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REVIEW

TRANSLATIONAL BIOPHOTONICS

Preclinical studies of transcranial photobiomodulation in the neurological diseases

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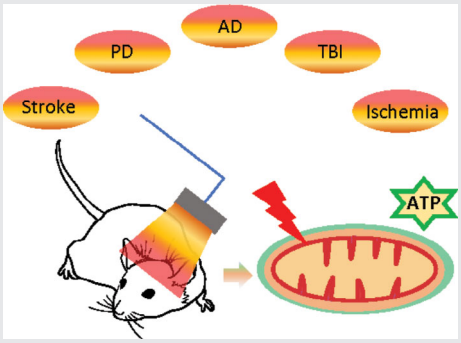
Abstract



Photobiomodulation (PBM) takes advantage of red and near-infrared light to induce therapeutic effects on various kinds of diseases, with transcranial PBM (tPBM) attracting most attention on neurological diseases. Displaying a noninvasive superiority over traditional treatment, tPBM is increasingly studied among research groups. Growing numbers of studies have been conducted in the last decade regarding neurological diseases; however, the research objects and lighting parameters among these papers varied from each other. This article introduces the biophotonics nature of PBM, records the experimental parameters of preclinical studies since 2014 and summarizes the application of tPBM on the neurobiological diseases in the past two decades. Under the summarized guidance of parameter setup, tPBM will be shining light in the prevention and treatment of neurological diseases.

KEYWORDS

Alzheimer's disease, neurological disease, parameter, Parkinson's disease, photobiomodulation

1 | INTRODUCTION

Soon after the invention of the ruby laser and helium-neon laser, photobiomodulation (PBM) came as a therapeutic technique in the 1960s, which was also known as low-level laser therapy (LLLT) [1]. Under PBM treatment, cells or tissues are exposed to low levels of 600 to 1100 nm wavelength red and near-infrared (NIR) light, containing relatively lower energy densities as compared to the lasers applied for ablation and cutting [2]. Mester et al first discovered the benefits of PBM in the year of 1967 [3], when he attempted to treat malignant cancer on shaved rats with a ruby laser at low power. Instead of destroying tumor cells, it stimulated the healing of skin incisions and the growth of hair. He carried out a series of experiments of various

Abbreviations: AD, Alzheimer's disease; CCO, cytochrome-*c*-oxidase; CSF, cerebrospinal fluid; ISF, interstitial fluid; LLLT, low-level laser therapy; NAD/NADH, nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide; NIR, near infrared; PD, Parkinson's disease; ROS, reactive oxygen species; TBI, traumatic brain injury; tPBM, transcranial photobiomodulation; TRP, transient receptor potential.

wound models and confirmed the faster wound healing effect of LLLT [4,5].

Transcranial PBM (tPBM), a noninvasive form of light energy delivered to the brain, was shortly introduced after the PBM. Accumulating evidence continues to show that tPBM is a potential brain stimulation technique capable of preventing and/or curing neurological diseases and neurodegenerative diseases [6–10]. In this stimulation process, a series of physiological reactions take place inside the brain, including increased cerebral blood flow, oxygen availability and consumption, elevated adenosine triphosphate (ATP) production and enhanced mitochondrial activity [11]. Furthermore, tPBM can modulate neuroprotection and neuroinflammation responses in the brain. Studies of tPBM have enormously increased in the last two decades [1], especially its application to neurological diseases. With increasing numbers of preclinical studies focused on neurological diseases, there is a big variance of parameters (such as wavelength, duration, power density) among these studies, which can be a limitation for making horizontal comparisons. Thus, this review aims to elucidate the mechanisms of tPBM, summarize the experimental parameters in the last 6 years, and integrate current tPBM research developments, while proposing optimal tPBM method to investigate neurological diseases. Our goal is to provide the optimal directions to initiate preclinical studies and to improve the utilization of PBM approaches focusing on neurological diseases.

1.1 | Biophotonics and tissue-photon interaction

Modern applications of light in the medical field date back to the 19th century, with the rapid development in the understanding of both the physical nature of light and its fundamental light-matter interactions. The laser invention even opened new medical avenues, bringing numerous laser-based diagnostic and therapeutic devices to the public [12–15].

The nature of light is electromagnetic radiation, composing a spectrum of wavelengths from radio waves to gamma rays [2]. Light propagates in the form of waves but interacts with matter as particles called photons. The primary interaction of photons with biological tissue can fall into two categories known as absorption and scattering [16]. Scattering can change the propagation path, polarization and spectrum of the scattered light. During the light absorption process, the energy of photons is transmitted to excite the absorbing molecules into the electronic or vibrational state. These light-tissue interactions have been applied in the diagnostic analysis and imaging-based mapping, especially by optical methods [17,18]. Some parts of the absorbing energy can be released through luminescence, inelastic scattering, or acoustomechanical waves, which provide the information of microstructure or molecular content of the tissue of interest [19]. Another part of the absorbing energy can invoke or support some physiological processes in the tissue.

Scattering increases the volume of tissue affected by light. However, due to the reflection or refraction at interfaces between different tissues, it can shorten the diffusing depth of light into the tissue. Absorption is also a leading factor in limiting the penetration depth of light. Most tissues are capable of absorbing light energy through the molecular absorption of photons. Molecules containing metal ions display a strong capacity for light absorption and absorbed photons can induce functional or conformational molecular changes.

The penetration of light through tissue is affected by several optical parameters such as wavelength, energy, attenuation coefficient (composed of scattering, refraction and absorption), area of irradiance, coherence and pulsing. Generally, longer wavelengths (>1000 nm) can penetrate further distances; however, the competing absorption by water starts to play an essential role in those wavelengths [20]. Also, enhancing power density can lead to higher penetration with more photons traversing the tissue.

Unlike other organs, light has to travel a long-distance in the brain from the scalp to the cerebral cortex. The action of tPBM emanates from the light shone on the scalp, where skin works as the first barrier and some light is reflected without penetration into the brain. Reflection and scattering continue at the second barrier of the skull, a solid bone structure, where penetrating light can reach the brain tissue (neurons and glial cells) and are further absorbed by interstitial fluid (ISF) or blood. The particular set of wavelengths known as the "optical window" has been determined from scientific investigation of deep brain therapies. Optical wavelengths of 650 to 1200 nm, which correspond to red and NIR lights, have been determined to provide the farthest and most effective penetration into the biological tissue [21]. Further validation studies have been done with functional resonance imaging [8]. Under the noninvasive induction approach, the effective distance of the NIR light that reaches into the human brain is 30 to 40 mm [22]. Considering the advantages of penetration depth and photon-tissue interactions, especially mitochondrial-based mechanisms (discussed in detail in Section 2), red and NIR light is chosen as the source of tPBM.

Beyond the wavelength dependencies of red and NIR light penetration into brain tissue, there have been

indications that specific adjustable parameters may influence neural activities. To compare parameters in preclinical studies of tPBM on neurological diseases, detailed experimental parameters including wavelength, light source, time duration, target site and spot size and power density are recorded based on diseases types: Tables 2 to 6 refer to PD, AD and dementia, traumatic brain injury (TBI), stroke and cerebral ischemia, respectively. An explanation of irradiation parameters and their effect on light-tissue interactions are summarized in Table S1.

1.2 | Light source: Light-emitting diode or laser?

PBM makes use of the light from visible red light to NIR at a relatively low power density to avoid heating or burning the tissue. Laser light and light-emitting diodes (LEDs) are the two main sources of light used in research and therapy by PBM. Laser light comes from the optical amplification based on the stimulated emission of photons. Laser-emitted light has an excellent reputation for its high-level spatial and temporal coherence, displayed as a diffraction-limited narrow beam [23]. As a result of the low divergence, laser light can concentrate its power at great distance [24]. Uniform irradiance is a noteworthy characteristic of laser light beam. Based on its characteristics, lasers are broadly used in applications that require high spatial or temporal coherence that cannot be achieved by other simple techniques.

Laser source held a dominant role in phototherapy until the end of the 1990s. The phenomena changed in 1998 when Prof Harry Whelan and his group invented the "NASA LED" [25]. Compared with older version of LED, NASA LED has less divergence, much higher and more stable output power and quasimonochromaticity whereby emitting photons at the rated wavelength. These characteristics made LED an alternative light source in PBM. Nowadays, with further development of semiconductors, LEDs are more frequently used as a light source. Modern versions of LEDs can emit light across the wavelengths of visible, ultraviolet and infrared with very high brightness [2]. The working principle for LED is based on electroluminescence and its color is determined by the energy gap of the semiconductor [26]. Constructed to form relatively large arrays, LEDs can treat wounds that commonly involve larger areas than that of a laser beam. Regarding biosafety, both low-level laser and LED display no thermal injury to tissues [27]. As a therapeutic device, the LED has achieved Food and Drug Administration (FDA) nonsignificant risk status based on its better tolerance with biological tissue and no reported detrimental effects [28]. Furthermore, LED devices are more compact, portable and affordable to customers. With costly laser light sources predominantly marketed to clinicians, LED equipment are more affordable and convenient to use personally at home.

Although the monochromatic nature and coherence of laser light were believed to be beneficial over noncoherent LED light for many years, this view is no longer widely held [29]. LED devices can also achieve the same or even better biological results with different sets of parameters. As a result, researchers reached an agreement to change the previously used name, "low-level laser therapy" (LLLT), to "PBM" in 2014, which means the laser is no longer a necessary light source for applicable treatments by red and NIR light [30]. PBM has had a comprehensive definition: "a form of light therapy that utilizes nonionizing forms of light sources, including lasers, LEDs and broadband light, in the visible and infrared spectrum. It is a nonthermal process involving endogenous chromophores-eliciting photophysical (ie, linear and nonlinear) and photochemical events at various biological scales" [30].

1.3 | Trend of tPBM in the neurological diseases

Since the beginning of the 21st century, enormous progress has been made toward the application of PBM. Compared with traditional pharmacotherapy, neuronal stimulation and brain surgery, tPBM has become a promising, noninvasive therapeutic method targeting neurological disease [1]. The trend of treating neurological diseases by tPBM and its increasing application over the last two decades are summarized in Figure 1 and Table 1. We carefully examined the critical parameters (wavelength, power density and duration) that have been used in the application of PBM. We also summarized the studies under different disease categories. Among a total of 56 studies, 40 of them are animal studies, and 16 are human results. Then, 20 studies utilized LED as light sources, and the remaining 36 studies used lasers.

Along with the summarized studies, we separated PBM applications into six groups in response to the types of neuronal diseases: (a) TBI, (b) stroke, (c) Alzheimer's disease (AD)/dementia, (d) brain cerebral ischemia, (e) Parkinson's disease (PD) and (f) others. We also noticed that a wide range of light wavelengths were adapted in different PBM applications. Based on the optical window and tissue absorption features, we put together the light wavelengths that shared similar tissue optical properties, yielding seven categories: (a) 620 nm+, including 620, 625, 627, 629, 630 and 633 nm; (b) 650 nm+, including 650, 660, 665, 670 and 675 nm; (c) 780 nm+, including

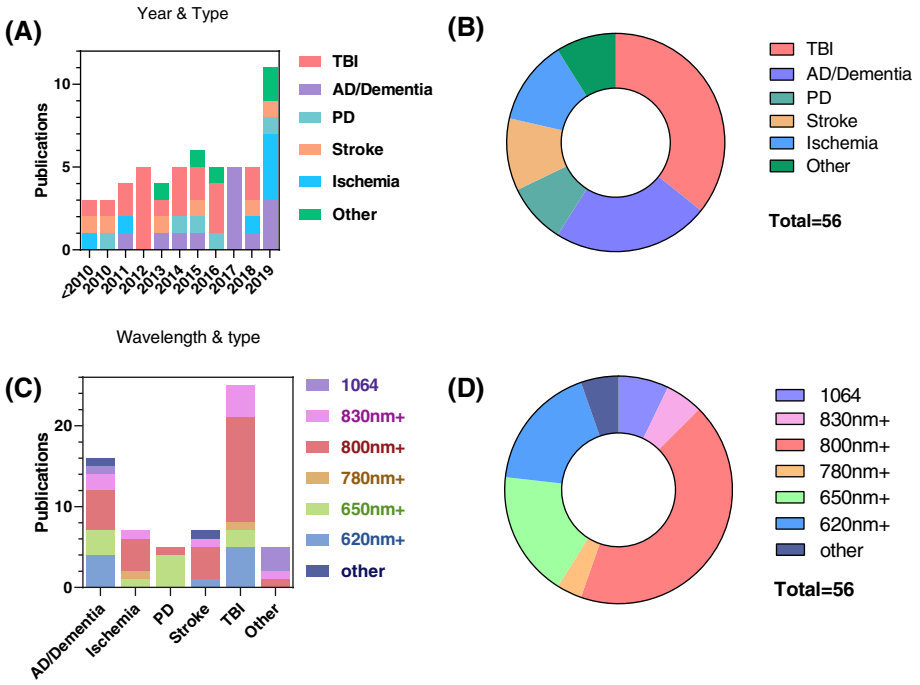


FIGURE 1 The number of publications utilizing photobiomodulation (PBM) in the neurobiology of diseases. A, The growing number of publications in the last 20 years, with different color blocks showing the numbers of neurological diseases individually. B, The percentage for each neurological disease in total publications during the last 20 years. C, The wavelength of red/near-infrared (NIR) light applied in different neurological diseases. D, The percentage of different wavelengths in all publications of two decades

780 and 785 nm; (d) 800 nm+, including 800, 808, 810 nm; (e) 830 nm+, including 830, 850 and 870 nm; (f) 1064 nm and (g) others (532 and 1267 nm) not mentioned in the former cases. Note that we only summarized the neurological diseases. The neuropsychological cases such as depression and anxiety disorder were not discussed in this review.

An overall increasing trend of PBM applications were observed (Figure 1A). Only three studies (5.4%) were found in the first decade of the 21st century. The rest of the studies were conducted in the latest 10 years (94.6%). The number of studies doubled in the year 2019 compared to previous years. Among these studies, TBI (35.7%) and AD/dementia (23.2%) take up to more than 50% of the total. The percentages of other types of applications were relatively close (PD 8.9%, ischemia 12.5%, stroke 10.7% and others 8.9%) (Figure 1B).

For the studies of PBM, a large variety of wavelengths were adapted for different types of diseases. In the AD/dementia group, 4 studies (n = 4) used 800 nm + as the primary wavelength. Likewise, a "favorite" wavelength can also be found in other types of diseases (800 nm + for ischemia [n = 4], stroke [n = 4] and TBI [n = 13], 650 nm + for PD [n = 4] and 1064 nm + for others [n = 3]; see more details in Figure 1C). Among the total studies, the major wavelength that has been used in PBM of neurological diseases is 800 nm+ (43%). The second and third preferred wavelengths are 650 nm+ (18%) and 620 nm+ (18%), respectively.

Power density and durations are also two critical parameters used in PBM. Among these studies, the average power density is (319 ± 1110 mW/cm^2), and the average duration is (36 ± 195 min). A vast range of power densities (2-6660 mW/cm^2) and durations (0-24 hours) have been described in previous studies. The wavelength/power density/durations that have been applied for different neurological diseases are discussed in more detail in Section 3.

2 | MECHANISM OF PBM

Research focused on PBM has been carried out for almost 50 years but still lacks widespread acceptance by the public. This limited acceptance is attributed to the uncertainty of its working mechanism [29]. Regarding the mechanism, there are two existing hypotheses: one is explained from the mitochondria field, the other is elucidated from light-sensitive ion channels on the cell membrane [1].

2.1 | Mitochondrial mechanism

The mitochondrial mechanism is based on the principle that absorbing light can give rise to biological reactions of the living system (Figure 2). When light strikes the biological tissue, most of the photons are absorbed by specific types of molecules called photoacceptors or photoreceptors [85]. The acting sites of photoacceptors are at chromophores, which are usually organic cofactors or metal ions containing electrons within a protein

TABLE 1 Summary of the PBM studies in the neurobiology of diseases between 1999 and 2019

Year [ref]	Light source	Wavelength (nm)	Subject	Power density (mW/cm^2)	Duration (min)	Disease	Mechanism
2020 [31]	Laser	808	Rat	350	2	TBI	Neuroprotection
2020 [32]	Laser	808	Rat	1000	5	TBI	Neuroprotection
2019 [33]	LED	904	Rat	11	63 s	Stroke	Neurogenesis
2019 [6]	Laser	1267	Mouse	200	17	AD	Neuroprotection
2019 [10]	Laser	808	Rat	100	2	Ischemia	Neuroprotection
2019 [34]	Laser	808	Rat	8	2	Ischemia	Neuroprotection
2019 [35]	Laser	808/905	Rat	8333/333	9	Other	Neuroprotection
2019 [36]	LED	635/810	Human	31/75	25	AD	Cognition
2019 [37]	Laser	810	Mouse	6660		Ischemia	Cognition
2019 [7]	LED	675	Rat	50	1.5	PD	Neuroprotection
2019 [8]	LED	633/870	Human	22.2	39	Stroke	Synaptogenesis
2019 [38]	LED	830	Human	33.2	20	Other	Cognition
2019 [39]	LED	850	Human	285	2.5	Dementia	Cognition
2019 [40]	LED	830	Rat	10	30	Ischemia	Neurogenesis
2018 [41]	LED	629/850	Human	6.4	20	TBI	Cognition
2018 [42]	Laser + LED	625/850	Mouse	28	10	AD	Neuroprotection
2018 [43]	Laser	808	Rat	25	2	Ischemia	Neuroprotection
2018 [44]	Laser	808	Rat	350	2	Stroke	Neuroprotection
2018 [9]	LED	627	Human	70	2	TBI	Cognition
2017 [45]	Laser	1064	Human	250	4	Dementia	Cognition
2017 [46]	Laser	808	Rat	25	2	AD	Neuroprotection
2017 [47]	Laser	660/810	Mouse	4750		Dementia	Cognition
2017 [48]	LED	810	Human	41	20	Dementia	Cognition
2017 [49]	LED	627	Rat	70	100 s	AD	Cognition
2016 [50]	Laser	810	Mouse	25	12	TBI	Neuroprotection
2016 [51]	Laser	785	Human	10	10	TBI	Behavior
2016 [52]	LED	633/810	Human	22.2	9.75	TBI	Neuroprotection
2016 [53]	Laser	1064	Human	250	8	Other	Cognition
2016 [54]	Laser	670	Monkey		24 h	PD	Neuroprotection
2015 [55]	Laser	810	Mouse	50	12	TBI	Synaptogenesis
2015 [56]	Laser	1064	Human	250	8	Other	Cognition
2015 [57]	LED	670	Mouse	2	1.5	Dementia	Neuroprotection
2015 [58]	Laser	808	Rat	2.5	100 s	PD	Neuroprotection
2015 [59]	Laser	532	Mouse	845	60	Stroke	Neurogenesis
2015 [60]	Laser	810	Mouse	150	4	TBI	
2014 [61]	Laser	810	Mouse	150	4	TBI	Anti-inflammation
2014 [62]	LED	670	Mouse	50	1.5	AD	neuroprotection
2014 [63]	Laser	810	Mouse	25	12	TBI	neurogenesis
2014 [64]	LED	633/870	Human	22.2	20	TBI	Cognition
2014 [65]	LED	670	Mouse	4	1.5	PD	Neuroprotection
2013 [66]	Laser	1064	Human	60	8	Other	cognition
2013 [67]	Laser	633	Mouse	12.74	5	AD	neuroprotection

(Continues)

TABLE 1 (Continued)

Year [ref]	Light source	Wavelength (nm)	Subject	Power density (mW/cm^2)	Duration (min)	Disease	Mechanism
2013 [68]	Laser	810	Mouse	25	12	TBI	Neuroprotection
2013 [69]	Laser	808.5	Rabbit	20	2	Stroke	Neuroprotection
2012 [70]	LED	670	Rat	50	5	TBI	Neuroprotection
2012 [71]	Laser	800	Mouse	500	2	TBI	Anti-inflammation
2012 [72]	Laser	810	Mouse	36	4	TBI	Cognition
2012 [73]	LED	850	Human	11.4	30	TBI	CBF
2012 [74]	Laser	808	Mouse	10	2	TBI	Neuroprotection
2011 [75]	LED	633/870	Human	25.8	10	TBI	Cognition
2011 [76]	Laser	780	Rat	1000	3 s	Ischemia	Neuroprotection
2011 [77]	Laser	808	Mouse	10	2	AD	Anti-inflammation
2011 [78]	Laser	810	Mouse	50	12	TBI	Neuroprotection
2010 [79]	LED	670	Mouse	7.5	1.5	PD	Neuroprotection
2010 [80]	Laser	808	Rabbit	25	2	Stroke	ATP
2010 [81]	Laser	665/810	Mouse	150	4	TBI	Behavior
2007 [82]	Laser	808	Mouse	20	2	TBI	Neuroprotection
2006 [83]	Laser	808	Rat	7.5	2	Stroke	Behavior
2002 [84]	Laser	660	Rat	44	5	Ischemia	Anti-inflammation

Abbreviations: AD, Alzheimer's disease; PD, Parkinson's disease; TBI, traumatic brain injury.

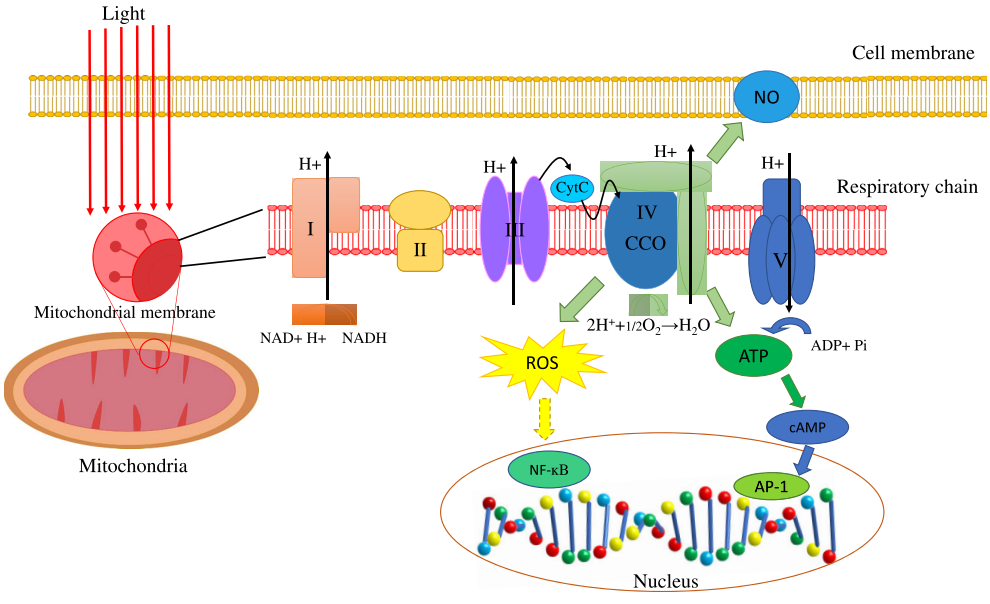


FIGURE 2 Mitochondrial mechanisms of photobiomodulation. Upon light shining on the tissue, photons pass through cell membranes to directly interact with mitochondria. In the inner membrane of a mitochondrion, photons induce a series of reactions on the respiratory chain, boosting ATP production and regulating downstream signaling pathways which may affect gene translation and expression

structure. Accepted photons can stimulate electrons from a ground state to an excited state, accompanying a conformation change of the photoacceptors. This process further affects the downstream signaling pathway such as DNA transcription and gene expression [86].

In PBM, the photoacceptor targeted by red light and NIR light is the mitochondrial enzyme called cytochrome-*c*-oxidase (CCO). Being the terminal enzyme of the mitochondrial electron transfer chain in eukaryotic cells, CCO is composed of 13 protein subunits, including

four redox-active metal centers—two copper centers (Cu_A and Cu_B) and two heme centers (Heme a and Heme a_3). Based on the biological structure, CCO can work as the photoreceptor absorbing the visible and infrared lights and further influences the related signaling pathway. Also, CCO can catalyze the transfer of electrons from cytochrome-*c* to molecular oxygen [87]. When light is shone on CCO, photon energy is accepted by the metal centers of CCO. As a result, cytochrome-*c* loses electrons to become oxidized, which can catalyze the reduction of oxygen to water in cellular respiration. Dissociation of nitric oxide (NO) happens at the same time, which originally binds to the heme irons and copper centers of CCO. NO competes with oxygen and inhibits the activity of CCO, further limiting the cellular respiration [29].

When red/NIR light strikes cells, it penetrates the cell membrane and is absorbed by the CCO on the mitochondria membrane. There is electron transport on the respiratory chain, which further produces ATP and reactive oxygen species (ROS) to change the cellular function. This process also triggers a series of downstream signaling pathways which affect gene translation and expression (see Fig. 2). Through the activation of related genes, PBM can affect other physiological processes indirectly.

Light absorption also results in the increased production of ATP. CCO, the terminal enzyme in the electron transport chain, is located in the outer mitochondrial membrane, where redox reactions take place to drive electrons moving across. The electron transfer produces a proton gradient across the mitochondrial membrane and further boosts the energy production by enhancing the activity of ATP synthase, which converts ADP to ATP [88]. Having the highest energy demand in the body, the brain requires a large amount of ATP to sustain the normal functions of neurons, such as maintaining membrane potential or conducting action potential. Of all neuron actions, active transport of ions against their concentration and electrical gradients serves as a mechanical basis and is the greatest energy-consuming activity [89,90]. As a result, neuronal activity and energy metabolism are closely connected with mitochondria—the primary source of energy supply. In some neurological diseases, such as AD and TBI, the main contributing factor of pathological symptoms is mitochondrial dysfunction [91,92]. Also, the distribution of mitochondria inside neurons displays different metabolic requirements; for example, the highest amount of mitochondria exist in dendrites, a moderate amount in cell bodies and the lowest amount in axons. Subcellular structure of mitochondria maximizes efficiency in energy utilization, providing immediate energy upon demand.

In addition to increased ATP formation, PBM may also initiate cell-signaling pathways known as secondary effects. These effects will take place in hours or in days after light exposure, mainly including an increase in the NAD/NADH (nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide) ratio and mitochondrial intermembrane potential, dissociation of nitric oxide from its binding site in cytochrome oxidase and changes in gene expression. These effects impact mitogenic signaling, surface molecule expression and expression of proteins regulating inflammation, redox states and apoptosis.

NO release also plays an essential role in the therapeutic effect of PBM. It competes with oxygen for the binding to CCO [29], so when the red/NIR light shines, the increase of oxygen consumption and NO production happen at the same pace (see Fig. 2). When combined with CCO, NO works as a cellular respiration inhibitor, so PBM therapy can reverse the mitochondria inhibition of cellular respiration by releasing the excessive binding of NO.

With an increase in the mitochondrial membrane potential by PBM, there is also an increase of ROS, which is linked to various pathologic conditions, such as hypoxia [93] and aging [94]. ROS starts from the superoxide produced by complexes I and III of electron-transport chain in mitochondria, and the superoxide further induces the production of hydrogen peroxide and other downstream products, which are called ROS in total [95]. Excessive ROS is linked to the dysfunction of mitochondria, so there exists a self-amplifying feedback loop called "ROS-induced ROS release." When cells undertake excessive or prolonged oxidative stress, the ROS level may reach the threshold and trigger the opening of the mitochondrial channel [96].

2.2 | Light-gated ion channels

In addition to CCO being the most potent chromophore in PBM, accumulating evidence has also found other primary chromophores playing essential roles in PBM such as opsins, flavins and cryptochromes. They can absorb light at shorter wavelengths (blue and green light), which induce protein configuration changes and further initiate downstream signaling pathways.

Although supported by limited research, the light-gated ion channel is another action mechanism of PBM. Transient receptor potential (TRP) channels are a leading group of light-gated ion channels in PBM. TRP channels are a superfamily consisting of over 28 distinct members, organized into six subfamilies based on their primary amino acid structures [97]. As pleiotropic cellular sensors, TRP channels can mediate the response to a wide range of external stimuli (heat, cold, pressure, taste, and smell) and are involved in many different cellular processes [97]. Activation of TRP causes nonselective permeabilization (mainly of the plasma membrane) to calcium, sodium and

magnesium [98]. TRP channels were recently reported to be involved in sensing the "redox status" [99]. Light-gated ion channels have attracted much attention in the application of optogenetics, and more evidence indicates green light activation of TRP channels [100, 101]. However, green light has reduced penetration distance as compared with red or infrared light, so its practical clinical application is limited.

3 | PBM IN THE NEUROLOGICAL DISEASES

3.1 | PBM in dementia and ADs

Dementia is a major neurocognitive disease caused by abnormal brain function and prompts confusion in daily activities [48]. AD accounts for the majority of dementia cases, affecting millions of older adults worldwide. There are histopathological changes in the AD brain characterized by extracellular accumulation of amyloid-beta (Aβ) plaques and intracellular tangles of hyperphosphorylated tau protein [88]. A large amount of effort has been put into figuring out the causative mechanism, but, unfortunately, it remains elusive.

Years of research has culminated in several commercialized drugs approved by the FDA, including Donepezil, Galantamine, Rivastigmine, Memantine and Namzaric. Disappointingly, none of these drugs are effective in reversing the symptoms of AD or stopping the progress of neurodegeneration. As a result of that, researchers are searching for alternative therapy methods for AD. As a noninvasive method, PBM can alleviate a broad spectrum of Aβ-induced pathologies that includes mitochondrial dysfunction, oxidative stress, neuroinflammation, neuronal apoptosis and tau pathology [46]. Therefore, PBM may be a promising therapy in the treatment of AD.

Highly promising results of PBM therapy on AD were provided in 2011 by de Taboada et al [77]. They discovered a significant reduction of Aβ in the mouse brain when treated with 810 nm laser light. There was also a dose-dependent reduction of soluble amyloid-β protein precursor and brain inflammatory markers [77]. This may due to the anti-inflammatory effect of tPBM therapy. Purushothuman et al confirmed the PBM potential on transgenic mouse models using 670 nm LED light [62]. There was an evident decrease of hyperphosphorylated tau protein, neurofibrillary tangles, oxidative stress markers in the hippocampus and neocortex and increased expression of CCO in surviving neurons [62].

Instead of tPBM therapy, Farfara et al used peripheral PBM targeting the bone marrow to study the therapeutic effects mesenchymal stem cells may have on AD [102]. Mesenchymal stem cells have the ability of multilineage differentiation from a single cell and reconstitution of injured tissues [103, 104]. In this aspect, neurogenesis may be able to reverse the neurodegeneration of the brain. At a wavelength of 810 nm, there is a significant reduction of Aβ and improved cognitive performance of mice [102]. PBM can stimulate the clearance of Aβ through meningeal lymphatic vessels (MLV). Newly discovered MLV are drainage routes for clearance of macromolecules, collecting wastes from cerebrospinal fluid and ISF and sending it to the cervical lymph nodes [105]. Accumulation of Aβ protein in the brain is associated with the reduction of synapses and cognitive dysfunction. Zinchenko et al used gold nanorods (GND) to mimic the deposition of Aβ in the hippocampus and cortex [6]. They found that when applying 1267 nm laser PBM to the mouse brain, there is a reduction of GND in these brain areas. Furthermore, in the Aβ-injected AD model, they discovered increased clearance of Aβ by tPBM and cognition improvement in the mouse [6].

3.2 | PBM in PD

PD is the second most common neurodegenerative disorder. Patients suffering PD will display typical symptoms related to motor deficits, such as resting tremors, rigidity and difficulty in initiating and sustaining voluntary movements [106, 107]. The widely acknowledged mechanism for explaining these symptoms is the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) of the midbrain [108, 109]. The loss of cells will contribute subsequently to a reduction in the levels of dopamine in the striatum, which is a hallmark of the disease. Along with this primary loss of dopaminergic cells in the brainstem, there are also pathological changes in the regions of the olfactory bulb, the dorsal motor nucleus of the vagus nerve and the locus coeruleus, while affecting the cortex as the disease progresses into the later stages.

PD can result from exposure to neurotoxins, such as paraquat, rotenone, 6-hydroxydopamine (6-OHDA) and methyl-4phenyl-1,2,3,6-tetrahydropyridine (MPTP). Based on this, current animal models are constructed with 6-OHDA or MPTP injections to specific brain areas. As an example, when MPTP is injected into the brain, MPTP can convert to an active form, MPP^+, which becomes concentrated in the mitochondria. MPP^+ can suppress the function of complex 1 of the electron transport chain, leading to ATP depletion and oxygen-free radical accumulation. This process causes a detrimental effect on cell proteins, including tyrosine hydroxylase (TH) [79,110–112]. To combat this, PBM therapy performs a neuroprotection role

through activation of the mitochondrial respiration chain and increases ATP synthesis.

In vitro tests by Liang et al [113] and Ying et al [114] have shown PBM (670 nm LED light) to reverse the effects of neurotoxins through increased ATP production and reduced oxidative stress in rat striatal and cortical cells, confirming its neuroprotective roles. Trimmer et al [115] have discovered the movement of mitochondria along axons when treated with PBM (810 nm laser light). The same neuroprotection effects of PBM are manifested in chemical-induced animal models and transgenic animal models. Purushothuman et al [116] used the K3 transgenic mouse model, which can overexpress tau protein after mutation of the pathogenic K369I gene. After applying a 670 nm LED light, they found decreased oxidative stress and hyperphosphorylated tau and increased dopaminergic cell survival in the SNc. There is also a promising result on nonhuman primate. PBM can affect gene expression through signaling pathways, and early onset of PD starts from gene mutations—presynaptic protein α-synuclein being the most important. Accumulation of synuclein in neuron cells is the leading cause of cell death [76].

A large degree of cell loss in the SNc (50%-70%) is the precondition of PD motor symptoms to become clinically evident [117, 118], offering possibilities to detect and arrest disease progress before clinical symptoms become too severe. PBM can perform its neuroprotective roles by activating downstream signaling pathways which increase the expression of trophic factors such as glia-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF). Massri et al [119] tested PBM therapy on a MPTP-induced PD monkey model with the stimulation of a 670 nm laser light and discovered a striking increase in striatal TH^+ cell numbers, accompanied by increases in GDNF expression. PBM also displays its function by controlling cerebrovascular leakage in the MPTP-induced PD mouse model. Miguel et al [120] perfused fluorescein isothiocyanate (FITC) labeled albumin into SNc and CPu (caudate-putamen complex) brain areas of MPTP-induced mice and noticed a significant reduction of leakage under 670 nm tPBM. Besides tPBM, remote PBM targeting on peripheral tissue also displays protective effects against PD mice. Johnstone et al [65] compared remote PBM with tPBM on the MPTP mouse model and noticed an increased number of TH^+ cells in SNc at mild MPTP dose (50 mg/kg) when 670 nm NIR was targeting the mouse dorsum, although not as robust as the effect of tPBM.

3.3 | PBM in TBI

As one of the leading causes of death and disability, TBI is affecting the daily life of 69 million people worldwide [121]. The trauma to the head usually comes from traffic accidents, sports injury, or even blast injury from military conflict. Based on the severity degree, TBI can be classified into three types: mild (loss of consciousness 0-30 minutes, altered mental state <24 hours, posttrauma amnesia <1 day), moderate (loss of consciousness 30 minutes to 24 hours, altered mental state >24 hours, posttrauma amnesia >1-7 days) and severe (loss of consciousness >24 hours; altered mental state >24 hours; posttrauma amnesia >7 days) [122]. Although having minimum severity, mild TBI may be induced by repeat concussions which cause cumulative damage to the neural system.

TBI results in cerebral structural damage and function deficits through both primary and secondary injuries. Survivors from TBI often develop chronic neurocognitive, psychological and neurological diseases that will profoundly affect the quality of daily life [123]. TBI is also a causative factor of acquired epilepsy, which is defined as recurrent and unprovoked seizures that occur at least 1 week after TBI, resulting in severe behavioral morbidity [124]. Recovery of function in TBI mostly occurs through behavioral practice and molecular and cellular routes, including upregulated gene expression, axon sprouting and neural connection remapping [125]. Although researchers widely study these phenomena, there are still no medical therapies to relieve these symptoms. As a noninvasive approach, tPBM may be an effective treatment for TBI.

tPBM can reduce neuroinflammation by reducing activated microglia. Zhang et al [61] took advantage of gene X-1 deficient mice to study the anti-inflammatory effect of PBM. Mice lacking the early responsive X-1 gene continuously suffer a secondary brain injury characterized by a pathologic lesion with extensive cell death, widespread leukocyte infiltrates and severe tissue loss. However, PBM treatment saved the mice from secondary brain injury and suppressed pro-inflammatory cytokine expression of interleukin (IL)-1b and IL-6.

tPBM can protect against apoptosis and reduce the lesion area. Using a hypoxic TBI model, Dong et al [60] observed a suppressive effect of 810 nm PBM therapy on cell apoptosis by downregulating the apoptotic protease activating factor. PBM blunted cytochrome-*c* leakage and retained cytochrome-*c* in the mitochondria in these hypoxic cells. PBM also protected blood vessels from a secondary injury of cerebral hypoxia.

tPBM can increase cerebral blood flow, leading to increased tissue oxygenation and oxidized CCO. Nawashiro et al [73] performed PBM therapy on a patient who suffered a vegetative state after severe head

injury. There was a significant increase in the regional cerebral blood flow after transcranial treatment of 850 nm LED light. Later on, the medical disability of this patient discontinued.

tPBM may also induce neurogenesis and synaptogenesis to cure brain injury. Xuan et al reported an improved neurological severity score with 810 nm laser light treatment on mice [55], and the immunohistochemical results on brain slices showed an increased expression of BDNF, a crucial regulator of synaptic plasticity. The induction of BDNF may lead to an increase of synaptogenesis in the cortex, which explains the improved neurological functions.

3.4 | PBM in stroke

Stroke is the second leading cause of death and disability worldwide, having a high incidence rate, high mortality rate and high disability rate. Based on the pathological mechanism, it can be divided into two types: ischemic stroke resulting from poor blood supply and hemorrhagic stroke caused by bleeding. Ischemic stroke has a higher incidence rate compared with hemorrhagic stroke, and it is induced by the occlusion of the cerebral vasculature, resulting in irreversible tissue infarction and abnormal cellular death.

Current stroke therapy includes the thrombolytic drug Alteplase, which is approved by the FDA for acute ischemic stroke. With increasing research in light therapy, PBM serves as a promising, noninvasive therapeutic method. It can increase cerebral blood flow through the release of NO from CCO and increase the energy supply by ATP production. In 2006, Detaboada et al [83] did the first animal experiment on rats to test PBM treatment on acute stroke. Then, 808-nm laser light was applied to three different sites on the shaved head. There were significant improvements in the neurological severity score after PBM therapy.

Ilic et al [126] tested the safety of PBM therapy under several different power densities and found there is no neurological and histological damage except under very high power density (750 mW/cm^2). As cells continue to die after stroke onset, an optical treatment window exists for stroke. Oron et al [127] tested the timing of PBM (either 4 or 24 hours poststroke). There was no significant difference in the 4 hours poststroke groups, but there were increased neural progenitor cells in the 24 hours poststroke group and increased expression of migration markers for these cells. This confirmed PBM could significantly reduce neurological deficits. Lapchak et al [128, 129] used a rabbit to construct a clot embolic stroke model. After PBM therapy with 808 nm laser light, the rabbit experienced improved motor function. They also found no difference between pulsed light and continuous-wave light. A series of clinical trials named NeuroThera Effectiveness and Safety Trials (NEST-1, NEST-2 and NEST-3) was carried out starting in 2007 [130]. They were international, double-blind, randomized, sham (placebo) controlled trials conducted at six medical centers in three countries: Israel, Peru and Sweden. The study evaluated the safety and effectiveness of PBM treatment on ischemic stroke. tPBM worked well in NEST-1 and NEST-2 but failed in NEST-3 [131, 132]. For the failure of tPBM in NEST-3, possible reasons include the selection of late therapeutic window which could influence the therapeutic performance of tPBM. Other reasons may lay by the lack of dosage to penetrate the thick human skull. To achieve better result in future clinical trials, more effective dosage as well as earlier therapeutic window are of primary consideration.

3.5 | PBM in cerebral ischemia

Cerebral ischemia is a pathological condition when blood supply cannot meet metabolic demand. This insufficient blood flow can further restrict oxygen-rich blood into the brain and cause brain injury. This symptom mainly occurs in neonatal and older people [34]. For infants, cerebral ischemia can be caused by impaired cerebral blood flow and oxygen deprivation, affecting the brain within the perinatal period. Moreover, for older adults, aging of the vasculature and heart attack are the primary causes of ischemia. It can induce severe life-long motor and cognitive deficits, which lowers the patient's quality of life and adds a burden to family and society [40].

As is known to all, the brain is an energy-consuming organ that needs a continuous supply of oxygen and glucose to maintain its survival and function. However, due to the deprivation of oxygen and glucose in cerebral ischemia, brain injury occurs due to delayed neuronal cell death in the cortex and hippocampus, resulting in impairments in hearing, learning, behavior, or even death. Mitochondria are the primary energy supply inside the brain, and their dysfunction will result in fission followed by the release of proapoptotic proteins into the cytosol. PBM is effective in regulating mitochondrial function, so it provides another choice of therapeutic intervention against brain ischemia. NO is a cytotoxin produced during the ischemia process; it has a protective function only during the very early stage (<2 hours) of cerebral ischemia, but its overproduction will be detrimental to neuronal survival. Transforming growth factor-β1 (TGF-β1) is a protective endogenous mediator in brain

ischemia. The action of these two mediators is closely related to neuronal survival and neurite growth.

Leung et al [84] studied PBM treatment by application of a 660 nm laser light with a brain ischemia rat model. Under more prolonged laser treatment (5 and 10 minutes), there was a significant reduction of nitric oxide synthase and increased TGF-β1 in the right hemisphere. Mitochondria undergo cycles of fission and fusion, and optic atrophy 1 is essential in the fusion process, while Dynamin-related protein 1 (Drp1) functions as a mitochondrial fission protein. Using a laser light of 808 nm wavelength, Wang et al [34] confirmed the therapeutic effect of PBM on neuronal protection, behavior improvement and suppression of mitochondrial fragmentation by Drp1 downregulation.

4 | FUTURE DIRECTIONS

In this review, we described potential PBM mechanisms from the perspectives of mitochondria and light-activated ion channels. The interaction between red/NIR light with mitochondria can trigger several different physiological reactions, including ATP synthesis, NO release, ROS production and trigger downstream signaling pathways. Compared with the mitochondrial mechanism, less is known in the field of light-activated ion channels, which remains a potential research focus.

The primary concern of applying PBM in clinical settings stems from uncertainty of its induced biochemical mechanisms, which has been confirmed through molecular-level studies. To increase its credibility among the public, other confirming methods and techniques, such as functional and structural brain mapping, can be used from cortical to subcortical levels to define the relationship between light absorption and neuronal activities. Future work should also implement electrophysiological assessments to understand transient neuronal activity and long-term network interactions in response to light stimulation.

According to our summary of PBM parameters (Tables 1-6), there are significant variations of power density and time duration. This variation comes from the light source (laser or LED) and power supply. Laser light tends to have a shorter acting duration with relatively higher power densities and a coherent light beam. In some studies, researchers preferred long period acting cycles, usually in days or weeks, while others prefer a one-time treatment. Moving forward, both longer periods and a one-time treatment should be considered in further research.

Biphasic dose response exists in PBM. It means insufficient power density or too short duration will

TABLE 2 Parameters of preclinical studies of tPBM on Parkinson's disease

Year [ref]	Species	Age	Gender	Mechanism	μ	Device brand	Type	Time	Target	Spot size	Power density
2019 [120]	C57BL/6 mouse	12 wk	Male	Neuroinflammation	670	Quantum Devices	LED	3 min×7 d	Head	Unknown	50 mW/cm^2
2019 [7]	SD rat	210-240 g	Male	Neuroinflammation	670	Quantum Devices	LED	88 s×2×6 d	Head	10 cm^2	50 mW/cm^2
2016 [54, 133]	Macaque Monkey	4-5 y	Male	Neuroprotection	670	Boston Scientific	Laser	5 s on 60 s off for 24 h	SNc	Optic fiber	35 J
2016 [134]	BALB/c mice	8–10 wk	Male	Neuroprotection	670	Quantum Devices	LED	90 s	Head	Unknown	5.3 mW/cm^2
2015 [135]	Wistar rat	8 wk	Male	Neuroprotection	670	Epitex	LED	90 s × 2 × 23 d	SNc	Optic fiber	634 mJ
2015 [58]	SD rat	180-200 g	Female	Neuroprotection	808	Roithner Lasertechnik	Laser	100 s/day×4 wk	Head	1 cm^2	2.5 and 5 mW/cm^2
2014 [136]	BALB/c mice	Unknown	Male	Neuroprotection	670	Epitex	LED	6 min/2.5 h	Lateral ventricles	Optic fiber	0.16 mW

Abbreviations: LED, light-emitting diode; SNc, substantia nigra pars compacta; tPBM, transcranial photobiomodulation.

TABLE 3 Parameters of preclinical studies of tPBM on Alzheimer's disease and dementia

Year [ref]	Species	Age	Gender	Mechanism	μ	Device brand	Type	Time	Target	Spot size	Power density
2019 [6]	Mongrel mice	25 g	Male	Ab clearance	1267	Innolume	Laser	17 min×3	Frontal cortex	5 mmd	50, 100, 150, 200 mW/cm^2
2018 [42]	Swiss mice	30-35 g	Male	Neuroprotection	850/625	REGEnLIFE	Laser + LED	10 min	Head	1 cm^2	28 mW/cm^2 skin surface
2017 [46]	SD rat	250-280 g	Male	Mitochondrial function	808	Dragon lasers	Laser	2 min	Between eye and ear	1 cm^2	25 mW/cm^2
2017 [49]	Wistar rat	200-250 g	Male	Neuroinflammation	627	Superbrightled	LED	100 s	Scalp	5 mmd	70 mW/cm^2
2017 [47]	BALB/c mice	25-30 g	Male	Mitochondrial function	660 + 810	Thor photomedicine	Laser	2.5 s × 3 d × 6 wk	Head	Unknown	8 J/cm^2 at cortical
2015 [102]/ 2014 [62]	APP/S1 and K3 mice	7 mo/5 mo	Unknown	Neuroprotection	670	Quantum Devices	LED	90 s × 5 d × 4 wk	Head	Unknown	2 mW/cm^2

Abbreviations: LED, light-emitting diode; tPBM, transcranial photobiomodulation.

TABLE 4 Parameters of preclinical studies of tPBM on traumatic brain injury

Year [ref]	Species	Age	Gender	Mechanism	μ	Device brand	Type	Time	Target	Spot size	Power density
2020 [31]	SD rat	300-320 g	Male	Neuroprotection	808	Dragon laser	Laser	2 min × 15	Scalp	Unknown	350 mW/cm^2
2016 [50]	BALB/c mice	6-8 wk	Male	Neurogenesis	810	HOYA ConBio	Laser	12 min	Head	1 cmd	25 mW/cm^2
2015 [55]	BALB/c mice	6-8 wk	Male	Neurogenesis	810	PhotoThera	Laser	12 min	Head	1 cmd	50 mW/cm^2
2015 [60]	C57BL/6 mice	8 wk	Unknown	Neuroprotection	810	Aculaser	Laser	4 min	Head	1 cmd	150 mW/cm^2
2014 [61]	C57BL/6 transgenic mice	8 wk	Unknown	Neuroinflammation	810	PhotoThera	Laser	4 min	Head	1 cmd	150 mW/cm^2

Abbreviation: tPBM, transcranial photobiomodulation.

TABLE 5 Parameters of preclinical studies of tPBM on stroke

Year [ref]	Species	Age	Gender	Mechanism	μ	Device brand	Type	Time	Target	Spot size	Power density
2019 [33]	Wistar rat	200 g	Unknown	Neurogenesis	904	Self-made	LED	63 s × 21 d	Frontal region of brain	5 mmd	7 J/cm^2
2018 [44]	SD rat	200-250 g	Male	Neurogenesis	808	Dragon lasers	Laser	2 min × 7 d	Infarct injury area	1 cm^2	350 mW/cm^2 on the scalp
2015 [59]	FVB mice	>60 postnatal	Unknown	Cell proliferation and migration	532	SUWTECH	Laser	60 min	Skull over left auditory cortex	7.1 mm^2	845 mW/cm^2

Abbreviations: LED, light-emitting diode; tPBM, transcranial photobiomodulation.

TABLE 6 Parameters of preclinical studies of tPBM on cerebral ischemia

Year [ref]	Species	Age	Gender	Mechanism	μ	Device brand	Type	Time	Target	Spot size	Power density
2019 [10]	SD rat	10 day	Hoth	Neuroprotection	808	Dragon lasers	Laser	2 min	Between eye and ear	1 cm^2	100 mW/cm^2
2019 [34]	SD rat	250-300 g	Male	Neuroprotection	808	Dragon lasers	Laser	500 s	Scalp	1 cm^2	8 mW/cm^2 at hippocampus
2019 [37]	BALB/c	8–10 wk	Male	Neuroinflammation	810	Thor photomedicine	Laser	5 s	Between eye and ear	0.03 cm^2	6.66 W/cm^2
2019 [40]	SD rat	12 wk	Male	Neurogenesis	830	Quantum devices	LED	30 min/day/wk × 12 wk	Head	1 cm^2	10 mW/cm^2
2018 [43]	rat	Postnatal	Both	Neuroprotection	808	Dragon lasers	Laser	2 min/7 d	Cerebral cortex	1 cm^2	25 mW/cm^2
2016 [137]	C57BL/6 mice	20-25 g	Male	Neuroinflammation	610	Color seven	LED	20 min	Head	4 mmd	17 mW/cm^2
2015 [59]	FVB mice	>60 postnatal		Proliferation and migration	532	SUWTECH	Laser	60 min	Auditory cortical area	7.1 mm^2	845 mW/cm^2

Abbreviations: LED, light-emitting diode; tPBM, transcranial photobiomodulation.

have little effect on the pathology, while too much power density and / or duration may have inhibitory effects. There may be an optimal balance between power density and time that produces a maximal beneficial effect [138]. This should be taken into great consideration.

As noted in Tables 2 to 6, locations of measuring power density are not uniform or standardized. Some measurements were taken at the surface of scalp, some from the surface of skull and others from the cortex level. Regulations need to be made regarding measurement location, so power density and other parameters can be comparable among different studies and useful for downstream research.

A difference in the size of the targeting area can also affect power density. Considering the coherence property of laser light, it is much easier to measure its spot size as compared to LED light, so the spot size of LED in tPBM should be clarified in future research.

Comparison of separate parameters on a fixed neurological disease is summarized in Tables 2 to 6. This practical toolbox can offer guidance in experimental design on further research regarding neurological diseases. Future studies should compare different power densities under fixed conditions as well as target size and acting duration of PBM.

Being a powerful noninvasive treatment method, PBM alone has shown promising results in treating neurological diseases such as neuroprotection and anti-inflammation. When combined with other therapeutic methods such as optogenetic tools and nanosized drug delivery, it is believed to improve the efficiency and outcome in curing neurological diseases.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Lin Li: Designed and directed the project. **Jing You**: Performed the article search and data analysis. **Jing You**, **Anatol Bragin**, **Hanli Liu** and **Lin Li**: Contributed to the writing of the manuscript.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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REFERENCES

[1] M. R. Hamblin, Y.-Y. Huang, *Photobiomodulation in the Brain: Low-Level Laser (Light) Therapy in Neurology and Neuroscience*, Academic Press, Cambridge, MA **2019**.
[2] H. Chung, T. Dai, S. K. Sharma, Y.-Y. Huang, J. D. Carroll, M. R. Hamblin, *Ann. Biomed. Eng.* **2012**, *40*(2), 516.
[3] E. Mester, G. Ludany, M. Selyei, B. Szende, G. Total, *The Stimulating Effect of Low Power Laser Rays on Biological Systems*, Medical University, Budapest **1968**.
[4] E. Mester, B. Szende, J. Tota, *Kiserl. Orvostud.* **1967**, *19*, 628.
[5] L. Gáspár, *J. Laser Dent.* **2009**, *17*(3), 146.
[6] E. Zinchenko, N. Navolokin, A. Shirokov, B. Khlebtsov, A. Dubrovsky, E. Saranceva, A. Abdurashitov, A. Khorovodov, A. Terskov, A. Mamedova, M. Klimova, I. Agranovich, D. Martinov, V. Tuchin, O. Semyachkina-Glushkovskaya, J. Kurts, *Biomed. Opt. Express* **2019**, *10*(8), 4003.
[7] J. A. O'Brien, P. J. Austin, *Biomolecules* **2019**, *9*(8), 381.
[8] M. A. Naeser, M. D. Ho, P. I. Martin, M. R. Hamblin, B.-B. Koo, *Photobiomod. Photomed. Laser Surg.* **2020**, *38*(2), 115.
[9] J. G. R. P. dos Santos, A. L. C. Zaninotto, R. A. Zângaro, A. M. C. Carneiro, I. S. Neville, A. F. de Andrade, M. J. Teixeira, W. S. Paiva, *Trials* **2018**, *19*(1), 249.
[10] L. Yang, Y. Dong, C. Wu, Y. Li, Y. Guo, B. Yang, X. Zong, M. R. Hamblin, T. C. Y. Liu, Q. Zhang, *J. Biophotonics* **2019**, *12*(6), e201800359.
[11] R. Zomorrodi, G. Loheswaran, A. Pushparaj, L. Lim, *Sci. Rep.* **2019**, *9*(1), 6309.
[12] S. H. Yun, S. J. J. Kwok, *Nat. Biomed. Eng.* **2017**, *1*(1), 8.
[13] S. Mihashi, G. J. Jako, J. Incze, M. S. Strong, C. W. Vaughan, *Ann. N. Y. Acad. Sci.* **1976**, *267*(1), 263.
[14] C. Raulin, S. Karsai, *Laser and IPL Technology in Dermatology and Aesthetic Medicine*, Springer Science & Business Media, Berlin, Germany **2011**.
[15] L. Goldman, *The Biomedical Laser: Technology and Clinical Applications*, Springer Science & Business Media, Berlin, Germany **2013**.
[16] D. N. Dederich, *J. Am. Dent. Assoc.* **1993**, *124*(2), 57.
[17] C. Kittrell, R. M. Cothren, M. S. Feld, Laser spectro-optic imaging for diagnosis and treatment of diseased tissue. Google Patents **1992**.
[18] C. Y. Mardin, F. K. Horn, J. B. Jonas, W. M. Budde, *Br. J. Ophthalmol.* **1999**, *83*(3), 299.
[19] V. V. Tuchin, *Tissue Optics: Light Scattering Methods and Instruments for Medical Diagnosis*, SPIE Press Book, Bellingham, WA **2007**.
[20] M. Hennessy, M. R. Hamblin, *J. Opt.* **2017**, *19*(1), 013003.
[21] F. Salehpour, P. Cassano, N. Rouhi, M. R. Hamblin, L. de Taboada, F. Farajdokht, J. Mahmoudi, *Photobiomodul. Photomed. Laser Surg.* **2019**, *37*(10), 581.
[22] F. Salehpour, J. Mahmoudi, F. Kamari, S. Sadigh-Eteghad, S. H. Rasta, M. R. Hamblin, *Mol. Neurobiol.* **2018**, *55*(8), 6601.
[23] P. E. McGuff, R. A. Deterling Jr., L. S. Gottlieb, H. D. Fahimi, D. Bushnell, *Ann. Surg.* **1964**, *160*(4), 765.
[24] V. Heiskanen, M. R. Hamblin, *Photochem. Photobiol. Sci.* **2018**, *17*(8), 1003.
[25] H. T. Whelan, J. M. Houle, N. T. Whelan, D. L. Donohoe, J. Cwiklinski, M. H. Schmidt, L. Gould, D. L. Larson, G. A. Meyer, V. Cevenini, *The NASA Light-Emitting Diode Medical Program—Progress in Space Flight and Terrestrial Applications.*

AIP Conference Proceedings, American Institute of Physics, Melville, NY **2000**.
[26] N. Holonyak Jr., S. Bevacqua, *Appl. Phys. Lett.* **1962**, *1*(4), 82.
[27] Y. Chen, L. de Taboada, M. O'Connor, S. Delapp, J. A. Zivin, *Neurosci. Lett.* **2013**, *553*, 99.
[28] J. C. Rojas, F. Gonzalez-Lima, *Biochem. Pharmacol.* **2013**, *86* (4), 447.
[29] L. F. de Freitas, M. R. Hamblin, *IEEE J. Sel. Top. Quantum Electron.* **2016**, *22*(3), 348.
[30] J. J. Anders, R. J. Lanzafame, P. R. Arany, *Photomed. Laser Surg.* **2015**, *33*(4), 183.
[31] B. Yang, J. Xu, Y. Li, Y. Dong, Y. Li, L. Tucker, L. Yang, X. Zong, C. Wu, T. Xu, *J. Biophotonics* **2020**, *13*(2), e201960117.
[32] 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, *J. Neurotrauma* **2020**, *37*(8), 1108.
[33] 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, *Lasers Med. Sci.* **2019**, *34*(8), 1619.
[34] R. Wang, Y. Dong, Y. Lu, W. Zhang, D. W. Brann, Q. Zhang, *Mol. Neurobiol.* **2019**, *56*(3), 1852.
[35] B. Svobodova, A. Kloudova, J. Ruzicka, L. Kajtmanova, L. Navratil, R. Sedlacek, T. Suchy, M. Jhanwar-Uniyal, P. Jendelova, L. Machova Urdzikova, *Sci. Rep.* **2019**, *9*(1), 7660.
[36] F. Salehpour, M. R. Hamblin, J. O. DiDuro, *Photobiomodul. Photomed. Laser Surg.* **2019**, *37*(3), 159.
[37] F. Salehpour, F. Farajdokht, J. Mahmoudi, M. Erfani, M. Farhoudi, P. Karimi, S. H. Rasta, S. Sadigh-Eteghad, M. R. Hamblin, A. Gjedde, *Front. Cell. Neurosci.* **2019**, *13*, 74.
[38] P. Mannu, M. Maiello, V. Spera, P. Cassano, *Photobiomodul. Photomed. Laser Surg.* **2019**, *37*, 579.
[39] A. Jahan, M. A. Nazari, J. Mahmoudi, F. Salehpour, M. M. Salimi, *Lasers Med. Sci.* **2019**, *34*, 1193.
[40] B. Argibay, F. Campos, M. Perez-Mato, A. Vieites-Prado, C. Correa-Paz, E. López-Arias, A. da Silva-Candal, V. Moreno, C. Montero, T. Sobrino, J. Castillo, R. Iglesias-Rey, *Front. Neurol.* **2019**, *10*, 911.
[41] S. G. Hipskind, F. L. Grover Jr., T. R. Fort, D. Helffenstein, T. J. Burke, S. A. Quint, G. Bussiere, M. Stone, T. Hurtado, *Photomed. Laser Surg.* **2018**, *37*, 2.
[42] G. Blivet, J. Meunier, F. J. Roman, J. Touchon, *Alzheimer's Dementia* **2018**, *4*, 54.
[43] L. D. Tucker, Y. Lu, Y. Dong, L. Yang, Y. Li, N. Zhao, Q. Zhang, *J. Mol. Neurosci.* **2018**, *65*(4), 514.
[44] L. Yang, D. Tucker, Y. Dong, C. Wu, Y. Lu, Y. Li, J. Zhang, T. C.-Y. Liu, Q. Zhang, *Exp. Neurol.* **2018**, *299*, 86.
[45] E. Vargas, D. W. Barrett, C. L. Saucedo, L.-D. Huang, J. A. Abraham, H. Tanaka, A. P. Haley, F. Gonzalez-Lima, *Lasers Med. Sci.* **2017**, *32*(5), 1153.
[46] Y. Lu, R. Wang, Y. Dong, D. Tucker, N. Zhao, M. E. Ahmed, L. Zhu, T. C.-Y. Liu, R. M. Cohen, Q. Zhang, *Neurobiol. Aging* **2017**, *49*, 165.
[47] F. Salehpour, N. Ahmadian, S. H. Rasta, M. Farhoudi, P. Karimi, S. Sadigh-Eteghad, *Neurobiol. Aging* **2017**, *58*, 140.
[48] A. E. Saltmarche, M. A. Naeser, K. F. Ho, M. R. Hamblin, L. Lim, *Photomed. Laser Surg.* **2017**, *35*(8), 432.
[49] C. da Luz Eltchechem, A. S. I. Salgado, R. A. Zângaro, M. C. da Silva Pereira, I. I. Kerppers, L. A. da Silva, R. B. Parreira, *Lasers Med. Sci.* **2017**, *32*(4), 749.
[50] W. Xuan, L. Huang, M. R. Hamblin, *J. Biophotonics* **2016**, *9* (11–12), 1263.
[51] C. Werner, M. Byhahn, S. Hesse, *Restor. Neurol. Neurosci.* **2016**, *34*(4), 561.
[52] M. A. Naeser, P. I. Martin, M. D. Ho, M. H. Krengel, Y. Bogdanova, J. A. Knight, M. K. Yee, R. Zafonte, J. Frazier, M. R. Hamblin, B.-B. Koo, *Photomed. Laser Surg.* **2016**, *34* (12), 610.
[53] J. Hwang, D. M. Castelli, F. Gonzalez-Lima, *Lasers Med. Sci.* **2016**, *31*(6), 1151.
[54] F. Darlot, C. Moro, N. el Massri, C. Chabrol, D. M. Johnstone, F. Reinhart, D. Agay, N. Torres, D. Bekha, V. Auboiroux, T. Costecalde, C. L. Peoples, H. D. T. Anastascio, V. E. Shaw, J. Stone, J. Mitrofanis, A.-L. Benabid, *Ann. Neurol.* **2016**, *79*(1), 59.
[55] W. Xuan, T. Agrawal, L. Huang, G. K. Gupta, M. R. Hamblin, *J Biophotonics* **2015**, *8*(6), 502.
[56] N. J. Blanco, W. T. Maddox, F. Gonzalez-Lima, *J. Neuropsychol.* **2017**, *11*, 14.
[57] S. Purushothuman, D. M. Johnstone, C. Nandasena, J. V. Eersel, L. M. Ittner, J. Mitrofanis, J. Stone, *Neurosci. Lett.* **2015**, *591*, 155.
[58] A. Oueslati, B. Lovisa, J. Perrin, G. Wagnières, H. van den Bergh, Y. Tardy, H. A. Lashuel, *PLoS One* **2015**, *10*(10), e0140880.
[59] Y. Fukuzaki, H. Shin, H. D. Kawai, B. Yamanoha, S. Kogure, *PLoS One* **2015**, *10*(4), e0123833.
[60] T. Dong, Q. Zhang, M. R. Hamblin, M. X. Wu, *J. Cereb. Blood Flow Metab.* **2015**, *35*(9), 1435.
[61] Q. Zhang, C. Zhou, M. R. Hamblin, M. X. Wu, *J. Cereb. Blood Flow Metab.* **2014**, *34*(8), 1391.
[62] S. Purushothuman, D. M. Johnstone, C. Nandasena, J. Mitrofanis, J. Stone, *Alzheimers Res. Ther.* **2014**, *6*(1), 2.
[63] W. Xuan, F. Vatansever, L. Huang, M. R. Hamblin, *J. Biomed. Opt.* **2014**, *19*(10), 108003.
[64] 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, *J. Neurotrauma* **2014**, *31*(11), 1008.
[65] D. M. Johnstone, N. El Massri, C. Moro, S. Spana, X. S. Wang, N. Torres, C. Chabrol, X. de Jaeger, F. Reinhart, S. Purushothuman, A. L. Benabid, J. Stone, J. Mitrofanis, *Neuroscience* **2014**, *274*, 93.
[66] D. W. Barrett, F. Gonzalez-Lima, *Neuroscience* **2013**, *230*, 13.
[67] C. Meng, Z. He, D. Xing, *J. Neurosci.* **2013**, *33*(33), 13505.
[68] W. Xuan, F. Vatansever, L. Huang, Q. Wu, Y. Xuan, T. Dai, T. Ando, T. Xu, Y.-Y. Huang, M. R. Hamblin, *PLoS One* **2013**, *8*(1), e53454.
[69] B. N. Huisa, Y. Chen, B. C. Meyer, G. M. Tafreshi, J. A. Zivin, *Lasers Med. Sci.* **2013**, *28*(4), 1085.
[70] B. J. Quirk, M. Torbey, E. Buchmann, S. Verma, H. T. Whelan, *Photomed. Laser Surg.* **2012**, *30*(9), 523.
[71] J. Khuman, J. Zhang, J. Park, J. D. Carroll, C. Donahue, M. J. Whalen, *J. Neurotrauma* **2012**, *29*(2), 408.
[72] 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, *Lasers Surg. Med.* **2012**, *44*(3), 218.
[73] H. Nawashiro, K. Wada, K. Nakai, S. Sato, *Photomed. Laser Surg.* **2012**, *30*(4), 231.

[74] A. Oron, U. Oron, J. Streeter, L. de Taboada, A. Alexandrovich, V. Trembovler, E. Shohami, *J. Neurotrauma* **2012**, *29*(2), 401.

[75] M. A. Naeser, A. Saltmarche, M. H. Krengel, M. R. Hamblin, J. A. Knight, *Photomed. Laser Surg.* **2011**, *29*(5), 351.

[76] M. S. Moreira, I. T. Velasco, L. S. Ferreira, S. K. Ariga, F. Abatepaulo, L. T. Grinberg, M. M. Marques, *J. Photochem. Photobiol. B: Biol.* **2011**, *105*(3), 207.

[77] L. de Taboada, J. Yu, S. El-Amouri, S. Gattoni-Celli, S. Richieri, T. McCarthy, J. Streeter, M. S. Kindy, *J. Alzheimer's Dis.* **2011**, *23*(3), 521.

[78] 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, *Comparat Study* **2011**, *6*(10), e26212.

[79] V. E. Shaw, S. Spana, K. Ashkan, A. L. Benabid, J. Stone, G. E. Baker, J. Mitrofanis, *J. Comp. Neurol.* **2010**, *518*(1), 25.

[80] P. A. Lapchak, J. Streeter, L. De Taboada, Transcranial near infrared laser therapy (NILT) to treat acute ischemic stroke: a review of efficacy, safety and possible mechanism of action derived from rabbit embolic stroke studies. in *Mechanisms for Low-Light Therapy V*, International Society for Optics and Photonics, Bellingham, WA **2010**.

[81] Q. Wu, Y.-Y. Huang, S. Dhital, S. K. Sharma, A. C.-H. Chen, M. J. Whalen, M. R. Hamblin, Low level laser therapy for traumatic brain injury. in *Mechanisms for Low-Light Therapy V*, International Society for Optics and Photonics, Bellingham, WA **2010**.

[82] A. Oron, U. Oron, J. Streeter, L. D. Taboada, A. Alexandrovich, V. Trembovler, E. Shohami, *J. Neurotrauma* **2007**, *24*(4), 651.

[83] L. Detaboada, S. Ilic, S. Leichliter-Martha, U. Oron, A. Oron, J. Streeter, *Lasers Surg. Med.* **2006**, *38*(1), 70.

[84] M. C. Leung, S. C. Lo, F. K. Siu, K. F. So, *Lasers Surg Med* **2002**, *31*(4), 283.

[85] F. Gonzalez-Lima, Rojas, *Eye Brain* **2011**, *3*, 49.

[86] J.-C. Heo, J.-A. Park, D.-K. Kim, J.-H. Lee, *Sci. Rep.* **2019**, *9* (1), 10114.

[87] T. I. Karu, L. V. Pyatibrat, S. F. Kolyakov, N. I. Afanasyeva, *J. Photochem. Photobiol. B* **2005**, *81*(2), 98.

[88] M. R. Hamblin, Photobiomodulation for Alzheimer's disease: has the light dawned? in *Photonics*, Multidisciplinary Digital Publishing Institute, Basel, Switzerland **2019**.

[89] D. Attwell, S. B. Laughlin, *J. Cereb. Blood Flow Metab.* **2001**, *21*(10), 1133.

[90] F. Gonzalez-Lima, B. R. Barksdale, J. C. Rojas, *Biochem. Pharmacol.* **2014**, *88*(4), 584.

[91] S. R. Pieczenik, J. Neustadt, *Exp. Mol. Pathol.* **2007**, *83*(1), 84.

[92] O. Kann, *Neurobiol. Dis.* **2016**, *90*, 75.

[93] L. B. Becker, T. L. van den Hoek, Z. H. Shao, C. Q. Li, P. T. Schumacker, *Am. J. Physiol.* **1999**, *277*(6), H2240.

[94] S. Moghaddas, C. L. Hoppel, E. J. Lesnefsky, *Arch. Biochem. Biophys.* **2003**, *414*(1), 59.

[95] M. P. Murphy, *Biochem. J.* **2009**, *417*(1), 1.

[96] X. Zhou, Y. Wang, J. Si, R. Zhou, L. Gan, C. Di, Y. Xie, H. Zhang, *Sci. Rep.* **2015**, *5*, 16925.

[97] M. J. Caterina, Z. Pang, *Pharmaceuticals* **2016**, *9*(4), 77.

[98] C. Montell, *Pflügers Archiv-Eur. J. Physiol.* **2011**, *461*(5), 499.

[99] N. Ogawa, T. Kurokawa, Y. Mori, *Cell Calcium* **2016**, *60* (2), 115.

[100] W. Z. Yang, J. Y. Chen, J. T. Yu, L. W. Zhou, *Photochem. Photobiol.* **2007**, *83*(4), 979.

[101] Q. Gu, L. Wang, F. Huang, W. Schwarz, *Evid. Based Complement Alternat. Med.* **2012**, *2012*, 1.

[102] D. Farfara, H. Tuby, D. Trudler, E. Doron-Mandel, L. Maltz, R. J. Vassar, D. Frenkel, U. Oron, *J. Mol. Neurosci.* **2015**, *55* (2), 430.

[103] A. Uccelli, L. Moretta, V. Pistoia, *Nat. Rev. Immunol.* **2008**, *8* (9), 726.

[104] S. M. Devine, A. M. Bartholomew, N. Mahmud, M. Nelson, S. Patil, W. Hardy, C. Sturgeon, T. Hewett, T. Chung, W. Stock, *Exp. Hematol.* **2001**, *29*(2), 244.

[105] A. Louveau, I. Smirnov, T. J. Keyes, J. D. Eccles, S. J. Rouhani, J. D. Peske, N. C. Derecki, D. Castle, J. W. Mandell, K. S. Lee, *Nature* **2015**, *523*(7560), 337.

[106] F. Blandini, G. Nappi, C. Tassorelli, E. Martignoni, *Prog. Neurobiol.* **2000**, *62*(1), 63.

[107] H. Bergman, G. Deuschl, *J. Mov. Disord.* **2002**, *17*(S3), S28.

[108] J. Rinne, *J. Mov. Disord.* **1993**, *8*(S1), S31.

[109] D. McRitchie, H. Cartwright, G. Halliday, *Exp. Neurol.* **1997**, *144*(1), 202.

[110] B. Bloem, I. Irwin, O. Buruma, J. Haan, R. Roos, J. Tetrud, J. Langston, *J. Neurol. Sci.* **1990**, *97*(2–3), 273.

[111] S. Przedborski, V. Jackson-Lewis, R. Djaldetti, G. Liberatore, M. Vila, S. Vukosavic, G. Almer, *Restor. Neurol. Neurosci.* **2000**, *16*(2), 135.

[112] N. Schmidt, B. Ferger, *J. Neural Transm.* **2001**, *108*(11), 1263.

[113] H. L. Liang, H. T. Whelan, J. T. Eells, M. T. T. Wong-Riley, *J. Neurosci.* **2008**, *153*(4), 963.

[114] R. Ying, H. L. Liang, H. T. Whelan, J. T. Eells, M. T. Wong-Riley, *Brain Res.* **2008**, *1243*, 167.

[115] P. A. Trimmer, K. M. Schwartz, M. K. Borland, L. De Taboada, J. Streeter, U. Oron, *Mol. Neurodegener.* **2009**, *4* (1), 26.

[116] S. Purushothuman, C. Nandasena, D. M. Johnstone, J. Stone, J. Mitrofanis, *Brain Res.* **2013**, *1535*, 61.

[117] H. Braak, K. del Tredici, U. Rüb, R. A. de Vos, E. N. J. Steur, E. Braak, *Neurobiol. Aging* **2003**, *24*(2), 197.

[118] J. M. Fearnley, A. J. Lees, *Brain* **1991**, *114*(5), 2283.

[119] N. el Massri, A. P. Lemgruber, I. J. Rowe, C. Moro, N. Torres, F. Reinhart, C. Chabrol, A.-L. Benabid, J. Mitrofanis, *Exp. Brain Res.* **2017**, *235*(6), 1861.

[120] M. San Miguel, K. L. Martin, J. Stone, D. M. Johnstone, *Biomolecules* **2019**, *9*(10), 564.

[121] M. C. Dewan, A. Rattani, S. Gupta, R. E. Baticulon, Y.-C. Hung, M. Punchak, A. Agrawal, A. O. Adeleye, M. G. Shrime, A. M. Rubiano, *J. Neurosurg.* **2018**, *1*, 1.

[122] M. R. Hamblin, *J. Neurosci. Res.* **2018**, *96*(4), 731.

[123] B. D. Semple, A. Zamani, G. Rayner, S. R. Shultz, N. C. Jones, *Neurobiol. Dis.* **2019**, *123*, 27.

[124] R. M. Verellen, J. E. Cavazos, *Therapy* **2010**, *7*(5), 527.

[125] M. T. Joy, E. Ben Assayag, D. Shabashov-Stone, S. Liraz-Zaltsman, J. Mazzitelli, M. Arenas, N. Abduljawad, E. Kliper, A. D. Korczyn, N. S. Thareja, E. L. Kesner, M. Zhou, S. Huang, T. K. Silva, N. Katz, N. M. Bornstein, A. J. Silva, E. Shohami, S. T. Carmichael, *Cell* **2019**, *176*(5), 1143.

[126] S. Ilic, S. Leichliter, J. Streeter, A. Oron, L. DeTaboada, U. Oron, *Photomed. Laser Therapy* **2006**, *24*(4), 458.

[127] A. Oron, U. Oron, J. Chen, A. Eilam, C. Zhang, M. Sadeh, Y. Lampl, J. Streeter, L. Detaboada, M. Chopp, *Stroke* **2006**, *37* (10), 2620.
[128] P. A. Lapchak, J. Wei, J. A. Zivin, *Stroke* **2004**, *35*(8), 1985.
[129] P. A. Lapchak, K. F. Salgado, C. H. Chao, J. A. Zivin, *Neuroscience* **2007**, *148*(4), 907.
[130] 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, *Stroke* **2007**, *38*(6), 1843.
[131] 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, *Stroke* **2014**, *45*(11), 3187.
[132] S. R. Levine, M. D. Hill, *Am. Heart Assoc.* **2014**, *45*, 3175.
[133] N. el Massri, C. Moro, N. Torres, F. Darlot, D. Agay, C. Chabrol, D. M. Johnstone, J. Stone, A.-L. Benabid, J. Mitrofanis, *Exp. Brain Res.* **2016**, *234*(11), 3225.
[134] N. el Massri, D. M. Johnstone, C. L. Peoples, C. Moro, F. Reinhart, N. Torres, J. Stone, A.-L. Benabid, J. Mitrofanis, *Int. J. Neurosci.* **2016**, *126*(1), 76.
[135] F. Reinhart, N. E. Massri, C. Chabrol, C. Cretallaz, D. M. Johnstone, N. Torres, F. Darlot, T. Costecalde, J. Stone, J. Mitrofanis, A.-L. Benabid, C. Moro, *J. Neurosurg.* **2016**, *124*, 1829.
[136] C. Moro, N. E. Massri, N. Torres, D. Ratel, X. de Jaeger, C. Chabrol, F. Perraut, A. Bourgerette, M. Berger, S. Purushothuman, D. Johnstone, J. Stone, J. Mitrofanis, A.-L. Benabid, *J. Neurosurg.* **2014**, *120*(3), 670.
[137] H. I. Lee, J. H. Park, M. Y. Park, N. G. Kim, K.-J. Park, B. T. Choi, Y.-I. Shin, H. K. Shin, *Restor. Neurol. Neurosci.* **2016**, *34*(2), 201.
[138] Y.-Y. Huang, S. K. Sharma, J. Carroll, M. R. Hamblin, *Dose-Response* **2011**, *9*(4), 602.

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SUPPORTING INFORMATION

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