Photobiomodulation and visual stimulation against cognitive decline and Alzheimer’s disease pathology: A systematic review

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Abstract
Introduction: Given the ineffectiveness of the available drug treatment against Alzheimer disease (AD), light-based therapeutic modalities have been increasingly receiving attention with photobiomodulation (PBM) and, more recently, visual stimulation (VS) being among the most promising approaches. However, the PBM and VS light parameters tested so far, as well as their outcomes, vary a lot with conflicting results being reported.

Methods: Based on Scopus, PubMed, and Web of Science databases search, this systematic review summarizes, compares, and discusses 43 cell, animal, and human studies of PBM and VS related to cognitive decline and AD pathology.

Results: Preclinical work suggests that PBM with 640±30-nm light and VS at 40 Hz attenuates Aβ and Tau pathology and improves neuronal and synaptic plasticity with most studies pointing towards enhancement of degradation/clearance mechanisms in the brain of AD animal models. Despite the gap of the translational evidence for both modalities, the few human studies performed so far support the use of PBM at 810-870 nm light pulsing at 40 Hz for improving brain network connectivity and memory in older subjects and AD patients, while 40 Hz VS in humans seems to improve cognition; further clinical investigation is urgently required to clarify the beneficial impact of PBM and VS in AD patients.

Discussion: This review highlights PBM and VS as promising light-based therapeutic approaches against AD brain neuropathology and related cognitive decline, clarifying the most effective light parameters for further preclinical and clinical testing and use.

Key words
Alzheimer’s disease, cognitive decline, light-based therapies, photobiomodulation, visual stimulation
Alzheimer’s disease (AD) is an age-related neurodegenerative disorder that progressively damages brain structure and function leading to memory loss and overall cognitive impairment.1,2 AD is the most prevalent cause of dementia1,3,4 affecting approx. 40 million people worldwide; importantly, this number will triple by 2050, turning AD and dementia into a high-priority health problem for the World Health Organization.5 The AD brain suffers from different lesions and deficits that include neuronal atrophy and synaptic loss in various brain areas (e.g., hippocampus and cerebral cortex), as well as aberrant connectivity and altered network oscillations.5–11 A plethora of preclinical and clinical studies correlated the brain deficits in plasticity and connectivity with the accumulation of different pathological species of amyloid beta (Aβ) peptide and Tau protein.12–14 Aβ is a proteolytic fragment of the transmembrane protein amyloid precursor protein (APP); the latter is abnormally processed to Aβ in the AD brain, leading to increased Aβ42/Aβ40 ratio and its deposition into the characteristic extracellular Aβ plaques. Moreover, Tau, a microtubule-associated protein involved in cytoskeletal regulation, is abnormally hyperphosphorylated and aggregated into intracellular neurofibrillary tangles in the AD brain.2,15 Different cellular mechanisms have been described regarding how the accumulation of Aβ42 and hyperphosphorylated Tau and their pathological species (e.g., Aβ oligomers, Tau oligomers and aggregates) interfere with and damage neuronal function and brain networks, causing neurodegeneration and cell death.5,9,12,16,17 In addition, different triggering parameters and risk factors for AD have been suggested including aging, genetics, sex, cardiovascular disorders, chronic stress, brain hypoperfusion, traumatic brain injury, and others.18–20

Despite the significant progress in understanding the mechanisms of neuronal malfunction and neurodegeneration in AD, there is a lack of effective strategies to stop or reverse AD pathological features related to brain lesions and cognitive impairment. In fact, the available pharmacological approaches currently used in AD patients offer a transient, not long-lasting, benefit in slowing down or alleviating the cognitive deficits but they don’t block or reverse Aβ or Tau pathology. Given the ineffectiveness of the available pharmacological treatment in AD, alternative therapeutic strategies have been suggested with some focusing on neuronal and brain connectivity, which are damaged in the AD brain.5,21–28 For example, functional disconnections among cortical regions and altered neural activity pattern, monitored by electroencephalogram (EEG), are often used in AD diagnosis.11,29 Moreover, AD patients present diminished power of gamma oscillations (30–100 Hz),30,31 which are associated with high-order cognitive functions.30,31 In light of evidence showing that the entrainment of brain oscillations and subsequent coordination of neural activity is shown to preserve normal neural function,32,33 recent studies have monitored the therapeutic potential of modulation of neural oscillations against AD. For instance, photobiomodulation (PBM), which consists of delivering red or near-infrared light for multiple therapeutic purposes (e.g., accelerating wound healing, destroying cancerous tumors, stimulating hair growth), is suggested to exhibit tissue-repairing properties and enhance synaptic function.25,27,28 More recently, visual stimulation (VS) has been shown to reduce AD neuropathology,26,34 supporting further exploration of this sensory stimulation modality against AD. As both PBM and VS may represent promising noninvasive and safe approaches to deliver therapeutic stimuli against brain pathology, different efforts have been focusing on the application of these light-based therapeutic modalities over the last years. However, the PBM and VS stimulation parameters tested against cognitive decline and AD brain pathology as well as their outcomes vary a lot, with conflicting results being reported. Thus, this systematic review summarizes, compares, and discusses the findings of different light-based protocols of PBM and VS against AD pathology and cognitive impairment, aiming to identify the most effective parameters used so far in basic, translational, and clinical efforts of light-therapy modalities against cognitive decline and AD and to highlight the main cellular mechanisms of the beneficial effects of PBM and VS.

2 | METHODS

2.1 | Search strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines35 based on the following questions:

1. What are the main outcomes of PBM and VS studies with respect to the mitigation of AD pathological features and symptomatology?
2. What light parameters are associated with the most effective stimulation protocols against AD neuropathology?

An electronic search was done in Scopus, PubMed, and Web of Science databases, performed from September 19 to 21, 2020. Other studies found in the search that were considered relevant for this review were also included. No year limitation was applied for the selection of publications. The following search strategy was used: (“Alzheimer’s disease” OR “cognitive decline” OR “mild cognitive impairment”) AND (photobiomodulation OR “light stimulus” OR “photic stimulation” OR photostimulation OR “visual stimulation” OR “laser therapy” OR “light therapy” OR “near infrared light” OR “near infra-red light”).

2.2 Inclusion and exclusion criteria

Articles were included in this review when the following requirements were met:

- Preclinical and clinical studies that report VS and PBM delivered noninvasively, in in vitro and/or in vivo AD animal models, as well as in older non-demented volunteers, cognitively impaired individuals, and demented and AD patients;
- Studies written in English.

In addition to the articles that did not satisfy the inclusion criteria, other studies were excluded, such as:

- Reviews, conference papers, proceedings papers, editorials, and surveys;
- Studies that used light to facilitate/interfere with the delivery of drugs, therapeutic agents/compounds, or nanoparticles;
- Studies in healthy non-demented < 60-year-old individuals;
- Studies in which the light stimulation is combined with other interventions (e.g., physical exercise);
- Studies that evaluate the effect of light stimulation in individuals suffering from cognitive decline derived from other disease conditions (e.g., stroke, ischemia, Parkinson’s disease);
- Studies in which VS was not delivered by flickering light at a defined frequency.

2.3 Data extraction and analysis

Titles and abstracts were screened to filter the search results, according to the above-defined criteria. When these criteria were satisfied, the articles were analyzed and organized in Table 1 (PBM studies) and Table 2 (VS studies) according to the type of experiment and year of publication, depicting their key aspects regarding the intervention parameters, experimental models/human subjects under study, and primary outcomes.

RESEARCH IN CONTEXT

1. Systematic review: Due to the lack of pharmacological treatment for Alzheimer’s disease (AD), light-based therapeutic modalities have been increasingly receiving attention in the last years; however, different stimulation protocols are proposed and no optimal regimen has yet been defined. To fill this gap, a systematic review was conducted according to PRISMA guidelines using Scopus, PubMed, and Web of Science databases.

2. Interpretation: Both preclinical and clinical evidence has emerged on the effectiveness of these light-based therapeutic modalities to positively impact different aspects of AD pathology, including Aβ and Tau pathologies, neuroinflammation, aberrant neural activity and brain functional connectivity, and cognitive function.

3. Future directions: By comparing and discussing the existing literature, we were able to propose the most suitable regimens for future clinical application. Still, future studies must provide information on: (a) physiological assessments after stimulation in humans, (b) neuroinflammation’s role in each disease stage, and (c) durability of the therapeutic effects.

2.4 Quality assessment

As previously described, the authors developed a customized criteria checklist to evaluate the methodological quality of the selected studies. The same checklist was applied to all studies and each criterion was scored with value 2 (when the criteria were completely met), value 1 (when the criteria were not fully met or met with some limitations), value 0 (when the studies failed to fulfill the criteria), or — (when no information is available). Each study was assessed independently by two authors (FM and OC) using this methodology and, in case of disagreement, the original paper was reevaluated until they reached a consensus. The established quality checklist criteria and the respective scores assigned for each study are presented in Table S1 in supporting information.

3 RESULTS

3.1 Articles’ selection and quality

Among the 2017 publications that were initially obtained in the electronic search performed and six additional articles found in the reviewed literature, 752 were duplicates. After screening titles and abstracts of the 1271 remaining papers, 75 full texts were scrutinized. A total of 43 studies met the eligibility criteria and were included in this systematic review. The article selection steps are shown in Figure 1.
The methodological quality assessment allowed the classification of the reviewed studies into (1) high quality when the score ranged from 85% to 100% (n = 19), (2) moderate quality for scores between 70% and 84% (n = 20), and (3) low quality when the score is less than or equal to 69% (n = 5). The overall data on the methodological quality assessment is provided in Table S1. The scores for criteria Q5, Q8, and Q11 presented high heterogeneity compared to the rest of the criteria, reflecting that many of the included studies (1) do not consider the light transmission through the skull and brain tissue (20 out of 28 PBM studies);22,37–55 (2) do not use devices designed for brain stimulation, adapting equipment designed for other purposes (five out of 11 clinical studies);44,52,53,56,57 or (3) do not clearly state their conclusions (19 out of 43 studies).21,26,34,37,40,45,46,50,51,56,58–65

3.2 Profile of the included articles

This systematic review focuses on both preclinical and clinical efforts that used light-based stimulation, with a particular focus on PBM and VS. The majority of the selected studies used PBM (35 out of 43) while different light sources (i.e., light-emitting diodes [LEDs] and lasers with different wavelengths), parameters (e.g., power density, energy density, duration), and targets (e.g., cells, head, whole body) were used. Furthermore, eight studies were focused on VS, two of those dedicated to multi-sensory stimulation, combining VS and auditory stimulation, in which similar VS protocols were used.

Concerning the type of experiment, eight in vitro studies in which cells were exposed to Aβ after or before the light treatment were
reviewed. Also, 25 articles used animals (i.e., aged wild-type mice, transgenic animal models of AD, or rodents injected with AD or Tau) to study the effect of light stimulation in AD-associated pathologies and impairments. Finally, 11 articles described clinical trials, most of them \( n = 7 \) with elderly subjects with cognitive impairment or diagnosed with AD. The selected articles were organized according to the type of experiment (cell, animal, or human) and their protocol specifications were summarized based on the respective light therapy modality. Tables 1 and 2 summarize the findings of the included studies of PBM and VS, respectively, and report the different light protocols used, as well as the different levels of conducted analysis (e.g., molecular, neuropathological, plasticity, behavioral read-outs). In addition, a direct comparison of the main categories of read-outs used in the 43 reviewed studies is presented in Table 3.

### 3.3 Impact of light-based stimulation on AD pathomechanisms

More than one third of the 43 articles in this systematic review report that light stimulation impacted AD pathology. The most common effect of PBM studies was the reduction in load and deposition of soluble AD and AD-injected mice, such as the cortex and hippocampus. Besides AD levels, a reduction of amyloid plaques (cardinal AD histopathological lesion), was also found in the hippocampus and cortex of AD mice using pulsed light or continuous wave PBM. Interestingly, AD deposits were found in the deep cervical lymph nodes of AD-injected mice after PBM, which was accompanied by an increase in blood-brain barrier (BBB) permeability. Moreover, one study also shows that PBM application induced a reduction in ex vivo synaptic vulnerability to AD oligomers in wild-type mice brain, rescuing deficits in synaptic plasticity mechanisms.

In addition, a combined delivery of PBM and magnetic emissions in AD-injected mice demonstrated that 10-Hz irradiation delivered simultaneously to the head and abdomen reduced AD levels in the brain. Similarly, VS or combined VS and auditory stimuli (the so-called gamma entrainment using sensory stimuli—GENUS) were shown to reduce soluble AD in the brain of AD mice, as well as amyloid plaques number and size. However, 2-Hz VS in 3xTg-AD mice did not produce a significant decrease in AD load, indicating that this frequency has no beneficial impact on AD pathology. There are no clinical studies related to the beneficial impact of either PBM or VS application on AD pathology. Indeed, only one recent human study conducted by Jeong has addressed this issue and found no significant differences in cortical AD load after a 10-day 40-Hz VS treatment in AD and mild cognitive impairment (MCI) patients, as assessed by cortical Pittsburgh compound B positron emission tomography (PET) imaging.

In contrast to AD, fewer studies \( n = 8 \) reported a beneficial impact of light-based modalities on Tau pathology. The most common effect induced by PBM was the reduction of hyperphosphorylated Tau levels in different AD transgenic mice or AD-injected rodents. Moreover, Tau oligomers and neurofibrillary tangles, the intermediate and final forms of Tau aggregation, respectively, were also reported to be reduced by PBM in AD transgenic mice. Here, it is worth noting that PBM treatment using near-infrared (NIR) light increased autophagy, which was positively correlated with a reduction in AD and Tau species in 3xTgAD mice. Note that deficits of autophagy and the related accumulation of protein aggregates are suggested to play a critical role in the early stages of AD neuropathology, and thus, PBM may exhibit an autophagy-stimulating role in AD and Tau clearance from the brain. Moreover, two VS protocols led to a significant decrease of levels of hyperphosphorylated Tau assessed by different Tau phosphoepitopes in the visual cortex of P301S-Tau mice. Hence, despite the preclinical evidence reporting the beneficial effect of PBM and VS on Tau pathology, no PBM or VS clinical study has monitored Tau pathology in the human brain.

### 3.4 Immunoregulation and light stimulation

Among the 43 included articles, 12 of them reported alterations in immunological activity induced by light stimulation. An in vitro study reported that mesenchymal stem cells (MSCs) from C57/B6 mice exposed to PBM therapy presented an increased phagocytic state toward AD whereas Yang et al. observed a PBM-driven normalization of inflammatory responses through the downregulation of pro-inflammatory factors in primary astrocytes exposed to AD. Accordingly, PBM animal studies have detected a decrease in pro-inflammatory markers in AD transgenic and non-transgenic models, such as interleukin 1β (IL-1β), tumor necrosis factor α (TNF-α), and transforming growth factor β (TGF-β), with some studies also demonstrating reduction of hyperactivated glial cells accompanied by decreased AD and/or Tau load.

On the contrary, one study using 40-Hz (gamma frequency band) VS and another combining 40-Hz VS and auditory stimulation reported enhanced microglia activation around AD plaques, accompanied by reduced AD levels in the hippocampus and different cortical regions of AD transgenic mice. In line with these findings, it has recently been shown that 40-Hz VS also increased expression of specific both pro- and anti-inflammatory cytokines associated with microglial phagocytosis and recruitment in C57BL/6J mice. Moreover, increased astrocytic reactivity was observed in 5xFAD mice after combined VS and auditory stimulation at 40 Hz. The above effects of VS or combined VS and auditory stimulation were accompanied by reduction of both soluble and insoluble AD deposits. However, different effects were reported after VS in CK-p25 and Tau P301S AD transgenic mice, in which a reduction in neuroinflammation and a normalization of hyperactivated glial activity were found. Overall, based on the available studies, it seems that PBM and VS had different effects on glia cells and the related inflammatory response. Someone should here consider the suggested dual role of inflammation in AD brain pathology in which the inflammatory response in the first stages of the AD neuropathology could be beneficial whereas inflammatory
| Publication       | Wavelength | Energy density | Duration & periodicity | Delivery mode | Model/Subjects | Primary outcomes of light-stimulation                                                                 |
|------------------|------------|----------------|------------------------|---------------|----------------|-----------------------------------------------------------------------------------------------------|
| Duan et al. (2003) | 640 ± 15 nm | 0.162 to 3.6 J/cm² | Single session of 30 to 60 min | - |  PC12 cells exposed to \( A\beta_{25-35} \) | Molecular and Cellular:  
- reduction of apoptosis after 0.9-W/m² 60-min irradiation (FCA);  
- decreased DNA fragmentation after 0.9-W/m² 60-min irradiation (electrophoresis). |
| Zhang et al. (2008) | 632.8 nm  | 0.156 J/cm² to 1.248 J/cm² | Single session of 5, 10, 20 or 40 min | - |  PC12 cells exposed to \( A\beta_{25-35} \) | Molecular and Cellular:  
- promotion of cell proliferation and inhibition of apoptosis after 5-20-min irradiation (CCK8 assay & morphological examination). |
| Yang et al. (2010) | 632.8 nm  | 16.2 J/cm² | 3 h/session | - |  Primary astrocytes exposed to \( A\beta_{1-42} \) | Molecular and Cellular:  
- suppression of oxidative stress and inflammatory responses (WB, dihydroethidium fluorescence and IHC). |
| Zhang and Wu (2011) | 632.8 nm  | 2 J/cm² | - | - |  PC12 cells exposed to \( A\beta_{25-35} \) | Molecular and Cellular:  
- reduction of apoptosis through the activation of the Akt/YAP/p73 pathway (CCK8 assay, Co-IP and FCA). |
| Liang, Liu and Xing (2012) | 632.8 nm  | 2 J/cm² | - | - |  PC12, HEK 293T & SH-SY5Y cells exposed to \( A\beta_{25-35} \) | Molecular and Cellular:  
- reduction of apoptosis in all cell lines through the activation of the Akt/GSK3β/β-catenin pathway (morphological analysis, Co-IP and FCA). |
| Meng, He and Xing (2013) | 632.8 nm  | 0.5, 1, 2 and 4 J/cm² | 0.7, 1.25, 2.5 and 5 min | - |  SH-SY5Y cells and APP/PS1 hippocampal neurons exposed to \( A\beta_{25-35} \) & \( A\beta_{1-42} \) | Molecular and Cellular:  
- reduction in \( A\beta \)-induced neurotoxicity after 2- and 4-J/cm² irradiation in both cell lines (CCK8 assay and FCA);  
- improved dendritic morphology and number in hippocampal neurons through the activation of the ERK/CREB/BDNF pathway after 2-J/cm² irradiation (IHC and phalloidin staining). |
| Duggett and Chazot (2014) | 1068 nm  | 0.9 J/cm² | 5 sets of 3 min each/day with 30-min intervals, for 3 days | - |  Neuronal cells exposed to \( A\beta_{1-42} \) | Molecular and Cellular:  
- reduction of cell death (non-radiative cytotoxicity assay);  
- no alteration of cell proliferation pattern (IHC). |
| Michalkikova et al. (2008) | 1072 nm  | - | 6 min/day, for 10 days | Whole-body exposure |  Aged CD1 mic | Functional and Behavioral:  
- no differences upon exploratory behavior & anxiety (3D maze - anxiety task);  
- improved working memory & spatial navigation (3D maze - spatial navigation task). |
| McCarthy et al. (2010) | 808 ± 10 nm | - 268 J/cm² (scalp); | 2 min/session | Transcranial |  Sprague Dawley rats | Safety and Feasibility:  
- the treatment was well-tolerated by all animals;  
- safe one year after single and multiple irradiations (behavioral and histopathological assessment). |
| Publication                        | Wavelength | Energy density                                      | Duration & periodicity                      | Delivery mode  | Model/Subjects                | Primary outcomes of light-stimulation                                                                 |
|----------------------------------|------------|----------------------------------------------------|--------------------------------------------|----------------|-----------------------------|-----------------------------------------------------------------------------------------------------|
| De Taboada et al. (2011)         | 808 ± 10 nm| - 68, 340 and 679 J/cm² (skin);                    | 2 min/day, 3 days/week over 6 months       | Transcranial   | AβPP transgenic mice        | Molecular and Cellular: - reduction of brain Aβ load & deposition after 100-Hz pulsed irradiation, for all doses (ELISA); - reduction of brain inflammatory markers after 100-Hz pulsed and continuous irradiation, for all doses (IHC); - improved mitochondrial function in the brain after 340-J/cm² 100-Hz pulsed irradiation (bioluminescent and bicin-chronic acid assays); - brain lesions after 679-J/cm² irradiation |
|                                  |            | - 1.20, 6 and 12 J/cm² (cortical surface).        |                                            |                |                             | Functional and Behavioral: - enhanced memory after 100-Hz pulsed and continuous irradiation, for all doses (MWM test). |
| Rojas, Bruchey and Gonzalez-Lima (2012) | 660 nm     | 1, 5, 5.4, 10.9, 16.2, 21.6 and 32.9 J/cm²        | 20 min, 40 min or 60 min                   | Transcranial   | Aged Long Evans rats        | Molecular and Cellular: - increased prefrontal oxygen consumption after 1- and 5-J/cm² irradiation (fluorometric oxygen quenching); - increased cortical metabolic capacity after 10.9-J/cm² irradiation (quantitative histochemistry) |
|                                  |            |                                                   |                                            | (dorsal head surface)  |                             | Functional and Behavioral: - enhanced memory (fear renewal test). |
| Grillo et al. (2013)             | 1,072 nm   | 1.8 J/cm²                                          | 6 min/day, for 2 consecutive days, 2 times/week, over 5 months. | Whole-body exposure | TASTPM mice                 | Molecular and Cellular: - downregulation of Aβ1-40, Aβ1-42, Tau-P and APP (WB); - reduction in small (< 10 μm) Aβ1-40/42 and Aβ1-42 plaque deposition throughout the brain (IHC); - upregulation of selective heat shock proteins (WB). |
|                                  |            |                                                   |                                            |                |                             | Functional and Behavioral: - enhanced memory (fear renewal test). |
| Farfara et al. (2014)            | -          | 1.0 J/cm²                                          | 20 s, 6 times over 2 months (mice); 20 s single treatment (MSCs). | To the bone marrow in the tibia | 5xFAD mice cultured MSCs from C57/B6 mice | Molecular and Cellular: - increased phagocytic state of MSCs towards Aβ1-42 (fluorescence-activated cell sorting); - reduction of brain Aβ load in 5xFAD mice (IHC) |
|                                  |            |                                                   |                                            |                |                             | Functional and Behavioral: - enhanced recognition and associative memory (NOR and fear conditioning tests); |
| Purushothuman et al. (2014)      | 670 nm     | 4 J/cm²                                            | 90 s/session, 5 days/week over 4 weeks    | Transcranial   | K3 and APP/PS1 mice         | Molecular and Cellular: - reduction of hTau levels and neurofibrillary tangles in the neocortex and HPC of K3 mice (histological analysis); - reduction of Aβ plaques burden, size, and number in the cortex and HPC of APP/PS1 mice (histological analysis); - reduction of mitochondrial dysfunction, oxidative stress and cell damage markers in the cortex and HPC of K3 mice (IHC). |
|                                  |            |                                                   |                                            |                |                             | (Continues) |
|                                  |            |                                                   |                                            |                |                             | (Continues) |
| Publication | Wavelength | Energy density | Duration & periodicity | Delivery mode | Model/Subjects | Primary outcomes of light-stimulation |
|-------------|------------|----------------|------------------------|---------------|---------------|--------------------------------------|
| Purushothuman et al. (2015) | 670 nm | 4 J/cm² | 90 s/session, 5 days/week over 4 consecutive weeks | Transcranial | K3 and APP/PS1 mice | Molecular and Cellular:  
- reduction of Aβ load and deposition in the APP/PS1 mice (IHC);  
- reduction of hTau levels in K3 mice (IHC);  
- regulation of mitochondrial activity in K3 mice (IHC). |
| Eltchechem et al. (2017) | 627 nm | 7 J/cm² | 100 s once a day over 7, 14 and 21 days | Transcranial | Wistar rats injected with Aβ25-35 | Molecular and Cellular:  
- reduction of Aβ plaque load in the HPC after 21-days irradiation (IHC);  
- reduction of glial cells activity in the HPC for all irradiation durations (IHC)  
Functional and Behavioral:  
- enhanced spatial memory after 14-days irradiation (MWM test). |
| Lu et al. (2017) | 808 nm | 15 J/cm² (cerebral cortex); around 5.0 J/cm² (HPC). | 2 min/day, for 5 consecutive days | Transcranial | Sprague Dawley rats injected with Aβ1-42 | Molecular and Cellular:  
- reduction of neurodegeneration in the HPC (histological assays);  
- regulation of mitochondrial function, oxidative stress and neuroinflammation in the HPC (WB and Co-IP);  
- inhibition of Tau phosphorylation in the HPC after irradiation (Co-IP).  
Functional and Behavioral:  
- improvement of impaired memory (Barnes maze and NOR test); |
| Comerota, Krishnan and Taglialetela (2017) | 670 nm | 4 J/cm² | 90 s/day, 5 days/week, for 4 consecutive weeks | Transcranial | Tg2576 mice (in vivo) synaptosomes exposed to Aβ1-42 (ex vivo) | Molecular and Cellular:  
- reduction of synaptic vulnerability to Aβ oligomer binding ex vivo (FCA, ELISA and WB);  
- reduction of Aβ oligomers at the synapse of Tg2576 mice (WB and ELISA);  
- mitigation of mitochondrial dysfunction (FCA)  
Functional and Behavioral:  
- attenuation of Aβ oligomer-induced damage of synaptic plasticity (EP). |
| Han et al. (2018) | 1040-1090 nm | 5.4 J/cm² | 6 min/day, for 40 days + 28 days of suspension + 15 days of irradiation | Whole-body exposure | APP/PS1 mice | Molecular and Cellular:  
- reduction of small (< 10 µm) Aβ plaques in the cortex and HPC (IHC)  
Functional and Behavioral:  
- improved spatial memory after the first phase of irradiation (MWM test);  
- after the treatment suspension, improvements were lost. |

(Continues)
| Publication                  | Wavelength                  | Energy density | Duration & periodicity | Delivery mode          | Model/Subjects                                      | Primary outcomes of light-stimulation                                                                                                                                                                                                 |
|------------------------------|-----------------------------|----------------|------------------------|------------------------|------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Blivet et al. (2018) \(^{22}\) | - 850 nm (NIR laser);       | 8.4 J/cm\(^2\) | 2.5, 5, 10 or 20 min,  | Transcranial & Abdominal | Swiss mice injected with \(A\beta_{25-35}\)          | Molecular and Cellular:  
- reduction of apoptotic markers after 10-Hz (head and abdomen) 10-min irradiation (ELISA);  
- reduction of oxidative stress and inflammation markers after 10-Hz (head) and 10- or 1000-Hz (abdomen) irradiation - different treatment durations for each biomarker (ELISA);  
- inhibition of hyperactivated glial cells after 10-Hz 10-min irradiation ex vivo (IHC);  
- reduction of \(A\beta_{1-42}\) and hTau levels after 10-Hz (head and abdomen), 10-min irradiation (ELISA);  
- all positive outcomes were associated to simultaneous irradiation of the head and abdomen  
Functional and Behavioral:  
- memory improvement (Barnes maze test). |
|                              | - 850 nm (NIR LED);        |                | once or twice a day over |                       |                                                      |                                                                                                                                  |
|                              | - 625 nm (red LED).        |                | 7 days                  |                        |                                                      |                                                                                                                                  |
|                              | (all combined in one device)|                |                         |                        |                                                      |                                                                                                                                  |
| Salehpour et al. (2018) \(^{23}\) | 660 nm                     | - 99.9 J/cm\(^2\) (scalp); | 15 s/session, once a day | Transcranial           | Aged BALB/c mice                                     | Molecular and Cellular:  
- increased ATP production in the HPC (spectrophotometric analysis)  
Functional and Behavioral:  
- improved spatial memory (Barnes maze test). |
|                              | - 16 J/cm\(^2\) (cortical surface). |                | for 2 consecutive weeks |                        |                                                      |                                                                                                                                  |
| Comerota et al. (2019) \(^{22}\) | 670 nm                     | -             | 90 s/day, 5 days/week,  | Transcranial           | hTau and 3xTgAD mice (in vivo) synaptosomes exposed to Tau oligomers (ex vivo) | Molecular and Cellular:  
- reduction of Tau in the cortex and HPC of both mouse models (WB, ELISA and IHC);  
- reduction of \(A\beta_{1-42}\) load in the cortex and HPC of 3xTgAD mice (WB, ELISA and IHC);  
- increased levels of heat shock protein 70 at the synapses in both mouse models (WB);  
- increased autophagy markers in 3xTgAD mice (WB)  
Functional and Behavioral:  
- no effect on synaptic deficits (LTP) induced by Tau oligomers (EP);  
- memory improvement in both mouse models (NOR test). |
|                              |                            |                | for 4 consecutive weeks |                        |                                                      |                                                                                                                                  |
| Zinchenko et al. (2019) \(^{22}\) | 1267 nm                    | 18, 25, 32 and 39 J/cm\(^2\) | 17 min-irradiation followed by 5-min interval, for 61 min, for 9 days | Transcranial (frontal cortex) | Mongrel mice injected with \(A\beta_{1-42}\) | Molecular and Cellular:  
- reduction of \(A\beta\) deposition in the cortex and HPC after 32-J/cm\(^2\) irradiation (IHC and CMA) in absence of brain injuries, temperature alterations and brain morphological changes in the brain;  
- increased brain lymphatic drainage after 32-J/cm\(^2\) irradiation (optical coherence tomography using gold nanorods)  
Functional and Behavioral:  
- improved memory, motor function and alertness (neuroseverity score and NOR test). |

(Continues)
| Publication          | Wavelength   | Energy density | Duration & periodicity | Delivery mode  | Model/Subjects                              | Primary outcomes of light-stimulation                                                                 |
|---------------------|--------------|----------------|------------------------|----------------|---------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Zhang et al. (2020) | 632.8 nm     | -2 J/cm² (in the HPC of mice); 0.5, 1.2 and 4 J/cm² (in cells). | 10 min, once a day, for 30 days (in mice); 0.7, 1.25, 2.5 and 5 min (in cells). | Transcranial (mice) | APP/PS1 mice (in vivo) APP/PS1 primary hippocampal neurons and SH-SY5Y-APP<sub>swe</sub> cells (in vitro) | Molecular and Cellular: reduction of Aβ levels in the cortex and HPC of APP/PS1 mice (ELISA and IHC); shift of APP processing towards the nonamyloidogenic pathway, in vivo and in vitro, after 2 J/cm² irradiation (WB, Co-IP, CMA, fluorometric assay, IHC, immunocytochemistry and semi-quantitative RT-PCR); enhanced mitochondrial membrane potential and increased ATP and cAMP levels in SH-SY5Y-APP<sub>swe</sub> cells after 2 J/cm² irradiation (ELISA, CMA and FCA); activation of SIRT1 in SH-SY5Y-APP<sub>swe</sub> cells after 2 J/cm² irradiation (fluorometric assays and WB) |
| Cho et al. (2020)   | 610 nm       | 2 J/cm²        | 20 min, 3 times/week, for 14 weeks | Transcranial | 5xFAD                                       | Molecular and Cellular: reduction of cortical Aβ plaque load (IHC); alleviation of neuronal degeneration in the cortical region (histological analysis); reduction in hyperactivation of microglia in the cortical region (IHC) |
| Wang et al. (2020)  | 770 – 1000 nm| -              | 1 h every day for 6 weeks | Whole-body exposure | APP/PS1 mice                                | Molecular and Cellular: reduced Aβ plaque load in the cortex and hippocampus (IHC); modulation of gut microbiota communities (RNA-sequencing and analysis) |
| Zinchenko et al. (2020) | 1267 nm     | -32 J/cm² (scalp); 9 J/cm² (cortical surface). | 17 min with 5-min break for 61 min, in alternate days, over 9 days | Transcranial (sagittal and triangle sinuses) | Mongrel mice injected with Aβ<sub>1-42</sub> | Molecular and Cellular: increased Aβ levels in the deep cervical lymph nodes (IHC); increased blood-brain barrier permeability (IHC and TEER measurements) |
|                     |              |                |                        |                | Functional and Behavioral: improved learning and memory abilities (MWM and Shuttle box tests). | Functional and Behavioral: improved neurological and cognitive function (neurological severe status scale); increased memory and recognition (NOR test); no changes in temperature in the cortical and external surface of the skull. |
| Publication | Wavelength | Energy density | Duration & periodicity | Delivery mode | Model/Subjects | Primary outcomes of light-stimulation |
|-------------|------------|----------------|------------------------|---------------|---------------|--------------------------------------|
| Salgado et al. (2015) | 627 nm | 10 J/cm² (per site) | 30 s/site (four sites), twice a week, for 4 weeks | Transcranial | Elderly, non-demented women | Molecular and Cellular:  
- enhanced cerebral blood flow (transcranial Doppler ultrasound). |
| Vargas et al. (2017) | 1064 nm | 60 J/cm² (per site) | 240 s/site (2 forehead sites), once a week, for 5 weeks | Transcranial | Adults with memory complaints and risk of cognitive decline. | Molecular and Cellular:  
- increased carotid intima-media thickness correlated with CD (ultrasounds);  
- enhanced cerebral blood flow in PFC (BOLD-fMRI signal)  
Functional and Behavioral:  
- increased resting-state in alpha, beta and gamma power in both cerebral hemispheres (EEG);  
- modulation of neural networks in the resting-state (EEG);  
- improvement of sustained attention and visual working memory (psychomotor vigilance and delayed matching tasks). |
| Saltmarche et al. (2017) | 810 nm | 10.65 J/cm² (inPBM-only); 24.6 J/cm² and 13.8 J/cm² (tPBM + inPBM, respectively). | 25 min (inPBM) and 20 min (tPBM + inPBM), twice a week for 2 weeks and, then, once a week for 10 weeks | Transcranial & Intranasal | AD & demented patient | Functional and Behavioral:  
- decrease of the severity of cognitive impairment (MMSE and ADAS-cog), functional disabilities, sleep disturbances and anxiety;  
- quality of life improvement;  
- discontinuation of positive cognitive outcomes when the treatment stopped. |
| Berman et al. (2017) | 1072 nm | - | 6 min/session/day for 28 consecutive sessions | Transcranial | AD & demented patient | Functional and Behavioral:  
- enhanced cognition and executive function (MMSE and ADAS-cog);  
- improved EEG amplitude and brain connectivity (quantitative EEG). |
| Chan et al. (2019) | 633 nm (red LEDs); 870 nm (NIR LEDs). | 20 J/cm² | Single session of 7.5 min | Transcranial (forehead and posterior midline) | Elderly, non-demented subject | Functional and Behavioral:  
- improved action selection and mental flexibility (modified Eriksen flanker and category fluency tasks). |
| Chao (2019) | 810 nm | - 60 J/cm² (posterior tPBM) and 45 J/cm² (anterior tPBM); - 15 J/cm² (inPBM). | 20 min/day, 3 times/week, for 12 weeks | Transcranial & Intranasal | AD & demented patients | Molecular and Cellular:  
- enhanced cerebral perfusion (arterial spin-labeled MRI)  
Functional and Behavioral:  
- decrease of the severity of cognitive impairment (ADAS-cog and neuropsychiatric inventory);  
- increased functional connectivity between specific nodes of the default mode network (MRI). |

(Continues)
### TABLE 1 (Continued)

| Publication | Wavelength       | Energy density | Duration & periodicity | Delivery mode       | Model/Subjects                  | Primary outcomes of light-stimulation                                                                 |
|-------------|------------------|----------------|------------------------|---------------------|--------------------------------|--------------------------------------------------------------------------------------------------------|
| Salehpour, Hamblin and Diduro (2019) | 635 nm (red LED) and 810 nm (NIR LED) (tPBM and body pad); 810 nm (inPBM). | 112.5 J/cm² (red LED) and 46.5 J/cm² (NIR LED) (tPBM and body pad); 10.65 J/cm² (inPBM). | 25 min/day, twice a day, over 4 weeks | Transcranial, Intranasal & Whole-body exposure | One female subject with cognitive decline | Functional and Behavioral: - enhanced cognitive function (Montreal cognitive assessment and working memory questionnaire); - mitigation of olfactory dysfunction (Alberta smell test and peanut butter odor detection test); - improvement in quality of life measures (physical self-maintenance and instrumental activities of daily living scales). |

**Abbreviations:** Aβ, amyloid beta; ADAS-cog, Alzheimer’s Disease Assessment Scale—Cognitive subscale; APP, amyloid precursor protein; ATP, adenosine triphosphate; BOLD-fMRI, blood oxygenation level dependent-functional magnetic resonance imaging; cAMP, cyclic adenosine monophosphate; CCK8, cell counting kit-8; CD, cognitive decline; CMA, confocal microscopy analysis; Co-IP, co-immunoprecipitation; EEG, electroencephalography; ELISA, enzyme-linked immunosorbent assay; EP, electrophysiology; FCA, flow cytometry analysis; hTau, hyperphosphorylated Tau; IHC, immunohistochemical; MSC, mesenchymal stem cell; MMSE, Mini-Mental State Examination; MWM, Morris water maze; NOR, novel object recognition; RT-PCR, reverse transcription polymerase chain reaction; WB, Western blot.
| Publication                        | Stimulation frequency          | Duration & periodicity | Model/subjects                              | Primary outcomes of light-stimulation                                                                 |
|-----------------------------------|-------------------------------|------------------------|---------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Zhang et al. (2015)26             | 2 Hz (duty cycle of 1/10)     | 6 hours/day, for 4 weeks | 3xTg-AD mice                               | Molecular and cellular: - upregulation of synaptic proteins and neurotrophic factors in the cortex and amygdala (qPCR and WB); - no significant effect in Aβ1-42 load (ELISA) |
|                                   |                               |                        |                                             | Functional and behavioral: - improvement of the impaired associative and spatial memory (MWM and fear conditioning tests); - facilitation of calcium-activated potassium channels activity in cortical pyramidal and lateral amygdala principal cells, normalizing their excitability (width of action potentials); - improve synaptic plasticity (LTP amplitude). |
| Iaccarino et al. (2016)26         | 20, 40, 80 Hz and random flickering | 1 hour/day, for 7 days | 5xFAD, APP/PS1 and Tau P301S mice           | Molecular and cellular: - reduction of Aβ1-40 and Aβ1-42 levels in the VC of 5xFAD mice and Aβ1-40 levels in the VC of APP/PS1 and wild-type mice after 40-Hz stimulation (IHC, WB and ELISA); - Aβ-bearing microglia response in the VC of 5xFAD and Tau P301S mice after 40-Hz stimulation (RNA-sequ, IHC, and FACS); - reduction in Aβ plaque number and size in the VC of all mouse models after 40-Hz stimulation (IHC); - reduction in pTau levels in the VC of Tau P301S mice after 40-Hz stimulation (IHC). |
|                                   |                               |                        |                                             | Functional and behavioral: - brainwave entrainment at 40 Hz in the VC of 5xFAD mice (EP).                |
| Adaikkan et al. (2019)34          | 40 and 80 Hz                  | 1 hour/day, for 22 days (Tau P301S and 5xFAD mice) and 1 hour/day, for 6 weeks (CK-p25 mice) | Tau P301S, CK-p25, 5xFAD and aged C57BL/6J mice | Molecular and cellular: - reduction of neuronal and synaptic loss and DNA damage in neural cells of Tau P301S and CK-p25 mice after 40-Hz stimulation (RNA-sequencing, phosphoproteomics, IHC and WB); - reduction of neuroinflammatory markers and alteration of glial cells activity in the VC, HPC, and cingulate cortex of CK-p25 and Tau P301S mice after 40-Hz stimulation (RNA-sequencing and IHC); - reduction of pTau levels in the VC of Tau P301S mice after 40-Hz stimulation (phosphoproteomics). |
|                                   |                               |                        |                                             | Functional and behavioral: - brainwave entrainment at gamma frequency in the VC, HPC, prefrontal cortex, and somatosensory cortex in Tau P301S and CK-p25 mice after 40-Hz stimulation (EP); - improved synaptic function in Tau P301S, CK-p25 and C57BL/6J mice after 40-Hz stimulation; - improved spatial memory in P301S and CK-p25 mice (novel object recognition and MWM tests). |
| Publication                  | Stimulation frequency | Duration & periodicity                      | Model/subjects            | Primary outcomes of light-stimulation                                                                 |
|-----------------------------|-----------------------|---------------------------------------------|---------------------------|--------------------------------------------------------------------------------------------------------|
| Martorell et al. (2019)     | 40 Hz and random      | 1 hour/day, for 7 days                      | SxFAD mice                | Molecular and cellular:                                                                                |
|                             | flickering and tone   |                                             |                           | - \(\text{A}\beta\)-bearing microglia-clustering response in the AC, HPC, and PFC after 40-Hz stimulation|
|                             | (VS + AS)             |                                             |                           | (IMARIS);                                                                                              |
|                             |                       |                                             |                           | - increase of astrocyte reactivity in the HPC and AC after 40-Hz stimulation (IHC);                     |
|                             |                       |                                             |                           | - reduction of \(\text{A}\beta_{1-42}\) load in the AC, HPC, and mPFC after 40-Hz stimulation (ELISA and IHC); |
|                             |                       |                                             |                           | - decreased \(\text{A}\beta\) plaque area and number in the AC, VS, HPC, and PFC after 40-Hz stimulation (IHC); |
|                             |                       |                                             |                           | - greater entrainment and therapeutic effects using combined VS and AS compared to each of the stimuli alone.|
|                             |                       |                                             |                           | Functional and behavioral:                                                                            |
|                             |                       |                                             |                           | - brainwave entrainment in the AC, HPC, and mPFC after 20-, 40-, and 80-Hz stimulation (EP).             |
| Garza et al. (2020)         | 20, 40 Hz, random     | Single session of 5, 15 minutes, or 1 hour   | C57BL/6J mice             | Molecular and cellular:                                                                                |
|                             | flickering averaged at |                                             |                           | - increased cytokine expression after 1 hour of 40-Hz stimulation, though the other flickering            |
|                             | 40 Hz and continuous  |                                             |                           | frequencies also led to distinct cytokines activity (cytokines assay);                                  |
|                             | stimulation           |                                             |                           | - upregulation of the NF-\(\kappa\)B pathway after 5 and 15 minutes of 40-Hz stimulation, though no    |
|                             |                       |                                             |                           | longer detectable after the 60-minute regimen (phosphoprotein assay);                                  |
|                             |                       |                                             |                           | - upregulation of the MAPK pathway after 60 minutes, but not after 5 or 15 minutes of 40-Hz stimulation (phosphoprotein assay); |
|                             |                       |                                             |                           | - 40-Hz light and lipopolysaccharide stimulation produce distinct immune profiles concerning the            |
|                             |                       |                                             |                           | activated cytokines and the magnitude of the response (cytokines assay).                                 |
|                             |                       |                                             |                           | Functional and behavioral:                                                                            |
|                             |                       |                                             |                           | - no significant differences between frequency conditions in behavioral performance and                   |
|                             |                       |                                             |                           | anxiety phenotype (active vs. freezing time, distance travelled, time spent in the center vs.            |
|                             |                       |                                             |                           | perimeter of the enclosure, among others).                                                            |
| Calomeni et al. (2017)      | 8, 10, 12, 14, and    | 15 minutes/day, 3-minute waves for each     | Elderly, non-demented     | Functional and behavioral:                                                                            |
|                             | 15 Hz (VS + AS)       | frequency band, 10 sessions on alternate    | subjects and AD patients | - gains in memory function associated with brain waves modulation in all subjects (EEG);              |
|                             |                       | days                                        |                           | - increase of alpha brain wave activity, but not of sensorimotor rhythm brain waves, in AD               |
|                             |                       |                                             |                           | patients (EEG);                                                                                        |
|                             |                       |                                             |                           | - improved working memory function in AD patients (Digit Span Test).                                   |
| Ismail et al. (2018)        | 40 Hz                 | 2 hours/day (1 hour in the morning and 1    | Mild-to-moderate AD       | Molecular and cellular:                                                                                |
|                             |                       | hour in the evening), for 10 consecutive     | patients                  | - no significant effect on \(\text{A}\beta\)load (cortical \(1^{11}\text{C}\)-PiB uptake monitored by PET); |
|                             |                       | days                                        |                           | Functional and behavioral:                                                                            |
|                             |                       |                                             |                           | - brainwave entrainment at 40 Hz throughout the cerebral cortex (EEG);                                 |
|                             |                       |                                             |                           | - greater neural entrainment using high-intensity than low-intensity visual stimuli (EEG).               |

**Abbreviations:** AC, auditory cortex; AD, Alzheimer’s disease; \(\text{A}\beta\), amyloid beta; AS, auditory stimulation; \(1^{11}\text{C}\)-PiB, Pittsburg compound B; EEG, electroencephalography; ELISA, enzyme-linked immunosorbent assay; EP, electrophysiology; FACS, fluorescence-activated cell sorting; HPC, hippocampus; IHC, immunohistochemical; IMARIS, microscopy image analysis software; mPFC, medial prefrontal cortex; MWM, Morris water maze; PET, positron emission tomography; RT-qPCR, quantitative reverse transcription polymerase chain reaction; VC, visual cortex; VS, visual stimulation; WB, Western blot.
Behavioral outcomes of light stimulation

Among the reviewed papers, 24 out of 43 studies monitored the behavioral performance of light-treated human subjects or animals while significant improvements were reported. Several animal PBM studies observed the enhancement of different types of memory (e.g., spatial, working, or associative memory) in multiple transgenic and non-transgenic (Aβ-injected) rodent models of AD, as well as in aged (wild-type) rodents. Associated with memory improvements, several behavioral abilities such as recognition, motor function, alertness, and navigation skills were also enhanced in animals. Similarly, clinical evidence also reported significant improvement in human behavioral performance. Specifically, PBM enhanced cognitive and olfactory functions in a female patient with cognitive decline. In addition, other clinical trials reported PBM-evoked enhancement of executive functioning, mental flexibility, and action selection ability, in AD and/or demented patients and healthy older adults as determined by different cognition tests (e.g., Mini-Mental State Examination, Eriksen flanker task). PBM therapy also improved recognition ability, working memory, and sustained attention skills in adults with memory complaints, as assessed by psychomotor vigilance and delayed match-to-sample tasks. Importantly, some of the referred cognitive enhancements were also accompanied by the quality of life improvement, as reported by the family, caregivers, and the patients themselves, after tPBM and intranasal PBM (inPBM) treatment. However, one study has reported that the beneficial impact of the 12-week-long PBM on the cognitive state of demented and possible AD patients was lost after the end of the treatment, indicating that longer periods of regimen may be necessary for a long-lasting cognitive effect.

Similar to PBM, beneficial effects were also reported by VS. Animal studies have found that different types of memory were enhanced after 2-Hz pulsed VS in 3xTgAD mice, and after 40-Hz VS in Tau P301S-Tau and CK-p25 mice. However, no impact on behavioral performance of wild-type animals (C57BL/6J mice) was found under different flickering regimens (i.e., 20 Hz, 40 Hz, random flickering averaged at 40 Hz, or continuous stimulation). Importantly, there was one clinical study in AD patients using VS combined with auditory stimulation that reported improvements in working and spatial memory (assessed by Digit Span Test). Interestingly, as mentioned above, the memory improvements were strongly correlated with brainwave modulation, suggesting that the increased neuronal activity in the alpha frequency band (i.e., 8–12 Hz) strongly impacted brain functioning and cognition of AD patients.

4 DISCUSSION

Despite the significant progress in understanding AD neuropathology over the last years, there is a lack of treatment that blocks AD brain pathology and subsequent cognitive decline. One of the main concerns related to the AD therapeutic trials is the fact that AD pathological features (e.g., Aβ and Tau accumulation, synaptic loss, and damaged brain connectivity) may start long (even 20 years) before the onset of symptoms. Thus, alternative, non-invasive therapeutic strategies that will be applied in the early stages of the disease and for a long period are urgently needed. In the light of the experimental evidence reporting that alteration of neural activity impacts AD neuropathology (e.g., Aβ and Tau pathomechanisms), recent attention has been given to the different light-based modalities that manipulate brain oscillations and brainwaves as a promising tool to alleviate AD brain pathology and related cognitive decline. In this systematic review, we summarize and discuss the therapeutic potential of light brain stimulation...
through VS and PBM based on both preclinical and clinical studies—see Figure 2. To the best of our knowledge, this is the first systematic review that focuses on these two light-based modalities offering (1) a comprehensive and detailed comparison of the different protocols used comparing their outputs in molecular, neuronal, brain network, and behavioral level; and (2) an overview of the development of different light-based approaches and devices of VS and PBM against AD neuropathology and related cognitive impairment.

4.1 PBM as an alternative strategy to fight AD

Multiple PBM studies included in this systematic review suggest that transcranially delivered light stimulation may exhibit beneficial effects on AD pathology and related cognitive decline. Different mechanisms are suggested to underlie this PBM effect. For instance, the transcranial PBM may reduce Aβ pathology by shifting the APP processing toward the nonamyloidogenic pathway, which leads to decreased Aβ generation and cognitive improvement. In addition, PBM is also shown to diminish Tau pathological species accompanied by upregulation of selective HSPs in AD transgenic mice. Indeed, specific HSPs, such as HSP70 and HSP90, are known to exhibit a critical role in the degradation mechanisms of Tau as, together with a complex network of other molecular chaperones, they are critically involved in protein quality control, helping to correct protein misfolding. When this is not possible (as occurs in heavily misfolded/aggregated proteins such as pathological Tau), HSPs deliver protein aggregates to proteasome or autophagosome for degradation. Dysregulation of molecular chaperones is shown to result in reduced Tau degradation and formation of neurotoxic Tau aggregates. Thus, the upregulation of these molecular chaperones by light stimulation could reflect a mechanism of mitigation of the accumulation of AD-related pathological molecules through the enhancement of their degradation. Accordingly, autophagy was also shown to be triggered by PBM treatment in AD transgenic mice that may help in the degradation of Aβ and Tau pathological aggregates, leading to the recovery of neuronal malfunction. Thus, degradation-related mechanisms appear to be regulated by PBM toward the reduction of Aβ and Tau pathologies in AD animal models, which could subsequently lead to decreased glial response and reduced inflammatory markers. Importantly, one of the reviewed studies showed that 268-J/m² PBM (a much higher energy density compared to the majority of the studies) is well tolerated by rats and safe 1 year after irradiation. More recently, the role of the brain–gut axis in neurodegeneration has gained attention in the AD field. Among the reviewed papers, we found that PBM was able to modulate gut microbiota flora, suggesting that non-invasive whole-body exposure to light can affect the communication between the central nervous system and the intestinal tract. Importantly, this alteration was accompanied by a reduction of the Aβ plaque load, attenuating learning and memory deficits in APP/PS1 mice. Alternatively, the activation of lymphatic drainage and the increased BBB permeability induced by PBM has been suggested as an intervention that may stimulate the clearance of
| Table 3 Comparison table of reviewed studies and different categories of the reported outcomes |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                | Aβ burden reduction            | Tau load reduction              | Immunoregulation                | Neuroplasticity and toxicity    | Brain connectivity and neural entrainment | Cognitive and other behavioral improvements |
|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| **Photobiomodulation**         |                                |                                |                                |                                |                                |                                |
| Duan et al. (2003)             | X                              |                                |                                |                                |                                |                                |
| Zhang et al. (2008)            |                                | X                              |                                |                                |                                |                                |
| Michalikova et al. (2008)      |                                |                                |                                | X                              |                                |                                |
| McCarthy et al. (2010)         |                                |                                |                                |                                |                                |                                |
| Yang et al. (2010)             |                                |                                | X                              | X                              |                                |                                |
| De Taboada et al. (2011)       |                                | X                              |                                |                                |                                |                                |
| Zhang and Wu (2011)            |                                |                                |                                | X                              |                                |                                |
| Liang, Liu and Xing (2012)     |                                |                                |                                |                                | X                              |                                |
| Rojas, Bruchey and Gonzalez-Lima (2012) | X                              |                                |                                | X                              |                                |                                |
| Meng, He and Xing (2013)       |                                |                                |                                | X                              |                                |                                |
| Grillo et al. (2013)           |                                | X                              | X                              |                                |                                | X                              |
| Farfara et al. (2014)          |                                | X                              | X                              |                                |                                |                                |
| Duggett and Chazot (2014)      |                                |                                |                                | X                              |                                |                                |
| Purushothuman et al. (2014)    |                                | X                              | X                              | X                              |                                |                                |
| Salgado et al. (2015)          |                                |                                |                                | X                              |                                |                                |
| Purushothuman et al. (2015)    |                                | X                              | X                              | X                              |                                |                                |
| Vargas et al. (2017)           |                                | X                              | X                              | X                              | X                              |                                |
| Eltchecham et al. (2017)       |                                |                                | X                              | X                              |                                |                                |
| Saltmarche et al. (2017)       |                                |                                |                                | X                              |                                |                                |
| Lu et al. (2017)               |                                | X                              | X                              | X                              |                                |                                |
| Berman et al. (2017)           |                                |                                |                                |                                |                                | X                              |
| Comerota, Krishnan and Taglialetela (2017) | X                              |                                |                                |                                |                                |                                |
| Han et al. (2018)              |                                |                                |                                |                                |                                | X                              |
| Blivet et al. (2018)           |                                | X                              | X                              | X                              |                                | X                              |
| Salehpour et al. (2018)        |                                |                                |                                | X                              |                                | X                              |
| Comerota et al. (2019)         |                                | X                              | X                              | X                              |                                | X                              |
| Chan et al. (2019)             |                                |                                |                                |                                |                                | X                              |
| Chao (2019)                    |                                | X                              | X                              |                                |                                | X                              |
| Salehpour, Hamblin and Diduro (2019) |                                |                                |                                |                                |                                | X                              |
| Zomorrodi et al. (2019)        |                                |                                |                                |                                |                                | X                              |
| Zinchenko et al. (2019)        |                                |                                |                                |                                |                                |                                |
| Zhang et al. (2020)            |                                |                                |                                |                                |                                | X                              |
| Cho et al. (2020)              |                                |                                | X                              | X                              |                                | X                              |
| Wang et al. (2020)             |                                |                                | X                              |                                |                                | X                              |
| Zinchenko et al. (2020)        |                                |                                |                                |                                |                                | X                              |

(Continues)
### Table 3 (Continued)

| Visual Stimulation (VS) | Aβ burden reduction | Tau load reduction | Immunoregulation | Neuroplasticity and toxicity | Brain connectivity and neural entrainment | Cognitive and other behavioral improvements |
|-------------------------|---------------------|-------------------|------------------|-----------------------------|------------------------------------------|-------------------------------------------|
| Zhang et al. (2015)68   | X                   | X                 | X                | X                          | X                                       | X                                         |
| Iaccarino et al. (2016)26 | X                   | X                 | X                | X                          | X                                       | X                                         |
| Calomeni et al. (2017)76 |                     |                   |                  |                            |                                         |                                           |
| Ismail et al. (2018)56  |                     |                   |                  |                            |                                         |                                           |
| Adikkan et al. (2019)34 | X                   | X                 | X                | X                          | X                                       | X                                         |
| Jones et al. (2019)57   |                     |                   |                  |                            |                                         | X                                         |
| Martorell et al. (2019)21 |                     |                   |                  |                            |                                         | X                                         |
| Garza et al. (2020)50   |                     |                   |                  |                            |                                         | X                                         |

Abbreviation: VS, visual stimulation.

Macromolecules, such as Aβ, promoting the reduction of Aβ levels in the AD brain.22,67

Despite the promising evidence of preclinical studies, the clinical support of the beneficial effect of PBM on AD patients remains limited (only three studies). Indeed, there is a significant translational gap between the preclinical and clinical proof. The few human studies conducted so far in AD patients or elderly with cognitive/memory decline show that PBM treatment improved different aspects of behavioral performance, increased cerebral perfusion, and enhanced brain connectivity, which is in line with the preclinical evidence.26,34 However, two studies reported loss of the positive outcomes achieved by PBM after the end of the treatment, indicating that this light-based approach may require a continuous stimulation regimen. In addition, there is a lack of information in humans about the beneficial (or not) effect of PBM on AD-related molecules and pathomechanisms (e.g., Aβ, Tau, inflammation) in the human brain or cerebrospinal fluid. The fast-evolving fields of PET imaging and peripheral biomarkers in AD could help to clarify the potential of PBM against cognitive decline and AD brain pathology.

Recent evidence supports the vascular hypothesis of AD underlying the synaptic failure and neuronal loss in the AD brain in which, prolonged brain hypoperfusion may progressively trigger neuronal malfunction and neurodegenerative processes precipitating AD brain pathology.84 Interestingly, some clinical studies observed PBM-driven improved cerebral blood flow of the brain. For instance, tPBM produced significant improvements in vasomotor behavior of the basilar and middle cerebral arteries in healthy elderly women, as assessed by transcranial Doppler ultrasound, reflecting an improved vascular function.52 Similarly, Vargas et al. (2017) tested the effect of tPBM in adults with memory complaints and detected decreased BOLD-fMRI signal (a proxy for enhanced brain perfusion) accompanied by increased carotid artery intima-media thickness, which was correlated with cognitive improvement.53 Also, Chao et al. observed enhancement of cerebral perfusion in AD and dementia patients after combined tPBM and inPBM treatment, as monitored using arterial spin-labeled MRI, one of the preferred neuroimaging examinations for AD. Hence, besides the effect of PBM on Aβ and Tau pathologies, behavioral deficits, and functional connectivity, these data also support the potential of PBM to improve cerebral blood flow, which may play a critical role in AD neurodegeneration.84

### 4.2 VS as a powerful therapeutic approach against AD neuropathology and cognitive deficits

The application of VS aims to modulate brain network excitability and synchrony with a particular focus on the gamma oscillatory activity, which is deregulated in AD patients. Different animal and human studies demonstrate that entrainment at 40 Hz through VS is an effective tool to restore normal neural activity in different brain regions. This VS effect was associated with reduction of AD-related pathomechanisms of Aβ and Tau in animals, as well as brain wave modulation and/or significant improvement of cognitive function in both animals and humans.21,26,34,57 It is noteworthy that VS in other frequencies, such as 8, 10, 12, 14, and 15 Hz (which are contained in alpha bands), applied in AD patients or 2 Hz (delta band) in AD transgenic mice were also associated with neuromodulation and memory improvement. Importantly, gamma oscillations are associated with high-order cognitive functions.30,31 In fact, previous studies in animals and humans show that VS at 40 Hz generated the greatest entrainment compared to other frequencies (i.e., 20, 60, 80 Hz).26,34,57 Nevertheless, the majority of the VS studies in animals and humans suggest that modulating brain network oscillations through VS seems to be an effective therapeutic strategy to ameliorate AD neuropathology and/or cognitive impairment.21,26,34,57 However, the clinical evidence of the beneficial application of VS in humans is very limited and requires further investigation, including studies with large cohorts of AD patients in different stages of the disorder, as well as prodromal conditions such as individuals suffering from mild cognitive impairment (MCI) or mild behavioral impairment (MBI).
Despite that our mechanistic understanding of how 40-Hz VS exhibits its beneficial action against AD remains unclear, the current hypothesis points toward the VS-driven reduction of the amyloidogenic pathway, as well as the activation of microglial responses that remove soluble and insoluble Aβ levels throughout the brain.²⁶,⁷⁰ Moreover, 40-Hz VS was shown to alter the expression profile of different cytokines associated with microglia activation. Note that, although different flickering frequencies impact cytokines’ profile, 40-Hz VS was found to induce the greater effect, independent of the severity of the brain pathology.⁷⁰ In addition, VS-driven restoration of normal neuronal activity could also attenuate various aspects of AD brain pathology in AD transgenic mice,²¹,³⁴ consistent with an increase in neuronal and glia interplay in the VS beneficial treatment.

4.3 The comparison between preclinical and clinical light-based therapeutic modalities

This systematic review summarizes and compares the use of VS and PBM in different in vitro and in vivo studies including both preclinical and clinical findings (see Tables 1–3). The limited number of clinical studies (only eight PBM³⁸,⁴¹,⁴⁴,⁴⁶,⁵²,⁵³,⁵⁵,⁷⁷ and three VS studies⁵⁶,⁵⁷,⁷⁶) hinders solid conclusions on the clinical translatability and safety of the aforementioned preclinical findings. Nevertheless, the few clinical studies in AD patients reviewed here suggest that light stimulation can positively affect cognition,³⁸,⁴¹,⁵⁵,⁷⁶ brain perfusion,⁴¹ brain oscillations,³⁸,⁷⁶ and functional connectivity between specific neuronal nodes³⁸,⁴¹ despite that the stimulation protocol may need to be optimized to obtain the maximum therapeutic effect. Specifically, comparing the light specifications among some PBM protocols associated with positive outcomes applied in vitro,⁶⁵,⁷³ in vivo,⁶²–⁶⁶ and in humans,⁷⁷ we conclude that the radiant energy density ranges remain similar. For instance, the optical fluence in in vitro experiments of neurons was 0.5 to 4 J/cm² while, in animal studies, the light that reached the rodent deep brain tissue (e.g., cerebral cortex, hippocampus) was between 0.058 and 16 J/cm² with the applied stimuli at the scalp of animals being at a fluence of 1 to 100 J/cm². In the human brain, different brain regions received different energy densities; 0.0 to 0.41 J/cm² in the temporal lobe, 0.56 to 0.97 J/cm² in the frontal lobe and 0.78 to 5.44 J/cm² in the occipital lobe, when 10.65 J/cm² was delivered intranasally and 46.5 and 112.5 J/cm² were delivered to the scalp. The referred studies used wavelengths ranging from 632.8 to 810 nm. It is important to highlight that the energy density applied to the target tissues in animals and humans is lower than the one applied in cells because the light in a live organism has to penetrate multiple tissues to reach the desired brain area; thus, higher optical fluences could damage the surrounding tissues. Moreover, the reviewed studies show that the optimal wavelength range for PBM treatment is 610 to 700 nm (red) and 810 to 870 nm (NIR) light in animals and humans, respectively.

Two factors that directly impact the energy density delivered to the tissues are the stimulation time and regularity. More than 70% of the applied VS protocols describe at least 1 hour of treatment from 7 days to 4 weeks with the majority of them showing beneficial results against AD neuropathology.²¹,²⁶,³⁴,⁵⁶,⁶⁸ Regarding PBM, in vitro studies show high heterogeneity concerning treatment duration, although similar cellular outcomes were reported – mainly related to the reduction of cell damage and death. In addition, despite that animal PBM studies also differ in both time (90 seconds to 10 minutes per day) and duration of stimulation (7 to 80 days), beneficial effects against Aβ or Tau pathology, as well as memory impairment, were detected.²²,⁴³,⁴⁵,⁵⁴ Similar variation in the period of the treatment is also found in clinical PBM protocols (e.g., 8–25 minutes, twice a day, over 1 day to 4 weeks); however, the vast majority of the studies reported beneficial PBM-driven effects such as improved cognition,³⁸,⁴¹,⁴⁴,⁵⁵,⁷⁷ enhanced cerebral perfusion,⁴¹,³⁵,³⁶ and brainwave entrainment.³⁸,⁴¹,⁵³ Although our knowledge about VS parameters in humans is very limited, animal evidence suggests 40-Hz VS as the most promising intermittence frequency for reverting AD neuropathology and cognitive decline. Moreover, different neurodegenerative disorders (e.g., AD, Parkinson’s disease, frontotemporal dementia, amyotrophic lateral sclerosis, vascular dementia) share common pathological mechanisms of neurodegeneration that include defective protein quality control and degradation pathways, synaptic failure, neuronal loss, dysfunctional mitochondria, and chronic neuroinflammation.⁸⁵–⁸⁸ Therefore, as light stimulation modalities in AD studies have recently shown beneficial results in protein degradation/removal mechanisms,²¹,²⁶,³⁴,³⁹,⁴³,⁴⁹,⁵¹,⁴²,⁶⁶,⁶⁸ metabolic function,²¹,³⁴,⁰⁴,⁴³,⁴⁹,⁶⁶,⁶⁸ immunological responses,²¹,²⁶,³⁴,⁴⁹ and brain connectivity and plasticity,²¹,³⁴,⁴³,⁴⁹,⁶⁶,⁷⁶ it is important that light stimulation modalities should also be tested in other neurodegenerative disorders that exhibit the same or similar brain lesions.

4.4 Limitations of light transmission in the brain

Although animal models are essential for accessing the feasibility, safety, and efficacy of light-based therapeutic approaches, it is important to consider that the anatomical and pathophysiological differences between humans and animals often cause inconsistencies in the outcomes obtained between species. One of the major concerns about this issue related to PBM application is the transmission of NIR light through different tissues such as the scalp, skull, meninges, and brain tissue in different brain areas. Tissue optics studies the interaction between light and tissues as absorption, scattering, and diffusion effects interfere with the light properties delivered to the target brain areas. To maximize the beneficial effect of PBM, the architecture and anatomy of the brain barriers associated with the referred structures must be taken into consideration, as well as the differences between
light specifications between species. Thus, Lapchak et al. conducted a study aiming to monitor the NIR laser transmission through the skull of four different species (mouse, rat, rabbit and human). Using similar NIR light treatment parameters to those applied in most of the PBM studies of this systematic review (wavelength of 800 nm and energy density of 84 J/cm²), this study found that light transmission has no correlation with skull density in human skulls. Additionally, light transmission was found to be reverse correlated with the skull thickness for all four species. In fact, they noticed that the penetration of light through the human skull was attenuated more than 95%, independent of the skull hydration state, which resulted in a power density of 29 mW/cm² below the skull surface. Considering that the scalp and the tissues under the skull have approximately 6 to 7 mm and 3 to 4 mm of thickness, respectively, the authors estimated that the delivered power density on the cortical surface would be about 2.9 to 14.5 mW/cm². Similarly, Tedford et al. also investigated how deep NIR light penetrates the brain tissue using 660, 808, and 940 nm LEDs, at 7 to 10 mW/cm². They showed that 808-nm NIR light was the most effective transcranial application because it penetrates the brain and surrounding tissues to a depth around 40 mm without difference between pulsed and continuous-wave PBM. Another study examined the transmission of 633-nm red and 830-nm NIR light in the temporal, parietal, frontal, and occipital skull and found that NIR light had a penetration rate of 0.90%, 9.12%, 2.13%, and 11.71% for each brain region, respectively. Also, lower penetration rates were associated with red light. Future detailed examination of the characteristics and profile of the light transmission through the brain and surrounding tissues will help to optimize the delivery efficacy of light stimuli for targeting specific brain areas.

4.5 Devices for delivery of light stimulation

Given the encouraging results of the use of VS and PBM against AD pathology, various devices delivering light stimulation have been patented, from which multiple commercial brain stimulation solutions appeared, with some of them using VS (Figure 3A-C) and others PBM (via intranasal, transcranial, and combined intranasal–transcranial delivery; Figure 3D-F note that these devices were used in some of the studies included in this systematic review). Regarding light stimulation to animals, researchers have recently developed an apparatus for LED-based VS in mice for flickering 40-Hz light providing an easy protocol for self-building this mouse VS apparatus. In addition, a new device for humans is recently developed as the first brain PBM device that delivers NIR light stimuli at 40 Hz (Figure 3D). This device aims to combine the previously reported beneficial effects of PBM and the brainwave entrainment effects produced by 40-Hz stimulation, as reported by VS studies. In fact, two recent studies that used this device reported that PBM treatment of NIR light at 40 Hz induced a significant cognitive enhancement accompanied by enhanced cerebral blood flow and neuronal functional connectivity in both demented patients and healthy adults. The beneficial effects reported in these two studies encourage further examination of the effects of transcranial PBM pulsing at 40 Hz.
in AD patients, including individuals in the early or prodromal stages of the disease (e.g., MCI). Indeed, new clinical trials have increasingly focused on the early phases of the disease, when memory loss is mild or absent, to block further neuronal and brain damage before it becomes irreversible.97

Usually, PBM and VS are not associated with side effects. However, light therapies require a thorough examination of the thermal effects caused by irradiation as sparse data are available on this topic among the reviewed studies. Future efforts may focus on temperature changes occurring inside the brain during transcranial PBM to avoid brain lesions as thermal effects are associated with the intensity and duration of irradiation. For instance, one animal study using AβPP transgenic mice found brain lesions in the brain of mice after 679-J/cm² irradiation, which did not occur for lower stimulation intensities.49

Also, the flickering frequency of the light stimulus delivered during VS should be carefully chosen, mainly when applied to older patients, as inappropriate flickering could cause confusion and disturb the individuals.

5 | CONCLUSIONS AND FUTURE PERSPECTIVES

Emerging evidence from different recent studies discussed in this systematic review strongly supports the beneficial impact of VS and PBM against different aspects of AD neuropathology that includes Aβ and Tau pathology, synaptic loss and neuronal malfunction, inflammation, disrupted network oscillations, and overall brain synchrony, as well as cognitive impairment. Despite the promising findings on AD patients (e.g., improved memory function, enhanced cerebral blood flow, increased brain oscillation and brain functional connectivity), clinical evidence on the effectiveness of PBM and VS against AD pathomechanisms is very limited and hence, further clinical studies must be conducted monitoring the brain pathology. Thus, the early diagnosis of AD combined with the proposed use of light-based brain stimulation, which is a low-cost and non-invasive procedure, may represent an effective therapeutic tool that can contribute to the fight against AD pathology and related cognitive impairment.

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REFERENCES

1. World Health Organization World Health Organization’S global action plan on the public health response to dementia 2017-2025. World Health Organization; 2017. Accessed November 19, 2019. https://apps.who.int/iris/bitstream/handle/10665/259615/9789241513487-eng.pdf?sequence=1

2. Querfurth HW, Laferla FM. Mechanisms of disease. N Engl J Med. 2010;362(4):329-344. https://www.area-c54.it/public/alzheimers/disease_0.pdf

3. Alzheimer’s Disease International. World Alzheimer report 2019—attitudes to dementia. 2019. https://doi.org/10.1007/978-3-030-10814-4_23

4. World Health Organization. Risk reduction of cognitive decline and dementia: WHO guidelines. World Health Organization; 2019. Accessed November 19, 2019. https://www.who.int/mental_health/neurology/dementia/risk_reduction_gdg_meeting/en/

5. Hong N. Photobiomodulation as a treatment for neurodegenerative disorders: current and future trends. Biomed Eng Lett. 2019;9(3):359-366.

6. Hou F, Liu C, Yu Z, et al. Age-related alterations in electroencephalography connectivity and network topology during n-back working memory task. Front Hum Neurosci. 2018;12(December):484.

7. Valero J, Bernardino L, Cardoso FL, et al. Impact of neuroinflammation on hippocampal neurogenesis: relevance to aging and Alzheimer’s disease. J Alzheimer’s Dis. 2017;60(1):S161-S168.

8. Gillespie AK, Jones EA, Lin YH, et al. Apolipoprotein E4 causes age-dependent disruption of slow gamma oscillations during hippocampal sharp-wave ripples. Neuron. 2016;90(4):740-751.

9. Palop JJ, Mucke L. Network abnormalities and interneuron dysfunction in Alzheimer disease. Nat Rev Neurosci. 2016;17(12):777-792.

10. Perl DP. Neuropathology of Alzheimer’s disease. Mt Sinai J Med A J Transl Pers Med. 2010;77(1):32-42.

11. Jeong J. EEG dynamics in patients with Alzheimer’s disease. Clin Neurophysiol. 2004;115(7):1490-1505.

12. Castano-Prat P, Perez-Mendez L, Perez-Zabalza M, Sancheliu C, Giménez-Llort L, Sanchez-Vives MV. Altered slow (~1 Hz) and fast (beta and gamma) neocortical oscillations in the 3xTg-AD mouse...
model of Alzheimer’s disease under anesthesia. Neurobiol Aging. 2019;79:142-151.

13. Nicholas E, Szoekoe CEI, Vollset SE, et al. Global, regional, and national burden of Alzheimer’s disease and other dementias, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;18(1):88-106. https://doi.org/10.1016/s1474-4422(18)30403-4

14. Palmqvist S, Schöll M, Strandberg O, et al. Earliest accumulation of β-amyloid occurs within the default-mode network and concurrently affects brain connectivity. Nat Commun. 2017;8(1):1-13.

15. Amemori T, Jenedelova P, Ruzicka J, Urzidzko LM, Sykova E. Alzheimer’s disease: mechanism and approach to cell therapy. Int J Mol Sci. 2015;16(11):26417-26451.

16. Silva JM, Rodrigues S, Sampaio-Marques B, et al. Dysregulation of autophagy and stress granule-related proteins in stress-driven Tau pathology. Cell Death Differ. 2019;26(8):1411-1427. https://doi.org/10.1038/s41418-018-0217-1

17. Mudher A, Colin M, Dujardin S, et al. What is the evidence that tau pathology spreads through prion-like propagation? Acta Neuropathol Commun. 2017;5(1):99.

18. Sotiropoulos I, Silva JM, Gomes P, Sousa N, Almeida OFX. Stress and the Etiopathogenesis of Alzheimer’s Disease and Depression. Advances in Experimental Medicine and Biology. Springer; 2019:241-257.

19. Vyas S, Rodrigues AJ, Silva JM, et al. Chronic stress and glucocorticoids: from neuronal plasticity to neurodegeneration. Neural Plast. 2016;2016:6391686.

20. Alzheimer’s Association. 2021 Alzheimer’s disease facts and figures—special report race, ethnicity and Alzheimer’s in America. 2021;17:327-406.

21. Martorell AJAJ, Paulson ALAL, Suk H-JHJ, et al. Multi-sensory entrainment attenuates amyloid load and modifies microglia. Front Neurosci. 2016;10(8):4003.

22. Lim L. The growing evidence for photobiomodulation as a promising treatment for Alzheimer’s disease. J Biosci Med. 2018;6:100-110.

23. Hennessy M, Hamblin MR. Photobiomodulation and the brain: a new paradigm. J Opt (United Kingdom). 2017;19(1):1-29.

24. Johnstone DM, Moro C, Stone J, Benabid AL, Mitrofanis J. Turning on lights to stop neurodegeneration: the potential of near infrared light therapy in Alzheimer’s and Parkinson’s disease. Front Neurosci. 2016;9(January):500.

25. Iaccarino HF, Singer AC, Martorell AJ, et al. Gamma frequency entrainment attenuates amyloid load and modifies microglia. Nature. 2016;540(7632):230-235.

26. Hamblin MR. Shining light on the head: photobiomodulation for brain disorders. BBA Clin. 2016;6:113-124.

27. Rojas JC, Gonzalez-Lima F. Neurological and psychological applications of transcranial lasers and LEDs. Biochem Pharmacol. 2013;86(4):447-457.

28. Rodrigues P, Teixeira JP. Artificial neural networks in the discrimination of Alzheimer’s disease. In International Conference on ENTERprise Information Systems. Springer, Berlin, Heidelberg; October 2011:272-281.

29. Fitzgerald SP, Pope KJ, MacKenzie L, Clark CR, Willoughby JO. Cognitive tasks augment gamma EEG power. Clin Neurophysiol. 2004;115(8):1802-1809.

30. Herrmann CS, Munk MHJ, Engel AK. Cognitive functions of gamma-band activity: memory match and utilization. Trends Cogn Sci. 2004;8(8):347-355.

31. Wu JW, Hussaini SA, Bastille IM, et al. Neuronal activity enhances tau propagation and tau pathology in vivo. Nat Neurosci. 2016;19(8):1085-1092.

32. Bero AW, Yan P, Roh JH, et al. Neuronal activity regulates the regional vulnerability to amyloid-β 2 deposition. Nat Neurosci. 2011:14(6):750-756.

33. Adai-Kan C, Middleton SJ, Marco A, et al. Gamma entrainment binds higher-order brain regions and offers neuroprotection. Neuron. 2019;102(5):929-943.

34. Moller D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264-269.

35. Moissenet F, Modenese L, Dumas R. Alterations of musculoskeletal models for a more accurate estimation of lower limb joint contact forces during normal gait: a systematic review. J Biomech. 2017;63:8-20.

36. Michalkova S, Ennaceur A, van Rensburg R, Chazot PL. Emotional responses and memory performance of middle-aged CD1 mice in a 3D maze: effects of low infrared light. Neurobiol Learn Mem. 2008;9(4):480-488.

37. Berman MH, Halper JP, Nichols TW, H J, Lundy A, Huang JH. Photobiomodulation with near infrared light helmet in a pilot, placebo controlled clinical trial in dementia patients testing memory and cognition. J Neurol Neurosci. 2017;8(1):1-15.

38. Comerota MM, Krishnan B, Tagliatela G. Near infrared light decreases synaptic vulnerability to amyloid beta oligomers. Sci Rep. 2017;7(1):1-11.

39. Han M, Wang Q, Wang X, et al. Near-infrared light treatment of Alzheimer’s disease. J Innov Opt Health Sci. 2018;11(01):1750012. https://doi.org/10.1142/s1793545817500122

40. Chao LL. Effects of home photobiomodulation treatments on cognitive and behavioral function, cerebral perfusion, and resting-state functional connectivity in patients with dementia: a pilot trial. Photobiomodulation, Photomedicine, Laser Surg. 2019;37(3):133-141.

41. Blivet G, Meunier J, Roman FJ, Touchon J. Neuroprotective effect of a new photobiomodulation technique against Aβ 25-35 peptide-induced toxicity in mice: novel hypothesis for therapeutic approach of Alzheimer’s disease suggested. Alzheimer’s Dement Transl Res Clin Interv. 2018:4:54-63.

42. Comerota MM, Tumurbaatar B, Krishnan B, Kayed R, Tagliatela G. Near infrared light treatment reduces synaptic levels of toxic tau oligomers in two transgenic mouse models of human tauopathies. Mol Neurobiol. 2018;56(5):3341-3355.

43. Chan AS, Lee TL, Yeung MK, Hamblin MR. Photobiomodulation improves the frontal cognitive function of older adults. Int J Geriatr Psychiatry. 2019;34(2):369-377.

44. Cho GM, Lee S-Y, Park JH, et al. Photobiomodulation using a low-level light-emitting diode improves cognitive dysfunction in the 5XFAD mouse model of Alzheimer’s disease. J Gerontol. 2018;75(4):631-639. https://doi.org/10.1093/gerona/gly240

45. Zomorodi R, Loeshwaran G, Pushparaj A, Lim L. Pulsed near infrared transcranial and intranasal photobiomodulation significantly modulates neural oscillations: a pilot exploratory study. Sci Rep. 2019;9(1):1-11.

46. Wang M, Cao J, Amakye WK, Gong C, Li Q, Ren J. Near infrared light treatment attenuates cognitive decline and alters the gut microbiota community in APP/PS1 mouse model. Biochem Biophys Res Commun. 2020;523(1):60-65.

47. McCarthy TJ, De Taboada L, Hildebrandt PK, Ziemer EL, Richieri SP. Streeter J. Long-term safety of single and multiple infrared transcranial laser treatments in Sprague-Dawley rats. Photomed Laser Surg. 2013;28(5):663-667.

48. De Taboada L, Yu J, El-Amouri S, et al. Transcranial Laser Therapy Attenuates Amyloid-β Peptide Neuropathology in Amyloid-β Protein
50. Grillo SL, Duggett NA, Ennaceur A, Chazot PL. Non-invasive infra-red therapy (1072 nm) reduces β-amyloid protein levels in the brain of an Alzheimer’s disease mouse model, TASTPM. J Photochem Photobiol B Biol. 2013;123:13-22.

51. Farfara D, Tuby H, Trudler D, et al. Low-level laser therapy ameliorates disease progression in a mouse model of Alzheimer’s disease. J Mol Neurosci. 2014;55(2):430-436.

52. Salgado ASI, Zângaro RA, Parreira RB, Kerpers II. The effects of transcranial LED therapy (TCTL) on cerebral blood flow in the elderly women. Lasers Med Sci. 2015;30(1):339-346. https://doi.org/10.1007/s10103-014-1669-2

53. Vargas E, Barrett DW, Saucedo CL, et al. Beneficial neurocognitive effects of transcranial laser in older adults. Lasers Med Sci. 2017;32(5):1153-1162.

54. da Luz Eltchechem C, Salgado ASI, Zângaro RA, et al. Transcranial LED therapy on amyloid-β toxin 25-35 in the hippocampal region of rats. Lasers Med Sci. 2017;32(4):749-756.

55. Saltmarche AE, Naeser MA, Ho KF, Hamblin MR, Lim L. Significant improvement in cognition in mild to moderately severe dementia cases treated with transcranial plus intranasal photobiomodulation: case series report. Photomed Laser Surg. 2017;35(8):432-441.

56. Ismail R, Hansen AK, Parbo P, et al. The effect of 40-Hz light therapy on amyloid load in patients with prodromal and clinical Alzheimer’s disease. Int J Alzheimers Dis. 2018;2018:10-15.

57. Jones M, McDermott B, Oliveira BL, et al. Gamma band light stimulation in human case studies: groundwork for potential Alzheimer’s disease treatment. J Alzheimers Dis. 2019;70(1):171-185.

58. Duan R, Zhu L, Liu T, et al. Light emitting diode irradiation protects against the amyloid beta 25-35 induced apoptosis of PC12 cell in vitro. Lasers Surg Med. 2003;33(3):199-203.

59. Zhang L, Xing D, Zhu D, Chen Q. Low-power Laser Irradiation Inhibiting Aβ25-35-induced PC12 Cell Apoptosis via PKC Activation. Cell Physiol Biochem. 2008;22(1-4):215-222. https://doi.org/10.1159/000149799

60. Yang X, Askarova S, Sheng W, et al. Low energy laser light (632.8 nm) suppresses amyloid-β peptide-induced oxidative and inflammatory responses in astrocytes. Neuroscience. 2010;171(3):859-868.

61. Duggett NA, Chazot PL. Low-intensity light therapy (1068 nm) protects CAD neuroblastoma cells from β-amyloid-mediated cell death. Biol Med. 2014;6(3). https://www.researchgate.net/profile/Natalie-Duggett/publication/286139387_Low-Intensity_light_therapy_1068_nm_protects_CAD_neuroblastoma_cells_from_b-Amyloid-Mediated_cell_death/links/57bdced508ae4e6f1845dba4/Low-Intensity-light-therapy-1068-nm-protects-CAD-neuroblastoma-cells-from-b-Amyloid-Mediated-cell-death.pdf

62. Purushothuman S, Johnstone DM, Nandasa C, et al. Near infrared light mitigates cerebellar pathology in transgenic mouse models of dementia. Neurosci Lett. 2015;591:155-159.

63. Lu Y, Wang R, Dong Y, et al. Low-level laser therapy for beta amyloid toxicity in rat hippocampus. Neurobiol Aging. 2017;49:165-182.

64. Salehpour F, Hamblin MR, Diduro JO. Rapid reversal of cognitive decline, olfactory dysfunction, and quality of life using multi-modality photobiomodulation therapy: case report. Photobiomodulation, Photomedicine, Laser Surg. 2019;37(3):159-167.

65. van Leeuwen FW, Kampinga HH. Heat shock proteins and protein quality control in Alzheimer’s disease. The Molecular and Cellular Basis of Neurodegenerative Diseases: Underlying Mechanisms. United States: Elsevier Inc.; 2018:269-298. https://doi.org/10.1016/B978-0-12-813004-2.00010-9

66. Kumar A, Singh A, Ekaavi. A review on Alzheimer’s disease pathophysiology and its management: an update. Pharmacol Rep. 2015; 67(2):195-203. https://doi.org/10.1016/j.pharep.2014.09.004

67. Cirrito JR, Yamada KA, Finn MB, et al. Synaptic Activity Regulates Protein Misfolding, Aggregation, and Conformational Strains in Neurodegenerative Diseases. Neurosci. 2018;21(10):1300-1309.

68. Soto C, Pritzkov S. Protein misfolding, aggregation, and conformational strains in neurodegenerative diseases. Nat Neurosci. 2018;21(10):1332-1340.

69. Zucker M, Walker LC. Propagation and spread of pathogenic protein assemblies in neurodegenerative diseases. Nat Neurosci. 2018;21(10):1341-1349.
88. Dugger BN, Dickson DW. Pathology of neurodegenerative diseases. *Cold Spring Harb Perspect Biol*. 2017;9(7):1-22.

89. Lapchak PA, Boitano PD, Butte PV, et al. Transcranial near-infrared laser transmission (NILT) profiles (800 nm): systematic comparison in four common research species. *PLoS One*. 2015;10(6):e0127580.

90. Tedford CE, Delapp S, Jacques S, Anders JJ. Quantitative analysis of transcranial and intraparenchymal light penetration in human cadaver brain tissue. *Lasers Surg Med*. 2015;47(4):312-322.

91. Jagdeo JR, Adams LE, Brody NI, Siegel DM. Transcranial red and near infrared light transmission in a cadaveric model. *PLoS One*. 2012;7(10):e47460.

92. Millard MD, Gonzales DA. Head worn device for treating Alzheimer’s disease. U.S. Patent Application No. 15/597,520. 2018.

93. Vyshedskiy A. Flashing light therapy with image presentation and interaction for treatment of Alzheimer’s disease and dementia. U.S. Patent Application No. 16/128,487. 2019.

94. Arasu M, Zoghi S, Zoghi B. Low-cost portable light therapy for Alzheimer’s patients. *ASEE Gulf-Southwest Section Annual Meeting 2018 Papers*. 2019. https://doi.org/10.26153/tsw/6922

95. Shanks SC. Treatment of neurodegenerative diseases using light therapy. U.S. Patent Application No. 15/604,363. 2018.

96. Singer AC, Martorell AJ, Douglas JM, et al. Noninvasive 40-Hz light flicker to recruit microglia and reduce amyloid beta load. *Nat Protoc*. 2018;13(8):1850-1868.

97. McDade E, Bateman RJ. Stop Alzheimer’s before it starts. *Nature*. 2017;547(7662):153-155.

98. Neuroscientifically Challenged. Squarespace. Accessed July 15, 2019. https://www.neuroscientificallychallenged.com/glossary/neuron

99. A/V Stim. MindSpa Personal Development System. https://www.avstim.com/

100. Gamma 40Hz Light and Sound Stimulation Device. https://gammalightandsound.com/

101. Optoeutics. Brain stimulation device. Accessed November 4, 2021. https://optoeutics.com/loesninger-2/

102. Vielight Inc. Neuro Gamma. Accessed November 4, 2021. https://www.vielight.com/devices/vielight-neuro-gamma/

103. Vielight Inc. Vielight X-Plus. Accessed November 4, 2021. https://www.vielight.com/devices/vielight-x-plus/

104. Shenzhen Guangyang Zhongkang Technology Co. L. Transcranial PBM near infrared brain treatment helmet brain photobiomodulation machine. Accessed November 19, 2019. http://www.sschgroup.com/transcranial-pbm-near-infrared-brain-treatment-helmet-brain-photobiomodulation-machine.html

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