Recent advances in photobiomodulation therapy for brain diseases

Abstract

Light therapy techniques, such as photobiomodulation therapy (PBMT), photodynamic therapy (PDT), and laser photoablation, have gained widespread attention and become indispensable physiotherapy methods in clinical practice. PBMT involves the application of low-level laser/LED to modulate the function of nerve cells, relieve neuroinflammation, promote neurogenesis and vascular growth. Recent studies have shown that PBMT holds promise as a complementary or alternative treatment of Alzheimer's disease (AD), traumatic brain injury (TBI), major depressive disorder (MDD), etc. However, the therapeutic effect of PBMT is influenced by various factors, such as the patients' condition, brain structure and function, illumination parameters, etc. Therefore, the optimized parameters, personalized therapeutic schedules, and precise evaluation of the therapeutic effect are crucial to the treatment success. In this review, we identified the recent experimental and clinical successes, existing obstacles, and future opportunities for PBMT in the treatment of the brain

diseases. As a non-invasive, side-effect-free, and highly accessible technique, PBMT brings a glimmer of light for the treatment of neuropsychiatric disorders and the neuro-rejuvenation of human brains.

1 INTRODUCTION

Photobiomodulation (PBM) is a therapeutic method that utilizes light with specific wavelengths, usually in the range of 400–1100 nm, to stimulate the photobiochemical reactions and trigger non-heating physical photonic effects at multiple living levels.[1, 2] These photon-tissue interactions have been demonstrated to have beneficial effects on promoting cell proliferation, suppressing neuroinflammation, reducing pain, and promoting the healing of wounds, deeper tissues and nerves.[3-6] Therefore, photobiomodulation therapy (PBMT), also known as low-level light therapy (LLLT), has evolved as an important physiotherapy, which applies low-level lasers or light emitting diodes (LED) to deliver light at a low power density (1–100 mW/cm^2) to pathologies or apply pulsed visual stimulations. Nowadays, PBMT has been widely applied in the fields of medical recovery and the treatment of various neurological disorders, such as neurodegenerative, neuropsychiatric, psychological, traumatic tissue injury, and cerebral infarction.[7] As a mild physical therapy, PBMT has almost no obvious side effects.[8] Besides, it has the advantages of being non-invasive, low-

cost, and suitable for home care of patients with brain diseases, such as AD, TBI and MDD. Hence, PBMT is expected to be a complementary or alternative technique of treating a wide range of brain diseases and tissue injuries in addition to pharmacotherapy.

The scientific basis of light therapy can be traced back to the late 19th century when researchers revealed that light plays a significant role in regulating various levels of animal life activities, such as gene expression, energy metabolism, cell proliferation, skeletal development, and ontogenesis.[7, 9, 10] In 1895, the Danish physician Niels R. Finsen discovered that red light helped the healing of skin lesions in patients with smallpox and lupus vulgaris.[11] Subsequently, he used this method to cure nearly a thousand patients, and then paved the way for scientific light therapy, for which he received the Nobel Prize in Medicine in 1903. In 1968, E. Mester, a pioneer of laser medicine, discovered that wound healing was markedly faster after repeated irradiation with a low-intensity laser on mice with back skin wounds.[12] In 1973, he successfully used this method to treat patients with skin ulcers,[13] and pioneered PBMT as a novel non-invasive technique for dermatological recovery.

In recent two decades, PBMT has received increasing attention from researchers and its application area has been broadened to the treatment of brain diseases (Figure 1). In

the figure, to assess the research trend of PBMT, 801 and 439 papers were collected respectively from the Web of Science (WOS) core collection and the Chinese National Knowledge Infrastructure (CNKI) English database with the topic of PBM or LLLT in the field of brain diseases. The data were pre-processed to avoid duplication or inconsistency. As the figure shows, there is a rapid increase in the number of publications after 2015, for the dominant reasons that (1) The development of advanced laser systems and much cheaper light emitting diodes (LEDs) has led to an unprecedented expansion of a multitude of therapy options.[14, 15] (2) The prevalence of dementia continues to increase worldwide and there is an urgent need for non-pharmaceutical treatments.[16] (3) The biochemical mechanisms underlying the positive effects of PBMT are gradually understood, and the consistence existing in the basic principles of PBMT intervention with various brain diseases have been found.[17] Brain diseases, including neurodegenerative diseases and neuropsychiatric disorders, have been a major public health problem. There is no drug that can completely reverse the progression without side effects, whereas PBMT has been demonstrated to be capable of delaying the progression of disability, promoting brain function recovery, and reducing the frequency of relapses.[7] Therefore, PBMT is expected to be a novel physiotherapy method for the treatment or prevention of cerebrovascular disease (stroke, cerebral ischemia),

neurodegenerative diseases (AD, Parkinson's disease), psychiatric disorders (depression, insomnia, addiction, obsessive-compulsive disorder, schizophrenia), and brain injury, etc.

FIGURE 1

Distribution of publications on the treatment of brain diseases with PBMT in the database of the CNKI and WOS core collections. Search strategy, Topic = ([PBM OR photobiomodulation OR LLLT OR low-level laser therapy] AND [brain disease OR neurology OR psychiatry]), Document Type = (Article OR Clinical Trial), Publication Date = (2000-01-01 to 2023-9-30).

2 MECHANISM OF ACTION OF PBMT

The prevailing view on the mechanism of action of transcranial PBMT is that low-level light activates mitochondrial cytochrome c oxidase (CCO) and certain molecular photo-acceptors to enhance the cellular energy metabolism. Hamblin et al. evaluated the results of light irradiation experiment on CCO conducted by Karu et al. and Pastore et al. with the results of irradiation experiments on TBI mice.[18-20] They found that the wavelength at the peak absorption of CCO matched the wavelength of light with the best therapeutic effect of PBMT in brain-injured mice. Moreover, they observed an improved adenosine triphosphate (ATP) level after the intervention of red and near-infrared (NIR) light.[21] Based on the fact that CCO belongs to the mitochondrial respiratory chain complex IV, it

is concluded that CCO is the most dominant intracellular chromophore to absorb red and NIR light, and thus enables the therapeutic effect during PBMT.[22, 23] When cells are exposed to the light, the activity of CCO is stimulated and its excessive binding with nitric oxide is dissociated by the photons, which contributes to an enhancement in the mitochondrial oxygen consumption and cellular energy metabolism.[5, 24] Since it has been reported that neurological dysfunction and neurodegeneration are closely related to impaired mitochondrial oxidative metabolism, it is hypothesized that PBMT improves the function of diseased or normal brains by enhancing mitochondrial metabolism.[25]

Another theory on the mechanism of PBMT is that light regulates the production of reactive oxygen species (ROS) and induces transcriptional changes. Chen et al. showed that light at a wavelength of 810 nm modulates the generation of ROS in mitochondria, activates retrograde signaling pathways from mitochondria to the nucleus and modulates the expression of transcription factors such as NF-κB in mouse embryonic cells.[26] NF-κB regulates the expression of hundreds of genes, including those with functions of antioxidant, anti-apoptotic, cell proliferation, migration promoting, etc. This work demonstrated that PBMT can reduce NF-κB levels in activated inflammatory neuronal cells, thus exerting a neuroinflammatory suppressive effect. In addition, Karkada et al. discovered an

effective rise in the antioxidant enzyme (i.e., malondialdehyde, superoxide dismutase and glutathione) of the rats treated with PBMT of dosages 4, 6, and 8 J/cm^2, which accelerates the scavenging of the ROS molecules during the wound healing process.[27]

Although the systemic mechanism of action of PBMT on human brain function has not been completely elucidated, several studies have observed that PBMT exerts beneficial effects on brain nerve cells and tissues. Giuliani et al. found that red and NIR light have neuroprotective effects, promoting neurogenesis and inhibiting neuronal apoptosis.[28] They found that the irradiation of rat PC12 neuronal cells cultured in vitro with low-intensity laser light at a wavelength of 670 nm resulted in neural protrusion growth and improved cell survival under oxidative stress. Naeser et al. found that transcranial irradiation of patients with chronic aphasia using light at 633 and 833 nm simultaneously increased functional connectivity in the default mode network of the brain.[29] Furthermore, many animal and clinical studies have shown that PBMT can promote angiogenesis and vasodilation, contributing to increased cerebral vascular density as well as improved cerebral blood flow and oxygenation.[30-32]

According to the analyses from the above-mentioned studies, conclusions on the mechanism of PBMT reached varied widely due to the different illumination parameters

(irradiation site, light wavelength, light power, etc.), targets (animal models, patient types) and detection methods selected in the previous experiments.[33] Despite the fact that the exact mechanism of PBMT remains controversial and has not been conclusively established, the positive effects of PBMT for brain diseases were demonstrated in various experiments conducted in vitro, in animal models and in clinical trials, which we discussed in the following parts in detail.

3 RECENT PROGRESS OF PBMT IN BRAIN DISEASES

3.1 PBMT for Alzheimer's disease

Alzheimer's disease (AD) is a chronic neurodegenerative disease and the most common form of dementia (Alzheimer's disease accounts for approximately 60%–70% of all dementia patients). The main clinical manifestations of AD are cognitive, executive and memory dysfunction in the brain, characterized pathologically by abnormal deposition of β-amyloid (Aβ) and plaques formed with hyperphosphorylated tau protein, which results in neurofibrillary tangles, triggers neuronal damage, apoptosis, neuroinflammation, and brain function disorders in AD patients.[34] The number of patients with AD and related dementias in China has exceeded 15 million in 2020,[35]

accounting for a quarter of the world. In addition, AD has been ranked 15th in the list of diseases with the highest number of deaths in China. With the increasing aging of the population, the impact of AD on the daily life of the population is becoming increasingly severe. However, the existing therapeutic drugs are unable to reverse the progression of AD patients, and thus there is an urgent need to develop new drugs or alternative treatments.

In recent years, a large number of basic studies and animal experiments have shown that PBMT can regulate the function of neurons and glial cells through various pathways, reduce the content of Aβ plaques in the brains of AD animal models and exert neuroprotective effects to restore their damaged brain functions. In 2018, Blivet et al. applied device RGn500, an innovative device that produced photonic and magnetic field emissions and exerted cranial parietal and abdominal irradiation on an AD mouse model generated by injecting the hippocampal region with Aβ25-35 protein.[36] After 8 consecutive days of daily 10-min irradiation with a pulse frequency of 10 Hz, the memory and spatial cognition of the AD mice were repaired. Besides, the content of Aβ1-42 with phosphorylated Tau-containing proteins in the mice decreased, and oxidative stress and neuroinflammation were suppressed.[36] In 2019, Tsai et al. found that stimulating AD mice with 40 Hz pulses of visual and auditory signals significantly reduced the number of amyloid plaques in their

brains and improved their cognitive function.[37] In May of the same year, the team elucidated the mechanism of this combined stimulation for AD mice from a novel perspective: 40 Hz light and sound signals could increase the gamma wave frequency in important brain regions of mice, alleviate synaptic dysfunction, reduce the inflammatory response of microglia, and thus improve their spatial learning and memory abilities (Figure 2A).[38] However, a recent study reported by Buzsáki et al. showed controversial results.[41] It was found that 40 Hz white light had only a small effect on the gamma rhythms of neurons in the visual cortices of AD mouse models of amyloidosis, with no reliable changes in plaque count or microglia morphology by either immunohistochemistry or in vivo two-photon imaging. Moreover, by measuring the electrical activity of the APP/PS1 mice, they found little effect the 40 Hz light or sound stimulus had on deeper brain regions, entraining only 7% of hippocampal neurons. This negative study indicated that native gamma oscillations and the steady-state oscillations evoked by 40 Hz sensory stimulation are likely distinct neurophysiological phenomena. Thus, replication studies are needed to study the cognitive benefits of PBMT and 40 Hz stimulation on mouse models and human subjects via its extension to clinical studies.[42]

FIGURE 2

Experiment setups of PBM for AD mouse models and AD patients. (A) Inducing gamma

oscillations with visual stimulation showed a preservation of neuronal and synaptic function across multiple brain areas, reduced inflammatory response in microglia, and modified cognitive performance. Reproduced with permission.[38] Copyright 2019, Elsevier. (B) The apparatus that treated the APP/PS1 mice with 1070-nm continuous, 10-Hz, or 40-Hz pulsed-light irradiation. Reproduced with permission.[31] Copyright 2021, Springer Nature. (C) The Targeted default mode network nodes of transcranial and transnasal PBMTs. Reproduced with permission.[39] Copyright 2017, Mary Ann Liebert, Inc. (D) Positions of the Vielight Neuro Gamma device generating transcranial LEDs irradiations on the brain regions of interest. Reproduced with permission.[40] Copyright 2019, Mary Ann Liebert, Inc.

Since 2016, Han et al. have pioneered the transcranial PBM (tPBM) using the NIR LED devices with wavelengths ranging from 1040 to 1090 nm to study its therapeutic effects on AD in APP/PS1 transgenic AD mice and AD patients.[43] In 2018, they observed prominent improvements in memory and spatial cognition of the tPBM-treated mice during the Morris water maze experiment. Besides, immunofluorescence analysis of the brain tissue sections showed significant decreases in Aβ content and the number of Aβ plaque-like deposits.[44] In 2021, they applied a novel LED device to irradiate AD mice with differently modulated irradiation modes (i.e., continuous, 10 Hz pulsed and 40 Hz pulsed modes) for 60 consecutive days (Figure 2B).[31] Then, they found that the mice irradiated by 10 Hz pulsed light had more significant improvements in their cognitive and memory abilities than other groups. In addition, they observed that the number of M1 microglia in the cerebral cortex decreased by 16.30% and inflammatory factors secreted by M1 microglia were reduced after the treatment.

They also revealed that the vascular density in the mouse brain increased by 24.26%, and the increase in vascular density and blood flow promoted the clearance of Aβ from the mouse brain tissue and the repair of cognitive function. This study investigated the mechanism of action of PBMT to improve Aβ clearance at both cellular and tissue levels, providing a new theoretical basis for tPBM treatment of AD.

Recent clinical studies have shown that PBMT can alleviate the AD symptoms and improve the memory and self-care abilities of the patients. In 2017, Saltmarche et al. conducted a PBMT which combined transcranial and transnasal irradiation (for 12 weeks, 20 min per day, using NIR light at a wavelength of 810 nm) in five AD patients with mild to severe cognitive impairment (Figure 2C).[39] They observed significant improvements in the mental status of the patients in the following 4 weeks and found the recovery of brain function in all five subjects, accompanied by better sleep quality, lower frequency of angry feelings and anxiety. Besides, no side effects of PBMT were detected. In 2019, Chao tested the efficacy of transcranial and transnasal PBMT home care in eight patients with dementia with a mean age of 80 years (Figure 2D).[40] He found that after 12 weeks of treatment, four patients receiving PBMT had their mean scores on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (a scale used to assess cognitive ability in patients with AD, with lower scores indicating better

cognitive performance) decreased by 13.9%, while the mean score in the conventional treatment group increased by 22.1%. In this study, PBMT was found to enhance cerebral perfusion and increase connectivity between the posterior cingulate cortex and the lateral parietal nodes by arterial spin-labeled perfusion magnetic resonance imaging. This experiment showed that at-home PBMT has sufficient efficacy in improving cognitive performance in AD patients and is a promising new home physiotherapy method.

In 2021, Cimenser et al. reported the results of the first clinical study of the curative effect of 40 Hz sensory stimulation therapy on AD patients.[45] They applied visual and auditory signal stimulation with 40 Hz pulses to a random sample of 14 out of 22 patients with mild to moderate AD and conducted sensory stimulation therapy for 1 h per day for 6 months. A significant decrease in nocturnal activity periods during the treatment period was recorded using a wrist motion detector, and the mean scores of these 14 patients increased gradually during the treatment period using the activities of daily living (ADL) scale for AD patients. In contrast, eight AD patients in the sham-treatment group who received irradiation with similar treatment conditions but without excitation of gamma waves at a frequency of 40 Hz in their cerebral cortex showed no improvement in their nighttime sleep quality or ADL scale scores. This clinical trial strongly supports the conclusion of Tsai's study

from animal experiments that sensory stimulation with 40 Hz pulses can increase γ-wave frequencies in important brain regions of AD patients and provide a significant curative effect on AD.[38]

3.2 PBMT for traumatic brain injury

Traumatic brain injury (TBI) is a sudden brain disease, usually caused by a severe blow or jolt to the head, resulting in secondary brain tissue damage and neuronal apoptosis and impairing brain functions such as memory, motor, and perception.[46] China has the largest number of TBI patients in the world, with an average of about 13 cases per 100,000 people.[47] Currently, there is no effective clinical treatment for TBI that can reverse the initial brain injury or prevent secondary injury. TBI has become an important public health issue that affects the health level of Chinese residents.

In recent years, many novel neuroprotective methods for acute TBI and neurorehabilitation methods for chronic TBI are in the testing phase, and PBMT is one of the non-invasive optical therapies with potential for treating TBI. In 2012, Hamblin et al. tested the therapeutic effects of low-level lasers with wavelengths of 665, 730, 810 and 980 nm in mice model with closed head injury.[20] They found that the experimental group of mice irradiated with 665 and 810 nm lasers had significantly improved neurological severity

scores (NSS) and reduced number of microcavities in brain tissue compared to the sham-treated group, while 730 and 980 nm laser irradiation did not produce significant therapeutic effects. This indicates that PBMT with specific wavelengths can have beneficial effects on post-injury recovery of TBI mice.

The therapeutic effects of PBMT on TBI patients have been reported in several clinical trials. In 2019, Hipskind et al. conducted a transcranial PBMT experiment on 12 veterans with chronic TBI (more than 18 months after brain injury).[48] After 6 weeks of 20-min sessions three times a week using both red and NIR light emitted from LED at a power density of 6.4 mW/cm^2, TBI patients showed significant improvement in 6 out of 15 neuropsychological test indicators, and increased regional cerebral blood flow was observed in 8 patients using SPECT imaging. This study suggests that PBMT may improve cognitive function in patients with chronic TBI. In 2020, Longo et al. conducted a randomized controlled trial (RCT) on 68 moderate TBI patients and found that PBMT was feasible in all participants, with no adverse reactions reported.[49] PBMT significantly altered multiple diffusion tensor parameters in the white matter of the brain in late subacute TBI patients. This study used a measurable method of multiple diffusion tensor imaging and was the first to discover the effect of PBMT on the neural matrix associated with moderate TBI in humans,

providing empirical evidence for the theory that PBMT affects the myelin repair pathway. Moreover, PBM serves as an alternative non-pharmacological intervention for TBI patients with crossed cerebellar diaschisis (CCD). In 2023, a longitudinal study was employed to confirm the effect of intravascular PBM (iPBM) on CCD in patients with TBI.[50] This study evaluated CCD in TBI patients (n = 30) from their brain perfusion images and identified that the occurrence of CCD decreased significantly ($p < 0.0001$) after 2–3 months of iPBM treatment.

3.3 PBMT for major depressive disorder

Major depressive disorder (MDD), also known as depression, is the most prevalent mental disorder with an estimated 322 million people with different degrees of MDD worldwide, according to a 2017 report by the World Health Organization.[51] The recognized treatments for MDD include pharmacotherapy, psychotherapy, and physical therapy. However, nearly 30% of patients do not show adequate relief of symptoms after multiple drug trials.[52] Furthermore, most MDD patients prefer non-pharmacological therapies when they are treatment-resistant or intolerant to antidepressants, whereas the effectiveness of psychotherapy is limited by multiple factors (i.e., environment, experiences of therapists, emotional shame of patients, etc.).[53, 54] Therefore, as a novel non-invasive and side-effect-free physical intervention

method, NIR light transcranial PBMT was demonstrated to hold the promise of alternative or adjuvant treatment for MDD patients.

In 2016, Mohammed et al. induced an MDD mouse model by intraperitoneal injection of chronic doses of reserpine (0.2 mg/kg per day) for 14 days. Then, they fully stimulated the entire cerebral cortex of the mice using a GaAlAs diode laser, which produced light with a wavelength of 804 nm and a power of 80 mW, from the 7th day of injection. In the forced swimming test on the 14th day, the swimming time of the MDD mice exposed to light increased by 63.3%, and 80% of the parameters in the cortical electroencephalogram (EEG) spectrum of the mice returned to levels close to those before reserpine injection.[55] In 2022, Mohammed et al. used a laser with a wavelength of 830 nm to irradiate the above-mentioned MDD mouse model.[56] They found that light exposure inhibited the oxidation of monoamines, increased the content of monoamines, and alleviated the oxidative stress in the cerebral cortex and hippocampus of the mice. These studies provided evidence that PBMT can improve the depressive symptoms of the MDD mouse model from multiple perspectives, including animal behavior, EEG spectrum analysis, oxidative stress marker detection, etc.

In 2018, Cassano et al. from Massachusetts General Hospital reported the first randomized, double-blind, sham-

controlled trial of transcranial PBMT for MDD patients.[57] They reported the antidepressant effects of PBMT. In this trial, out of 13 patients who completed the trial, 6 patients received PBMT with a wavelength of 823 nm and a power density of 36 mW/cm^2 for 20–30 min per day for 8 weeks. Their mean score on the Hamilton Depression Rating Scale ($HAM\text{-}D_{17}$) dropped from 22 to 6, while the mean score of the other 7 patients in the sham treatment group only dropped from 20 to 14 (most of the patients in the experiment still received medication treatment). This trial showed that PBMT has significant antidepressant properties, but it has limitations such as small sample size and short follow-up time. Hence, more replicated clinical trials are needed in the future to further test the efficacy of PBMT for MDD.

Moreover, the therapeutic effect of PBMT is related to the irradiation site, and the intervention results of PBMT on MDD at different irradiation sites have been observed.[58, 59] Disner et al. conducted an RCT of PBMT as an adjunctive treatment for major depression.[59] They randomly assigned 51 patients to three groups (left, right prefrontal irradiation group and sham treatment group). The treatment effect was assessed using the Center for Epidemiologic Studies Depression Scale (CESD) after 2 weeks of treatment. They found that the depressive symptoms of patients who received right prefrontal irradiation were significantly improved, while there

was no obvious improvement in the symptoms of patients who received left prefrontal irradiation or sham treatment. They speculated that the reason was that depression was more strongly related to the activity of the right prefrontal cortex. Therefore, when conducting PBMT, the irradiation site should be reasonably selected, which can help to achieve precise treatment. The above-mentioned RCT suggested that the illumination sites should be set on the right forehead when using PBMT to treat MDD.

4 FUTURE OPPORTUNITIES AND CHALLENGES OF PBMT

4.1 Toward elucidating the systemic mechanisms of PBMT

PBMT uses light at various wavelengths to treat a wide range of brain diseases and brain injuries (Table 1), but the different mechanism of action underlying different illumination parameters have not been fully understood. Although previous studies suggested that the cell proliferation enhancement triggered by PBM involves the activation of the mitochondrial respiratory chain CCO, some recent studies have shown controversial results.[68-70] Lima et al. applied PBM (660 nm) to cell lines with complete absence of assembled CCO, and found increased cell proliferation in both control and CCO negative cells.[68] This

result indicated that CCO is not a molecular target for light at specific wavelengths such as 660 nm. Besides, Fuchs et al. reported the demonstration of differing kinetics in response to PBM therapy at red (660 nm) versus NIR wavelength (980 nm).[71] The PBM response from 660 nm was more durable than that from 980 nm, and COX-1 protein levels were increased following 660 nm treatment but were unaffected by 980 nm. In addition, Xing et al. found that low level laser irradiation at a wavelength of 633 nm suppressed glycogen synthase kinase 3β (GSK3β) activity by activating Akt to inhibit Aβ-induced apoptosis, which triggered the transduction of a series of downstream signals, enhancing cell proliferation signals, inhibiting cell apoptosis signals, and thus resisting neuronal death.[69] Therefore, it is necessary to further explore the initial reaction process of low-level laser-tissue interaction and clarify the mechanisms of different wavelengths of laser and different modes of action, in order to reach the consensus on optimal wavelengths or dosimetry guide the development and clinical application of PBMT.

TABLE 1. Research on PBMT for other common and vital brain diseases.

Type	Subjects	Illumination parameters	Therapeu effect
Intraventricular hemorrhage	A mouse IVH model and a neonatal rat IVH	1267 nm wavelength locked laser diode, 3–	PBM provide recovery afte due to photo improvement

(IVH)	model[60]	27 J/cm^2, transcranial	lymphatic dra and clearing functions
Stroke	A rat model for photothrombotic stroke[61]	808 nm continuous wave (CW) laser, 350 mW/cm^2, transcranial	PBM could in neurotoxic astrocytic polarization, preserve syn integrity and protect neuro against strok injury
	18 post-stroke hemiplegic patients[62]	660, 808, 980 nm laser diode beams, 648 J energy per session, transcranial	PBM treated showed improvement cognitive fun pain relief, an greater manu dexterity
Post-traumatic stress disorder (PTSD)	A rat model for complex PTSD[63]	808 nm CW laser, 350 mW/cm^2, transcranial	PBM protect contextual fe memory and prevent the development PTSD-like psychopatho fear
	22 PD patients[64]	904 nm laser diode, 60 mW/diode, 50 Hz, combined transcranial and intra-oral	With regular the spiral (wr test and the dynamic step were most sensitive to c in a positive

Parkinson's disease (PD)		PBMT	direction
	7 PD patients[65]	904 nm laser diode, 30 mW/diode, remote PBMT to the abdomen and neck	Participants showed improvement spiral test an Montreal cog assessment (MoCA) after PBMT
Generalized anxiety disorder (GAD)	36 GAD patients[66]	820 nm continuous laser, 310 mW/cm^2, transcranial	PBMT had a significant improvement the HAMA sc of GAD patie and appeare reverse the abnormality c time-varying network connections
	22 GAD patients[67]	945-nm LED, 9.25 J/cm^2, transcranial	PBMT improv brain activity may clinically decrease anx and depressi

Further research is needed to elucidate the systemic mechanisms of remote PBM for brain diseases in addition to intranasal and transcranial PBMT. Recent studies have shown that targeting PBM at the body also protects the brain by a mechanism that spreads from the irradiated tissue.[72] For example, Gordon et al. found that remote PBM targeting

the abdomen or leg provides neuroprotection against MPTP-induced destruction of the key circuitry underlying PD mice.[73] Zhu et al. found that after irradiating the backs of mice with low-level ultraviolet light, the blood levels of urocanic acid (UCA) increased. UCA promoted the synthesis of excitatory neurotransmitter glutamate in the cortical neurons of the mouse brain after passing through the blood-brain barrier, and thus enhanced the learning ability and memory of the mice. This work elucidates a novel and exciting view of the molecular mechanism for the phenomenon of light improving memory and learning ability.[74] Although the remote PBM treatment modality is likely to play an important role in the treatment of brain diseases, many unanswered questions remain to be studied further, such as optimal target tissue/organ, dosimetry, illumination parameters, as well as a therapeutic effect, which require more focused investigations to assess.[69]

4.2 Toward precise evaluation of the therapeutic effect

In order to evaluate the therapeutic effects of PBMT on pre-clinical models of AD or other brain diseases, the conventional solution is to develop animal models and evaluate the PBMT outcomes using imaging methods and behavioral assays in the laboratory.[75, 76] However, this solution has several limitations to be overcome in the future.

First, the most commonly used animal AD models are transgenic rodent models which overexpress human genes involved in the production of amyloid plaques and neurofibrillary tangles.[77] But most of these models do not develop neurodegeneration and their pathology and symptomatology relates poorly to those seen in the majority of humans with AD.[75] Second, current imaging techniques cannot simultaneously achieve high resolution and in vivo imaging, hindering the consecutive assessment of the improvement of brain structure and function during the PBMT. Third, the dominant behavioral assays used in mice have limited predictive validity, such as water maze, forced swim, three-chamber social test, etc. To address the above-mentioned problems, recent studies have developed novel alternative disease models and measures that enable a more precise evaluation of the cognitive and behavioral outcomes. For example, next-generation models of transgenic rodents, aged dogs, non-human primates, etc. of brain diseases have been proposed.[78-80] Besides, multi-modality medical imaging has been applied to obtain complementary information with adequate resolution for animal models.[81] In addition, some recently developed neurobehavioral experiments enable assessments of the cognitive improvements by PBMT across multiple physiological systems.[82] These emerging animal models and measures show better abilities to reflect corresponding phenotypes in humans and thus create confidence in clinical translation of

PBMT with a 64-channel EEG.

New insights from an interdisciplinary approach have been applied to describe and prove the effectiveness of PBMT applied in human clinical trials.[83] For example, Wang et al. recorded the ability of PBMT to alter electrophysiological activity of 44 health volunteers.[84] They demonstrated that prefrontal PBMT neuromodulated the alpha and gamma powers in the default-mode network, frontal-parietal network, and executive control network. In addition, Holmes et al. used functional near-infrared spectroscopy (fNIRS) as a safe, non-invasive method to monitor hemodynamics.[85] They observed significantly increased cerebrovascular oxygenation after PBMT, which is associated with neurocognitive enhancement in 18 healthy adults from the experimental group compared with 16 sham operative adults. These techniques have facilitated the validation of therapeutic interventions and enabled precision medicine approaches of PBMT.

4.3 Toward optimization of the illumination parameters

To maximize the therapeutic outcome of PBMT, it is necessary to set appropriate treatment plans and protocols, among which the most important is to choose suitable illumination parameters.[33, 86] The types of illumination

parameters that can be set for PBMT are numerous, including light wavelength, light source size, position, light power, illumination time, pulse modulation, etc. Suitable illumination parameters have the following characteristics: the incident light has a deep penetration depth in the cranial and brain tissue, and a uniform light flux distribution within a large range, so that an appropriate amount of photon energy deposition is achieved in the target brain regions. Moreover, it should not cause photothermal effects or obvious skin temperature rise and other discomfort symptoms in the brain tissue. However, it is difficult to accurately and quantitatively determine the optimal illumination parameters by the clinical trial methods mentioned above because (1) the sample size of existing clinical trials is small. (2) The cost of conducting large-scale clinical trials to optimize treatment protocols is high. (3) There are individual differences in brain function and structure among patients. (4) The current methods for evaluating PBMT efficacy are not sufficiently precise. Therefore, there is an urgent need for an accurate, efficient, and low-cost means of assessing PBMT dose in clinical practice.

With the development of computer numerical simulation technology, simulation methods represented by Monte Carlo (MC) optical simulation have created possibilities for solving this problem. MC method, also known as statistical simulation method, is a method that takes probability

phenomena as research objects. It is an ideal optical simulation strategy that can quantitatively characterize the treatment effect of PBMT under different light parameters. The pioneers of applying the MC method to the field of biomedical photonics were Jacques and Wang, who developed an MC algorithm named MCML in multi-layer homogeneous media and constructed a theoretical framework for MC optical simulation.[87] However, this algorithm cannot be applied to fine heterogeneous models and introduces approximation in the calculation of light flux. Dunn et al. at Harvard Medical School improved the MCML algorithm and developed the tMCimg algorithm, which greatly improved the simulation efficiency and ensured high simulation accuracy.[88] In 2019, Fang et al. used their own developed MCX algorithm to examine various approaches to deliver red and near-infrared light to the dorsolateral prefrontal cortex (dlPFC) and ventromedial prefrontal cortex (vmPFC) in the human brain, simulating the intranasal and transcranial PBMT for MDD (Figure 3A,C).[89] In the following year, they successfully conducted simulated illumination experiments with five different wavelengths of light (670, 810, 850, 980 and 1064 nm) at F3-F4 and Fp1-FpZ-Fp2 sites (based on the international 10–20 system) on 18 MRI brain atlas models with the age range between 5 and 89 years (Figure 3B,D).[90] They quantitatively calculated the total photon energy absorbed by the target brain region, speculated out the optimal parameter setting scheme for

transcranial PBMT for patients with depression in different age groups, and further simulated and verified the safety and effectiveness of using different irradiation schemes to treat MDD.

FIGURE 3

Light source configurations of (A) three intranasal positions, including the nostril (red), mid-nose (green), and near cribriform plate (blue) positions, and (B) three extracranial source positions, including F3 (green), F4 (red), and Fpz (blue). Sagittal section plots of the normalized energy deposition (in log-scale) results for (C) the cribriform plate illumination, and (D) transcranial illumination. (A, C) Reproduced with permission.[89] Copyright 2019, SPIE. (B, D) Reproduced with permission.[90] Copyright 2020, SPIE.

MC optical simulation can provide guidance for the design of human clinical trials and enable precision medicine approaches. This is because it has many advantages such as flexibility, efficiency, quantification and low cost. This technique can apply incident photons at any site, simulates the motion trajectory of each photon, and then calculates the energy density and light flux of photons absorbed by various regions in the brain model. In addition, a large number of parameter settings can be simulated and verified quickly through numerical simulation and parallel computing. However, the MC simulation experiment of PBMT needs further development and matching the evaluation criteria for clinical dose assessment and lacks simple and effective verification methods. Hence, further research is needed to enhance its practicality and reliability.

4.4 Integration with novel translational strategies

Original, smart and targeted multifunctional solutions as well as novel nanomedicines could be integrated with PBMT, and thus facilitate its clinical and translational application in the treatment of the brain diseases. For example, Li et al. synthesized gold nanoparticles (AuNPs) and specifically targeted the tight junction.[91] The tight junction is a kind of intercellular adhesion complex in epithelia and endothelia that control paracellular permeability.[92] Li et al. then demonstrated that transcranial laser stimulation of these AuNPs after intravenous injection increased the blood–brain barrier permeability, which is useful for drug screening and therapeutic interventions in the central nervous system. Recently, the protective effect of curcumin against some neurodegenerative diseases has been proven by in vivo and in vitro studies.[93] Curcumin, the dietary polyphenol isolated from *Curcuma longa* (turmeric), is a kind of photosensitizer that can be activated by the intravenous PBMT and downregulate the expression of various proinflammatory cytokines in patients.[93, 94] PBMT integrated with the above-mentioned nanomedicines offers promising therapeutic avenues in brain diseases.

Neurobiology is making steady progress in elucidating the basic biophysical mechanism and accurately evaluating the

therapeutic effect of PBMT, especially after the combined with integration with the computational methods and machine learning. For example, Ambrosetti et al. demonstrated the molecular forces induced by optical excitations using computational chemistry methods and presented a deep understanding of light-matter interactions in living complex molecular systems.[95] Ardakani et al. developed an effective image denoising technique using deep learning (DL) to dramatically improve the low-photon MC simulation result quality, equivalently bringing further acceleration to the evaluation the efficiency of transcranial PBMT for brain diseases.[96] Alexandrov et al. developed a platform capable of identifying the therapeutic efficacy of PBMT in rodents, which incorporated high-throughput behavioral and physiological assays with innovative machine learning. They have demonstrated the ability of these behavioral assessment platforms to identify early and robust phenotypes in a variety of disease models including Alzheimer's and Huntington disease mouse models.[97]

5 CONCLUSIONS

To sum up, it has been demonstrated that PBMT could play a beneficial role in the treatment of brain diseases in numerous animal experiments and clinical trials for neurodegenerative diseases, brain injury, mental diseases and the improvement of normal brain function (such as enhancement of mood,

sleep quality, cognitive abilities, etc.). Since PBMT utilizes low-intensity and non-ionizing light irradiation, no obvious side effects have been observed in the current studies. Moreover, the advantage of low cost and the capability of home-based care make PBMT a promising new physical therapy method. At present, several companies have already carried out the research and development of related equipment. However, there are still some unresolved issues that limit the further promotion and broader application of PBMT. On the one hand, the systematic mechanism of PBMT for treating specific types of brain diseases has not been elucidated. On the other hand, there is no unified standard for evaluating the efficacy and dosage of PBMT in clinical and industrial fields. To solve these problems, more in-depth basic research and large-scale clinical RCTs are needed to study the mechanism and efficacy of PBMT. Besides, the formulation of industry norms and clinical dose evaluation standards should be accelerated. Furthermore, computation methods such as Monte Carlo simulation and artificial intelligence algorithms can be used to assist in optimizing the illumination parameters and developing treatment strategies. PBMT has a broad application prospect in the adjuvant treatment of various types of brain diseases, and thus the continuous development of novel PBMT devices and the formulation of complementary comprehensive treatment strategies will bring tangible help to the treatment of patients with brain diseases.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests.

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