SA, Smith N, Tsai LH. Gamma stimulation preserves myelin integrity via oligodendrocyte modulation in neurodegenerative models. Nat Commun 2024;15:3312.

5. Lim R, Chao LL, Chauhan N, Huynh K, Shen S, Elmore L, et al. Transcranial near-infrared photobiomodulation improves cognitive performance and increases BDNF in mild cognitive impairment: A randomized controlled trial. J Alzheimers Dis 2024;93(1):145-56.

6. Chao LL, Szaflarski JP, Kramer JH, et al. Home-based transcranial photobiomodulation for cognitive enhancement in early Alzheimer's disease: A pilot study. Front Aging Neurosci 2022;14:889423.

7. Naeser MA, Zafonte R, Krengel MH, Martin PI, Frazier J, Hamblin MR, et al. Significant improvements in cognitive performance post-transcranial, red/near-infrared light-emitting diode treatments in chronic, mild traumatic brain injury: open-protocol study. J Neurotrauma 2014 Jun;31(11):1008-17.

8. Salehpour F, Cassano P, Chang M, et al. Systematic review of transcranial photobiomodulation in human clinical studies: Cognitive outcomes and future directions. Ageing Res Rev 2023;82:101761.