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Bright light therapy in Parkinson's disease: a pilot study on visual pathway improvements

Wei-ye Xie[1†], Hui Lou[2†], Jia-ying Liu[3], Jie-yun Yin[4], Tian-qi Zhang[2], Cheng-jie Mao[1], Fen Wang[3], Chun-feng Liu[1,3*] and Yun Shen[1*]

Abstract

Background Bright light therapy (BLT) has been proved to have beneficial effects on Parkinson's disease (PD), the mechanisms remained unclear. Improvements of visual pathways might be key to BLT.

Objective The aim of this study is to validate whether BLT improves clinical symptoms in PD and explore the possible mechanisms of visual pathways evaluated by optical coherence tomography (OCT), pattern electroretinogram (PERG) and visual evoked potentials (VEP).

Methods Twenty-three PD patients were enrolled in this crossover randomized placebo-controlled study. Participants received either one month of BLT or dim light therapy (DLT), separated by one-month wash-out period, followed by another intervention. Participants underwent clinical scales, and visual-related evaluations including OCT, PERG and VEP before and after each intervention. Mixed-effects regression models were used to determine the effect between BLT and DLT on improving the differentials of clinical scales (Δscales), OCT (Δretinal thickness), PERG (ΔPERG values) and VEP (ΔP100 latencies). Correlations between clinical symptoms and visual evaluations improvements were analyzed in PD patients receiving BLT.

Results Excessive daytime sleepiness, anxiety, life quality and autonomic function were improved after BLT. Compared with DLT, bilateral ΔN95 latencies for PERG and ΔP100 latencies for VEP were improved after BLT. We did not observe the changes of four quadrants retinal nerve fiber layer (RNFL) thickness after BLT or DLT.

Conclusions BLT is a valuable and safe non-pharmacological intervention for improving visual function in PD patients.

Significance These findings extend neural mechanisms of BLT to visual pathways improvements.

Keywords Optical coherence tomography, Pattern electroretinogram, Visual evoked potentials, Parkinson's disease, Bright light therapy, Randomized crossover controlled trial

[†]Wei-ye Xie and Hui Lou contributed equally to this work.

*Correspondence:
Chun-feng Liu
liuchunfeng@suda.edu.cn
Yun Shen
shenyun127@126.com
[1]Department of Neurology and Clinical Research Center of Neurological Disease, The Second Affiliated Hospital of Soochow University, Suzhou 215004, China
[2]Department of Ophthalmology, The Second Affiliated Hospital of Soochow University, Suzhou 215004, China
[3]Jiangsu Key Laboratory of Neuropsychiatric Diseases and Institute of Neuroscience, Soochow University, Suzhou 215123, China
[4]Jiangsu Key Laboratory of Preventive and Translational Medicine for Major Chronic Non-communicable Diseases, Soochow University, Suzhou 215123, China

Introduction

Parkinson's disease (PD), one of the common neurodegenerative disorders, is characterized with various motor and non-motor symptoms. It has been well reported that up to 70% of patients with PD will express recurrent visual complaints [1] which are associated with poorer outcomes including depression, dementia and shorter survival [2, 3]. The retina shares similar innervation by the dopaminergic system with the cortex in terms of dopamine 1 and dopamine 2 receptors [4]. Optical coherence tomography (OCT), pattern electroretinogram (PERG) and visual evoked potentials (VEP) are used to evaluate the structural and functional changes in the retina and its downstream visual pathways [5]. Recently, a growing number of studies have evaluated the retina of patients with PD using OCT, PERG and VEP, and found significant abnormalities such as thickness of the retinal nerve fiber layer (RNFL), as well as delays in latencies, and reduced wave amplitude [4–6]. We have previously demonstrated that OCT can detect the changes in retinal morphology for diagnosis of PD and may predict cognitive dysfunction in PD patients [7–9]. Thus, whether these retina-related examinations can provide good clinical therapeutic biomarkers of PD is a promising direction.

Circadian rhythm abnormality is one of the non-motor symptoms in patients with PD. Light therapy (LT), especially bright light therapy (BLT), has positive effects on emotion, sleep and even motor dysfunction of PD patients [10–12]. However, the specific mechanism of BLT is still lacking.

In this crossover randomized placebo-controlled clinical intervention of LT in PD patients, we explored whether BLT significantly improved the retinal functional and structural changes measured by OCT, PERG and VEP.

Methods

Study population

This was a crossover randomized placebo-controlled clinical light therapy trial in PD patients. All participants were recruited through networks and social media. Ethics approval was obtained from the hospital's Ethical Committee and was registered with the ClinicalTrials.gov (ClinicalTrials: NCT06129942, Registration Date: November 12, 2023, Clinical Trial Registry: The Second Affiliated Hospital of Soochow University). All participants gave written informed consent in accordance with the Declaration of Helsinki.

Twenty-nine patients were recruited between September 2022 and September 2023 from the movement disorder unit at the Second Affiliated Hospital of Soochow University. No medication changes occurred throughout the study.

Patients were enrolled in the study if they (1) had a diagnosis of idiopathic PD, as defined by the 2015 Movement Disorder Society clinical diagnostic criteria [13]; (2) were classified according to Hoehn and Yahr stages (H&Y) 1 to 3; (3) had a stable PD medication regimen for at least 6 months before screening; and (4) were willing and able to give written informed consent.

Patients enrolled were excluded from this study if they (1) had atypical parkinsonian syndrome; (2) had untreated hallucinations or psychosis; (3) had visual diseases that may interfere with light intervention, such as severe cataracts or blindness; (4) traveled across 2 or more time zones within 90 days before study screening; (5) had diabetes mellitus, poor sitting stability, had history of severe visual loss including cataract, glaucoma, age-related macular degeneration, hypermyopia (refractive diopter > – 4.0D), or any ocular surgery history.

Study design

The patients enrolled were randomized to order 1 or 2, using a computer-generated randomization schedule.

At the screening visit (T0), participants enrolled in this study underwent standard ophthalmologic and clinical evaluations including Hoehn and Yahr stages, disease duration, levodopa equivalent doses according to Tomlinson et al. [14], which were all evaluated in the "on" state. After the baseline phase, participants were then randomized to order 1 or order 2. In each period, participants received 2 h of BLT (10000 lx) or dim light therapy (DLT) (200 lx, as placebo light therapy) [10] at about 45-degree angle from the direction of gaze (for minimizing the side effects of bright light) in the morning (one hour within 9–11 AM) and in the afternoon (one hour within 5–7 PM) daily for 30 days. The LT procedure has been reported in our previous study [15].

We have previously proved that after 14 days of LT, the effect almost disappeared [16]. After a 30-day of intervention, participants experienced 30-day wash-out period and then began next intervention. Examinations of the above mentioned were also conducted in other three stages: end of first LT (T1), end of wash-out period (T2) and end of the second intervention (T3).

Clinical evaluations

Clinical assessments in all PD patients, including the Hoehn and Yahr stage, disease duration, Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scales I-III (MDS-UPDRS I-III) [17], Parkinson's Disease Questionnaire-39 (PDQ-39) [18], Fatigue Severity Scale (FSS) [19] and Non-Motor Symptoms Questionnaire (NMSQ) [20] were conducted in all participants. Cognitive function was assessed by the Montreal Cognitive Assessment scale (MoCA) [21] scale. Subjective sleep quality was assessed by The Pittsburgh

Sleep Quality Index (PSQI) [22], Epworth Sleepiness Scale (ESS) [23] and the Parkinson's Disease Sleep Scale 2nd version (PDSS-2) [24] scales. Autonomic dysfunction was assessed by The Autonomic Scale for Outcomes in Parkinson's disease (SCOPA-AUT) [25] scale. Emotion status was assessed by 24 item-Hamilton Depression Scale (HAMD-24) [26], and 14-item Hamilton Anxiety Scale (HAMA-14) [27] scales. RBD was assessed by the RBD questionnaire-Hong Kong (RBDQ-HK) [28] scale. A neurologist who was blinded to this study performed the assessment.

High-definition OCT examination

We used high-definition OCT (Cirrus HD-OCT, Carl Zeiss Meditec, Inc., Dublin, CA) in all patients to measure RNFL thickness as previously demonstrated [9, 29]. The RNFL thickness was assessed using an Optic Disc Cube 200 × 200 scanning. This protocol analyzed a 6-mm^2-based spatial cube surrounding the optic disc and performs 200 × 200 A-scans in approximately 1.5 s. The Optic Disc acquired 200 B-scans with 200 A-scans per B-scan (40,000 points). The temporal, nasal, superior and inferior RNFL thickness was measured in each eye and we calculated the mean RNFL.

PERG examination

PERG (Visual Electrophysiologic test instrument, MKWHBMD, Medconova, Huzhou, China) was obtained using a neurophysiology device for ERG record (Neuronic) and following the International Society for Clinical Electrophysiology of Vision (ISCEV) standards [30]. Stimuli were checkerboard patterns with a check size of 30 min of visual angle (min arc; contrast 90%; mean luminance, 93 cd/m^2). Each PERG included at least two trials. The evaluated parameters were P35, N95 and P50 latencies (ms) and amplitudes.

VEP examination

VEP examinations were processed by an integrative electromyography system (Keypoint.net, Denmark) in the tessellated pattern flip-flop. The participants were seated in a dark, quiet environment and were asked to pay attention to the screen. The evaluated eye was 100 cm away from the screen and at the same level. Both eyes were examined separately, with one eye covered while the other was examined. According to the international Electroencephalogram (EEG) 10/20 system, the recording electrode was placed in Oz, the reference electrode was placed in FPz, the size of the checkerboard grid was 12/16, the sensitivity was 5 μV, the filtering was 2–50 Hz, the recording length was 300 ms, the repetition frequency was 1.7 Hz, and each was repeated at least 2 trials, and the average was taken for P100 latencies (ms).

Statistical analysis

Statistical analysis was performed with SPSS 26.0 and R software. Data were reported as mean and SD or median and interquartile range (IQR). We used paired samples Wilcoxon Signed Rank test to compare OCT, PERG and VEP parameters and scale scores before and after BLT or DLT. The difference of scales values and parameters before and after LT and expressed as ΔOCT, ΔPERG and ΔVEP parameters. Mixed-effects regression models were next used to explore whether there was an effect between the two interventions on improving the differentials of scales, OCT, PERG and VEP parameters. In our mixed linear model, Δscales values, ΔOCT, ΔPERG and ΔVEP parameters were the dependent variables, and intervention kind was the independent variable. The order, stage, age, sex, H&Y, LED and disease duration were covariates, while the participant was a random effect. Correlations between ΔVEP and ΔPERG parameters and Δscales values were evaluated using nonparametric Spearman's ρ. A significance level of $P < 0.05$ was used for all tests.

Results

Basic demographics analysis

After screening 29 participants, 23 were randomly assigned to order 1 ($n = 11$) or order 2 ($n = 12$) (Fig. 1). Over the course of the intervention period, 2 participants in order 1 discontinued DLT intervention due to being conflict with daily working hours. baseline demographic data are presented in table 1. there were no significant differences in demographic, disease duration and severity and other disease characteristics between two order groups ($P > 0.05$). Because of the presence of eyes tremor in PD patients which might affect the examination, some data of OCT, PERG and VEP was excluded. the numbers of eyes after exclusion were presented in Supplementary table (1) the missing clinical scales due to incompleteness of evaluation or inconvenience of participants were presented in Supplementary table (2) baseline PERG and VEP data was presented in Supplementary table 3.

Adherence metrics

All participants enrolled in final analysis completed BLT and DLT intervention. We monitored the adherence by the following: 1). Participants were asked by follow-up staff by phone regularly; 2). Huawei Zhengtai remote control smart socket was used to connect the light box to display the time period during when the light boxes were energized each day and could automatically timed to switch on and off the light box.

Effects of light therapy on clinical symptoms

Paired samples Wilcoxon signed rank test of different scales before and after BLT were performed to evaluate the effects of BLT (Supplementary Table 4a). There were

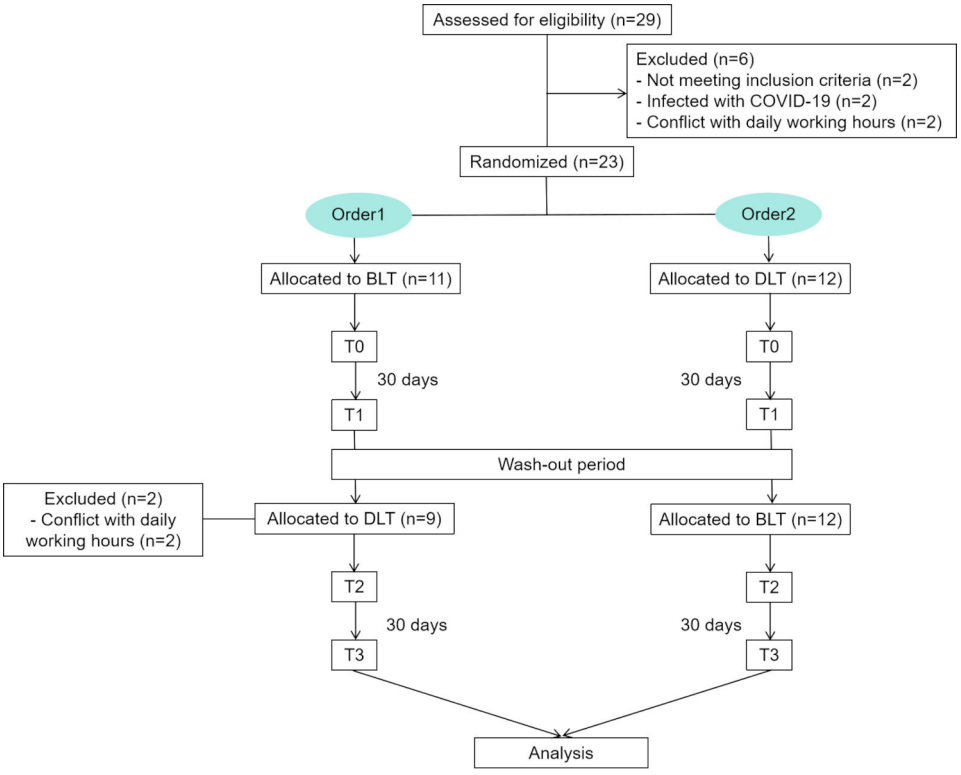

Fig. 1 Study flow diagram. A total of 29 participants were screened, 6 were excluded following screening, 23 consented and started baseline and were randomly assigned. A total of 23 completed the first period, 21 completed both periods (2 participants discontinued due to being conflict with daily working hours). Abbreviations: COVID-19 = coronavirus disease 2019, Order 1 = intervention order starting with BLT first, Order 2 = intervention order starting with DLT first, BLT = bright light therapy, DLT = dim light therapy

Table 1 Demographic characteristics and disease metrics of the study cohort

	Randomization			
Variable	**Order1**	**Order2**	**Final sample**	***P* value**
Number of participants	11	12	23	-
Sex, Female/Male	5/6	4/8	9/14	0.552[a]
Age, y	63.36 ± 7.38	64.00 ± 6.77	63.70 ± 6.91	0.831[b]
Disease duration, m	60 (48, 92)	63 (49, 81)	60 (48, 84)	0.786[c]
H&Y	1.5 (1.5, 2.5)	2.0 (2.0, 2.9)	2.0 (1.5, 2.5)	0.104[c]
LED	450 (375, 750)	688 (406, 872)	525 (375, 865)	0.288[c]

Values are expressed as mean ± SD or median (interquartile range) or frequency

Abbreviations: y = years, m = months, H&Y = Hoehn and Yahr stages, LED = levodopa equivalent dose

[a] Chi-square test between groups Order 1 and Order 2

[b] Independent Samples t-test between groups Order 1 and Order 2

[c] Mann-Whitney U tests between groups Order 1 and Order 2

significant improvements in ESS ($P = 0.025$), HAMA-14 ($P = 0.040$), PDQ-39 ($P = 0.035$) and SCOPA-AUT ($P = 0.020$) scales after BLT. For DLT intervention, PSQI showed significant improvement ($P = 0.006$) (Supplementary Table 4b). Mixed-effects regression models for Δscales comparisons between BLT and DLT showed no differences (Table 2).

Effects of light therapy on RNFL thickness

We preformed paired samples Wilcoxon signed rank test of RNFL before and after BLT (Supplementary Table 5a) and DLT (Supplementary Table 5b). There was no significant change in the four quadrants of RNFL thickness before and after two light interventions. Mixed-effects regression models for ΔRNFL comparisons between BLT and DLT showed no differences (Table 3).

Effects of light therapy on PERG and VEP parameters

We evaluated the difference before and after BLT or DLT. We conducted paired samples Wilcoxon signed rank test of PERG and VEP parameters between before BLT and after BLT groups (Supplementary Table 6a). There were significant differences of bilateral N95 latencies for PERG ($P < 0.01$) and P100 latencies ($P < 0.01$) for VEP after BLT. Although oculus Dexter (OD) N35 amplitude ($P = 0.013$) and P50 latency ($P = 0.036$) showed significant differences after DLT (Supplementary Table 6b), this result became insignificant in mixed effects models. Table 4 illustrated the effect of light therapy on ΔPERG and ΔVEP parameters. Compared with DLT, BLT significantly improved

Table 2 Effect of bright light therapy or dim light therapy on subjective scale scores

Scales	BLT	DLT	*P* value[a]
ΔMDS-UPDRS I	0.00(-3.00, 2.00)	-4.50(0.00, 2.00)	0.603
ΔMDS-UPDRS II	0.00(-2.00, 0.00)	-1.00(-2.00, 2.50)	0.769
ΔMDS-UPDRS III	0.00(-3.00, 5.00)	0.00(-3.50, 10.50)	0.746
ΔESS	-2.00(-4.00, 0.00)	-2.00(-6.00, 2.00)	0.870
ΔFSS	0.00(-4.00, 3.00)	3.00(-9.50, 9.50)	0.802
ΔHAMA-14	0.00(-2.00, 1.00)	0.00(-1.00, 1.00)	0.705
ΔHAMD-24	0.00(-1.00, 3.00)	1.00(-1.00, 2.75)	0.922
ΔMoCA	0.00(0.00, 2.00)	0.00(-3.00, 1.50)	0.111
ΔNMSQ	0.00(-1.00, 0.50)	-0.50(-4.50, 2.75)	0.424
ΔPDQ-39	-2.00(-4.00, 0.00)	-1.00(-4.50, 3.25)	0.222
ΔPDSS-2	0.00(-2.75, 2.00)	-1.00(-8.50, 0.50)	0.780
ΔPSQI	-1.00(-5.00, 1.00)	-2.00(-4.50, -0.50)	0.398
ΔRBDQ-HK	0.00(0.00, 0.00)	0.00(-5.75, 6.00)	0.415
ΔSCOPA-AUT	0.00(-1.50, 0.00)	-2.00(-2.00, 0.00)	0.290

Scale scores are expressed as median (interquartile range) and as differences before and after BLT or DLT

[a] *P* values were estimated with a mixed-effects regression model with participant as a random effect

Abbreviations: BLT = bright light therapy, DLT = dim light therapy, MDS-UPDRS = Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale, ESS = Epworth Sleepiness Scale, FSS = Fatigue Severity Scale, HAMA-14 = 14-item Hamilton Anxiety Scale, HAMD-24 = 24-item Hamilton Depression Scale, MoCA = Montreal Cognitive Assessment, NMSQ = Non-Motor Symptoms Questionnaire, PDQ-39 = Parkinson's Disease Questionnaire-39, PDSS-2 = Parkinson's Disease Sleep Scale 2nd version, PSQI = Pittsburgh Sleep Quality Index, RBDQ-HK = RBD questionnaire-Hong Kong, SCOPA-AUT = The Autonomic Scale for Outcomes in Parkinson's disease

Table 3 Effect of bright light therapy or dim light therapy on RNFL using HD-OCT

RNFL thickness	BLT	DLT	*P* value[a]
OD			
ΔAverage (μm)	1.00 (-2.00, 2.00)	0.00 (-1.75, 2.00)	0.636
ΔTemporal quadrant thickness (μm)	0.00 (-3.00, 4.75)	1.00 (-4.75, 4.75)	0.134
ΔNasal quadrant thickness (μm)	2.00 (-1.00, 5.50)	-0.50 (-5.75, 1.75)	0.101
ΔSuperior quadrant thickness (μm)	1.00 (-4.00, 4.50)	-3.50 (-7.75, 2.75)	0.384
ΔInferior quadrant thickness (μm)	1.50 (-2.50, 5.00)	2.50 (-0.75, 5.75)	0.996
OS			
ΔAverage (μm)	0.00 (-2.00, 1.00)	1.00 (0.00, 4.00)	0.334
ΔTemporal quadrant thickness (μm)	0.00 (-3.75, 3.00)	1.00 (-3.00, 4.00)	0.741
ΔNasal quadrant thickness (μm)	-1.50 (-7.75, 0.75)	1.00 (-2.00, 6.00)	0.233
ΔSuperior quadrant thickness (μm)	1.00 (-3.75, 7.25)	1.00 (-2.00, 5.00)	0.723
ΔInferior quadrant thickness (μm)	0.00 (-4.75, 3.00)	3.00 (-2.00, 7.00)	0.356

Values of HD-OCT parameters are expressed as median (interquartile range) and as differences before and after BLT or DLT

[a] *P* values were estimated with a mixed-effects regression model with participant as a random effect

Abbreviations: HD-OCT = high-definition optical coherence tomography, RNFL = retinal nerve fiber layer, BLT = bright light therapy, DLT = dim light therapy, OD = oculus dexter, OS = oculus sinister

bilateral N95 latencies ($P = 0.003$ for OD and $P = 0.018$ for oculus sinister (OS)) and P100 latencies ($P < 0.001$ for OD and $P = 0.001$ for OS). We found no significant correlations between ΔN95, ΔP100 latencies and Δscales scores in BLT (Table 5).

Adverse effects of LT

Light therapy was well tolerated. Only 2 participants reported mild headache during the BLT intervention. These adverse effects resolved spontaneously.

Discussion

To our knowledge, this study was the first to illustrate that safety and effectiveness of BLT in PD patients using ophthalmological-related examinations. The RNFL was not significantly altered before or after BLT, suggesting that BLT did not affect the structural function of the retina. Furthermore, we found that visual pathways improvement might be crucial mechanisms for BLT in PD patients. Together, these findings suggested that BLT was important for enhancing visual pathways function in PD patients.

The exploration of biomarkers for PD has been a promising research direction [31]. By using OCT and PERG, visual biomarkers such as retina and its downstream pathways have been confirmed by numerous studies to be abnormal in patients with PD [5]. OCT could provide accurate and reproducible cross-sectional imaging of the retina and optic nerve including RNFL [32]. Although the precise origin of PERG waveform was not be fully elucidated, N95 component was hypothesized to originate mainly in retinal ganglion, while P50 component was derived form ganglion cells and its downstream visual pathways [33]. Human and animal-related studies have identified the presence of α-synuclein deposits in the retina in PD, suggesting that retinal structural and functional changes might serve as a neglected but important biomarker of PD [34]. Previous studies also confirmed the presence of RNFL thinning and decreased retinal function in PD patients [7–9]. Therefore, it is significant to assess the changes of retina function in PD patients before and after treatment using retinal related examinations. Previous studies found significant improvement in PERG responses [31, 35] in PD patients with the use of levodopa, and we observed an ameliorative effect on retinal dysfunction in PD patients by using BLT for up to one month.

As the use of BLT in PD has gradually increased, its safety and mechanisms have been emphasized [36]. Although animal studies have demonstrated that it might

Table 4 Effect of bright light therapy or dim light therapy on PERG and VEP

Functional parameters	BLT	DLT	*P* value[a]
PERG-OD			
ΔN35 latency (ms)	-6.00 (-14.00, 5.00)	-2.00 (-9.50, 7.50)	0.366
ΔN35 amplitude (μV)	-0.60 (-1.80, 0.80)	1.20 (-0.35, 2.75)	0.034
ΔP50 latency (ms)	0.00 (-6.00, 16.00)	2.00 (-7.00, 10.50)	0.694
ΔP50 amplitude (μV)	-0.40 (-2.50, 0.70)	1.30 (-0.50, 3.00)	0.047
ΔN95 latency (ms)	-27.00 (-44.00, -2.00)	4.00 (-13.50, 38.00)	0.003
ΔN95 amplitude (μV)	-0.90 (-1.30, 0.10)	1.30 (-0.85, 1.60)	0.270
PERG-OS			
ΔN35 latency (ms)	-6.00 (-18.25, 13.50)	0.00 (-13.00, 4.00)	0.980
ΔN35 amplitude (μV)	-0.25 (-3.43, 0.63)	-0.10 (-1.60, 1.55)	0.324
ΔP50 latency (ms)	0.00 (-8.50, 6.00)	4.00 (-7.00, 13.00)	0.141
ΔP50 amplitude (μV)	-0.45 (-2.48, 0.20)	-0.30 (-2.05, 0.80)	0.443
ΔN95 latency (ms)	-15.50 (-35.75, 0.50)	-5.00 (-22.00, 15.50)	0.018
ΔN95 amplitude (μV)	-0.20 (-1.05, 1.00)	0.70 (-1.05, 1.65)	0.365
VEP			
ΔP100-OD (ms)	-7.66 ± 8.50	1.24 ± 6.34	< 0.001
ΔP100-OS (ms)	-8.03 ± 7.00	0.52 ± 8.92	0.001

Values of PERG and VEP are expressed as median (interquartile range) or mean ± SD and as differences before and after BLT or DLT

[a] *P* values were estimated with a mixed-effects regression model with participant as a random effect

Abbreviations: BLT = bright light therapy, DLT = dim light therapy, PERG = pattern electroretinogram, VEP = visual evoked potentials, OD = oculus dexter, OS = oculus sinister

activate the retina and its downstream neural circuits to improve sleep [37] and spatial memory [38], the mechanism of BLT in PD was currently unknown. The N95 latency of PERG examination was significantly reduced by BLT, suggesting that the connectivity of retinal ganglion cells and visual pathways were alleviated by BLT, but unfortunately no changes in RNFL were observed. A possible explanation is that retinal function might improve before structure did, as previously found by Huang et al. that it might not be found the difference of RNFL until PD patients are in the H-Y III stage [8], while ERG abnormalities might be detected in the early stage of disease. BLT is a long-lasting non-pharmacological intervention [16]. We might need to follow up longer in the future. From a therapeutic point of view, the insignificant changes in the RNFL after BLT might indicate that BLT used in this study did not cause damage to retina and is safe and effective.

VEP waveform mainly generated form the occipital cortex and could reflect the integrity of the ascending visual pathways. The morphology and latency of P100 were important electrophysiological parameters for evaluating the integrity of light pathways as well [39]. Thus, the prolonged latency of P100 indicated the connectivity of visual neurons was impaired in PD patients [40]. In terms of neural circuits, since retinal ganglion cells could secrete dopamine, it could be hypothesized that the integrity of its downstream visual pathway was closely related to the dopamine system. Therefore, dopamine might play an important role in the BLT which in turn activated the entire visual circuits. Due to the lack of PET imaging of retinal dopamine transporters, we currently lack direct evidence demonstrating retinal release of dopamine after BLT. Future studies need to validate this hypothesis.

Although BLT improved non-motor symptoms in Parkinson's disease, such as daytime sleepiness, anxiety, and quality of life, the effect was minimal in the mixed-regression model. Meanwhile, no association was found between visual pathway improvements and clinical symptoms. As pointed by our previous research [15], BLT might induce more extensive and intense neural activity than DLT. Here, we also observed that the visual pathways were activated by BLT, but it was well acknowledged that non-motor symptoms were associated with various neural pathways [41], brain regions [42]. Thus the one-month activation of the visual pathways here was not sufficient to provide significant symptom alleviation.

We acknowledge some limitations in this study. First, our results were limited by our small sample size of 21

Table 5 Correlations between Δscales scores and ΔPERG or ΔVEP values in participants receiving bright light therapy

	ΔScales							
	ΔESS		ΔHAMA-14		ΔPDQ-39		ΔSCOPA-AUT	
	Spearman's ρ	*P* value	Spearman's ρ	*P* value	Spearman's ρ	*P* value	Spearman's ρ	*P* value
PERG								
OD-N95 latency (ms)	0.350	0.141	-0.057	0.815	0.163	0.533	0.031	0.907
OS-N95 latency (ms)	0.033	0.896	-0.181	0.472	-0.193	0.474	-0.029	0.914
VEP								
P100-OD (ms)	0.016	0.942	0.108	0.625	-0.206	0.371	-0.324	0.152
P100-OS (ms)	0.244	0.263	-0.200	0.360	-0.006	0.979	0.105	0.650

Correlations between Δscales scores and ΔVEP or ΔPERG values are analyzed by Spearman correlation test

Abbreviations: ESS = Epworth Sleepiness Scale, HAMA-14 = 14-item Hamilton Anxiety Scale, PDQ-39 = Parkinson's Disease Questionnaire-39, SCOPA-AUT = The Autonomic Scale for Outcomes in Parkinson's disease, PERG = pattern electroretinogram, VEP = visual evoked potentials, OD = oculus dexter, OS = oculus sinister

patients enrolled in the final analysis, which limited the further exploration of our results. Second, we observed differences of OD N95 and P100-OS latencies between two orders in T0. Though the numbers of N95 and P100 latencies of Order 1 participants were larger than those of Order 2, it is noteworthy that they were significantly decreased after BLT. Nevertheless, these two values were increased after DLT. Thus, BLT was more able to improve the visual neural pathways compared to DLT. Last, PD patients who did not receive LT rather than 200 lx could be the true Sham group in our study. Thus, this result might be confirmed in the future.

Conclusion

By means of OCT, PERG and VEP, we concluded that BLT is a safe and valuable intervention for improving visual pathways in PD patients, thus providing novel mechanisms of BLT in PD.

Abbreviations

BLT	Bright light therapy
PD	Parkinson's disease
OCT	Optical coherence tomography
PERG	Pattern electroretinogram
VEP	Visual evoked potentials
DLT	Dim light therapy
RNFL	Retinal nerve fiber layer
LT	Light therapy
H&Y	Hoehn and Yahr stages
LED	Levodopa equivalent doses
MDS-UPDRS	Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scales
PDQ-39	Parkinson's Disease Questionnaire-39
FSS	Fatigue Severity Scale
NMSQ	Non-Motor Symptoms Questionnaire
MoCA	Montreal Cognitive Assessment
PSQI	Pittsburgh Sleep Quality Index
ESS	Epworth Sleepiness Scale
PDSS-2	Parkinson's Disease Sleep Scale 2nd version
SCOPA-AUT	The Autonomic Scale for Outcomes in Parkinson's disease
HAMD-24	24-item Hamilton Depression Scale
HAMA-14	14-item Hamilton Anxiety Scale
RBDQ-HK	RBD questionnaire-Hong Kong
IQR	Interquartile range
Y	Years
m	Months
OD	Oculus dexter
OS	Oculus sinister
HD-OCT	High-definition optical coherence tomography
COVID-19	Coronavirus disease 2019

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-025-06915-z.

Supplementary Material 1

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Author contributions

Chun-feng Liu and Yun Shen: Conceptualization, Methodology; Wei-ye Xie and Hui Lou: Data curation, writing original draft; Jia-ying Liu and Tian-qi Zhang: statistical analysis; Cheng-jie Mao and Fen Wang: manuscript revision; Jie-yun Yin: Statistical analysis assistance; All authors: Visualization, Investigation; Chun-feng Liu: Supervision; All authors: Writing- Reviewing and Editing.

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Data availability

The data underlying this article are available in the article and its online supplementary materials.

Declarations

Ethics approval and consent to participate

Statement that all methods are performed in accordance with relevant guidelines and regulations. This study received approval from the Ethics Committee of The Second Affiliated Hospital of Soochow University, China (JD-LK-2020-062-01). Having explained the nature of the survey, confirming that informed consent was obtained from all subjects and/or their legal guardian(s). Each participant's privacy was safeguarded with respect to the processing of personal data and the confidentiality of individual records and accounts was ensured.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

Conflict of interest

None declared.

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References

1. Urwyler P, Nef T, Killen A, et al. Visual complaints and visual hallucinations in Parkinson's disease. Parkinsonism Relat Disord. 2014;20(3):318–22.
2. HAMEDANI A G, ABRAHAM D S, MAGUIRE M G, et al. Visual impairment is more common in Parkinson's disease and is a risk factor for poor health Outcomes[J]. Mov Disord. 2020;35(9):1542–9.
3. ZARKALI A, MCCOLGAN P, LEYLAND L A, et al. Visual dysfunction predicts cognitive impairment and white matter degeneration in Parkinson's Disease[J]. Mov Disord. 2021;36(5):1191–202.
4. ELMERS J, COLZATO L S, ZIEMSSEN F, et al. Optical coherence tomography as a potential surrogate marker of dopaminergic modulation across the life span[J]. Ageing Res Rev. 2024;96:102280.
5. ALVES J N, WESTNER B U, HØJLUND A, et al. Structural and functional changes in the retina in Parkinson's disease[J]. J Neurol Neurosurg Psychiatry. 2023;94(6):448–56.
6. GARCIA-MARTIN E, RODRIGUEZ-MENA D, SATUE M, et al. Electrophysiology and optical coherence tomography to evaluate Parkinson disease severity[J]. Invest Ophthalmol Vis Sci. 2014;55(2):696–705.
7. HUANG J, LI Y, XIAO J et al. Combination of Multifocal Electroretinogram and Spectral-Domain OCT Can Increase Diagnostic Efficacy of Parkinson's Disease[J]. Parkinsons Dis, 2018,2018:4163239.
8. HUANG J, WANG Q, LI K, et al. Spectral domain OCT can differentiate the retinal morphological changes of patients with Parkinson's disease in clinical middle stages[J]. Neurol Sci. 2020;41(7):1909–12.

9. ZHANG JR, CAO Y L, LI K, et al. Correlations between retinal nerve fiber layer thickness and cognitive progression in Parkinson's disease: A longitudinal study[J]. Parkinsonism Relat Disord. 2021;82:92–7.
10. Videnovic A, Klerman EB, Wang W, Marconi A, Kuhta T, Zee PC. Timed light therapy for sleep and daytime sleepiness associated with Parkinson disease: A randomized clinical trial. JAMA Neurol. 2017;74(4):411–8.
11. LIU Y L, GONG S Y, XIA S T, et al. Light therapy: a new option for neurodegenerative diseases[J]. Chin Med J (Engl). 2020;134(6):634–45.
12. FEIGL B, BURR L D LEWISS, et al. Efficacy of biologically-directed daylight therapy on sleep and circadian rhythm in Parkinson's disease: a randomised, double-blind, parallel-group, active-controlled, phase 2 clinical trial[J]. EClinicalMedicine. 2024;69:102474.
13. BERG POSTUMARB. MDS clinical diagnostic criteria for Parkinson's disease[J]. Mov Disord. 2015;30(12):1591–601.
14. TOMLINSON CL, STOWE R, PATEL S, et al. Systematic review of Levodopa dose equivalency reporting in Parkinson's disease[J]. Mov Disord. 2010;25(15):2649–53.
15. Xie WY, Duan WX, Chen Y, et al. The impact of bright light therapy on Parkinson's disease: A pilot study using vestibular-evoked myogenic potentials. Parkinsonism Relat Disord. 2025;134:107776.
16. SHEN Y, GONG S, LIU Y, et al. Therapeutic potential of bright light therapy for the non-motor symptoms in Parkinson's disease[J]. Chin Med J (Engl). 2021;135(2):243–4.
17. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement disorder Society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord. 2008;23(15):2129–70.
18. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The Parkinson's disease questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. Age Ageing. 1997;26(5):353–7.
19. Elbers RG, Verhoef J, van Wegen EE, Berendse HW, Kwakkel G. Interventions for fatigue in Parkinson's disease. Cochrane Database Syst Rev. 2015;2015(10):CD010925.
20. Chaudhuri KR, Martinez-Martin P, Schapira AH, Stocchi F, Sethi K, Odin P, Olanow CW, et al. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. Mov Disord. 2006;21(7):916–23.
21. Hoops S, Nazem S, Siderowf AD, Duda JE, Xie SX, Stern MB, Weintraub D. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. Neurology. 2009;73(21):1738–45.
22. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193–213.
23. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540–5.
24. Muntean ML, Benes H, Sixel-Döring F, Chaudhuri KR, Suzuki K, Hirata K, Trenkwalder C, et al. Clinically relevant cut-off values for the Parkinson's disease sleep Scale-2 (PDSS-2): a validation study. Sleep Med. 2016;24:87–92.
25. Visser M, Marinus J, Stiggelbout AM, Van Hilten JJ. Assessment of autonomic dysfunction in Parkinson's disease: the SCOPA-AUT. Mov Disord. 2004;19(11):1306–12.
26. Liu H, Ou R, Wei Q, Hou Y, Zhang L, Cao B, et al. Shang H. Apathy in drug-naïve patients with Parkinson's disease. Parkinsonism Relat Disord. 2017;44:28–32.
27. Clark DB, Donovan JE. Reliability and validity of the Hamilton anxiety rating scale in an adolescent sample. J Am Acad Child Adolesc Psychiatry. 1994;33(3):354–60.
28. Li SX, Wing YK, Lam SP, Zhang J, Yu MW, Ho CK, et al. Mok V. Validation of a new REM sleep behavior disorder questionnaire (RBDQ-HK). Sleep Med. 2010;11(1):43–8.
29. YANG Z J, WEI J, MAO C J, et al. Retinal nerve fiber layer thinning: a window into rapid eye movement sleep behavior disorders in Parkinson's disease[J]. Sleep Breath. 2016;20(4):1285–92.
30. HOLDER G E, BRIGELL M G, HAWLINA M, et al. ISCEV standard for clinical pattern electroretinography–2007 update[J]. Doc Ophthalmol. 2007;114(3):111–6.
31. GUO L, NORMANDO E M, SHAH PA, et al. Oculo-visual abnormalities in Parkinson's disease: possible value as biomarkers[J]. Mov Disord. 2018;33(9):1390–406.
32. WAGNER SK, ROMERO-BASCONES D, CORTINA-BORJA M, et al. Retinal optical coherence tomography features associated with incident and prevalent Parkinson Disease[J]. Neurology. 2023;101(16):e1581–93.
33. ALMARCEGUI C, DOLZ I. Correlation between functional and structural assessments of the optic nerve and retina in multiple sclerosis patients[J]. Neurophysiol Clin. 2010;40(3):129–35.
34. HARNOIS C, DI PAOLO T. Decreased dopamine in the retinas of patients with Parkinson's disease[J]. Invest Ophthalmol Vis Sci. 1990;31(11):2473–5.
35. INDRIERI A, PIZZARELLI R, FRANCO B, et al. Dopamine, Alpha-Synuclein, and mitochondrial dysfunctions in parkinsonian Eyes[J]. Front Neurosci. 2020;14:567129.
36. FIFEL K. Light therapy in Parkinson's disease: towards Mechanism-Based Protocols[J]. Trends Neurosci. 2018;41(5):252–4.
37. HUANG L, CHEN X, TAO Q, et al. Bright light treatment counteracts stress-induced sleep alterations in mice, via a visual circuit related to the Rostromedial tegmental nucleus[J]. PLoS Biol. 2023;21(9):e3002282.
38. HUANG X, HUANG P, HUANG L, et al. A visual circuit related to the nucleus reuniens for the Spatial-Memory-Promoting effects of light Treatment[J]. Neuron. 2021;109(2):347–e3627.
39. MIURA G. Visual evoked potentials for the detection of diabetic retinal Neuropathy[J]. Int J Mol Sci, 2023,24(8):7361.
40. HE S B, LIU C Y, CHEN LD et al. Meta-Analysis of Visual Evoked Potential and Parkinson's Disease[J]. Parkinsons Dis, 2018,2018:3201308.
41. Zhang Y, Roy DS, Zhu Y, Chen Y, Aida T, Hou Y, Feng G, et al. Targeting thalamic circuits rescues motor and mood deficits in PD mice. Nature. 2022;607(7918):321–9.
42. Salehi N, Nahrgang S, Petershagen W, Dembek TA, Pedrosa D, Timmermann L, Oehrn CR, et al. Theta frequency deep brain stimulation in the subthalamic nucleus improves working memory in Parkinson's disease. Brain. 2024;147(4):1190–6.

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