Photobiomodulation for cognitive dysfunction (Brain Fog) in post-COVID-19 condition: a randomized double-blind sham-controlled pilot trial

Summary

Background

Post-COVID-19 condition (PCC) affects millions globally, with cognitive dysfunction (“brain fog”) impairing daily functioning in up to 88% of patients. No effective treatments exist for PCC-related cognitive impairment. Photobiomodulation (PBM), a non-invasive therapy delivering near-infrared light, enhances mitochondrial function and reduces neuroinflammation, showing promise in neurological disorders. This study aimed to evaluate the efficacy and safety of home-based intranasal and transcranial PBM (itPBM) for PCC cognitive dysfunction.

Methods

This randomized, double-blind, sham-controlled pilot trial in the USA (ClinicalTrials.govNCT05857124) enrolled 43 adults (18–65 years) with PCC cognitive symptoms ≥12 weeks post-infection. Participants were randomized 1:1, stratified by age (<45 vs ≥ 45 years), using computer-generated assignment to 8 weeks of daily 20-min itPBM, 6 days per week, with the Vielight Neuro RX Gamma device or sham, targeting the brain's default mode network, followed by 4 weeks of observation. Participants, investigators, and assessors were masked to group assignment. The primary outcome was mean change in Creyos cognitive battery composite score at Day 56. Secondary outcomes included fatigue, quality of life, and safety. Analyses used mixed-model repeated measures in the per-protocol population.

Findings

The trial was completed, with 43 participants randomized (23 active, 20 sham) and 41 analyzed (21 active, 20 sham). They were recruited between July 5, 2023, and September 1, 2024. Active itPBM improved composite cognitive scores more than sham (mean difference 0.043, 95% CI −0.007 to 0.092, $p = 0.088$), with significant gains in participants <45 years (prespecified but exploratory, $p = 0.028$). Attention tasks improved consistently ($p < 0.050$ at multiple timepoints). Secondary outcomes mobility favored sham ($p = 0.007$), and fatigue also favored sham. No serious adverse

events occurred; compliance was high (median 55 days, interquartile range 2 days).

Interpretation

Home-based itPBM is safe and feasible, showing potential cognitive benefits for PCC brain fog, particularly in younger adults. Larger trials are needed to confirm efficacy and optimize parameters.

Keywords

1. Post (long)-COVID-19
2. Cognitive dysfunction
3. Brain fog
4. Photobiomodulation

Research in context

Evidence before this study

We searched PubMed and Google Scholar for studies on photobiomodulation (PBM) for cognitive impairment in post-COVID-19 condition (PCC) from January 2020 to March 2025, using terms “photobiomodulation,” “long COVID,” and “cognitive dysfunction.” No randomized controlled trials were found, but open-label studies suggested PBM improved cognitive function in PCC and related conditions like traumatic brain injury and dementia. A prior trial showed that PBM targeting the upper respiratory system accelerated recovery in acute COVID-19 cases, including mental clarity improvements, prompting exploration of brain-targeted PBM for PCC brain fog. Given shared pathophysiology, such as neuroinflammation and mitochondrial dysfunction; preclinical data indicated PBM enhances mitochondrial function, reduces

oxidative stress, and modulates microglial activity, aligning with PCC's mechanisms and supporting its potential for cognitive recovery.

Added value of this study

This pilot randomized, double-blind, sham-controlled trial provides the first controlled evidence of itPBM's efficacy for PCC cognitive impairment, showing significant improvements in attention and composite cognitive scores in younger adults (<45 years).

Implications of all the available evidence

PBM is a safe, feasible intervention with potential to alleviate PCC cognitive dysfunction, particularly in younger patients. Larger and longer trials are needed to confirm efficacy, optimize parameters for broader populations, and explore its role in global health systems.

Introduction

Post-COVID-19 condition (PCC), or long COVID, affects millions globally, with cognitive dysfunction (“brain fog”) reported in up to 88% of patients, impairing attention, memory, and executive function.[1–3] This debilitating symptom disrupts daily functioning, yet no effective treatments exist.[4]

PCC brain fog is believed to arise from neuroinflammation, blood–brain barrier compromise, and disrupted default mode network (DMN) connectivity, compounded by mitochondrial dysfunction.[5–8] Neuroinflammation, driven by cytokine storms and microglial activation, compromises the blood–brain barrier, leading to cortical thinning and myelin dysregulation, impairing attentional and memory

networks.[6,7,9] These collective neurological disruptions contribute to persistent cognitive deficits.[10]

No pharmacologic treatments target PCC cognitive symptoms, and while cognitive rehabilitation is under study, evidence-based therapies are urgently needed.[4,11]

Photobiomodulation (PBM), or low-level light therapy, is a promising non-invasive strategy. PBM delivers near-infrared light (600–1100 nm wavelengths) to modulate biological activity. Between 600 and 850 nm, PBM enhances mitochondrial function, increases ATP production, reduces oxidative stress, and modulates inflammation.[12] PBM delivering 40 Hz gamma oscillations could reduce amyloid burden and modify microglial activity for neuroprotection, and targeting the DMN may aid the recovery of impaired cognition.[13,14] An open-label study suggests transcranial PBM (tPBM) improves cognitive function in PCC.[15]

Intranasal PBM (iPBM) offers a complementary route of brain stimulation, as illumination through the nasal cavity delivers light to the cribriform plate, potentially influencing cerebrospinal fluid dynamics, and to the olfactory bulb, which has direct projections to the hippocampal and thalamic regions involved in memory and cognition.[16,17] Despite using relatively low irradiance, iPBM achieves high relative intracranial irradiance efficiency.[17] In contrast, transcranial PBM (tPBM) primarily targets cortical regions; in this study, stimulation was directed toward hubs of the DMN, a network consistently disrupted in cognitive impairment,

including PCC-related brain fog.[14] Both modalities, iPBM and tPBM, have been shown to modulate neural activity in deep and cortical brain regions, albeit through distinct anatomical routes.

By combining these two modalities (itPBM), the intervention leverages the strengths of each approach: enhancing mitochondrial metabolism, improving neurovascular coupling, and modulating oscillatory brain networks across both deep and cortical structures. This dual engagement offers broader network coverage that may be especially relevant to PCC pathophysiology.[16–18] Importantly, the combined approach may also address the complex, multifactorial pathophysiology observed in related conditions such as traumatic brain injury.[16] A recent dosimetry study further supports the efficiency of the intranasal route, highlighting its high relative power efficiency compared with transcranial illumination.[17]

A previous trial of another PBM device for acute COVID-19 demonstrated that PBM targeting the upper respiratory system accelerated overall recovery, including improvements in mental clarity.[19] These findings informed the current study's targeted approach, using the Vielight Neuro RX Gamma device to deliver itPBM with 810 nm near-infrared light, pulsing at 40 Hz to the DMN hubs to address cognitive dysfunction.

We conducted a randomized, double-blind, sham-controlled

pilot clinical trial to evaluate the efficacy of home-based itPBM in adults with PCC-related cognitive dysfunction. The primary aim was to assess improvements in cognitive performance, with secondary outcomes including fatigue, quality of life, and safety.

Methods

Study design

This prospective, randomized, double-blind, sham-controlled pilot clinical trial in the USA (Supplementary 1: Protocol), reported per CONSORT guidelines, evaluated the efficacy of itPBM for cognitive impairment in PCC. The home-based study was conducted remotely using an electronic data capture (EDC) system, with all assessments performed online. The protocol received IRB approval from Biomedical Research Alliance of New York LLC Institutional Review Board (BRANY IRB, # 211750), followed ethical guidelines, and was registered at ClinicalTrials.gov (NCT05857124).

Key design elements of the protocol were informed by prior PBM research. Specifically, the wavelength of 810 nm was selected because it has been the most consistently effective in neurological PBM studies, demonstrating substantial tissue penetration and mitochondrial effects.[12] The protocol incorporated intranasal PBM, adding to transcranial delivery

and increasing cerebral engagement through dual pathways.[18] A pulse frequency of 40 Hz was chosen based on evidence linking gamma-band stimulation to improved memory and cognition.[13] Finally, light placement targeted hubs of the default mode network (DMN), a network disrupted in PCC and other cognitive disorders.[14] These considerations provided the mechanistic rationale for the protocol design.

This pilot study targeted 36 participants but enrolled 43 to assess preliminary efficacy, safety, and feasibility, ensuring adequate power for exploratory analyses. Participants were randomized 1:1 to active itPBM or sham equivalent for 8 weeks (56 days), followed by a 4-week observation period. Blinding was maintained for participants, investigators, and assessors.

Participants

Adults aged 18–65 meeting World Health Organization (WHO) PCC criteria with cognitive symptoms ≥12 weeks post-COVID were eligible.[1] WHO criteria were operationalized via physician diagnosis of cognitive dysfunction and documented SARS-CoV-2 infection (positive PCR/antigen test or clinical diagnosis). English proficiency and internet access were required. Exclusion criteria included neurological or psychiatric conditions (e.g.,

dementia, uncontrolled depression, significant brain injury, unstable illness, pregnancy, photosensitivity, seizure risk, or use of cognition-impairing substances (Supplementary 1: Protocol)).

Sex and race/ethnicity were self-reported using U.S. Census categories to assess representativeness. All procedures, including screening and device shipment, were remotely managed. Electronic informed consent was obtained through Castor eConsent.

Randomization and blinding

Randomization used computer-generated treatment assignment, stratified by age (<45 vs ≥ 45 years) because younger and older adults were hypothesized to differ in neuroplasticity and PBM response. Active and sham devices were identical visually with similar auditory cues and identified by randomization codes. Study personnel and participants were blinded to device allocation.

Intervention

Participants used the Vielight Neuro RX Gamma v2 (LED-based itPBM device; Vielight Inc., Toronto, Canada). For readability, we refer to this unit as 'Neuro RX Gamma' throughout. The active device delivered 810 nm near-infrared light at 40 Hz intranasally and transcranially via

LEDs targeting DMN hubs (Fig. 1a and b). The device uses six transcranial and one intranasal LED to optimize cerebral perfusion and neural oscillation modulation, with the 40 Hz pulse rate chosen to enhance gamma entrainment.[18] Sessions lasted 20 min daily, six days per week for 8 weeks. Supplementary document (Supplementary 2) contains detailed itPBM device parameters (wavelength, frequency, duty cycle, irradiance and total energy (dosage) per session).

Fig. 1 **a: The intervention itPBM device, Vielight Neuro RX Gamma. b: The near infrared (NIR) LEDs target the hubs of the default mode network (DMN) and cerebellum**.

Participants were trained using a 10-min video tutorial and written manual to ensure consistent home use. Participants recorded session completion and were asked to avoid other treatments or maintain stable medication doses. Sham

devices mimicked operation without light delivery, using internal sensors to disable output on scalp contact. Compliance was monitored via daily electronic diaries and device usage logs, with reminders sent for missed sessions.

Outcome measures

Primary outcome

The primary efficacy endpoint was the composite change in cognitive performance from baseline to Day 56, measured from the mean of seven tasks from the Creyos Research cognitive battery (formerly Cambridge Brain Sciences). These tasks assessed key cognitive domains: short-term memory (Monkey Ladder, Token Search, Paired Associates), executive function and reasoning (Spatial Planning, Rotations), attention (Feature Match), and visuospatial processing (Polygons). Online testing with the Creyos battery demonstrated comparable strength to comprehensive in-person assessment of cognitive performance.[20] Table 1 sets out the purposes of each task. Each task generated quantitative scores (higher = better), and a global composite score was calculated by averaging Z-scores across all Creyos tasks at each time point. Brain fog in long COVID was operationalized as impairment across these domains, with improvements in the composite score interpreted as cognitive recovery.

Cognitive task	Cognitive domain assessed

Spatial planning	Planning Ability
Monkey ladder	Visuospatial Short-term Memory
Rotations	Reasoning/Executive Function
Feature match	Attention/Concentration
Paired associates	Episodic Memory
Token search	Short-term Memory
Polygons	Visuospatial Processing

Table 1

Key cognitive tasks—components of primary endpoints.

Secondary outcomes

Secondary outcomes included additional Creyos cognitive tasks (Grammatical Reasoning, Spatial Span, Digit Span, Odd One Out, and Double Trouble) to capture broader cognitive function beyond the primary composite. Quality of life was assessed using the EQ-5D-5L, which evaluates mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analog scale rating overall health from 0 to 100. Fatigue was measured using the 10-item Fatigue Assessment Scale (FAS), a validated instrument in chronic illness populations, with lower scores indicating less fatigue.[21] Cognitive symptoms were evaluated using the PDQ-20, which assesses perceived difficulties in memory, attention, planning, and organization. Symptom burden was captured using the modified Symptom Burden Questionnaire (MSBQ), which measures PCC-related symptoms such as fatigue and memory problems.

Safety

Adverse events (AEs) were self-reported in diaries and categorized per MedDRA (see Supplementary 3 Adverse Events table numbers).

Data collection

All data were collected electronically via Castor secure portal at baseline, Days 14, 28, 56 (endpoint), and 84 (for follow up). Participants maintained daily diaries for device usage, AEs, and health changes. Study staff sent reminders to ensure compliance.

Fig. 2 presents the schedule of interventions and assessments. All entries were time-stamped and monitored for completion by the study team.

Fig. 2 **Study timeline depicting enrollment, itPBM/sham administration, interim assessments, and follow-up**.

Statistical analysis

This pilot study targeted 36 participants but enrolled 43 to assess preliminary efficacy, safety, and feasibility, ensuring adequate power for exploratory analyses. The Safety Population, equivalent to the Intent-to-Treat (ITT) population, included all randomized participants who received the device. The Per-Protocol (PP) Population included those with valid Creyos data at baseline and adhered to the protocol, excluding subjects with major protocol deviations.

Cognitive task outcomes were standardized to z-scores and percentiles using age-adjusted norms; treatment effects are reported as least-squares (LS) mean changes with 95% confidence intervals. Here, “percentile” denotes the normative scoring metric of the Creyos battery, not the percentage of participants improved.

All least-squares (LS) means and treatment effects (overall and by age subgroup) were estimated from a single, prespecified mixed-model for repeated measures (MMRM) fitted by restricted maximum likelihood. We used an unstructured within-subject covariance matrix with the Satterthwaite approximation for denominator degrees of freedom and assumed missing at random (MAR) for intermittent missingness; no ad hoc imputation was performed within the MMRM. Fixed effects were treatment

group, visit (categorical), age stratum (<45 vs ≥ 45 years), and treatment-by-visit interactions; the corresponding baseline value of each outcome was included as a covariate. The MMRM was applied to continuous outcomes (e.g., Creyos composite, EQ-5D index, EQ-5D VAS). From this unified model, we obtained LS-mean changes from baseline and their 95% confidence intervals for each treatment–age subgroup at each visit (Fig. 3a–c). Age-stratified analyses were prespecified and exploratory; p values are two-sided and nominal (no multiplicity adjustment). See Supplementary 4 for full model specification and Supplementary 5 for ITT sensitivity results.

Fig. 3 **a: Primary endpoint by age stratum, showing the change in the least-squares (LS) mean difference in composite cognitive score between active and sham groups by age group on day 56**. Each bar or column represents the LS mean difference, includes 95% confidence intervals (CI) bars and p values. Age-stratified analyses are prespecified but exploratory; p values are nominal (no multiplicity adjustment). **b: Change in composite cognitive score from baseline (Active-Sham) by age group in LS mean.** The columns display the change from baseline in composite cognitive score by treatment group and age stratum across the time points (Days 14, 28, 56, 84) with 95% confidence intervals (CI) bars. Statistical significance (∗) of p = 0.0280 on day 56 was demonstrated by the <45-year-old age stratum. The remaining timepoints showed the trend although not statistically

significant improvement. Age-stratified analyses are prespecified and exploratory; p values are nominal (no multiplicity adjustment). **c: Component cognitive task outcomes by age group at day 56.** The bar chart displays the LS mean differences (Active-Sham) for each component cognitive task at Day 56, grouped by age, the blue columns for participants under 45 years and the magenta-colored columns for those 45 years and older. Error bars represent the 95% CI of the LS mean difference. At the primary endpoint, Feature Match showed a statistically significant improvement in the ≥45-year subgroup (∗, p = 0.034), but this isolated, exploratory finding did not alter the overall interpretation—on the composite cognitive score, the pattern of effects favored the <45-year cohort. Age-stratified analyses are prespecified but exploratory; p values are nominal (no multiplicity adjustment).

The EQ-5D index and VAS were treated as continuous measures and analyzed using MMRM, consistent with their scale properties. In contrast, domain-level EQ-5D-5L scores (Mobility, Self-care, Usual activities, Pain/Discomfort, Anxiety/Depression) are ordinal and were therefore considered exploratory. In this pilot, no additional rank-based sensitivity analysis was performed due to the small sample size, and we acknowledge this as a limitation. Domain-level results are presented descriptively and interpreted with caution.

No adjustments for multiple comparisons were applied for secondary outcomes or timepoints, consistent with the exploratory nature of this pilot study. Effect sizes (Cohen's d) were calculated for the primary composite endpoint overall and by age subgroup to aid interpretation of clinical relevance. For secondary outcomes, continuous measures (e.g., EQ-5D index, VAS, FAS, PDQ-20, MSBQ) were analyzed using ANCOVA for change from baseline to Day 56,

while EQ-5D domain-level scores were presented as exploratory ordinal outcomes. Analyses were conducted using SAS v9.4 and R v4.1.

Role of funding source

The funding source, Vielight Inc. provided the study devices and sponsored the trial and through author-employees played a large role in the study design, and writing of the report, but played no role in data collection, analysis and interpretation.

Results

Participant disposition and baseline characteristics

Participants were recruited between July 5, 2023 and September 1, 2024. Of 90 screened individuals, 47 were excluded (10 failed cognitive dysfunction criteria, 29 lost to follow-up, 8 withdrew). Forty-three participants were randomized (23 active, 20 sham); 41 were analyzed (21 active, 20 sham) in the per-protocol population. Thirty-three (76.7%) were female. Two active group participants were excluded from PP analysis due to incomplete Day 56 assessments or non-compliance. Most (98%) completed Day 84 follow-up (Fig. 4).

Fig. 4 **CONSORT flow diagram detailing recruitment, allocation, follow-up, and analysis.** It illustrates the screening of 90 individuals, exclusion of 47 before randomization, and the flow through to final efficacy analysis with 41 participants. No sham participants were lost to follow-up; two active participants were excluded due to protocol deviations.

Table 2 summarizes baseline characteristics. Mean age was 40.6 years (SD 10.6), with 76.7% female and 93% White, non-Hispanic. The active/sham groups were each balanced for age, sex, and Body Mass Index (BMI). Sex differences were not considered in the endpoint analyses, justified by their balance at baseline (Supplementary 3 Table S1).

Characteristic	Active itPBM (n = 23)	Sham (n = 20)	Total (N = 43)	p value (between groups)
Sex—Female	17 (73.9%)	16	33	0.641

		(80.0%)	(76.7%)	
Sex—Male	6 (26.1%)	4 (20.0%)	10 (23.3%)	–
Age (years)	39.2 ± 10.9	42.2 ± 10.3	40.6 ± 10.6	0.365
Age <45 years	17 (73.9%)	14 (70.0%)	31 (72.1%)	0.778
Age ≥45 years	6 (26.1%)	6 (30.0%)	12 (27.9%)	–
Race—White	22 (95.7%)	18 (90.0%)	40 (93.0%)	0.557
Race—Black	1 (4.3%)	1 (5.0%)	2 (4.7%)	–
Race—Other[a]	0 (0%)	1 (5.0%)	1 (2.3%)	–
Ethnicity—Hispanic/Latino	1 (4.3%)	2 (10.0%)	3 (7.0%)	0.473
Ethnicity—Non-Hispanic	22 (95.7%)	18 (90.0%)	40 (93.0%)	–
BMI (kg/m^2)	27.1 ± 5.3	26.4 ± 4.8	26.8 ± 5.1	0.684
Current smoker	0 (0%)	0 (0%)	0 (0%)	–
Former smoker	8 (34.8%)	2 (10.0%)	10 (23.3%)	0.082[b]

Table 2

Demographics and baseline characteristics (Safety Population, n = 43).

Values are n (%) or mean ± SD. No significant differences between active and sham population within the age groups.

a

“Other” race category includes participants who identified with a race not listed (e.g., multi-racial).

b

Fisher's exact test for former smoker status.

Cognitive outcomes (Primary Endpoint)

By Day 56 (primary end timepoint and end of treatment), the

composite cognitive score—representing the aggregate of seven Creyos tasks—improved more in the active itPBM group (LS mean +0.050) than in sham (+0.007), with a between-group difference of 0.043 (95% CI −0.007 to 0.092; p = 0.088). Although not statistically significant overall, this trend favored active itPBM (Fig. 3a and b, Table 3). The overall effect size for this difference was small (Cohen's d ≈ 0.28), consistent with a modest but potentially meaningful improvement in a condition with no established treatments.

Cognitive outcome	Active itPBM vs Sham: outcome at day 56	p value
Composite cognitive score (all ages)	Greater improvement in Active (mean increase vs baseline higher than Sham)	0.088 (n.s.)
Composite cognitive score (<45 subgroup)	Active significantly > Sham (notable improvement in Active group)	0.028[a]
Feature match task (attention)	Active significantly > Sham overall at Day 28 and Day 84; not significant overall at Day 56 (see[b]).	<0.05[b]
Other individual cognitive tasks (6 tasks)	No significant group differences (trends favoring Active on some tasks)	n.s.

Table 3

Primary cognitive outcome results at Day 56 (change from baseline) in the Per-Protocol population.

a

Statistically significant difference favoring Active itPBM in participants <45 years old.

b

Statistically significant difference favoring Active itPBM in the overall group for the Feature Match task at Day 28 (p = 0.019), Day 56 (p = 0.133), Day 84 (p = 0.017).

Prespecified, age-stratified exploratory analyses indicated that the pattern of effects favored the <45-year cohort on

the composite cognitive score at Day 56; these subgroup findings are exploratory and not multiplicity-adjusted. In this group, active itPBM improved significantly more than sham (LS mean + 0.082 vs + 0.023; difference 0.059, 95% CI 0.007–0.111; p = 0.028), corresponding to a moderate effect size (Cohen's d ≈ 0.44). No significant difference was seen in participants ≥45 years (LS mean + 0.026 vs + 0.016; p = 0.873), with a negligible effect size (Cohen's d ≈ 0.05). These trajectories across time, with follow-up to Day 84, are shown in Fig. 3b and detailed in Supplementary 3.

Because age stratification was pre-specified in the protocol for randomization and included as a covariate in the primary analysis model, these findings were expected to be clinically relevant. However, the study was not powered for definitive subgroup conclusions, and the age-related differences should be regarded as exploratory and hypothesis-generating.

When the seven tasks were analyzed individually, Feature Match showed a significant between-group difference overall at Day 28 (p = 0.019) and Day 84 (p = 0.017); at Day 56, significance was observed only in the ≥45-year subgroup (p = 0.034), while the <45-year subgroup was not significant (p = 0.171) (nominal p values; see Fig. 3c and Table 3).[22] Other tasks, such as Spatial Planning and Paired Associates, showed non-significant trends favoring active

itPBM, while Rotations and Token Search improved in both groups without clear separation. Monkey Ladder and Polygons showed minimal change.

Intention-to-Treat (ITT) sensitivity analysis

In addition to the per-protocol (PP) analysis, we conducted an ITT sensitivity analysis including all 43 randomized participants. For the two active participants with missing Day 56 data, we conservatively imputed no change from baseline (0 improvement). This assumption biases against the active group. The ITT comparison was highly consistent with the PP analysis: the active-minus-sham difference in composite score at Day 56 remained approximately 0.04 ($p \approx 0.09$). Thus, the direction and magnitude of the treatment effect were unchanged by inclusion of all randomized participants (See Supplementary 5 for PP vs ITT comparison).

Secondary outcomes

Secondary outcome analyses showed mixed results that did not consistently align with the primary cognitive endpoint. On the EQ-5D-5L, sham participants younger than 45 years demonstrated greater improvement in Mobility at Day 56 ($p = 0.007$; Supplementary 3 Table S2; Table 4), while no significant between-group differences emerged in the remaining domains (Self-care, Usual activities, Pain/Discomfort, Anxiety/Depression). The EQ-5D index and

visual analog scale improved similarly in both groups, and domain-level scores were treated as exploratory ordinal measures. Fatigue outcomes, assessed using the FAS, generally favored the sham group, with older participants showing significant improvement on items such as “I get tired very quickly” and “I am bothered by fatigue” ($p < 0.05$). For cognitive symptoms measured by the PDQ-20, younger participants receiving active itPBM reported modest memory gains, whereas older participants exhibited some worsening after treatment cessation (Supplementary 3 Table S6). Symptom burden, assessed using the MSBQ, decreased slightly in both groups but did not reveal consistent between-group differences (Supplementary 3 Table S7).

Outcome measure	Between-Group comparison (Active itPBM vs Sham)	p value
EQ-5D-5L mobility (function)	Sham improved more (greater reduction in mobility limitations)	0.007
EQ-5D-5L other domains (Self-care, Usual activities, Pain/Discomfort, Anxiety/Depression)	Favoring active itPBM but not significant	>0.05 (NS)
EQ-5D VAS (overall health)	No significant difference (trend: sham higher VAS)	0.10 (NS)
Fatigue (FAS total score)	No significant difference (fatigue improved in both groups)	0.67 (NS)
FAS key items (fatigue perception)	Sham better on some (less “bothered by fatigue”)	<0.05 on select items
Cognitive symptoms (PDQ-20 total)	No significant difference overall	0.75 (NS)
PDQ-20 key items	Mixed: Active better on some (younger	<0.05 on

(memory, attention)	memory), Sham better on others (older concentration)	select items
Symptom Burden (MSBQ total)	No significant difference	>0.05 (NS)
MSBQ specific symptoms	No significant differences (trend toward sham reporting less fatigue, cognitive issues and 'Memory' in Sham was superior at Day 56 (p = 0.011) in older adults)	>0.05 (NS)

Table 4

Summary of secondary outcome results at Day 56 (change from baseline).

Note: itPBM, intranasal and transcranial photobiomodulation; NS, not significant. EQ-5D index and VAS were analyzed as continuous outcomes using MMRM. Domain-level EQ-5D-5L scores (Mobility, Self-care, Usual activities, Pain/Discomfort, Anxiety/Depression) are ordinal and were treated as exploratory. No rank-based sensitivity analysis was performed in this pilot. For Mobility, a negative change indicates improvement; at Day 56 the significant effect (p = 0.007) favored Sham over Active.

Table 4 summarizes the secondary outcome results at the primary endpoint (Day 56), with full numeric data provided in Supplementary 3.

Overall summary for outcomes

Overall, while subjective outcomes such as mobility and fatigue favored sham, the protocol-defined primary endpoint—objective cognitive performance—was improved by active itPBM, reaching statistical significance in participants under 45 years at Day 56. This indicates that the study successfully met its main objective of evaluating itPBM's potential to alleviate brain fog in PCC. The age-specific effect highlights where efficacy is most evident and guides future protocol optimization, but does not detract from the

central finding that itPBM can potentially improve cognition in younger adults with long COVID.

Adverse events and tolerability

No serious adverse events (AEs) occurred. Common AEs included mild headache (7/43, 16.3%) and skin irritation (6/43, 14.0%), resolving without intervention (Supplementary 3, Table S9). One active participant reported nasal pressure discomfort, alleviated with saline gel. Treatment adherence was high (median 45/48 sessions), with high compliance (median 55 days, interquartile range 2 days).

Discussion

This pilot randomized controlled trial provides encouraging evidence that home-based intranasal and transcranial photobiomodulation (itPBM) is a safe and feasible intervention for cognitive impairment in long COVID. Active itPBM improved composite cognitive scores more than sham ($p = 0.088$), with significant gains in participants <45 years ($p = 0.028$), likely due to enhanced neuroplasticity, as 40 Hz gamma oscillations strengthen synaptic connectivity in neural networks.[23] Older adults may require higher itPBM doses to achieve similar effects.[24]

The protocol incorporated age stratification (<45 vs. ≥45

years) at randomization to ensure treatment balance, and age stratum (<45, ≥45) was included as a covariate in the primary mixed-model analysis, acknowledging its potential influence on cognitive recovery. Although younger participants demonstrated greater improvement, the protocol designated age subgroup analyses as exploratory. Thus, the observed age effect should be interpreted with caution—as hypothesis-generating rather than confirmatory—given the limited sample size. Larger, adequately powered trials are needed to determine whether age moderates treatment response.

The between-group mean difference of 0.043 on the composite cognitive score is modest. On a standardized measure such as the Creyos composite, a 4.3% difference (95% CI –0.7% to 9.2%) on Day 56 corresponds to a small improvement in performance and, by itself, may not translate into a large functional change for an individual patient. Nonetheless, given that PCC currently has no established treatments for cognitive dysfunction, even small objective gains could be clinically meaningful if reproducible in larger studies. We therefore emphasize that the observed effect is best regarded as hypothesis-generating, warranting confirmation in adequately powered trials before clinical conclusions can be drawn.

We also conducted an ITT sensitivity analysis to assess

potential bias from the two active participants who did not complete Day 56 assessments. By imputing no change from baseline for these participants, the active-minus-sham difference remained consistent with the per-protocol analysis (≈0.04, p ≈ 0.09). This confirms the robustness of the primary finding and indicates that the observed effects were not attributable to dropout bias.

Among the seven individual tasks, only Feature Match (visual attention and pattern recognition) showed consistent statistically significant group differences. Other tasks showed smaller, non-significant trends favoring active itPBM. The significant improvements in the Feature Match task across groups align with itPBM's modulation of gamma oscillations, known to enhance attentional processing.[23] This finding is consistent with prior brain stimulation work linking gamma-frequency stimulation to attentional gains in both preclinical and human studies.

Younger participants' greater responsiveness may reflect higher baseline neuroplasticity, enabling more robust neural repair. itPBM's anti-inflammatory and mitochondrial-enhancing effects likely mitigate PCC's neuropathophysiology, restoring cortical function.[25,26]

Secondary outcomes were mixed and did not consistently align with the primary endpoint. For example, sham itPBM participants reported greater improvements in mobility on the EQ-5D-5L (p = 0.007), and fatigue outcomes (FAS)

generally favored sham. Similarly, perceived cognitive difficulties on the PDQ-20 improved in both groups with no significant overall difference, aside from isolated item-level changes by age subgroup. The MSBQ also showed slight improvements in both groups without significant between-group differences. These discordant findings indicate that the objective cognitive gains observed with active itPBM were not mirrored by patient-reported functional outcomes, particularly for mobility and fatigue. Two explanations may account for this discrepancy: (1) symptom perception bias, whereby participants in the active group, experiencing clearer cognition, may have become more aware of other persisting symptoms such as fatigue; and (2) an energy trade-off, whereby improvement in one domain (cognition) could temporarily detract from another (physical energy or mobility).[27] We emphasize that these interpretations are speculative, and we acknowledge this discordance as a limitation of the study. Larger and longer trials incorporating biomarkers are needed to reconcile objective and subjective outcomes.

Through the PDQ-20 assessments, the younger participants reported better memory (e.g., recalling names), whereas older participants were more forgetful after treatment cessation. This suggests that itPBM may have temporarily arrested neurodegenerative-like processes in older PCC patients, which resumed once therapy ended.[28] Evidence from dementia and chronic traumatic encephalopathy (CTE)

studies indicates that resuming itPBM can potentially reverse progressive degeneration,[29,30] reinforcing the biological plausibility of our findings.

Open-label studies, such as Bowen et al., have reported improvements in “brain fog” and fatigue with transcranial or whole-body PBM in COVID-19 survivors, providing preliminary evidence for its potential role in PCC.[15] Our randomized controlled trial extends this early work by introducing a sham comparator and focusing specifically on cognitive endpoints.

Intranasal PBM has also shown promise for other post-COVID symptoms, most notably olfactory dysfunction. In a Brazilian multicenter case series, intranasal PBM improved anosmia in COVID-19 survivors, demonstrating feasibility and neurological benefits through this route.[31] This supports the plausibility of intranasal delivery in modulating neurological pathways beyond cognition.

Similarly, recent reviews of transcranial PBM in acquired brain injury have highlighted its capacity to reduce neuroinflammation, enhance mitochondrial function, and promote neuroplasticity, with evidence of improved cognitive and behavioral outcomes.[32] These findings reinforce the translational rationale for applying combined itPBM to the multifactorial pathophysiology of PCC, which shares features with acquired brain injury, such as disrupted network connectivity, oxidative stress, and impaired neurovascular regulation.

Together, these studies strengthen the biological and clinical plausibility of our findings: itPBM may improve cognition in PCC by addressing convergent mechanisms observed in related neurological disorders.

Compared to cognitive rehabilitation's mixed efficacy or unproven pharmacological treatments, itPBM offers a non-invasive, safe alternative, though efficacy is more predictable in younger adults. While the primary endpoint was met as specified, the pattern of results underscores the need for larger, fully powered trials to validate multi-domain cognitive benefits. Clinical Implications: Even modest improvements in attention may meaningfully enhance daily functioning in PCC patients, supporting the potential utility of itPBM in clinical care.

The clinical implications of this trial are that cognitive gains, particularly in attention, could enhance daily functioning and work productivity for PCC patients. Continuous treatment is suggested for the older patients to avoid some potential post-treatment memory decline. Supporting this suggestion, itPBM is delivered through a home-based device. Its application offers a scalable, cost-effective intervention, potentially integrating with cognitive rehabilitation to enhance functional recovery.

This study has several limitations. As a pilot, the trial was exploratory and not powered to detect definitively clinically

meaningful differences. The sample size was chosen to observe preliminary efficacy trends, assess feasibility, and evaluate a range of outcome measures; any positive findings should therefore be regarded as hypothesis-generating and interpreted with caution. The 8-week treatment duration may not capture longer-term recovery trajectories. Remote assessments introduced the potential for variability due to environmental distractions. The predominantly White (93%) and female (76.7%) cohort limits generalizability, and more diverse recruitment will be important in future trials. Sex/gender-based analyses were conducted despite the small sample size, with limited generalizability. The absence of biomarkers (e.g., EEG, inflammatory markers) restricted mechanistic insight into potential treatment effects. Finally, while the EQ-5D index and VAS were analyzed as continuous outcomes using MMRM, the domain-level EQ-5D-5L scores are ordinal and were therefore treated as exploratory. A sensitivity analysis using rank-based or ordinal regression methods was not performed in this pilot but will be important in larger studies.

As future directions, larger trials should explore alternative itPBM parameters (e.g., higher dose) for older adults and incorporate EEG and inflammatory biomarkers to elucidate mechanisms. Diverse populations and sex/gender analyses are critical to ensure equitable outcomes, addressing the current study's demographic limitations.

Contributors

LL, NH, MVB, AP, JL, ZA, AP designed the study and wrote the protocol. KO and JR were the clinical investigators; AB managed data collection and participant follow-up; LL, NH, AB, MVB and RZ accessed and verified the data; MVB performed statistical analyses and interpretation. JD was the medical monitor; RZ provided supervision on the study quality, objectivity, and contributed to statistical analyses and interpretation; LL wrote the main manuscript; all authors contributed to the manuscript content and approved the final version. ZA was unresponsive so signatures could not be obtained.

Data sharing statement

De-identified participant data and a data dictionary will be available upon request after publication, subject to approval of a proposal and a signed data access agreement. Data will be accessible via the corresponding author for 5 years post-publication.

Declaration of interests

All authors received compensation from Vielight either as employees or consultants/advisors. We declare no other competing interests.

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Appendix A Supplementary data (5)

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Supplementary material (5)