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Whole-body photobiomodulation therapy in Parkinson's disease: a single-arm feasibility and safety pilot trial with exploratory cognitive signals

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Abstract

Background: Beyond dopaminergic loss, Parkinson's disease (PD) involves mitochondrial dysfunction, ATP/NAD^+ depletion, neuroinflammation, and reduced cerebral perfusion. Photobiomodulation (PBM)—red and near-infrared light absorbed by mitochondrial cytochrome c oxidase—raises ATP synthesis, increases nitric-oxide–mediated blood flow, and reduces inflammation, and so could act on several of these pathways at once. In PD, PBM has been applied almost exclusively transcranially; whole-body PBM (WB-PBM) has not been evaluated. We conducted an early-phase pilot to characterise its safety, feasibility, and preliminary effects ahead of a future sham-controlled trial.

Methods: This single-centre, single-arm, prospective pilot trial enrolled 15 patients with idiopathic PD (Hoehn & Yahr 1–3); 14 completed 30 WB-PBM sessions (660/810/850/930 nm; skin-surface irradiance 35–65 mW/cm²; 20 min; three times

weekly for 10 weeks). The pre-specified registered primary efficacy outcome was the UPDRS total score; exploratory motor and cognitive outcomes were also assessed. Pre–post changes used the Wilcoxon signed-rank test (effect size r = Z/√N), with Benjamini–Hochberg false-discovery-rate (FDR) correction applied within a pre-specified memory family (SVLT, RCFT).

Results: The registered primary outcome, UPDRS total, fell from 24.86 ± 15.98 to 20.29 ± 8.71—a moderate-sized reduction (r = −0.42) that did not reach significance in this small sample (p = 0.127). Within the memory family, verbal learning improved with a large effect and survived FDR correction: SVLT total score (r = −0.74; p = 0.006; p_adj = 0.041) and its constituent immediate recall (r = −0.69; p = 0.009; p_adj = 0.041). Visuospatial memory (RCFT immediate recall, delayed recall, total score) also improved with large effects, significant before but not after correction (all p_adj = 0.076). Motor outcomes were maintained without deterioration. One participant had mild localised hyperpigmentation, judged unrelated to the study device and resolving during the study; no serious adverse events occurred.

Conclusions: WB-PBM was safe and feasible in PD. Verbal memory improved robustly enough to survive FDR correction, visuospatial memory showed a promising signal requiring confirmation, and the registered primary outcome showed a non-significant, moderate-sized reduction. A sham-controlled randomised trial should follow.

Trial registration: ClinicalTrials.gov, NCT07271927 (https://clinicaltrials.gov/study/NCT07271927); registered 9 December 2025; retrospectively registered (first participant enrolled 12 February 2025).

Keywords

Photobiomodulation; Parkinson's disease; Cognition; Verbal memory; Near-infrared light; Pilot study; Safety; Feasibility

Background

Parkinson's disease (PD) is a progressive neurodegenerative disorder marked by the gradual loss of dopaminergic neurons in the substantia nigra pars compacta, accompanied by abnormal aggregation of α-synuclein and the formation of Lewy bodies [1, 2]. Patients experience motor symptoms—tremor, rigidity, bradykinesia, and postural instability—alongside non-motor symptoms such as cognitive decline, mood disturbance, and disrupted sleep [1].

Dopaminergic loss is not the whole story. PD is increasingly understood as a disorder in which cellular energy metabolism breaks down. Reduced levels of adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide (NAD^+) have been reported in neural and muscle tissue, and mitochondrial dysfunction has been tied not only to symptom severity but also to large-scale disruption of neural networks [3, 4]. Vascular dysfunction at both cerebrovascular and systemic levels—reduced blood flow, microvascular abnormality—can add to neuronal stress and promote α-synuclein pathology [5, 6].

A further shift in perspective is that PD may not be confined to the central nervous system but is instead a systemic, multi-organ disorder. In the influential hypothesis proposed by Braak and colleagues, pathological α-synuclein aggregation may begin relatively early in the enteric nervous system of the gut and ascend along the vagus nerve, through the dorsal motor nucleus, into the brainstem [7]. This "gut–brain axis" hypothesis is supported by preclinical and epidemiological evidence. In animals given pathological α-synuclein in the gastrointestinal tract, the protein has been directly observed spreading to the brain along the vagus nerve [8], and large epidemiological studies have found a lower subsequent risk of PD in people who have undergone vagotomy [9]. Evidence also continues to accumulate that changes in the gut microbiome are linked to the onset and progression of PD; indeed, altered gut microbiota have been reported in patients with PD after PBM treatment [10]. Taken together, these observations suggest that PD pathophysiology reaches beyond the cranial vault to involve the gut, the vagus nerve, and the systemic circulation. Put the other way around, a localised therapy confined to the head is unlikely to reach the peripheral components of the disease.

Current treatment is predominantly pharmacological—levodopa, dopamine agonists, and monoamine oxidase B and catechol-O-methyltransferase inhibitors—with deep brain stimulation (DBS) reserved for selected patients [11, 12]. Long-term dopaminergic therapy, however, is commonly complicated by motor fluctuations and dyskinesia, and surgical options are constrained by cost, risk, and eligibility [13, 14]. These limitations have driven interest in non-invasive neuromodulation.

Photobiomodulation (PBM) is a non-invasive intervention that uses red and near-infrared light (roughly 600–1064 nm) to elicit physiological cellular responses [15, 16]. Its central mechanism is the direct activation of mitochondrial cytochrome c oxidase (CCO), which improves electron transport chain efficiency and increases ATP synthesis [17–19]. In addition, PBM releases nitric oxide (NO) from mitochondria, relaxing vascular smooth muscle and increasing cerebral blood flow [20, 21], and it modulates immune activity to dampen inflammation at sites of neural injury [22–24]. Across the red-to-near-infrared range, individual wavelengths have been reported to produce somewhat different effects [25–30].

The action of PBM need not remain confined to the site of irradiation but can extend systemically—and this is the theoretical starting point for whole-body irradiation (WB-PBM). Unlike localised transcranial or abdominal delivery, whole-body irradiation targets the trunk, limbs, and head at once. It may therefore act on several fronts simultaneously: (i) improving systemic and cerebral perfusion through NO-mediated vasodilation [20, 21]; (ii) lowering systemic inflammatory load through modulation of immune-cell activity and anti-inflammatory responses [22–24], with a downstream effect on neuroinflammation [31]; and (iii) opening the possibility of influencing the gut, enteric nervous system, and microbiome through irradiation of the abdomen and trunk [10]. The third of these connects directly to the gut–brain axis pathophysiology outlined above. Moreover, PBM is known to produce remote systemic effects beyond the irradiated area—so-called abscopal or systemic effects—mediated by circulating factors and immune cells [32, 33], so it may act indirectly on the central nervous system through systemic routes even when light does not sufficiently penetrate the skull [32]. Light itself, of course, does not "cross" the blood–brain barrier (BBB). The

hypothesis is rather that improved systemic perfusion and reduced systemic inflammation support the BBB, which is known to be compromised in PD [6], and the surrounding cerebral microenvironment. In short, given that PD is a systemic, multi-organ disease, there is a reasonable rationale for whole-body irradiation to encompass peripheral pathophysiology that head-restricted PBM cannot reach.

In animal models, PBM has improved cognitive and motor function in neurodegenerative disease through complex IV activation, increased ATP production, and reductions in reactive oxygen species and inflammation [34–36]. In the clinic, Liebert and colleagues reported in a prospective proof-of-concept study that combining transcranial and remote (including abdominal) stimulation improved UPDRS scores and cognitive measures in patients with PD, with effects sustained for up to a year, and noted the need for a large randomised controlled trial (RCT) [37]. The same group later confirmed, in a five-year follow-up, that the effects persisted [38]. Hamilton and colleagues likewise reported improvements in gait and cognition following transcranial PBM [39].

No clinical study has yet evaluated whole-body PBM (WB-PBM) in PD. Prior work has applied PBM only to limited regions such as the transcranial or abdominal areas, and it remains unknown what whole-body irradiation would produce. With the clinical evidence for PBM in PD accumulating from earlier work, and with the need for a large confirmatory trial already raised, an early-phase pilot that first establishes the safety, feasibility, and exploratory clinical signals of whole-body irradiation is a reasonable preparatory step towards designing a subsequent sham-controlled confirmatory trial. We therefore conducted the first WB-PBM pilot trial in patients with PD. The primary aim was to assess safety and feasibility; the secondary aim was to estimate preliminary effect sizes for motor and cognitive function to inform a future confirmatory trial. We set out to explore, in an exploratory fashion, whether whole-body irradiation—acting through pathways spanning systemic blood flow, immune (anti-inflammatory) modulation, and the gut–brain axis—could produce measurable change in the central and non-motor symptoms of PD.

Methods

Study design

This was an investigator-initiated, single-centre, single-arm, prospective pilot clinical trial conducted at Pusan National University Yangsan Hospital. It was approved by the institutional review board (IRB No. 23-2024-005), and the clinical trial plan was approved by the Ministry of Food and Drug Safety (MFDS approval No. 1730)—initially on 24 May 2024, after which amendments to the eligibility criteria, sample size, and study methods were approved on 22 January 2025. The first participant was enrolled on 12 February 2025 under this finally approved protocol; accordingly, the eligibility criteria, sample size, and assessment methods reported here all follow the final (22 January 2025) protocol. The trial was registered at ClinicalTrials.gov (NCT07271927; first posted 9 December 2025, first submitted 21 August 2025). Because registry posting occurred after enrolment of the first participant (12 February 2025), the trial was registered retrospectively; this is disclosed openly in the manuscript. The study followed the ethical principles of the Declaration of Helsinki, and written informed

consent was obtained from every participant before enrolment. Given the single-arm, non-randomised pilot design, reporting followed the CONSORT 2010 extension for pilot and feasibility trials together with the TREND statement for non-randomised designs, and participant flow is shown in a CONSORT-based diagram (Figure 1).

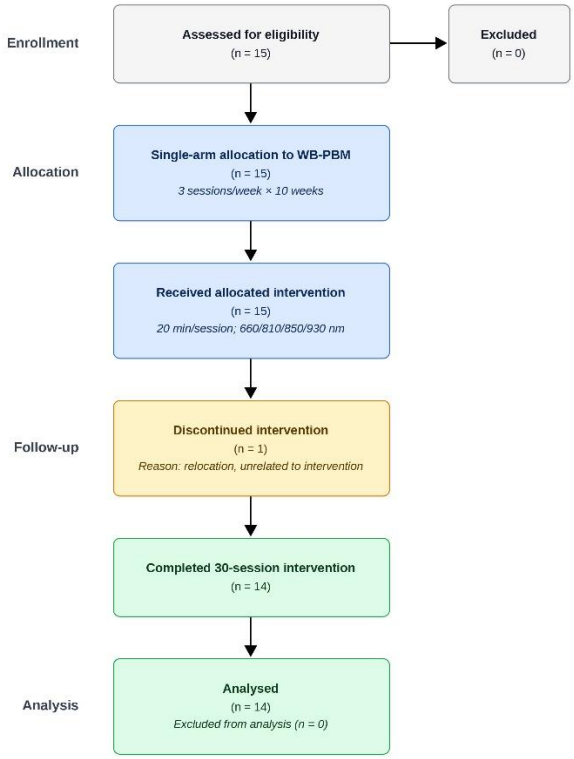


Figure 1. CONSORT participant flow diagram.

Participants

Patients were eligible if they met all of the following: (1) aged ≥40 years; (2) idiopathic PD by the UK Parkinson's Disease Society Brain Bank criteria; (3) Hoehn & Yahr stage 1–3; (4) mild cognitive impairment or greater (Korean Montreal Cognitive Assessment [K-MoCA] ≤23); (5) able to walk independently; and (6) stable medication dose during the study period.

Exclusion criteria were: severe cognitive impairment or other dementia; major psychiatric disorder (e.g., schizophrenia, bipolar disorder); photosensitivity disorder; an incompatible implanted device (e.g., pacemaker); alcohol dependence within the preceding 6 months; a history of seizures; a history of suicide attempt; a major uncorrected sensory deficit that would interfere with testing; participation in another clinical trial within the preceding 3 months; pregnancy or refusal of contraception in women of childbearing potential; active malignancy; and any other condition judged inappropriate by the investigators.

Intervention

The intervention used a WB-PBM device (WB-PBM-M01; Hue Light Co., Ltd., Gwangmyeong-si, Gyeonggi-do, Republic of Korea), a capsule-shaped system that delivers three-dimensional whole-body irradiation from a light-emitting diode (LED) array while the participant lies supine (Figure 2). Four wavelengths—660 nm (red) and 810, 850, and 930 nm (near-infrared)—were delivered simultaneously at fixed ratios, with a skin-surface irradiance of 35–65 mW/cm². Pulsed operation used seven Nogier frequencies (73, 146, 292, 584, 1168, 2336, and 4672 Hz), applied sequentially within each session. Each session lasted 20 minutes and was given three times weekly for 10 weeks, for a total of 30 sessions. The estimated skin-surface fluence was 42–78 J/cm² per session and 1,260–2,340 J/cm² cumulatively. The full delivery parameters are summarised in Table 1. As noted in Table 1, transcranial cortical fluence was not directly measured and regional in-vivo dosimetry was not performed. All sessions were carried out under the supervision of trained personnel in a controlled clinical setting.

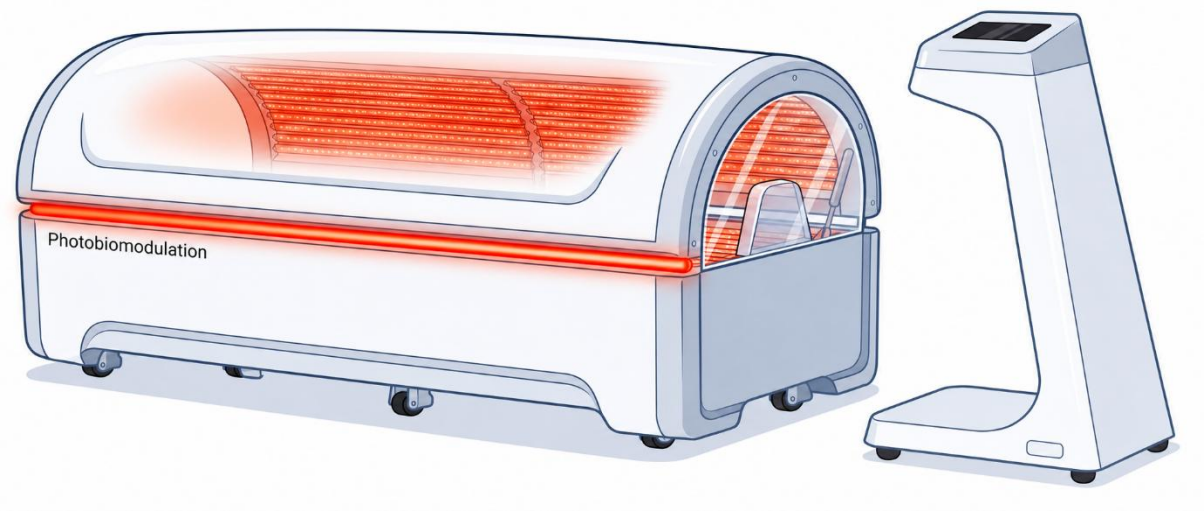


Figure 2. Whole-body photobiomodulation therapy device (WB-PBM-M01, Hue Light Co., Ltd.) and its control unit.

Table 1. Whole-body photobiomodulation light delivery parameters.

Parameter	Specification
Device	WB-PBM-M01 (Hue Light Co., Ltd., Gwangmyeong-si, Gyeonggi-do, Republic of Korea)
Light source	Light-emitting diode (LED) array
Device dimensions	200 cm (L) × 84 cm (W) × 106 cm (H); 220 kg
Wavelengths	660, 810, 850, 930 nm (simultaneous delivery at fixed ratios)
Skin-surface irradiance	35–65 mW/cm² (varies by Nogier pulse frequency)
Operating mode	Pulsed (Nogier frequencies, sequential within each session)
Pulse frequencies	73, 146, 292, 584, 1168, 2336, 4672 Hz (7 frequencies, sequential per session)
Treatment position	Supine
Session duration	20 minutes

Parameter	Specification
Estimated fluence per session	42–78 J/cm² (skin surface)
Treatment frequency	3 sessions/week
Treatment duration	10 weeks (30 sessions total)
Cumulative fluence	1,260–2,340 J/cm² (skin surface; 42–78 J/cm² × 30 sessions)
Panel configuration	LED panels on lower bed, upper canopy, bilateral side walls, and vertex/occipital head positions (360° circumferential array)
Panel-to-skin distance	Upper canopy 15–22 cm; lower bed 8–10 cm
Body coverage	Dorsal, ventral, bilateral lateral, cranial (vertex and occiput), and limb regions simultaneously irradiated; no shielded region (supine)
Skin-surface irradiance uniformity	±10% across body regions under continuous-wave operation; ±5% per Nogier frequency under sequential pulse operation
Regional in-vivo dosimetry	Not directly measured in this pilot

Abbreviations: LED, light-emitting diode; L, length; W, width; H, height. Footnote: Skin-surface irradiance values represent measurements at the skin surface. Transcranial cortical fluence depends on individual tissue optical properties (skull thickness, scalp pigmentation, hair density) and was not directly measured in the present study.

Outcome measures

Outcomes were measured by a trained assessor at baseline (V1) and after the 30-session course (approximately 10 weeks, V2).

Primary efficacy outcome. The pre-specified registered primary efficacy outcome was the UPDRS total score, where lower scores indicate milder symptoms. The total (= Part I + Part II + Part III) was analysed as the primary outcome; pre–post changes in the individual Part I–III subscales were also reported as an exploratory, post-hoc decomposition to show which domains drove any change in the total.

Exploratory motor outcomes. Berg Balance Scale (BBS), Functional Reach Test (FRT), Timed Up-and-Go (TUG), hand strength (power grip, three-jaw chuck pinch, and tip pinch; measured on the more affected side, defined as the side with lower grip strength at baseline), and the Clinical Rating Scale for Tremor (CRTS).

Exploratory cognitive outcomes. Cognition was assessed with the Seoul Neuropsychological Screening Battery [40]: the Seoul Verbal Learning Test (SVLT: immediate recall, delayed recall, recognition, total score), the Rey Complex Figure Test (RCFT: copy, immediate recall, delayed recall, recognition, total score), the Digit Span Test (DST: forward, backward, total score), the Trail Making Test (TMT: parts A and B), and the Korean Color–Word Stroop Test (K-CWST). The K-MoCA was used for screening (eligibility) only. For the SVLT, the alternate word list provided in the SNSB-II [40] was administered at V2, ensuring that participants were not retested on the word list presented at V1. By contrast, the RCFT was administered using the same complex figure at both visits because the battery does not provide an alternate figure.

Mood. Depressive symptoms were assessed with the Geriatric Depression Scale (GDS).

Safety. Adverse events were collected through voluntary reporting and a structured interview at every visit, coded with MedDRA, and assessed for severity and causality; serious adverse events (SAEs) were also monitored.

Sample size

Following conventions for pilot studies, 15 participants were enrolled (≥12 evaluable, allowing for dropout). The trial was not powered for hypothesis testing; its purpose was to estimate effect sizes, feasibility parameters, and variability to inform a subsequent confirmatory trial.

Statistical analysis

Analyses were performed in Python 3.10 (Python Software Foundation) using pandas, NumPy, and SciPy. Continuous variables were summarised as mean ± standard deviation and categorical variables as n (%). Within-participant pre–post comparisons used the non-parametric Wilcoxon signed-rank test, chosen because of the small sample and the uncertain normality of the data. Effect sizes were calculated as $r = Z/\sqrt{N}$ ($N = 14$). To handle multiplicity transparently, the Benjamini–Hochberg method was used to control the false discovery rate (FDR) within a pre-specified memory family (SVLT and RCFT, 9 measures), and both uncorrected (p) and corrected (p_adj) values are reported (Table 5). The remaining outcomes—the registered primary outcome (UPDRS total) and its exploratory subscale decomposition (Part I–III), the motor outcomes (Table 4), GDS, and the DST, TMT, and K-CWST—did not belong to the pre-specified FDR family and are reported with uncorrected p-values only. All tests were two-tailed exact Wilcoxon signed-rank tests, with significance set at two-tailed $p < 0.05$. Consistent with the single-arm pilot design, all outcomes, including the registered primary outcome, were interpreted as exploratory clinical signals (effect-size estimates) rather than as confirmatory tests of efficacy.

Results

Participant flow and baseline characteristics

Fifteen patients with PD were enrolled. One withdrew because of relocation (unrelated to the intervention), and 14 completed all 30 sessions and were included in the analysis (dropout 1/15, 6.7%; Figure 1). Baseline characteristics are shown in Table 2. Mean age was 60.07 ± 6.06 years, with an even sex distribution (7 women, 7 men; 50.0% each). The more affected side was the right in 9 participants (64.3%) and the left in 5 (35.7%). Mean disease duration was 3.36 ± 2.13 years, and the mean Hoehn & Yahr stage was 1.54 ± 0.57, indicating largely mild-to-moderate disease. The baseline UPDRS total score was 24.86 ± 15.98 and the baseline K-MoCA was 19.93 ± 1.91.

Table 2. Baseline demographic and clinical characteristics of study participants (N = 14).

Variable	Mean ± SD or n (%)
Demographic characteristics	
Age (years)	60.07 ± 6.06
Sex — Female	7 (50.0)
Sex — Male	7 (50.0)
More affected side — Right	9 (64.3)
More affected side — Left	5 (35.7)
Disease characteristics	
Disease duration (years)	3.36 ± 2.13
Hoehn & Yahr stage	1.54 ± 0.57
Baseline UPDRS scores	
UPDRS total score	24.86 ± 15.98
UPDRS Part I (mentation/behaviour/mood)	2.57 ± 0.76
UPDRS Part II (activities of daily living)	8.79 ± 7.03
UPDRS Part III (motor)	13.50 ± 10.89
Baseline motor function measures	
Berg Balance Scale	54.14 ± 1.83
Timed Up-and-Go (s)	8.56 ± 2.10
Functional Reach Test (cm)	30.30 ± 5.95
Baseline cognitive function measures	
K-MoCA	19.93 ± 1.91
SVLT immediate recall	17.93 ± 3.34
RCFT immediate recall	13.39 ± 6.60

Abbreviations: SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale; K-MoCA, Korean Montreal Cognitive Assessment; SVLT, Seoul Verbal Learning Test; RCFT, Rey Complex Figure Test.

Primary efficacy outcome and exploratory subscale decomposition (UPDRS)

The registered primary efficacy outcome, the UPDRS total score, fell from 24.86 ± 15.98 at baseline to 20.29 ± 8.71 after the intervention (Table 3; Figure 3). The direction of change favoured improvement and the effect size was moderate ($r = -0.42$), but in this small pilot sample the change did not reach statistical significance ($Z = -1.576$; $p = 0.127$; $p_{adj} = 0.127$). Consistent with the single-arm design, this result is reported as an exploratory clinical signal. It should be read not as evidence of "no effect" but as a moderate-sized reduction whose statistical significance is not established at the present sample size. Inspection of individual trajectories showed that most participants had a lower UPDRS total after the intervention, with a minority stable or increased (Figure 3).

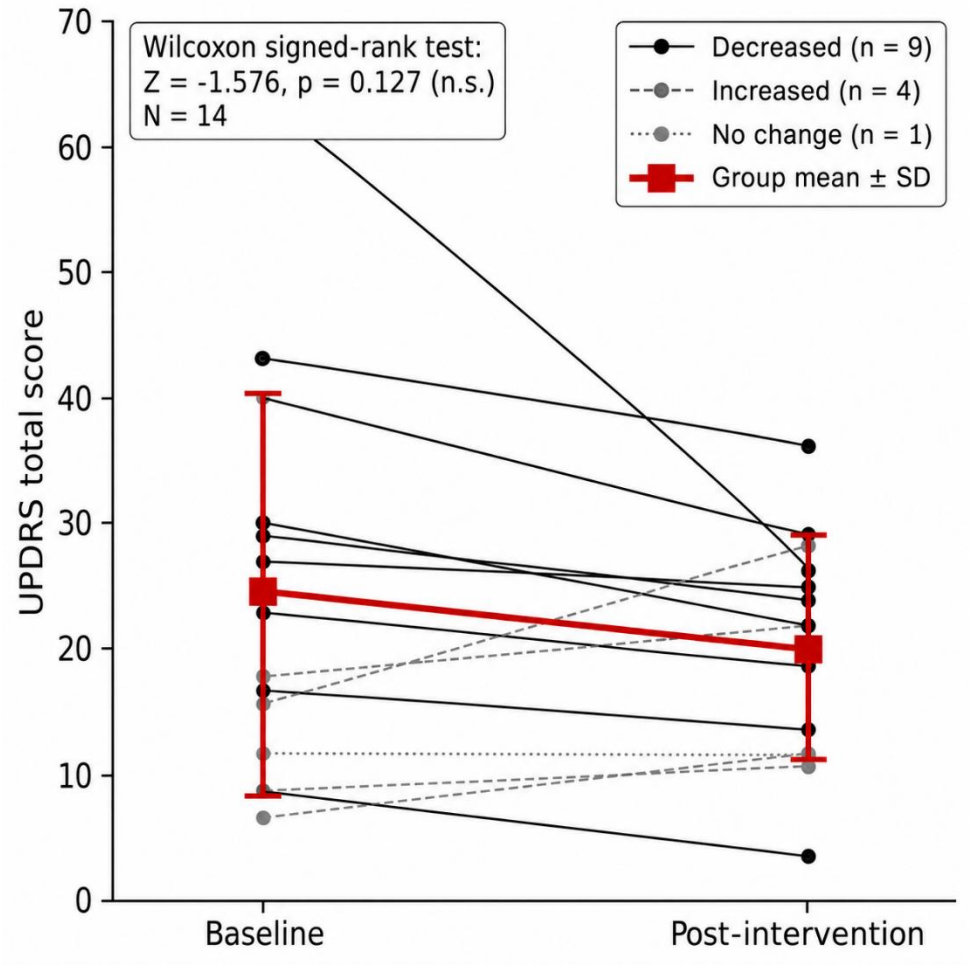


Figure 3. Individual changes in the total Unified Parkinson's Disease Rating Scale (UPDRS) scores before and after intervention

An exploratory decomposition of the total into its subscales indicated that this numerical reduction was driven by the non-motor domains (Table 3). UPDRS Part I (mentation, behaviour, and mood) improved with a large effect size (2.57 ± 0.76 → 1.86 ± 0.95; Z = −2.673; r = −0.71; p = 0.014), and Part II (activities of daily living, ADL) trended toward improvement, again with a large effect size (8.79 ± 7.03 → 6.50 ± 4.38; Z = −1.938; r = −0.52; p = 0.068). Part III (motor) was essentially unchanged (13.50 ± 10.89 → 11.93 ± 5.68; Z = −0.045; r = −0.01; p = 1.000). In other words, the numerical reduction in the total arose from the mentation and daily-living domains rather than from motor function. Because this subscale analysis was a post-hoc, exploratory decomposition that was not part of the pre-specified FDR family (SVLT/RCFT), it is reported without correction and interpreted only as a hypothesis-generating signal.

Table 3. Pre–post changes in the UPDRS total score (registered primary efficacy outcome) with exploratory subscale decomposition (N = 14).

Variable	Baseline	Post-treatment	Z	r	p	p_adj
UPDRS total score (registered primary)	24.86 ± 15.98	20.29 ± 8.71	−1.576	−0.42	0.127	0.127
Exploratory subscale decomposition						
UPDRS Part I (mentation/behaviour/mood)	2.57 ± 0.76	1.86 ± 0.95	−2.673	−0.71 (large)	0.014	—‡
UPDRS Part II (activities of daily living)	8.79 ± 7.03	6.50 ± 4.38	−1.938	−0.52 (large)	0.068	—‡
UPDRS Part III (motor)	13.50 ± 10.89	11.93 ± 5.68	−0.045	−0.01	1.000	—‡

Abbreviations: UPDRS, Unified Parkinson's Disease Rating Scale; p_adj, p-value adjusted by the Benjamini–Hochberg method to control the false discovery rate. Footnote: UPDRS total (= Part I + Part II + Part III) was the pre-specified registered primary efficacy outcome (ClinicalTrials.gov NCT07271927). Values are mean ± standard deviation; Z and r (= Z/√N) were derived from the Wilcoxon signed-rank test (effect size), and p-values are exact two-tailed Wilcoxon. ‡Part I–III represent an exploratory, post-hoc decomposition of the total and were not part of any pre-specified FDR-corrected family; their p-values are uncorrected. Lower UPDRS scores indicate milder symptoms. Given the single-arm design without sham control, all outcomes are reported and interpreted as exploratory clinical signals.

Exploratory motor outcomes

No motor outcome reached significance (Table 4). The BBS was essentially unchanged (54.14 ± 1.83 → 54.21 ± 2.78; r = −0.17; p = 0.527), and the TUG was stable (8.56 ± 2.10 → 8.38 ± 2.15 s; r = −0.147; p = 0.583). The FRT changed from 30.30 ± 5.95 to 28.66 ± 4.27 cm (r = −0.262; p = 0.326). Hand strength on the more affected side did not change: power grip (35.14 ± 11.13 → 35.29 ± 12.07 kg; p = 0.814), three-jaw chuck pinch (8.69 ± 2.77 → 8.50 ± 2.53 kg; p = 0.420), and tip pinch (4.99 ± 2.05 → 4.90 ± 1.89 kg; p = 0.340). The CRTS total score fell from 47.64 ± 15.99 to 43.07 ± 12.00 (r = −0.346; p = 0.195). Motor outcomes were not part of the pre-specified FDR family and are reported without correction; overall, motor and balance function was maintained without deterioration over the 10 weeks.

Table 4. Pre–post changes in exploratory motor function outcomes (N = 14).

Variable	Baseline	Post-treatment	Z	r	p
Berg Balance Scale	54.14 ± 1.83	54.21 ± 2.78	−0.632	−0.17	0.527
Timed Up-and-Go (s)	8.56 ± 2.10	8.38 ± 2.15	−0.549	−0.147	0.583
Functional Reach Test (cm)	30.30 ± 5.95	28.66 ± 4.27	−0.980	−0.262	0.326
Power grip, more affected side (kg)	35.14 ± 11.13	35.29 ± 12.07	−0.236	−0.063	0.814

Variable	Baseline	Post-treatment	Z	r	p
Three-jaw chuck pinch, more affected side (kg)	8.69 ± 2.77	8.50 ± 2.53	−0.806	−0.215	0.420
Tip pinch, more affected side (kg)	4.99 ± 2.05	4.90 ± 1.89	−0.957	−0.256	0.340
CRTS total score	47.64 ± 15.99	43.07 ± 12.00	−1.296	−0.346	0.195

Abbreviations: CRTS, Clinical Rating Scale for Tremor. Footnote: Values are mean ± standard deviation. Z and r (= Z/√N, N = 14) were derived from the Wilcoxon signed-rank test. Lower scores indicate better function for the Timed Up-and-Go and CRTS. For participants with bilateral involvement, hand strength was measured on the more affected side, defined as the side with the lower grip strength at baseline. Motor outcomes were not part of a pre-specified FDR-corrected family and are reported with uncorrected p-values only; no motor outcome reached nominal significance (all $p > 0.05$).

Exploratory cognitive outcomes

Cognitive outcomes are summarised in Table 5, and the clearest signals are plotted in Figure 4.

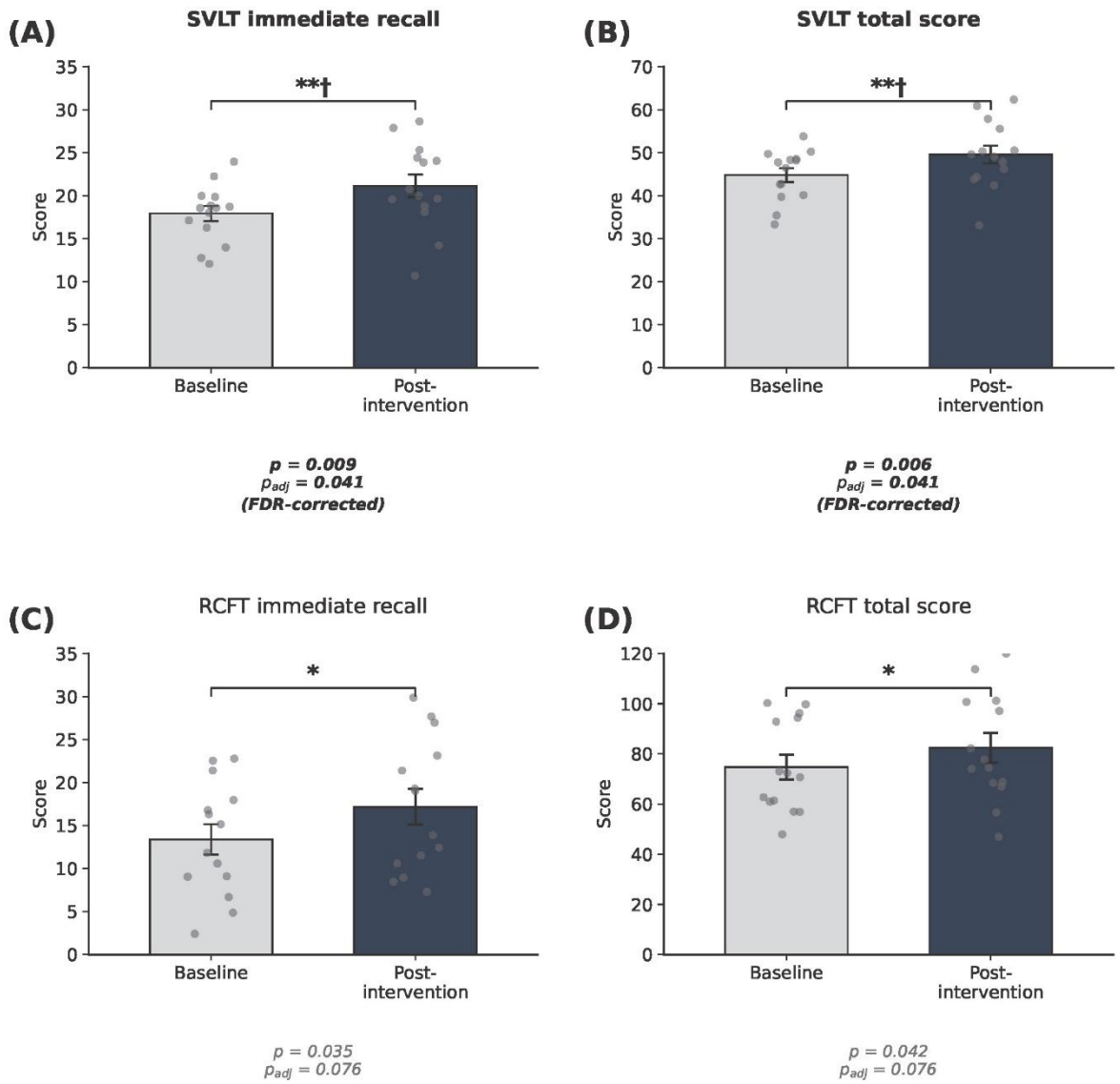


Figure 4. Pre–post changes in cognitive function showing statistically significant differences. SVLT, Seoul Verbal Learning Test; RCFT, Rey Complex Figure Test.

Verbal memory (survived FDR). Within the pre-specified memory family, the most robust improvement was in verbal learning. The SVLT total score rose from 44.79 ± 5.95 to 49.57 ± 7.82, a large effect that remained significant after FDR correction (Z = −2.76; r = −0.74; p = 0.006; p_adj = 0.041). Its constituent, SVLT immediate recall, likewise rose from 17.93 ± 3.34 to 21.14 ± 4.99—again a large effect that survived FDR (Z = −2.59; r = −0.69; p = 0.009; p_adj = 0.041). Because SVLT total = immediate recall + delayed recall + recognition, immediate recall is a component of the total; the two values are not statistically independent and point to a single verbal-learning construct rather than two separate findings. SVLT delayed recall (r = −0.48; p = 0.074; p_adj = 0.111) and recognition (r = −0.42; p = 0.117; p_adj = 0.150) moved in the same direction but did not reach significance.

Visuospatial memory (promising; significant before correction, did not survive FDR). RCFT immediate recall rose from 13.39 ± 6.60 to 17.18 ± 7.74 (Z = −2.11; r = −0.56, large; p = 0.035; p_adj = 0.076), delayed recall from 13.21 ± 6.89 to 16.64 ± 7.91 (Z = −2.07; r = −0.55, large; p = 0.039; p_adj = 0.076), and the total score from 74.75 ± 18.29 to 82.43 ± 22.19 (Z = −2.07; r = −0.55, large; p = 0.042; p_adj = 0.076). All three improved with large effect sizes and were significant before correction but did not survive FDR (all p_adj = 0.076). This is therefore best read not as an absence of effect but as a promising visuospatial-memory signal, accompanied by a large effect size, that requires confirmation. RCFT copy and recognition were unchanged (p = 0.844 and p = 0.192).

Other cognitive domains (outside the FDR family). The DST, TMT, and K-CWST were not part of the pre-specified FDR family and are reported with uncorrected p-values only. None reached significance. In terms of direction, several measures moved toward improvement—for example, TMT completion times shortened (part A 23.97 ± 8.62 → 21.53 ± 9.06 s, p = 0.296; part B 36.87 ± 12.21 → 34.73 ± 25.44 s, p = 0.135) and the number of correct K-CWST responses increased (92.71 ± 20.83 → 94.79 ± 16.88, p = 0.169)—but no claim of significance is made for these directional observations.

Table 5. Pre–post changes in exploratory cognitive function outcomes (N = 14).

Variable	Baseline	Post-treatment	Z	r	p	p_adj
SVLT						
Immediate recall	17.93 ± 3.34	21.14 ± 4.99	−2.59	−0.69 (large)	0.009**	0.041†
Delayed recall	6.36 ± 1.82	6.93 ± 1.94	−1.79	−0.48 (medium)	0.074	0.111
Recognition	20.50 ± 2.28	21.50 ± 1.56	−1.57	−0.42 (medium)	0.117	0.150
Total score	44.79 ± 5.95	49.57 ± 7.82	−2.76	−0.74 (large)	0.006**	0.041†
RCFT						
Copy	28.00 ± 7.27	27.82 ± 7.46	−0.20	−0.05	0.844	0.844
Immediate recall	13.39 ± 6.60	17.18 ± 7.74	−2.11	−0.56 (large)	0.035*	0.076
Delayed recall	13.21 ± 6.89	16.64 ± 7.91	−2.07	−0.55 (large)	0.039*	0.076
Recognition	20.14 ± 1.51	20.79 ± 1.25	−1.31	−0.35 (medium)	0.192	0.216
Total score	74.75 ± 18.29	82.43 ± 22.19	−2.07	−0.55 (large)	0.042*	0.076
DST						
Forward	7.57 ± 1.34	7.64 ± 1.34	−0.24	−0.06	0.813	—‡
Backward	3.64 ± 0.93	4.21 ± 1.58	−1.31	−0.35 (medium)	0.190	—‡
Total score	11.21 ± 1.85	11.86 ± 2.32	−1.26	−0.34 (medium)	0.208	—‡
TMT						
Part A (s)	23.97 ± 8.62	21.53 ± 9.06	−1.10	−0.29 (small)	0.296	—‡
Part B (s)	36.87 ± 12.21	34.73 ± 25.44	−1.54	−0.41 (medium)	0.135	—‡
K-CWST						
Correct responses	92.71 ± 20.83	94.79 ± 16.88	−1.38	−0.37 (medium)	0.169	—‡

Abbreviations: SVLT, Seoul Verbal Learning Test; RCFT, Rey Complex Figure Test; DST, Digit Span Test; TMT, Trail Making Test; K-CWST, Korean Color–Word Stroop Test; p_adj, Benjamini–Hochberg FDR-adjusted p. Significance markers: *p < 0.05; **p < 0.01 (uncorrected, two-tailed Wilcoxon signed-rank test). †p_adj < 0.05 after Benjamini–Hochberg FDR correction within the pre-specified memory family (SVLT and RCFT; 9 measures). ‡Not part of a pre-specified FDR correction family; reported with uncorrected p-values only. Footnote: Values are mean ± standard deviation; Z from the Wilcoxon signed-rank test; r = Z/√N (N = 14). SVLT total score and SVLT immediate recall both remained significant after FDR correction (p_adj = 0.041). Because SVLT total = immediate recall + delayed recall + recognition, immediate recall is a constituent of the total and the two are not statistically independent (a single verbal-learning construct). All cognitive outcomes are reported as exploratory signals given the single-arm pilot design.

Mood

Depressive symptoms on the GDS decreased slightly from 4.57 ± 3.76 to 3.71 ± 3.41 but were not significantly changed (Z = −1.123; r = −0.30; p = 0.320). Given the single-arm design, this is interpreted only as a hypothesis-generating signal.

Safety

The intervention was well tolerated. One participant developed mild localised hyperpigmentation after about three sessions; the investigators judged this to be related to a pre-existing dermatological treatment the participant had been receiving rather than to the study intervention (WB-PBM). The finding was mild, the participant continued both the pre-existing skin treatment and the study intervention, it did not interfere with daily life, and it resolved during the study. No other adverse events were reported, and the events commonly of concern with PBM—skin burns, eye injury, headache, dizziness—did not occur at all. No serious adverse events occurred over the study period, and all 14 completers finished the intervention safely.

Discussion

In this first pilot trial of whole-body PBM in PD, WB-PBM was safe and feasible over a 10-week, 30-session course. The clearest efficacy signal was in verbal memory: the SVLT total score and its constituent immediate recall both improved with large effect sizes and remained significant after Benjamini–Hochberg FDR correction. Visuospatial memory, as assessed by RCFT immediate recall, delayed recall, and total scores, improved with large effect sizes; these improvements were statistically significant before correction but did not survive FDR correction, representing a promising signal that requires confirmation in future studies. The registered primary outcome, the UPDRS total score, showed a non-significant, moderate-sized reduction (r = −0.42). Exploratory subscale analysis indicated that the reduction in total score was driven by non-motor domains: Part I (mentation and mood) showed a large effect, and Part II (ADL) showed a large effect, whereas Part III (motor function) remained unchanged. This pattern is consistent with the study's overall findings, where signals were concentrated in cognitive and non-motor domains while

motor function was maintained. However, because this decomposition was conducted post hoc and was not prespecified, these findings should be considered hypothesis-generating. Although efficacy cannot be established from a single-arm study, the large effect sizes and consistent direction of improvement provide a promising signal that warrants evaluation in a confirmatory trial.

Several PBM-related mechanisms can plausibly be invoked as a backdrop for the memory signals. Increased mitochondrial CCO activity raises ATP synthesis, which supports the neural function and synaptic plasticity involved in memory encoding and retrieval [17–19] and could to some extent offset the ATP/NAD^+ deficiency reported in PD [3, 4]. PBM-induced NO release can improve cerebral perfusion and the delivery of oxygen and nutrients to metabolically demanding regions [20, 21], and the anti-inflammatory effects of PBM may dampen the neuroinflammation entangled with cognitive decline in PD [22–24, 31]. These mechanistic explanations are consistent with our observations but were not directly investigated or demonstrated in the present study.

Whole-body irradiation in this study included the head, trunk, and abdomen and therefore, unlike localized PBM, may have influenced peripheral aspects of PD pathophysiology. In the context of the gut–brain axis hypothesis, which proposes that pathological α-synuclein may originate in the enteric nervous system and ascend to the brainstem via the vagus nerve [7–9], as well as reports of altered gut microbiota in patients with PD following PBM [10], abdominal and truncal irradiation may have contributed indirectly to central symptoms through gut, vagal, or microbiome-mediated pathways. These pathways cannot be easily targeted by transcranial irradiation and may represent a potential advantage of whole-body delivery. However, because gastrointestinal measures, vagal function, and the microbiome were not assessed in the present study, this interpretation remains hypothesis-generating and requires direct investigation.

Our findings are broadly consistent with earlier PBM research in PD and related models. Preclinical studies have reported neuroprotective and cognitive benefits of PBM associated with enhanced mitochondrial activity and reduced oxidative stress [34, 35], while clinical studies of transcranial and abdominal PBM have described cognitive and broader clinical improvements in patients with PD [37–39]. However, in the randomized placebo-controlled study of a transcranial PBM helmet conducted by McGee and colleagues, the total MDS-UPDRS-III score did not significantly differ between the active and sham groups, although improvements were observed in selected motor subitems [43]. Thus, the study did not establish a clear overall motor benefit from the localized transcranial irradiation.

By contrast, improvements in cognitive and non-motor domains have been reported in proof-of-concept studies of transcranial and abdominal PBM [37]. The signals observed in both verbal memory and, at the nominal level, visuospatial memory are compatible with the hypothesis that whole-body irradiation may influence multiple brain regions or physiological systems. Nevertheless, studies that differ in device, population, intervention protocol, and outcome measures cannot be directly compared to establish that whole-body delivery is superior to transcranial PBM for cognition. Addressing this question requires a trial comparing both delivery

approaches within a single study design. Even then, mechanistic interpretations would remain conjectural unless the proposed pathways were directly assessed.

These cognitive signals take on clinical significance when considered against the limitations of current pharmacotherapy. Dopaminergic medications such as levodopa are highly effective for motor symptoms; an acute response alone typically improves the UPDRS Part III score by 30% or more, and this responsiveness is itself used as a diagnostic feature of PD [45]. In contrast, their effects on cognition are limited and inconsistent. According to the dopamine overdose hypothesis, dopamine replacement may overstimulate non-denervated ventral striatal–prefrontal circuits, such that treatment in early PD may improve certain executive functions while impairing other cognitive domains [46]. Consequently, cognitive and memory decline remain important unmet therapeutic needs in PD.

Because all participants maintained stable medication doses throughout the study, the observed memory signals emerged in addition to the effects of existing pharmacotherapy. This finding is consistent with the possibility that WB-PBM, by targeting non-dopaminergic pathways involved in cellular energy metabolism, inflammation, and blood flow, could serve as an adjunct to rather than a replacement for drug therapy. However, because the study did not directly compare WB-PBM with pharmacotherapy, no conclusions can be drawn regarding their relative effects on cognition.

Motor and balance measures, including UPDRS motor items, BBS, TUG, hand strength, and tremor, did not change significantly and remained stable over 10 weeks. This stability should be interpreted cautiously and not as evidence of slowed disease progression. Because motor decline in early PD is generally gradual [44], measurable deterioration would not necessarily be expected over such a short period, particularly while participants remained on stable medication regimens. Short-term stability in an uncontrolled, single-arm cohort therefore cannot support claims of neuroprotection or disease modification.

Considered alongside the randomized trial of transcranial PBM, which likewise found no significant improvement in motor outcomes relative to sham during the study period [43], these findings suggest that any motor effects of PBM, if present, may require a longer intervention period to detect, such as 24 weeks or longer, potentially extending to 6–12 months. The effects of PBM on motor function should therefore be reassessed in longer-term, controlled trials.

This study has several limitations that should be acknowledged. First, as a single-arm pilot with a small sample size (n = 14) and no control group, the observed changes cannot be directly attributed to WB-PBM, as placebo effects, natural symptom fluctuations, and regression to the mean cannot be excluded. Second, repeated neuropsychological testing carries a risk of practice effects, and the two memory assessments differed in the extent to which these effects were mitigated. For the SVLT, the standard alternate word list was administered at V2. Therefore, the verbal-memory improvement, the only cognitive finding that remained significant after FDR correction, is unlikely to be explained by re-exposure to the same words. However, alternate forms do not eliminate procedural learning, as familiarity with the

task format, testing environment, and recall demands may persist across assessments. For the RCFT, the same complex figure was used at both visits. Therefore, practice effects may have contributed to the observed visuospatial-memory improvement. Together with its failure to remain significant after FDR correction, this supports interpreting the RCFT finding as a preliminary, unconfirmed signal. Without a sham-control group, the contribution of residual practice effects cannot be determined. Third, objective biomarkers, such as neuroimaging (fMRI/fNIRS), electrophysiology (EEG), and biochemical markers, were not assessed. Fourth, because the four wavelengths were delivered simultaneously at fixed ratios, the individual contribution of each wavelength could not be determined; additionally, neither regional in vivo dosimetry nor transcranial fluence was measured (Table 1). Fifth, the single-center design and absence of long-term follow-up limit the generalizability of these findings and preclude evaluating their durability.

These results provide a clear rationale for proceeding to a confirmatory trial. The pilot study met its primary aims of evaluating safety and feasibility. Furthermore, the improvement in verbal memory, which demonstrated a large effect size that remained significant after FDR correction despite the small sample, represents a notable signal warranting further investigation. The next step is to evaluate this signal in a larger, adequately powered, multicenter, randomized, sham-controlled trial. In parallel, wavelength-specific and dose–response studies could help optimize the protocol, while objective biomarkers (including neuroimaging, electrophysiological measures, and biochemical markers) could help clarify underlying mechanisms. The intervention and follow-up periods should also be extended to 6–12 months or longer to assess potential changes in motor outcomes. Effect-size estimates from the present study, particularly the large verbal memory effect, can directly inform sample size and power calculations for future confirmatory trials.

Finally, during structured interviews at follow-up visits, several participants spontaneously reported falling into deep sleep during treatment sessions or experiencing more regular bowel habits. Although these reports reflect participants' lived experiences, they were not prespecified outcomes and were not systematically assessed using validated instruments; consequently, they should not be interpreted as definitive findings of this study. Nevertheless, because similar observations were noted by multiple participants, they warrant systematic evaluation in future research. Slow-wave sleep is linked to the clearance of pathological proteins via AQP4-mediated glymphatic flow [41, 42], while gastrointestinal function is closely tied to the gut–brain axis implicated in PD pathophysiology [10]. Future trials should therefore include prespecified measures of sleep (utilizing polysomnography or actigraphy) as well as gastrointestinal function and gut microbiota, incorporating objective assessments where feasible.

Conclusions

In this pilot study, whole-body photobiomodulation was safe and feasible in patients with Parkinson's disease, with one mild adverse event judged unrelated to the study device and no serious adverse events. Verbal memory, as assessed by the SVLT, improved with a large effect size and remained significant after FDR correction,

representing the clearest positive signal observed in the study. Visuospatial memory, as assessed by the RCFT, also showed a promising large effect signal that requires confirmation. The registered primary outcome, the total UPDRS score, showed a non-significant reduction of moderate magnitude.

The improvement in verbal memory is particularly noteworthy because it occurred in a cognitive domain not adequately addressed by current pharmacotherapy, which remains primarily focused on motor symptoms. However, given the single-arm, uncontrolled design, these findings should be interpreted as hypothesis-generating signals and preliminary effect-size estimates rather than evidence of efficacy. Nevertheless, the demonstration of safety and feasibility, together with the large verbal memory effect, provides a rationale and preliminary design basis for a randomized, sham-controlled trial to evaluate the therapeutic potential of WB-PBM in PD.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board of Pusan National University Yangsan Hospital (IRB No. 23-2024-005), and the clinical trial plan was approved by the Ministry of Food and Drug Safety (MFDS approval No. 1730; initial approval 24 May 2024, amendment approval 22 January 2025). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before enrolment.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available because of patient privacy and confidentiality restrictions under the IRB approval and the Personal Information Protection Act of the Republic of Korea. Reasonable requests may be directed to the corresponding author and will be considered subject to IRB approval and the establishment of an appropriate data transfer agreement.

Competing interests

The device used in this study was provided by Hue Light Co., Ltd., and partial research funding was received from the same company. However, all scientific procedures—study design, data collection, analysis, and manuscript preparation—were conducted independently by the research team, and Hue Light Co., Ltd. had no involvement in the research content, interpretation of results, or publication decisions.

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This study received partial funding from Hue Light Co., Ltd. The funder had no role in the study design, data collection and analysis, interpretation, or manuscript preparation.

Authors' contributions

SYL and YIS conceptualized the study and designed the whole-body photobiomodulation trial protocol. SYL and JB developed the methodology, including selection of the outcome measures and the pre-specified statistical analysis plan, and jointly performed the formal analysis comprising the Wilcoxon signed-rank tests, effect-size estimation and the Benjamini–Hochberg false discovery rate correction. J-HL performed the neurological diagnosis, confirmed eligibility against the diagnostic criteria, and carried out the clinical evaluation of participants. SYL, JB and CA conducted the investigation, administering the intervention sessions, performing the clinical and neuropsychological assessments at baseline and after 30 sessions, and monitoring adverse events. JB curated the data, including verification and quality control of the assessment dataset. SYL wrote the original draft and prepared the figures and tables. YIS critically reviewed and edited the manuscript, supervised the conduct of the trial, and acquired the funding. All authors critically reviewed the manuscript for important intellectual content, and read and approved the final version.

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List of abbreviations

ADL: activities of daily living; AE: adverse event; AQP4: aquaporin-4; ATP: adenosine triphosphate; BBB: blood–brain barrier; BBS: Berg Balance Scale; CCO: cytochrome c oxidase; CRTS: Clinical Rating Scale for Tremor; DST: Digit Span Test; EEG: electroencephalography; FDR: false discovery rate; fMRI: functional magnetic resonance imaging; fNIRS: functional near-infrared spectroscopy; FRT: Functional Reach Test; GDS: Geriatric Depression Scale; IRB: institutional review board; K-CWST: Korean Color–Word Stroop Test; K-MoCA: Korean Montreal Cognitive Assessment; LED: light-emitting diode; MFDS: Ministry of Food and Drug Safety; NAD^+: nicotinamide adenine dinucleotide; NO: nitric oxide; PBM: photobiomodulation; PD: Parkinson's disease; RCFT: Rey Complex Figure Test; SAE: serious adverse event; SVLT: Seoul Verbal Learning Test; TMT: Trail Making Test; TUG: Timed Up-and-Go; UPDRS: Unified Parkinson's Disease Rating Scale; WB-PBM: whole-body photobiomodulation.

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Figure legends

Figure 1. CONSORT-based participant flow diagram. Fifteen patients were assessed and enrolled, one discontinued (relocation, unrelated to the intervention), and 14 completed the 30-session course and were included in the analysis. Intervention: WB-PBM, 20 min per session, three times weekly for 10 weeks, at 660/810/850/930 nm.

Figure 2. The whole-body photobiomodulation therapy device (WB-PBM-M01, Hue Light Co., Ltd.) and its control unit, as used in the study.

Figure 3. Individual changes in the total UPDRS score before and after the intervention. Each line represents one participant, and the bold line with error bars shows the group mean ± SD. Most participants decreased (n = 9), one was unchanged (n = 1), and a minority increased (n = 4). Wilcoxon signed-rank test: $Z = -1.576$, $p = 0.127$ (n.s.); $N = 14$.

Figure 4. Pre–post changes in the cognitive outcomes with the clearest signals: (A) SVLT immediate recall, (B) SVLT total score, (C) RCFT immediate recall, (D) RCFT total score. Bars show group means (light, baseline; dark, post-intervention) with individual values overlaid as dots; error bars represent the standard error of the mean (SEM). N = 14. Significance markers: *p < 0.05; **p < 0.01 (uncorrected, two-tailed Wilcoxon signed-rank test); †p_adj < 0.05 after Benjamini–Hochberg FDR correction. Panels A and B (SVLT immediate recall and SVLT total score) carry both ** and †, indicating that they remained significant after FDR correction (p_adj = 0.041); panels C and D (RCFT immediate recall and total score) carry * only, being significant before correction but not surviving FDR (p_adj = 0.076).