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Recent advances in near-infrared photobiomodulation for the intervention of acquired brain injury

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Acquired brain injury (ABI) is an injury that affects the brain structure and function. Traditional ABI treatment strategies, including medications and rehabilitation therapy, exhibit their ability to improve its impairments in cognition, emotion, and physical activity. Recently, near-infrared (NIR) photobiomodulation (PBM) has emerged as a promising physical intervention method for ABI, demonstrating that low-level light therapy can modulate cellular metabolic processes, reduce the inflammation and reactive oxygen species of ABI microenvironments, and promote neural repair and regeneration. Preclinical studies using ABI models have been carried out, revealing the potential of PBM in promoting brain injury recovery although its clinical application is still in its early stages. In this review, we first inspected the possible physical and biological mechanisms of NIR-PBM, and then reported the pathophysiology and physiology of ABI underlying NIR-PBM intervention. Therefore, the potential of NIR-PBM as a therapeutic intervention in ABI was demonstrated and it is also expected that further work can facilitate its clinical applications.

Keywords: Near-infrared photobiomodulation; acquired brain injury; traumatic brain injury; ischemic stroke.

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1. Introduction

Acquired brain injury (ABI) encompasses any form of brain damage resulting from traumatic or non-traumatic incidents like traumatic brain injury (TBI), stroke, neoplasm, infection, and anoxia.[1,2] These injuries can result in devastating consequences, causing cognitive, motor, and behavioral impairments that might have profound impact on the patient's quality of life.[2–5] With the greatest population in the world, China's absolute numbers of patients with TBI and stroke exceed those of most other nations, imposing a significant burden on society and families.[6,7] Despite advancements in medical care, effective treatments for ABI remain very limited, highlighting the urgent need for the development of innovative therapeutic methods.

Photobiomodulation (PBM), also known as low-level laser therapy (LLLT), has the ability to induce biochemical changes,[8] reduce the inflammation,[9] and promote tissue regeneration by activating cellular signaling pathways and modulating gene expression.[10,11] The noninvasive and low-intensity light therapy makes PBM an attractive candidate for therapeutic use in the intervention of brain disorders including psychiatric disorders and neurodegenerative diseases.[12,13] More importantly, PBM is now approved by the U.S. Food and Drug Administration (FDA) for stimulating healing. Besides, previous research has used PBM to enhance human cognitive performance. Improved inhibition and cognitive flexibility were observed in healthy individuals,[14] while patients with traumatic brain injury showed improvements in executive function.[15,16] Therefore, PBM can promote damage repair and cognitive improvement in patients with ABI.

Near-infrared photobiomodulation (NIR-PBM) is based on the interaction between near-infrared (NIR) light (700–1100 nm) and biological tissues through the mitochondrial respiratory chain. In particular, NIR-PBM has exhibited its obvious efficacy for the intervention of various categories of ABI.[17–21] The unique properties of near-infrared light, including its ability to penetrate deep into tissue and its minimal risk of adverse effects, make it an attractive candidate for therapeutic use in neurological disorders such as stroke and various categories of ABI.[22–26] Herein, we aim to provide a comprehensive overview on the recent work on NIR-PBM as a therapeutic modality for the treatment of ABI.

2. The Biological Mechanism of Near-Infrared Photobiomodulation Therapy

NIR-PBM is able to irritate brain parenchyma with multifaceted effects, eliciting immediate cascades of key signaling regulatory molecules through evoked local and distant systemic responses. Previous studies showed that cytochrome c oxidase plays an important role in mediating the effects of PBM. In particular, low-intensity NIR light stimulation is able to prompt the dissociation of inhibitory nitric oxide from the enzyme, thereby facilitating electron transport and ATP synthesis. This cascade potentiates mitochondrial membrane potential, augments ATP production, and engenders the expression of transcription factors pivotal in governing gene expression, protein synthesis, and diverse cellular and tissue functions.[27,28] Currently, NIR-PBM shows the ability to modulate Meningeal lymphatic vessels (mLVs) drainage and attenuate cognitive decline in aged mice and Alzheimer's disease (AD) mice.[29] Importantly, the local responses underlying NIR-PBM consist of a number of therapeutic effects[23–30]: (1) augmentation of intracellular adenosine triphosphate (ATP) generation; (2) enhancement of mitochondrial function; (3) mitigation of oxidative stress; (4) attenuation of neuroinflammation; (5) facilitation of synaptogenesis and restoration of damaged synaptic connections; (6) induction of neurotrophic factors and promotion of neurogenesis; and (7) instigation of angiogenesis (Fig. 1(B)).

Interestingly, the therapeutic effects of NIR-PBM are due to the optical absorption of cytochrome c oxidase. NIR light can prompt redox changes within cytochrome c oxidase, thereby initiating intracellular signaling cascades that positively modulate mitochondrial function and confer intracellular protection through the upregulation of cytoprotective factors (Fig. 1(B)).[30–32] Besides, NIR light is able to facilitate the expression and accumulation of antioxidants and cytoprotective factors,[33] with gene profile analyses revealing the promotion of noncoding RNAs (ncRNAs) under its influence,[34] thereby delineating a compelling avenue for further investigation into the role of noncoding sequences. Further, NIR light exerts robust neuroprotective effects, facilitating functional restoration and improvement in damaged cortical regions through enhancements in mitochondrial function,

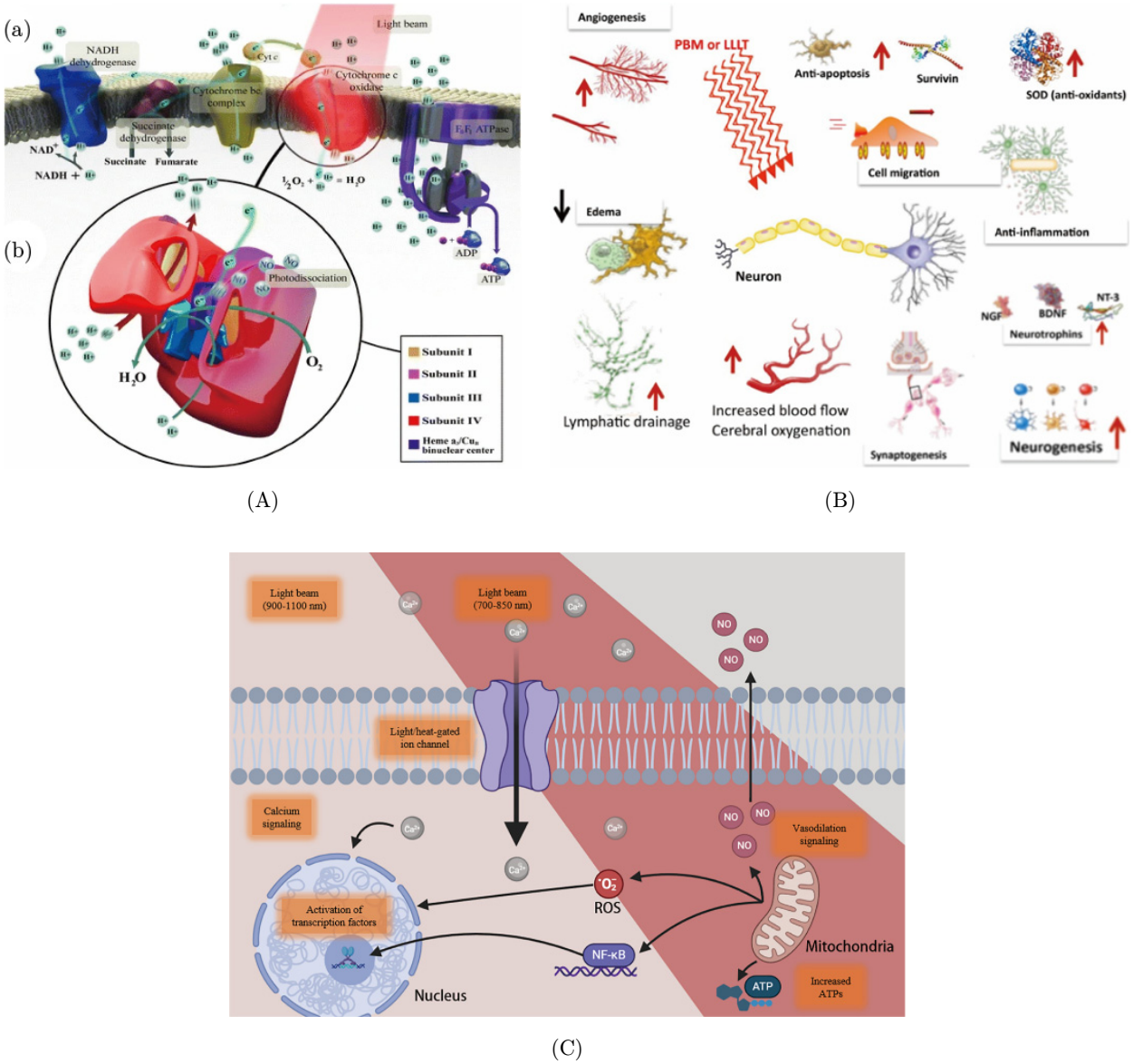

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Fig. 1. (A) The underlying mitochondrial biological mechanism of PBM. (B) Brain-focused mechanisms of transcranial PBM. (C) Mechanisms of NIR-PBM at the cellular and molecular levels.

augmenting blood flow to injured neurons, and amplifying cell survival factors (Fig. 1(C)).

To sum up, NIR-PBM can reduce inflammation and neuronal mortality, enhance neurotrophic factor expression and neural progenitor cell proliferation, and overexpress protrusion proteins to enhance the cognitive performances in ABI patients.[13] Additionally, NIR-PBM has been shown by electroencephalography (EEG) and magnetoencephalography (MEG) to influence neurophysiological activity both locally and in distant cortical regions.[35–37] Another research indicated that NIR-PBM can modulate brain connectivity to improve cognitive function in ABI patients, which can be detected in functional magnetic resonance imaging (fMRI).[13,15,16,38]

3. Pathophysiology of Acquired Brain Injury

Since ABI is characterized by distinct pathophysiological mechanisms, it is essential to inspect the underlying processes for developing effective therapeutic interventions. ABI consists of two primary

categories: traumatic brain injury (TBI) and non-traumatic brain injury (non-TBI) (Figs. 2(A) and 2(B)).[2,32–34] TBI is caused by external traumatic incidents while non-TBI is due to internal pathological processes causing similar brain tissue impairments. Interestingly, various factors contribute to TBI such as motor vehicle accidents, falls, sports-related incidents, and acts of violence. By contrast, non-TBI can be instigated by events such as strokes, neoplasms, infections, and oxygen deprivation.[2] Likewise, clinical outcomes of ABI exhibit considerable diversity, affected by both the specific disease mechanisms and demographic factors such as age, genetic predispositions, and, socioeconomic status.

3.1. *Traumatic brain injury*

TBI resulting from external mechanical forces shows primary and secondary injury cascades.[41] Intracranial bleeding, diffuse axonal damage, and localized contusions are examples of primary injuries that occur at the time of impact. The mechanisms for secondary damage transpire in the hours to days following the original insult and include a multifaceted interaction between neuroinflammation, excitotoxicity, oxidative stress, and altered cerebral blood flow.[42,43] These processes exacerbate neuronal injury, demonstrating long-term neurological deficits.

3.2. *Ischemic stroke*

Ischemic stroke arises from impaired cerebral blood flow, depriving neurons of oxygen and nutrients. Numerous harmful events, such as energy failure, excitotoxicity, oxidative stress, and inflammation, are a part of the ischemia cascade.[44,45] The most prevalent kind of ischemic brain damage, ischemic stroke, is caused by thrombotic or embolic blockage of the cerebral arteries.[46] Subsequent neuronal death and tissue damage occur in the core ischemic zone, while surrounding regions undergo a cascade of molecular and cellular changes, termed the penumbra, which may be salvageable with timely intervention.[47,48]

3.3. *Other forms of acquired brain injury*

In addition to TBI and ischemic stroke, ABI encompasses a variety of other insults, including anoxia, epidural or subdural hematomas and subarachnoid hemorrhage, infection and neoplasm.[2,49–51] Each condition is characterized by distinct pathophysiological mechanisms, yet shares common themes of neuronal injury, inflammation, and impaired neuroplasticity.

3.4. *Challenges in treatment*

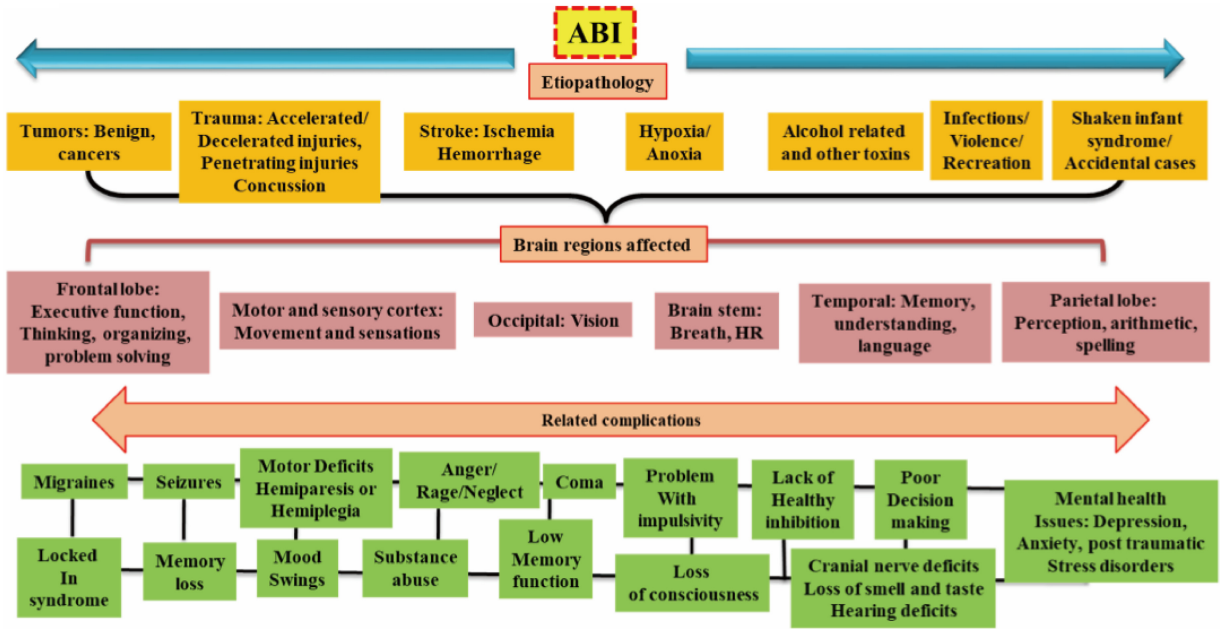
Despite advances in acute care and rehabilitation, treatment options for ABI remain limited. Most of the therapeutic strategies target specific aspects of the injury cascade, such as reducing intracranial pressure or restoring cerebral perfusion. However, challenges persist in translating preclinical findings into effective clinical interventions, highlighting the need for innovative approaches to address the multifaceted nature of ABI pathophysiology.[52]

4. Potential Mechanisms of NIR-PBM in ABI

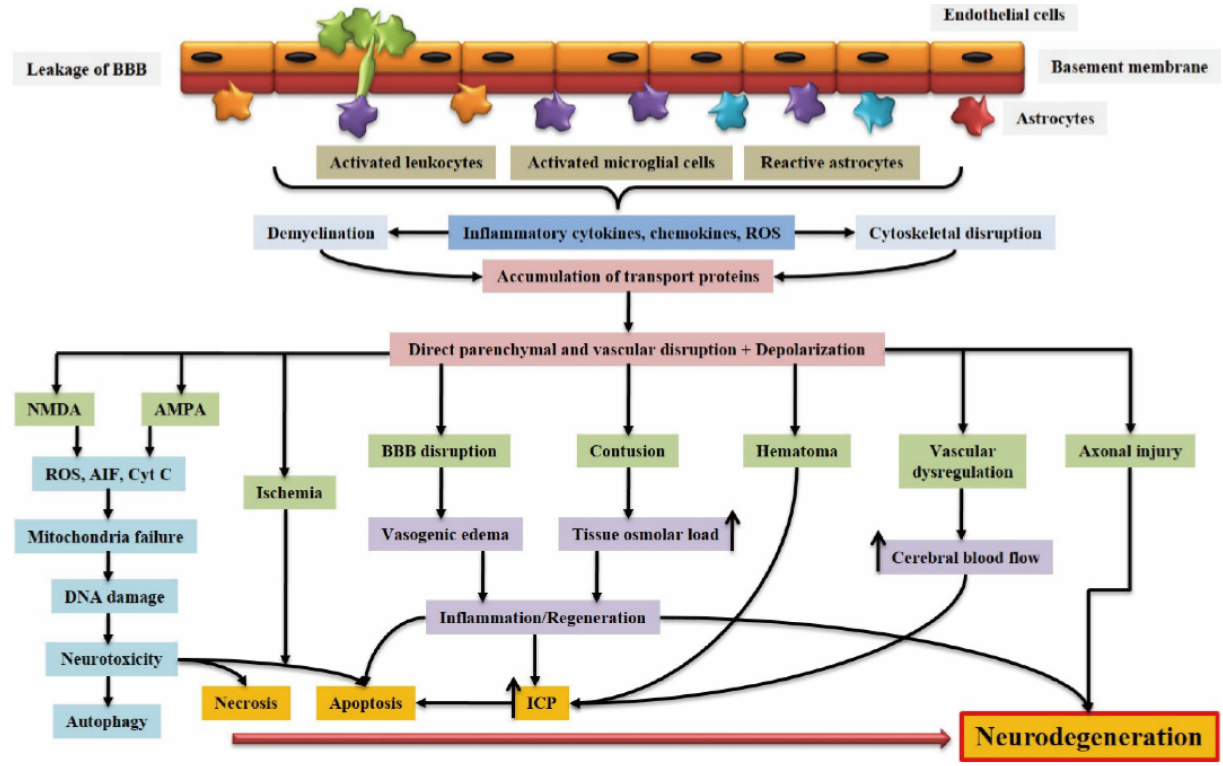
NIR-PBM has shown promising results in the treatment of acquired brain injuries, but the exact mechanisms behind its effectiveness are yet not fully understood. One potential mechanism of action is the stimulation of mitochondrial function through the absorption of photons by cytochrome c oxidase, leading to increased ATP production and improved cellular energy metabolism.[29] In addition, NIR-PBM shows its ability to reduce inflammation and oxidative stress in the brain, which are common factors in ABI pathophysiology. Further, NIR-PBM may also promote neurogenesis and synaptogenesis, leading to improved neuronal connectivity and function.[53]

4.1. *Mitochondrial function and energy metabolism*

Mitochondrial function and energy metabolism stand as central focal points through which NIR-PBM exerts its effects. NIR light, absorbed by chromophores within the mitochondria, orchestrates a series of events culminating in heightened adenosine triphosphate (ATP) production, augmented mitochondrial respiration, and enhanced cellular energy metabolism.[54] This restoration of mitochondrial function holds promise for mitigating cellular dysfunction and fostering neuronal survival post-injury.



(a)



(b)

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Fig. 2. (a) ABI: Etiopathology, classifications, the brain region affected, and related complications. (b) Schematic representation of pathophysiology of ABI.

Extensive investigations across diverse cell types underscore the efficacy of PBM in bolstering mitochondrial function and metabolic equilibrium.[55] Given the abundant mitochondrial density in neuronal tissues, exposure to light precipitates the activation of cytochrome c oxidase (CCO), thereby enhancing energy metabolism via increased oxygen consumption and subsequent ATP generation.[56,57]

The complex effects of NIR light on neuronal ATP production have been outlined in earlier research. *In vitro* experiment has demonstrated significant restoration of ATP levels in potassium cyanide (KCN)-treated neurons following exposure to NIR-PBM by 770 nm, 830 nm, and 880 nm LED sources.[31] Moreover, as shown in Fig. 3(A), in SH-SY5Y cells, NIR laser PBM at 970 nm elicited a notable increase in ATP production on days 2 and 4.[58] Complementing these findings, numerous *in vivo* investigations have affirmed the capacity of NIR-PBM to augment cerebral ATP production across other neuropathological models.[59,60]

The restoration of mitochondrial membrane potential (MMP) is crucial in alleviating cellular dysfunction, as evidenced by its key role in ATP generation. Studies showed promising efficacious of NIR-PBM in MMP restoration in pink1 mutant Drosophila fruit flies.[61] Furthermore, in a variety of animal models, transcranial laser PBM at around 810 nm has shown the capacity to restore cerebral MMP.[62,63] Notably, the quantity and efficiency of mitochondria in neurons are directly linked to the preservation of regular respiration and ATP synthesis in the brain. Investigations have revealed that both short and long-term exposure to 810 nm laser PBM can increase mitochondrial number and function within brain tissue.[21,60]

4.2. *Anti-inflammatory, antioxidant and anti-apoptotic effects*

One significant advantage of PBM lies in its potent anti-neuroinflammatory properties. NIR-PBM has demonstrated efficacy in attenuating neuroinflammation by suppressing the expression of pro-inflammatory cytokines and modulating microglial activation.[64] Notably, an 808 nm laser PBM, administered at lower fluences ranging from 0.2 J/cm^2 to 10 J/cm^2, has been shown to induce the expression of M2 polarization markers such as CD206, in BV2 microglia.[65] Moreover, a plethora of studies has corroborated the anti-neuroinflammatory effects of NIR-PBM across various animal models of TBI.[66]

Additionally, NIR-PBM's antioxidant qualities may provide neuroprotection by efficiently scavenging reactive oxygen species (ROS) and reducing oxidative stress. *In vitro* studies have underscored the neuroprotective efficacy of PBM against ROS-induced neurotoxicity, particularly against damage instigated by hydrogen peroxide (H_2O_2) and potassium cyanide (KCN) (Fig. 3(B)).[30,67] Additionally, in various animal models, PBM has demonstrated the ability to bolster cerebral antioxidant defense systems, further enhancing its neuroprotective potential.[62]

Apoptosis represents a pivotal pathophysiological mechanism implicated in a myriad of brain injuries and disorders. Notably, an 810 nm laser PBM intervention has exhibited significant mitigation of neuronal apoptosis induced by oxygen-glucose deprivation (OGD) via regulation of protein level in cell death/survival pathways such as Akt, p-Akt and Bcl-2, coupled with reduction of NO level (Figs. 3(C) and 3(D)).[68] Some *in vivo* studies have reported the attenuation of apoptosis in models of TBI[24] and cerebral ischemia.[62]

4.3. *Neurotrophic factors and neurogenesis*

Neurotrophic factors, a pivotal family of proteins, play integral roles in fostering the growth, viability, and differentiation of neurons.[69] Among the primary members of this family are Brain-Derived Neurotrophic Factor (BDNF), Glial Cell-Derived Neurotrophic Factor (GDNF), and Neuronal Growth Factor (NGF).[70] BDNF, notably, exhibits the capability to enhance the expression of Growth-Associated Protein 43 (GAP-43), a crucial regulator involved in neurite growth cone extension.[71] GDNF is expressed by various cellular entities including astrocytes, neurons and microglia. It exerts neuroprotective effects primarily on dopaminergic neurons.[72] The upregulation of BDNF and NGF expression is thought to underpin the basement of synaptogenesis and neurogenesis.[70]

The pioneering *in vitro* evidence showcasing the efficacy of 810 nm laser PBM in augmenting BDNF and GDNF expression has profound implications. This elevation in neurotrophic factor levels

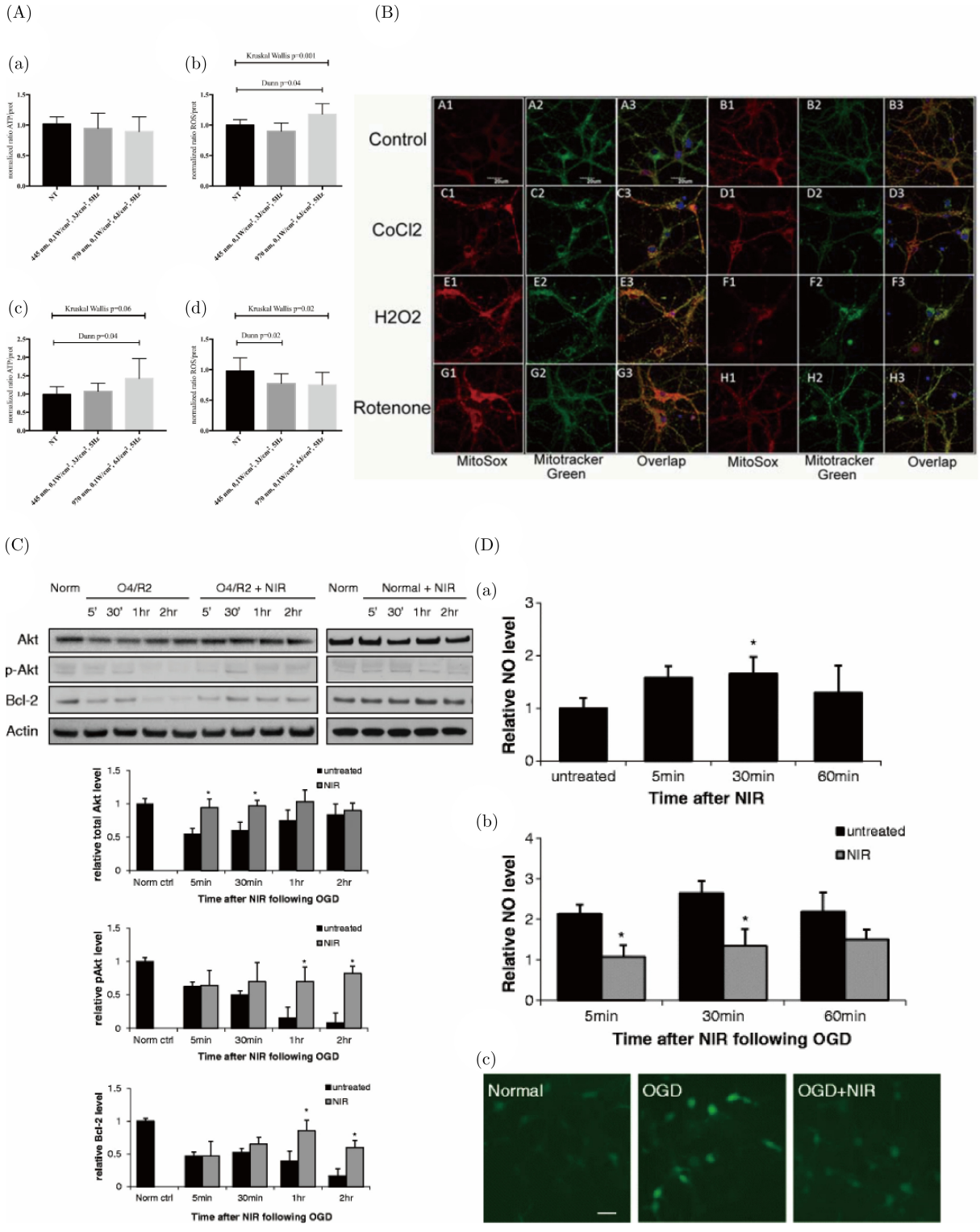

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Fig. 3. (A) Reactive oxygen species (ROS) and ATP generation in SH-SY5Y cells treated with 445-nm and 970-nm wavelengths in comparison to untreated cells on days 2 and 4. (B) Representative images of cortical neurons in different treatment groups. Mitochondrial ROS was shown by MitoRox (red), mitochondrial colocalization was shown by Mitotracker green, and nuclei was shown by Hoescht (blue) which can be observed in triple overlay. (C) Effects of NIR on pivotal cell death/survival signaling pathways. Representative Western blot images and quantitation of p-Akt and Bcl-2 protein levels following Oxygen Glucose Deprivation (OGD) and NIR. (D) Effects of NIR on Nitric Oxide (NO) production in primary cultured mouse cortical neurons.

correlates with an increased proliferation of olfactory ensheathing cells.[73] In murine models of TBI, Hamblin and colleagues demonstrated that transcranial 810 nm laser PBM robustly promotes neurogenesis, enhancing the migration and differentiation of neural progenitor cells.[74–77] Additionally, higher levels of BDNF expression were noted in areas including the subventricular zone and dentate gyrus, which coincided with the cortical stimulation of synaptogenesis and neurogenesis.[74] Anders *et al.* compared the treatment outcomes of different parameters for 810 nm and 980 nm lasers using an *in vitro* model, and subsequently confirmed that PBM could enhance axonal regrowth in a rabbit mode.[78] PBM significantly increased cortical neurogenesis while maintaining the survival of developing neurons in a photothrombotic rat paradigm that mimics an ischemic stroke. Furthermore, PBM promoted synaptogenesis in recently created cortical neurons.[64]

4.4. *Cerebral blood flow and angiogenesis*

NIR-PBM enhances cerebral blood flow (CBF) and promotes angiogenesis, both crucial for mitigating neuronal damage and promoting recovery in acquired brain injury. By inducing vasodilation through nitric oxide release and reducing vascular resistance, NIR-PBM improves blood flow to injured brain regions.[79] This enhanced CBF ensures an adequate supply of oxygen and nutrients while facilitating the removal of metabolic waste, crucial for neuronal survival.[80] Additionally, NIR-PBM stimulates angiogenesis by upregulating angiogenic growth factors like VEGF and bFGF, activating endothelial cells, and remodeling the extracellular matrix.[81] These processes promote the formation of new blood vessels, further improving blood supply to the affected areas. The combined effects of enhanced CBF and angiogenesis create a favorable environment for neuroprotection and neurogenesis, supporting the brain's natural repair mechanisms and significantly contributing to the therapeutic potential of NIR-PBM in treating ABI.[82,83]

In summary, NIR-PBM represents a novel therapeutic approach that capitalizes on the unique properties of NIR light to modulate cellular function and promote tissue repair. By elucidating the fundamental principles and mechanisms of NIR-PBM, we can gain insight into its therapeutic potential for neurological disorders such as ABI. Subsequent sections will explore the application of NIR-PBM in the context of ABI, including preclinical studies, clinical applications, and future directions for research and translation.

5. Current Applications of NIR-PBM

The promising therapeutic effects of near-infrared photobiomodulation in preclinical studies have spurred interest in its clinical application for acquired brain injury. This section reviews existing clinical research and case reports, evaluating the effectiveness and safety of NIR-PBM in human populations with ABI.

5.1. *Traumatic brain injury*

Current applications of NIR-PBM in TBI are summarized in Table 1. The initial use of NIR-PBM in an animal model of traumatic brain injury was documented by Oron *et al.*[84] A transcranial 808-nm Ga-As diode laser was utilized 4 h post-trauma to illuminate the entire brain cortex, resulting in a significant long-term functional neurological improvement in TBI. Regarding the PBM parameter, various groups conducted different studies. Oron *et al.* further explored the effects of continuous wave (CW) or pulsed wave (PW) mode using an 808-nm Ga-As diode laser and determined that the pulsed laser mode at 100 Hz is the optimal choice for TBI treatment.[85] Ando *et al.* concluded that an 810 nm Ga-Al-As diode laser pulsed at 10-Hz was the most effective approach based on improvements in NSS and body weight.[86] Additionally, they observed that PBM could reduce brain lesion volume and exhibit an antidepressant effect in forced swim and tail suspension tests. Wu *et al.* compared the treatment effects of PBM in TBI mice using different wavelengths (Figs. 4(A) and 4(B)).[87] They discovered that 665 nm and 810 nm (excluding 730 nm and 980 nm) provided benefits for TBI.

Several studies have explored the underlying mechanisms. Moreira *et al.* discovered that PBM can impact TNF-α, IL-1β, and IL-6 levels in the brain and circulation within the initial 24 h following cryogenic brain injury.[88] They also demonstrated that PBM using a 780 nm AlGaAs diode laser can enhance wound healing by preventing neuronal death and severe astrogliosis (Figs. 4(D) and 4).[89] Khuman *et al.* indicated that NIR-PBM

Table 1. Summary of studies on the effects of NIR-PBM in TBI from 2007 to 2022.

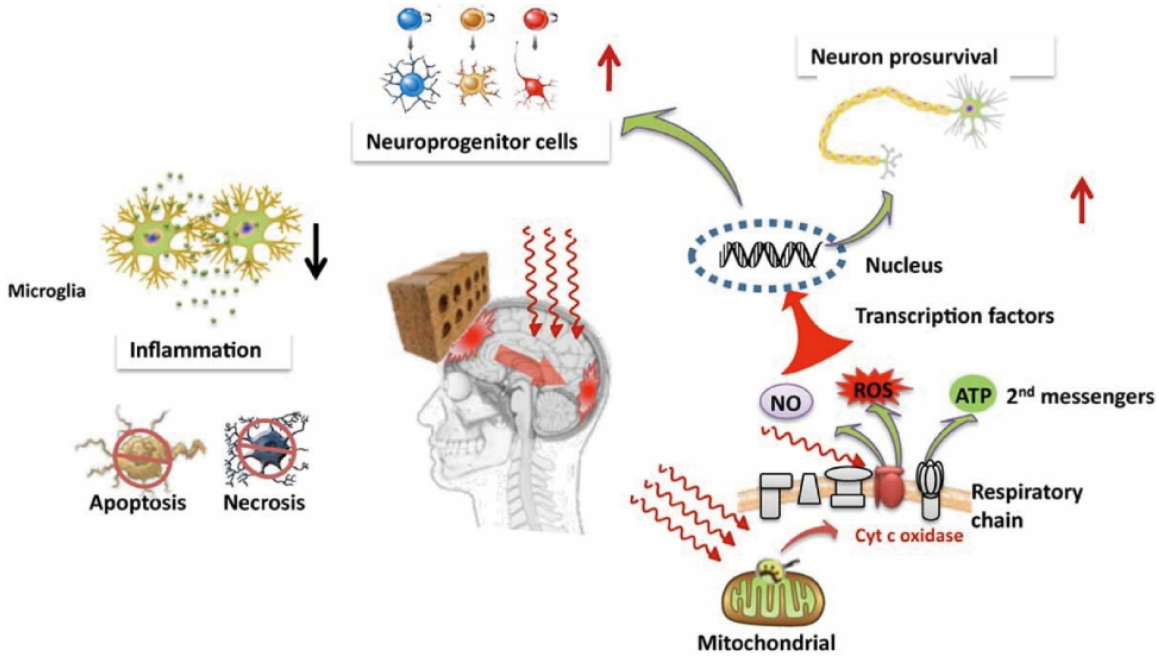
Preclinical studies	Animal models	Wavelength	Irradiation parameters	Irradiation approaches	Effects and findings
Oron *et al.*[84]	Weight-drop device model mice	808 nm	CW; 10 or 20 mW/cm^2; 1.2 J/cm^2 or 2 2.4 J/cm^2	Transcranial	Reduced neurological deficits, reduced lesion volumes, showed long-term benefits.
Oron *et al.*[85]	Weight-drop device model mice	808 nm	CW or PW at 100 Hz; 10 mW/cm^2; 1.2 J/cm^2	Transcranial	PW at 100 Hz performed better than CW.
Ando *et al.*[86]	Weight-drop device model mice/rabbit	810 nm	CW or PW at 10 Hz or 100 Hz; 50 mW/cm^2; 36 J/cm^2	Transcranial	Improvement in NSS and body weight, reduced lesion volumes, antidepressant effect. The effect of 10 Hz was better than 100 Hz and CW.
Wu *et al.*[87]	CCI model mice	665 nm, 730 nm, 810 nm, and 980 nm	CW; 150 mW/cm^2; 36 J/cm^2	Transcranial	665 nm and 810 nm (excluding 730 nm and 980 nm) provided benefits for TBI.
Moreira *et al.*[88]	Cryogenic brain injury adult male Wistar rats	660 nm or 780 nm	CW; 40 mW; 3 J/cm^2 or 5 J/cm^2	Contact irradiation	Affected TNF-α, IL-1β, IL-6 levels.
Moreira *et al.*[89]	Cryogenic brain injury adult male Wistar rats	780 nm	CW; 40 mW; 3 J/cm^2	Contact irradiation	Enhanced wound healing by preventing neuronal death and severe astrogliosis.
Khuman *et al.*[66]	C57BL/6Mice CCI	800 nm	CW; 500 mW/cm^2; 60 J/cm^2	Directly to the contused parenchyma or Transcranial	Reduced microgliosis, improved cognitive recovery and limited inflammation after TBI.
Xuan *et al.*[76]	Adult male BALB/c mice CCI	810 nm	CW; 25 mW/cm^2; 18 J/cm^2	Transcranial	Increased neurogenesis, prevented or slowed down the development of the secondary brain injury.
Xuan *et al.*[74,77]	Young adult male BALB/c mice CCI	810 nm	CW; 25 mW/cm^2; 18 J/cm^2	Transcranial	Reduced cell death and stimulating neurogenesis, which partly mediated by stimulation of BDNF production.
Xuan *et al.*[75]	Male BALB/c mice CCI	810 nm	CW; 50 mW/cm^2; 15 J/cm^2	Transcranial	Biphasic dose-response relationship.
Zhang *et al.*[90]	WT and IEX-1 KO mice CCI	810 nm	PW at 10 Hz; 150 mW/cm^2; 36 J/cm^2	Transcranial	Increased ATP synthesis and specific proinflammatory mediator regulation.

Table 1. (*Continued*)

Preclinical studies	Animal models	Wavelength	Irradiation parameters	Irradiation approaches	Effects and findings
Dong *et al.*[59]	C57BL/6Mice CCI	810 nm	PW at 10 Hz; 150 mW/cm^2; 36 J/cm^2	Transcranial	Energy metabolic modulators may improve the therapeutic efficacy of NIR-PBM in energy-producing inadequate tissue, such as wounded brain, by maintaining the mitochondrial membrane potential, limiting cytochrome c leakage in hypoxic cells, and shielding them from apoptosis.
Mocciaro *et al.*[91]	Rat Fluid percussion injury (FPI)	808 nm	PW at 20 Hz; 300 J/cm	Transcranial	Enhanced cognitive performance, reduced TBI-dependent defective neural progenitor development and aberrant migration, and inhibited TBI-induced overexpression of certain microRNAs.
Clinical studies	**Human cases**	**Wavelength**	**Irradiation parameters**	**Irradiation approaches**	**Effects and findings**
Naeser *et al.*[15]	TBI cases	633 nm, and 870 nm	CW; 19.39 mW/cm^2	Transcranial	Improve Cognitive, executive function and memory. Reduce PTSD.
Naeser *et al.*[16]	mTBI participants with nonpenetrating brain injury	633 nm, and 870 nm	CW; 22.2 mW/cm^2; 13 J/cm^2	Transcranial	Improved sleep, and lowered PTSD symptoms
Hipskind *et al.*[92]	Twelve symptomatic military veterans diagnosed with chronic TBI	629 nm, and 850 nm	CW; 6.4 mW/cm^2; 7.7 J/cm^2	Transcranial	Improved cognitive function and rCBF
Chao *et al.*[93]	A 23-year-old white male TBI patient	810 nm	CW; 100 mW/cm^2; 60 J/cm^2; 75 mW/cm^2; 45 J/cm^2	Transcranial	Improved learning and memory, executive function, attention and processing speed
Longo *et al.*[94]	68 patients with mTBI	665 nm, 730 nm, 810 nm, and 980 nm	CW; 43 J/cm^2; 0.036 W/cm^2	Transcranial	Show the feasibility and safety on NIR-LLLT
Rindner *et al.*[95]	11 TBI patients	1064 nm	CW; 500 mW/cm^2	Transcranial	Supporting the safety and potential efficacy of TILS

Notes: *Abbreviation: PTSD: post-traumatic stress disorder; TNF-α: tumor necrosis factor-alpha; IL-1β: interleukin1 beta; IL-6: interleukin-6; rCBF: regional cerebral blood flow; TILS: transcranial infrared laser stimulation; CCI: controlled cortical impact; WT: wild-type; KO: knockout; BDNF: brain-derived neurotrophic factor; mTBI: mild traumatic brain injury; NSS: neurological severity score; LLLT: low-level laser therapy.

(800 nm) can enhance cognitive function in a TBI model by inhibiting microglial activation.[66] Additionally, Xuan *et al.* proposed that PBM therapy with a continuous wave 810 nm laser could promote neurogenesis and reduce the lesion size of TBI.[76] They further revealed that NIR-PBM might benefit TBI by decreasing cell death in the lesion and stimulating neurogenesis.[77] Specifically, this advantage could be mediated by the stimulation of brain-derived neurotrophic factor (BDNF)



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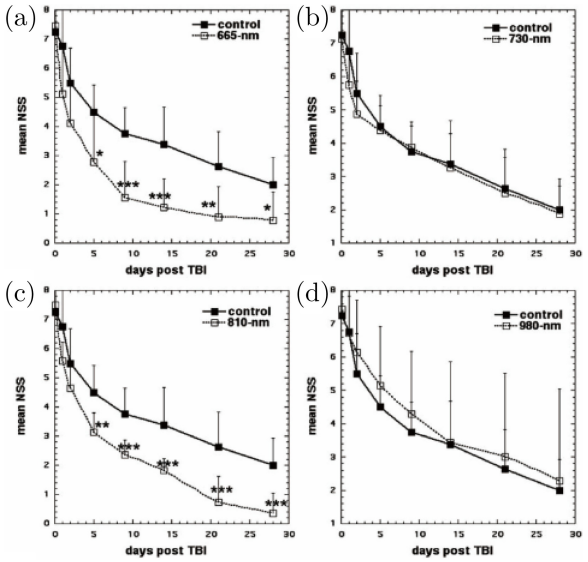

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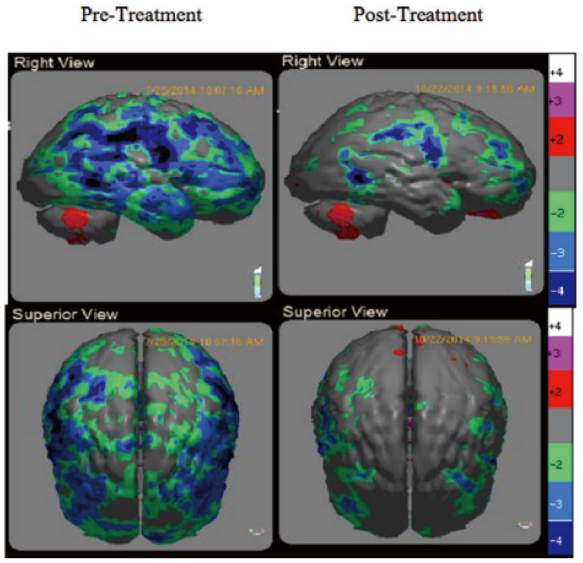

(C)

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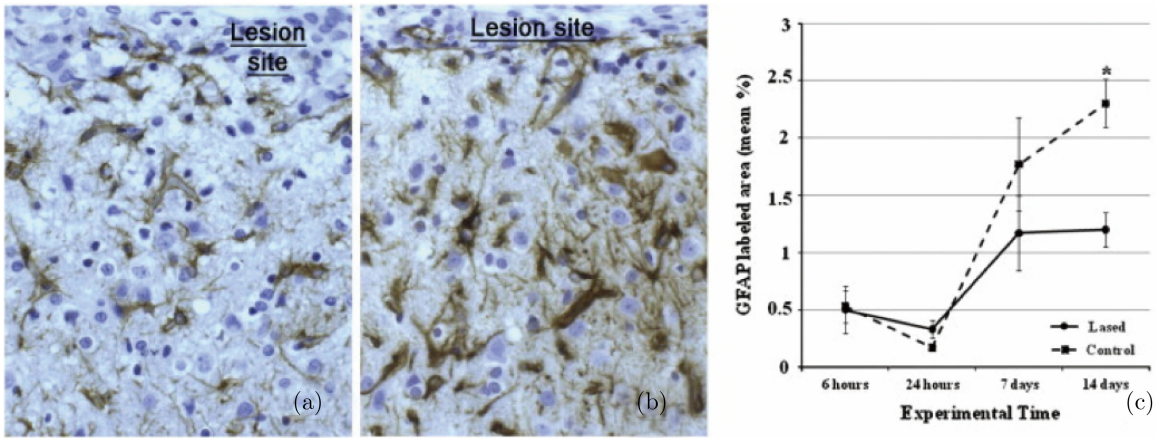
Fig. 4. (A) Scheme illustration of the possible mechanisms of transcranial LLLT for TBI. (B) Time course of NSS scores of shams and laser-treated mice. (C) Changes in regional cerebral blood flow following 6 weeks of treatment (P3). Sagittal and superior views. (D) Illustrative photomicrographs of immunohistochemical reactions for GFAP-positive cells of lased animals and control animals in 14 days. (E) Evolution of the healing process of the cryogenic lesions of both experimental groups.



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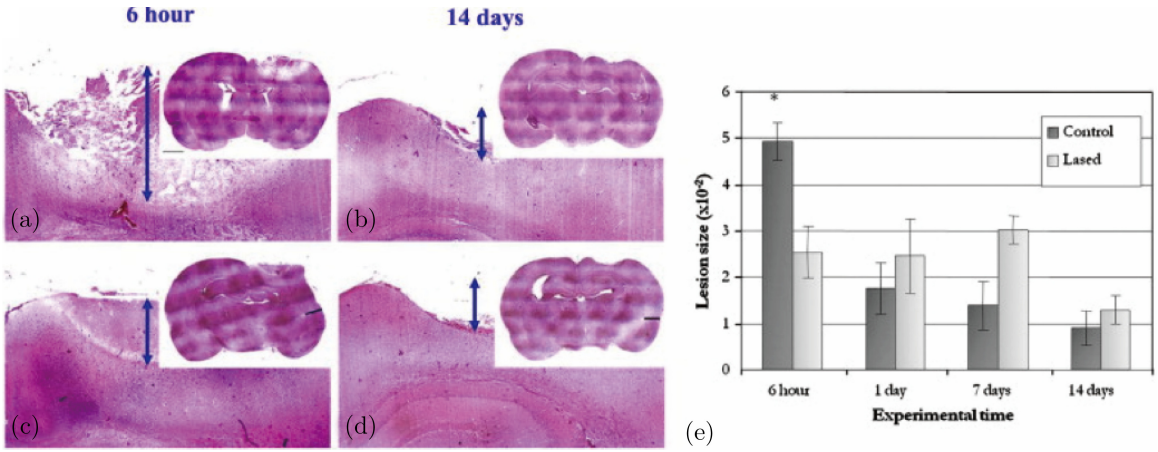


(E)

Fig. 4. (*Continued*)

production, which might promote synaptogenesis.[74] Xuan *et al.* observed an intriguing biphasic dose response in 3 or 14 daily sessions of NIR-PBM treatment.[76] Another study was conducted to compare two groups receiving 3 or 14 daily sessions of NIR-PBM treatment. They found that excessive PBM might induce reactive gliosis and temporarily impede the brain repair process stimulated by NIR-PBM.[75] Zhang *et al.* examined the impact of NIR-PBM on secondary brain injury in immediate early responsive gene X-1 (IEX-1) knockout mice.[90] They observed that NIR-PBM provided significant protection by enhancing ATP production and selectively modulating proinflammatory mediators. Dong *et al.* demonstrated that NIR-PBM shielded cells from apoptosis by maintaining the mitochondrial membrane potential and preventing cytochrome c leakage.[59] They suggested that combining NIR-PBM with energy metabolic modulators could enhance the therapeutic effects on TBI mice.

A novel NIR-PBM technique called nano-pulsed laser therapy (NPLT) system was developed by Esenaliev *et al.*[24] This system combines the advantages of near-infrared laser light and optoacoustic waves, which are produced with each short laser pulse within the tissue. TBI rats treated by NPLT showed better performance in cognitive tests with lower apoptosis protein levels and higher BDNF levels. Then they further investigated the neuroprotective effects of NPLT probably due to modulating the specific microRNAs (miRNAs) in neural stem cells (NSC) in the dentate gyrus (DG).[91]

For the clinical studies, Naeser *et al.* initially reported an improvement in the cognitive function of two chronic TBI patients after the application of transcranial LED with 61 diodes (9×633 nm,

52×870 nm).[15] Subsequently, Naeser *et al.* conducted an open-protocol study to confirm the positive effects in 11 chronic TBI patients following transcranial red/NIR LED therapy.[16] These patients exhibited significant enhancements in executive function, verbal learning, and memory. Hipskind *et al.* utilized pulsed transcranial red/infrared LED (220 infrared and 180 red) PBM to enhance cognitive function and regional cerebral blood flow in chronic TBI patients (Fig. 4(C)).[92] Chao *et al.* implemented a self-administered home photobiomodulation in a 23-year-old professional hockey player with a history of concussions using a LED device emitting 810 nm light pulses.[93] This study detailed increased brain volumes, improved functional connectivity, increased cerebral perfusion, and enhancements in neuropsychological test scores after 8 weeks of PBM treatments, suggesting a promising treatment option for TBI. In addition to the benefits for long-term chronic TBI, a randomized, single-center, prospective, double-blind, placebo-controlled parallel-group trial was carried out by Longo *et al.*[94] Sixty-eight moderate TBI patients were enrolled and received transcranial LLLT using a custom-built helmet (360 LED sources emitting at a center wavelength of 810 nm) within 72 h post-trauma. The findings demonstrated the feasibility of LLLT in all patients without any adverse events. This study provided the first human evidence indicating that light therapy activates neural substrates involved in the pathophysiologic mechanisms of moderate TBI. Rindner *et al.* presented a promising clinical trial involving 1064 nm laser PBM.[95] All participants in this study were able to undergo the procedures without experiencing any negative effects. Nine out of eleven individuals showed clinically meaningful enhancements in the participant-rated global rating of change score (GRS). Results from neuropsychological assessments and mood questionnaires also indicated a favorable therapeutic impact.

5.2. *Ischemic brain injury*

As shown in Table 2, PBM has been assessed in stroke animal models and patients. Lapchak *et al.* initially studied the effectiveness of NIR-PBM (808 nm) for stroke in a rabbit small clot embolic stroke model (RSCEM).[96] They discovered that PBM enhanced behavioral performance and had lasting benefits when started within 6 h of an embolic stroke. Subsequently, they compared the impacts of continuous wave or pulse wave NIR-PBM and determined that PW offers superior benefits.[97] In a separate study, DeTaboada *et al.* contrasted the effects of NIR-PBM applied ipsilaterally, contralaterally, and bilaterally to the induced stroke.[98] They observed that all treated groups exhibited significant improvement compared to the no-laser control group. Huisa *et al.* proposed that additional NIR-PBM treatments yield greater behavioral improvement than a single laser treatment when administered during the acute ischemic stroke phase (Fig. 5(D)).[99]

For the mechanism study, Oron *et al.*, the notable functional enhancement in stroke outcomes attributed to NIR-PBM may be linked to the stimulation of neurogenesis (Fig. 5(A)).[100] Lapchak *et al.* first demonstrated that embolization can lower the amount of ATP in rabbit cortex and that NIR-PBM dramatically raised the amount of ATP in the cortex in embolized rabbits.[26] Yang *et al.* investigated PBM's effects on neurogenesis in a rat photothrombotic (PT) model of ischemic stroke.[64] PBM may improve the neural microenvironment by enhancing mitochondrial function and altering the inflammatory state. It may also increase neurogenesis by encouraging the proliferation and differentiation of internal neuroprogenitor cells in the peri-infarct zone. Turker *et al.* investigated the possible advantages of NIR-PBM for newborn brain damage brought on by hypoxia-ischemia (HI) in a rat model.[62] They concluded that NIR-PBM therapy significantly reduced neuronal apoptosis, oxidative stress, and mitochondrial dysfunction in the newborn HI brain. Wang *et al.* proposed that NIR-PBM could help preserve the dynamics and activities of the mitochondria while preventing delayed apoptotic neuronal death (Fig. 5(E)).[101] According to de Jesus Fonseca *et al.*, neurogenesis, muscular resistance, and animal motor behavior after ischemic stroke may all benefit from exposure to 904-nm LED light PBM.[102] Vogel *et al.* demonstrated that 780 nm NIR-PBM could decrease epileptiform discharges in stroke-induced epilepsy (Figs. 5(B) and 5(C)).[103] Additionally, they confirmed that NIR-PBM might increase astroglial activity in the peri-lesioned area following stroke while decreasing levels of TNF-α, IL-1β, IL-6, brain injury, neuroinflammation, and microglial activation. According to Feng *et al.*, NIR-PBM can prevent stroke

Table 2. Summary of studies on the effects of NIR-PBM in stroke and from 2004 to 2024.

Preclinical studies	Animal models	Wavelength	Irradiation parameters	Irradiation approaches	Effects and findings
Lapchak *et al.*[96]	RSCEM stroke model	808 nm	CW, 7.5 mW/cm^2 or 25 mW/cm^2; 0.9 J/cm^2 or 15 J/cm^2	Transcranial	Improved behavioral performance and the effect of laser treatment is durable.
Lapchak *et al.*[97]	RSCEM stroke model	808 nm	CW, 10 mW/cm^2, PW 1 kHz or PW 100 Hz, 7.5 mW/cm^2,	Transcranial	Better clinical improvement provided by PW.
DeTaboada *et al.*[98]	Rat atherothrombotic model	808 nm	CW; 7.5 mW/cm^2; 0.9 J/cm^2	Transcranial	Improved neurological function at 14, 21, and 28 days after acute stroke in rats.
Huisa *et al.*[99]	RSCEM stroke model	808.5 nm	CW; 7.5 mW/cm^2, 10.8 mW/cm^2 or 20 mW/cm^2	Transcranial	Giving the extra NIR-PBM treatments during the acute ischemic stroke phase resulted in further behavioral improvement.
Oron *et al.*[100]	Rat atherothrombotic model	808 nm	PW at 70 Hz or CW; 7.5 mW/cm^2; 0.9 J/cm	Transcranial	The notable functional enhancement in stroke outcomes attributed to NIR-PBM may be linked to the stimulation of neurogenesis.
Lapchak *et al.*[26]	RSCEM stroke model	808 nm	PW at 100 Hz or CW; 7.5 mW/cm^2, 37.5 mW/cm^2, or 262.5 mW/cm^2; 0.9 J/cm^2, 24.5 J/cm^2, or 31.5 J/cm^2	Transcranial	NIR-PBM markedly elevated the cortical ATP level in embolized rabbits.
Lapchak *et al.*[109]	RSCEM stroke model	808 nm	CW, 7.5 mW/cm^2; 0.9 J/cm^2	Transcranial	NIR-PBM combined with tPA increased ATP generation and improved the treatment outcome.
Yang *et al.*[64]	Photothrombotic model of ischemic stroke in rats	808 nm	CW; 350 mW/cm^2	Transcranial	Enhanced neuronal microenvironment and encouraged internal neuroprogenitor cell multiplication and differentiation.
Tucker *et al.*[62]	Hypoxia ischemia rat model	808 nm	CW; 25 mW/cm^2; 3 J/cm^2	Transcranial	Reduced neuronal apoptosis, oxidative stress, and mitochondrial malfunction.

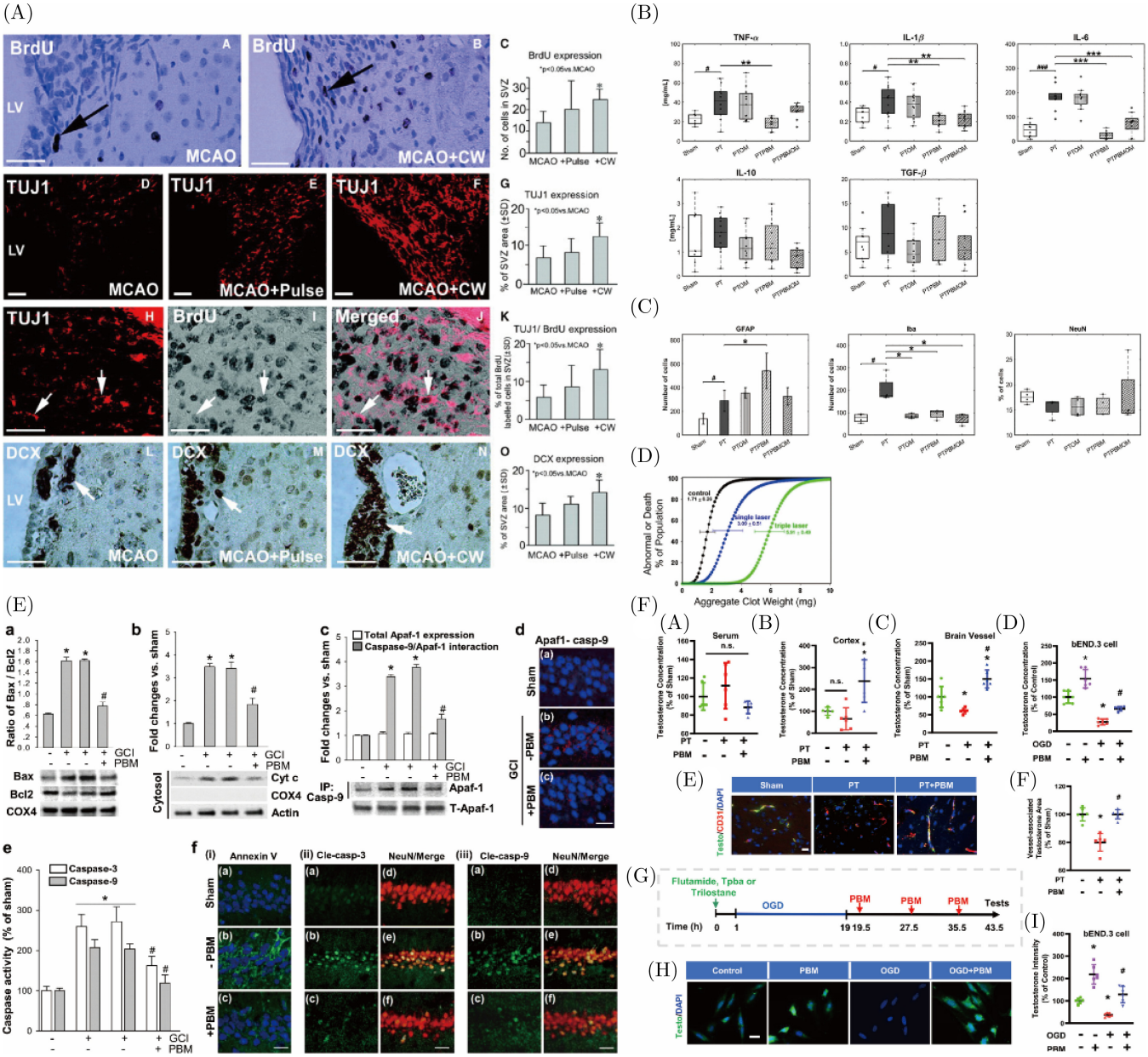
Table 2. (*Continued*)

Preclinical studies	Animal models	Wavelength	Irradiation parameters	Irradiation approaches	Effects and findings
Wang *et al.*[101]	Global cerebral ischemia SD rat model	808 nm	CW; 8.0 mW/cm^2	Transcranial	Preserved the dynamics and activities of the mitochondria while preventing delayed apoptotic neuronal death.
de Jesus Fonseca *et al.*[102]	Electrolytic injury ischemic stroke model rats	904 nm	CW; 110 mW, 7 J/cm^2	Transcranial	Positively impact muscular resistance, neurogenesis, and animal motor behavior.
Vogel *et al.*[103]	Photothrombotic model of ischemic stroke in rats	780 nm	CW; 10 mW/cm^2; 10 J/cm ^{2}	Transcranial	Epileptiform discharges and inflammatory factors reduced.
Feng *et al.*[25]	Photothrombotic model rats	808 nm	CW; 350 mW/cm^2	Transcranial	Preserved synaptic integrity, prevented neurotoxic astrocytic polarization, and shielded neurons from stroke damage in both *vitro* and *in vivo*.
Feng *et al.*[104]	Photothrombotic model rats	808 nm	CW; 350 mW/cm^2; 42 J/cm^2	Transcranial	Reduced brain damage and testosterone-related behavioral abnormalities after ischemic stroke.
Yokomizo *et al.*[105]	Ischemic stroke mice model	1064 nm	CW; 50 mW/cm^2	Transcranial	Enhanced cerebral blood flow, phosphorylation of eNOS, and results of stroke.
Clinical studies	Human cases	Wavelength	Irradiation parameters	Irradiation approaches	Effects and findings
Lampl *et al.*[106]	120 ischemic stroke patients	808 nm	1 J/cm^2	Transcranial	Show initial safety and effectiveness for treatment in humans.
Zivin *et al.*[107]	Ischemic stroke patients, 40 to 90 years of age	808 nm	/	Transcranial	Individuals with moderate to moderately severe ischemic stroke showed improvement within 24 h after the start of the stroke.
Karabegović *et al.*[110]	70 patients after stroke with pain in shoulder and oedema of paralyzed hand	830 nm	CW	Transcranial	Reduced pain, swelling, disability, and improved independency.

Table 2. (*Continued*)

Clinical studies	Human cases	Wavelength	Irradiation parameters	Irradiation approaches	Effects and findings
Boonswang *et al.*[111]	29-year-woman brainstem stroke	660 nm, and 850 nm	CW	Transcranial	Muscle, bone, and joint recovery facilitated.
dos Reis *et al.*[112] das Neves *et al.*[113]	15 volunteers post- CVA with spasticity	808 nm	CW; 100 mw; 4.77 J/cm^2/ 100 mW; 127.39 J/cm^2	Skin contacts with slight pressure	Muscle function improved, and pain intensity reduced. Increased recruitment of muscle fibers, reduce pain intensity.
das Neves *et al.*[114]	12-healthy volunteers 15-poststroke patients	780 nm	CW; 100 mW; 159.24 J/cm^2	Skin contact	Muscle strength and signal conduction on spastic muscle fibers increased.
Casalechi *et al.*[115]	15 patients	905 nm, 875 nm, and 640 nm	10 J/30 J/50 J	Skin contact	Functional mobility shows positive effects.
Dumont *et al.*[116]	10 hemiparesis stroke patients	905 nm, 875 nm, and 640 nm	10 J/30 J/50 J	Skin contact	Promoted immediate effects in the kinematic variables of the hip.
Naeser *et al.* (2020).[117]	Person PWA due to LH stroke	633 nm, and 870 nm	CW; 500 mW; 22.2 mW/cm^2	Transcranial	Improved and accelerated the results from speech-language therapy.
Paolillo *et al.*[118]	Hemiplegic patients	660 nm, 808 nm, and 980 nm	0∼150 mW; 43.2 J	Transcranial	Improved cognitive function, pain relief, greater manual dexterity.
Estrada-Rojas *et al.*[119]	38-year-old woman ischemic stroke on the left side	630 nm, 660 nm, and 850 nm	200 mW/cm^2; 12 J/cm^2	Transcranial	Improvements in expressive language and dysarthria were observed with simultaneous speech-language treatment and tPBM to both hemispheres.

Notes: *Abbreviations: RSCEM: rabbit small clot embolic; SD rat: Sprague-Dawley rat; CVA: cerebrovascular accident; PWA: persons with aphasia; LH: left hemisphere; tPA: tissue plasminogen activator; eNOS: endothelial nitric oxide synthase.



Source: Adapted from Refs. 109–101, 103 and 104 with permission.

Fig. 5. (A) Representative micrographs and quantified immunoreactivity of control and laser-irradiated rat brain slices of the SVZ of the ipsilateral hemisphere (a–c) for bromodeoxyuridine (BrdU), (d–g) for tubulin isotype III (TUJI), and (h–k) for double staining of TUJ1 and BrdU and (l–o) for doublecortin (DCX). (B) Levels of inflammatory cytokines in brain tissue. (C) Number of cells GFAP+, Iba+ and percentage of cells NeuN+ in the peri-lesional region. (D) Effects of laser treatments on stroke outcomes in rabbits (triple laser curves). (E) Effect of PBM on the mitochondria-mediated caspase activation pathway in hippocampal CA1 subregion following GCI. (F) Photobiomodulation treatment (PBMT) increases vascular testosterone concentrations in photothrombosis (PT)-stroke rats and OGD-treated bEND.3 cells.

damage to neurons *in vivo* and *in vitro*, preserve synaptic integrity, and inhibit neurotoxic astrocytic polarization.[25] Another study by Feng *et al.* presented evidence that NIR-PBM mitigates cerebrovascular injury and behavioral deficits associated with testosterone following ischemic stroke (Fig. 5(F)).[104] Yokomizo *et al.* demonstrated that pretreatment with a 1064-nm laser enhanced cerebral blood flow, endothelial nitric oxide synthase (eNOS) phosphorylation, and stroke outcomes.[105]

The PBM clinical trials for patients with acute ischemic stroke were conducted as part of the neurothera efficacy and safety trials (NEST) set of investigations. The safety and effectiveness of infrared laser treatment for treating ischemic stroke in humans was first assessed by Lampl *et al.* within 24 h of the stroke start.[106] 120 patients with acute ischemic stroke were recruited for the NEST-1 experiment; 79 of them received head treatment with an 808 nm laser, while the remaining patients were placed in a sham treatment group that did not receive any laser energy. Compared to the sham treatment group, the patients undergoing laser therapy exhibited improvement after 90 days. Subsequently, Zivin *et al.* conducted the NEST-2 trial involving 660 patients aged 40 to 90 with acute ischemic stroke.[107] Although TLT was proven to be safe when administered within 24 h after the beginning of a stroke, its effectiveness did not achieve formal statistical significance. NEST-1 and NEST-2 both showed that PBM had no effect on adverse events or death rates. Unfortunately, the lack of anticipated statistical significance led to the premature termination of NEST-3.[108]

A clinical study on painful shoulder and shoulder-hand syndrome after stroke was reported in 2009.[110] Seventy stroke patients with shoulder pain and edema in the paralyzed hand were examined. They were split into two groups of 35 each. The experimental group received treatment with a laser probe (830 nm), while the control group received electrotherapy. The laser therapy administered to the experimental group showed significantly better outcomes in reducing pain, swelling, disability, and enhancing independence compared to the control group. A case report in 2012 suggested that PBM conducted using an LED device (combining 660 nm and 850 nm) on cerebral cortices, brainstem, cervical spine, core musculature, and lymphatics, along with subsequent muscle/bone/joint recovery techniques, could aid in the rehabilitation of stroke patients.[111] Two clinical studies by dos Reis *et al.* and das Neves *et al.* indicated that 808 nm laser PBM could enhance muscle function and decrease pain intensity in stroke patients with spasticity.[112,113] In 2020, das Neves *et al.* presented a long-term analysis showing that 808 nm laser PBM could improve signal conduction in spastic muscle fibers of chronic post-stroke spastic patients, leading to increased elbow motion range, muscle fiber recruitment, and muscle strength.[114] Most recently, das Neves *et al.* reported that 780 nm PBM demonstrated significant enhancements in muscle performance, reduction in fatigue and pain levels, and improvement in range of motion in post-stroke patients with spastic hemiparesis.[48]

Casalechi *et al.* used a combination of various light sources (12 diodes: four laser diodes at 905 nm, four LED diodes at 875 nm, and four LED diodes at 640 nm) along with a static magnetic field to treat stroke patients.[115] They discovered that this approach had positive immediate effects on functional mobility. Two years later, Dumont *et al.* further examined the impact of this combined therapy at varying doses.[116] They noted that there were no significant differences in spatiotemporal variables observed among the different doses when compared to the initial assessment. However, there were significant differences ($p < 0.05$) in the kinematic variable of the hip in both the affected and unaffected limbs.

Besides the research on PBM in stroke-related muscle disorders, Naeser *et al.* conducted a series of studies on Red/Near-Infrared Transcranial PBM in individuals with aphasia resulting from left hemisphere stroke.[117] Six patients received different PBM protocols using LED cluster heads (633 nm and 870 nm). They discovered that NIR photons can impact surface areas of the brain cortex beneath the placement of the LED. Enhanced naming ability was observed with the optimal Protocol: LED placement on the left hemisphere along with the medial prefrontal cortex and precuneus. This is the initial study to demonstrate positive effects from PBM therapy in chronic stroke cases, revealing a significant increase in functional connectivity within neural networks on functional magnetic resonance imaging. A case study indicated that transcranial photobiomodulation (tPBM) in combination with traditional speech-language therapy can enhance and expedite the outcomes of speech-language therapy in stroke patients with aphasia.[119] Subsequently, Paolillo *et al.* explored the impacts of transcranial laser photobiomodulation in conjunction with neuromuscular electrical stimulation (NMES) in post-stroke individuals.[118] The laser cluster comprised 12 diode laser beams (4×660 nm, 4×808 nm, and 4×980 nm). This clinical trial demonstrated enhancements in cognitive function, pain relief, increased manual dexterity, and improvements in physical and social-emotional well-being, suggesting that transcranial laser photobiomodulation

Table 3. Summary of studies on the effects of NIR-PBM in other forms of ABI.

Preclinical studies	Animal models	Wavelength	Irradiation parameters	Irradiation approaches	Effects and findings
Shirokov *et al.*[120]	Wistar rats injected by C6 rat glioma cell	1050 nm	CW; 500 mW/cm^2; 10 J/cm^2	Skull contact	PBM course during sleep as opposed to wakefulness more successfully inhibits glioma development and promotes survival compared with the control by raising the amount of CD8$^+$ in glioma cells, triggering apoptosis, and preventing glioma cell proliferation.[120]
Clinical studies	**Human cases**	**Wavelength**	**Irradiation parameters**	**Irradiation approaches**	**Effects and findings**
Bowen *et al.*[122]	People who recovered from the acute phase of COVID-19 and presented with brain fog	1070 nm, 660 nm, and 850 nm	CW; 24 mW/cm^2; 20.2 J/cm^2	Helmet	Cognitive test scores significantly improved with each PBM delivery device.

Notes: *Abbreviation: COVID-19: coronavirus disease 2019.

combined with NMES could serve as a valuable therapeutic option for post-stroke rehabilitation.

5.3. *Other forms of acquired brain injury*

Beyond TBI and ischemic stroke, NIR-PBM has shown promise in other forms of ABI, such as infection, glioma.[120] Shirokov *et al.* compared the effects of NIR-PBM for rat glioma during sleep and wakefulness using a device for PBM under EEG control.[121] They found that taking PBM during sleep was more effective in inhibiting glioma growth and improving survival than taking PBM during wakefulness. These benefits may be due to an increase in the number of CD8$^+$ in glioma cells, activation of apoptosis, and blocking of glioma cell proliferation. There is growing recognition that the after-effects of COVID-19 include chronic fatigue and brain fog. To investigate the effect of PBM on COVID-19 brain fog, Bowen *et al.* utilized a 1070 nm helmet for transcranial PBM (tPBM) and a light bed with 660 nm and 850 nm for whole-body PBM (wbPBM).[122] This pilot clinical study demonstrated that each PBM delivery device was associated with significant improvements in cognitive tests, highlighting the benefits of using PBM therapy to treat long-COVID brain fog.

We can see the application of NIR-PBM to another form of ABI is still an initial stage. The primary reason may be that NIR-PBM cannot directly eliminate tumors or infection. However, NIR-PBM could potentially be used in tumor or infection prognosis recovery.

5.4. *Safety and considerations*

Overall, NIR-PBM with low power density laser or LED sources, appears to be well-tolerated with minimal adverse effects reported in preclinical and clinical studies. But there are still some safety issues that need consideration.

First, the photon of NIR with a wavelength > 700 nm cannot be perceived by the human eye, so a safety concern arises from unintentionally exposing the naked eye to NIR radiation.[123] Before and during NIR-PBM treatment, goggles that have a light density appropriate to the power and

wavelength may need to be applied. Secondly, the thermal effects of NIR-PBM also need consideration.[124,125] Some animal studies have shown a slight temperature rise in the laser region, but no obvious side effects have been detected.[79,96,126] Data comparing CW and PW modes showed that the PW laser had a smaller temperature rise on the scalp and brain tissue surface.[127] The transcranial 1064 nm laser (3.4 W) was used to irradiate the human forehead. The skin temperature rose gradually from 32°C to 41°C over the 4-minute irradiation period and then remained constant at 41°C for the next 4 min.[128] Therefore, the use of a thermal imaging camera and cooling system may be necessary. Thirdly, some side effects of NIR-PBM applied to ABI have been reported. In a study on patients with depression comorbidity along with TBI, 15 percent reported headaches and 28 percent felt tired or fatigued after the first one to three sessions of IR-PBM. However, these symptoms were released with further treatment.[129]

In summary, clinical studies conducted to date suggest that NIR-PBM holds promise as a safe and effective adjunctive therapy for ABI. However, additional research is needed to establish its efficacy, optimize treatment protocols, and translate preclinical findings into clinical practice.

6. Conclusion and Future Direction

Near-infrared photobiomodulation delivered noninvasively to deep brain tissue represents a promising therapeutic modality for acquired brain injury. It offers the potential to mitigate neuronal damage and promote recovery through its effects on mitochondrial function, neuroprotection, and neurogenesis. Numerous studies have demonstrated its efficacy in treating traumatic brain injury, stroke, and other forms of ABI.

Despite the growing evidence affirming the therapeutic efficacy of NIR-PBM, several critical questions remain. Future research should prioritize elucidating optimal treatment parameters, including the most efficacious wavelength, mode, intensity, irradiation approach, and duration. Recent studies have shown that wavelengths in the near-infrared region, such as 780 nm to 1070 nm, are effective, with 808 nm being the most widely used. Combining different wavelengths may yield more favorable outcomes and become a trend in clinical studies. In addition, NIR-PBM with energy densities of 0.1–15 J/cm^2 is effective for neurons in animal models, while 10–84 J/cm^2 is effective in humans. While PW mode has shown better outcomes in animal studies, CW mode is more preferred in clinical settings. Transcranial stimulation is commonly used, but for acute trauma or cerebral infarction, focusing NIR-PBM on the injured site may provide more benefits. The biphasic dose response of NIR-PBM highlights the importance of optimizing treatment dose and duration for different situations. Furthermore, identifying biomarkers indicative of treatment response and establishing patient selection criteria are essential to optimize therapeutic outcomes.

Translational investigations are imperative to ascertain the enduring effects of NIR-PBM in human cohorts with ABI. Large-scale, multicenter clinical trials are crucial to establish the safety, efficacy, and cost-effectiveness of NIR-PBM as a standard adjunctive therapy for ABI. Additionally, exploring combination therapies that integrate NIR-PBM with pharmacological agents or rehabilitation strategies holds promise for synergistically enhancing therapeutic outcomes.

In conclusion, NIR-PBM represents a burgeoning frontier in the therapeutic armamentarium for ABI. By unraveling its underlying mechanisms of action and conducting meticulous clinical investigations, we stand poised to unlock the full therapeutic potential of NIR-PBM, thereby improving outcomes for individuals with ABI. Persistent dedication to research in this domain is essential for advancing our understanding of NIR-PBM and facilitating its integration into clinical practice.

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Conflicts of Interest

The authors declare that there are no conflicts of interest relevant to this paper.

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References

1. J. Bruns Jr., W. A. Hauser, "The epidemiology of traumatic brain injury: A review," *Epilepsia* **44**, 2–10 (2003).
2. L. Goldman, E. M. Siddiqui, A. Khan, S. Jahan, M. U. Rehman, S. Mehan, R. Sharma, S. Budkin, S. N. Kumar, A. Sahu, M. Kumar, K. Vaibhav, "Understanding acquired brain injury: A review," *Biomedicines* **10**, 2167 (2022).
3. J. Ghajar, "Traumatic brain injury," *Lancet* **356**, 923–929 (2000).
4. S. Fleminger, J. Ponsford, "Long term outcome after traumatic brain injury," *BMJ* **331**, 1419–1420 (2005).
5. D. N. Cope, K. Hall, "Head injury rehabilitation: Benefit of early intervention," *Arch. Phys. Med. Rehabil.* **63**, 433–437 (1982).
6. J.-Y. Jiang, G.-Y. Gao, J.-F. Feng, Q. Mao, L.-G. Chen, X.-F. Yang, J.-F. Liu, Y.-H. Wang, B.-H. Qiu, X.-J. Huang, "Traumatic brain injury in China," *Lancet Neurol.* **18**, 286–295 (2019).
7. V. Saini, L. Guada, D. R. Yavagal, "Global epidemiology of stroke and access to acute ischemic stroke interventions," *Neurology* **97**, S6–S16 (2021).
8. T. G. da Silva, R. S. Ribeiro, A. L. Mencalha, A. de Souza Fonseca, "Photobiomodulation at molecular, cellular, and systemic levels," *Lasers Med. Sci.* **38**, 136 (2023).
9. S. Shamloo, E. Defensor, P. Ciari, G. Ogawa, L. Vidano, J. S. Lin, J. A. Fortkort, M. Shamloo, A. E. Barron, "The anti-inflammatory effects of photobiomodulation are mediated by cytokines: Evidence from a mouse model of inflammation," *Front. Neurosci.* **17**, 1150156 (2023).
10. S. W. Jere, H. Abrahamse, N. N. Houreld, "Interaction of the AKT and β-catenin signalling pathways and the influence of photobiomodulation on cellular signalling proteins in diabetic wound healing," *J. Biomed. Sci.* **30**, 81 (2023).
11. S. Song, F. Zhou, W. R. Chen, "Low-level laser therapy regulates microglial function through Src-mediated signaling pathways: implications for neurodegenerative diseases," *J. Neuroinflammation* **9**, 219 (2012).
12. F. Fernandes, S. Oliveira, F. Monteiro, M. Gasik, F. S. Silva, N. Sousa, Ó. Carvalho, S. O. Catarino, "Devices used for photobiomodulation of the brain — a comprehensive and systematic review," *J. NeuroEngineering Rehabil.* **21**, 53 (2024).
13. W. Pan, P. Liu, D. Ma, J. Yang, "Advances in photobiomodulation for cognitive improvement by near-infrared derived multiple strategies," *J. Transl. Med.* **21**, 135 (2023).
14. A. S. Chan, T. L. Lee, M. K. Yeung, M. R. Hamblin, "Photobiomodulation improves the frontal cognitive function of older adults," *Int. J. Geriatr. Psychiatry* **34**, 369–377 (2019).
15. M. A. Naeser, A. Saltmarche, M. H. Krengel, M. R. Hamblin, J. A. Knight, "Improved cognitive function after transcranial, light-emitting diode treatments in chronic, traumatic brain injury: Two case reports," *Photomed. Laser Surg.* **29**, 351–358 (2011).
16. M. A. Naeser, R. Zafonte, M. H. Krengel, P. I. Martin, J. Frazier, M. R. Hamblin, J. A. Knight, W. P. Meehan, E. H. Baker, "Significant improvements in cognitive performance post-transcranial, red/near-infrared light-emitting diode treatments in chronic, mild traumatic brain injury: Open-protocol study," *J. Neurotrauma* **31**, 1008–1017 (2014).
17. B. J. Quirk, M. Torbey, E. Buchmann, S. Verma, H. T. Whelan, "Near-infrared photobiomodulation in an animal model of traumatic brain injury: Improvements at the behavioral and biochemical levels," *Photomed. Laser Surg.* **30**, 523–529 (2012).
18. D. Nizamutdinov, C. Ezeudu, E. Wu, J. H. Huang, S. S. Yi, "Transcranial near-infrared light in treatment of neurodegenerative diseases," *Front. Pharmacol.* **13**, 965788 (2022).
19. M. R. Hamblin, "Photobiomodulation for traumatic brain injury and stroke," *J. Neurosci. Res.* **96**, 731–743 (2018).
20. L. D. Morries, P. Cassano, T. A. Henderson, "Treatments for traumatic brain injury with emphasis on transcranial near-infrared laser phototherapy," *Neuropsychiatr. Dis. Treat.* **11**, 2159–2175 (2015).
21. F. Salehpour, J. Mahmoudi, F. Kamari, S. Sadigh-Eteghad, S. H. Rasta, M. R. Hamblin, "Brain photobiomodulation therapy: A narrative review," *Mol. Neurobiol.* **55**, 6601–6636 (2018).
22. S.-Y. Chang, M. Y. Lee, "Photobiomodulation of neurogenesis through the enhancement of stem cell

and neural progenitor differentiation in the central and peripheral nervous systems," *Int. J. Mol. Sci.* **24**, 15427 (2023).
23. R. Zomorrodi, G. Loheswaran, A. Pushparaj, L. Lim, "Pulsed near infrared transcranial and intranasal photobiomodulation significantly modulates neural oscillations: A pilot exploratory study," *Sci. Rep.* **9**, 1–11 (2019).
24. R. O. Esenaliev, I. Y. Petrov, Y. Petrov, J. Guptarak, D. R. Boone, E. Mocciaro, H. Weisz, M. A. Parsley, S. L. Sell, H. Hellmich, J. M. Ford, C. Pogue, D. DeWitt, D. S. Prough, M.-A. Micci, "Nano-pulsed laser therapy is neuroprotective in a rat model of blast-induced neurotrauma," *J. Neurotrauma* **35**, 1510–1522 (2018).
25. Y. Feng, L. Yang, X. Ma, Z. Huang, X. Zong, C. T. Citadin, H. W. Lin, Q. Zhang, "Photobiomodulation treatment inhibits neurotoxic astrocytic polarization and protects neurons in *in vitro* and *in vivo* stroke models," *Neurochem. Int.* **162**, 105464 (2023).
26. P. A. Lapchak, L. De Taboada, "Transcranial near infrared laser treatment (NILT) increases cortical adenosine-5'-triphosphate (ATP) content following embolic strokes in rabbits," *Brain Res.* **1306**, 100–105 (2010).
27. L. F. de Freitas, M. R. Hamblin, "Proposed mechanisms of photobiomodulation or low-level light therapy," *IEEE J. Sel. Top. Quantum Electron.* **22**, 7000417 (2016).
28. M. R. Hamblin, "Shining light on the head: Photobiomodulation for brain disorders," *BBA Clinical* **6**, 113–124 (2016).
29. M. Wang, C. Yan, X. Li, T. Yang, S. Wu, Q. Liu, Q. Luo, F. Zhou, "Non-invasive modulation of meningeal lymphatics ameliorates ageing and Alzheimer's disease-associated pathology and cognition in mice," *Nat. Commun.* **15**, 1453 (2024).
30. H. L. Liang, H. T. Whelan, J. T. Eells, H. Meng, E. Buchmann, A. Lerch-Gaggl, M. Wong-Riley, "Photobiomodulation partially rescues visual cortical neurons from cyanide-induced apoptosis," *Neuroscience* **139**, 639–649 (2006).
31. M. T. T. Wong-Riley, H. L. Liang, J. T. Eells, B. Chance, M. M. Henry, E. Buchmann, M. Kane, H. T. Whelan, "Photobiomodulation directly benefits primary neurons functionally inactivated by toxins: ROLE OF CYTOCHROME *c* OXIDASE *," *J. Biol. Chem.* **280**, 4761–4771 (2005).
32. T. I. Karu, L. V. Pyatibrat, G. S. Kalendo, "Photobiological modulation of cell attachment via cytochrome c oxidase," *Photochem. Photobiol. Sci.* **3**, 211–216 (2004).
33. R. Ying, H. L. Liang, H. T. Whelan, J. T. Eells, M. T. T. Wong-Riley, "Pretreatment with near-infrared light via light-emitting diode provides added benefit against rotenone- and MPP+-induced neurotoxicity," *Brain Res.* **1243**, 167–173 (2008).
34. R. Natoli, Y. Zhu, K. Valter, S. Bisti, J. Eells, J. Stone, "Gene and noncoding RNA regulation underlying photoreceptor protection: microarray study of dietary antioxidant saffron and photobiomodulation in rat retina," *Mol. Vis.* **16**, 1801–1822 (2010).
35. T. Pruitt, E. M. Davenport, A. L. Proskovec, J. A. Maldjian, H. Liu, "Simultaneous MEG and EEG source imaging of electrophysiological activity in response to acute transcranial photobiomodulation," *Front. Neurosci.* **18**, 1368172 (2024).
36. R. Zomorrodi, G. Loheswaran, A. Pushparaj, L. Lim, "Modulation of neural oscillation power spectral density with transcranial photobiomodulation," *Brain Stimul.* **12**, 457–458 (2019).
37. X. Wang, J. P. Dmochowski, L. Zeng, E. Kallioniemi, M. Husain, F. Gonzalez-Lima, H. Liu, "Transcranial photobiomodulation with 1064-nm laser modulates brain electroencephalogram rhythms," *Neurophotonics* **6**, 025013 (2019).
38. E. Vargas, D. W. Barrett, C. L. Saucedo, L.-D. Huang, J. A. Abraham, H. Tanaka, A. P. Haley, F. Gonzalez-Lima, "Beneficial neurocognitive effects of transcranial laser in older adults," *Lasers Med. Sci.* **32**, 1153–1162 (2017).
39. B. S. Subbarao, J. Stokke, S. J. Martin, "Telerehabilitation in acquired brain injury," *Phys. Med. Rehabil. Clin. N Am.* **32**, 223–238 (2021).
40. H. Thielen, N. Tuts, L. Welkenhuyzen, I. M. C. Huenges Wajer, C. Lafosse, C. R. Gillebert, "Sensory sensitivity after acquired brain injury: A systematic review," *J. Neuropsychol.* **17**, 1–31 (2023).
41. A. Capizzi, J. Woo, M. Verduzco-Gutierrez, "Traumatic brain injury: An overview of epidemiology, pathophysiology, and medical management," *Med. Clin.* **104**, 213–238 (2020).
42. N. Stocchetti, M. Carbonara, G. Citerio, A. Ercole, M. B. Skrifvars, P. Smielewski, T. Zoerle, D. K. Menon, "Severe traumatic brain injury: Targeted management in the intensive care unit," *Lancet Neurol.* **16**, 452–464 (2017).
43. A. Khellaf, D. Z. Khan, A. Helmy, "Recent advances in traumatic brain injury," *J. Neurol.* **266**, 2878–2889 (2019).
44. S. K. Feske, "Ischemic stroke," *Am. J. Med.* **134**, 1457–1464 (2021).
45. J. H. DeLong, S. N. Ohashi, K. C. O'Connor, L. H. Sansing, "Inflammatory responses after ischemic stroke," *Semin. Immunopathol.* **44**, 625–648 (2022).

46. F. Herpich, F. Rincon, "Management of acute ischemic stroke," *Crit. Care Med.* **48**, 1654–1663 (2020).
47. A. Ajoolabady, S. Wang, G. Kroemer, J. M. Penninger, V. N. Uversky, D. Pratico, N. Henninger, R. J. Reiter, A. Bruno, K. Joshipura, H. Aslkhodapasandhokmabad, D. J. Klionsky, J. Ren, "Targeting autophagy in ischemic stroke: From molecular mechanisms to clinical therapeutics," *Pharmacol. Ther.* **225**, 107848 (2021).
48. M. F. das Neves, A. P. Pinto, L. T. Maegima, F. P. S. Lima, R. Œ. B. Lopes-Martins, E. A. Lo Schiavo Arisawa, M. O. Lima, "Effects of photobiomodulation on pain, lactate and muscle performance (ROM, torque, and EMG parameters) of paretic upper limb in patients with post-stroke spastic hemiparesis-a randomized controlled clinical trial," *Lasers Med. Sci.* **39**, 88 (2024).
49. T. M. Yoshida, A. Wang, D. A. Hafler, "Basic principles of neuroimmunology," *Semin. Immunopathol.* **44**, 685–695 (2022).
50. T. N. Seyfried, P. Mukherjee, "Targeting energy metabolism in brain cancer: Review and hypothesis," *Nutr. Metab. (Lond.)* **2**, 30 (2005).
51. S. Wilkes, E. McCormack, K. Kenney, B. Stephens, R. Passo, L. Harburg, E. Silverman, C. Moore, T. Bogoslovsky, D. Pham, R. Diaz-Arrastia, "Evolution of traumatic parenchymal intracranial hematomas (ICHs): Comparison of hematoma and edema components," *Front. Neurol.* **9**, 527 (2018).
52. G. Morrison, D. D. Fraser, G. Cepinskas, "Mechanisms and consequences of acquired brain injury during development," *Pathophysiology* **20**, 49–57 (2013).
53. N. L. Gaggi, N. L. Roy, X. Song, A. L. Peterson, D. V. Iosifescu, R. Diaz-Arrastia, P. Cassano, J. J. Kim, "Transcranial photobiomodulation and chronic traumatic brain injury," *Photonics* **11**, 260 (2024).
54. F. Gonzalez-Lima, B. R. Barksdale, J. C. Rojas, "Mitochondrial respiration as a target for neuroprotection and cognitive enhancement," *Biochem. Pharmacol.* **88**, 584–593 (2014).
55. S. Passarella, T. Karu, "Absorption of monochromatic and narrow band radiation in the visible and near IR by both mitochondrial and non-mitochondrial photoacceptors results in photobiomodulation," *J. Photochem. Photobiol. B* **140**, 344–358 (2014).
56. L. Yang, H. Youngblood, C. Wu, Q. Zhang, "Mitochondria as a target for neuroprotection: Role of methylene blue and photobiomodulation," *Transl. Neurodegener.* **9**, 19 (2020).
57. J. C. de la Torre, A. D. Olmo, S. Valles, "Can mild cognitive impairment be stabilized by showering brain mitochondria with laser photons?," *Neuropharmacology* **171**, 107841 (2020).
58. L. Zupin, F. Celsi, G. Ottaviani, S. Crovella, "Photobiomodulation therapy at different wavelength impacts on retinoid acid–dependent SH-SY5Y differentiation," *Lasers Med. Sci.* **35**, 221–226 (2020).
59. T. Dong, Q. Zhang, M. R. Hamblin, M. X. Wu, "Low-level light in combination with metabolic modulators for effective therapy of injured brain," *J. Cereb. Blood Flow Metab.* **35**, 1435–1444 (2015).
60. F. Salehpour, N. Ahmadian, S. H. Rasta, M. Farhoudi, P. Karimi, S. Sadigh-Eteghad, "Transcranial low-level laser therapy improves brain mitochondrial function and cognitive impairment in D-galactose-induced aging mice," *Neurobiol. Aging* **58**, 140–150 (2017).
61. M. Vos, B. Lovisa, A. Geens, V. A. Morais, G. Wagnières, H. van den Bergh, A. Ginggen, B. De Strooper, Y. Tardy, P. Verstreken, "Near-infrared 808 nm light boosts complex IV-dependent respiration and rescues a Parkinson-related pink1 model," *PLoS One* **8**, e78562 (2013).
62. L. D. Tucker, Y. Lu, Y. Dong, L. Yang, Y. Li, N. Zhao, Q. Zhang, "Photobiomodulation therapy attenuates hypoxic-ischemic injury in a neonatal rat model," *J. Mol. Neurosci.* **65**, 514–526 (2018).
63. F. Salehpour, F. Farajdokht, P. Cassano, S. Sadigh-Eteghad, M. Erfani, M. R. Hamblin, M. M. Salimi, P. Karimi, S. H. Rasta, J. Mahmoudi, "Near-infrared photobiomodulation combined with coenzyme Q10 for depression in a mouse model of restraint stress: reduction in oxidative stress, neuroinflammation, and apoptosis," *Brain Res. Bull.* **144**, 213–222 (2019).
64. L. Yang, D. Tucker, Y. Dong, C. Wu, Y. Lu, Y. Li, J. Zhang, T. C.-Y. Liu, Q. Zhang, "Photobiomodulation therapy promotes neurogenesis by improving post-stroke local microenvironment and stimulating neuroprogenitor cells," *Exp. Neurol.* **299**, 86–96 (2018).
65. R. E. von Leden, S. J. Cooney, T. M. Ferrara, Y. Zhao, C. L. Dalgard, J. J. Anders, K. R. Byrnes, "808 nm wavelength light induces a dose-dependent alteration in microglial polarization and resultant microglial induced neurite growth," *Lasers Surg. Med.* **45**, 253–263 (2013).
66. J. Khuman, J. Zhang, J. Park, J. D. Carroll, C. Donahue, M. J. Whalen, "Low-Level Laser Light Therapy Improves Cognitive Deficits and Inhibits Microglial Activation after Controlled Cortical Impact in Mice," *J. Neurotrauma* **29**, 408–417 (2012).
67. Y.-Y. Huang, K. Nagata, C. E. Tedford, T. McCarthy, M. R. Hamblin, "Low-level laser

therapy (LLLT) reduces oxidative stress in primary cortical neurons in vitro," *J. Biophotonics* **6**, 829–838 (2013).
68. Z. Yu, Z. Li, N. Liu, Y. Jizhang, T. J. McCarthy, C. E. Tedford, E. H. Lo, X. Wang, "Near infrared radiation protects against oxygen-glucose deprivation-induced neurotoxicity by down-regulating neuronal nitric oxide synthase (nNOS) activity in vitro," *Metab. Brain Dis.* **30**, 829–837 (2015).
69. I. Mocchetti, J. R. Wrathall, "Neurotrophic factors in central nervous system trauma," *J. Neurotrauma* **12**, 853–870 (1995).
70. S. J. Allen, J. J. Watson, D. K. Shoemark, N. U. Barua, N. K. Patel, "GDNF, NGF and BDNF as therapeutic options for neurodegeneration," *Pharmacol. Ther.* **138**, 155–175 (2013).
71. D. L. Emery, N. C. Royo, I. Fischer, K. E. Saatman, T. K. McIntosh, "Plasticity following injury to the adult central nervous system: Is recapitulation of a developmental state worth promoting?," *J. Neurotrauma* **20**, 1271–1292 (2003).
72. L. F. Lin, D. H. Doherty, J. D. Lile, S. Bektesh, F. Collins, "GDNF: A glial cell line-derived neurotrophic factor for midbrain dopaminergic neurons," *Science* **260**, 1130–1132 (1993).
73. K. R. Byrnes, X. Wu, R. W. Waynant, I. K. Ilev, J. J. Anders, "Low power laser irradiation alters gene expression of olfactory ensheathing cells in vitro," *Lasers Surg. Med.* **37**, 161–171 (2005).
74. W. Xuan, T. Agrawal, L. Huang, G. K. Gupta, M. R. Hamblin, "Low-level laser therapy for traumatic brain injury in mice increases brain derived neurotrophic factor (BDNF) and synaptogenesis," *J. Biophotonics* **8**, 502–511 (2015).
75. W. Xuan, L. Huang, M. R. Hamblin, "Repeated transcranial low-level laser therapy for traumatic brain injury in mice: Biphasic dose response and long-term treatment outcome," *J. Biophotonics* **9**, 1263–1272 (2016).
76. W. Xuan, F. Vatansever, L. Huang, Q. Wu, Y. Xuan, T. Dai, T. Ando, T. Xu, Y.-Y. Huang, M. R. Hamblin, "Transcranial low-level laser therapy improves neurological performance in traumatic brain injury in mice: Effect of treatment repetition regimen," *PLoS One* **8**, e53454 (2013).
77. W. Xuan, F. Vatansever, L. Huang, M. R. Hamblin, "Transcranial low-level laser therapy enhances learning, memory, and neuroprogenitor cells after traumatic brain injury in mice," *J. Biomed. Opt.* **19**, 108003 (2014).
78. J. J. Anders, H. Moges, X. Wu, I. D. Erbele, S. L. Alberico, E. K. Saidu, J. T. Smith, B. A. Pryor, "In vitro and in vivo optimization of infrared laser treatment for injured peripheral nerves," *Lasers Surg. Med.* **46**, 34–45 (2014).
79. Y. Uozumi, H. Nawashiro, S. Sato, S. Kawauchi, K. Shima, M. Kikuchi, "Targeted increase in cerebral blood flow by transcranial near-infrared laser irradiation," *Lasers Surg. Med.* **42**, 566–576 (2010).
80. H. Engquist, A. Lewén, L. Hillered, E. Ronne-Engström, P. Nilsson, P. Enblad, E. Rostami, "CBF changes and cerebral energy metabolism during hypervolemia, hemodilution, and hypertension therapy in patients with poor-grade subarachnoid hemorrhage," *J. Neurosurg.* **134**, 555–564 (2021).
81. Y. V. Stepanov, I. Golovynska, S. Golovynskyi, L. V. Garmanchuk, O. Gorbach, L. I. Stepanova, N. Khranovska, L. I. Ostapchenko, T. Y. Ohulchanskyy, J. Qu, "Red and near infrared light-stimulated angiogenesis mediated via Ca2+ influx, VEGF production and NO synthesis in endothelial cells in macrophage or malignant environments," *J. Photochem. Photobiol. B* **227**, 112388 (2022).
82. J. F. Dunn, Q. Zhang, Y. Wu, S. Srinivasan, M. R. Smith, R. A. Shaw, "Monitoring angiogenesis noninvasively with near-infrared spectroscopy," *J. Biomed. Opt.* **13**, 064043 (2008).
83. C. Rau, J. C. Yang, S. Jeng, Y. Chen, C. Lin, C. Wu, T. Lu, C. Hsieh, "Far-infrared radiation promotes angiogenesis in human microvascular endothelial cells *via* extracellular signal-regulated kinase activation," *Photochem. Photobiol.* **87**, 441–446 (2011).
84. A. Oron, U. Oron, J. Streeter, L. De Taboada, A. Alexandrovich, V. Trembovler, E. Shohami, "Low-level laser therapy applied transcranially to mice following traumatic brain injury significantly reduces long-term neurological deficits," *J. Neurotrauma* **24**, 651–656 (2007).
85. A. Oron, U. Oron, J. Streeter, L. De Taboada, A. Alexandrovich, V. Trembovler, E. Shohami, "Near infrared transcranial laser therapy applied at various modes to mice following traumatic brain injury significantly reduces long-term neurological deficits," *J. Neurotrauma* **29**, 401–407 (2012).
86. T. Ando, W. Xuan, T. Xu, T. Dai, S. K. Sharma, G. B. Kharkwal, Y.-Y. Huang, Q. Wu, M. J. Whalen, S. Sato, M. Obara, M. R. Hamblin, "Comparison of therapeutic effects between pulsed and continuous wave 810-nm wavelength laser irradiation for traumatic brain injury in mice," *PLoS One* **6**, e26212 (2011).
87. Q. Wu, W. Xuan, T. Ando, T. Xu, L. Huang, Y.-Y. Huang, T. Dai, S. Dhital, S. K. Sharma, M. J. Whalen, M. R. Hamblin, "Low-level laser therapy for closed-head traumatic brain injury in mice: Effect of different wavelengths," *Lasers Surg. Med.* **44**, 218–226 (2012).

88. M. S. Moreira, I. T. Velasco, L. S. Ferreira, S. K. K. Ariga, D. F. Barbeiro, D. T. Meneguzzo, F. Abatepaulo, M. M. Marques, "Effect of phototherapy with low intensity laser on local and systemic immunomodulation following focal brain damage in rat," *J. Photochem. Photobiol. B* **97**, 145–151 (2009).
89. M. S. Moreira, I. T. Velasco, L. S. Ferreira, S. K. K. Ariga, F. Abatepaulo, L. T. Grinberg, M. M. Marques, "Effect of laser phototherapy on wound healing following cerebral ischemia by cryogenic injury," *J. Photochem. Photobiol. B* **105**, 207–215 (2011).
90. Q. Zhang, C. Zhou, M. R. Hamblin, M. X. Wu, "Low-level laser therapy effectively prevents secondary brain injury induced by immediate early responsive gene X-1 deficiency," *J. Cereb. Blood Flow Metab.* **34**, 1391–1401 (2014).
91. E. Mocciaro, A. Grant, R. O. Esenaliev, I. Y. Petrov, Y. Petrov, S. L. Sell, N. L. Hausser, J. Guptarak, E. Bishop, M. A. Parsley, I. J. Bolding, K. M. Johnson, M. Lidstone, D. S. Prough, M.-A. Micci, "Non-invasive transcranial nano-pulsed laser therapy ameliorates cognitive function and prevents aberrant migration of neural progenitor cells in the hippocampus of rats subjected to traumatic brain injury," *J. Neurotrauma* **37**, 1108–1123 (2020).
92. S. G. Hipskind, F. L. Grover, T. R. Fort, D. Helffenstein, T. J. Burke, S. A. Quint, G. Bussiere, M. Stone, T. Hurtado, "Pulsed transcranial red/near-infrared light therapy using light-emitting diodes improves cerebral blood flow and cognitive function in veterans with chronic traumatic brain injury: A case series," *Photobiomodul. Photomed. Laser Surg.* **37**, 77–84 (2019).
93. L. L. Chao, C. Barlow, M. Karimpoor, L. Lim, "Changes in brain function and structure after self-administered home photobiomodulation treatment in a concussion case," *Front. Neurol.* **11**, 952 (2020), doi: 10.3389/fneur.2020.00952.
94. M. G. F. Longo, C. O. Tan, S. Chan, J. Welt, A. Avesta, E. Ratai, N. D. Mercaldo, A. Yendiki, J. Namati, I. Chico-Calero, B. A. Parry, L. Drake, R. Anderson, T. Rauch, R. Diaz-Arrastia, M. Lev, J. Lee, M. Hamblin, B. Vakoc, R. Gupta, "Effect of Transcranial Low-Level Light Therapy vs Sham Therapy Among Patients With Moderate Traumatic Brain Injury: A Randomized Clinical Trial," *JAMA Netw. Open* **3**, e2017337 (2020).
95. E. S. Rindner, J. M. Haroon, K. G. Jordan, K. D. Mahdavi, J. R. Surya, M. A. Zielinski, B. Habelhah, V. Venkatraman, S. A. Becerra, L. Chan, T. P. Kuhn, S. E. Jordan, "Transcranial infrared laser stimulation for the treatment of traumatic brain injury: A case series," *J. Lasers Med. Sci.* **13**, e65 (2022).
96. P. A. Lapchak, J. Wei, J. A. Zivin, "Transcranial infrared laser therapy improves clinical rating scores after embolic strokes in rabbits," *Stroke* **35**, 1985–1988 (2004).
97. P. A. Lapchak, K. F. Salgado, C. H. Chao, J. A. Zivin, "DeTaboada," *Neuroscience* **148**, 907–914 (2007).
98. L. Detaboada, S. Ilic, S. Leichliter-Martha, U. Oron, A. Oron, J. Streeter, "Transcranial application of low-energy laser irradiation improves neurological deficits in rats following acute stroke," *Lasers Surg. Med.* **38**, 70–73 (2006).
99. B. N. Huisa, Y. Chen, B. C. Meyer, G. M. Tafreshi, J. A. Zivin, "Incremental treatments with laser therapy augments good behavioral outcome in the rabbit small clot embolic stroke model," *Lasers Med. Sci.* **28**, 1085–1089 (2013).
100. A. Oron, U. Oron, J. Chen, A. Eilam, C. Zhang, M. Sadeh, Y. Lampl, J. Streeter, L. DeTaboada, M. Chopp, "Low-level laser therapy applied transcranially to rats after induction of stroke significantly reduces long-term neurological deficits," *Stroke* **37**, 2620–2624 (2006).
101. R. Wang, Y. Dong, Y. Lu, W. Zhang, D. W. Brann, Q. Zhang, "Photobiomodulation for global cerebral ischemia: Targeting mitochondrial dynamics and functions," *Mol. Neurobiol.* **56**, 1852–1869 (2019).
102. E. G. de Jesus Fonseca, A. Pedroso, D. Neuls, D. Barbosa, F. J. Cidral-Filho, A. S. I. Salgado, A. Dubiela, E. Carraro, I. I. Kerppers, "Study of transcranial therapy 904 nm in experimental model of stroke," *Lasers Med. Sci.* **34**, 1619–1625 (2019).
103. D. D. S. Vogel, N. N. Ortiz-Villatoro, N. S. Araújo, M. J. G. Marques, F. Aimbire, F. A. Scorza, C. A. Scorza, R. Albertini, "Transcranial low-level laser therapy in an in vivo model of stroke: Relevance to the brain infarct, microglia activation and neuroinflammation," *J. Biophotonics* **14**, e202000500 (2021).
104. Y. Feng, Z. Huang, X. Ma, X. Zong, C. Y.-C. Wu, R. H.-C. Lee, H. W. Lin, M. R. Hamblin, Q. Zhang, "Activation of testosterone-androgen receptor mediates cerebrovascular protection by photobiomodulation treatment in photothrombosis-induced stroke rats," *CNS Neurosci. Ther.* **30**, e14574 (2024).
105. S. Yokomizo, T. Kopp, M. Roessing, A. Morita, S. Lee, S. Cho, E. Ogawa, E. Komai, K. Inoue, M. Fukushi, S. Feil, H.-H. Kim, D. E. Bragin, D. Gerashchenko, P. L. Huang, S. Kashiwagi, D. N. Atochin, "Near-infrared II photobiomodulation preconditioning ameliorates stroke injury via

phosphorylation of eNOS," *Stroke* **55**, 1641–1649 (2024), doi: 10.1161/STROKEAHA.123.045358.

106. Y. Lampl, J. A. Zivin, M. Fisher, R. Lew, L. Welin, B. Dahlof, P. Borenstein, B. Andersson, J. Perez, C. Caparo, S. Ilic, U. Oron, "Infrared laser therapy for ischemic stroke: A new treatment strategy," *Stroke* **38**, 1843–1849 (2007).
107. J. A. Zivin, G. W. Albers, N. Bornstein, T. Chippendale, B. Dahlof, T. Devlin, M. Fisher, W. Hacke, W. Holt, S. Ilic, S. Kasner, R. Lew, M. Nash, J. Perez, M. Rymer, P. Schellinger, D. Schneider, S. Schwab, R. Veltkamp, M. Walker, J. Streeter, NeuroThera Effectiveness and Safety Trial-2 Investigators, "Effectiveness and safety of transcranial laser therapy for acute ischemic stroke," *Stroke* **40**, 1359–1364 (2009).
108. W. Hacke, P. D. Schellinger, G. W. Albers, N. M. Bornstein, B. L. Dahlof, R. Fulton, S. E. Kasner, A. Shuaib, S. P. Richieri, S. G. Dilly, J. Zivin, K. R. Lees, J. A. Zivin, J. Broderick, A. Ivanova, K. Johnston, B. Norrving, G. Albars, A. Alexandrov, D. Brown, P. Capone, D. Chiu, W. Clark, J. Cochran, C. Deredyn, T. Devlin, W. Hickling, G. Howell, D. Huang, S. Hussain, S. Mallenbaum, M. Moonis, M. Nash, M. Rymer, R. Taylor, M. Tremwel, B. Buck, J. Perez, C. Gerloff, B. Greiwing, M. Grond, G. Hamman, T. Haarmeiter, S. Jander, M. Köhrmann, M. Ritter, P. Schallinger, D. Schneider, J. Sobesky, T. Steiner, H. Steinmetz, R. Veltkamp, C. Weimar, F. Gruber, B. Andersson, L. Welin, D. Leys, T. Tatlisumak, A. Luft, P. Lyrer, P. Michel, C. Molina, T. Segura, "Transcranial laser therapy in acute stroke treatment: Results of neurothera effectiveness and safety trial 3, a phase III clinical end point device trial," *Stroke* **45**, 3187–3193 (2014).
109. P. A. Lapchak, P. D. Boitano, "Transcranial near-infrared laser therapy for stroke: How to recover from futility in the NEST-3 clinical trial," *Acta Neurochir. Suppl.* **121**, 7–12 (2016).
110. A. Karabegović, S. Kapidzić-Duraković, F. Ljuca, "Laser therapy of painful shoulder and shoulder-hand syndrome in treatment of patients after the stroke," *Bosn. J. Basic Med. Sci.* **9**, 59–65 (2009).
111. N. A. Boonswang, M. Chicchi, A. Lukachek, D. Curtiss, "A new treatment protocol using photobiomodulation and muscle/bone/joint recovery techniques having a dramatic effect on a stroke patient's recovery: A new weapon for clinicians," *BMJ Case Rep.* **2012**, bcr0820114689 (2012).
112. M. C. R. dos Reis, E. A. F. de Andrade, A. C. L. Borges, D. Q. de Souza, F. P. S. Lima, R. A. Nicolau, A. O. Andrade, M. O. Lima, "Immediate effects of low-intensity laser (808 nm) on fatigue and strength of spastic muscle," *Lasers Med. Sci.* **30**, 1089–1096 (2015).
113. M. F. das Neves, M. C. R. Dos Reis, E. A. F. de Andrade, F. P. S. Lima, R. A. Nicolau, E. Â. L. Arisawa, A. O. Andrade, M. O. Lima, "Effects of low-level laser therapy (LLLT 808 nm) on lower limb spastic muscle activity in chronic stroke patients," *Lasers Med. Sci.* **31**, 1293–1300 (2016).
114. M. F. das Neves, D. C. Aleixo, I. S. Mendes, F. P. S. Lima, R. A. Nicolau, E. A. L. Arisawa, R. A. B. Lopes-Martins, M. O. Lima, "Long-term analyses of spastic muscle behavior in chronic poststroke patients after near-infrared low-level laser therapy (808 nm): a double-blinded placebo-controlled clinical trial," *Lasers Med. Sci.* **35**, 1459–1467 (2020).
115. H. L. Casalechi, A. J. L. Dumont, L. A. B. Ferreira, P. R. V. de Paiva, C. dos S. M. Machado, P. de T. C. de Carvalho, C. S. Oliveira, E. C. P. Leal-Junior, "Acute effects of photobiomodulation therapy and magnetic field on functional mobility in stroke survivors: a randomized, sham-controlled, triple-blind, crossover, clinical trial," *Lasers Med. Sci.* **35**, 1253–1262 (2020).
116. A. J. L. Dumont, H. L. Casalechi, S. S. Tomazoni, L. C. Grecco, M. Galli, C. S. Oliveira, E. C. P. Leal-Junior, "Photobiomodulation therapy combined with static magnetic field (PBMT–SMF) on spatiotemporal and kinematics gait parameters in post-stroke: A pilot study," *Life* **12**, 186 (2022).
117. M. A. Naeser, M. D. Ho, P. I. Martin, M. R. Hamblin, B.-B. Koo, "Increased functional connectivity within intrinsic neural networks in chronic stroke following treatment with red/near-infrared transcranial photobiomodulation: Case series with improved naming in aphasia," *Photobiomodul. Photomed. Laser Surg.* **38**, 115–131 (2020).
118. F. R. Paolillo, G. A. A. Luccas, N. A. Parizotto, A. R. Paolillo, J. C. de Castro Neto, V. S. Bagnato, "The effects of transcranial laser photobiomodulation and neuromuscular electrical stimulation in the treatment of post-stroke dysfunctions," *J. Biophotonics* **16**, e202200260 (2023).
119. K. Estrada-Rojas, N. P. Cedeño Ortiz, "Increased improvement in speech-language skills after transcranial photobiomodulation plus speech-language therapy, compared to speech-language therapy alone: Case report with aphasia," *Photobiomodul. Photomed. Laser Surg.* **41**, 234–240 (2023).
120. A. Shirokov, I. Blokhina, I. Fedosov, E. Ilyukov, A. Terskov, D. Myagkov, D. Tuktarov, M. Tzoy, V. Adushkina, D. Zlatogosrkaya, A. Evsyukova, V. Telnova, A. Dubrovsky, A. Dmitrenko,

M. Manzhaeva, V. Krupnova, M. Tuzhilkin, I. Elezarova, N. Navolokin, E. Saranceva, T. Iskra, E. Lykova, O. Semyachkina-Glushkovskaya, "Different effects of phototherapy for rat glioma during sleep and wakefulness," *Biomedicines* **12**, 262 (2024).

121. O. Semyachkina-Glushkovskaya, I. Fedosov, A. Zaikin, V. Ageev, E. Ilyukov, D. Myagkov, D. Tuktarov, I. Blokhina, A. Shirokov, A. Terskov, D. Zlatogorskaya, V. Adushkina, A. Evsukova, A. Dubrovsky, M. Tsoy, V. Telnova, M. Manzhaeva, A. Dmitrenko, V. Krupnova, J. Kurths, "Technology of the photobiostimulation of the brain's drainage system during sleep for improvement of learning and memory in male mice," *Biomed. Opt. Express* **15**, 44–58 (2024).
122. R. Bowen, P. R. Arany, "Use of either transcranial or whole-body photobiomodulation treatments improves COVID-19 brain fog," *J. Biophotonics* **16**, e202200391 (2023).
123. Y. Ma, J. Bao, Y. Zhang, Z. Li, X. Zhou, C. Wan, L. Huang, Y. Zhao, G. Han, T. Xue, "Mammalian near-infrared image vision through injectable and self-powered retinal nanoantennae," *Cell* **177**, 243–255.e15 (2019).
124. C. Bastiancich, A. Da Silva, M.-A. Estève, "Photothermal therapy for the treatment of glioblastoma: Potential and preclinical challenges," *Front. Oncol.* **10**, 610356 (2020).
125. Z. Li, H. Chen, F. Zhou, H. Li, W. R. Chen, "Interstitial photoacoustic sensor for the measurement of tissue temperature during interstitial laser phototherapy," *Sensors* **15**, 5583–5593 (2015).
126. Y. Chen, L. De Taboada, M. O'Connor, S. Delapp, J. A. Zivin, "Thermal effects of transcranial near-infrared laser irradiation on rabbit cortex," *Neurosci. Lett.* **553**, 99–103 (2013).
127. T. A. Henderson, L. D. Morries, "Near-infrared photonic energy penetration: can infrared phototherapy effectively reach the human brain?," *Neuropsychiatr. Dis. Treat.* **11**, 2191–2208 (2015).
128. X. Wang, D. D. Reddy, S. S. Nalawade, S. Pal, F. Gonzalez-Lima, H. Liu, "Impact of heat on metabolic and hemodynamic changes in transcranial infrared laser stimulation measured by broadband near-infrared spectroscopy," *Neurophotonics* **5**, 011004 (2017).
129. T. A. Henderson, L. D. Morries, "Multi-watt near-infrared phototherapy for the treatment of comorbid depression: An open-label single-arm study," *Front. Psychiatry* **8**, 187 (2017).