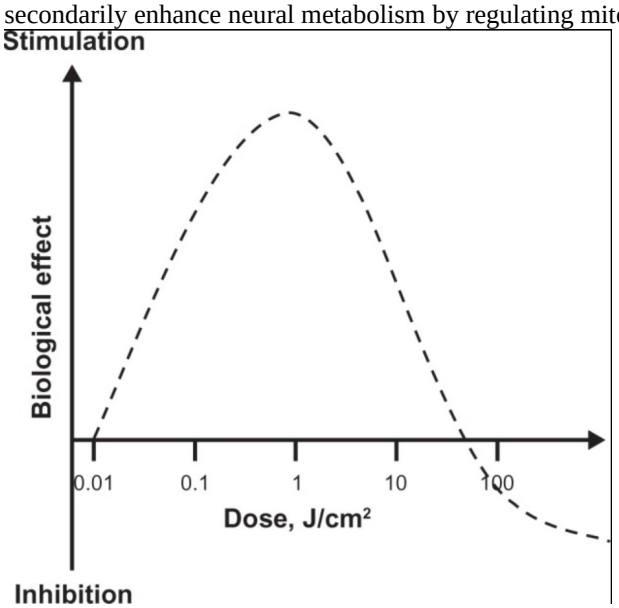
Infrared: Photobiomodulation for Alzheimer's

Summary: The main consensus is that Photobiomodulation activates the mitochondrial enzyme cytochrome c oxidase, improving the mitochondrial respiration and oxygen consumption. Research also points out that Alzheimer's death is higher in low sun countries, and that people who have skin cancer have a lower incidence of Alzheimers. The photobiomodulation also show up on brain electroencephalogram rhythms. Studies have shown decreased reaction times, and improved attention and motor skills with PBM. On a related note visual stimulation (flickering light) at 40Hz may promote gamma-wave brain activity. Another variation is "Bright Light Therapy" Also a studys shows significant increased risk of dementia in people with cataracts, BUT reduced risk of dementia with cataract extraction. The relationship of light on the eyes/transcranial and the relation to Alzheimer's seems overwhelming.
Canadian-based biotech company, Vielight might be a leader in PBM but seems very profit motivated. (Price of products very high compared to cost of components)

https://en.wikipedia.org/wiki/Radiative_cooling
Infrared radiation can pass through dry, clear air in the wavelength range of 8–13 μm. Materials that can absorb energy and radiate it in those wavelengths exhibit a strong cooling effect. Materials that can also reflect 95% or more of sunlight in the 200 nanometres to 2.5 μm range can exhibit cooling even in direct sunlight.[9]

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8211253/pdf/pone.0253320.pdf
Effects of far infrared light on Alzheimer's disease-transgenic mice 2020
Although some reports have indicated that FIR therapy promotes blood circulation [12], the detailed relationship between FIR exposure and AD-related cognitive dysfunction has not yet been elucidated. Here we evaluated the effects of FIR light in a transgenic mouse model of AD The highest emission wavelength was between 8 to 10 μm, and it produced about 1 W/cm2/sr. We also used normal mice in this study, but the number of animals was small and could not clearly detect the biological effect of FIR exposure. However, changes were seen in body weight and in the levels of neurotrophic factors in specific brain segments in AD mice exposed to FIR light

https://pubmed.ncbi.nlm.nih.gov/28539775/
Low-level light therapy of the eye and brain 2011
Cytochrome oxidase is the primary photoacceptor of light in the red to near-infrared region of the electromagnetic spectrum. It is also a key mitochondrial enzyme for cellular bioenergetics, especially for nerve cells in the retina and the brain. Evidence shows that LLLT can secondarily enhance neural metabolism by regulating mitochondrial function, intraneuronal signaling systems, and redox states.



https://pubmed.ncbi.nlm.nih.gov/36404359/
Photobiomodulation therapy in mood disorders: a systematic review 2022
Sixteen studies, which included four randomized controlled trials (RCTs), met the inclusion criteria. Infrared wavelength ranges from 800 to 830 nm, power density of 250 mW/cm2 and energy density of 60 to 120 J/ cm2 were the most used PBMT parameters.

https://pubmed.ncbi.nlm.nih.gov/22850314/

Low-level light therapy improves cortical metabolic capacity and memory retention 2012

Cerebral hypometabolism characterizes mild cognitive impairment and Alzheimer's disease. Low-level light therapy (LLLT) enhances the metabolic capacity of neurons in culture through photostimulation of cytochrome oxidase, the mitochondrial enzyme that catalyzes oxygen consumption in cellular respiration. Growing evidence supports that neuronal metabolic enhancement by LLLT positively impacts neuronal function in vitro and in vivo. Based on its effects on energy metabolism, it is proposed that LLLT will also affect the cerebral cortex in vivo and modulate higher-order cognitive functions such as memory. In vivo effects of LLLT on brain and behavior are poorly characterized. We tested the hypothesis that in vivo LLLT facilitates cortical oxygenation and metabolic energy capacity and thereby improves memory retention. Specifically, we tested this hypothesis in rats using fear extinction memory, a form of memory modulated by prefrontal cortex activation. Effects of LLLT on brain metabolism were determined through measurement of prefrontal cortex oxygen concentration with fluorescent quenching oximetry and by quantitative cytochrome oxidase histochemistry. Experiment 1 verified that LLLT increased the rate of oxygen consumption in the prefrontal cortex in vivo. Experiment 2 showed that LLLT-treated rats had an enhanced extinction memory as compared to controls. Experiment 3 showed that LLLT reduced fear renewal and prevented the reemergence of extinguished conditioned fear responses. Experiment 4 showed that LLLT induced hormetic dose-response effects on the metabolic capacity of the prefrontal cortex. These data suggest that LLLT can enhance cortical metabolic capacity and retention of extinction memories, and implicate LLLT as a novel intervention to improve memory.

https://pubmed.ncbi.nlm.nih.gov/35368252/

Photobiomodulation of Cytochrome c Oxidase by Chronic Transcranial Laser in Young and Aged Brains 2022

In cellular bioenergetics, cytochrome c oxidase (CCO) is the enzyme responsible for oxygen consumption in the mitochondrial electron transport chain, which drives oxidative phosphorylation for adenosine triphosphate (ATP) production. CCO is also the major intracellular acceptor of photons in the light wavelengths used for photobiomodulation (PBM). Brain function is critically dependent on oxygen consumption by CCO for ATP production. Therefore, our objectives were (1) to conduct the first detailed brain mapping study of the effects of PBM on regional CCO activity, and (2) to compare the chronic effects of PBM on young and aged brains. Specifically, we used quantitative CCO histochemistry to map the differences in CCO activity of brain regions in healthy young (4 months old) and aged (20 months old) rats from control groups with sham stimulation and from treated groups with 58 consecutive days of transcranial laser PBM (810 nm wavelength and 100 mW power). We found that aging predominantly decreased regional brain CCO activity and systems-level functional connectivity, while the chronic laser stimulation predominantly reversed these age-related effects. We concluded that chronic PBM modified the effects of aging by causing the CCO activity on brain regions in laser-treated aged rats to reach levels similar to those found in young rats. Given the crucial role of CCO in bioenergetics, PBM may be used to augment brain and behavioral functions of older individuals by improving oxidative energy metabolism.

810nm, 100mW laser diode
Exposure duration/point (s): 30.
Radiant exposure (J/cm2) per point per session: 121.8.
Number of points irradiated: Five.
Delivery mode: Contact mode.
Number and frequency of sessions: one session/day for 58
consecutive days.
Total radiant energy (J) per head: 15

https://pubmed.ncbi.nlm.nih.gov/33998008/

Photobiomodulation Response From 660 nm is Different and More Durable Than That From 980 nm 2021

Keratinocytes and fibroblasts responded differently to exposures at 660 nm (red) and 980 nm (NIR). Although 980 nm required much lower fluence for cell stimulation, the resulting increase in ATP levels was short-term, whereas 660 nm stimulation elevated ATP levels for at least 24 hours. COX-1 protein levels were increased following 660 nm treatment but were unaffected by 980 nm. In fibroblasts, SDH-A levels were affected by both wavelengths, whereas in keratinocytes only 660 nm light impacted SDH-A levels. Inhibition of ATP synthase nearly completely abolished the effects of both wavelengths on ATP synthesis. Interestingly, inhibiting cytochrome c oxidase did not prevent the rise in ATP levels in response to PBM treatment.
These findings confirm that different response pathways are involved after 660 and 980 nm exposures and suggest that 660 nm causes a more durable response.

https://pubmed.ncbi.nlm.nih.gov/36317341/

Neuromodulation of brain power topography and network topology by prefrontal transcranial photobiomodulation 2022

Transcranial photobiomodulation (tPBM) has shown promising benefits, including cognitive improvement, in healthy humans and in patients with Alzheimer's disease. In this study, we aimed to identify key cortical regions that present significant changes caused by tPBM in the electroencephalogram (EEG) oscillation powers and functional connectivity in the healthy human brain.*Approach*. A 64-channel EEG was recorded from 45 healthy participants during a 13 min period consisting of a 2 min baseline, 8 min tPBM/sham intervention, and 3 min recovery. After pre-processing and normalizing the EEG data at the five EEG rhythms, cluster-based permutation tests were performed for multiple comparisons of spectral power topographies, followed by graph-theory analysis as a topological approach for quantification of brain connectivity metrics at global and nodal/cluster levels.*Main results*. EEG power enhancement was observed in clusters of channels over the frontoparietal regions in the alpha band and the centroparietal regions in the beta band. The global measures of the network revealed a reduction in synchronization, global efficiency, and small-worldness of beta band connectivity, implying an enhancement of brain network complexity. In addition, in the beta band, nodal graphical analysis demonstrated significant increases in local information integration and centrality over the frontal clusters, accompanied by a decrease in segregation over the bilateral frontal, left parietal, and left occipital regions.*Significance*.Frontal tPBM increased EEG alpha and beta powers in the frontal-central-parietal regions, enhanced the complexity of the global beta-wave brain network, and augmented local information flow and integration of beta oscillations across

prefrontal cortical regions. This study sheds light on the potential link between electrophysiological effects and human cognitive improvement induced by tPBM.

https://pubmed.ncbi.nlm.nih.gov/34092636/

Pilot Study on Dose-Dependent Effects of Transcranial Photobiomodulation on Brain Electrical Oscillations: A Potential Therapeutic Target in Alzheimer's Disease 2021

Methods: We conducted a single-blind, sham-controlled pilot study to test the effect of continuous (c-tPBM), pulse (p-tPBM), and sham (s-tPBM) transcranial photobiomodulation on EEG oscillations and CBF using diffuse correlation spectroscopy (DCS) in a sample of ten healthy subjects [6F/4 M; mean age 28.6±12.9 years]. c-tPBM near-infrared radiation (NIR) (830 nm; 54.8 mW/cm2; 65.8 J/cm2; 2.3 kJ) and p-tPBM (830 nm; 10 Hz; 54.8 mW/cm2; 33%; 21.7 J/cm2; 0.8 kJ) were delivered concurrently to the frontal areas by four LED clusters. EEG and DCS recordings were performed weekly before, during, and after each tPBM session.
Results: c-tPBM significantly boosted gamma ($t = 3.02$, $df = 7$, $p < 0.02$) and beta ($t = 2.91$, $df = 7$, $p < 0.03$) EEG spectral powers in eyes-open recordings and gamma power ($t = 3.61$, $df = 6$, $p < 0.015$) in eyes-closed recordings, with a widespread increase over frontal-central scalp regions. There was no significant effect of tPBM on CBF compared to sham.
Conclusion: Our data suggest a dose-dependent effect of tPBM with NIR on cerebral gamma and beta neuronal activity. Altogether, our findings support the neuromodulatory effect of transcranial NIR.

https://pubmed.ncbi.nlm.nih.gov/31259198/

Transcranial photobiomodulation with 1064-nm laser modulates brain electroencephalogram rhythms 2019

Noninvasive transcranial photobiomodulation (tPBM) with a 1064-nm laser has been reported to improve human performance on cognitive tasks as well as locally upregulate cerebral oxygen metabolism and hemodynamics. However, it is unknown whether 1064-nm tPBM also modulates electrophysiology, and specifically neural oscillations, in the human brain. The hypothesis guiding our study is that applying 1064-nm tPBM of the right prefrontal cortex enhances neurophysiological rhythms at specific frequency bands in the human brain under resting conditions. To test this hypothesis, we recorded the 64-channel scalp electroencephalogram (EEG) before, during, and after the application of 11 min of 4-cm-diameter tPBM (CW 1064-nm laser with 162mW/cm2 and 107J/cm2) to the right forehead of human subjects (n=20) using a within-subject, sham-controlled design. Time-resolved scalp topographies of EEG power at five frequency bands were computed to examine the tPBM-induced EEG power changes across the scalp. The results show time-dependent, significant increases of EEG spectral powers at the alpha (8 to 13 Hz) and beta (13 to 30 Hz) bands at broad scalp regions, exhibiting a front-to-back pattern. The findings provide the first sham-controlled topographic mapping that tPBM increases the strength of electrophysiological oscillations (alpha and beta bands) while also shedding light on the mechanisms of tPBM in the human brain.

https://www.liebertpub.com/doi/10.1089/pho.2016.4227

Significant Improvement in Cognition in Mild to Moderately Severe Dementia Cases Treated with Transcranial Plus Intranasal Photobiomodulation: Case Series Report 2017

This study investigated whether patients with mild to moderately severe dementia or possible Alzheimer's disease (AD) with Mini-Mental State Exam (MMSE) Baseline scores of 10–24 would improve when treated with near-infrared photobiomodulation (PBM) therapy. The study used 810 nm, 10 Hz pulsed, light-emitting diode devices combining transcranial plus intranasal PBM to treat the cortical nodes of the DMN. There was significant improvement after 12 weeks of PBM (MMSE, $p < 0.003$; ADAS-cog, $p < 0.023$). Increased function, better sleep, fewer angry outbursts, less anxiety, and wandering were reported post-PBM. There were no negative side effects. Precipitous declines were observed during the follow-up no-treatment, 4 week period. This is the first completed PBM case series to report significant, cognitive improvement in mild to moderately severe dementia and possible AD cases.

All diodes emitted light of 810 nm wavelength, synchronized to pulse at 10 Hz, 50% duty cycle (Fig. 1b and c). The device shut off automatically after 20 min of treatment time (powered by rechargeable NiMH batteries). Each of the four LED cluster heads on the headset contained three LEDs. The ‘‘Neuro’’ also consisted of a single intranasal diode with higher power than the intranasal-only ‘‘810’’ device. See Table 2 for the ‘‘Neuro’s’’ specifications and parameters.

Table 2. Vielight Intranasal-Only ‘‘810’’ and ‘‘Neuro’’ Parameters

	‘‘810’’ Intranasal device	‘‘Neuro’’ transcranial-intranasal device
Source	LED	LED
Wavelength, nm	810	810
Power output, mW	14.2	41 (transcranial) 23 (intranasal)
Power density per LED, mW/cm 2	14.2	41 (transcranial) 23 (intranasal)
Pulse frequency, Hz	10	10
Pulse duty cycle, percentage	50	50
Duration of each treatment session, minutes	25	20
Beam spot size, cm 2	~1	~1
Energy delivered, Joules	10.65	24.6 (transcranial) 13.8 (intranasal)
Energy density per LED, J/cm 2	10.65	24.6 (transcranial) 13.8 (intranasal)
Cumulative energy density per LED, per week during weeks 1 and 2, J/cm 2	53.25	49.2 (transcranial) 27.6 (intranasal)
Cumulative energy density per LED, per week during weeks 3 to 12, J/cm 2	63.90	24.6 (transcranial) 13.8 (intranasal)
Dose of each treatment session, Joules	10.65	309
Cumulative dose per week during weeks 1 and 2,	Joules 639 total	
Cumulative dose per week during weeks 3 to 12,	Joules 375 total	

The 14.2 mW/cm2 power density for the ‘‘810’’ intranasal device is similar to the one used in previous research (650 nm wavelength, 8.32 mW/cm 2 , used daily for 30 min for 20 days, 10 days on, 3 days off, then 10 days on). That research demonstrated efficacy for improving blood lipid levels and rheology of the blood; there were no negative side effects.32 Based on that research and our clinical experience with the intranasal device, the daily intranasal treatments were deemed to be safe. The ‘‘Neuro’’ delivers 41 mW/cm2 , which is much less than the 250 mW/cm 2 used in research by Schiffer et al. 7 but almost twice the transcranial power density used by Naeser et al.

(22 mW/cm2). 33 Both research studies demonstrated efficacy, and no negative side effects were present.33 There is no method to measure/calculate the loss of energy in the transmission of light through living tissues. It is a biological fact, however, that the scalp and hair are major barriers. To compensate for this, the transcranial diodes in the ‘‘Neuro’’ had almost twice the power density (41 mW/cm 2) than the single intranasal diode (23 mW/cm 2). A recent transcranial study with human cadaver brains has measured the penetration of near-infrared photons (808 nm) to a depth of 40 mm

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4331044/?report=classic
Re-evaluation of the near infrared spectra of mitochondrial cytochrome c oxidase: Implications for non invasive in vivo monitoring of tissues 2014
We re-determined the near infrared (NIR) spectral signatures (650–980 nm) of the different cytochrome *c* oxidase redox centres, in the process separating them into their component species. We confirm that the primary contributor to the oxidase NIR spectrum between 700 and 980 nm is cupric Cu_A, which in the beef heart enzyme has a maximum at 835 nm.

https://www.nature.com/articles/s41598-018-21869-x
Inhibitory modulation of cytochrome c oxidase activity with specific near-infrared light wavelengths attenuates brain ischemia/reperfusion injury 2018
The interaction of light with biological tissue has been successfully utilized for multiple therapeutic purposes. Previous studies have suggested that near infrared light (NIR) enhances the activity of mitochondria by increasing cytochrome c oxidase (COX) activity, which we confirmed for 810 nm NIR. In contrast, scanning the NIR spectrum between 700 nm and 1000 nm revealed two NIR wavelengths (750 nm and 950 nm) that reduced the activity of isolated COX.
We systematically screened the NIR electromagnetic spectrum in the “therapeutic window of opportunity” of 700 nm to 1000 nm, where NIR absorptions by water and blood are minimal, allowing deep tissue penetration of the NIR for possible medical applications.
To establish the effect of NIR on mitochondria, we next isolated intact mitochondria. Mitochondrial respiration, shown as a % of basal respiratory rate, was reduced by NIR irradiation at 750 and 950 nm in the range of 24–25%, whereas 810 nm NIR increased mitochondrial oxygen consumption (Fig. 1D). Simultaneous irradiation with 750 and 950 nm NIR reduced mitochondrial respiration by 34%.
Interestingly, the inhibitory effect of both 750 nm and 950 nm IRL was more pronounced in isolated mitochondria compared to purified COX.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9195249/pdf/12974_2022_Article_2521.pdf
Far infrared light irradiation enhances Aβ clearance via increased exocytotic microglial ATP and ameliorates cognitive deficit in Alzheimer’s disease-like mice
Exposure to sunlight may decrease the risk of developing Alzheimer’s disease (AD), and visible and near infrared light have been proposed as a possible therapeutic strategy for AD. Here, we investigated the effects of the visible, near infrared and far infrared (FIR) light on the cognitive ability of AD mice, and found that FIR light also showed potential in the improvement of cognitive dysfunction in AD. However, the related mechanism remains to be elucidated.
Results: Our results showed that FIR light reduced Aβ burden, a hallmark of AD neuropathology, alleviated neuroin-flammation, restored the expression of the presynaptic protein synaptophysin, and ameliorated learning and memory impairment in the AD mice. FIR light enhanced mitochondrial oxidative phosphorylation pathway to increase ATP production. This increased intracellular ATP promoted the extracellular ATP release from microglia stimulated by Aβ, leading to the enhanced Aβ phagocytosis through phosphoinositide 3-kinase/mammalian target of rapamycin path-ways for Aβ clearance
Conclusions: Our findings have uncovered a previously unappreciated function of FIR light in inducing microglial phagocytosis to clean Aβ, which may be the mechanisms for FIR light to improve cognitive dysfunction in AD mice. These results suggest that FIR light treatment is a potential therapeutic strategy for AD
Mice in all groups were allowed free feeding during light irra-diation that was for 60 min at 0.13 mW/cm2 per day for 1.5 months
Conclusions
In summary, our study revealed that FIR light at wave-lengths of 3–25 μm could enhance mitochondrial OXPHOS pathway to increase ATP production. This increased intracellular ATP promoted the extracellular ATP release of microglia stimulated by Aβ, leading to the enhanced Aβ phagocytosis of microglia treated with FIR light through the PI3K/mTOR pathways, which was beneficial to the Aβ clearance. Thus, FIR light was able to reduce Aβ burden in the brain of AD mice, resulting in beneficial effects, including decreased neuroinflammatory cytokines and restored expression of presynaptic protein synaptophysin. As a result, FIR light ameliorated the learning and memory impairment of these AD mice, suggesting a therapeutic potential of FIR light for AD.

https://pubmed.ncbi.nlm.nih.gov/31831179/
Mid infrared light treatment attenuates cognitive decline and alters the gut microbiota community in APP/PS1 mouse model
Alzheimer's disease (AD) as the first most neurodegenerative disease in the elderly still has no effective therapy, suggesting that the intervention toolbox for AD should be expanded. One newly developed strategy involves the use of photobiomodulation, such as near infrared or far infrared light, which has proven to attenuate AD-associated pathology. However, the efficacy of mid infrared light (MIR) in treating AD is under investigated. With this in mind, we assessed the benefits of MIR light of peak wavelength 7.7-10 μm treatment on APP/PS1 transgenic mice. We found that APP/PS1 mice treated with MIR light had improved learning and memory abilities and reduced amyloid-β (Aβ) plaque load in the brain. We also surprisingly found that the gut microbiota composition in APP/PS1 mice treated with MIR light returned to normal (wild type mice) levels. Together, these findings suggested a novel non-invasive and promising avenue for AD treatment via photobiomodulation, and also proposed that future target for AD might be the gut microbiota via the brain-gut-skin axis.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8260213/pdf/cureus-0013-00000016188.pdf
Gender Differences of Dementia in Response to Intensive Self-Administered Transcranial and Intraocular Near-Infrared Stimulation
Transcranial near-infrared (tNIR) stimulation was proven to be a safe, reliable, and effective treatment for cognitive and behavioral symptoms of dementia. he tNIR light has a wavelength of 1,060 nm to 1,080 nm and was delivered via a

photobiomodulation (PBM) unit. The treatment consists of a six-minute tNIR light stimulation session twice daily for eight weeks
Results
Over the course of treatment, active-arm female subjects had a 20.2% improvement in Mini-Mental State Exam (MMSE) (mean 4.8 points increase, $p < 0.001$) and active-arm male cohort had 19.3% improvement ($p < 0.001$).
Photobiomodulation (PBM) therapy employing transcranial near-infrared (tNIR) stimulation has recently been shown to be a safe, low-cost, easily deployed and reliable treatment for both cognitive and behavioral symptoms of dementia. The tNIR at 1072 nm proves to lower brain beta-amyloid protein in AD mouse model, and improves memory performance and emotional response [2,3]. Photic stimulation of cortical mitochondria is now widely accepted as a primary mechanism of action, i.e., elevating intracellular adenosine triphosphate (ATP) by stimulating cytochrome c oxidase (CCO) - a chromophore that reacts to light within the 700 nm-1,100 nm spectrum. The increased ATP is of direct benefit to people with dementia, as many neuropathologies are characterized by markedly decreased ATP [4-6]. tNIR stimulation also improves endothelial flexibility thus improving cortical perfusion and regional cerebral blood flow, thereby increasing oxygenation of cortical white matter by upregulating the production of nitric oxide (NO), a potent vasodilator [7-9]. Additionally, tNIR stimulation mitigates inflammatory reaction by modulating the NF-κB system [10], tumor necrosis factor (TNFα), and other inflammatory cytokines in brain parenchyma [11]; activates anti-apoptotic, and anti-senescence cascades via complex regulation of transcription factors [12-15]; and promotes neurogenesis, synaptogenesis and neurogenesis through activation of brain-derived neurotrophic factor (BDNF) [16,17]. Numerous clinical trials utilizing tNIR stimulation for the treatment of neurological and neuropsychiatric disorders have been proven safe and effective [18-23].
Both active and sham PBM units have 12 LED modules covering the skull and two retractable modules to provide intraocular stimulation. Each cranial module contains 70 LEDs and each eye module contains 14 LEDs. The sham PBM units were identical in design, except that it does not emit NIR light. Subjects and investigators could not tell which device was active or placebo because infrared light at 1068nm is invisible to the naked eye. The active PBM unit emitted NIR light with a wavelength of 1,060-1,080 nm, and 15,000 mW, irradiance or power density is 23.1 mW/cm2, ~650 cm2 per treatment area. The treatment protocol consisted of twice-daily six-minute stimulation sessions conducted at home over eight consecutive weeks The statistically significant improvements observed in this study indicate that subjects of both genders can respond positively to the tNIR stimulation. During the trial, mood elevation had been observed either through direct assessor-patient interaction or reports from dedicated caregivers. This has been reported more often in people receiving active PBM treatment. Despite anatomical, chemical, genetic and socio-psychological differences, both male and female dementia subjects responded quite positively to intensive, self-administered tNIR stimulation.

https://www.sciencedirect.com/science/article/abs/pii/S1011134413000420?via%3Dihub
Non-invasive infra-red therapy (1072 nm) reduces β-amyloid protein levels in the brain of an Alzheimer's disease mouse model, TASTPM 2013
IR1072 treatment provides a novel non-invasive and safe way to upregulate a panel of stress response proteins in the brain, known to both reduce protein aggregation and neuronal apoptosis. This approach recently entered clinical trials for AD in the USA, and may provide a novel disease modifying therapy for a range of neuropathologies.

https://www.sciencedirect.com/science/article/pii/S1568163721001628
Photobiomodulation for the aging brain 2021
Longevity is one of the great triumphs of humanity. Worldwide, the elderly is the fastest growing segment of the population. As a consequence, the number of cases of age-related cognitive decline and neurological diseases associated with aging, such as Alzheimer's and Parkinson's, has been increasing. Among the non-pharmacological interventions studied for the treatment or prevention of age-related neurocognitive impairment, photobiomodulation (PBM) has gained prominence for its beneficial effects on brain functions relevant to aging brains. In animal models, the neuroprotective and neuromodulatory capacity of PBM has been observed. Studies using both animals and humans have shown promising metabolic and hemodynamic effects of PBM on the brain, such as improved mitochondrial and vascular functions. Studies in humans have shown that PBM can improve electrophysiological activity and cognitive functions such as attention, learning, memory and mood in older people. In this paper we will review the main brain effects of PBM during aging, discuss its mechanisms of action relevant to the aging brain, and call for more controlled studies in older populations.

https://www.sciencedirect.com/science/article/abs/pii/S0304394022002385
Transcranial photobiomodulation changes neuronal morphology in the cerebral cortex of rats 2022
We hypothesized that chronic laser treatment may stimulate neuronal growth. To test this hypothesis, we investigated the morphology of neurons in the cerebral cortex of rats submitted to brief (2.5 min) daily sham or transcranial laser treatment (810 nm wavelength at 100 mW) for 58 consecutive days. Laser treatment increased the number of dendritic nodes and ends, and reduced the total dendritic length in neurons of the cerebral cortex. Taken together, our data indicate that chronic transcranial photobiomodulation induces morphological neuroplasticity in the cerebral cortex of rats.

https://pubmed.ncbi.nlm.nih.gov/35887386/
Therapeutic Potential of Photobiomodulation for Chronic Kidney Disease
Photobiomodulation (PBM), a form of non-thermal light therapy, effectively mitigates mitochondrial dysfunction, reactive oxidative stress, inflammation, and gut microbiota dysbiosis, all of which are inherent in CKD. Preliminary studies suggest the benefits of PBM in multiple diseases, including CKD.
PBM, previously known as low-level laser (light) therapy (LLLT), uses visible and near-infrared light with a wavelength from 450 to 1100 nm to trigger photochemical changes within intracellular cellular structures. PBM has been used clinically for more than 50 years and studied in various diseases and conditions, such as muscle [5], wound healing [6], pain relief [7], arthritis [8], hair loss [9], orthodontic mini-implant stability [10], neurodegenera-

tive diseases [11] and most recently in COVID-19 patients [12]. PBM has been shown over decades to be a patient-directed, adjunctive, effective, non-invasive, and safe treatment option to mitigate mitochondrial dysfunction [13], oxidative stress [14 ,15], inflammatory conditions [16], and, more recently, gut microbiota dysbiosis [17], which are all primary contributors to CKD. Notably, several studies have demonstrated a positive effect of PBM in different models of kidney diseases, including acute kidney injury, glomerulonephritis, and metabolic syndrome-related kidney injury [18]

The parameters of PBM that influence PBM's effectiveness on the target cells and tissues include the light source, wavelength, power output, energy density, duration of irradiation, number of treatments, and the mode of light delivery (continuous or pulsed). For example, different wavelengths of light have different degrees of absorption, scattering coefficient, and reflection in the human body [72, 73]. Near-infrared wavelengths have lower scattering factors and much higher penetration into tissues [74 , 75]. In addition, skin contact with the PBM source also increases penetration into tissues since reflection is reduced, resulting in greater power density in the target tissue [76]. Moreover, PBM in a pulsed mode has been suggested to result in improved therapeutic outcomes compared to continuous mode [77].

Although the action mechanisms underlying the beneficial effect of PBM are not fully understood, the most widely accepted mechanism is that PBM improves mitochondrial function, leading to increased ATP production, inhibiting oxidative stress, and reducing inflammation [15 ,80 , 81]. Furthermore, recent studies have demonstrated that PBM can modulate the gut microbiota and may be a novel gut microbiota intervention in different animal disease models, including Alzheimer's disease and osteoporosis [17 ,82 ,83] and, more recently, in patients with Parkinson's disease [84,85].

PBM and Mitochodrial Activity

PBM works on the principle that light-sensitive molecules in the body known as chromophores are excited by photonic stimulation. It is generally recognized that the principal chromophore responsible for light absorption is complex IV (cytochrome c oxidase, CCO) of the mitochondrial electron transport chain [13]. The photon absorption by CCO can restore the rate of respiration, increase ATP production and improve cellular metabolism, which is likely to work through the photodissociation of the inhibitory nitric oxide from the enzyme [87].

The Role of PBM on Inflammation

One of the well-known effects of PBM is an overall inhibition of inflammation, as evidenced in various inflammatory conditions, such as diabetic wounds [94], retinal dis-
eases [95], asthma [96], and the aging brain [72]. PBM exerts its anti-inflammatory effect by reducing many cytokines and inflammatory mediators in different inflammatory condi-
tions such as carrageenan-induced paw edema, blepharitis, and osteoarthritis [10 , 97, 98]. In human periodontal ligament fibroblasts stimulated with IL-1μ, PBM with 810 nm alone
or combined with 660 nm or 980 nm showed more potent inhibition of INF-γ, IL-17A/F, monocyte chemoattractant protein 1 (MCP-1), and IL-6 as compared to 660 nm + 980 nm
irradiation, demonstrating the beneficial effect of PBM with 810 nm in regulating inflammatory responses [99].

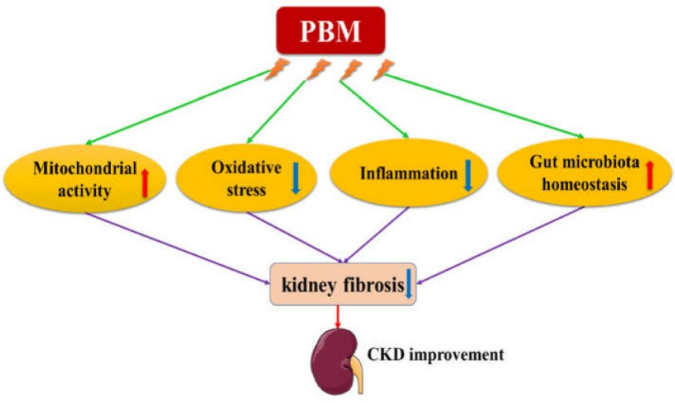
PBM and Gut Microbiota Dysbiosis

Moreover, PBM has beneficial effects on various neurodegenerative diseases via regulating gut microflora [82, 106]. For example, in amyloid precursor protein/presenilin 1 (APP/PS1) transgenic mice (an Alzheimer's disease (AD)-like mouse model), the application of PBM (peak wavelength 7.7–10 μm) for six weeks reversed the gut microbiota composition in the APP/PS1 mice, suggesting that the positive effect of PBM for AD treatment is likely via the brain-gut axis [107]. In line with this finding, Chen et al. reported that PBM at wavelengths of 630 nm, 730 nm, and 850 nm for eight weeks improved the AD condition in an amyloid-β (Aß)-induced AD mouse model. Finally, they found that PBM increased the diversity and abundance of Helicobacter, uncultured Baterioidales, and decreased Rikenella in AD mice. These findings further confirmed that gut flora-targeted PBM provided the therapeutic potential for AD treatment by restoring the dysbiosis of gut flora [82].

PBM Therapies in Kidney Diseases

Oron et al., reported that the administration of PBM (804 nm;1 J/cm2) to areas remote from the kidney, specifically the tibia of rats, significantly improved pathological changes and kidney function. They suggested that promoted stem cells in bone marrow to migrate to injured kidneys, thus providing an indirect mechanism to improve kidney function [109].

In summary, PBM might exert its beneficial effect by targeting kidney directly or indirectly (PBM being applied remote from the kidney area) through systemic effects. As shown in Figure 1, PBM might have the potential to improve kidney function via promoting mitochondrial activity, suppressing oxidative stress, inhibiting inflammation, and restoring gut microbiota homeostasis.



https://www.frontiersin.org/articles/10.3389/fnins.2022.1006031/full
Photobiomodulation for the treatment of neuroinflammation: A systematic review of controlled laboratory animal studies 2022
Results: The studies showed that PBM has anti-inflammatory properties in several conditions, such as traumatic brain injury, edema formation and hyperalgesia, ischemia, neurodegenerative conditions, aging, epilepsy, depression, and spinal cord injury.
Conclusion: Taken together, these results indicate that transcranial PBM therapy is a promising strategy to treat brain pathological conditions induced by neuroinflammation.

https://journals.sagepub.com/doi/10.2203/dose-response.09-027.Hamblin
Biphasic Dose Response in Low Level Light Therapy 2009
Low level laser therapy (LLLT) is the application of light (usually a low power laser or LED in the range of 1mW – 500mW) to a pathology to promote tissue regeneration, reduce inflammation and relieve pain. The light is typically of narrow spectral width in the red or near infrared (NIR) spectrum (600nm – 1000nm), with a power density (irradiance) between 1mw–5W/cm^2. It is typically applied to the injury for a minute or so, a few times a week for several weeks. Unlike other medical laser procedures, LLLT is not an ablative or thermal mechanism, but rather a photochemical effect comparable to photosynthesis in plants whereby the light is absorbed and exerts a chemical change.
1mW to 50mW/cm2. But over time the range is 0.01J/cm2 to 1J/cm2.
In this model the severity of the arthritis is quantified by
measuring the diameter of the swollen joint every day and plotting a time
course for each joint. We compared illumination regimens consisting of
a high and low fluence (3 and 30 J/cm2), delivered at high and low irradiance (5 and 50 mW/cm 2) using 810-nm laser light daily for 5 days, with the positive control of conventional corticosteroid (dexamethasone)therapy.
As shown in Figure 12 three of the illumination regimens were effective in reducing the mean integrated knee swelling almost as much as the positive control of the powerful steroid, dexamathasone; these were 3 J/cm2 delivered at 5 mW/cm2 and 30 J/cm 2 delivered at 50 mW/cm 2 both of which took 10 minutes, and 30 J/cm 2 delivered at 5 mW/cm2 which took 100 minutes.
In general, fluences of red or NIR as low as 3 or 5 J/cm2 will be beneficial in vivo, but a large dose like 50 or 100 J/cm2 will lose the beneficial effect and may even become detrimental.

https://pubmed.ncbi.nlm.nih.gov/33935090/
Photobiomodulation Therapy for Dementia: A Systematic Review of Pre-Clinical and Clinical Studies. 2021
Results: Out of 10,473 initial articles, 36 studies met the inclusion criteria. Nine articles reported in vitro studies, 17 articles reported studies in animal models of dementia, and 10 studies were conducted in dementia patients. All of the included studies reported positive results.

https://pubmed.ncbi.nlm.nih.gov/28186867/
Significant Improvement in Cognition in Mild to Moderately Severe Dementia Cases Treated with Transcranial Plus Intranasal Photobiomodulation: Case Series Report. 2017
Materials and methods: The study used 810 nm, 10 Hz pulsed, light-emitting diode devices combining transcranial plus intranasal PBM to treat the cortical nodes of the DMN (bilateral mesial prefrontal cortex, precuneus/posterior cingulate cortex, angular gyrus, and hippocampus). Five patients with mild to moderately severe cognitive impairment were entered into 12 weeks of active treatment as well as a follow-up no-treatment, 4-week period. Patients were assessed with the MMSE and Alzheimer's Disease Assessment Scale (ADAS-cog) tests. The protocol involved weekly, in-clinic use of a transcranial-intranasal PBM device; and daily at-home use of an intranasal-only device.
Results: There was significant improvement after 12 weeks of PBM (MMSE, $p < 0.003$; ADAS-cog, $p < 0.023$). Increased function, better sleep, fewer angry outbursts, less anxiety, and wandering were reported post-PBM. There were no negative side effects. Precipitous declines were observed during the follow-up no-treatment, 4-week period. This is the first completed PBM case series to report significant, cognitive improvement in mild to moderately severe dementia and possible AD cases.

https://pubmed.ncbi.nlm.nih.gov/33610085/
Gut flora-targeted photobiomodulation therapy improves senile dementia in an Aß-induced Alzheimer's disease animal model 2021
Methods: PBM was performed on the abdomen of the mice at the wavelengths of 630 nm, 730 nm, and 850 nm at 100 J/cm2 for 8 weeks. Morris water maze test, immunofluorescence and proteomic of hippocampus, and intestinal flora detection of fecal were used to evaluate the treatment effects of gf-targeted PBM on AD rats.
Results: PBM at all three wavelengths (especially 630 nm and 730 nm) significantly improved learning retention as measured by the Morris water maze. In addition, we found reduced amyloidosis and tau phosphorylation in the hippocampus by immunofluorescence in AD mice. By

https://pubmed.ncbi.nlm.nih.gov/33336891/
Photobiomodulation suppresses JNK3 by activation of ERK/MKP7 to attenuate AMPA receptor endocytosis in Alzheimer's disease 2021
Our previous research showed that a physical method named photobiomodulation (PBM) therapy rescues Aβ-induced dendritic atrophy in vitro. However, it remains to be further investigated the mechanism by which PBM affects AD-related multiple pathological features to improve learning and memory deficits. Here, we found that PBM attenuated Aβ-induced synaptic dysfunction and neuronal death through MKP7-dependent suppression of JNK3, a brain-specific JNK isoform related to neurodegeneration.

https://pubmed.ncbi.nlm.nih.gov/31050946/

Rapid Reversal of Cognitive Decline, Olfactory Dysfunction, and Quality of Life Using Multi-Modality Photobiomodulation Therapy: Case Report. 2019
Materials and methods: Patient received twice-daily PBM therapy at home using three different wearable light-emitting diode (LED) devices. For the first week containing a mixture of continuous wave mode red (635 nm) and NIR (810 nm) LEDs, a prototype transcranial light helmet and a body pad were used. The body pad was placed on various areas on the lower back and the helmet was worn while seated. After the first week of treatment, an intranasal LED device, 10-Hz pulsed wave mode NIR (810 nm), was initiated in the left nostril twice daily. All three devices were applied simultaneously for an irradiation time of 25 min per session. Results: The patient showed a significant improvement in the Montreal Cognitive Assessment score from 18 to 24 and in the Working Memory Questionnaire score from 53 to 10. The cognitive enhancement was accompanied by reversal of olfactory dysfunction as measured by the Alberta Smell Test and peanut butter odor detection test. Quality-of-life measures improved and caregiver stress was reduced. No adverse effects were reported.

https://surfershealth.com.au/news/2020/09/01/can-infrared-light-therapy-help-with-alzheimers-disease/
Finnish dental student Vladimir Heiskanen has collated an extensive list of trials carried out on the therapeutic effects of red and near-infrared light on his website www.valtsus.blogspot.com. His database lists over 3800 scientific articles which includes over 1100 animal studies, 500 randomised studies and 140 randomised and controlled trials in humans.
Her treatment is delivered via a mobile infrared light device produced and marketed by Vielight, a company based in Canada. This device delivers 810 nm wavelength infrared light for 20 minutes per treatment session, six days a week.

http://valtsus.blogspot.com/
Red light and near-infrared are able to induce significant physiological changes inside the tissue. According to modern knowledge, the red light inside the cells activates the mitochondrial enzyme cytochrome c oxidase, improving the mitochondrial respiration and oxygen consumption (de Freitas&Hamblin 2016, Wang et al. 2017).
This shift in cellular metabolism leads to other changes in cell function, eg. gene expression and growth factor production (Prindeze et al. 2012).

https://sunlightinstitute.org/get-your-sun-alzheimers-disease-brain/
Hence, it is no surprise that the latest research paper found high risk in low-sunlight countries. Consequently, the researchers stated: “According to sunlight data, we can conclude that countries with low average sunlight have high AD (Alzheimer’s disease) death rate.[4]”
Sun exposure directly correlates to non-melanoma skin cancer (NMSC). Therefore, the latter is often used as a sun-exposure indicator. It is thus compared with various diseases to evaluate the relationship between them and sun exposure. A 2013 article, published in the journal Neurology, reveals that among people with NMSC, the risk of Alzheimer’s disease (AD) is profoundly decreased:[5] Those with NMSC had a 79% reduction in disease risk. Stated another way, those without NMSC had about five times the risk of Alzheimer’s! Of course, this demonstrates the importance of sun exposure in reducing the risk, whether due to vitamin D production of from other photoproducts of the sun.

https://pubmed.ncbi.nlm.nih.gov/29565713/
Sunlight Incidence, Vitamin D Deficiency, and Alzheimer's Disease 2018
According to sunlight data, we can conclude that countries with low average sunlight have high AD death rate.

https://pubmed.ncbi.nlm.nih.gov/23677746/
Nonmelanoma skin cancer is associated with reduced Alzheimer disease risk. 2013
Results: We followed 1,102 adults with a mean age of 79 years at enrollment. Prevalent NMSC was associated with reduced risk of only AD (hazard ratio = 0.21; 95% confidence interval = 0.051-0.87; p = 0.031) among subjects after adjustment for demographics, hypertension, diabetes, and coronary heart disease. APOE ε4 genotypes were available in 769 individuals. The association was similar in magnitude, but nonsignificant, when the number of APOE ε4 alleles was included in the model. No significant association was found between NMSC and subsequent development of any AD or all-cause dementia.
Conclusions: This population-based longitudinal study shows that individuals older than 70 years with NMSC have a significantly reduced risk of developing AD compared with individuals without NMSC. We deduce Alzheimer-specific neuroprotection, because the effect is attenuated or eliminated when considering less-specific diagnoses such as AD with another diagnosis (any AD) or all-cause dementia.

https://pubmed.ncbi.nlm.nih.gov/28225789/
Non-melanoma skin cancer and risk of Alzheimer's disease and all-cause dementia 2017
In conclusion, NMSC was associated with 2%-10% reductions in relative risks of Alzheimer's disease and all-cause dementia. However, these small inverse associations may have been caused by ascertainment bias due to decreased awareness of NMSC tumors in persons with undiagnosed early cognitive impairment or by confounding from a more neuroprotective lifestyle among persons with NMSC

https://pubmed.ncbi.nlm.nih.gov/29573497/
Inverse association for diagnosis of Alzheimer's disease subsequent to both melanoma and non-melanoma skin cancers in a large, urban, single-centre, Midwestern US patient population. 2018
Although literature demonstrates a decreased risk of Alzheimer's disease (AD) in individuals with various cancers, including squamous cell cancers (SCC) and basal cell cancers (BCC) comprising non-melanoma skin cancers (NMSC), there is a paucity of literature to substantiate an association between malignant melanoma (MM) and AD.

(ORs).
Results: Data for a total of 82 925 patients with known race and gender and were detected. After adjusting for confounding factors (race, gender, age, cerebrovascular disease, peripheral vascular disease and diabetes), there was a significant decreased risk of subsequent AD in patients with MM (OR: 0.39; 95% CI: 0.16-0.96; P = 0.042) as well as in patients with BCC (OR: 0.18; 95% CI: 0.08-0.45; P < 0.0001) and for patients with SCC (OR: 0.08; 95% CI: 0.01-0.56; P = 0.013).
Conclusion: These findings add to the growing body of evidence for a decreased risk of AD in patients with various cancers and highlight the need for ongoing research to elucidate both neurologic and biologic mechanisms that may underlie this apparent inverse association.

https://pubmed.ncbi.nlm.nih.gov/34729018/
The Relationship Between Alzheimer's Disease and Skin Diseases: A Review 2021
Epidemiologic studies have demonstrated that patients with neurodegenerative disorders have lower malignancy rates, such as prostate cancer, breast cancer, and nonmelanoma skin cancer.86 In 2020, a meta-analysis including 9,630,435 individuals was conducted to investigate the association between Alzheimer's disease and cancer, and concluded that the risk for people with a cancer history to develop Alzheimer's disease was weakly but significantly decreased (OR=0.75 from case-control studies, HR=0.89 from cohort studies). 86

https://pubmed.ncbi.nlm.nih.gov/32224926/
Risk of Alzheimer's Disease in Cancer Patients: Analysis of Mortality Data from the US SEER Population-Based Registries. 2020
Previous studies have reported an inverse association between cancer and Alzheimer's disease (AD), which are leading causes of human morbidity and mortality. We analyzed the SEER (Surveillance, Epidemiology, and End Results) data to estimate the risk of AD death in (i) cancer patients relative to reference populations stratified on demographic and clinical variables, and (ii) female breast cancer (BC) patients treated with chemotherapy or radiotherapy, relative to those with no/unknown treatment status. Our results demonstrate the impact of race, cancer type, age and time since cancer diagnosis on the risk of AD death in cancer patients. While the risk of AD death was decreased in white patients diagnosed with various cancers at 45 or more years of age, it was increased in black patients diagnosed with cancers before 45 years of age (likely due to early onset AD). Chemotherapy decreased the risk of AD death in white women diagnosed with BC at the age of 65 or more, however radiotherapy displayed a more complex pattern with early decrease and late increase in the risk of AD death during a prolonged time interval after the treatment. Our data point to links between molecular mechanisms involved in cancer and AD, and to the potential applicability of some anti-cancer treatments against AD.

https://pubmed.ncbi.nlm.nih.gov/32098507/
Death from Alzheimer's disease among cancer survivors: a population-based study. 2020
.Conclusion: Long-term cancer survivors (≥10 years) are more likely to die from Alzheimer's disease compared to the US general population. This risk seems to be higher among patients with older age at the time of cancer diagnosis, American Indian race and those with brain tumors.

https://pubmed.ncbi.nlm.nih.gov/18003939/
Race/ethnic differences in AD survival in US Alzheimer's Disease Centers. 2007
Conclusions: African American and Latino Alzheimer disease (AD) patients may have longer survival compared with white AD patients. Neuropathology findings did not explain survival differences by race. Determining the underlying factors behind survival differences may lead to longer survival for AD patients of all race/ethnic backgrounds.

https://pubmed.ncbi.nlm.nih.gov/32432415/
Cancer and risk of Alzheimer's disease: Small association in a nationwide cohort study 2020
Discussion: Inverse associations between cancer and AD were small and diminished over time. Incidence rates in cancer survivors approached those of the general population, suggesting limited association between cancer and AD risk.

https://pubmed.ncbi.nlm.nih.gov/27875990/
Inverse relationship between Alzheimer's disease and cancer, and other factors contributing to Alzheimer's disease: a systematic review. 2016
Conclusions: Alzheimer's disease and Cancer have inverse relationship; many factors that are upregulated in any cancer to sustain growth and survival are downregulated in Alzheimer's disease contributing to neuro-degeneration. When aged neurons or genetically susceptible neurons have weakened growth, cell survival and anti-stress responses, age related gene expression changes, altered regulation of cell death and maintenance mechanisms, they contribute to Alzheimer's disease. Countermeasures by AD neurons such as Beta Amyloid Plaques, NFTs, S100, are last attempts for survival and this provides neuroprotection for certain time and ultimately may become pathological and speed up AD. This study may contribute in developing new potential diagnostic tests, interventions and treatments.

https://www.researchgate.net/publication/348632044_Neuro-Photobiomodulation_Stimulation_of_the_Brain_Using_Different_Frequencies
Neuro-Photobiomodulation: Stimulation of the Brain Using Different Frequencies 2021
Iaccarino et al. (2016) [14] first reported the positive effects of restoring gamma (40 Hz) oscillations in the visual cortex of a transgenic mice model in Alzheimer's disease; also optogenetically driving FS-PV-interneurons at gamma (40 Hz), but not other frequencies, reduced the levels of amyloid-ß (A ß)1–40 and A ß1–42 isoforms. Despite several subsequent studies, consensus on using 40 Hz stimulation for new strategies in the possible treatment of Alzheimer's disease remains elusive. Nevertheless, our experimentally performed BIS measurements showed that at least the stimulation frequency of 40 Hz could have a (possibly sedative) influence on the bioelectrical function of the brain, which in individual cases can be larger than that compared to continuous stimulation, but does not reach the level of a longer- lasting effect with 136.1 Hz frequency [10]. These

preliminary findings are corroborated by the results of the neuromodulatory parameters [10], which were also collected in our experiments. The reduction in the heart rate at a frequency of 136.1 Hz also showed the soothing effects of this frequency [10]

https://pubmed.ncbi.nlm.nih.gov/32390621/
Photobiomodulation for Alzheimer's Disease: Translating Basic Research to Clinical Application 2020
This review covers the mechanistic action of photobiomodulation therapy against Alzheimer's disease at a cellular level. Safe and effective doses have been found in animal models, and the first human case studies have provided reasons to undertake large-scale clinical trials. A brief discussion of the minimally effective and maximum tolerated dose concludes this review, and provides the basis for a successful translation from bench to bedside. The rradiation intensity of a suitable device for photobiomodulation therapy for AD needs to permit elivery of a dose of up to 60 J/cm 2 to the scalp ithin a reasonable period of time while providing power density below the risk of thermal damage <250 mW/cm2).

https://pubmed.ncbi.nlm.nih.gov/36633696/
Photobiomodulation for Alzheimer's disease: photoelectric coupling effect on attenuating Aβ neurotoxicity 2023
Alzheimer's disease (AD) and dementia are the most worrying health problems faced by people globally today. Although the pathological features of AD consisting of amyloid-beta (Aβ) plaques in the extracellular space (ECS) and intracellular tau tangles are well established, the developed medicines targeting these two proteins have not obtained the expected clinical effects. Photobiomodulation (PBM) describes the therapeutic use of red light (RL) or near-infrared light (NIR) to serve as a noninvasive neuroprotective strategy for brain diseases. The present review discusses the mechanisms of the photoelectric coupling effect (light energy-induced special electronic transition-related alterations in protein structure) of PBM on reducing Aβ toxicity. On the one hand, RL or NIR can directly disassemble Aβ in vitro and in vivo. On the other hand, formaldehyde (FA)-inhibited catalase (CAT) and H2O2-inactived formaldehyde dehydrogenase (FDH) are formed a vicious circle in AD; however, light energy not only activates FDH to degrade excessive FA (which crosslinks Aβ monomer to form Aβ oligomers and senile plaques) but also sensitizes CAT to reduce hydrogen peroxide levels (H2O2, which can facilitate Aβ aggregation and enhance FA generation). In addition, it also activates mitochondrial cytochrome-c to produce ATP in the neurons. Clinical trials of phototherapeutics or oral coenzyme Q10 have shown positive effects in AD patients. Hence, a promising strategy combined PBM with nanopacked Q10 has been proposed to apply for treating AD

https://pubmed.ncbi.nlm.nih.gov/36034819/
Transcranial near-infrared light in treatment of neurodegenerative diseases 2022
Transcranial brain stimulations with NIR light PBM in recent animal and human studies revealed a positive impact of treatment on the progression and improvement of neurodegenerative processes, management of brain energy metabolism, and regulation of chronic brain inflammation associated with various conditions, including traumatic brain injury. This scientific overview incorporates the most recent cellular and functional findings in PBM with NIR light in treating neurodegenerative diseases, presents the discussion of the proposed mechanisms of action, and describes the benefits of this treatment in neuroprotection, cell preservation/detoxification, anti-inflammatory properties, and regulation of brain energy metabolism. This review will also discuss the novel aspects and pathophysiological role of the glymphatic and brain lymphatics system in treating neurodegenerative diseases with NIR light stimulations. Scientific evidence presented in this overview will support a combined effort in the scientific community to increase attention to the understudied NIR light area of research as a natural agent in the treatment of neurodegenerative diseases to promote more research and raise awareness of PBM in the treatment of brain disorders.

https://pubmed.ncbi.nlm.nih.gov/31875125/
Short-term Effects of Transcranial Near-Infrared Photobiomodulation on Motor Performance in Healthy Human Subjects: An Experimental SingleBlind Randomized Clinical Trial 2019
In this experimental single-blind randomized clinical trial study, 56 right-handed healthy participants, whose ages ranged from 18 to 30, were randomly assigned to (1) Real transcranial NIR-PBMC3 group (n=14), (2) Sham transcranial NIR-PBMC3 group (n=14), (3) Real transcranial NIR-PBMC4 group (n=14), and (4) Sham transcranial NIR-PBMC4 group (n=14). We applied the 808 nm laser with irradiation energy density of 60 J/cm2 and power density of 200 mw/cm2 to the C3 or C4 points of the scalp. The number of finger taps as an indicator of motor performance was assessed by the finger-tapping test (FTT) before and after irradiation of transcranial NIR-PBM on the corresponding points of the scalp for 5 minutes. Results: The results showed that the number of finger taps in both right and left hands following the use of transcranial NIR-PBM in the real transcranial NIR-PBMC3 group significantly increased (P<0.05). Conclusion: We concluded that using transcranial NIR-PBM with a laser source on C3 point of the motor cortex in right-handed healthy people can increase the number of finger taps in both hands as an indicator of motor performance improvement.

https://pubmed.ncbi.nlm.nih.gov/36254133/
The effect of transcranial photobiomodulation on cognitive function and attentional performance of older women with mild cognitive impairment: a randomized controlled trial 2022
In this study, tPBM was used for 5 daily sessions (in compliance with Circadian Rhythms 9–12 a.m.). We used an 850-nm multi-array LED device (20 NIR LEDs, total power: 400 mW, power density: 285 mW/ cm $_2$, energy density: 42.75 J/cm $_2$, total dose delivered to the scalp:
The cognitive function was tested using an MMSE questionnaire. The results showed that after 5 sessions of tPBM, the cognitive score improved, which was consistent with previous studies reporting that tPBM was useful in enhancing cognitive functioning in healthy elderly adults and in clinical situations [15]. Research has shown that tPBM can improve cognitive

function in individuals with neurodegenerative diseases such Alzheimer's disease [33], dementia, Parkinson's disease [34], and chronic traumatic brain injury [35].
This study also demonstrated that the intervention significantly decreased the reaction time, which was consistent with the studies [39, 40], reporting that cognitive abilities significantly improved in participants receiving the treatment. In their study, individuals who underwent tPBM had a faster reaction time (measured by the psychomotor vigilance test). According to another study by Chan et al., tPBM improved the cognitive function of the elderly people, and only the mean reaction time significantly changed in the experimental group [14].
In our study, the PCT was also improved. The improved attention and motor skills in response to the proper stimulus are indicated by a higher PCT score. As this score rises, the performance of the irradiated area in controlling the inhibition of response to the requested task may improve; this has been supported in some previous research [39, 40]. In the study by Holmes et al. [41], psychomotor performance improved and patients showed faster reaction times and a higher number of accurate experiments after tPBM treatment.

https://pubmed.ncbi.nlm.nih.gov/36177151/
Repeated transcranial photobiomodulation improves working memory of healthy older adults: behavioral outcomes of poststimulation including a three-week follow-up 2022
Approach: In a sham-controlled and within-subject design, 61 healthy older adults were recruited to participate in a longitudinal study involving an experimental baseline, seven days of tPBM treatment (12 min daily, 1064-nm laser, 250 mW/cm 2) in the left dorsolateral prefrontal cortex and three weeks of follow-ups. Behavioral performance in the N-back (N ¼ 1;2; 3) was recorded poststimulation during the baseline, the first and seventh days of the tPBM session, and the three weekly follow-ups. A control group with 25 participants was included in this study to rule out the practice and placebo effects. The accuracy rate and response time were used in the statistical analysis.
Results: Repeated and single tPBM significantly improved accuracy rate in 1- and 3-back tasks and decreased response time in 3-back compared to the baseline. Moreover, the repeated tPBM resulted in a significantly higher improvement in accuracy rate than the single tPBM. These improvements in accuracy rate and response time lasted at least three weeks following repeated tPBM. In contrast, the control group showed no significant improvement in behavioral performance. Conclusions: This study demonstrated that seven-day repeated tPBM improved the working memory of healthy older adults more efficiently, with the beneficial effect lasting at least three weeks. These findings provide fundamental evidence that repeated tPBM may be a potential intervention for older individuals with memory decline.

https://pubmed.ncbi.nlm.nih.gov/36371017/
Can transcranial photobiomodulation improve cognitive function? A systematic review of human studies 2023
Of the 35 studies identified, 29 (82.9 %) studies reported positive improvement in cognitive functions after tPBM. All nine studies on participants with subjective memory complaints, mild cognitive impairment, and dementia, showed positive outcomes. Seven (87.5 %) studies on traumatic brain injury (TBI) patients also showed positive results. A series of clinical trials on stroke patients showed positive trends on improved neurological deficit at first, but was prematurely terminated later at phase III due to the lack of statistical significance. One of the most common protocols for clinical populations employed devices delivering near-infrared light (810 nm), the irradiance of 20-25 mW/cm2, and fluence of 1-10 J/cm2. While this was common, the reviewed protocols also included other wavelengths of light ranging from visible, red (630-635 nm) to invisible near-infrared maximum wavelengths of 1060-1068 nm.
Conclusions: tPBM seems to improve cognitive function. However, only half of the reviewed clinical trials were randomized control trials, further investigation is warranted.

https://pubmed.ncbi.nlm.nih.gov/36459562/
Transcranial photobiomodulation enhances visual working memory capacity in humans 2022
Transcranial photobiomodulation (tPBM) is a safe and noninvasive intervention that has shown promise for improving cognitive performance. Whether tPBM can modulate brain activity and thereby enhance working memory (WM) capacity in humans remains unclear. In this study, we found that 1064-nm tPBM applied to the right prefrontal cortex (PFC) improves visual working memory capacity and increases occipitoparietal contralateral delay activity (CDA). The CDA set-size effect during retention mediated the effect between the 1064-nm tPBM and subsequent WM capacity. The behavioral benefits and the corresponding changes in the CDA set-size effect were absent with tPBM at a wavelength of 852 nm or with stimulation of the left PFC. Our findings provide converging evidence that 1064-nm tPBM applied to the right PFC can improve WM capacity.
. The measured uniform laser beam has an area of 13.57 cm2 (4 cm in diameter) and a continuous power output of 2271 mW, resulting in an irradiance or power density of 167 mW/cm2 (2271 mW/13.57 cm 2 = 167 mW/cm 2).
At this power level, the energy emitted by the laser is one-fifth of the skin's maximum permissible exposure (the exposure not deemed harmful to tissue and causing no detectable physical damage or imperceptible heat).

https://pubmed.ncbi.nlm.nih.gov/32173886/
Transcranial Photobiomodulation (tPBM) With 1,064-nm Laser to Improve Cerebral Metabolism of the Human Brain In Vivo 2020
This study provided strong evidence to validate/confirm our previous findings that tPBM with 1,064-nm laser enables to increase cerebral Δ[HbO] and Δ[oxi-CCO] in the human brain, as measured by bb-NIRS. Overall, it demonstrated the robust reproducibility of tPBM being able to improve cerebral hemodynamics and metabolism of the human brain in vivo in both young and older adults.
Light from the aperture was well-collimated and the illumination area on the human forehead was 13.6 cm2 , giving rise to a constant power density of 3.4 W/13.6 cm2 = 0.25 W/cm2

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https://pubmed.ncbi.nlm.nih.gov/35757526/

Enhancement of Frequency-Specific Hemodynamic Power and Functional Connectivity by Transcranial Photobiomodulation in Healthy Humans 2022

Transcranial photobiomodulation (tPBM) has been considered a safe and effective brain stimulation modality being able to enhance cerebral oxygenation and neurocognitive function. To better understand the underlying neurophysiological effects of tPBM in the human brain, we utilized a 111-channel functional near infrared spectroscopy (fNIRS) system to map cerebral hemodynamic responses over the whole head to 8-min tPBM with 1,064-nm laser given on the forehead of 19 healthy participants. Instead of analyzing broad-frequency hemodynamic signals (0-0.2 Hz), we investigated frequency-specific effects of tPBM on three infra-slow oscillation (ISO) components consisting of endogenic, neurogenic, and myogenic vasomotions. Significant changes induced by tPBM in spectral power of oxygenated hemoglobin concentration (Δ[HbO]), functional connectivity (FC), and global network metrics at each of the three ISO frequency bands were identified and mapped topographically for frequency-specific comparisons. Our novel findings revealed that tPBM significantly increased endogenic Δ[HbO] powers over the right frontopolar area near the stimulation site. Also, we demonstrated that tPBM enabled significant enhancements of endogenic and myogenic FC across cortical regions as well as of several global network metrics. These findings were consistent with recent reports and met the expectation that myogenic oscillation is highly associated with endothelial activity, which is stimulated by tPBM-evoked nitric oxide (NO) release.

https://pubmed.ncbi.nlm.nih.gov/35050164/

Metabolic Connectivity and Hemodynamic-Metabolic Coherence of Human Prefrontal Cortex at Rest and Post Photobiomodulation Assessed by Dual-Channel Broadband NIRS 2022

For post-tPBM/sham comparison, our analyses revealed three key findings: 8-min, right-forehead, 1064-nm tPBM (1) enhanced the amplitude of metabolic oscillation bilaterally, (2) promoted the bilateral metabolic connectivity of neurogenic rhythm, and (3) made the main effect on endothelial cells, causing alteration of hemodynamic-metabolic coherence on each side of the prefrontal cortex.

https://pubmed.ncbi.nlm.nih.gov/28178891/

Up-regulation of cerebral cytochrome-c-oxidase and hemodynamics by transcranial infrared laser stimulation: A broadband near-infrared spectroscopy study 2017

Transcranial infrared laser stimulation (TILS) is a noninvasive form of brain photobiomulation. Cytochrome-c-oxidase (CCO), the terminal enzyme in the mitochondrial electron transport chain, is hypothesized to be the primary intracellular photoacceptor. We hypothesized that TILS up-regulates cerebral CCO and causes hemodynamic changes. We delivered 1064-nm laser stimulation to the forehead of healthy participants (n = 11), while broadband near-infrared spectroscopy was utilized to acquire light reflectance from the TILS-treated cortical region before, during, and after TILS. Placebo experiments were also performed for accurate comparison. Time course of spectroscopic readings were analyzed and fitted to the modified Beer-Lambert law. With respect to the placebo readings, we observed (1) significant increases in cerebral concentrations of oxidized CCO (Δ[CCO]; >0.08 μM; $p < 0.01$), oxygenated hemoglobin (Δ[HbO]; >0.8 μM; $p < 0.01$), and total hemoglobin (Δ[HbT]; >0.5 μM; $p < 0.01$) during and after TILS, and (2) linear interplays between Δ[CCO] versus Δ[HbO] and between Δ[CCO] versus Δ[HbT]. Ratios of Δ[CCO]/Δ[HbO] and Δ[CCO]/Δ[HbT] were introduced as TILS-induced metabolic-hemodynamic coupling indices to quantify the coupling strength between TILS-enhanced cerebral metabolism and blood oxygen supply. This study provides the first demonstration that TILS causes up-regulation of oxidized CCO in the human brain, and contributes important insight into the physiological mechanisms.

https://pubmed.ncbi.nlm.nih.gov/36462596/

Photobiomodulation and nitric oxide signaling 2023

Nitric oxide (NO) is a well-known gaseous mediator that maintains vascular homeostasis. Extensive evidence supports that a hallmark of endothelial dysfunction, which leads to cardiovascular diseases, is endothelial NO deficiency. Thus, restoring endothelial NO represents a promising approach to treating cardiovascular complications. Despite many therapeutic agents having been shown to augment NO bioavailability under various pathological conditions, success in resulting clinical trials has remained elusive. There is solid evidence of diverse beneficial effects of the treatment with low-power near-infrared (NIR) light, defined as photobiomodulation (PBM). Although the precise mechanisms of action of PBM are still elusive, recent studies consistently report that PBM improves endothelial dysfunction via increasing bioavailable NO in a dose-dependent manner and open a feasible path to the use of PBM for treating cardiovascular diseases via augmenting NO bioavailability. In particular, the use of NIR light in the NIR-II window (1000-1700 nm) for PBM, which has reduced scattering and minimal tissue absorption with the largest penetration depth, is emerging as a promising therapy. In this review, we update recent findings on PBM and NO.

https://www.medicalnewstoday.com/articles/infrared-light-therapy-a-new-approach-to-dementia

Infrared light therapy: A new approach to dementia?

https://pubmed.ncbi.nlm.nih.gov/33166061/

Cytochrome c oxidase-modulatory near-infrared light penetration into the human brain: Implications for the noninvasive treatment of ischemia/reperfusion injury 2021

Near-infrared light (IRL) has been evaluated as a therapeutic for a variety of pathological conditions, including ischemia/reperfusion injury of the brain, which can be caused by an ischemic stroke or cardiac arrest. Strategies have focused on modulating the activity of mitochondrial electron transport chain (ETC) enzyme cytochrome c oxidase (COX), which has copper centers that broadly absorb IRL between 700 and 1,000 nm. We have recently identified specific COX-inhibitory IRL wavelengths that are profoundly neuroprotective in rodent models of brain ischemia/reperfusion through the following mechanism: COX inhibition by IRL limits mitochondrial membrane potential hyperpolarization during reperfusion, which otherwise causes reactive oxygen species (ROS) production and cell death. Prior to clinical application of IRL on humans, IRL penetration must be tested, which may be wavelength dependent. In the present study, four fresh (unfixed) cadavers and

isolated cadaver tissues were used to examine the transmission of infrared light through human biological tissues. We conclude that the transmission of 750 and 940 nm IRL through 4 cm of cadaver head supports the viability of IRL to treat human brain ischemia/reperfusion injury and is similar for skin with different skin pigmentation. We discuss experimental difficulties of working with fresh cadavers and strategies to overcome them as a guide for future studies.

https://pubmed.ncbi.nlm.nih.gov/31112450/

Non-invasive treatment with near-infrared light: A novel mechanisms-based strategy that evokes sustained reduction in brain injury after stroke 2020

Ischemic stroke is a debilitating disease that causes significant brain injury. While restoration of blood flow is critical to salvage the ischemic brain, reperfusion can exacerbate damage by inducing generation of reactive oxygen species (ROS). Recent studies by our group found that non-invasive mitochondrial modulation with near-infrared (NIR) light limits ROS generation following global brain ischemia. NIR interacts with cytochrome *c* oxidase (COX) to transiently reduce COX activity, attenuate mitochondrial membrane potential hyperpolarization, and thus reduce ROS production. We evaluated a specific combination of COX-inhibitory NIR (750 nm and 950 nm) in a rat stroke model with longitudinal analysis of brain injury using magnetic resonance imaging. Treatment with NIR for 2 h resulted in a 21% reduction in brain injury at 24 h of reperfusion measured by diffusion-weighted imaging (DWI) and a 25% reduction in infarct volume measured by T2-weighted imaging (T2WI) at 7 and 14 days of reperfusion, respectively. Additionally, extended treatment reduced brain injury in the acute phase of brain injury, and 7 and 14 days of reperfusion, demonstrating a >50% reduction in infarction. Our data suggest that mitochondrial modulation with NIR attenuates ischemia-reperfusion injury and evokes a sustained reduction in infarct volume following ischemic stroke.

https://pubmed.ncbi.nlm.nih.gov/36066188/

Sometimes less is more: inhibitory infrared light during early reperfusion calms hyperactive mitochondria and suppresses reperfusion injury 2022

Finally, we discuss the use of near infrared light (IRL) to treat stroke. IRL can both stimulate or inhibit mitochondrial activity depending on the wavelength. We emphasize that the use of the correct wavelength is crucial for outcome: inhibitory IRL, applied early during reperfusion, can prevent the ROS burst from occurring, thus preserving neurological tissue.

https://pubmed.ncbi.nlm.nih.gov/32716711/

What Lies at the Heart of Photobiomodulation: Light, Cytochrome C Oxidase, and Nitric Oxide-Review of the Evidence 2020

A novel nitrite reductase activity of solubilized mitochondria has been demonstrated attributable to CCO. NO production was optimal under hypoxic conditions. It was also found that 590 nm irradiation increased NO production by enhancing NO release. The presence of cellular NO has usually been considered metabolically detrimental, but current thinking has expanded the importance and the physiological roles of NO. Evidence shows that NO production is likely to play a role in cardioprotection and defenses against hypoxic damage. ***Conclusions****:* Studies combining PBM and hypoxia also point to a connection between light irradiation, hypoxia protection, and NO production. This leads the authors to the possibility that the intrinsic nature of PBM involves the production of NO. The combination of CCO and hemoglobin/myoglobin NO production with photorelease of NO may constitute the heart of PBM.

https://pubmed.ncbi.nlm.nih.gov/34115530/

Effect of Red-to-Near Infrared Light and a Nitric Oxide Donor on the Oxygen Consumption of Isolated Cytochrome c Oxidase 2021

Objective: To study the effects of 670 and 830 nm irradiation on oxygen consumption by cytochrome c oxidase (CCO) in a Clark electrode type reaction chamber. To explore the effect of irradiation on the nitric oxide (NO) donor-induced inhibition of oxygen consumption. Background: Most theories of photobiomodulation (PBM) involve the enzyme CCO as a cellular target for red-to-near infrared light (R-NIR) irradiation. Attempts to measure the effect of irradiation on the kinetics of CCO have failed to demonstrate a significant effect. It remains to explore the effects of irradiation on the consumption of oxygen. NO has been proposed as a possible mediator for PBM due to its inhibitory effects on CCO. Studying the effect of R-NIR on NO-induced inhibition of oxygen consumption is needed to explore this thesis. Methods: Oxygen consumption assays at 22°C were performed in a Mitocell MT200A system equipped with a 1302 oxygen electrode. R-NIR irradiation at 670 nm (41 mW/cm2) or 830 nm (31 mW/cm2) was provided to the reaction mixture. Calculated second-order rate constants were compared with control runs at four cytochrome c concentrations. Assays were also performed with or without NO donor and/or light for two substrate concentrations. Results: Kinetics constants for oxygen consumption with or without R-NIR showed no significant differences with either wavelength at any substrate concentration. The NO donor showed significant inhibition that was not relieved by irradiation. Conclusions: This lack of effect by R-NIR calls into question both the CCO activity model and the NO inhibition relief model of PBM.

https://pubmed.ncbi.nlm.nih.gov/31107170/

Revisiting the Photon/Cell Interaction Mechanism in Low-Level Light Therapy 2019

Objective: Several reports claim that the enzyme cytochrome c oxidase (CCO) is the primary absorber for red-to-near-infrared (R-NIR) light in cells and causal for mitochondrial adenosine triphosphate (ATP) upregulation, and that pulsed R-NIR light has frequent therapeutic effects, which are superior to those of the continuous wave (CW) mode used in low-level light therapy (LLLT). ***Background data:*** Convincing evidence that the absorption of R-NIR photons by CCO is involved in mitochondrial ATP upregulations as well as a coherent explanation for the superiority of the pulsed irradiation mode is presently lacking in the literature. ***Methods:*** A comprehensive literature search and rigorous analysis of the data published on the idea that CCO is the primary absorber for R-NIR light, and of the claim that the effectivity of the pulsed irradiation mode can be derived from the absorption of R-NIR photons by CCO, reveal a number of severe inconsistencies. ***Results:*** A systematical analysis covering both the theory that CCO is the primary acceptor for R-NIR light and of its use to interpret differences between the biological effect of pulsed light and CW casts doubt on the general validity of the CCO-based hypothesis. Instead, we are offered a simple and conflict-free model accounting for both ATP upregulation and superiority of the pulsed mode in LLLT, which is in agreement with the results of recent laboratory experiments. ***Conclusions:*** CCO is not the primary acceptor for R-NIR light.

https://pubmed.ncbi.nlm.nih.gov/29472564/

Inhibitory modulation of cytochrome c oxidase activity with specific near-infrared light wavelengths attenuates brain ischemia/reperfusion injury 2018

The interaction of light with biological tissue has been successfully utilized for multiple therapeutic purposes. Previous studies have suggested that near infrared light (NIR) enhances the activity of mitochondria by increasing cytochrome c oxidase (COX) activity, which we confirmed for 810 nm NIR. In contrast, scanning the NIR spectrum between 700 nm and 1000 nm revealed two NIR wavelengths (750 nm and 950 nm) that reduced the activity of isolated COX. COX-inhibitory wavelengths reduced mitochondrial respiration, reduced the mitochondrial membrane potential ($\Delta\Psi_m$), attenuated mitochondrial superoxide production, and attenuated neuronal death following oxygen glucose deprivation, whereas NIR that activates COX provided no benefit. We evaluated COX-inhibitory NIR as a potential therapy for cerebral reperfusion injury using a rat model of global brain ischemia. Untreated animals demonstrated an 86% loss of neurons in the CA1 hippocampus post-reperfusion whereas inhibitory NIR groups were robustly protected, with neuronal loss ranging from 11% to 35%. Moreover, neurologic function, assessed by radial arm maze performance, was preserved at control levels in rats treated with a combination of both COX-inhibitory NIR wavelengths. Taken together, our data suggest that COX-inhibitory NIR may be a viable non-pharmacologic and noninvasive therapy for the treatment of cerebral reperfusion injury.

https://pubmed.ncbi.nlm.nih.gov/35746943/

Brighten the Future: Photobiomodulation and Optogenetics 2022

Safe, noninvasive, and effective treatments for brain conditions are everyone's dream. Low-level light therapy (LLLT) based on the photobiomodulation (PBM) phenomenon has recently been adopted in practice, with solid scientific evidence. Optogenetics provides high spatiotemporal resolution to precisely switch on and off a particular circuitry in the brain. However, there are currently no human trials of optogenetics on the human brain. These two approaches-PBM and optogenetics-are promising photonic treatments that target the brain using completely different technologies. PBM is based on the mitochondrial reaction to the photons for up- or downregulation on the cytochrome c oxidase synthase in cellular respiration. It is safe, noninvasive, and good for long-term treatments, with wide applications using light wavelengths ranging from 650 nm to ≈1,100 nm, the red to near-infrared range. Optogenetics is based on the expression of engineered opsins on targeted tissues through viral vectors. The opsins are engineered to be sensors, actuators, or switches and could be precisely controlled by light wavelength ranging from 450 nm to ≈650 nm, the visible light range. The penetration of visible light is limited, and thus the photons cannot be applied directly outside the head without surgical means to create a physical window. PBM using near-infrared light could reach deeper tissues for light directly applied outside the head. Detailed scientific foundations and the state of the art for both technologies are reviewed. Ongoing developments are discussed to provide insight for future research and applications.

https://pubmed.ncbi.nlm.nih.gov/35208178/

Photobiomodulation at Different Wavelengths Boosts Mitochondrial Redox Metabolism and Hemoglobin Oxygenation: Lasers vs. Light-Emitting Diodes In Vivo 2022

Our group previously examined 8 min photobiomodulation (PBM) by 1064 nm laser on the human forearm in vivo to determine its significant effects on vascular hemodynamics and cytochrome c oxidase redox activity. Since PBM uses a wide array of wavelengths, in this paper, we investigated (i) whether different wavelengths of lasers induced different PBM effects, and (ii) if a light-emitting diode (LED) at a similar wavelength to a laser could induce similar PBM effects. A broadband near-infrared spectroscopy (bbNIRS) system was utilized to assess concentration changes in oxygenated hemoglobin (Δ[HbO]) and oxidized cytochrome c oxidase (Δ[oxCCO]) during and after PBM with lasers at 800 nm, 850 nm, and 1064 nm, as well as a LED at 810 nm. Two groups of 10 healthy participants were measured before, during, and after active and sham PBM on their forearms. All results were tested for significance using repeated measures ANOVA. Our results showed that (i) lasers at all three wavelengths enabled significant increases in Δ[HbO] and Δ[oxCCO] of the human forearm while the 1064 nm laser sustained the increases longer, and that (ii) the 810-nm LED with a moderate irradiance (≈135 mW/cm^2) induced measurable and significant rises in Δ[HbO] and Δ[oxCCO] with respect to the sham stimulation on the human forearm.

https://pubmed.ncbi.nlm.nih.gov/31553265/

Penetration Profiles of Visible and Near-Infrared Lasers and Light-Emitting Diode Light Through the Head Tissues in Animal and Human Species: A Review of Literature 2019

Background and objective: Photobiomodulation (PBM) therapy is a promising and noninvasive approach to stimulate neuronal function and improve brain repair. The optimization of PBM parameters is important to maximize effectiveness and tolerability. Several studies have reported on the penetration of visible-to-near-infrared (NIR) light through various animal and human tissues. Scientific findings on the penetration of PBM light vary, likely due to use of different irradiation parameters and to different characteristics of the subject such as species, age, and gender. ***Materials and methods:*** In this article, we review published data on PBM penetration through the tissues of the head in both animal and human species. The patterns of visible-to-NIR light penetration are summarized based on the following study specifications: wavelength, coherence, operation mode, beam type and size, irradiation site, species, age, and gender. ***Results:*** The average penetration of transcranial red/NIR (630-810 nm) light ranged 60-70% in C57BL/6 mouse (skull), 1-10% in BALB/c mouse (skull), 10-40% in Sprague-Dawley rats (scalp plus skull), 20% in *Oryctolagus cuniculus* rabbit (skull), 0.11% in pig (scalp plus skull), and 0.2-10% in humans (scalp plus skull). The observed variation in the reported values is due to the difference in factors (e.g., wavelengths, light coherence, tissue thickness, and anatomic irradiation site) used by researchers. It seems that these data challenge the applicability of the animal model data on transcranial PBM to humans. Nevertheless, two animal models seem particularly promising, as they approximate penetration in humans: (I) Penetration of 808 nm laser through the scalp plus skull was 0.11% in the pig head; (II) Penetration of 810 nm laser through intact skull was 1.75% in BALB/c mouse. ***Conclusions:*** In conclusion, it is worthwhile mentioning that since the effectiveness of brain PBM is closely dependent on the amount of light energy reaching the target neurons, further quantitative estimation of light penetration depth should be performed to validate the current findings.

https://pubmed.ncbi.nlm.nih.gov/27070113/

Effect of Photobiomodulation on Mesenchymal Stem Cells 2016

Results: After evaluation, 30 articles were deemed relevant according to the inclusion criteria. The energy density of the laser was 0.7-9 J/cm^2. The power used for visible light was 30-110 mW and that used for infrared light was 50-800 mW. Nearly all studies showed that low-level laser therapy had a positive effect on cell proliferation. Similar outcomes were found for LED; however, some studies suggest that the laser alone is not effective, and should be used as an adjunct tool.

https://pubmed.ncbi.nlm.nih.gov/30145725/

Photobiomodulation with 808-nm diode laser light promotes wound healing of human endothelial cells through increased reactive oxygen species production stimulating mitochondrial oxidative phosphorylation 2019

Photobiomodulation of cells using near-infrared (NIR) monochromatic light can affect cell functions such as proliferation, viability, and metabolism in a range of cell types. Evidence for the effects of near-infrared light on endothelial cells has been reported, but the studies were mainly performed using VIS light emitted by low-energy lasers, because NIR wavelengths seemed negatively stimulate these cells. Cell viability, free radical-induced oxidative stress, NF-κB activation, nitric oxide release, mitochondrial respiration, and wound healing repair were assessed in human endothelial cells (HECV) irradiated with 808-nm diode laser light (laser setup = 1 W/cm^2, 60 s, 60 J/cm^2, CW vs measured energy parameter = 0.95 W/cm^2, 60 s, 57 J/cm^2, mode CW) emitted by an handpiece with flat-top profile. No difference in viability was detected between controls and HECV cells irradiated with 808-nm diode laser light for 60 s. Irradiated cells demonstrated higher proliferation rate and increased migration ability associated to moderate increase in ROS production without a significant increase in oxidative stress and oxidative stress-activated processes. Near-infrared light stimulated mitochondrial oxygen consumption and ATP synthesis in HECV cells. Short near-infrared irradiation did not affect viability of HECV cells, rather led to a stimulation of wound healing rate, likely sustained by ROS-mediated stimulation of mitochondrial activity. Our results demonstrating that near-infrared led to a shift from anaerobic to aerobic metabolism provide new insight into the possible molecular mechanisms by which photobiomodulation with 808-nm diode laser light protects against inflammation-induced endothelial dysfunction, seemingly promising to enhance their therapeutic properties.

https://pubmed.ncbi.nlm.nih.gov/32027411/

Role of 904 nm superpulsed laser-mediated photobiomodulation on nitroxidative stress and redox homeostasis in burn wound healing 2020

Background: Burn wound healing is delayed due to several critical factors such as sustained inflammation, vascular disorder, neuropathy, enhanced proteolysis, infection, and oxidative stress. Burn wounds have limited oxygen supply owing to compromised blood circulation. Hypoxic burn milieu leads to free radicals overproduction incurring oxidative injury, which impedes repair process causing damage to cell membranes, proteins, lipids, and DNA. Photobiomodulation (PBM) with 904 nm superpulsed laser had shown potent healing efficacy via attenuating inflammation while enhancing proliferation, angiogenesis, collagen accumulation, and bioenergetic activation in burn wounds.

Methods: This study investigated the effects of 904 nm superpulsed laser at 0.4 mW/cm2 average power density, 0.2 J/cm2 total energy density, 100 Hz frequency, and 200 ns pulse width for 10 min daily for seven days postburn injury on nitroxidative stress, endogenous antioxidants status, and redox homeostasis.

Results: Photobiomodulation treatment significantly decreased reactive oxygen species, nitric oxide, and lipid peroxidation levels as compared to non-irradiated control. Further, protective action of PBM against protein oxidative damage was evidenced by reduced protein carbonylation and advanced oxidation protein product levels along with significantly enhanced endogenous antioxidants levels of SOD, catalase, GPx, GST, reduced glutathione, and thiol (T-SH, Np-SH, P-SH). Biochemical changes aid in reduction of oxidative stress and maintenance of redox homeostasis, which further well corroborated by significantly up-regulated protein expression of Nrf 2, hemeoxygenase (HO-1), and thioredoxin reductase 2 (Txnrd2).

Conclusion: Photobiomodulation with 904 nm superpulsed laser led to reduction of nitroxidative stress, induction of endogenous antioxidants, and maintenance of redox homeostasis that could play a vital role in augmentation of burn wound healing.

Note: 0.4mW/cm2 average (10ms/200ns=50,000) so peak would be 20W (WOW)

https://pubmed.ncbi.nlm.nih.gov/29970828/

Red (635 nm), Near-Infrared (808 nm) and Violet-Blue (405 nm) Photobiomodulation Potentiality on Human Osteoblasts and Mesenchymal Stromal Cells: A Morphological and Molecular In Vitro Study 2018

Photobiomodulation (PBM) has been used for bone regenerative purposes in different fields of medicine and dentistry, but contradictory results demand a skeptical look for its potential benefits. This in vitro study compared PBM potentiality by red (635 ± 5 nm) or near-infrared (NIR, 808 ± 10 nm) diode lasers and violet-blue (405 ± 5 nm) light-emitting diode operating in a continuous wave with a 0.4 J/cm² energy density, on human osteoblast and mesenchymal stromal cell (hMSC) viability, proliferation, adhesion and osteogenic differentiation. PBM treatments did not alter viability (PI/Syto16 and MTS assays). Confocal immunofluorescence and RT-PCR analyses indicated that red PBM (i) on both cell types increased vinculin-rich clusters, osteogenic markers expression (Runx-2, alkaline phosphatase, osteopontin) and mineralized bone-like nodule structure deposition and (ii) on hMSCs induced stress fiber formation and upregulated the expression of proliferation marker Ki67. Interestingly, osteoblast responses to red light were mediated by Akt signaling activation, which seems to positively modulate reactive oxygen species levels. Violet-blue light-irradiated cells behaved essentially as untreated ones and NIR irradiated ones displayed modifications of cytoskeleton assembly, Runx-2 expression and mineralization pattern. Although within the limitations of an in vitro experimentation, this study may suggest PBM with 635 nm laser as potential effective option for promoting/improving bone regeneration.

https://pubmed.ncbi.nlm.nih.gov/28593105/

Photobiomodulation with Near Infrared Light Helmet in a Pilot, Placebo Controlled Clinical Trial in Dementia Patients Testing Memory and Cognition 2017

Alzheimer's disease (AD) is a common, chronic expensive debilitating neurodegenerative disease with no current treatments to prevent the physical deterioration of the brain and the consequent cognitive deficits. The current pathophysiology of

Alzheimer's disease is the accumulation of neurofibrillary tangles (NFTs) of hyperphosphorylated tau protein and amyloid-beta (Aβ) plaques. Antibody therapy of Tau and Amyloid beta, vaccines and other methods to decrease Tau and or Amyloid have not been successful after considerable pharmaceutical and biotech efforts. For example, Eli Lilly announced a major change to its closely watched clinical trial for the Alzheimer's drug solanezumab which failed to reach statistical significance. Recently, a report on animal models using photomodulation with near infrared light to treat AD pathology in K369I tau transgenic model (K3) l engineered to develop neurofibrillary tangles, and the APPs/PSEN1dE9 transgenic model (APP/PS1) to develop amyloid plaques. Mice were treated with NIR 20 times over a four-week period and NIR treatment (600-1000 nm) was associated with a reduction in the size and number of amyloid-β plaques in the neocortex and hippocampus. We now report a small pilot double blind, placebo-controlled trial (n=11) 6 active, 3 controls and 2 dropouts assessing the effect of 28 consecutive, sixminute transcranial sessions of near infrared (NIR) stimulation using 1060-1080 nm light emitting diodes. Subjects were independently diagnosed with dementia conducted in an outpatient behavioral healthcare clinic. IRB approval was obtained through the Quietmind Foundation's institutional review Board (IRB). Results showed changes in executive functioning; clock drawing, immediate recall, praxis memory, visual attention and task switching (Trails A&B) as well as a trend of improved EEG amplitude and connectivity measures. Neuroplasticity has also been reported with NIR light stimulation and mitochondrial enhancement.
The experimental device used 1100 LEDs set in 15 arrays of 70 LEDs/array with all matched to 1060–1080 nm and pulsed at 10 hz with a 50% duty cycle. Stimulation was administered for 6 minutes daily over 28 consecutive days.
Delta power increase = improved alertness, attention. Alpha decrease = less anxiety
Quietmind Foundation has had experience now in several Alzheimer's patients treated with PBM adding Neurobiofeedback (NBB) with marked improvement in executive function and memory using a two year treatment protocol. Patients are being observed over 4–5 years who are showing continued cognitive and functional improvement with no medications other than vitamins and supplements for improve gut flora and chelation of heavy metals and other neurotoxins.

https://pubmed.ncbi.nlm.nih.gov/36291206/
The Transcranial Light Therapy Improves Synaptic Plasticity in the Alzheimer's Disease Mouse Model 2022
Alzheimer's disease (AD) is the main cause of dementia worldwide. Emerging non-invasive treatments such as photobiomodulation target the mitochondria to minimize brain damage, improving cognitive functions. In this work, an experimental design was carried out to evaluate the effect of transcranial light therapy (TLTC) on synaptic plasticity (SP) and cognitive functions in an AD animal model. Twenty-three mice were separated into two general groups: an APP/PS1 (ALZ) transgenic group and a wild-type (WT) group. Each group was randomly subdivided into two subgroups: mice with and without TLTC, depending on whether they would undergo treatment with TLTC. Cognitive function, measured through an object recognition task, showed non-significant improvement after TLTC. SP, on the other hand, was evaluated using four electrophysiological parameters from the Schaffer-CA1 collateral hippocampal synapses: excitatory field potentials (fEPSP), paired pulse facilitation (PPF), long-term depression (LTD), and long-term potentiation (LTP). An improvement was observed in subjects treated with TLTC, showing higher levels of LTP than those transgenic mice that were not exposed to the treatment. Therefore, the results obtained in this work showed that TLTC could be an efficient non-invasive treatment for AD-associated SP deficits.
TLTC Device
The designed TLTC device complies with fundamental characteristics to achieve neuronal stimulation, such as: optical power less than 500 mW, power density between 1 and 5 W/cm2, electromagnetic spectrum between 600 and 1100 nm [41], and light penetration into the brain no greater than 3 cm. Specifically, our device uses a radiation source in the red range (visible) and with a peak at 630 nm, which according to Hamblin (2017) [42] is the most efficient wavelength for TLTC application, leading to low power consumption, small physical size, durability, and high reliability
Light module: The module is based on the LSMCC-x4X3-LP single-color LED module. The module contains four high-power 5050SMD LEDs. Each LED has a viewing angle of 120 degrees, a wavelength of 630 nm, and 1 W of power. The coverage area of the module is 2.3 cm2. The module is powered by 12 volts and is controlled by a relay in the control unit. The light module is mounted on the top of the box. When the push button is pressed, the microcontroller turns on the relay for 125 s, turning on the light module. The TLTC device delivers a constant light intensity of 74.5 lx during the 125 s the light module is on. This corresponds to an energy equal to 100 J, an energy density of 43.5 J/cm2 , and a power density of 0.35 W/cm2.
Given that other studies showed that PBM at 630 nm generates a positive effect on the brain, we believed that a PBM for longer exposure times could emphasize the statistical differences in our behavioral results.
In general, the present study shows the beneficial effect of TLTC on neuronal plasticity in a murine model of AD, showing higher levels of LTP than those transgenic mice that were not exposed to the treatment, supporting the idea that TLTC may be a good alternative treatment for AD and associated synaptic deficit in humans. Our results also emphasize the importance of considering the use of non-pharmacological tools in AD, whose exposure times must be controlled, just as the therapeutic dose of a drug must be adjusted.

https://pubmed.ncbi.nlm.nih.gov/36447479/
Photobiomodulation and visual stimulation against cognitive decline and Alzheimer's disease pathology: A systematic review 2022
Preclinical work suggests that PBM with 640±30-nm light and visual stimulation (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.

https://www.alzheimers.gov/clinical-trials/light-and-cognitive-therapy-alzheimers-disease
What Is This Study About?
Electrical activity in the brain known as gamma brainwaves helps connect and process information throughout the brain. Research suggests that exposure to a light flickering at 40 Hz may promote gamma-wave brain activity, which could

potentially activate cells in the brain to eliminate beta-amyloid plaques that are common in Alzheimer's disease. This one-year observational study will test the ability of an iPad application, also called an app, to improve cognition, function, and quality of life in people with Alzheimer's disease. Participants will use the iPad app on a daily basis to play cognitive games (e.g., Sudoku, Tic-Tac-Toe) while being exposed to light therapy at 40 Hz. Each month, the participant's caregiver will use the app to report on the participant's functioning in daily living activities.

https://pubmed.ncbi.nlm.nih.gov/26817446/

Transcranial laser stimulation improves human cerebral oxygenation 2016

Two separate experiments were conducted in which 1,064-nm laser stimulation was administered at (1) the center and (2) the right side of the forehead, respectively. The laser emitted at a power of 3.4 W and in an area of 13.6 cm2, corresponding to 0.25 W/cm2 irradiance. Stimulation duration was 10 minutes. Nine healthy male and female human participants of any ethnic background, in an age range of 18-40 years old were included in each experiment.

Results: In both experiments, transcranial laser stimulation induced an increase of oxygenated hemoglobin concentration (Δ[HbO2]) and a decrease of deoxygenated hemoglobin concentration (Δ[Hb]) in both cerebral hemispheres. Improvements in cerebral oxygenation were indicated by a significant increase of differential hemoglobin concentration (Δ[HbD] = Δ[HbO2] - Δ[Hb]). These effects increased in a dose-dependent manner over time during laser stimulation (10 minutes) and persisted after laser stimulation (6 minutes). The total hemoglobin concentration (Δ[HbT] = Δ[HbO2] + Δ[Hb]) remained nearly unchanged in most cases.

Conclusion: Near-infrared laser stimulation applied to the forehead can transcranially improve cerebral oxygenation in healthy humans.

https://www.verywellhealth.com/bright-light-therapy-and-its-use-in-alzheimers-disease-98668

Bright Light Therapy and Its Use in Alzheimer's Disease 2023

Bright light therapy consists of regular exposure to a light anywhere from five to 30 times brighter than typical office lights. The light is placed in a box with a screen that diffuses it. The person receiving bright light therapy is asked to sit in front of the light source for a set amount of time each day.

https://getmebright.com/

In ongoing clinical trails daily exposure to 40Hz light shows dramatic improvement in sleep and cognitive function.

https://pubmed.ncbi.nlm.nih.gov/28127845/

Bright light therapy for sleep disturbance in dementia is most effective for mild to moderate Alzheimer's type dementia: a case series 2017

In this study, we explored the efficacy of BLT in the treatment of 17 participants, including those with Alzheimer's type dementia (AD) (n = 8), vascular dementia (n = 4), and dementia with Lewy bodies (n = 5). Patients sat in front of the light box for 1 h/day from 0900 to 1000. The patients underwent treatment every day for 2 weeks.

Results: BLT led to the improvement of sleep disturbance in four participants, all of whom were AD patients. The four AD patients showed a shorter duration of illness and/or had mild to moderate AD.

Conclusion: BLT could be an effective strategy for treating dementia patients, depending on their type and grade of their dementia. To confirm this hypothesis, it would be necessary to study a larger number of cases. Non-pharmacological therapies for sleep disorders should be emphasized as a safe form of treatment for patients with dementia.

https://pubmed.ncbi.nlm.nih.gov/35891052/

Tunable White Light for Elders (TWLITE): A Protocol Demonstrating Feasibility and Acceptability for Deployment, Remote Data Collection, and Analysis of a Home-Based Lighting Intervention in Older Adults 2022

Sleep disturbances are common in older adults and may contribute to disease progression in certain populations (e.g., Alzheimer's disease). Light therapy is a simple and cost-effective intervention to improve sleep. Primary barriers to light therapy are: (1) poor acceptability of the use of devices, and (2) inflexibility of current devices to deliver beyond a fixed light spectrum and throughout the entirety of the day. However, dynamic, tunable lighting integrated into the native home lighting system can potentially overcome these limitations. Herein, we describe our protocol to implement a whole-home tunable lighting system installed throughout the homes of healthy older adults already enrolled in an existing study with embedded home assessment platforms (Oregon Center for Aging & Technology-ORCATECH). Within ORCATECH, continuous data on room location, activity, sleep, and general health parameters are collected at a minute-to-minute resolution over years of participation. This single-arm longitudinal protocol collected participants' light usage in addition to ORCATECH outcome measures over a several month period before and after light installation. The protocol was implemented with four subjects living in three ORCATECH homes. Technical/usability challenges and feasibility/acceptability outcomes were explored. The successful implementation of our protocol supports the feasibility of implementing and integrating tunable whole-home lighting systems into an automated home-based assessment platform for continuous data collection of outcome variables, including long-term sleep measures. Challenges and iterative approaches are discussed. This protocol will inform the implementation of future clinical intervention trials using light therapy in patients at risk for developing Alzheimer's disease and related conditions.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4168854/

Tailored lighting intervention improves measures of sleep, depression, and agitation in persons with Alzheimer's disease and related dementia living in long-term care facilities 2014

Conclusion: A lighting intervention, tailored to increase daytime circadian stimulation, can be used to increase sleep quality and improve behavior in patients with ADRD.

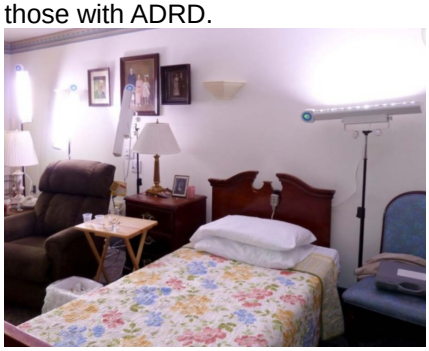
Several studies have found that exposure to bright white light (at least 2,500 lux and as high as 8,000 lux at the cornea) for at least 1 hour in the morning for a period of at least 2 weeks consolidated rest–activity patterns in ADRD patients, resulting in greater nighttime sleep duration and sleep efficiency, and more wakefulness during daytime hours.2–4 Unattended exposure to

bright white light (>1,000 lux at the cornea) during the entire day was shown to improve rest–activity patterns of ADRD patients.5 Data from Riemersma-van der Lek et al6 showed, in the largest randomized placebo-controlled, double-blind study ever conducted with this population, that high levels of unattended exposures to white light (>2,500 lux at the cornea) could not only improve sleep but also slow down cognitive decline in ADRD patients.

Recent research has shown that the human circadian system is maximally sensitive to short-wavelength (blue) light, with peak wavelength close to 460 nanometers (nm).18–20 This finding opens the door for the potential application of lower, more targeted light levels in therapeutic settings. Using this knowledge, two pilot studies showed that evening exposure to 2 hours of short-wavelength light (30 lux at the cornea) from light-emitting diodes (LEDs) peaking at 470 nm consolidated rest–activity rhythms and increased the sleep efficiency of persons with ADRD.21,22 However, delivering light to ADRD patients via light boxes or light goggles is a challenge and would likely have low compliance rates.

A logical compromise solution would be to illuminate the occupied room with a white light source with a high proportion of short-wavelength radiation delivering lower corneal photopic light levels than those previously employed.5,6,17,23 Although studies have shown that short-wavelength light or “blue-enriched” light sources can be effective at correcting circadian sleep disorders,24,25 other studies failed to show differences between lamps of different correlated color temperatures (CCTs). Smith and Eastman26 compared the effectiveness of a 17,000 K lamp and a 4,100 K lamp in phase shifting the human circadian clock, under controlled laboratory conditions. The researchers did not find any significant differences between the light sources, most likely because they were using light levels above the saturation response of the circadian system. In fact, calculations performed using the model of human circadian phototransduction by Rea et al19 showed that both light sources should have the same impact on acute melatonin suppression. Therefore, from the studies to date, it has not been empirically demonstrated that white light sources with more short-wavelength content delivered at lower light levels than the ones used in previous studies can be as or more efficacious at treating circadian sleep disorders in ADRD patients.

The present study was designed to investigate the efficacy and feasibility of a tailored lighting intervention designed to deliver high circadian stimulation at moderate light levels from a high-CCT white light source.19 The lighting intervention illuminated the occupied room during daytime hours and was energized for 8–10 hours per day. The combined effect of a high-CCT lamp delivering moderately high light levels was calculated to be 40 times more effective at stimulating the circadian system than the lighting conditions commonly found in facilities for the elderly, where low-CCT sources deliver low light levels. Importantly, the plug-in luminaires used in the present study were inexpensive and easy to install. It was hypothesized that the lighting intervention would improve objective and subjective measures of sleep as well as reduce depression and agitation scores in those with ADRD.



https://pubmed.ncbi.nlm.nih.gov/31855161/

Effects of a Tailored Lighting Intervention on Sleep Quality, Rest-Activity, Mood, and Behavior in Older Adults With Alzheimer Disease and Related Dementias: A Randomized Clinical Trial 2019

Study objectives: We investigated the effectiveness of a lighting intervention tailored to maximally affect the circadian system as a nonpharmacological therapy for treating problems with sleep, mood, and behavior in persons with Alzheimer disease and related dementias (ADRD).

Methods: This 14-week randomized, placebo-controlled, crossover design clinical trial administered an all-day active or control lighting intervention to 46 patients with ADRD in 8 long-term care facilities for two 4-week periods (separated by a 4-week washout). The study employed wrist-worn actigraphy measures and standardized measures of sleep quality, mood, and behavior.

Results: The active intervention significantly improved Pittsburgh Sleep Quality Index scores compared to the active baseline and control intervention (mean ± SEM: 6.67 ± 0.48 after active intervention, 10.30 ± 0.40 at active baseline, 8.41 ± 0.47 after control intervention). The active intervention also resulted in significantly greater active versus control differences in intradaily variability. As for secondary outcomes, the active intervention resulted in significant improvements in Cornell Scale for Depression in Dementia scores (mean ± SEM: 10.30 ± 1.02 at baseline, 7.05 ± 0.67 after active intervention) and significantly greater active versus control differences in Cohen-Mansfield Agitation Inventory scores (mean ± SEM: -5.51 ± 1.03 for the active intervention, -1.50 ± 1.24 for the control intervention).

Conclusions: A lighting intervention tailored to maximally entrain the circadian system can improve sleep, mood, and behavior in patients with dementia living in controlled environments.

https://onlinelibrary.wiley.com/doi/abs/10.1002/1099-1166%28200101%2916%3A1%3C106%3A%3AAID-GPS288%3E3.0.CO%3B2-9

Bright light therapy and melatonin in motor restless behaviour in dementia: a placebo-controlled study 2001

All subjects were exposed during 2×5 consecutive days for 30 minutes to 10,000 lux bright light and randomly administered 2.5 mg melatonin or placebo at 22.00 h.

Results: Six demented inpatients completed the trial. Positive effects were found for the treatment combined with placebo. Patients were less restless and more co-operative. The condition with melatonin showed no additional positive effects, additionally, patients became more aggressive and showed the same or more disturbed behaviour.
Conclusions: Bright light therapy has a positive effect on motor restless behaviour. Light therapy in combination with melatonin has no positive effects. The results might be explained by a possible overshoot of chronobiological synchronisation or the timing of the melatonin intake.

https://www.alzheimers.org.uk/about-dementia/treatments/alternative-therapies/light-therapy-and-dementia
A small number of studies have suggested that bright light therapy may be beneficial for people with dementia. One small but well-conducted study showed promising effects of bright light therapy on restlessness and disturbed sleep for people with dementia.
A large and well-conducted research review found that bright light therapy can result in less daytime sleeping and increased night-time sleeping.
Current findings indicate that bright light therapy may beneficial for people with dementia. However, there are a limited number of studies, and most include a small number of people. Further research is therefore needed before we can come to make any definitive conclusions.

https://pubmed.ncbi.nlm.nih.gov/34870676/
Association Between Cataract Extraction and Development of Dementia 2022
Results: In total, 3038 participants were included (mean [SD] age at first cataract diagnosis, 74.4 (6.2) years; 1800 women (59%) and 1238 men (41%); and 2752 (91%) self-reported White race). Based on 23 554 person-years of follow-up, cataract extraction was associated with significantly reduced risk (hazard ratio, 0.71; 95% CI, 0.62-0.83; P < .001) of dementia compared with participants without surgery after controlling for years of education, self-reported White race, and smoking history and stratifying by apolipoprotein E genotype, sex, and age group at cataract diagnosis. Similar results were obtained in marginal structural models after adjusting for an extensive list of potential confounders. Glaucoma surgery did not have a significant association with dementia risk (hazard ratio, 1.08; 95% CI, 0.75-1.56; P = .68). Similar results were found with the development of Alzheimer disease dementia.

https://pubmed.ncbi.nlm.nih.gov/32538850/
Association of Glaucoma and Cataract with Incident Dementia: A 5-Year Follow-Up in the Shanghai Aging Study 2020
Conclusion: Glaucoma is an independent risk factor of incident dementia and AD. The comorbidity of glaucoma and cataract may significantly increase the risk of dementia and AD.

https://pubmed.ncbi.nlm.nih.gov/33788406/
Ophthalmic conditions associated with dementia risk: The Cardiovascular Health Study 2021
Methods: Diagnoses of cataracts, age-related macular degeneration (AMD), diabetic retinopathy (DR), and glaucoma were based on medical histories and International Classification of Diseases, Ninth Revision (ICD-9) codes for 3375 participants from the Cardiovascular Health Study. Dementia, including Alzheimer's disease (AD) and vascular dementia (VaD), was classified using standardized research criteria.
Results: Cataracts were associated with AD (hazard ratio [HR] = 1.34; 95% confidence interval [CI] = 1.01-1.80) and VaD/mixed dementia (HR = 1.41; 95% CI = 1.02-1.95). AMD was associated with AD only (HR = 1.87; 95% CI = 1.13-3.09), whereas DR was associated with VaD/mixed dementia only (HR = 2.63; 95% CI = 1.10-6.27).
Discussion: Differential associations between specific ophthalmic conditions and dementia subtypes may elucidate pathophysiologic pathways. Lack of association between glaucoma and dementia was most surprising from these analyses.

https://www.nia.nih.gov/news/cataract-removal-linked-reduction-dementia-risk
Cataract removal linked to a reduction in dementia risk 2022
Researchers found that participants who underwent cataract removal surgery had nearly 30% lower risk of developing dementia compared with participants without surgery, even after controlling for numerous additional demographic and health risks.

https://link.springer.com/article/10.1007/s10654-014-9903-6
Cataract may be a non-memory feature of Alzheimer's disease in older people 2014
The overall incidence of Alzheimer's disease was 1.21 per 1,000 person-years in the cataract group and 0.73 per 1,000 person-years in the non-cataract group (crude hazard ratio 1.62, 95 % CI 1.28, 2.04). After adjustment for potential confounders, the adjusted HR of Alzheimer's disease was 1.43 (95 % CI 1.13, 1.82) for the cataract group, compared to the non-cataract group. Male (HR 1.36, 95 % CI 1.09, 1.70), age (every 1 year, HR 1.08, 95 % CI 1.06, 1.10) and head injury (HR 1.79, 95 % CI 1.08, 2.96) were other factors significantly associated with Alzheimer's disease. Older people with cataract are at 1.43-fold increased risk of developing Alzheimer's disease. More research is necessary to determine whether cataract is one of non-memory features of Alzheimer's disease.

https://pubmed.ncbi.nlm.nih.gov/8247229/
Incomplete achromatopsia in Alzheimer's disease 1993
We report that patients with Alzheimer's disease (AD) have a selective deficit in blue hue discrimination, as assessed with three clinical measures of color vision. The Farnsworth D-15 Test, the Lanthony New Color Test, and the City University Color Vision Test were administered to 32 patients with AD (ranging in dementia severity from mild to severe) and 32 age-matched normal control subjects (NCS). Of the AD patients, 11 who were representative of the larger group for age, education level, and dementia severity received a complete neuro-ophthalmological examination that ruled out obvious disorders of the anterior visual structures. AD patients made significantly more tritan (blue) errors than NCS on all three color vision tests but did not make more protan (red) or deutan (green) errors on two of the three tests. The results support the conclusion that there is a deficit in color discrimination in AD that is specific to blue hues, and oppose the hypothesis that AD does not deleteriously

affect the color-opponent visual channel. In the absence of obvious damage to anterior visual structures, the likely substrates for the observed deficit are peristriate and inferotemporal visual cortices, which are subject to significant neuropathology in AD.

https://pubmed.ncbi.nlm.nih.gov/35579902/

The Association Between Acquired Color Deficiency and PET Imaging of Neurodegeneration in Mild Cognitive Impairment and Alzheimer Disease 2022

Results: Patients with AD presented higher mean values indicating poorer color discrimination for protan (P = 0.04) and deutan (P = 0.001) axes compared with the controls. Along the tritan axis, both patients with AD and patients with MCI showed decreased color vision (P = 0.001 and P = 0.001) compared with controls. The analyses from the HF-ERG protocol revealed no differences between the groups (P = 0.31 and P = 0.41). Diffuse color vision loss was found in individuals with signs of neurodegeneration (protan P = 0.002, deutan P = 0.003 and tritan P = 0.01), but not in individuals with signs of β-amyloid deposition only (protan P = 0.39, deutan P = 0.48, tritan P = 0.63), regardless of their clinical classification.
Conclusions: Here, patients with AD and patients with MCI present acquired color vision deficiency that may be linked with impaired brain metabolism.

https://pubmed.ncbi.nlm.nih.gov/18331219/

Color vision in the tritan axis is predominantly affected at high altitude 2008

The purpose of this study was to evaluate color vision during high altitude mountain climbing by applying the Mollon-Reffin Minimalist test to 14 climbers, all of whom were participating in the expedition to Ama Dablam (6,812 m) in Nepal. Before leaving for Nepal (at 300 m), all 28 eyes showed normal color vision in all 3 axes. At 1,300 m, 100% of eyes showed normal color vision in the protan and deutan axes, while 25% showed minimally reduced color discrimination in the tritan axis. At 4,000 m, 100% showed normal deutan axis, 4% minimally reduced protan axis, and 72% minimally reduced tritan axis discrimination. At 5,400 m 100% of eyes tested showed normal protan and deutan axis discrimination, while 75% showed minimally and 25% moderately reduced tritan axis discrimination. Back home at 300 m 3 days after return, 100% showed normal deutan, 4% minimally reduced protan, and 38% minimally reduced tritan axis discrimination. One year later, all eyes showed normal color vision in all three axes. Changes in tritan axis discrimination correlated well with increased heart rate (r = 0.69; p = 0.0001) and decreased oxygen saturation (r = 0.71; p = 0.001) at high altitude. This study shows that the tritan color vision axis is predominantly affected at high altitude, but that this reduced color discrimination is transient.

https://pubmed.ncbi.nlm.nih.gov/20733026/

Effects on colour discrimination during long term exposure to high altitudes on Mt Everest 2010

Conclusions: Chronic hypoxia induced by high altitude exposure transiently affects colour discrimination, in particular tritan axis discrimination. Decreased tritan discrimination is partly reversible upon physiological adaptation to high altitude and completely normalised upon return to low altitude.