Light therapy: a new option for neurodegenerative diseases

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Abstract

Given the increasing incidence of neurodegenerative disease (ND), recent research efforts have intensified the search for curative treatments. Despite significant research, however, existing therapeutic options for ND can only slow down the progression of the disease, but not provide a cure. Light therapy (LT) has been used to treat some mental and sleep disorders. This review illustrates recent studies of the use of LT in patients with ND and highlights its potential for clinical applications. The literature was collected from PubMed through June 2020. Selected studies were primarily English articles or articles that could be obtained with English abstracts and Chinese main text. Articles were not limited by type. Additional potential publications were also identified from the bibliographies of identified articles and the authors' reference libraries. The identified literature suggests that LT is a safe and convenient physical method of treatment. It may alleviate sleep disorders, depression, cognitive function, and other clinical symptoms. However, some studies have reported limited or no effects. Therefore, LT represents an attractive therapeutic approach for further investigation in ND. LT is an effective physical form of therapy and a new direction for research into treatments for ND. However, it requires further animal experiments to elucidate mechanisms of action and large, double-blind, randomized, and controlled trials to explore true efficacy in patients with ND.

Keywords: Neurodegenerative diseases; Light therapy; Circadian rhythm

Introduction

Neurodegenerative diseases (NDs) are a broad, highly heterogeneous group of disorders affecting both the central nervous system (CNS) and the peripheral nervous system and are characterized by irreversible, progressive loss of previously intact neurological function, worsening with age.[1] It includes Alzheimer disease (AD), Parkinson disease (PD), Huntington disease (HD), motor neuron disease, and others. The pathogenesis of ND is still unclear and may vary across specific diseases. Despite significant global morbidity and mortality, there are no curative treatments for ND. ND reduces the quality of life of patients and their families. At present, the mainstay treatments of ND are pharmaceutics, but the available drugs provide only symptomatic relief and usually carry the risk of adverse reactions, such as diarrhea, nausea, headache, and others. In contrast, physical therapies and chronotherapies, such as transcranial magnetic stimulation (TMS), light therapy (LT), and physical exercise (like Tai Chi), have attracted the attention of researchers due to their high safety, low cost, and feasibility of implementation.[2-7]

The LT, sometimes referred to as heliotherapy, consists of controlled exposure to either daylight or a comparable source of artificial light, and has been reported to be an economic, convenient, safe, and effective way to ease symptoms of sleep disorders, depression, and cognitive disorders.[8-10] There have been some researches investigating the effectiveness of light in the treatment of ND.[10-13] In this article, we review the current evidence on the mechanism, therapeutic methods, and efficacy of LT in ND.

Mechanisms of LT

The circadian rhythm refers to behavioral and biological cycles that are regulated by an endogenous system. This biological cycle repeats roughly every 24 h, even in the absence of environmental influence. Although circadian

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rhythms persist in the absence of external cues, many extrinsic stimuli can entrain the intrinsic time-keeping system to maintain synchrony with the earth's light-dark cycle. Environmental stimuli signaling the progression of time are known as zeitgeber, a German word meaning "time giver," and include light as the most prominent signal, as well as others, such as patterns of exercise,[14] food consumption,[15] social activity, and more.

Clock gene

The master circadian clock in human beings is localized in the hypothalamus over the optic chiasm and is thus named the suprachiasmatic nucleus (SCN) [Figure 1]. The clock gene plays an important role in the circadian regulation mechanism. Clock genes include *Per1*, *Per2*, *CRY1*, *CRY2*, *Bmal1/Clock*, and others. In addition, some studies have found that clock genes are related to the pathological mechanisms of metabolic diseases, tumors, and other diseases, suggesting that clock genes may be important not only for regulating the circadian rhythm but also for driving the occurrence or progression of certain diseases. In general, light, activity, and food intake send signals to the SCN as important feedback for the circadian timing system. The clock genes form the molecular machinery of this circadian system, operating via autoregulatory feedback loops. However, of interest, prior studies have found that there is a complex relationship between the circadian rhythm and the clinical symptoms of ND.[16]

Melatonin (MT)

MT, a hormone that regulates the circadian rhythm and promotes sleep, is mainly secreted by the pineal gland. The secretion of MT is regulated by the SCN and follows the patterns of the circadian rhythm. Specifically, secretion increases at night and decreases during the day. The SCN interacts with the pineal gland to influence this cycle of production. After light stimulation during the day, the SCN acts on the pineal gland to suppress the secretion of MT, leading to a low concentration of MT in the blood and thus reducing drowsiness. In contrast, in the absence of light at night, the SCN no longer inhibits the pineal gland, leading to increased production of MT which reaches a peak in the early morning and then decreases slowly, promoting wakefulness.[17] Through this pathway, MT converts the neural information initiated after the perception of light into biochemical information through the SCN's action on the pineal gland, ultimately affecting the human body's rhythm.[18] In ND, changes in the secretion of MT can cause disorders in the circadian rhythm of the human body.

Other physiological impacts of light

However, of interest, light appears to stimulate biochemical responses without a strict requirement for visual perception. Recent evidence from animal experiments has suggested that illumination of the trunk (and not the head or eyes) still affords neuroprotective effects.[19-21] Though the concrete mechanisms underlying this effect, called remote photobiomodulation (PBM), are not entirely clear, it is likely that light activates one or more molecules or cells in the body, such as immune cells, inflammatory mediators, or bone marrow-derived stem cells. These cells presumably rescue neuronal functions by releasing nerve growth factors or brain-derived neurotrophic factors. Different lights have different wavelengths that are absorbed, reflected, or scattered by various cellular organelles or tissues. In the body, the number of chromophores drives circadian photoentrainment after stimulation with a wide range of light wavelengths.

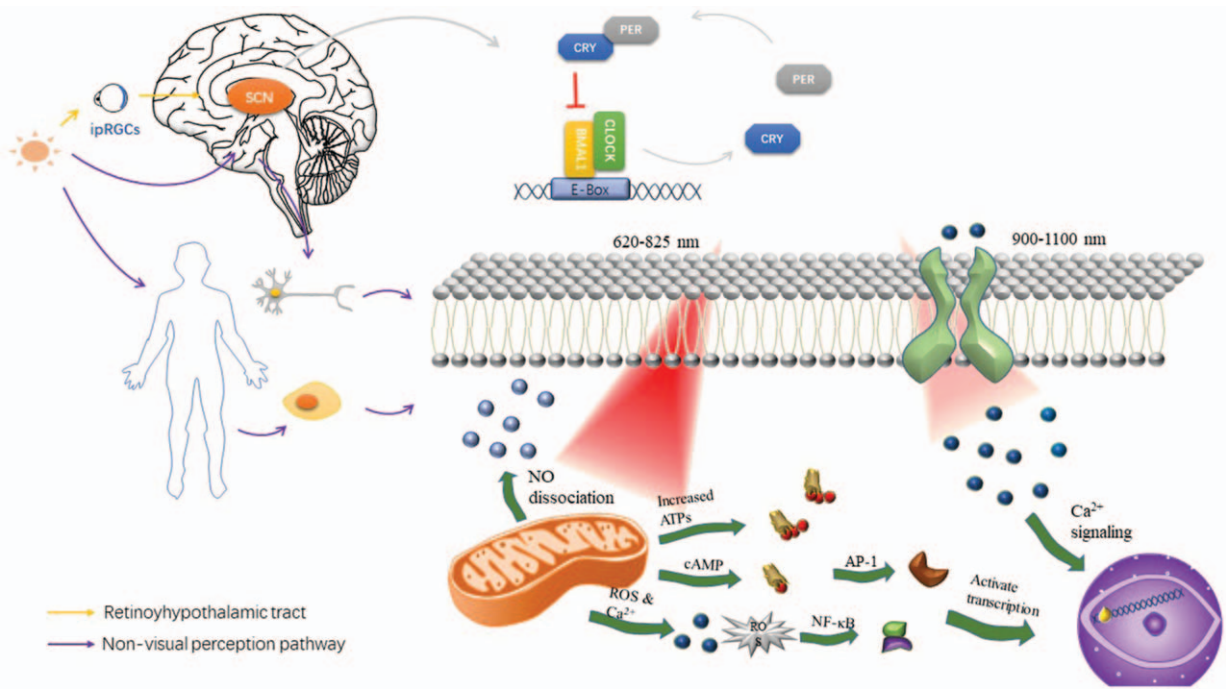

Figure 1: Schematic representation of the mechanism underlying LT. In general, light exerts its function through visual and non-visual perception pathways. As the circadian master, SCN regulates clock gene oscillations, thus synchronizing multiple central and peripheral structures. LT: Light therapy; SCN: Suprachiasmatic nucleus; ipRGCs: Intrinsically photosensitive retinal ganglion cells; AP-1: Activator protein-1; ROS: Reactive oxygen species; NF-κB: Nuclear factor-κB.

However, each specific chromophore responds to a certain range of wavelengths. For example, for red and near-infrared (NIr) light, cytochrome c oxidase (CCO), the last enzyme in the respiratory chain, is the main photoreceptor and serves a vital role in the mechanism of PBM. CCO is composed of 13 protein subunits, including two heme centers and two copper centers. The absorption peaks of them appear to be different in the reduced and oxidized forms, mainly distributed in the range of the red spectrum (620–760 nm) and NIr spectrum (780–825 nm).[22-24] When the source emits the light ray, metal molecules in the CCO absorb photons and are stimulated from the ground state into upper, excited states.[25] During this process, nitric oxide (NO) photodissociates from CCO. In fact, NO typically inhibits electron transportation. Therefore, the mitochondrial membrane potential is increased after NO dissociation. Then, oxygen consumption levels are elevated and a proton gradient is established, ultimately resulting in a boost in ATP production.[26] These steps are followed by the production of reactive oxygen species, Ca^{2+}, and cyclic adenosine monophosphate.[27] As second messengers, they could further activate a battery of signaling pathways and transcription factors.

Another hypothesis is the presence of a special signaling system between mitochondria across different organ systems. According to this theory, mitochondria under stress release an as-of-yet unidentified signaling molecule called mitokine, which consequently triggers a mitochondrial stress response in other areas of the body.[28] Of interest, light with wavelengths longer than the NIr spectrum, such as 980 nm,[29] 1064 nm,[30] and 1072 nm,[31] appear to be capable of exerting effects on biological tissues or cells, which strongly suggests the existence of other chromophores beyond CCO. Although no such evidence exists to date, it is possible that water molecules in light/heat sensitive channel play a role in mediating these effects. Although the results of prior experiments on PBM appear promising, many details supporting the theory require substantially more evidence, and further studies are needed to determine the mechanisms that are involved [Figure 1].

Application of Light in ND

AD

The AD is a degenerative disease of the CNS characterized by progressive cognitive and behavioral impairments and occurs in the elderly and pre-senile. Clinical symptoms include dysmnesia, aphasia, agnosia, impairment of visuospatial ability, abstraction, computational power, and changes in personality and behavior.[32] At present, there is no cure. The therapeutics used for the treatment only alleviate the symptoms of AD, and sometimes present side effects which may actually aggravate the patients' condition.[32] Studies have shown that there is a bidirectional relationship between sleep and AD, in which sleep disturbance is associated with increased expression of biomarkers of AD. Sunset syndrome describes a set of emotional and cognitive changes sometimes seen in patients with AD and occurs when the light begins to fade (eg, at dusk), including emotional disorders, anxiety, hyperactivity, and a loss of sense of direction, lasting for several hours or the whole night. However, of interest, recent data have suggested that LT may play a role in addressing some of these effects by restoring the circadian rhythm, cognitive capacity, and emotional control.[33]

Animal models

A growing body of evidence has shown that intervention with NIr light ameliorates the negative cognitive effects of AD in mouse models, restoring memory capacity and leading to a reduction in amyloid-β (Aβ) burden in the brain. Several key findings have been summarized in Table 1.

In 2011, Luis De Taboada carried the first experiment reporting the beneficial effects of PBM in AD animal models. By applying transcranial photobiomodulation (tPBM), amyloid-β protein precursor (AβPP) transgenic mice were examined and their behavioral abnormalities were alleviated with soluble AβPP increased and inflammatory markers decreased. In addition, a reduction of Aβ plaques was detected in a dose-dependent manner associated with NIr treatment.[34] Meng and colleagues discovered that low-level light therapy (LLLT) in APP/PS1 mice up-regulated brain-derived neurotrophic factor to reverse dendrite atrophy, during which ERK/CREB pathway would be activated as well.[36] Later, Sivaraman Purushothuman demonstrated the neuroprotective effects of NIr treatment in two mouse strains, K3 and amyloid precursor protein/presenilin 1 (APP/PS1) transgenic mice. Specifically, neurofibrillary tangles, hyperphosphorylated tau proteins, and oxidative stress markers decreased while cytochrome oxidase increased in the hippocampus and neocortex of K3 transgenic mice. In APP/PS1 mice, the number of Aβ declined and the size of the protein shrunk after NIr intervention.[37] The research team kept on evaluating whether NIr treatment had the protective effects for cerebellum in two mouse strains and the results proved the capability of NIr to ameliorate the neurodegeneration in cerebellum and possibly in any part of the brain.[39] In 2014, Farfara and her colleagues[38] creatively applied the LLLT to the bone marrow in 5XFAD transgenic mice model, placing the distal fiber on the middle part of the tibia, and the results showed an improvement of spatial learning with Aβ load decreased in brain and proliferation of mesenchymal stem cells increased. Another study employing 5XFAD mice but in a different animal background showed similar results. In detail, tPBM leads to the reduction in neuronal loss, microgliosis, Aβ accumulation, and improvement in cognitive function in 5XFAD mice. In 2019, Russian scientists first discovered that it is via the lymphatic system of the neck and the brain that tPBM removed Aβ to improve the cognitive, memory functions in Mongrel male mice.[42] In fact, NIr light treatment can accelerate Aβ degradation in extracellular space, therefore, recovering the interstitial fluid flow and reversing the cognitive function in APP/PS1 transgenic mice.[44] Intriguingly as well, Min Wang[43] reported the normalization of gut microbiota compositions in APP/PS1 transgenic mice after the application of Mid-infrared light (2.5–4.0 μm) for about 6 weeks.

In conclusion, tPBM effectively rescues the cognitive and memory functions in AD animal models primarily through the removal of Aβ proteins in the brain.

Table 1: Effect of light on animal models of Alzheimer disease.

First author, year, reference	Subject	Models	PBM parameters	Results/effects
Luis De Taboada, 2011[34]	C57BL/6 mice	Aβ protein precursor transgenic mice	Transcranial, 2 min, 3 times/week, 6 months, 808 ± 10 nm, 10 mw/cm^2	Dose-dependent reduction in amyloid load Behavioral abnormalities ↓ SaβPPα↑ CTFβ↓
Julio C. Rojas, 2012[35]	Adult male rats obtained from Harlan	Fear conditioning	Transcranial PBM, 660 nm, LLLT 1 J/cm^2 (1 min 51 s) or LLLT 5 J/cm^2 (9 min 25 s), 9 mw/cm^2	Cortical metabolic capacity↑ Retention of extinction memories
Chengbo Meng, 2013[36]	C57BL/6 mice	APP/PS1 transgenic mice	Illuminate at cells, 632.8 nm, 10 mw, 12.74 mw/cm^2	Rescue dendrite atrophy BDNF upregulation by activation of ERK/CREB pathway
Sivaraman Purushothuman, 2014[37]	C57BL/6 mice	K369I tau transgenic mice (K3) APP/PS1 transgenic mice	Transcranial PBM, 670 nm, 90 s, 5 days/week for 4 weeks, 4 J/cm^2	K3: hyperphosphorylated tau, neurofibrillary tangles, oxidative stress markers (4-hydroxynonenal and 8-hydroxy-2'-dexyguanosine) ↓, CCO↑ (in neocortex and hippocampus) APP/PS1: size and number of Aβ plaques ↓
Dorit Farfara, 2014[38]	C57/B6 male mice	5XFAD transgenic male mice (Tg6799)	LLLT, implanted in skin on tibia, start at 4 months of age, weekly for 2 months, 1 J/cm^2	Cognitive capacity and spatial learning ↑ Aβ in brain ↓ Proliferation of mesenchymal stem cells (mscs) ↑
Sivaraman Purushothuman, 2015[39]	C57BL/6 mice	APP/PS1 transgenic mice K3 transgenic mice	Transcranial PBM, 670 nm, 90 s, 5 days/week for 4 weeks, 2 mw/cm^2, 4 J/cm^2	K3 mice: hyperphosphorylated tau, neurofibrillary tangles, oxidative stress↓, CCO↑ in cerebellum APP/PS1 mice: Aβ deposition in cerebellar cortex ↓
Yujiao Lu, 2016[100]	Male Sprague Dawley rats	Aβ1–42 peptide injection	Transcranial PBM, 2 mins daily for 5 consecutive days for 4 weeks, 808 nm, continuous wave, 8.33 ± 0.27 mw/cm^2, 15 J/cm^2	Aβ-induced hippocampal neurodegeneration ↓ Long-term spatial and recognition memory impairments ↓
Gwang Moo Cho, 2018[40]	B6SJLF1. J mice	5XFAD mice	Transcranial PBM, 610 nm, 1.7 mw/cm^2, 2.0 J/cm^2, 20 min, 3 times/week for 14 weeks.	Amyloid accumulation, neuronal loss, and microgliosis↓ Cognitive function↑ Insulin degrading enzyme (IDE) ↑
Guillaume Blivet, 2018[41]	Male Swiss mice	Amyloid β 25–35 peptide-induced toxicity	Rgn500, laser (850 nm), LED (850 nm, 625 nm), on top of the head or center of abdomen,10 mins daily for 7 days, 28 mw/cm^2, 8.4 J/cm^2.	Memory restoration, normalization of amyloid β 1–42, ptau, oxidative stress, apoptosis (Bax/Bcl2), neuroinflammation.
Ekaterina Zinchenko, 2019 [42]	Mongrel male mice	Injection of amyloid β (1–42) peptide (1 μL, 200 μmol)	Transcranial PBM, 1267 nm, 32 J/cm^2, 9 days each second day	Cognitive, memory and neurological status↑ Clearance of Aβ via the lymphatic system
Min Wang, 2019[43]	–	APP/PS1 transgenic mice	Mid-infrared light (2.5–4.0 μm) with peak wavelength 7.7–10 μm, 6weeks	Learning and memory↑ Aβ in brain ↓ Gut microbiota compositions return to normal
Xiangpei Yue, 2019[44]	C57BL/6 mice	APP/PS1 transgenic mice	Illuminate at skull and abdomen, 630 nm, 40 mins daily, 5 days/week for 2 consecutive months, 0.55 mw/cm^2	Destroy Aβ assembly *in vitro* and *in vivo* Activate FA dehydrogenase, facilitated Aβ aggregation Smash Aβ deposition in ECS, recover ISF flow, rescue cognitive function

Aβ: Amyloid-β; LLLT: Low level light therapy; PBM: Photobiomodulation; CCO: Cytochrome C oxidase; LED: Light-emitting diode; ECS: Extracellular space; ISF: Intersitial fluid; BDNF: Brain-derived neurotrophic factor; ERK/ CREB: Extracellular signal-regulated kinases/cyclic AMP response element binding protein.

Patients

Sleep disorders

Sleep disorders in AD patients become increasingly serious with the progression and aggravation of the disease. Previous studies have confirmed the bidirectional relationship between AD and sleep disorders.[45] Light is often used to treat AD patients in clinical trials. Although different in several ways, LT has been suggested to be effective in improving sleep disorders in patients with AD, improving sleep quality, prolonging sleep time, stabilizing the circadian rhythm, and shortening the sleep latency.[46] One such study exposed patients with AD (and related dementias) to light at 350 to 400 lux for an average of 92 min of treatment (median 102 min) per 120 min

Table 2: Effect of light in AD patients.

First author, year, reference	Participants	Head-to-light distance	Intervention	Duration and frequency	Assessment tools	Outcome
Sonia Ancoli-Israel, 2010[59]	92 probable or possible Alzheimer's disease patients	1.0 m	2500 lux bright light or <300 lux red light	9:30 AM to 11:30 AM and 5:30 PM to 7:30 PM for 10 days	The Actillume recorder	Both morning and evening bright light resulted in more consolidated sleep at night
Sonia Ancoli-Israel, 2002[48]	77 dementia patients	1.0 m	2500 lux bright ligh tor <50 lux red light	9:30 AM to 11:30 AM and 5:30 PM to 7:30 PM for 10 days	Scales and actillume recorder	Increasing exposure to morning bright light delayed the acrophase of the activity rhythm and made the circadian rhythm more robust.
Constantine G Lyketsos, 1999[53]	15 AD patients	3 feet	10,000 lux bright light and dim, digital, low-frequency blinking light	1 h in the morning for 4 weeks and for an additional 4 weeks in the other condition	Scales and sleep diaries	Patients sleep more hours at night when administered morning BLT.
Glenna A. 2008[47]	70 AD patients	4 feet	2500 lux bright light or indoor light	09:30 AM to 10:30 AM or 3.30 PM to 4.30 PM Monday through Friday for 10 weeks	Scales and actigraphy	One hour of bright light, administered to subjects with AD either in the morning or afternoon, did not improve nighttime sleep or daytime wake compared to a control group of similar subjects.
Lisa L. Onega, 2016[56]	60 dementia patients	27 inches	10,000 lux bright light or 250 lux dim light	30 min twice a day (8:00 AM to 12:00 PM, and 2:00 PM to 8:00 PM), five times a week for 8 weeks	Scales and actigraphy	Bright light exposure was associated with significant improvement in depression and agitation.
Barbara B, 1995[57]	6 dementia patients	1.0 m	2500 lux bright light	09:30 AM to 11:30 AM for two 10-day periods.	Scales	BLT can reduce agitation.
Alistair Burns, 2009[12]	48 dementia patients	–	10,000 lux bright light or 100 lux dim light	10:00 AM –12:00 AM for 2 weeks	Scales and actigraphy	BLT is a potential alternative to drug treatment in people with dementia who are agitated.
Andre Graf, 2001[55]	23 AD or VD patients	90 cm	3000 lux bright light or 100 lux dim light	2 h from 5:00 PM to 7:00 PM for 10 days	Scales and body temperature	Short-term evening BLT may exert beneficial effects on cognitive functioning in patients with dementia.
Rixt F, 2008[10]	189 dementia patients	–	1000 lux bright light or 300 lux dim light	Between 10:00 AM and 5:00 PM for 15 months	Scales and actigraphy	Light can improve some cognitive and noncognitive symptoms of dementia.
Ann Louise Barrick, 2010[58]	66 dementia patients	–	2000 lux bright light	AM bright light (7–11 AM), PM bright light (4–8 PM), all day bright light (7 AM –8 PM); or standard light for 3 weeks	Actigraphy	BLT does not appear promising as a treatment for agitation.

AD: Alzheimer disease; BLT: Bright light therapy; VD: Vascular dementia.

treatment session for 4 weeks, and concluded that the mean percent time awake increased from 65% during baseline to 68% during treatment.[47] To further verify the effectiveness of LT in patients with sleep disorders, another study included 11 AD patients with sleep-wakefulness disorders. Those patients were exposed to 6000 to 8000 lux of morning light for 2 weeks for 2 h a day. This study found that, 2 weeks later, sleep efficiency was significantly improved and the amount of time spent sleeping during the day or spent awake at night was dramatically reduced.[48] The patients were followed to observe the long-term effects of LT, remarkable, sleep efficiency was still significantly better than the baseline 12 weeks after the last treatment. Additionally, light markedly decreased the sleep latency at 12 weeks [Table 2].[49]

In contrast with those studies, several case-control studies have reported a total lack of effect of LT in some patients. Dowling *et al*[46] divided 70 AD patients into the experimental group and the control group. The experimental group was treated with 2500 lux (or more) in the morning (9:30–10:30 AM) or in the afternoon (3:30–4:30 PM) every Monday through Friday for 10 weeks. The control group, however, received normal indoor light (150–200 lux). The outcomes of interest included sleep at night, awakening during the day, and rest-activity, and were determined by actigraphy. Disappointingly, their experiments showed the circadian rhythm and cognitive function improved remarkably in the questionable and mildly demented patients group, but not so in the moderately and severely demented patients. This could be because responses to light varied in AD patients undergoing different courses of treatment, and the severity of dementia also appeared to affect patients' sensitivity to light.[56] Overall, previous studies have suggested mixed effects of LT on sleep disorders in AD patients, however, there appears to be a general trend toward a positive effect of LT on sleep. Since LT does not have significant adverse effects, larger studies with longer follow-up periods are

warranted to verify whether the effects on sleep are significant and persist over time[57] [Table 2].

Cognitive impairment

Patients with AD experience various forms of cognitive impairment including impaired memory, language, visual-spatial skills, task execution, comprehension, and judgment, even during symptomatic treatment.[51] Defects in two or more of the above cognitive domains may seriously affect the individual's daily or social abilities.[58] The positive effect of light on cognition has been reported in many clinical studies. A balanced, placebo-controlled study of 23 AD patients which was randomly assigned to either evening bright light therapy (BLT) or dim light therapy showed that scores on the mini-mental state exam (MMSE), a test measuring cognitive function, were significantly improved after light treatment ($P = 0.012$).[54] A similar result was reported by another study, in which 27 patients received 3000 lux of light every morning for 4 weeks, resulting in a significant improvement in MMSE (7.8 ± 5.2 *vs.* 8.6 ± 6.3, $P < 0.05$).[56] However, some studies have suggested that LT does not improve cognitive function in patients with AD. For example, one study with 22 cases in the LT group and 26 cases in the control group were, respectively, given 10,000 lux and <100 lux of light from 10:00 AM to 12:00 AM, but the MMSE scale assessment results revealed no significant improvement in the cognitive level of the patients between two groups after light exposure.[12] Additionally, a double-blind randomized controlled trial divided 168 patients from nursing homes into two groups, who were exposed to either 1000 or 300 lux of daily light for between 15 months and 3.5 years. After treatment, the average score of MMSE in the LT group was reduced by 0.9 points relative to baseline. In contrast, the control group did not experience a significant change relative to the baseline.[10] However, taken altogether, the effects of light on cognitive function in patients with AD remains controversial. Of note, the MMSE scale used to assess the cognitive functions in most studies is a relatively insensitive screening test. Furthermore, repeated measurements with the same test may cause bias. Therefore, it is necessary to develop more comprehensive and objective methods for assessing the cognitive functions of AD patients [Table 2].

Mental disorders

AD patients often present with anxiety, depression, and other mental disorders. Studies on the impacts of light on associated mental disorders have shown that light may play a role in reducing agitation in dementia patients.[12] Similarly, Onega *et al*[52] demonstrated that bright environments significantly alleviate depression and agitation in patients with dementia. At the same time, LT is suggested to alleviate depression and restlessness in AD patients.[12,53] However, some studies have shown that bright environments may actually aggravate agitation in patients with dementia.[55] In short, the question of whether light alleviates emotional disorders remains a topic for further investigation [Table 2].

In conclusion, LT appears to generally have a positive effect on AD patients[51] and several clinical studies demonstrated that BLT can alleviate issues related to sleep disorders, depression, cognition, and agitation in AD patients. However, most studies are unable to exclude the influence of external light on the research results, and more data are required to provide unambiguous recommendation for or against the use of BLT in AD.

PD

PD, also known as paralysis agitans, is a common degenerative disease of the nervous system. It is characterized by tremor, bradykinesia, myotonia, and postural balance disorder. The incidence of PD is increasing annually alongside the progressively aging population of China. Currently, PD remains an incurable neurological disease. However, since it was developed 50 years ago, levodopa has been widely used as an effective treatment to relieve the motor symptoms associated with PD.[59] However, over time, patients experience diminishing the therapeutic effects of levodopa. After 5 years of treatment, fluctuation of motor symptoms and dyskinesia begin to reappear. Furthermore, dopaminergic drugs may have adverse reactions, such as daytime sleepiness and dopamine imbalance syndrome. The non-motor symptoms of PD are diverse and universal, but there are limited pharmaceutic options to address them. Increasing evidence has suggested that non-drug treatments for PD, such as BLT, physical exercise, and TMS, may be useful, cheap, and non-invasive treatment methods.[7] LT has an important impact on the circadian rhythm. First, the light activates the SCN via the hypothalamic bundle of the retina; second, light-sensing inhibits the secretion of MT; third, light promotes the connection between thalamus and cortex through indirectly activating sympathetic activity in the brainstem.[60] Currently, the primary treatments for PD are pharmaceutics, which can greatly alleviate the motor symptoms of PD.[61] However, there are very few treatments for the non-motor symptoms of PD, which sometimes precede the motor symptoms and also affect patients' quality of life.[62] Several studies have shown that light alleviates some non-motor symptoms of PD patients, such as insomnia, depression, autonomic dysfunction, and fatigue.[63] However, publications on biological rhythms and PD are still rare.

Animal models

The majority of experimental data on animal models of PD come from John Mitrofanis laboratory in Australia. Specifically, for PD, the most used animal model is the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced mouse model. MPTP is a neurotoxin that destroys dopaminergic cells in the substantia nigra to produce symptoms similar to PD and thus has been widely used in PD research. Details about the effects of red and NIr LT in different animal models are mentioned in Table 1. Below are the main experiments of interest, described in chronological order [Table 3].

Patients

Motor symptoms

Motor symptoms, such as resting tremor, myotonia, bradykinesia, and postural balance disorder have signifi-

Table 3: Effect of light on animal models of PD.

First author, year, reference	Subject	Model	PBM Parameters	Effects
Victoria E Shaw, 2010[64]	BALB/c albino Mice	Acute MPTP	Transcranial PBM, 1 cm above the head, 670 nm, 40 mw/cm^2, 90 s, 10 cm^2, 2 J/cm^2	Dopaminergic cells in SNc↑
Cassandra Peoples, 2012[65]	BALB/c male mice	Chronic, Acute MPTP	Transcranial PBM, 670 nm, 90 s, 0.5 J/cm^2	Dopaminergic amacrine cells and TH+ cells in retina↑
Victoria E Shaw, 2012[66]	BALB/c Mice	Acute, chronic MPTP	Transcranial PBM, 1–2 cm above the head, 670 nm, 90 s, 0.5 J/cm^2	Fos+ cells in subthalamic nucleus and zona incerta ↓
Cassandra Peoples, 2012[67]	BALB/c Mice	Chronic MPTP	Transcranial PBM, 1–2 cm above the head, 670 nm, 90 s, 5 J/cm^2, 3–5 weeks	TH+ cells in SNc↑
Melissa Vos, 2013[68]	Dorsophila	Pink 1 mutants	Transcranial PBM, 808 nm, 25 mw/cm^2, 2.5 J/cm^2	Partially rescue the behavioral abnormalities and mitochondrial function of pink1 mutant
Cecile Moro, 2013[69]	C57BL/6 pigmented mice	Acute MPTP	Transcranial PBM, 1–2 cm above the head, 670 nm, 90 s, 4 times, 2 J/cm^2	TH+ cells ↑ Behavioral impairment ↓
Purushothuman S 2013[70]	Mice	K3 (tau transgenic mice)	–	Loss of TH+ cells↓ stress biomarkers: increase of 4-HNE, 8-OHDG, AT-8↓
Cecile Moro 2014[71]	BALB/c Mice Sprague-Dawley rats	Acute MPTP	Implanted (lateral ventricles), 0.16 mw, 67 mw	Dopaminergic cells ↑
Johnstone DM, 2014[19]	Male BALB/c Mice	MPTP	Remote PBM (applied on the trunk and leg instead of head), 670 nm, 50 mw/cm^2, 4 J/cm^2	Damage of TH+ cells in SNc↓ Effects of direct transcranial application is better than remote PBM
Oueslati A, 2015[72]	Sprague-Dawley female Rat	AAV-based α-synuclein overexpression	Transcranial PBM, 808 nm, 2.5–5 mw/cm^2, 100 s, once daily for 28 days	Behavioral damage↓ Loss of dopaminergic cells↓
Florian Reinhart, 2016[73]	Male BALB/c Mice	Acute MPTP	Transcranial PBM, 670 nm, 90 s, twice daily, 1 J/cm^2/d	Whether PBM is simultaneously, before or after the MPTP injection, MPTP induced behavioral impairment↓ cell survival ↑
Darlot F, 2016[74]	Macaque Monkey	Subacute MPTP	Implanted, 670 nm, 10 mw, 25 J/5 d, 35 J/7 d	Clinical and behavioral impairment↓ Dopaminergic cells and their terminations in SN, TH+ cells in stratum↑
Nabil El Massri, 2016[75]	Macaque Monkey	Subacute MPTP	Implanted (substantia nigra next to the midline of midbrain) 670 nm, 25/35 J, before injection: NIr delivery (5 s ON/ 60 s OFF); after injection: 24 h, 10 mw	Astrogliosis in SNc and stratum ↓
Florian Reinhart, 2016[76]	Wistar Rat	6-OHDA	Implanted (Bergma coordinate (–5.6 mm, +2.9 mm, –8.5 mm) 20°), continuous or pulsed, 670 nm, 0.16 mw, twice daily for 23 days, 90 s per time, total dose of 634 mJ	At the stronger power, apomorphine induced rotation↓ TH+ cells ↑
Nabil El Massri, 2017[77]	Macaque Monkey	MPTP	Implanted (midbrain midline), 670 nm, 10 mw	TH+ cells in stratum ↑ GDNF↑
Florian Reinhart, 2017[78]	Male BALB/c Mice	MPTP	670 nm and 810 nm (simultaneously or sequentially) 22 J, 2 days	Motility ↑ TH+ cells in SNpc↑
Boaz Kim, 2018[20]	Male C57BL/6 mice	MPTP	remote PBM before MPTP injection, 670 nm, 50 mw/cm^2, 3 min	Loss of dopaminergic cells↓
O'Brien, 2019[79]	Sprague-Dawley Mice (Male)	LPS	Transcranial PBM, 670 nm, 50 mw/cm^2, 88 s, twice daily for 6 days	Loss of dopaminergic cells ↓
Varshika Ganeshan, 2019[21]	BALB/c mice	MPTP	Remote PBM before MPTP injection, 670 nm, continuous wave, 4 J/cm^2, 50 mw/cm^2	Loss of TH+ cells in midbrain ↓ increase of FOS+ neurons in putamen and caudate nucleus↓

PBM: Photobiomodulation; SNc: Substantia Nigra compacta; SNpc: Substantia Nigra pars compacta; GDNF: Glial cell-derived Neuro trophic factor.

cant impacts on the quality of life and prognosis of PD patients.[80] The Movement Disorder Society Unified PD Rating Scale, Part III (MDS-UPDRS III) is commonly used to assess motor symptoms. Motor symptoms are mainly alleviated through dopamine-based therapies. Interestingly, studies have shown that LT can reduce the need for dopamine drugs.[81] The effect of light on PD motor symptoms is less investigated and is a topic requiring further exploration. In one study, some of the PD patients were treated with 1 h of 10,000 lux of light after waking up (no later than 9 o'clock) for 30 min daily for 10 days, and the patients of the control group were exposed to <2500 lux of light. This study found that BLT led to significant alleviation of tremor, UPDRS III and IV, and depression in the active treatment group.[8] However, since the effect of environmental light may not have been adequately controlled, this may be a biased result. Another study found that 14 days of LT led to significant improvements in the total UPDRS score and the UPDRS parts I, II, and III scores [Table 4].[82] Importantly, the mechanism of the effect of light on improving motor symptoms in PD patients lacks theoretical support and requires further clinical and mechanistic verification.

Table 4: Effect of light in PD patients.

First author, year, reference	Participants	Head-to-light distance	Intervention	Duration and frequency	Assessment tools	Outcome
Sebastian Paus, 2007[8]	36 PD patients	20 cm in the active treatment, and 100 cm in the placebo group	7500 lux in the active treatment group and 950 lux in the placebo group	15 days in the morning, 30 min daily for 1 week	Scales	BLT led to significant improvement of tremor, UPDRS I, II, and IV, and depression in the active treatment group but not in the placebo group.
Aleksandar Videnovic, 2017[83]	31 PD patients	86.4 cm	BLT (±10,000 lux) or dim red light (<300 lux).	In the morning (9–11 AM) and in the afternoon (5–7 PM) daily for 2 weeks.	Scales, Actigraphy	Light therapy was well tolerated and maybe a feasible intervention for improving the sleep-wake cycles in patients with PD.
Jessica K, 2018[92]	140 PD patients	0.8–1.0 m	3000 to 4000 lux for one to four hours	Daily bright light exposure for 2–5 years	Scales and diaries	The application of LT before retiring can improve the quality of sleep and reduce the incidence of nocturnal movement.
Gregory L. Willis, 2018[95]	30 PD patients	0.8–1.0 m	3000 lux polychromatic light, red light and discontinued polychromatic light	11 AM to 1 PM daily for 2 weeks	Scales	Continued exposure to polychromatic light over a 2-week period results in incremental improvement in motor and psychiatric parameters associated with PD.
Sonja Rutten, 2019[6]	83 patients with PD and MDD	30–40 cm	BLT (±10,000 lux) or a control light (±200 lux)	Daily for 30 min in the morning and evening for 3 consecutive months	Cortisol, scales and diary	BLT was not more effective in reducing depressive symptoms than a control light. Mood and subjective sleep improved in both groups. BLT was more effective in improving subjective sleep quality than control light.

PD: Parkinson disease; BLT: Bright light therapy; UPDRS: Unified PD rating scale; MDD: Major depressive disorder.

Non-motor symptoms

Recently, there has been increasing research focus on the non-motor symptoms of PD, which include depression, sleep disorders, constipation, salivation, dysphagia, hyperhidrosis, weight loss, orthostatic hypotension, frequent micturition, sexual dysfunction, and others.[85] These non-motor symptoms have negative impacts on quality of life throughout the course of the disease and thus urgently require the development of safe and effective therapeutic options.[59,61,62]

Sleep disorders are a common non-motor symptom of PD and mainly manifest as daytime sleepiness, insomnia, rapid eye movement behavior disorder, restless legs syndrome, and sleep-disordered breathing.[86] Notably, sleep disturbances affect 40% to 98% of PD patients in the world.[87-89] In China, the prevalence of sleep disturbance among PD patients ranges from 47.66% to 89.10%.[90] Sleep disorders can reduce the quality of life and impair daytime function.

Interestingly, clinical studies have confirmed the safety and effectiveness of light in improving insomnia and daytime sleepiness of PD patients. Indeed, a study of patients with PD with sleep disorders found that stronger light had a more significant treatment effect. Videnovic *et al*[82] randomly assigned patients with daytime sleepiness into two sex- and age-matched groups, who received 10,000 and 200 lux of irradiation for 2 weeks. The Epworth sleepiness scale was used to evaluate outcomes and revealed that daytime sleepiness symptoms were significantly alleviated in the experimental group relative to the control group. Long-term follow-up studies of PD patients with insomnia have indicated that 2 to 5 years of light treatment can alleviate insomnia symptoms.[91] Some studies have also confirmed that LT can alleviate rapid-eye-movement sleep behavior disorder, suggesting that symptoms were gradually alleviated from the third month through the 60th month of treatment, with better effects between the 6th and 11th months than the first 2 months of treatment.[91]

Strikingly, up to 35% of patients with PD have clinically relevant symptoms of depression.[92] Several studies have compared the changes of depression symptoms in PD patients, as evaluated by the Hamilton Depression Scale (HAMD/HDRS) and other scales, before and after LT. One such study recently gave patients with PD and depression either 10,000 or 200 lux of light separately for 3 months and followed up at the first, second, and sixth months after treatment. Disappointingly, they found that there was no difference in depressive symptoms between the groups. This study suggests that LT does not significantly alleviate the depressive symptoms of PD patients.[6] In contrast, Sonja Rutten *et al*[9] used bright light (±10,000 lux) or a control light (±200 lux) daily for 30 min in the morning and evening for at least 1 week in 83 patients and found that BLT was more effective in improving subjective sleep quality than control light. In terms of cognitive impairment in PD patients, the study has suggested that BLT may improve the cognitive function of PD patients, mainly through the MMSE scale.[8] However, this result may be caused by repeated measurements. We

should adopt more precise cognitive function assessment methods to avoid the change of scores caused by repeated measurement. In terms of autonomic nerve function, fatigue, and other non-motor symptoms of PD, more researches are needed.

In summary, the light may alleviate motor symptoms and some non-motor symptoms in PD patients, such as sleep disorders, but these results require further confirmation [Table 4].

LT in Other ND

Little research has been conducted on the therapeutic use of light in other types of ND, and most such studies are still at preclinical, experimental studies in model mice. HD is an ND that lacks a specific treatment.[93] It has been shown that, after exposure to blue light for 6 h a day for 3 months, the activity rhythms of both bacterial artificial chromosome-mediated transgenic mouse model and Q175 mice were alleviated, but no significant improvement in sleep behavior was observed. Compared with the untreated control group, the motor function of the treated mice of both genotypes was alleviated. Given the changes in the expression of some HD-related markers in the striatum and cortex of the treated mice, the authors speculated that light may alleviate the motor symptoms of the HD model mice. This makes sense in the context of other research suggesting that stimulation of the circadian system can delay the progression of HD.[94]

Other studies have explored the effect of light treatment in mice models with familial amyotrophic lateral sclerosis, but there was no significant difference in the survival rate or exercise ability of mice between groups, suggesting that LT may not be helpful for familial amyotrophic lateral sclerosis disease.[95]

There is a lack of animal experiments and clinical trials on the use of light in treating other types of ND at present, but we believe that the broad safety and potential efficacy of light should facilitate more research on the use of LT for other NDs.

Although the tolerance of LT is generally good, about 45% of patients may have mild adverse reactions during the early stages of treatment, including headache, visual fatigue, blurred vision, eye irritation, or elevated blood pressure. Inappropriate LT may also cause insomnia. Rare adverse reactions, such as mania, mood instability, and attempted suicide, may be due to light-induced alertness and should be carefully assessed. However, this assumption is not very certain at present, and it is not clear whether there is a true causal link between LT and aggravated symptoms in some people. Adverse reactions can be reduced by reducing exposure time.[6,11,12,46-48,51,54,82,96,97]

Future Perspectives

LT as a treatment for NDs presents the advantages of being low cost and having relatively minor side effects. The rapid advancements in research on LT as a treatment for ND in recent years have provided a mechanistic basis for its clinical effects by acting on the circadian rhythm, but there have been conflicting reports of efficacy across trials, potentially due to varying light intensities, light equipment, and treatment times across studies.

Studies have shown that the body reaches its lowest temperature at approximately 4:00 AM; after which light exposure will adjust the biological clock to an earlier schedule, according to the light phase curve.[98] Similarly, light exposure before arriving at the lowest body temperature has the opposite effect of setting the biological clock to a later time. The effects of light on the biological clock are strongest near the time at which the human body reaches its lowest temperature. The further light exposure occurs from this time point, the smaller the effect. This implies that LT should be started as early in the morning as possible. In addition, some studies have classified the "time type" of the patients using the morning-night type scale, and determined light time accordingly.[6,99] Between 1000 and 10,000 lux of visible light is often applied to ND patients for times ranging from 1 week to several years and for daily treatment periods ranging from 30 min to 24 h a day.[3-6,8-12,46-58,82,84,91] The light is typically 20 cm to 1 m away from the human eyes. However, the application of light treatment in ND is still very much at the research stage, and there are no unified treatment guidelines outlining the time, intensity, or other parameters required for successful LT. With increasing research, such a guide will be crucial to standardize LT in the future.

Thus LT still has its limitations. It is inherently difficult to study light quantitatively because both the time of year and natural exposure to the sun have important effects on circadian rhythm.[12] To quantify the impact of outdoor light exposure on the results of the study, some scholars have suggested that different seasons should be equally distributed between the treatment and control groups in future research,[55,83] thereby mitigating the effects of the season. Moreover, the baseline light level, clear light intensity, color temperature, wavelength, duration of treatment, and daily treatment time should be taken into account and clearly reported.[82] The influence of external light can also be eliminated by calculating the light using quantitative instruments. It is possible that, in the next few years, light-related research may be developed into a safe and effective treatment for ND. Last but not least, because of the different pathogenesis of the ND, it is difficult to explain the effectiveness of LT in different ND, which needs more mechanism research.

LT represents a new, non-pharmaceutic, well-tolerated therapy with global applicability. The improvement of ND symptoms observed in some studies of LT is encouraging. However, in the future, large, randomized, and controlled studies are needed to better clarify the potential mechanisms through which LT effects ND and to determine the optimal frequency, duration, intensity, and other parameters for safe and effective LT.

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Conflicts of interest

None.

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