

**Use of either Transcranial or Whole-Body
Photobiomodulation Treatments improve COVID-19 Brain
Fog**

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Use of either Transcranial or Whole-Body Photobiomodulation Treatments improve COVID-19 Brain Fog

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Abstract

There is increasing recognition of post-COVID-19 sequelae involving chronic fatigue and brain fog for which Photobiomodulation (PBM) therapy has been utilized. This open-label, pilot, human clinical study examined the efficacy of two PBM devices namely a light bed (660 and 850 nm, 35.7pJ/cm², 7.9 Einstein) for whole body (WbPBM) and a helmet (1070 nm, 27.2 p.J/cm² or 6 Einstein) for transcranial (tPBM) over a four-week period, with 12 treatments in two separate groups (n = 7 each). Subjects were evaluated with a comprehensive neurocognition array including Montreal Cognitive Assessment (MoCA), digit symbol substitution test (DSST), trail-making tests A and B, physical reaction time (PRT), and quantitative electroencephalograph system (WAVi) at visits 1, 6, and 12. Each approach for PBM delivery, individually, was associated with improvement in cognition, executive functions, and neuromuscular coordination (p < 0.05). This study outlines the benefits of utilizing PBM therapy to treat long COVID brain fog.

INTRODUCTION

COVID-19 has had a devastating impact on global public health. However, the major brunt of this pandemic has affected patients with underlying chronic disease and other morbidities (obesity, diabetes, etc.), secondary to the cytokine storm and acute respiratory distress syndrome (ARDS).(1,2) COVID-19 has been managed with vaccinations, monoclonal antibodies, immunomodulators, and anti-viral agents. However, the global population is now dealing with the major effects of post-pandemic complications termed 'long COVID'.(3-5) Two specific symptoms that stand out are general fatigue, and cognitive dysfunction, also termed 'brain fog'. (6-8) There are no directed therapeutics for this complication developed to date.

Given the relatively high sensitivity of the coronavirus to physicochemical modalities, several forms of light treatments have been attempted. A popular approach is using Ultraviolet ionizing radiation extrinsically or a combination of dye and light for systemic use, termed Photodynamic therapy (PDT). (9-11) In contrast, biophotonics treatments directed at shoring up the antimicrobial host immune response and reducing the inflammatory cytokine storm damage are termed Photobiomodulation (PBM) Therapy. (12-14) A rationalized combination of the two treatments is conceivable but requires careful application. (15) The presence of multisystem dysfunctions noted with COVID-19 has raised significant interest in both targeted (eg; transcranial) and transdermal, whole-body treatments and how these treatments can be effectively employed.(12,14,16-19) There has been tremendous progress in our understanding of the photobiological mechanisms of PBM. (20) Three discrete sites of interactions, namely the mitochondrial cytochrome C oxidase, cell membrane receptors and transporters, and extracellular activation of a growth factor, TGF- β . These mechanisms appear to be cell and tissue response-specific that may often be concurrently involved.

There have been some recent publications outlining the evidence for the use of PBM treatments for acute COVID-19 complications.(17,21-31) The use of PBM in **COVID-19** management was prompted by its efficacy in relieving Acute respiratory distress syndrome (ARDS). (32-36) PBM treatments have focused on mitigating acute pulmonary inflammatory complications that have been supported by several controlled lab and animal studies. (37-39) The use of multiple inflammatory stimuli in these studies is

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3 particularly worth emphasizing as this suggests that PBM appears to target the underlying
4 pathophysiological process. Although, severe acute phase SARS-CoV-2 infections are not
5 known to directly cause neurological damage; the long-term effects of systemic
6 inflammation and vascular dysfunction could indirectly contribute to neurological damage.
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8 The role of the ACE2 receptor in mediating viral attachment in a wide range of cells in the
9 cardiovascular and immune systems has been noted. (40,41) The ACE2/Ang (1–9) receptor
10 is essential in maintaining blood pressure and vasodilation. With infection, the virus binds
11 ACE2 and disables this protective mechanism, and can result in a cytokine storm,
12 coagulation, increased vascular permeability, and acute lung injury. (42-44) Persons with
13 pre-existing ACE2 deficiencies, such as those with diabetes or hypertension, are at even
14 greater risk. In the brain, loss of ACE2 impairs autoregulation of blood pressure and
15 endothelial cell function. (45) Cognitive alterations have been observed in patients who
16 have recovered from the acute phase of COVID-19. These include concentration memory,
17 executive function, information processing, and language. (46)

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19 A major question in the field has been the delivery of PBM dose to precise
20 anatomical sites for optimal efficacy. There have been elegant, controlled animal studies
21 with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-induced Parkinson's disease
22 model as well as MOG (myelin oligodendrocyte glycoprotein)-induced experimental
23 autoimmune encephalitis (EAE) model of Multiple Sclerosis. (47,48) These groups utilized
24 whole-body systemic PBM treatments and observed reduced clinical symptoms,
25 biochemical, molecular, and histological changes demonstrating therapeutic efficacy.
26 Strikingly, the MPTP-induced PD model in rodents and primates demonstrated equivalent
27 efficacy when either systemic whole body or transcranial PBM treatments were
28 performed.(49) In contrast, studies on depression, Alzheimer's and traumatic brain injury
29 have utilized transcranial treatments with PBM helmets or headsets. (50-52) The striking
30 clinical efficacy of PBM treatments in supportive cancer care have also highlighted the
31 equivalence of intraoral and extraoral treatments. (53-55) The growing interest in
32 extending PBM treatments to the broader supportive cancer care complications such as
33 tissue fibroses, malaise, fatigue, cancer cachexia, and cancer brain has led to practical
34 clinical considerations of systemic, multiorgan treatments for optimal benefit. These

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3 treatments have now become clinically viable with large light (LED) panels and beds that
4 are cost effective for both providers and patients.
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6 Hence, this pilot study was aimed at examining the effectiveness of a PBM bed and
7 helmet in relieving long COVID symptoms. As a proof of principle study, a longitudinal
8 study design with active treatments was employed. A battery of qualitative neurocognitive
9 and quantitative EEG assessments were performed with PBM treatments. The PBM
10 treatments were delivered three times a week for 4 weeks using either a [light bed for whole](#)
11 [body \(WbPBM\) or helmet for transcranial \(tPBM\) therapy](#).
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18 **MATERIALS AND METHODS**

19 ***Clinical study design:*** The study design was approved by the Institutional Review Board
20 (QuietMind Foundation 06092022). Subjects were recruited who presented with cognitive
21 decline (brain fog) of at least 5 months duration with minimal or no improvement. Subjects
22 were recruited from word of mouth and social media (Facebook) announcement. All
23 subjects had a positive PCR test for COVID-19 and had recovered from the acute phase of
24 infection. Subjects under the age of 18, prisoners, military recruits, persons with other
25 disorders that might result in cognitive impairment, persons not competent to give informed
26 consent, and other vulnerable persons were excluded. [Subjects described their symptoms](#)
27 [with statements such as slow thinking, poor articulation, lack of recall-especially numbers,](#)
28 [slow reactions, forgetting names and directions, clumsy, easily confused, losing train of](#)
29 [thought, mentally overwhelmed, and mentally fatigued.](#) Participants received 3 treatments
30 a week (48 hours between treatments), for 4 weeks. Neuropsychological testing was
31 performed on the day of the first treatment, before the first treatment. Post- testing was
32 performed after the [6th treatment and again after the 12th treatment.](#) A total of 16 subjects
33 were initially recruited for the study along with 5 age- and education-matched healthy
34 controls for baseline evaluations.
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50 ***Cognitive Assessments:*** Subjects were evaluated using the Montreal Cognitive Assessment
51 (MoCA), digit symbol substitution test (DSST), trail-making tests A and B, physical
52 reaction time (PRT) at visits 1, 6, and 12 [before the PBM treatments.](#) The MoCA is a 30-
53 items test that assesses language, memory, visual [and spatial thinking, reasoning, and](#)
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3 orientation skills. It is thought to be more useful for mild cognitive impairment than the
4 mini-mental status exam, and normal subjects usually score 25 to 30. (56) The digit symbol
5 substitution test (DSST) assesses cognitive impairment.(57) Nine-digit symbol pairs are
6 listed at the top of a page, followed by a list of digits. Under each of the digits, the subject
7 records the corresponding symbol. The number of correct answers in 90 seconds is
8 recorded. A higher score indicates improved function. Trail-making tests are useful for
9 assessing visual attention and task switching.(58) The Trails A test consists of numbers
10 only, where each number is inside a circle randomly arranged on a page. The task is to
11 draw a line to connect the correct number/circle in ascending order, as quickly as possible.
12 The Trails B test consists of numbers and letters, each inside a circle randomly placed on
13 the page. The task is to draw a line switching between connecting a number and then
14 connecting a letter, in ascending order of each, as quickly as possible. There are 25 circles.
15 Shorter test completion times indicate improved cognitive performance. The Physical
16 reaction time test consists of the time to respond to an auditory signal response on a
17 computer-based software.

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29 ***Cognitive Assessments using Electroencephalography:*** The EEG was recorded using the
30 WAVi system (WAVi Boulder, CO, USA) sampled at 250hz and bandpass filtered between
31 0.5-30hz. Electrodes were placed according to the 10-20 system using a cap with 19
32 electrodes and 2 reference electrodes on the earlobes. Electrode impedances below 30 ohms
33 were established prior to testing. The P300 event-related potential measures the stimulus-
34 evoked subject response with the EEG that is best assessed over the parietal lobe. The time
35 to response (lower P300T) and amplitude (voltage) of current (higher P300V) reflect
36 improved cognitive function in this test. The Eriksen Flanker tasks examine the ability of
37 the subject to suppress inappropriate responses in a particular context representing
38 cognitive processing in the presence of distracting information (noise). The target is
39 flanked by non-target stimuli corresponding to either the same direction as the target
40 (congruent flankers), or opposite response (incongruent flankers), or neither (neutral
41 flankers). This assessment is focused on the anterior cingulate cortex (ACC) in the frontal
42 lobe, which is responsible for a wide variety of autonomic functions. The time to response
43 (lower Flanker T) and amplitude (voltage) of current (higher Flanker V) reflect improved
44 cognitive functions.

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5 **Photobiomodulation (PBM) Treatments:** All subjects received either the whole body
6 PBM treatment in the NovoTHOR (THOR photomedicine, London, UK) light pod or
7 Neuroradiant 1070 helmet (Neuronic Devices Ltd., Ireland). Subjects were randomly
8 allocated to receive either PBM treatment using a digital randomizer program. **Treatments**
9 **were given thrice a week for 4 consecutive weeks (Figs. 1A and B).** The NovoTHOR light
10 pod is designed to deliver photons from light-emitting diodes (LEDs) of 660 nm and 850
11 nm (100% duty cycle, CW) to the whole body (WbPBM) simultaneously at the treatment
12 surface irradiance (power density) of 25 mW/cm² for 14 min for a fluence of 21 J/cm²,
13 photon fluence of 35.8 p.J/cm² and 7.9 Einstein. The Neuroradiant 1070 is a LEDs helmet
14 device for transcranial (tPBM) that emits photons at a wavelength of 1070 nm (100% duty
15 cycle, CW) at the tissue surface irradiance of 27 mW/cm² for a fluence of 22.7 J/cm²,
16 photon fluence of 27.2 p.J/cm² and 6 Einstein.

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26 **Statistical Analysis:** Data was organized in Excel (Microsoft) and analyzed using
27 Pearson's linear regression for correlation and two-tailed, paired T-test for pre- and post-
28 treatment comparison using GraphPad Prism (v9.0.0, GraphPad Inc, San Diego CA).

31 32 33 **RESULTS**

34 **Study demographics**

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36 Of the 16 subjects initially recruited for the study, one subject failed to report for testing
37 and treatment. Another subject withdrew from the study after a single session due to the
38 inability to participate in repeated treatments and evaluations schedule. Fourteen subjects
39 completed all evaluations and treatments, 10 females and 4 males with ages ranging from
40 37-42 years, with a median age of 56 years, and an equal number (7 each) received either
41 PBM treatment (**Fig. 1C**). All subjects reported improvements in their symptoms and no
42 adverse (anticipated or unanticipated) were encountered during the course of the study.
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50 **Neuropsychological Cognitive assessments**

51 *Montreal Cognitive Assessments (MoCA):* **Assessing the cognitive status pre-PBM**
52 **treatment (Day 1) versus post-PBM treatments (Day 12) noted significant improvements**
53 **in MoCA scores following tPBM (27 ± 1.53 to 29.42 ± 0.97 , $n = 7$, $p = 0.052$), wbPBM**
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(25 ± 3.21 to 29.14 ± 1.21 , $n = 7$, $p = 0.052$), and combined PBM group (26 ± 2.6 to 29 ± 1 , $n = 14$, $p < 0.0005$) (**Fig. 2A-C**). This improvement was not affected by gender (Female 3.5 ± 2.5 , $n = 10$ versus Male 3.2 ± 2.6 , $n = 4$, $p = 0.88$). In contrast, younger subjects below 65 years (4.6 ± 2.3 , $n = 9$, $p < 0.005$) appear to benefit more significantly from PBM treatments compared to subjects above 65 years (1.4 ± 1.1 , $n = 5$). However, this could be ascribed to unequal recruitment numbers in this study which needs to be investigated further.

Digital Symbol Substitution Test: This test combines visual neurocognitive perception, processing, and digital execution. Assessments of subjects at pre-PBM treatment (Day 1) versus post-PBM treatments (Day 12) noted significant successful completion scores following tPBM (50.28 ± 8.34 to 64.71 ± 4.11 , $n = 7$, $p = 0.0028$), wbPBM (42.14 ± 13.56 to 57.57 ± 10.47 , $n = 7$, $p = 0.036$), and combined PBM group (46.2 ± 11.6 to 61.6 ± 8.2 , $n = 14$, $p < 0.0005$) (**Fig. 2A-B, D**). This test did not demonstrate any statistically significant difference among gender (Female 14.4 ± 8.1 , $n = 10$ versus Male 18 ± 12 , $n = 4$, $p = 0.61$) or age (< 65 years 16 ± 10.3 , $n = 9$ versus > 65 years 14.4 ± 7.3 , $n = 5$, $p = 0.74$).

Trail A and B test: This test also assesses the combination of visual neurocognitive perception, processing, and digital execution. Assessments of subjects at pre-PBM treatment (Day 1) versus post-PBM treatments (Day 12) noted reduction in time to successful completion of the Trail A following tPBM (65.43 ± 14.59 to 43.43 ± 7.11 , $n = 7$, $p = 0.0062$), wbPBM (60.29 ± 27.09 to 52 ± 16.93 , $n = 7$, $p = 0.508$), and combined PBM group (62.9 ± 21.1 to 45.6 ± 9.82 sec, $n = 14$, $p < 0.0005$) (**Fig. 2A-B, E**). Although the wbPBM demonstrated a reduced test completion time, it was not statistically significant. Similarly, the Trail B test analysis demonstrated reduced completion times following tPBM (111.86 ± 50.67 to 58.57 ± 13.07 , $n = 7$, $p = 0.0318$), wbPBM (102.43 ± 39.16 to 64.14 ± 14.25 , $n = 7$, $p = 0.043$), and combined PBM group (107.1 ± 43.8 to 61.3 ± 13.5 sec, $n = 14$, $p < 0.0005$) (**Fig. 2A-B, F**). This test also did not demonstrate any statistically significant difference for either Trail A or B test scores among gender (Female -11.7 ± 9.9 sec and -36.1 ± 44.7 sec, $n = 10$ versus Male -31 ± 18.4 sec and -70.2 ± 26.6

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3 sec, $n = 4$, $p = 0.12$ and 0.11 paired T-test respectively), age (< 65 years -16.3 ± 15.4 sec
4 and -45.8 ± 50 sec, $n = 9$ versus > 65 years -18.8 ± 16 sec and -46 ± 29.1 sec, $n = 5$, $p =$
5 0.79 and 0.99 paired T-test respectively).
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10 *Physical reaction time:* This test assesses the combination of auditory neurocognitive
11 perception and processing followed by digital execution. Assessments of subjects at pre-
12 PBM treatment (Day 1) versus PBM post-treatments (Day 12) noted reduction in response
13 time following tPBM (0.36 ± 0.12 to 0.26 ± 0.03 , $n = 7$, $p = 0.069$), wbPBM (0.36 ± 0.05
14 to 0.32 ± 0.07 , $n = 7$, $p = 0.23$), and combined PBM group (0.36 ± 0.09 to 0.29 ± 0.6 sec,
15 $n = 14$, $p < 0.005$ paired T-test) (Fig. 2A-B, G). Although the data from all the three groups
16 noted reduced reaction times and the combined group showed statistical significance,
17 neither tPBM nor wbPBM individually noted any statistical significance. The trend for
18 improved response times did not appear to be affected by age (< 65 years -0.08 ± 0.1 sec,
19 $n = 9$ versus > 65 years -0.05 ± 0.5 sec, $n = 5$, $p = 0.56$). However, a statistically significant
20 difference was noted with gender (Female -0.92 ± 0.1 sec, $n = 10$ versus Male -0.02 ± 0.01
21 sec, $n = 4$, $p = 0.04$ paired T-test). However, the increased improvement in females could
22 be ascribed to increased subject numbers ($n = 10$ versus 4) that need to be investigated
23 more carefully.
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36 **Quantitative EEG assessments**

37 *P300 – Time and Voltage:*

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39 The functional EEG assessments demonstrated a significant reduction in P300T following
40 tPBM (0.307 ± 0.03 to 0.277 ± 0.01 sec, $n = 7$, $p = 0.028$), wbPBM (0.3 ± 0.03 to $0.29 \pm$
41 0.04 sec, $n = 7$, $p = 0.583$), and combined PBM group (0.3 ± 0.03 to 0.28 ± 0.06 sec, $n =$
42 14 , $p < 0.005$ paired T-test) (Fig. 3A-B, C). While both tPBM and combined PBM group
43 noted statistically significant reduction in P300V, wbPBM noted a similar reduction but
44 was not statistically significant. Concurrently, an increase in P300V was noted following
45 tPBM (12.34 ± 5 to 16.43 ± 4.2 mV, $n = 7$, $p = 0.125$), wbPBM (9.34 ± 6.13 to 15.71 ± 4.3
46 mV, $n = 7$, $p = 0.046$), and combined PBM group (10.8 ± 5.6 to 15.8 ± 4.2 mV, $n = 14$, p
47 < 0.0005) (Fig. 3A-B, D). In contrast to P300V, the P300T noted consistent increase in
48 wbPBM and combined PBM group that was statistically significant while tPBM increase
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3 was not. This assessment did not demonstrate any statistically significant difference in
4 either P300T or P300V among gender (Female -0.017 ± 0.37 sec and 5.34 ± 3.4 mV, $n =$
5 10 versus Male -0.42 ± 0.05 sec and 4 ± 3.3 mV, $n = 4$, $p = 0.37$ and 0.52 respectively), or
6 age (< 65 years -0.02 ± 0.03 sec and 5.24 ± 2.97 mV, $n = 9$ versus > 65 years -0.03 ± 0.05
7 sec and 4.4 ± 4.12 mV, $n = 5$, $p = 0.71$ and 0.71 respectively).
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10 11 12 13 *Flanker – Time and Voltage:*

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15 The functional EEG assessments demonstrated a reduction in FlankerT following tPBM
16 (0.52 ± 0.08 to 0.45 ± 0.08 sec, $n = 7$, $p = 0.1$), wbPBM (0.56 ± 0.09 to 0.47 ± 0.07 sec, $n =$
17 7, $p = 0.045$), and combined PBM group (0.54 ± 0.08 to 0.45 ± 0.07 sec, $n = 14$, $p <$
18 0.0005) (Fig. 3A-B, E). While both wbPBM and combined PBM groups noted statistically
19 significant reduction in FlankerT, wbPBM noted a similar reduction but was not
20 statistically significant. An increase in FlankerV was noted following tPBM (13.14 ± 9.7
21 to 20.87 ± 12.2 mV, $n = 7$, $p = 0.215$), wbPBM (7.61 ± 2.89 to 13.1 ± 3.53 mV, $n = 7$, $p =$
22 0.008), and combined PBM group (10.4 ± 7.4 to 16.8 ± 9.6 mV, $n = 14$, $p < 0.005$) (Fig.
23 3A-B, F). Thus, the FlankerV noted statistically significant increase in wbPBM and
24 combined PBM groups, while the increase evident in the tPBM group was not statistically
25 significant. No statistically significant differences in either P300T or P300V among gender
26 (Female -0.099 ± 0.47 sec and 6.37 ± 6.65 mV, $n = 10$ versus Male -0.052 ± 0.06 sec and
27 6.4 ± 5.14 mV, $n = 4$, $p = 0.22$ and 0.99 paired T-test respectively), age (< 65 years $- 0.10$
28 ± 0.05 sec and 6.67 ± 7.02 mV, $n = 9$ versus > 65 years $- 0.07 \pm 0.65$ sec and 5.86 ± 4.52
29 mV, $n = 5$, $p = 0.41$ and 0.80 paired T-test respectively).
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43 **Correlation among neuropsychological test results and qEEG measures**

44 There were no significant correlations between the TrA, TrB, and MoCA assessments and
45 quantitative brain reaction times and voltage. The DSST, however, did correlate with P300
46 voltage ($r = 0.37$, $p = 0.0006$), Flanker voltage ($r = 0.40$, $p = 0.0002$) and Flanker time ($r =$
47 -0.29 , $p = 0.0064$) respectively.
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DISCUSSION

The COVID-19 pandemic has had far-reaching implications on [many](#) aspects of global society, including public health, access to medical care, the global economy, policy, and politics. It has also demonstrated our tremendous capabilities in biomedicine, such as vaccination, monoclonal antibodies, immunomodulators, and anti-viral agents. While it is anticipated that SARS-CoV-2 infections will become less prevalent and less severe, its long-term impact on the global health of approximately 200 million known cases is yet to be fully confronted.(59-61) One of the most serious of these is emerging reports on cognitive problems among those with pre-existing neurological conditions such as Parkinson's Disease, Alzheimer's Disease, and mild cognitive impairment. [Cognitive impairment has been recognized as a part of chronic illness resulting in immobility and social isolation.](#)

Transcranial Photobiomodulation (PBM) treatments with near-infrared light have been noted to penetrate deeper anatomical sites effectively. (62-64). The use of PBM therapy has shown significant therapeutic efficacy in acute and chronic brain conditions such as Parkinson's, Alzheimer's disease, Dementia, mild cognitive impairment, traumatic brain injury, Post-traumatic stress disorder, gulf war illness, and depression, among many others.(48,65-79) Besides these disease models with compromised neurocognition, there have been clear demonstrations of the ability of PBM to improve memory, attention, emotion and executive functions.(80-84) An improvement in local circulation and modulation of Cytochrome C oxidase activity in the discrete parts of the brain, especially the pre-frontal cortex, following PBM treatments that have been proposed as potential therapeutic mechanisms. (85-87) There has been significant progress in our understanding of the molecular mechanisms of PBM [that have been noted](#) three discrete cellular sites. The first PBM mechanism described involves intracellular mitochondrial cytochrome C oxidase that transiently increases ATP and ROS generation following photoabsorption.(88,89) The second site of PBM interactions has been the description of specific photoresponsive cell membrane receptors and transporters such as non-visual Opsins, and TRPV-1, among others. (90-94) Finally, an extracellular PBM mechanism involving direct activation of latent TGF- β 1 involving a redox-mediated conformational change has been described. (95) [The role of these specific pathways in enabling improved](#)

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3 neuroplasticity and reducing neuroinflammation contribute to improve neurocognition has
4 been previously demonstrated. (96-98)

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6 In designing this study, our major hypothesis was that transcranial treatments with
7 a 1070 nm PBM device would be more effective in alleviating COVID brain fog than whole
8 body PBM treatments with a 660-850nm bed.(66) In contrast to our expectations, both
9 devices performed equivocal and the bed in fact appears to have more, albeit statistically
10 insignificant, improvement. The clinical safety of these transcranial PBM treatments has
11 been demonstrated. (16) A recent human clinical study demonstrated the utility of a whole
12 body, transdermal PBM treatment in COVID patients. (18) This motivated us to compare
13 the two PBM delivery modalities in this pilot study focusing on potential mitigation of
14 multiple long COVID symptoms. It has been well documented that assessment of outcomes
15 are usually a combination of musculoskeletal and neurocognitive functions.(99-101) In
16 fact, a recent study noted several similarities between chronic fatigue syndrome and post-
17 COVID-19 sequelae on physical fatigue and cognitive impairment sequelae in terms of
18 physical fatigue, poor sleep quality, increased anxiety, depressive symptoms, and
19 perturbation of a wide range of attention and visuospatial cognitive domains.(102) This is,
20 to our knowledge, the first human clinical report on utilizing a whole-body PBM treatment
21 to target a central neural ailment, although similar approaches have been successfully
22 employed in animal models.(49) The equipoise noted with both PBM treatment approaches
23 as noted in prior studies as well indicates the evoked therapeutic biological responses have
24 a prominent systemic component. The nature of the mechanism mediating these responses
25 remains to be investigated.

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27 The cognitive impairment, brain fog in patients who have recovered from acute
28 SARS-CoV-2 is typically less pronounced than in neurodegenerative conditions such as
29 Alzheimer's disease.(41,103) Assessments which have been developed for these
30 conditions are less useful for assessing brain fog, as patients typically score in the normal
31 range for MMSE, MoCA, and trail making tests. Some traditional methods of assessing
32 cognitive impairment developed for evaluating patients with Alzheimer's Disease or
33 Lewy-body Dementia including the Montreal Cognitive Assessment (MoCA) and Trail
34 making tests A and B (TRA, TRB), were not useful in evaluating subjects with the milder,
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3 but still quite troublesome, brain fog.(104,105) We observed improvements in the MoCA,
4 TrA and B and DSST scores after PBM treatments with each modalities.

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6 The qEEG has been used in a clinical setting to assess evoked potential differences
7 between patients with lower vs higher cardiac risk. Further, a prior study has demonstrated
8 the utility of qEEG in assessing the utility of PBM in mitigating dementia.(106) There was
9 no difference in effect on delay times or voltages between participants treated with wbPBM
10 or tPBM; neither after the first treatment nor cumulatively over the full course of
11 treatments. Each method significantly improved decrease in the Flanker (visual ERP)
12 response time, and increase in the Flanker voltage and P300 (auditory ERP) voltage,
13 implying an improvement in physical brain processing speed and power. Only one of the
14 14 participants failed to improve on the Flanker or P300 voltages, but that participant did
15 shorten the Flanker response time; he/she had been treated with. It is of note that this
16 subject had the least improvement (6/10 to 7/10) on the self-assessment score. The use of
17 qEEG allowed assessment of brain function, specifically neurological responses to
18 auditory (P300) and visual (Flanker) evoked potentials. These responses included both
19 processing speed (delay time) and processing power (voltage). There was little correlation
20 between the neuropsychological (MoCA, TRA, TrB and PRT) and the qEEG. However,
21 the DSST was an exception and correlated to auditory and visual evoked potentials with
22 P300 voltage, Flanker delay, and Flanker voltage. We postulated that measuring brain
23 processing speed and power by using auditory and visual evoked potentials could be more
24 sensitive than cognitive tests, and could be practically employed in a clinic setting for
25 diagnostic purposes, as well as evaluation of interventional efficacy.

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27 We would like to draw attention to the utility of the recently described photon
28 fluence and Einstein PBM dose concept. This dose equivalence includes the individual
29 wavelength photon energy of the tPBM with the helmet (1070 nm 1.2 eV) and the wbPBM
30 with the bed (red 660 nm 1.9 eV and infrared 850 nm 1.5 eV). This is particularly relevant
31 for two reasons. Firstly, accounting for the discrete wavelengths accounts for delivering
32 precise amounts of low dose energy that enables PBM efficacy. Moreover, this approach
33 provides a rationalized comparative assessment of the a single versus dual combined
34 wavelength as evident with the wbPBM (7.9 Einstein) versus tPBM (6.0 Einstein). A major
35 advantage of this approach is its ability to enable harmonized dose interpretation and

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3 communication that can be universally implemented with accessible PBM wavelength
4 devices that may otherwise be globally restrictive.

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6 This study is limited by both the number of subjects and the lack of a placebo arm.
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8 The limitations of the subject numbers are evident particularly when comparing the
9 individual tPBM versus wbPBM responses, hence a consolidated group analysis is also
10 included. Further study with a larger population as well as subject masking is currently
11 being planned. Repeated neurophysiological testing (6 tests over 4 weeks) with MoCA,
12 DSST, and Trail making tests could conceivably improve performance as a result of
13 gaining familiarity with the test and practice; however, no papers have been published for
14 a learning effect on these tests. Such an effect is less likely with qEEG parameters as there
15 is no evidence that processing speeds or power can be influenced by repeated practice and
16 placebo effects are less likely to persist over a full course of treatment.(70,107) In addition,
17 further examination of current data is planned to determine if biomarkers provided by
18 qEEG can be used to predict, early in the clinical treatment course, which patients would
19 most likely benefit from PBM treatment. Other treatment modalities could likewise use
20 these biomarkers to determine possible treatment efficacy for those other modalities in each
21 individual patient.
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32 In summary, PBM delivered by either whole body or by transcranial treatment was
33 effective in improving parameters of brain performance in subjects with at least 5 months
34 duration of cognitive impairment after infection with COVID-19. The choice of WbPBM
35 in an office setting versus at-home tPBM, that has shown efficacy with TBI and dementia,
36 should be explored further. It is conceivable that a synergistic combination of the in-clinic
37 and at-home PBM treatments along with emphasis on nutrition and exercise could ideally
38 address access, costs, and compliance issues especially with chronic diseases.
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46 **Conflicts of Interests**

47 The authors declare they have no conflicts of interest with this study.
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Figure Legends

Figure 1. Outline of PBM therapy clinical study **A.** Timeline of evaluations and PBM interventions; **B.** PBM devices used in this study denoting the treatment parameters and delivery format; **C.** Demographics of subjects include in the study depicting distributions of age ($> < 65$ years), gender (male or female), and mode of PBM treatment (bed versus head).

Figure 2. Cognitive assessments utilized in the study included **A.** Tabular presentation of the neurophysiological assessments following tPBM with helmet; **B.** Tabular presentation of the neurophysiological assessments following wbPBM in the bed; **C.** Montreal Cognitive Assessment (MoCA); **D.** Digit symbol substitution test (DSST); **E.** Trail-making test A; **F.** Trail-making test B; **G.** Physical reaction time (PRT). All data **C-G** outline individual tPBM or wbPBM modalities (left) and combined (right) treatments. Data is shown as mean with standard deviations and statistical significance is noted as $** = p < 0.005$, and $*** = p < 0.0005$.

Figure 3. Using a quantitative EEG device to assess PBM treatment efficacy. **A.** Tabular presentation of the qEEG assessments following tPBM with helmet; **B.** Tabular presentation of the qEEG assessments following wbPBM in the bed; **C.** P300T assessment in time (sec); **D.** P300V assessment in milli-volts; **E.** FlankerT assessment in time (sec); **F.** FlankerV assessment in milli-volts. All data **C-F** outline individual tPBM or wbPBM modalities (left) and combined (right) treatments. Data is shown as mean with standard deviations and statistical significance is noted as $* = p < 0.05$, $** = p < 0.005$, and $**** = p < 0.00005$.

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Figure. 1

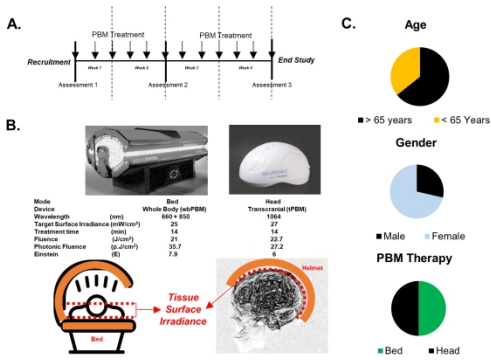


Figure 1

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Figure 2

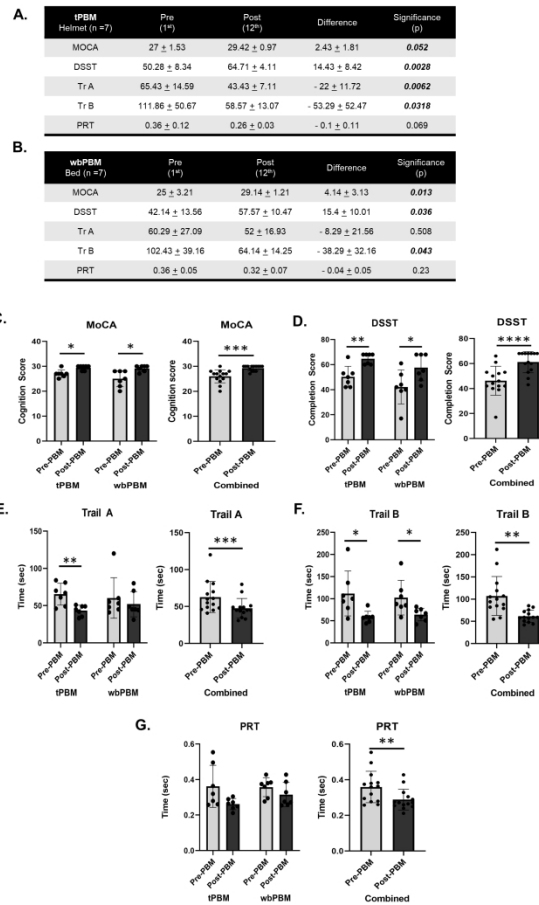


Figure 2

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Figure 3

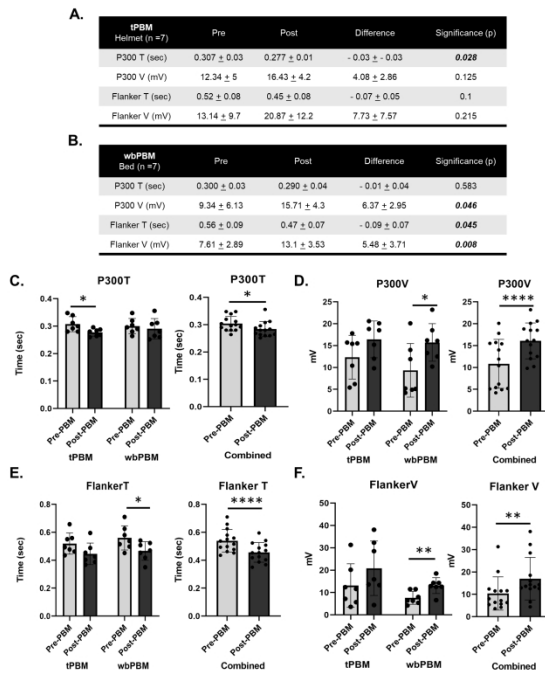


Figure 3

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