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Transcranial Photobiomodulation for Neuromodulation of Brain Disorders: A Perspective

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ABSTRACT

Introduction: Photobiomodulation (PBM) uses light to modulate biological activity. Because red and near-infrared wavelengths penetrate the skin and skull, PBM can be applied transcranially (tPBM) to noninvasively modulate brain activity, offering therapeutic potential for neurologic, psychiatric, neurodevelopmental, neurodegenerative, and neuroimmunologic disorders, and for cognitive enhancement.

Materials and Methods: A scoping review is performed integrating literature on tPBM in humans, excluding indications for which only preclinical data exist.

Results: tPBM can be delivered through the scalp, nose, oral cavity, or external ear canal, in continuous or pulsed modes, with varying wavelengths and doses. It exhibits a biphasic dose-response, meaning both under- and overstimulation are possible. tPBM directly enhances cellular energy metabolism, oxygenation, and neuroprotection by stimulating mitochondria, promoting repair, reducing apoptosis, and modulating neuroinflammation. It supports neurogenesis, synaptogenesis, angiogenesis, and microtubule plasticity, and activates the glymphatic clearance system. Additional effects include transient receptor potential vanilloid 1 calcium channel modulation, intercellular mitochondrial transfer, and immune cell recruitment. Preclinical studies indicate benefits in epilepsy, hypoxic-ischemic lesions, intraventricular hemorrhage, and posttraumatic stress disorder, whereas clinical studies cover stroke, traumatic brain injury, chronic traumatic encephalopathy, autism spectrum disorder, attention-deficit/hyperactivity disorder, Down syndrome, Alzheimer's and Parkinson's diseases, anxiety, depression, insomnia, sexual dysfunction, and multiple sclerosis.

Discussion and Perspective: Optimal tPBM outcomes may depend on multitarget, multiwavelength approaches, and pulsed delivery, likely owing to complementary mechanisms and prevention of excessive reactive oxygen species production. Understanding the full range of illumination parameters is essential to develop personalized protocols. Future research should determine whether tPBM can serve as a standalone therapy or as part of multimodal interventions including pharmacology, psychotherapy, or other neuromodulation techniques.

Keywords: ATP, brain, inflammation, mental disorders, photobiomodulation

INTRODUCTION

Photobiomodulation (PBM) uses light to modulate biological activity. Transcranial photobiomodulation (tPBM) applies light to the surface of the head to enhance underlying physiologic, or modulate and treat, pathologic brain activity and connectivity. Light is applied at a low power level (1–100 mW/cm^2) using low-power lasers or light-emitting diodes (LEDs) especially in the red and near-infrared spectral regions. Hence, photobiomodulation is sometimes called red light therapy or photobiostimulation, and when applied with a laser, it also is called low-level laser therapy, low-intensity laser therapy, low-power laser therapy, soft laser

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therapy, cold laser therapy, and since the development of LEDs, LED phototherapy or LED therapy.[1] PBM differs from high-power laser therapy, which uses lasers to cut or destroy tissue. Photobiomodulation also should be differentiated from photodynamic therapy (PDT). In PDT, light-sensitive compounds called photosensitizers are combined with LED or laser light to generate reactive oxygen species, which selectively target and destroy abnormal or unwanted cells. PDT is primarily used in oncology, dermatology, and infectious diseases. In a different application, light stimuli can selectively control the activity of a genetically modified set of neurons using the technique of optogenetics.[2]

Transcranial photobiomodulation applies LED or low-level laser light without the use of photosensitizing agents or any genetic modification of neurons, to increase adenosine triphosphate (ATP) generation, improve oxygenation, and stimulate cellular repair and blood flow, in addition to reducing inflammation and apoptotic cell death.

What is Light?

Light is part of the electromagnetic spectrum of waves that penetrate the earth's atmosphere. The energy of the waves is described by wavelength or frequency. From low to high frequency, these are radio waves, microwaves, infrared, visible light, ultraviolet, x-rays, and gamma rays. Visible light is defined as electromagnetic radiation that can be perceived by the human eye with wavelengths ranging between 400 and 700 nanometers (nm). This corresponds to a frequency range of 750 and 420 THz. Visible light sits between the UV band, with shorter wavelengths and higher frequencies, and the infrared band, with longer wavelengths and lower frequencies, both of which are invisible.

However, in physics, the term light may refer to electromagnetic radiation of any wavelength, whether visible or not. In this sense, gamma rays, x-rays, microwaves, and radio waves also are called light. In this manuscript, we follow the physics terminology and include the infrared spectrum as light.

Light comprises electromagnetic oscillations, which differ from the electrical oscillations in alternating current electricity. Electromagnetic waves can travel through a vacuum without the need for a physical medium, in contrast to electricity, which requires a physical medium (wires or a circuit component) to propagate by the movement of electrons. Both types of oscillations can be described by frequency/wavelength, pulse width, and amplitude.

History of Light Therapy

The sun has been linked to life and health in ancient Egyptian, Indo-European, and meso-American culture, and consequently, the sun gods of many ancient religions have been worshipped for healing human diseases. The eye of Ra, the Egyptian sun god, was linked to healing; Apollo, the Greek god of the sun, was associated with healing, as were the Hindu god Surya and the Aztec god Piltzintecuhtli.

In 1903, the physician Niels Finsen from the Faroe Islands received the third Nobel Prize in Medicine and Physiology "in recognition of his contribution to the treatment of diseases, especially lupus vulgaris, with concentrated light radiation, whereby he has opened a new avenue for medical science." His research was motivated by having Niemann-Pick disease, and noting that his health benefited from going out in the sun.[3] By the mid-1920s, light therapy using the Finsen lamp was enjoying a boom in popularity. The public "began to demand the treatment for every ill under the sun," and medical practitioners, including the most eminent and influential of the day, adopted it widely.[4] King George V received light treatment for his near-fatal pneumonia in 1928.[4] In contrast, meticulous research conducted in the late 1920s by Dora Colebrook, who was unable to detect any beneficial effects of light therapy, was ridiculed and ignored until the 1940s.[4] In the 1950s, light therapy faded in popularity, only to resurge in the 1960s when lasers were invented, and a serendipitous result was noted. When performing a study to evaluate high-energy 694-nm ruby laser treatment for tumors, it was accidentally discovered that a faulty laser delivering only low power, which was insufficient to destroy the tumor, made the hair grow back more quickly on the treated mice than on the control group.[5] This stimulated the idea that "laser is a solution which is looking for a new problem."[6] Subsequently, it also was shown that low-level Helium-Neon laser light could accelerate wound healing in mice.[7] Later, LEDs were more often used for light therapy because they were safer and less expensive than lasers. Since then, PBM has seen a dramatic resurgence and become a hot topic again.[8] More than 90 medical indications are currently being investigated,[9] among them brain disorders,[10,11] in both the neurologic and psychiatric realm.[10,11]

Difference Between Laser and LED Light Therapy

For dermatologic indications, three different kinds of light therapy are commonly used, laser, LED, and intense pulsed light, but the latter is not used in transcranial PBM.

Low-level laser light differs in many physical aspects from LED light. Laser is coherent, monochromatic light at a very specific frequency/wavelength, with a specific pulse width, high intensity, and high directionality.[9,12] Laser light is most often polarized owing to the fixed geometry of the laser cavity. LEDs, in contrast, emit polychromatic light at multiple frequencies/wavelengths, with different pulse widths, low intensity, low directionality, and no polarization.[9,12] Although lasers offer high precision, spatial selectivity, high intensity, and deep tissue penetration, advantages of LEDs include no laser safety considerations, ease of home use, ability to irradiate a large area of tissue at once, possibility of wearable devices, and much lower cost per megawatt.[9] In other words, LED PBM may be able to treat broader areas of the body, is safer, and yields more accessible light therapy options (Table 1).

Can Light Reach the Brain?

There is an inverse relationship between wavelength and energy. Shorter wavelengths of radiation have higher energy.[13] Radio waves have the lowest frequency and longest wavelengths (10–1000 m) and consequently have the lowest photon energy. Gamma rays have the highest frequency and the shortest wavelengths (less than the size of an atomic nucleus) and carry the highest photon energies.

All the high-energy cosmic, gamma, and x-rays reaching the Earth are reflected or absorbed by the ozone layer of the atmosphere; most of the UV is absorbed, but visible light and infrared light pass more readily through the atmosphere.[13] Approximately 5% of UV light reaches the Earth's surface, as do 39% of visible light and 56% of infrared light.[13] High-energy UV rays (10–280 nm) can break chemical bonds, and UV photons carry enough energy to excite DNA bases into permanent chemical rearrangement, which can cause lasting damage.[14] DNA also is indirectly damaged by reactive oxygen species produced by longer-wavelength UV light (280–400 nm).

Table 1. Differences Between Laser and LED for PBM.

Characteristic	Laser	LED
Intensity	High, thermal effects	Moderate, no thermal effect
Pulse width	Fixed	Continuous and adjustable
Coherence	Coherent (synchronized in phase and direction)	Noncoherent (out of phase and scattered)
Polarization state	Linear or circular polarized	Not polarized
Penetration depth	Deep (high intensity, coherent)	Superficial (low intensity, noncoherent)
Wavelength	Single (monochromatic)	Broad band or polychromatic
Spot size	<1 × 1 cm, narrow focused beam	30 × 0 cm, broad and diffuse beam
Form and portability	Larger, complex cooling and power system, less portable	Compact, portable
Ease of use	Requires a therapist for application	Wearable LED devices are becoming common
Expense and access	More expensive, requires specialized safety training	Less expensive, easy to use at home

Life started in water, and hence, light between 100 and 1200 nm could serve as an energy source for the self-organization of molecules that counteracted the second law of thermodynamics.[14,15] Water absorbs light <100 nm and >1200 nm, with the lowest absorption between 400 and 500 nm, thus accounting for the bluish hue of the ocean. Visible light and infrared light, which carry less damaging energy, are preferentially used by cyanobacteria and plants to convert water and carbon dioxide (CO_2) into sugar and oxygen by means of chlorophyll, in the process known as photosynthesis. This converts light energy into chemical energy, essential for sustaining life. The highest absorption of light by chromophores such as chlorophyll involves the blue (400–500 nm), red (620–750), and near-infrared (750–1200 nm) wavelengths, causing the green color of plants.[16]

Only a narrow band of electromagnetic waves, between 650 and 1200 nm, can penetrate the skull and reach the brain directly.[17–19] Radio waves pass straight though living tissue, whereas microwaves and high-energy UV waves are absorbed by water and protein in the skin, respectively.[14] The electromagnetic waves that can reach the brain fall in the visible red (600–700 nm) and near-infrared spectrum (700–1400 nm). Below 600 nm, blood (hemoglobin) absorbs photons, and >1250 nm, water absorbs them, creating a small optical window of light penetration to the brain.[19] On the basis of simulations, it has been proposed that 810-nm wavelength delivers the highest energy into the brain, closely followed by 850- and 1064-nm wavelengths, which all deliver more energy than 670- and 980-nm wavelengths.[20] Depending on the location on the head of the application of PBM, different amounts of energy are deposited in different brain areas.[21] For example, when applying PBM to the dorsolateral prefrontal cortex (DLPFC) located at F3 to F4 on the bilateral forehead, most energy is deposited in the underlying frontal areas but less in the deep brain structures such as thalamus and caudate nucleus, and intermediate doses in the amygdala, hippocampus, putamen, and accumbens. However, when PBM is applied intranasally, these deeper areas receive more energy deposited, and the DLPFC receives less energy. Orbitofrontal application (FP1–FP2) leads to intermediate results. There are no substantial differences between 670, 810, 850, 980, and 1064 nm regarding the amount of energy that is deposited in different areas of the brain,[21] which seems counter to the simulations that suggested 810 nm was optimal.[21] This may result from different light wavelengths having different amounts of absorption and scattering in biological media and tissues, in addition to varying degrees of penetration through different bone densities, not fully reflected in the cadaver-based models.[18]

A second demonstration that light can reach the brain was based on a neuroimaging technique called functional near-infrared spectroscopy (fNIRS). fNIRS is an optical imaging technique that emits and detects light in the red to near-infrared (NIR) range, and measures hemodynamic changes in living tissues by measuring the differences in light absorption of oxygenated and deoxygenated hemoglobin.[22] It can be used transcranially, given the 650-to-1200 nm optical window permits these wavelengths to pass the skull.[22] In other words, near-infrared light can cross the skull in both directions. fNIRS measures the same changes in oxygen consumption as the blood oxygen dependent (BOLD) signal in functional magnetic resonance imaging (fMRI), as confirmed by simultaneous fNIRS and fMRI measurements.[23,24] Using broadband NIRS, changes in the oxidation state of mitochondrial cytochrome-c-oxidase (CCO) can be monitored.[25] CCO is the terminal enzyme and electron acceptor in the electron/respiratory transport chain in the mitochondria and is responsible for >95% of oxygen metabolism and ATP production. Because fNIRS sends NIR light into the brain and detects the reflection of these NIR frequencies from the brain's blood vessels, the functional imaging device might have a tPBM effect on its own. Indeed, when using a classical fNIRS device, it was shown that fNIRS itself induced faster reaction times and better accuracy in some cognitive tests than in a well-matched control group wearing the same but inactive device.[26]

In summary, red and NIR light (600-1250 nm) can reach the brain directly from the outside, and the reemitted light can be detected. Therefore, red and NIR light can be used to modulate the brain but also as a functional imaging technique.

How is Light Delivered to the Brain?

Different lasers and LED devices have been developed to target the brain. Most devices use an external, that is, transcranial approach, but some devices have been developed for intracranial PBM. Commonly used tPBM devices target cortical areas, but intranasal, intraoral, and intraear devices also exist (Fig. 1). When light is delivered through the nasal route, the medial temporal lobe (amygdala, hippocampus) can be reached more readily, which can be beneficial for Alzheimer's disease (AD).[27] Moreover, the orbitofrontal lobe, in addition to the hypothalamus, thalamus, and substantia nigra also could be reached.[28] When light is delivered through the oral cavity, the brainstem and midbrain may be reached, which may be beneficial for Parkinson's disease (PD).[28] When light is delivered through the ear canal, the posterior inferior temporal lobe and cerebellum could be reached.[29] The intracranial

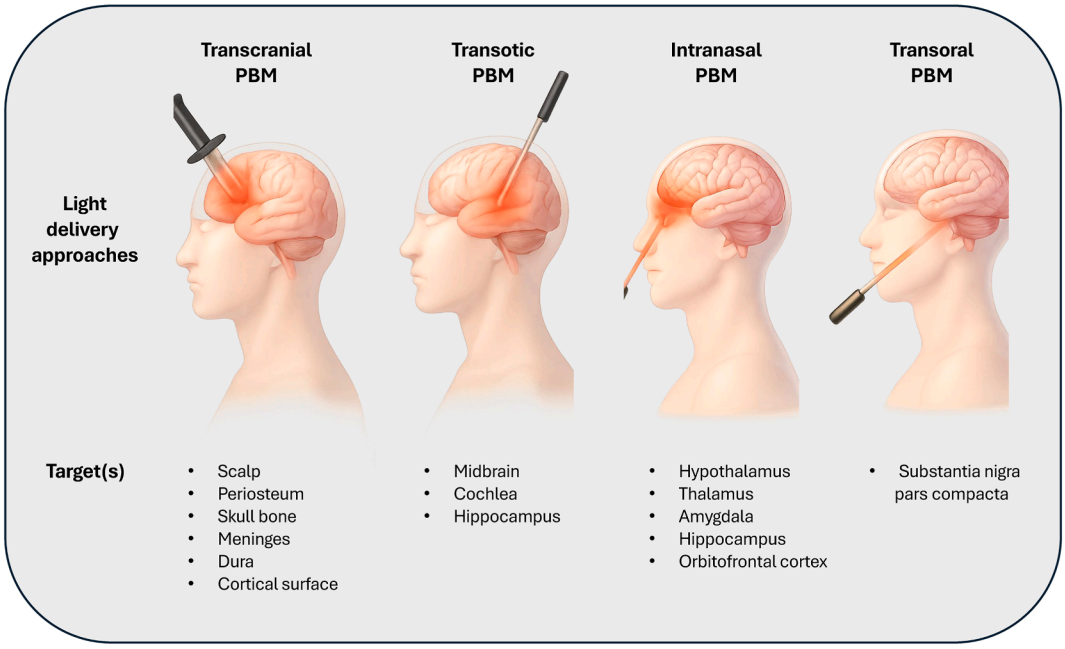

Figure 1. Different approaches to reach different targets in the brain. Figure modified from Nairuz et al.[28] [Color figure can be viewed at www.neuromodulationjournal.org]

approach could reach any part of the brain, depending on the chosen trajectory.[28] Figure 1 presents an overview.

tPBM Parameters

"For every substance, small doses stimulate, moderate doses inhibit, and large doses kill." (Arndt-Schulz law).

The Arndt-Schulz law is reminiscent of Paracelsus's (1493–-1541) famous saying that "the dose makes the poison." This concept of Paracelsus is clearly shown by the beneficial effect of UV light on vitamin D production, and the protective effects of UV-induced melanin production that permits humans to tan and be protected against increasing UV levels. In contrast, the damage done by high levels of UV causes immediate sunburns, and at later stages, skin photoaging and UV-induced skin cancer.[14]

The Arndt-Schulz law extends Paracelsus's adage, leading to the inverted-U–curve concept, or biphasic dose response,[30] also called hormesis in pharmacology.[31–33] This inverted-U dose response profile also exists in tPBM[30,34–38] (Fig. 2) and accords with descriptions of transcranial electrical neuromodulation such as transcranial direct current stimulation (tDCS).[39] This means that both under- and overstimulation are possible, depending on the dose administered,[36,37] so that a dose that is too low achieves nothing, whereas too high a dose inhibits the brain function, and an in-between dose of tPBM stimulates the brain function. Even though this inverted-U–curve profile has been revealed in in vitro and animal studies, in humans, this profile has not been convincingly shown. One study comparing a single with a double dose has shown that too much stimulation (double dose) may be less efficacious than less stimulation (single dose).[40] Another study showed that a lower dose did not yield a cognitive benefit, in comparison with a higher dose, also compatible with the inverted-U–curve profile,[41] but no formal dose-escalation study has yet been performed.

The dose can be expressed as the fluence or energy density that is delivered (J/cm^2) and as the intensity, power density, or irradiance (mW/cm^2). The fluence (J/cm^2) = the irradiance (mW/cm^2) ÷ 1000 × time (seconds) (Fluence = Irradiance × Time).[30]

The photobiological responses of cells and tissue usually involve a sequence of interacting biological reactions, which makes a linear dose-time relationship unlikely,[42] so it is difficult to simply propose an optimal dose. Intriguingly, this inverted U-curve exists at the level of the individual mitochondria. When 810-nm PBM is applied to cell cultures at different doses, low doses produce little ATP; optimal doses produce the maximal increase in ATP, and high doses produce less ATP again.[43]

The average penetration of transcranial NIR (630–810 nm) light into the surface of the brain ranges from 0.2% to 10% in humans (scalp plus skull),[44] and some light could penetrate to a depth of approximately 40 mm.[45]

The wide range of parameters that can be applied in PBM, including wavelength (nm), total energy (J), fluence (J/cm2), power (W), irradiance (mW/cm2), pulse frequency (Hz), pulse duration (seconds) treatment duration (seconds), and repetition (times) has led to some contradictory results in the PBM literature.[46] Therefore, it has been proposed that these key parameters should be reported to permit reproducible studies: wavelength, total energy (J), fluence (J/cm^2) irradiance (mW/cm^2), irradiation time, beam area (cm^2), pulse parameters (frequency and pulse duration), anatomical location, number of treatments, and the interval between treatments.[47]

Dose: Energy, Fluence, and Irradiance

The biological effects of red/NIR light depend on the dose and intensity, power, or irradiance of the applied light. At high levels of intensity, light heats the tissue and eventually destroys it, so lasers are used to cut or destroy brain tissue in laser-induced interstitial thermotherapy (LITT) or interstitial laser photocoagulation. This

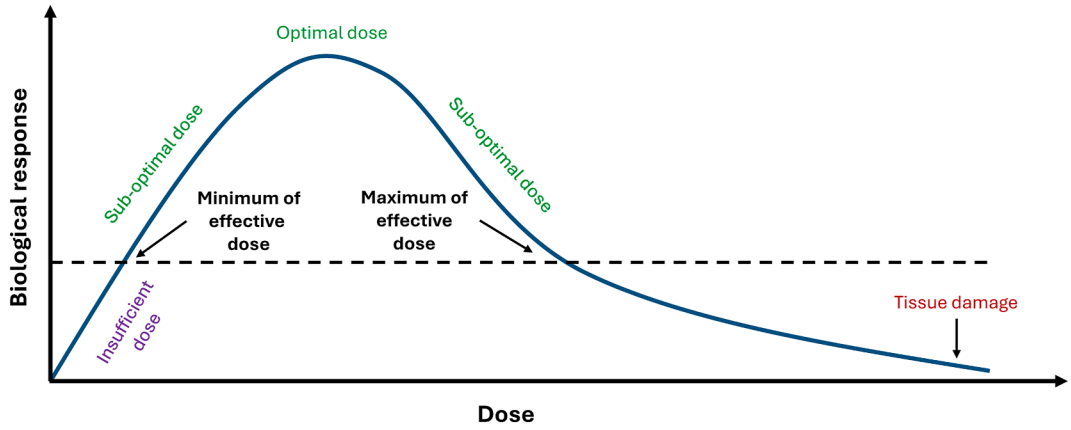

Figure 2. Dose-response effect (Arndt-Schulz law): hormesis or the inverted-U curve profile of tPBM. [Color figure can be viewed at www.neuromodulationjournal.org]

technique is currently being applied for ablation of brain tumors and epilepsy generating foci in the brain, and for stereotactic lesioning in movement disorders.[48,49] The intensity or irradiance values that produce unacceptable heating of the tissue are governed by the wavelength and are approximately 500 mW/cm^2 at 800 to 900 nm, approximately 200 to 300 mW/cm^2 at 600 to 700 nm, and as low as 100 mW/cm^2 at 400 to 500 nm.[46] The light intensity used for LITT is many times higher at 12 W/cm^2 at 1064 nm or 15 W/cm^2 at 980 nm.[50] There is a minimal intensity required for generating a clinical effect, given that <0.5 mW/cm^2, the illumination time could be infinite but not differ from daylight and therefore would provide no extra benefit.[46]

At lower intensities but still >0.5 mW/cm^2, PBM does not have any destructive effects, and when red or NIR light penetrates the skin, skull, dura, and cerebrospinal fluid (CSF) and reaches the brain, it activates CCO. The optimal dose at the target may be from 1 to 10 J/cm^2, but for deeper tissues such as the brain, 10 to 50 J/cm^2 may be better.[46]

It should be noted that both the fluence/energy density (J/cm^2) and the total energy in Joule should be specified in PBM protocols. This is because a small spot of 1 cm^2 with a power density of 100 mW/cm^2 would deliver 90 J/cm^2 or 90 Jouls in 15 minutes, but if the area was 10 cm × 10 cm with the same power density of 100 mW/cm^2, the total energy delivered in 15 minutes would be 9000 Joule (100 times higher), but the fluence would remain at 90 J/cm^2.

Wavelength

In the visible spectrum, different spectrums yield different colors: blue (400–500 nm), green (500–575nm), yellow (575–585 nm), orange (585–620 nm), and red light (620–750 nm). Infrared light is not visible and has wavelengths between 750 and 1,000,000 nm.

Blue and green light have not been very well studied in PBM, for multiple reasons. Blue light carries the highest energy in the visible spectrum, being adjacent to UV-A. Thus, blue light carries a potential risk of carcinogenesis, analogous to UV light. Blue and green light also do not penetrate tissue and are unlikely to reach the brain directly.[51] Blue and green PBM exerted a beneficial effect in almost 75% of published studies, predominantly involving reduction of inflammation in superficial tissues, promoting wound healing, in addition to being able to limit bacterial growth.[51]

CCO is activated by four peak absorption wavelengths, 620, 680, 760, and 820 nm,[52] in the red and NIR spectral regions. On the basis of Monte Carlo simulations using a Chinese head model, it was calculated that 660 and 810 nm wavelengths were superior to 980 and 1064 nm, with 660 nm indicating slightly better penetration into cerebral tissue.[53] Human intraparenchymal brain cadaver studies showed lower absorption and scattering for 808 nm wavelength light than for the 660- or 940 nm wavelengths.[45] In a mouse model of traumatic brain injury (TBI), both 665 nm and 810 nm had beneficial effects on neurologic outcome measures, but not 730 or 980 nm,[54] suggesting a wavelength-dependent effect. This alleviation in TBI may relate to an increase in brain-derived neurotrophic factor (BDNF) and synapsin-1 induced by 810 nm tPBM[55] because BDNF is related to neural repair and regeneration in TBI,[56] and synapsin is related to synaptogenesis.[55] However, an excessive number of laser treatments (daily for 14 days) could temporarily inhibit the process of brain repair stimulated by tPBM, owing to transient reactive gliosis as shown by increased glial fibrillary acidic protein expression in the brain.[57] When the inhibitory effect ceases (six weeks), the process of brain repair can resume, leading to better results than without any tPBM.[57]

That CCO has four different absorption peaks has led to the suggestion that combining red (660 nm) and infrared (810 nm) PBM may be superior to single wavelengths alone.[58,59] Although single-wavelength PBM affected the metabolic activity in superficial brain areas as well as did combined-wavelength PBM, the deeper structures (hippocampus, infralimbic, subgenual anterior cingulate cortex) were only affected by the combined wavelength stimulation.[58] In a mouse model of PD, combining 670-nm and 810-nm increased locomotor activity and number of tyrosine hydroxylase immunoreactive cells in the substantia nigra pars compacta to a greater extent than when single wavelengths were applied.[59] This also applies to humans, as shown by a meta-analysis confirming that cognitive improvement in humans is better achieved by combining multiple wavelengths.[60] In a single case report, 635-nm red light tPBM was combined with 810-nm NIR tPBM and transnasal 10-Hz pulsed 810-nm NIR tPBM, producing a rapid reversal of cognitive decline and olfactory dysfunction, and improved quality of life.[61]

In rats, the activation of CCO by 1064-nm tPBM persists after stimulation for two to four weeks and extends beyond the area of stimulation.[62] Nevertheless, even though the light absorption spectra of the mitochondria do not show a peak at 1064 nm, 1064-nm PBM does upregulate CCO in humans and thereby increases

hemoglobin oxygenation both peripherally[63] and in the brain.[64] Furthermore, this metabolic effect is not only local but extends to a metabolic network functionally connected to the target area, as shown by histochemical mapping in rats,[62] in addition to electroencephalography (EEG),[65,66] magnetoencephalography,[67] and fNIRS[68] in humans. There is a significant increase in mitochondrial oxidative energy metabolism produced by 1064-nm PBM, as shown by more oxidized CCO during laser stimulation in humans, followed by a significant poststimulation increase in brain oxygenation as reflected by increased oxygenated hemoglobin and a decrease in deoxygenated hemoglobin.[64,69] This extends beyond the stimulation site and does not occur with placebo stimulation.[64] Because 1064-nm tPBM may produce a little heat, it has been argued that brain changes could be due to the heat and not to tPBM per se. By comparing heat stimulation using a thermal probe to 1064-nm tPBM on the human forehead, it was shown that the laser-induced heat was not the explanation for increases in EEG power during and after tPBM.[65]

Interestingly, the mitochondrial oxidative energy metabolism increases were especially marked in older people, whereas the cerebral oxygenation was predominantly increased in younger people.[64] Furthermore, it has been proposed that NIR 1064-nm tPBM also acts on microglial cells, transforming resting microglia into the M2 state, in which they exert an anti-inflammatory effect,[70] in addition to affecting light-sensitive calcium permeable ion channels known as transient receptor potential (TRP) channels, especially the vanilloid type (TRPV).[71]

Moreover, 1064-nm light undergoes less scattering and can penetrate deeper into the brain (3 cm) than can 808-nm wavelength, despite its slightly higher water absorption[72,73]; 1064 nm (in common with other PBM wavelengths) also has no known carcinogenic or mutagenic effects.[73,74]

Even longer wavelengths, such as 1267-nm tPBM, could stimulate the brain waste removal system (BWRS) in mice, thus contributing to neuroprotection in the central nervous system.[75,76] However, 1267 nm is more absorbed by water and may therefore not reach the brain in humans.

In addition, 808-, 1064-, and 1267-nm wavelengths induce nitric oxide (NO) release, suggesting that the effect of NIR tPBM may be mediated not only by the direct effect of NIR light on oxygen metabolism in neuronal cells but also by improved blood flow due to increased NO generation/release in endothelial cells.[74,77] Furthermore, given NO controls lymphatic vessel contractility and has been postulated to be one of the major underlying mechanisms for PBM-induced lymphatic clearance of macromolecules from the brain (glymphatic drainage), other NIR tPBM wavelengths may have a similar glymphatic pumping effect.[77]

In summary, different wavelengths seem to exert different but potentially complementary effects on the brain, suggesting that combining different wavelengths may be a useful avenue in PBM.

Pulsed Vs Continuous tPBM

Pulsed light has been found to penetrate deeper into tissues than does continuous wave light with the same average power.[73,78,79] Three parameters are used to describe the pulsing of light, frequency (Hz), pulse duration (milliseconds), and duty cycle (%), and two of three should be specified in each case. Pulsed tPBM also may influence ion channels if the half-life of the channel opening is similar to the pulse duration of the light.[73] Moreover, pulsed 1070-nm light at 10 Hz has an anti-inflammatory effect by triggering microglia rather than astrocyte responses and promoting angiogenesis.[80] Similar results were obtained by 810-nm 10-Hz PBM, in comparison with continuous or 100-Hz pulsed PBM.[81] Pulsing has clinical repercussions because in a TBI model in animals, pulsed 10-Hz laser PBM was better at limiting the spread of the lesion and improving neurologic performance.[82] This was confirmed in an animal study of depression, in which 10-Hz pulsed NIR laser light (810 nm) was as effective as citalopram and more effective than red laser (630 nm) in the treatment of depressive-like behavior.[83]

In addition, 40-Hz pulsed light exerts a stronger metabolic effect on neuron-like cells than does continuous or 100- or 1000-Hz pulsed PBM, as shown by more ATP production, a raised mitochondrial membrane potential, more reactive oxygen species (ROS) production, and increased viability.[84] In contrast to continuous PBM, there was no clear inverted-U–curve effect, possibly because the progressive ROS build-up was prevented by pulsing,[85] which permits ROS to be removed in the stimulation-free periods. Furthermore, 40-Hz pulsed 810-nm tPBM significantly increased the power of the higher oscillatory EEG frequencies (alpha, beta, and gamma) and reduced the power of the slower frequencies (delta and theta).[86] Continuous wave 1064-nm tPBM elicited no changes in delta, theta, and gamma bands but did increase alpha and beta power, extending beyond the site of stimulation.[66]

In a comparative study of 40-Hz, 100-Hz pulsed, and continuous 850-nm tPBM, 40 Hz was superior to continuous tPBM in enhancing cognitive function in healthy volunteers and was associated with increased gamma band spectral power.[87] That only pulsed 40-Hz tPBM increases gamma power suggests that the mechanism of action differs between continuous and pulsed tPBM. Another study found that continuous 830-nm tPBM exerted a more pronounced effect on EEG gamma spectral power than did 10-Hz pulsed tPBM,[41] suggesting that pulsing at 40 Hz may differ from pulsing at 10 Hz. In a mouse model of AD, cerebral amyloid angiopathy decreased specifically after 40-Hz pulsed 808-nm LED and not with visible light PBM.[88] A systematic review has shown that PBM with 640 ± 30 nm light attenuates Aβ and tau pathology and improves neuronal and synaptic plasticity in most studies, suggesting enhancement of protein degradation or clearance mechanisms in the brain of AD animal models.[89] This does suggest that not only 1267 nm but other NIR tPBM wavelengths can activate the waste clearance mechanism, as previously mentioned, but that red light also has the capacity to do so. The few human studies performed so far support the use of PBM at 810 to 870 nm with pulsing at 40 Hz for improving brain network connectivity and memory in older subjects and patients with AD.[89]

In summary, pulsed and continuous PBM appear to have different mechanisms of action, and most studies suggest that pulsed tPBM may be more powerful than continuous tPBM for brain conditions.

Duration and Timing

According to the reciprocity rule of Bunsen and Roscoe, a photochemical reaction is directly proportional to the total energy delivered, irrespective of the time over which this dose is delivered.[90] However, most studies have shown that the rule of reciprocity is invalid or of limited validity for many photobiological reactions.[91] For UV-induced cell death, photocarcinogenesis, psoralen photochemistry, and the effects of low level laser radiation, it has been shown that at a constant total dose, the intensity

of the source is a major factor that determines the type and extent of the response.[91] Indeed, applying low intensity (sun)light for a very long time may not produce any therapeutic effect.[46]

A systematic review has shown that most PBM sessions last 20 minutes, irrespective of the indication treated,[92] but a meta-analysis found that 30 minutes showed the best results in the treatment of depression.[93]

Another meta-analysis found that in cognitive dysfunction, the cumulative irradiation time was the most important parameter for improving cognitive function, suggesting that more sessions were better than fewer.[60]

In a sports trial with participants who were untrained healthy subjects, it was shown that 905-nm PBM applied to the quadriceps muscle (combined with static magnetic fields) could be used from 5 minutes to six hours before exercise, and the effects could last for up to 54 hours after treatment.[94] The effects started to decrease when a one-day (24-hour) time-response window was used.[94]

For children, the timing and duration are less studied. Moreover, given the skull thickness, brain metabolism, vascular dynamics, synaptic development, and plasticity are different in children, light penetration, dose-response, and safety margins with regards to timing and illuminating duration may differ. The few studies performed in children used very different timing and duration parameters. Although one study was limited to 5 minutes per session, twice weekly for four weeks,[95] another study used 20 minutes twice daily for six months.[96]

Summary and Proposal of the Parameter Ranges Used in Human tPBM Trials

On the basis of four systematic reviews, the ranges of the parameters used in human tPBM trials can be tabulated (Table 2). The parameter values in each condition category (degenerative, mental, brain injury, etc) are based on Fernandes et al,[92] and the disease-specific ranges (especially AD/PD, TBI, stroke) are based on several recent studies.[73,97,98]

Human brain tPBM studies cluster around a relatively narrow and well-tolerated region of parameter space, allowing a set of evidence-aligned starting ranges for new protocols. Most human trials use brain-penetrating wavelengths between 810 and 830 nm or 1060 and 1080 nm for cognitive indications through helmets, with 660 to 670 nm used primarily for superficial or historical reasons. A practical, safe starting average irradiance is 30 to 100 mW/cm^2 at the scalp, staying generally <250 mW/cm^2 unless temperature is monitored. Correspondingly, a reasonable exploratory fluence for a focal site is 10 to 20 J/cm^2, with 20 to 40 J/cm^2 representing the upper part of the midrange used in psychiatric and cognitive studies; higher doses (60–100 J/cm^2) appear only in a few high-dose depression trials. These doses typically produce session durations of 8 to 15 minutes for two to four PFC sites or 15 to 20 minutes for helmets. In addition to the dose measured by energy density, the dose measured by total energy in Joules is important. For instance, 2300 J per session in the Evaluation of LEDs' Antidepressant Therapeutic Effect in Depression (ELATED)3 trial was ineffective for depression, whereas 3400 J in the ELATED2 trial was effective.[99] Continuous wave light is simplest and dominates psychiatric, stroke, and TBI work, but pulsed light with 40 Hz at 40% to 50% duty cycle is used when gamma-entrainment is desired, especially in cognitive enhancement or dementia studies. Session schedules typically fall between two and three times per

Table 2. Summary of Parameter Ranges Used in Human Brain tPBM Based on Systematic Reviews.

Parameter type	Approximate range observed in human brain-tPBM trials	Most common values/patterns
Wavelength λ	627–1080 nm (brain-penetrating red–NIR)	660–670 nm (red); 780–850 nm (especially 808, 810, 830, 850); 904–940 nm; 1060–1080 nm, especially dementia and helmet trials.
Power density (irradiance at scalp)	4–800 mW/cm^2	Mode ~250 mW/cm^2 for physiologic/cognitive studies; <50 mW/cm^2 in many TBI, dementia, anxiety, and DoC protocols; isolated SZ trial at 800 mW/cm^2 (75 Hz, 20% duty) without thermal AEs.
Fluence (J/cm^2 at scalp) Total energy per session	~4–120 J/cm^2 per site/session when reported Tens of Joules (small spot) to 2–3 kJ (large areas/helmets)	ELATED-2 MDD uses 100 J/cm^2; many dementia/TBI protocols sit ~8–40 J/cm^2 per site. ELATED-2: 3.4 kJ; dementia helmets: hundreds of joules per session; Vielight Neuro Gamma: ~240 J total.
Session duration	30 s–40 min	Focal MDD/TBI protocols: 4–20 min; DMN helmets/Neuro devices: 20 min; dementia 1060–1080 nm helmet: 6-min twice daily.
Mode of operation	Continuous or pulsed	Continuous dominates for depression, TBI, stroke. Pulsed (10–40 Hz; occasionally 50–75 Hz) common in dementia/AD and some psychiatric EEG studies.
Duty cycle (pulsed)	Typically 20%–50% when reported	Many 40-Hz gamma-entrainment protocols use ~50% duty; some SZ work used 20% at high irradiance.
Session frequency	1× to 14× per wk	Mechanistic/proof-of-concept: single or few sessions. Clinical protocols: 2–3×/wk is very common; home-use dementia devices: daily or twice daily.
Total course length	Single session–16 wk	MDD: often 4–8 wk; dementia: 8–12 wk; AD Gamma/Alpha device trials: 12–16 wk; acute stroke: single session.
Targets	Local spots to whole-head helmets + intranasal	PFC (F3/F4/Fp1/Fp2) is the most common single region across psychiatric and cognitive studies; dementia adds DMN nodes (mPFC, PCC, angular gyrus) and whole cortex; stroke/TBI often use multispot whole scalp coverage or perilesional cortex.

AE, adverse event; DMN, default mode network; DoC, disorder of consciousness; mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex.

week for clinic-based protocols and daily for home-use dementia devices, with course lengths of four to eight weeks for exploratory or depression studies and eight to 12 weeks for dementia. For target selection, psychiatry and cognitive work generally stimulates PFC regions (F3/F4/Fp1/Fp2), whereas dementia studies extend to default mode network hubs or whole-head helmets, and TBI or stroke protocols target perilesional cortex with modest multispot dosing.

Biological Effects of tPBM

Structural Effects on the Brain

Repetitive 810-nm tPBM with a laser increased the number of dendritic nodes and ends, and reduced the total dendritic length in neurons of the cerebral cortex, suggesting that chronic transcranial PBM could induce morphologic neuroplasticity in the cerebral cortex of rats.[100] Furthermore, red light can increase neurite (= axon or dendrite) growth more than green light,[101,102] and 10-Hz seems to be more effective than 1- and 100-Hz pulsed illumination.[103] The rescue of dendritic atrophy occurs through upregulation of BDNF, mediated through photoactivation of transcription factor cAMP response element-binding protein (CREB).[104] It can be hypothesized that these energy-requiring structural changes influence long-lasting functional changes as later described.

tPBM and Mitochondria

It is generally accepted that the primary effect of PBM involves the modulation of mitochondria,[36,62,64,73] and specifically the upregulation of ATP (energy) production and the reduction of ROS to help oxidatively stressed cells.[105] Mitochondria act as the energy plants of the brain and body, and are under the influence of a circadian clock.[106]

The brain requires basic energy to fuel its structural integrity and extra energy to interact and survive in a changing environment.[15] It consumes energy in both cognition and emotion. Cognition arises from neural dynamics in large-scale brain systems and their context-dependent neuromodulation. Glucose is the primary source of energy for these processes and provides most of the energy "currency," ATP, which fuels neurotransmission, neurotransmitter biosynthesis, and recycling, managing oxidative stress, and maintaining resting potentials,[107] all to preserve its integrity and adapt to the everchanging environment.

One of the most important metabolic processes that provide energy within the cell is amino acid metabolism. Almost all the 20 amino acids that are building blocks of proteins are produced or degraded in the mitochondria.[108] Mitochondria also are involved in iron and calcium homeostasis, and production of hormones such as steroids and melatonin, in addition to neurotransmitters.[106] This is not surprising because neurotransmitters are formed from amino acids. Mitochondria are actively involved in each step of synaptic transmission through their critical functions in providing energy, maintaining an intracellular redox balance and intrasynaptic calcium homeostasis, and by regulating key signaling transduction pathways and promoting the synthesis of the intermediates and/or end products of several key neurotransmitters such as acetylcholine, noradrenaline, γ-aminobutyric acid (GABA), and serotonin.[109]

Furthermore, mitochondria are involved in the production and homeostasis of DNA, RNA, proteins, and lipids.[110] This multifaceted energy-driven biological function of mitochondria enables and governs communications between the nervous system, the microbiome, the circadian system, and the immune system.[106,110]

Some mechanisms beyond mitochondria have been proposed for tPBM because some infrared wavelengths such as 1064 or 1267 nm may not activate CCO directly,[105] including photophysical mechanisms such as biophotonic effects and microtubule modulation, and photophysical effects involving the TRPV ion channels and molecular oscillations of other proteins.[111]

The brain requires a continuous supply of energy in the form of ATP, 95% of which is produced from glucose by oxidative phosphorylation within the mitochondria, complemented by aerobic glycolysis in the cytoplasm.[112] Stored nutrients such as proteins, glucose, fat, and lactate are turned into pyruvate and into acetyl coenzyme A and enter the tricarboxylic acid (TCA) cycle, also known as the Krebs orcitric acid circle. This produces fatty acids, water, CO_2, amino acids, and nicotinamide adenine dinucleotide (NADH); the latter is then used in oxidative phosphorylation through the mitochondrial respiratory chain (also known as electron transport chain) to generate ATP and ROS. Amino acids are used as building blocks for neurotransmitters, and fatty acids are involved in both catabolic processes that generate energy and anabolic processes in which they serve as building blocks for other compounds. Some metabolites of the TCA cycle influence expression of genes in the nucleus through epigenetic mechanisms such as chromatin modification and DNA methylation.[113]

Mitochondria respond to signals from the nucleus, but mitochondria also can regulate the expression of different genes.[113] Thus, the communication between mitochondria and nucleus is bidirectional.[113] Gene expression changes in the nucleus promote mitochondrial biogenesis or increase mitochondrial respiratory activity to meet cellular needs, but the nucleus determines whether mitochondrial metabolism is sufficient before engaging in complex and highly demanding cellular functions, including differentiation or adaptation to stress.[113] Five mechanisms by which mitochondria communicate with the rest of the cell include 1) the release of cytochrome c to induce cell death; 2) activation of adenosine monophosphate-activated protein kinase to control mitochondrial fission and fusion; 3) production of ROS to activate transcription factors such as nuclear factor κ of activated B-cells (NF-kB); 4) the release of mitochondrial DNA (mtDNA) to activate immune responses; and 5) release TCA cycle metabolites to control cell fate and function.[113] Consequently, PBM may exert its effects through altering gene expression in the nucleus.[114]

Some neurons, especially high-frequency (gamma ≥30 Hz) firing neurons (ie, GABAergic cortical interneurons) require much energy and therefore contain high numbers of mitochondria.[115] These neurons also are most sensitive to energy depletion.[116–120] When glucose levels are limited, ketone bodies generated in the liver and lactate derived from exercised skeletal muscle also can become important energy substrates for the brain.[121] However, high energetic demand cannot be satisfied solely by lactate, and these neurons become more susceptible to glutamate toxicity.[122] Mitochondria undergo glutamate toxicity owing to impairments in the TCA cycle, and then experience disruptions to oxidative phosphorylation.[123] Aging is associated with a decrease (~10%) in ATP production in the brain.[112] In most neurodegenerative conditions, such as AD, PD, Huntington's disease, frontotemporal dementia, and amyotrophic lateral sclerosis, ATP production is reduced by a further 20% in a progressive manner, and this reduction is both region-specific and disease-specific.[112] Indeed, meta-analyses have identified complex I (NADH dehydrogenase) and complex IV (CCO)

in the mitochondrial electron transport chain as being implicated in the pathophysiology of many psychiatric disorders, such as major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SZ), in addition to in neurodegenerative disorders, such as AD and PD.[124] Because tPBM may shift the mitochondrial metabolism from glycolysis to oxidative phosphorylation (generating ATP), this causes increased activation of stem cells and an anti-inflammatory response.[125,126] Therefore, PBM could theoretically be an optimal approach for degenerative brain pathologies.

In addition to degenerative brain disorders, some neurodevelopmental pathologies such as autism spectrum disorder[127,128] and attention-deficit/hyperactivity disorder (ADHD)[129] are characterized by mitochondrial dysfunction with impaired ATP production. In addition to degenerative and neurodevelopmental brain disorders, TBI has been associated with mitochondrial dysfunction, including impaired calcium homeostasis, reduced ATP production, and elevated ROS production, and decreased cortical blood flow through impaired neurovascular coupling.[130] Obstruction of blood flow in the brain leads to cerebral ischemia, hypoxia, and decreased cellular ATP production,[131] causing an ischemic or cryptogenic stroke, which is associated with strong metabolic remodeling generating pronounced oxidative and energetic stress.[132] In fact, acute stress, such as that induced by sleep deprivation, generates mitochondrial structural damage leading to decreased mitochondrial energy metabolism, often clinically expressed as anxiety.[133] Both sleep-deprived young and aged rats exhibited decreased anxiety (mania)-like behavior after receiving PBM.[134] Chronic stress also causes mitochondrial damage characterized by abnormal mitochondrial morphology, compromised function, impaired biogenesis, and alterations in mitochondrial marker proteins, often clinically expressed as depression.[135] It thus appears that many brain disorders are associated with dysfunctional mitochondria and insufficient ATP production.

At a molecular level, mitochondrial activation by NIR tPBM yields more ATP production, that is, more energy availability, in addition to increased tissue oxygenation, but also production of low levels of RNS and ROS, which can function as signaling molecules that activate early response genes and NF-kB production.[17,73] NF-kB is a transcription factor that controls expression of many genes in DNA; that is, it can both induce and repress gene expression by binding to discrete DNA sequences, known as κB elements, within certain gene promoters and enhancers.[136] NF-kB is activated by stimuli such as stress, cytokines, free radicals, heavy metals, UV irradiation, oxidized low-density lipoprotein, and bacterial or viral antigens; therefore, NF-kB is involved in immune responses, stress responses, synaptic plasticity, and memory formation through induction of inflammatory mediators, growth factors, synaptogenesis, and neurogenesis.[17] NIR PBM has an inhibitory effect on acetylcholinesterase, enhances the production of acetylcholine, attenuates ROS, and regulates cellular apoptosis factors such as B-cell lymphoma 2 (BCL-2) and BCL-2 associated X.[28] Furthermore, NIR increases mRNA expression of BDNF and glucagon-like peptide-1, thereby facilitating neuronal survival and differentiation.[134]

At a systemic level, PBM may preserve mitochondria, enhance cerebral blood flow and oxygenation, inhibit neuronal apoptosis, induce neurogenesis, synaptogenesis, and angiogenesis, exert an antineuroinflammatory effect, and reduce the amyloid-β burden by increasing glymphatic drainage.[73,137] Tissues with high numbers of mitochondria (brain, spinal cord, retina, muscles, liver, and kidney) respond to lower doses of light than do tissues with lower numbers of mitochondria,[46] suggesting that mitochondrial activation is indeed critically important for tPBM success. Furthermore, ineffective PBM studies in cells with high mitochondrial activity are more often due to overdosing than to underdosing, and ineffective studies in cells with lower numbers of mitochondria are mostly due to underdosing[46] (Fig. 2).

In summary, tPBM targets CCO in the mitochondria in the brain. Red and NIR wavelengths of light can enhance the activity of CCO, leading to increased electron transport, improved oxygen consumption, and enhanced ATP production. This boost in cellular energy can prevent neurons from dying (antiapoptotic),[134,138] stimulate stem cells to migrate to where they are needed and form new neurons (neurogenesis), and increase synapses (synaptogenesis).[139] tPBM can stimulate the formation of new blood vessels (angiogenesis),[28] and can help in cell repair and improving overall cellular function,[8] for example, by increasing production of neurotransmitters and growth factors.[134] Consequently, neuroinflammation can be reduced,[140] causing less edema, reduced temperature, and less pain. Intriguingly, these effects occur both locally and at a distance, and for a time that extends beyond the stimulation period. The prolonged effect can be attributed to tPBM's influence on gene expression through transcription factors,[28,139,141] causing angiogenesis, neurogenesis, and synaptogenesis, which all require time to develop.

Microtubule Plasticity

Microtubules are tubulin polymers that form part of the cytoskeleton and provide structure and shape to eukaryotic cells, especially axons and dendrites. They provide a scaffold for intracellular transport, and allow the responsive and adaptative aspects of basic neuronal function.[142] Microtubules adapt their structure to changes in function and are intrinsically involved in neuron excitability, neurotransmission, plasticity, and memory.[142,143] Mitochondria are the central hubs in synaptic plasticity,[144] and the biphasic changes produced by tPBM lead to an increase in mitochondrial instability in the early stage, followed by increased stability in the later phase.[145] The early phase may be associated with adaptive flexibility, followed by memory consolidation.[142] Given neurotransmission and synaptic plasticity are energy dependent, the mitochondria in the cell body need to be transported to the synapses, through the microtubules, so they can provide the energy where it is required.[146] There also is a calcium-mediated response under the influence of neurotransmitters such as serotonin and dopamine, which has an opposite effect.[146]

Animal studies have identified a progressive increase in microtubule dysfunction with increasing AD burden.[147] Microtubules are highly charged polymers that behave as biological transistors supporting, amplifying, and axially propagating electrical signals from the dendrites through the cell body to the axons.[148] Consequently, some of the brain's electrical oscillations may be generated by microtubules, especially the 40-Hz oscillations.[149,150] Microtubule depolymerization and the subsequent accumulation of dopamine and ROS in the dopaminergic neuronal cytosol may cause mitochondrial dysfunction and an increased risk of PD.[151] Tau, a microtubule-associated protein critical for axonal stability and transport, becomes hyperphosphorylated and detached under pathologic conditions (eg, oxidative stress, mitochondrial dysfunction,…), leading to microtubule destabilization, impaired neurotransmission, and aggregation into neurotoxic oligomers and tangles. These

misfolded tau species propagate transsynaptically, driving synaptic loss, axonal degeneration, and neuronal death—the hallmarks of tauopathies such as AD, PD, progressive supranuclear palsy, corticobasal degeneration, frontotemporal dementia, and amyotrophic lateral sclerosis.[152]

α-Synuclein is localized primarily in axon terminals, where it regulates synaptic vesicle trafficking and subsequent neurotransmitter release and is involved in PD, Lewy body disease, and other neurodegenerative disorders.[153] α-Synuclein and tau polymerize into amyloid fibrils and form intraneuronal filamentous inclusions characteristic of neurodegenerative diseases.[154]

Moreover, 808-nm tPBM reduced α-synuclein induced toxicity in an animal model of PD,[155] and 670-nm PBM reduced hyperphosphorylated tau, neurofibrillary tangles, and oxidative stress markers in an animal model of AD[156]; 810-nm tPBM at 10-Hz modulated microtubules[157] reduced microtubule stability, and affected the protein dynamics to allow the remodeling and refreshing of microtubule structures.[158]

In summary, tPBM may modulate microtubules and their associate proteins and thus modulate mitochondrial transport required for adaptive neuroplasticity.

Ion Channel Modulation

TRPV ion channels are calcium ion channels that can be activated by light and increased temperature.[159–161] TRPV1 receptors have evolved to detect and regulate the body temperature, and to allow the detection of noxious environmental stimuli.[162] This happened two billion years ago, antedating the development of mitochondria. Green or infrared PBM can activate[163] or inhibit TRPV1 calcium channels.[164] Although green light has less practical clinical use owing to its limited tissue penetration, infrared and NIR light are more promising.[28] Similarly, 1875-nm pulsed infrared stimulation can modulate TRPV4[165] channels, but this wavelength is mostly absorbed by water. Exposure to even longer wavelengths such as 2780 nm can attenuate TRPV1 activation, reducing a pain stimulus.[28] Figure 3 presents an overview.

Biophoton Emission

Biophoton emission is the spontaneous emission of ultraweak light that emanates from all living systems and cells, including humans. The emission is linked to the endogenous production of the excited states of certain molecules within the living system.[166] These biophotons are ROS-dependent[167] intercellular signals that are emitted as red and NIR light and can be "seen" by other cells, permitting, for example, cell alignment.[168] The effect on neurons involves potassium channels.[169] Neurons also can emit biophotons, and it has been proposed that myelinated axons could serve as photonic waveguides for optical communication between neurons.[170–173] Similar to electrical transmission, the gaps in the myelin sheath known as the nodes of Ranvier have been proposed to be instrumental in the propagation of biophotons as a communication signal,[174] on the basis of the presence of some light-sensitive structures in the nodes of Ranvier.[111] However, on the basis of some simple physics calculations of tPBM and even sunlight, it has been suggested that this mechanism may be impossible because the biophotons are drowned in the background of ambient light, and that the intensity of the light used in PBM drastically exceeds the biophoton intensity by many orders of magnitude.[175–177]

In summary, tPBN has been hypothesized to influence biophoton emission and thus may enable optical transmission of information,[111] but physics suggest the biophoton signal may be

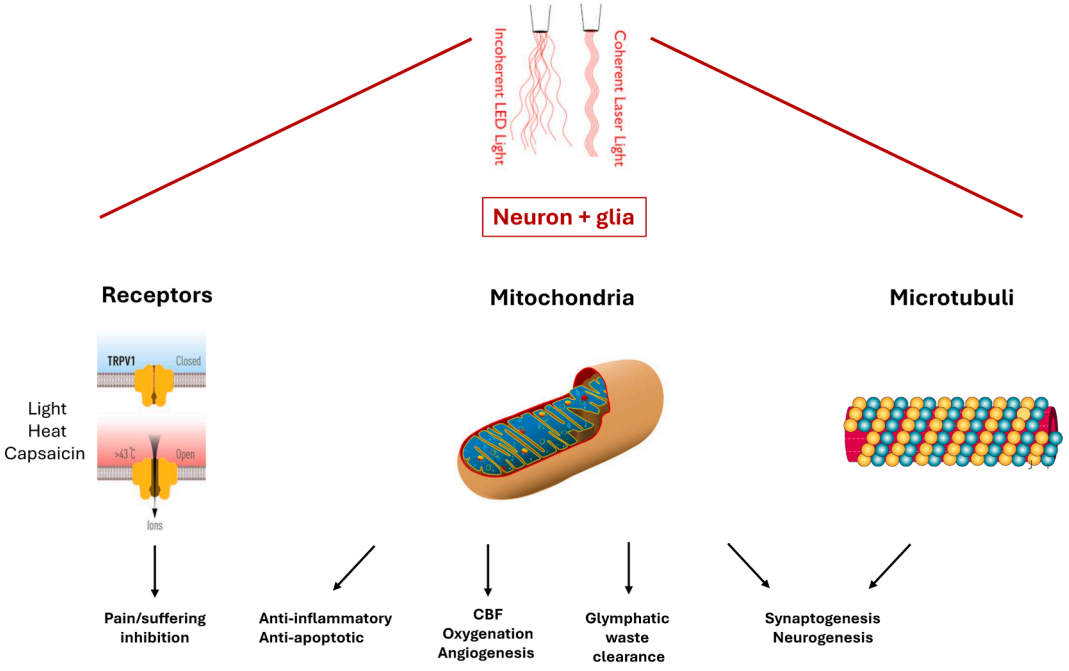

Figure 3. Direct effects of tPBM through TRPV1 channel modulation (left) mitochondrial stimulation (middle), and microtubule plasticity (right). tPBM can 1) reduce pain and suffering through TRPV1 calcium channel modulation, and 2) influence mitochondria in neurons and glial cells yielding anti-inflammatory and anti-apoptotic effects in cerebral blood flow modulation leading to changes in oxygenation and angiogenesis, modulation of glymphatic waste clearance, and synaptogenesis and neurogenesis, which also is mediated through 3) microtubule plasticity. [Color figure can be viewed at www.neuromodulationjournal.org]

drowned in light noise, so more research is required to know whether biophoton transmission could play a role in tPBM.

Biological Effects at a Distance

PBM can affect the brain in animals[178–181] and humans[182] when the light is applied to remote areas of the body and not the head. For example, remote application of PBM on the abdomen and neck improves several clinical signs of PD (mobility, cognition, dynamic balance, spiral test, and sense of smell), with some improvements being maintained for 45 weeks.[182] Improvements in clinical signs were similar to those observed with the application of remote plus transcranial PBM treatment.[182] A comparative study evaluating 1064-nm tPBM vs whole-body 660-nm and 850-nm PBM showed a similar benefit in cognitive improvement for brain fog with both approaches,[183] again indicating that PBM on the body may have a remote effect in the brain.

A mechanistic explanation may be found in a recently discovered mechanism of mitochondrial intercellular transfer.[184] Some cell types export their mitochondria for uptake by developmentally unrelated cell types, a process called intercellular mitochondrial transfer.[184] Cells can transfer mitochondria between themselves through several mechanisms, including transient connections such as tunneling nanotubes, extracellular vesicles formed by budding off from the plasma membrane, and free mitochondria released from source cells and then captured by recipient cells. Some vesicles or free mitochondria can enter the bloodstream, and cell-free mitochondria are an abundant, normal component of blood.[185] Even though these cell-free mitochondria may not be capable of oxidative phosphorylation,[186] they may become functional once incorporated into cells. Mitochondrial transfer is involved in regulating cellular metabolism, cancer biology, the immune system, maintenance of tissue homeostasis, mitochondrial quality control, wound healing, and adipose tissue function.[184] The mitochondria released by astrocytes and gathered by neurons support neuron survival in the central nervous system during stroke or oxygen deprivation. The mitochondria released by macrophages in the dorsal root ganglia can reduce the transmission of pain signals caused by neuroinflammation.[184] Platelets also can release mitochondria, which are picked up by mesenchymal stem cells and neutrophils involved in angiogenesis, wound healing, and antimicrobial activity. Moreover, mesenchymal stem cells can transfer mitochondria into T cells to promote regulatory T cell differentiation and inhibit proinflammatory cytokine production.[184]

A second pathway in remote PBM may involve stem cell-related CXC chemokine receptor type 4 (CXCR4) signaling, oxidative stress response pathways, and modulation of the blood-brain barrier.[73,180,181] CXCR4 is evolutionarily conserved and is highly expressed in microglia and astrocytes, making it one of the important mediators involved in neuroinflammation caused by microglia and astrocytes.[187] Circulating leucocytes can be recruited into the perivascular space through CXCR4, which is critical for neuroinflammation.[188] The chemoattraction of leukocytes through CXCR4 may explain ways remote PBM potentially influences the brain.

A third mechanism may involve biophoton emission by circulating neutrophils,[189] which emit biophotons owing to oxidative stress[190] that can be used as a real-time measurement of ongoing ROS-related oxidative stress.[191] Considering that tPBM modulates ROS, this may be due to modulation of biophoton emission by circulating neutrophils. However, as previously mentioned, it is not yet certain that biophoton emission really plays a role in PBM.

In summary, apart from the local effects of tPBM, there also is a pronounced systemic effect or action at a distance, which may be explained by intercellular mitochondrial transfer, CXCR4 mediated leucocyte attraction into the brain (and/or biophoton modulation).

PBM and Brain Disorders

Considering that many brain disorders are associated with mitochondrial dysfunction, it is not surprising that many studies have attempted to treat neurologic and psychiatric disorders with tPBM (reviews by[8,10,11,28,73,92,141,192]). Only those brain pathologies in which human trials have been performed are reported in the next sections including related preclinical data. Promising preclinical trials that have been performed for additional brain disorders but without human trials are not discussed, including epilepsy,[193–199] intraventricular haemorrhage,[200] hypoxic-ischemic lesions,[201,202] and PTSD.[203,204]

Clinical research has revealed that tPBM may be beneficial in the repair of conditions involving trauma to the brain (stroke, TBI, chronic traumatic encephalopathy [CTE]), neurodegenerative diseases (AD, PD), developmental disorders (autism spectrum disorder [ASD], ADHD, Down syndrome [DS]), neuroimmunologic diseases (multiple sclerosis, amytrophic lateral sclerosis), and psychiatric disorders (depression, anxiety, insomnia, obsessive compulsive disorder, addiction). Furthermore, tPBM may be beneficial for neuro-enhancement in healthy individuals,[10,11,34,73] which means it could be used as prevention from decrease or to improve normal brain functioning. Table 3 presents an overview.

Trauma to the brain, whether caused by stroke, acute TBI, or chronic TBI has been treated by tPBM.[10,73,92,141]

Stroke

Preclinical studies using different wavelength tPBM (660, 780, 808, 810, 904 nm) have all shown alleviation in stroke in animal models by direct neuroprotective effects, inflammation reduction,

Table 3. Preclinical, Clinical, and Enhancement Applications of tPBM.

Preclinical	Clinical	Enhancement
Epilepsy	Trauma (stroke, TBI, CTE)	Older
PTSD	Degenerative (AD, PD)	Young
Hypoxia-ischemic injury	Developmental (ASD, ADHD, DS)	
IVH	Immune (MS)	
Sleep deprivation	Mood (anxiety-depression)	
Low gravity (spaceflight)	Insomnia, sexual dysfunction	

IVH, intraventricular hemorrhage; MS, multiple sclerosis.

prevention of apoptosis, and induction of angiogenesis and neurogenesis.[73] tPBM causes reduced infarct size and improved clinical outcomes in animals, in both the motor and cognitive domain. Too low or too high a dose of tPBM may, however, have a negative effect caused by the biphasic inverted-U profile of tPBM. This may be mitigated by applying pulsed tPBM or reducing or increasing the dose and/or frequency of sessions depending on whether the dose was too low or too high.

Clinical studies, however, are not as promising for stroke because two clinical trials found no difference between tPBM and no tPBM with 808 nm laser treatment.[205–207] This failure may be related to the trials using only one tPBM session and both the stroke side and contralateral hemisphere being illuminated.[73] Indeed, in patients with aphasia related to stroke, there was only benefit if the stroke side was treated and not when tPBM was bilaterally applied.[208]

Traumatic Brain Injury

Many preclinical studies have been performed for TBI. One session of red 660-nm or NIR 810-nm tPBM applied within four hours of a TBI can reduce lesion volumes, analogous to observations in stroke, in addition to improving neurologic outcomes in animal models.[54] Performing three sessions produced an even better result,[57] but 14 daily sessions gave no benefit,[57,209] in keeping with the biphasic inverted-U response. The beneficial results were due to release of BDNF, stimulation of synaptogenesis and neurogenesis, and inhibition of neuroinflammation. The best neuroprotective results were obtained with 660 and 810 nm, but not with 730 or 980 nm.[54] This could be due to weak light absorption by CCO at 730 and 980 nm.[54]

In clinical trials, 633-nm and 870-nm tPBM improved cognitive performance in patients with mild TBI,[210] potentially by increasing brain neural activity, as shown by single-photon emission computed tomography (SPECT) imaging.[211] Furthermore, tPBM in chronic TBI increases the volume of total cortical gray matter (GM), subcortical GM, and thalamic, and improves cerebral blood flow, functional connectivity (FC), and cerebral oxygenation, improving brain function.[210]

In summary, tPBM for trauma, whether stroke or TBI, mitigates the death of brain neurons, decreases neuroinflammation, and improves the self-repair ability of the brain by stimulating synapse formation and proliferation of nerve cells, indicating high potential of tPBM for the clinical treatment of TBI.[73]

Chronic Traumatic Encephalopathy

CTE is a chronic brain condition linked to repeated head injuries and blows to the head. It is often diagnosed in long-term players of sports such as boxing, rugby, or American football. No preclinical data are available, but in an open-label clinical trial in four former players of football, clinically relevant improvement was found in two of four patients after 18 sessions tPBM (three times per week for six weeks). This was followed by 12 home-based sessions yielding further improvements.[212] No controlled studies have been performed.

In chronic TBI, tPBM increases activity (SPECT), in addition to the volume of total cortical GM, subcortical GM, and thalamic, improves cerebral blood flow, FC, and cerebral oxygenation, all producing improving brain function.[210] In some tPBM studies for TBI, structural and functional imaging were performed both post and pretreatment, which showed that tPBM affected brain structure and functioning, but only one study also performed correlation analyses.[212] This study found that the brain changes did indeed correlate with clinical outcome measures. FC within the salience network correlated with executive function, attention, PTSD, pain, and improved sleep. The increase in FC within the central executive network correlated with improved verbal learning and memory, and with relief of depression. The increase in N-acetyl-aspartate in the anterior cingulate cortex measured by spectroscopy was correlated with reduced pain and PTSD severity.[212]

Neurodevelopmental Disorders

The most prevalent neurodevelopmental condition is ASD. One preclinical[213] and five clinical tPBM studies have been performed for ASD.[214] They involved three randomized controlled trials (RCTs) ($N = 40, 40, 30$) and two open label studies ($N = 21$, $N = 10$). tPBM showed efficacy in improving disruptive behavior, social communication, cognitive rigidity, sleep quality, and attention in ASD.[214]

tPBM also has been performed for other developmental disorders, including ADHD and DS.[214] Two open-label clinical studies were performed for ADHD, with seven and nine participants, respectively. tPBM improved both self-rated and clinician-rated attentional performance.[73] One open-label study in DS with three participants[215] revealed that tPBM improved behavioral and cognitive outcomes.[215]

The high prevalence of comorbidity, and broadly overlapping symptoms in these conditions, suggests a shared common pathophysiology, involving mitochondrial dysfunction, increased oxidative stress with ROS, and neuroinflammation.[214] A range of wavelengths between 635 nm (red light) and 905 nm (NIR) have been used in these studies.[214] Taken together, these studies have indicated that tPBM can improve disruptive behavior,[96,213,216] social communication,[217] cognitive and behavioral rigidity,[96] sleep quality,[96] and attentional functions[96] in developmental disorders. In summary, there is promising early evidence for tPBM in ASD, and hints for ADHD and DS that tPBM may be a useful neuromodulation approach warranting further scientific investigation.

Alzheimer's Disease

A good deal of preclinical research has been performed on the use of tPBM in AD animal models, showing beneficial effects in this neurodegenerative disorder. tPBM, especially when performed at night, is capable of decreasing the amyloid-β burden and ameliorating cognitive and memory impairments in AD animal models by affecting various pathways.[73,218] Various wavelengths including 630, 633, 810, 1070, and 1267 nm have shown a beneficial effect on either reducing the production of amyloid β or removing amyloid β from the AD brain, associated with behavioral and cognitive improvement.[73] It must be mentioned, however, that amyloid deposition alone does not correlate with AD disease severity because in humans, amyloid levels do not correlate with clinical progression. The presence of intercellular amyloid plus intracellular tau does correlate with disease progression, especially lateral temporal deposition in the brain.[219,220]

Clinical research using tPBM in human patients with AD also has shown some benefit in four studies.[27,61,221,222] Illuminating the brain with NIR tPBM at 1070 nm for 28 days in a placebo-controlled trial with 11 patients indicated improved changes in executive function, clock drawing, immediate recall, praxis memory, visual attention, and task switching (Trails A and B) in addition to a trend for improved EEG amplitude and connectivity measures.[221]

Another 12-week study in five patients reported improved function in Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale-cognitive (ADAS-cog) tests, better sleep, fewer angry outbursts, and less anxiety and wandering.[27] But this effect was transient because after one month, the MMSE scores decreased again,[27] suggesting that either continuous treatment or booster sessions may be required to maintain the beneficial improvements. A home-based tPBM study in eight patients showed that after 12 weeks of treatment, there were significant improvements in the ADAS-cog and neuropsychiatric index tests in the four patients treated with tPBM in comparison with standard of care.[222] A case report suggested that multimodal treatment with tPBM, intranasal and remote tPBM, could yield a rapid improvement in cognition, sense of smell, and quality of life.[61] The patient showed a significant improvement in the Montreal Cognitive Assessment score from 18 to 24 and in the Working Memory Questionnaire score from 53 to 10.[61]

Parkinson's Disease

Preclinical studies in animals using a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced model of PD showed that tPBM at 670 or 810 nm could alleviate PD symptoms. The neuroprotective effects of tPBM also were observed in other PD models in rats, including the lipopolysaccharide-induced PD model, the 6-hydroxydopamine-induced PD model, the adeno-associated virus 2/6-induced PD model, and even in transgenic PD rat models, showing the robustness of the therapeutic benefits.[73] Intriguingly, irradiation of the back and hindlimb areas in rats also exerted neuroprotective effects, although not as effectively as tPBM.[180] This is an example of the remote effects of PBM either by intercellular mitochondrial transfer, stem cell-related CXCR4 signaling, and oxidative stress response pathways, or more speculatively by biophoton modulation, as previously mentioned.

A clinical study using a randomized placebo-controlled design in humans, with a multiwavelength approach, showed that tPBM at 635 nm plus 810 nm using LEDs could safely and meaningfully relieve individual motor symptoms in PD.[223] Adding a third tPBM wavelength (670, 810, and 850 nm) also caused slowing PD progression.[224] It is proposed that multitarget approaches seem to benefit PD. For example, combining abdominal and brain PBM[182] may allow the brain to be modulated directly through tPBM and indirectly through modification of the gut-brain axis.[182] Other multitarget approaches involve brain, neck, plus intranasal illumination[225] in an attempt to reach the brainstem. Not only multitarget but also multimodal approaches have been attempted: Combining hydrogen water with 940 nm tPBM also improved the unified PD rating scale significantly.[226] A five-year follow-up study revealed that tPBM might safely reduce important clinical motor signs and nonmotor symptoms in some patients with PD, with the improvements being maintained for the long term.[227]

In summary, both the preclinical and clinical data suggest that PBM may be effective for neurodegenerative disorders. Clinical studies support this: PBM applied to the brain through different approaches (tPBM, intranasal, neck) at different wavelengths (both red and different NIR wavelengths) in different combinations seems to exert a beneficial effect on degenerative diseases (both AD and PD). This warrants more placebo-controlled randomized trials to be conducted to verify the specific effects, mechanisms, and effect size of PBM in the setting of degenerative brain disorders.

Multiple Sclerosis

Considering that tPBM has an anti-inflammatory effect in addition to the potential to stimulate neural repair, it has been trialed in autoimmune diseases of the nervous system, such as multiple sclerosis. In preclinical animal studies, tPBM has been shown to improve motor performance in mice with demyelination.[228] This improvement is associated with the attenuation of demyelination, proliferation of oligodendrocyte precursor cells, and inhibition of neuroinflammation.[228]

In a clinical study in humans, tPBM increased the amount of the anti-inflammatory cytokine interleukin-10 in blood samples associated with a subjective improvement in fatigue but without a significant difference in the Modified Fatigue Impact Scale.[229]

Depression and Anxiety

In preclinical studies, 810-nm tPBM significantly improved the behavioral status in animal models of depression caused by sleep deprivation, chronic restraint, or stress.[230] This may be related to reversing oxidative stress and increasing ATP production, attenuating neuroinflammation, and arresting neuronal apoptosis in the prefrontal cortex and hippocampus. This was shown by the expression of immediate-early genes, such as Arc and c-fos in the hippocampus and amygdala.[230,231] This gene activation may cause increased production of BDNF, tropomyosin receptor kinase B, and phospho-CREB/CREB in the hippocampus, and downregulation of corticosterone levels.[232] Pulsing at 10 Hz with an 808-nm NIR laser was more effective than using a red laser (660 nm) but was as effective as the antidepressant citalopram in alleviating depressive-like behaviors in rats.[83] The difference between the red (660 nm) and NIR (810 nm) laser could be related to the better penetration depth and higher absorption by CCO of the 808-nm laser.[83]

Multiple human clinical trials have been performed for anxiety and depression. Safety and effectiveness were established using 830-nm tPBM in patients with MDD,[233] permitting further clinical trials to be performed. tPBM at 810 nm and 940 nm significantly improved the Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale scores in patients with depression, associated with increased cerebral blood flow in both cerebral hemispheres.[234] At two weeks post treatment, six of ten patients had a remission (a score ≤10) on the Hamilton Depression Rating Scale, and this improvement was achieved in seven of ten on the Hamilton Anxiety Rating Scale.[234] Applying 820-nm tPBM targeting the left DLPFC for 14 consecutive days yielded an improvement on the Hamilton Anxiety and Depression Scale that was maintained for ≥eight weeks.[196] The clinical improvement was associated with normalization of repetitive transcranial magnetic stimulation (rTMS)-induced FC.[196] Illuminating the right prefrontal lobe enhanced attention in depression, suggesting the right-sided lateralization of the attentional networks in the human brain.[235,236] Nevertheless, a minimum dose of tPBM needs to be delivered because it was shown that very low levels of tPBM (830 nm; continuous wave; 35.8 cm[2] treatment area; 54.8 mW/cm[2] irradiance; 65.8 J/cm[2] fluence, 20 min/session; ~2 W total power; 2.3 kJ total energy per session) did not yield any benefit.[99]

A systematic review with meta-analysis of tPBM for depression showed that it was beneficial, with a medium-to-large effect size (standardized mean difference: SMD 0.55).[93] The best results were obtained with 830 nm and a duration of 30 minutes per session,

and performing >three sessions per week for a minimum total of 15 treatments.[93]

In summary, depression is a good evidence-based indication for tPBM. More mechanistic preclinical and human placebo-controlled trials are needed, given the placebo effects in depression treatment can be sizable.[237]

Addiction

In a retrospective analysis in 42 patients treated for opioid addiction, 62% received major benefit from unilateral tPBM; 19% had a minor benefit and 19% no benefit.[238] A comparative study of three groups, a cognitive rehabilitation group, a PBM group, and a control group, on drug craving in patients seeking treatment for opioid addiction indicated that either intervention significantly reduced drug craving in both the posttest and follow-up phases compared with the control group.[239] However, tPBM was more effective than cognitive rehabilitation in terms of working memory (WM) and inhibitory control for reducing drug craving.[239] In a controlled study, tPBM showed statistically significant reductions in the intensity, time, frequency, and total scores of opioid cravings, in addition to relief of depression symptoms in comparison with the control group.[240]

In summary, the studies suggest that tPBM may be a promising indication for opioid addiction. Further studies need to be performed in a placebo-controlled manner, and should verify whether tPBM also could be used for other addictions.

Sexual Dysfunction

In a double-blind placebo-controlled trial on tPBM for MDD in 20 patients,[233] the patient's sexual function was investigated, evaluating sexual desire, arousal, and orgasm using the Systematic Assessment for Treatment-Emergent Effects-Specific Inquiry (SAFTEE). The mean improvement in sexual function (decrease in SAFTEE sex total score) in subjects receiving tPBM in NIR mode was significantly greater than in subjects receiving sham mode.[241] Whether this was a direct effect, for example, through NO release, or related to the improvement in depression, is hard to discern, but the study suggests that it is worthwhile to investigate this finding in more detail in patients without depression who experience sexual dysfunction.

PBM Effects on the Healthy Brain

Cognitive Enhancement in Older Participants

Transcranial red (660 nm) and NIR (810 nm) light treatment significantly alleviated memory and cognitive decline, mitochondrial dysfunction, oxidative stress, and cell apoptosis in a D-galactose-induced mouse model of age-related cognitive reduction.[231,242–244] This effect was dose dependent, with a biphasic inverted-U curve, with low and high doses providing no beneficial effects. Red light (660 nm) and NIR light (810 nm) were equally effective, and 1070 nm also exerted a similar benefit.[245] tPBM (670 nm) had a beneficial effect on the inhibition of age-related glial cell proliferation (astrocytes and microglia).[246] tPBM (810 nm) reversed the age-related decrease in regional brain mitochondrial CCO activity in addition to mitigating inflammation, and disrupted intracellular signaling pathways linked to vascular function, cell survival, and glucose metabolism in the aged brain.[247] In animal studies, improvements in spatial memory, episodic-like memory, and social memory were found, whereas different results were found in recognition memory.[248]

A clinical trial of tPBM (627 nm) significantly increased the systolic and diastolic velocity of the left middle cerebral artery and the basilar artery, and decreased the fluctuation index and resistance index, as measured by transcranial ultrasound doppler.[249] Using NIRS, the CCO level was elevated during the irradiation period, followed by a significant poststimulation increase in oxygenated hemoglobin and a decrease in deoxygenated hemoglobin.[64] Furthermore, tPBM (1064 nm) also induced resting-state increases in alpha, beta, and gamma power using EEG, and prefrontal BOLD activity increases were found using fMRI.[250] In other words, the functional imaging technology presently available confirmed the benefits of tPBM in improving clinical cognitive functions. The combination of red (633 nm) and NIR (870 nm) tPBM improved depressive state and cognitive function in older patients, and the WM improvements lasted for ≥three weeks.[251] Improvements were shown especially in WM, cognitive inhibition, and lexical/semantic access.[248] The cognitive benefits were associated with an increase in BDNF,[252] a mechanism already identified in preclinical studies.[55,134] Those older individuals who will respond to tPBM for cognitive enhancement can be predicted by performing fNIRS during a recognition memory task with approximately 80% accuracy.[253]

In summary, based on the preclinical and mechanistic investigations and the preliminary clinical trials, 627, 800, 810, or 1064 nm tPBM may each be a promising approach for cognitive and mood improvement in older patients. These improvements are mediated by neuroprotective, anti-inflammatory, immunomodulatory, and hemodynamic effects.[248] On the basis of tPBM potential in reversing metabolic alterations and enhancing mitochondrial function, as shown by restored CCO activity and ATP levels,[248] the potential for preventing cognitive decline in older patients should be further investigated, in addition to the optimal dosing.

Cognitive Enhancement in Young Subjects

Preclinical studies have shown that tPBM in rats significantly enhances the metabolic pathways in young rats, particularly for excitatory neurotransmission and oxidative metabolism, and similarly restores the altered metabolic pathways in aged rats almost to levels found in younger rats, primarily in the cerebral cortex.[254] This is paralleled by increases in energetic metabolism in young rats and restoration of levels in aged rats to those detected in young animals.[247]

Several tPBM studies in young volunteers have been performed showing that tPBM may improve cognitive functions. After four minutes of right frontal 1064-nm tPBM in 40 human volunteers, enhancements in reaction time during the Psychomotor Vigilance Task (PVT) and performance in a delayed match-to-sample memory task (DMS) were observed. Interestingly, another study reported that sustained positive emotional states persisted for two weeks after tPBM treatment.[255]

In clinical studies, one meta-analysis showed significant, beneficial effects of tPBM on cognitive performance in young, healthy individuals, with a very large effect size (0.949 SMD).[256] The cognitive enhancement on a PVT and DMS in young healthy individuals was more pronounced with pulsed tPBM than with continuous wave tPBM, for sleepiness, memory, and attention.[87] This finding was associated with increased gamma band activity in the EEG.[87] A placebo-controlled study indicated a clear benefit in the learning of syntactically complex Mandarin Chinese sentences, and the authors proposed that tPBM may be a cost-effective tool to upregulate language acquisition and possible learning in general.[257]

Insomnia

An RCT evaluating sleep and life quality in patients with hemodialysis found that after 830-nm laser tPBM, lower global Pittsburgh Sleep Quality Index and Athens Insomnia Scale scores were observed, accompanied by higher physical and mental component summary scores in Medical Outcomes Study 36-Item Short-Form Health Survey Version 2 and a global World Health Organization Quality of Life Brief Version score.[258]

Future Perspectives

Cognitive Enhancement

tPBM seems to exert a more powerful effect on the brains of healthy people for improving cognitive function than that historically achieved by other neuromodulation approaches such as rTMS or tDCS. One study comparing the effects of tPBM and TMS targeting the human somatomotor cortex on brain structural and FC showed increases in left-lateralized functional and structural connectivity from M1 to thalamus after tPBM, but not TMS.[259] Thus, tPBM may be superior to TMS at inducing changes in connected nodes in the somatomotor cortex during a finger-tapping task.[259]

These three neuromodulation methods (rTMS, tDCS, tPBM) have been used to improve attention, perception, memory, and other cognitive functions in healthy individuals, leading to better performance in many aspects of everyday life.[260] These techniques also may reduce the cost, duration, and overall impact of brain disorders and mental illness in patients with neurologic or psychiatric conditions. Given that the benefits of neuro-enhancement outweigh the potential costs, tPBM could potentially reduce suffering and improve the quality of life for everyone while further increasing our knowledge about the mechanisms of human cognition.[260] Indeed, tPBM can act as a reversible "metabolic perturbation," thereby revealing the energetic and network dynamics and requirements underlying cognition, for example, by correlating molecular (ATP), physiologic (oscillations, blood flow), and behavioral levels of brain function. Furthermore, tPBM could be considered as a preventive approach against aging and mood disorders. It should be noted that the neuro-enhancement results of tDCS and rTMS have been limited in scope and effect size. The most impressive improvements have probably been obtained by neurofeedback, yet very few placebo-controlled neurofeedback studies have been performed.

In a randomized placebo-controlled study using 660- or 850-nm tPBM, 56 healthy young adults (28 male and 28 female participants) were randomized to receive either sham, continuous, 40-Hz pulsed, or 100-Hz pulsed tPBM for 8 minutes.[87] Several cognitive tests were performed including the Karolinska Sleepiness Scale questionnaire, PVT, and DMS tasks before and after the intervention, with EEG as a neurophysiologic marker.[87] The results indicated that 40-Hz pulsed tPBM yielded more alertness, more correct answers on the PVT and DMS,[87] and increased gamma activity in the EEG; 100-Hz pulsed tPBM also yielded more correct answers on the DMS.

In summary, these impressive results suggest that neuro-enhancement may be a potential application of tPBM, either as prevention against brain pathology or to improve the quality of life.

Brain Diseases

Because only a few placebo-controlled studies have been performed, it may be concluded that from an evidence-based point of view, tPBM is not yet ready for introduction into routine clinical practice. However, it has been proposed that evidence-based medicine and mechanism-based evidence should be merged to determine whether a novel treatment may enter routine clinical practice.[261–265] In the realm of neuromodulation, this mechanism-based approach has been advocated to be even more important than traditional evidence-based medicine.[261] That does not mean that the scientific world should abandon evidence-based medicine, but in some circumstances, mechanism-based evidence can be sufficient. The famous article in the 2003 *British Medical Journal* Christmas edition questioning whether parachutes are effective in preventing major trauma due to gravitational challenge is one such, albeit humorous, example.[266] Moreover, there has never been any single randomized placebo-controlled study to evaluate the effect of insulin in diabetes, and its introduction into routine clinical practice was based solely on mechanism-based evidence. Ideally, the mechanism-based hypothesis of ways tPBM exerts its effect on the brain could be further elucidated so that placebo-controlled clinical trials can be performed. If the mechanism-based data and the clinical trials agree with each other, a rapid introduction into the clinic can be envisioned.

Traditional evidence-based approaches have so far failed to produce highly efficacious treatments for many mental disorders. The effect size for psychotherapy is 0.34, and pharmacology hovers around 0.36,[267] which translates to a number needed to treat of approximately seven.[268,269] These depressing data are derived from a meta-analysis of 102 meta-analyses, including 3782 RCTs and 650,514 patients, covering a wide assortment of mental disorders, including depressive disorders, anxiety disorders, PTSD, obsessive-compulsive disorder, somatoform disorders, eating disorders, ADHD, substance use disorders, insomnia, SZ spectrum disorders, and BD.[267] Thus, a new strategy to treat mental illness and brain disorders is required.

Can we learn from the concept of war to develop better treatments for brain disorders?

In combined arms warfare, the complementary strengths of the air force, ground troops, and navy act in concert to exert the maximal effect.[270] The concept is that combined forces hit the enemy with ≥two types of weapons simultaneously, such that the actions the enemy must take to defend themselves from one make them more vulnerable to another.[270] Its purpose is to defeat the enemy by disrupting the opponent's ability to react, rather than by overwhelming physical destruction of forces.[270] Translating combined arms tactics into mental disorders, the question arises of whether we should adopt a multitarget and/or multimodal approach. Multitarget tPBM means combining different targets, such as the brain and the abdomen for tPBM. Multimodal, in contrast, means combining multiple modalities, for example, pharmacology plus neuromodulation, or pharmacology and psychology, or all three approaches combined, rather than limiting oneself to a unimodal approach. In essence, multitarget tPBM is defined as having multiple tPBM targets; multimodal tPBM means applying tPBM plus another modality such as pharmacology, psychology, and so forth. Moreover, within each modality, multiple approaches may be combined, for example, drug cocktails, electrical stimulation combined with magnetic stimulation, or PBM combined with neurofeedback. The pharmacologic cocktail approach has been proved highly successful in fighting AIDS. Using four different drugs that each work through a different mechanism, survival has increased from nearly 2 years with one drug, to 5 years with two drugs, 20 with three drugs, and a normal life expectancy (>40 years) with four drugs.[271]

The "war on mental disorders" concept suggests that combining tPBM with other treatment approaches may increase treatment success. One example could be to combine tPBM with neurofeedback. It has been shown that neurofeedback does not help patients with fibromyalgia who also are fatigued, in contrast to patients without fatigue.[272] This makes sense because an exhausted brain is not amenable to learning.[273] Consequently, providing more energy by increasing mitochondrial ATP production through tPBM before neurofeedback seems logical from a mechanism-based point of view, especially in those patients who are mentally fatigued. Evidence-based medicine suggests a clinical trial that compares neurofeedback with tPBM followed by neurofeedback to verify the hypothesis. If a sufficiently large, controlled study could confirm the hypothesis, it could be concluded that no meta-analyses would be required before this combination could transition into routine clinical practice.

Another example would be to combine tPBM with medications. Multiple studies have looked at combining medications with tPBM. tPBM can be used as an add-on therapy to valproic acid to control epileptic seizures.[274] However, this combination follows an inverted-U curve[274] so that care needs to be taken not to use excessively high doses of medication combined with tPBM. Methylene blue easily crosses the blood-brain barrier (BBB) and neutralizes ROS, and therefore can have an additive effect when used with tPBM.[275] A combined methylene blue plus tPBM study indicated improved learning in sleep-deprived rats, associated with increased neuroplasticity biomarker levels (growth-associated protein 43, postsynaptic density protein 95, and synaptophysin[276]) and changes in NO, ROS, and superoxide dismutase antioxidant levels.[277] An open-label clinical study in eight people with long COVID showed a very rapid improvement within four days that extended to the end of the study after two months.[278] tPBM plus oxytocin was effective in relieving the neuropathic pain induced by trigeminal nerve injury.[279] Both these studies were mechanism-based. Methylene blue scavenges ROS that are generated in the mitochondria by oxidative phosphorylation. Although low levels of ROS function as signaling molecules for gene expression, at high doses, ROS are damaging. Thus, methylene blue could be complementary to tPBM by preventing ROS overproduction due to overstimulation by tPBM, on the basis of the biphasic inverted-U curve of tPBM.[34] The second example involves the combination of oxytocin and tPBM. Sensory stimulation of the paw in rodents elicits separate activation of the primary (S1) and secondary (S2) somatosensory cortex. When the infraorbital nerve is ligated, S1 and S2 activation fuses in one large hyperactivated region, not two separate zones. Using either oxytocin or tPBM can reduce the size of spontaneous cortical hyperactivity that covers S1 and S2 but not separate S1 and S2 activation. Combining tPBM and oxytocin normalizes the neurophysiologic activity in S1 and S2.[279] These data suggest that pharmacologic enhancement of tPBM may be useful in clinical practice.

This idea accords with findings for rTMS. Excitatory drugs[280] in addition to drugs that affect neuroplasticity such as N-methyl-D-aspartate modulating drugs (D-cycloserine) can enhance the efficacy of neuromodulation.[281–284] Meta-analyses have confirmed that an antidepressant plus rTMS is superior to rTMS or pharmacologic treatment alone.[285,286] The same holds for medication plus tDCS.[287] A meta-analysis has shown that tDCS plus medication has a superior clinical effect to medication plus sham tDCS in treating addiction.[288]

The meta-meta-analysis mentioned above also confirmed that combining drugs and psychotherapy does increase the effect size by 0.31,[267] suggesting that the complementary treatment approach, that is, a war on brain disorders, makes sense.

In summary, from a mechanism-based approach, tPBM could be combined with medication, other forms of neuromodulation such as rTMS, tDCS, or neurofeedback, or with psychotherapy to obtain maximal results. There is one caveat, however, in that the combined treatments need to be complementary and not cancel each other out. For example, combining a drug that blocks TRPV channels with tPBM at 1064 nm (which activates TRPV channels) may not be beneficial. In contrast, combining tPBM and antioxidants does make sense. For example, combining PBM with acetylcysteine has been shown to reduce ROS in alveola,[289] and because acetylcysteine readily crosses the BBB, it also could be considered in tPBM.

tPBM and Food Supplements

tPBM Plus Amino Acids as Building Blocks for Neurotransmitters. Although drugs plus tPBM may exert a complementary effect on brain disorders, theoretically, food supplements also may be complementary with tPBM. The major effect of tPBM is the production of energy in the form of ATP, which involves the Krebbs cycle. This requires glucose, fat, or protein as substrates for oxidative phosphorylation. However, the mitochondria also produce neurotransmitters from amino acid building blocks, and tPBM in rats has been shown to improve oxidative stress-related decrease in noradrenaline, dopamine, and serotonin levels in the brain.[290] The amino acid building blocks can become depleted in stressful conditions,[291] leading to acute or chronic physical and mental disorders.[292] Literature from researchers in extreme sports and military medicine has discussed the relative deficiencies that can ensue after severe, acute, or less severe long-term stress. When focusing on the most relevant neurotransmitters in the brain, it has been shown in military medicine that L-tyrosine supplementation under extreme stress benefits cognitive performance.[293,294] L-tyrosine is the building block for dopamine, noradrenaline, and adrenaline, all involved in the sympathetic fight or flight response,[294] in addition to the thyroid hormone L-tyroxine (T4). L-tyrosine was depleted in acute and chronic stress, whereas L-tryptophan (the building block of serotonin, which counterbalances the sympathetic nervous system) was only depleted during acute stress.[291] Moreover, histidine may be relevant because it is the building block for histamine, playing a role in brain-immune interactions and arousal. Glutamine, the building block for glutamate and GABA, is known to be deficient in elite athletes and military personnel who overtrain[295] or overreach.[296] Conceptually, if tPBM activates the mitochondria to work harder but there is not a sufficient supply of material (building blocks), the increased activity of the mitochondria may lead to nothing because the ingredients are missing to generate enough neurotransmitters. Even though this is a metaphorical concept, this hypothesis can be tested very easily by comparing tPBM with and without amino acid supplementation.

In addition to tyrosine, tryptophan, and glutamine, some other nutrients change under physical or mental stress. Alanine and arginine levels might have a role in overtraining-related performance loss and fatigue.[296] In endurance athletes, phenylalanine, methionine, lysine, cysteine, and serine also were lower, in addition to glutamine and tyrosine, suggesting a more general depletion ensues over time.[297] In short-duration high-intensity

sports, glutamine, histidine, citrulline, and ornithine were all decreased.[298]

In summary, the addition of amino acid supplements to tPBM makes theoretical sense but still requires scientific confirmation in clinical trials.

tPBM Plus Antioxidants to Prevent Overstimulation. Given it is impossible to know the exact tPBM dose that is optimal for each individual, a treatment provider needs to select a dose, which could be either underdosing, be the perfect dose, or overdosing based on the inverted-U curve. Selecting high tPBM doses at the risk of overstimulation may be an option on the condition that overproduction of ROS can be prevented or blocked. ROS also are homeostatically controlled in the mitochondrion by enzymatic antioxidant defenses and nonenzymatic antioxidants such as ubiquinol (= coenzyme Q10) and glutathione.[299] tPBM overstimulation could exhaust their production. Theoretically, it would make sense to supply endogenous mitochondrial antioxidants (coenzyme Q10, melatonin, glutathione) to prevent tPBM overstimulation. Exogenous antioxidants such as vitamin C or E, alpha-lipoic acid, or polyphenols such as quercetin, curcumin, or resveratrol could be considered,[299] as could methylene blue[276,277] and acetylcysteine.[299]

tPBM Plus Other Therapies

A systematic review evaluated tPBM in combination with other interventions, such as physical therapy, exercise, stem cells, and external biomaterials, in neurologic disorders in both animal models and humans. The conditions included neuropsychiatric diseases, neurodegenerative diseases, ischemia, nerve injury, pain, paresis, and neuropathy. The results indicated clear synergistic effects, leading to better results for a wide range of neurologic and psychiatric disorders by relieving symptoms and reducing side effects.[300]

Multimodal approaches involve the combination of different treatments, yet different variations of the same treatment may be beneficial when combined, as clearly shown by the success of multipharmacologic treatment in AIDS. The same may hold for tPBM if combinations of multiple different wavelengths/frequencies, or continuous and pulsed illumination produce more benefits. The same idea is behind the application of PBM directly to the brain and to other parts of the body such as the abdomen, at the same time.

As mentioned above, combining multiple wavelengths may be synergistic because they can exert complementary effects.[70,301] A meta-analysis of clinical studies confirmed that a combination of multiple wavelengths was superior for cognitive enhancement.[60] This could be explained by a combination of red and NIR tPBM possibly being complementary, because red light exerts a direct effect on chromophores in the mitochondria, whereas NIR may exert extra benefits through affecting TRPV channels and microglial phenotypes.[70] Thus, this method is in keeping with the war on mental disorders approach.

tPBM and Remote PBM

On the basis of a small case series ($N = 12$),[225] single case reports,[61] and some animal studies, it appears that combining abdominal or neck PBM plus transcranial PBM may exert a beneficial effect that surpasses each approach separately.[302] However, no comparative studies have yet been performed. This also is in keeping with the war on mental disorders approach.

Predictive Biomarkers for tPBM?

The discovery of predictive biomarkers to suggest that the application of PBM may be beneficial would be highly desirable. Considering tPBM's primary mechanism of action is through the mitochondria, measuring mitochondrial dysfunction may enable the selection and follow-up of patients who would benefit from targeting mitochondria.[303] This could be achieved by tissue biopsies, magnetic resonance spectroscopy imaging,[304] or wet laboratory tests (blood/CSF/urine/saliva).[303] The ideal mitochondrial marker has not been identified because longitudinal studies are mostly lacking, and no potential biomarkers have been validated. Those that have been proposed are either not feasible, are expensive, or are not widely available.[305] Biopsies are not practical in human clinical neuromodulation, and magnetic resonance spectroscopy imaging is only performed in highly specialized neuroimaging centers, limiting its accessibility. Therefore, blood, urine, saliva or CSF biomarkers would be preferable. Considering that performing a lumbar puncture for CSF is invasive, and few analyses have been conducted with saliva or urine, it is suggested that blood biomarkers would be most promising. These blood biomarkers can be divided into three classes, functional markers measured in blood cells, biochemical markers in serum/plasma, and DNA markers.[303]

An expert review found that there was no single biomarker with 100% sensitivity and specificity for all types of mitochondrial dysfunction in patients.[303] Therefore, combining multiple biomarkers is probably the best strategy. This combination of biomarkers could include examples of three separate types: firstly, a functional marker measured in white blood cells, which would be a direct measurement of mitochondrial dysfunction;[306] secondly, a panel of biochemical markers, covering a different aspect of the mitochondrial defect spectrum, such as lactate, pyruvate and lactate/pyruvate, carnitine, acylcarnitine, coenzyme Q10, and amino acids all involved in the TCA cycle, or else oxidative stress markers evaluating oxidative phosphorylation; and thirdly, analysis of the mtDNA and RNA species.[303,307,308] For example, mitochondrial long noncoding 7S RNA in plasma could be a potential predictive biomarker for both depression/anxiety and the treatment response for these disorders, because mitochondrial 7S RNA is increased in anxiety and depression and is decreased in response to successful treatment.[309] Similarly, the mtDNA copy number is associated with symptoms of depression, anxiety, and stress, and also changes with treatment response.[310] Furthermore, in cognitive decline, a higher mtDNA copy number is associated with better general cognitive function.[311]

CONCLUSIONS

PBM exerts many different effects on the body and the brain. Mechanistically, the improvements may relate to focal effects in regions of the brain, in addition to remote effects in other tissues and parts of the body. These include mitochondrial CCO activity and increasing energy availability through increased ATP production. Apart from mitochondrial activation, PBM also activates immediate early gene expression and the NF-kB transcription factor. This causes protein production that modulates intracellular signaling, up-regulates cell survival and proliferation, and generates neurotrophic factors, while down-regulating proapoptotic markers and preventing cell death. Consequently, tPBM exerts beneficial effects on synaptic plasticity, neurotransmitter levels, and cholinergic neurotransmission, highlighting its potential for

promoting neuronal function and cognitive enhancement. tPBM not only targets neurons but also glial cells such as astrocytes and microglia, thereby producing antineuroinflammatory effects and synapse remodeling effects. Furthermore, owing to its NO production, tPBM can increase blood flow and brain oxygenation. tPBM also activates the glymphatic BWRS, reducing Aβ plaque levels, and in the long run can even modify structural plasticity by microtubule generation and restructuring.

The indirect effects exerted by remote (nonbrain) PBM may be mediated by free-floating intravascular mitochondria or immune cells, in addition to stem cells residing in bone marrow that are mobilized and then migrate to the distressed brain. Remote PBM also may reduce systemic inflammation, which has been shown to benefit the brain.

On the basis of these widely different but cooperative physiologic and metabolic processes induced by tPBM, this novel neuromodulation technology has been investigated preclinically and clinically for a vast array of brain disorders, including traumatic (stroke, TBI, CTE), developmental (ASD, ADHD, DS), neurodegenerative (AD, PD), psychiatric (anxiety, depression, insomnia, and sexual dysfunction), and neuroimmunologic (multiple sclerosis) disorders.

However, it remains unclear whether the tPBM effects on the energy, metabolic, hemodynamic, drainage, and immune processes of the brain are nonspecific or whether they depend on specific characteristics of brain diseases and on specific illumination parameters.

Some studies have suggested that both multitarget and multiwavelength tPBM with red and NIR tPBM may be superior to single-target and single-wavelength illumination. This could be due to the complementary mechanisms of action exerted by the different wavelengths. Moreover, pulsed tPBM appears to be superior to continuous wave tPBM, possibly owing to preventing overproduction of ROS, which in low dose acts as a signaling molecule but in high levels is damaging. The biphasic inverted-U curve effect of tPBM on the brain physiology and mechanisms of tPBM needs to be considered.

In short, a better understanding of the large range of illumination parameters will help to develop optimal and personalized standards and guidelines for tPBM for brain diseases and neuroenhancement alike.

It needs to be determined whether tPBM will be used in routine clinical practice as a stand-alone treatment or whether it may become part of a multimodal approach that could involve pharmacology (medication and/or food supplements), psychotherapy, and/or other forms of neuromodulation.

Key issues

- Light in the red and NIR spectrum can penetrate the skin and skull
- Red and NIR light can be delivered in continuous or pulsed mode
  a. Red and NIR light can be delivered by lasers
  b. Red and NIR light can be delivered by LED
- Red and NIR light can be applied at low and high intensities
- Low-intensity NIR light can be used for imaging purposes, called fNIRS
- Low-intensity red and NIR light can be used as a neuromodulation device, called tPBM
- High-intensity light can be used to destroy tissue and is predominantly a surgical tool
- tPBM targets CCO in the mitochondria in the brain leading to
  a. improved oxygen consumption
  b. enhanced ATP production
- tPBM boost in cellular energy can help in
  a. overall improved cellular function
  b. cell repair
  c. production of neurotransmitters and growth factors
  d. reduction of inflammation
  e. both locally and at a distance
  f. for a time that extends beyond the stimulation period
- tPBM can have long-term effects due to transcription factor activation and genetic expression or inhibition involved in
  a. synaptic plasticity
  b. angiogenesis
  c. neurogenesis
  d. reduced apoptosis
- tPBM also exerts structural changes in neurons and glia
- Remote PBM (eg, abdomen, neck) also affects the brain
- tPBM has been investigated in trauma to the brain, developmental anomalies, degenerative disorders, and psychiatric and neuroimmunologic disorders
- tPBM has also been investigated in preclinical trials not yet translated to humans (epilepsy, intraventricular hemorrhage, hypoxic-ischemic lesions, and PTSD)
- tPBM can be used as a standalone treatment or be part of a multimodal approach for brain diseases, involving neurologic and psychiatric disorders

Authorship Statements

Dirk De Ridder, Michael R. Hamblin, and Sven Vanneste drafted and revised the manuscript. All authors approved the final manuscript.

Conflict of Interest

The authors reported no conflict of interest.

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COMMENTS

The manuscript provides valuable guidance for clinicians planning to use tPBM in their practice, and for researchers.

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This review was very comprehensive of cellular, animal, and human work using photobiomodulation, low-level laser therapy, and LEDs and covers the mechanisms of this neuromodulation technique, which differs from other techniques such as TMS and TDCS.

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