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The Effect of Intranasal Plus Transcranial Photobiomodulation on Neuromuscular Control in Individuals with Repetitive Head Acceleration Events

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Abstract

Objective: This proof-of-concept study was to investigate the relationship between photobiomodulation (PBM) and neuromuscular control.

Background: The effects of concussion and repetitive head acceleration events (RHAEs) are associated with decreased motor control and balance. Simultaneous intranasal and transcranial PBM (itPBM) is emerging as a possible treatment for cognitive and psychological sequelae of brain injury with evidence of remote effects on other body systems.

Methods: In total, 43 (39 male) participants, age 18–69 years (mean, 49.5; SD, 14.45), with a self-reported history of concussive and/or RHAE and complaints of their related effects (e.g., mood dysregulation, impaired cognition, and poor sleep quality), completed baseline and posttreatment motor assessments including clinical reaction time, grip strength, grooved pegboard, and the Mini Balance Evaluation Systems Test (MiniBEST). In the 8-week interim, participants self-administered itPBM treatments by wearing a headset comprising four near-infrared light-emitting diodes (LED) and a near-infrared LED nasal clip.

Results: Posttreatment group averages in reaction time, MiniBEST reactive control subscores, and bilateral grip strength significantly improved with effect sizes of $g = 0.75$, $g = 0.63$, $g = 0.22$ (dominant hand), and $g = 0.34$ (nondominant hand), respectively.

Conclusion: This study provides a framework for more robust studies and suggests that itPBM may serve as a noninvasive solution for improved neuromuscular health.

Keywords: photobiomodulation, light therapy, neuromuscular control, repetitive head acceleration events, motor control

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Introduction

Approximately 3.8 million sport- and recreation-related concussions occur annually in the United States.[1] The effects of concussion, including persistent long-term issues with concentration and physical skills,[2,3] is a growing concern. Equally concerning are the effects of repetitive head impacts (RHIs), also known as repetitive head acceleration events (RHAEs). RHAE has the same meaning as RHI; however, it is emerging as a preferred term because it inherently indicates that the brain is experiencing translational and/or rotational movement because of external forces regardless of the source (blast or mechanical blow) or location (head or body) of the impact forces. Although RHAE may include concussions or mild traumatic brain injury (mTBI), most do not result in any acute detectable clinical symptoms. However, the cumulative effect of RHAE, like concussion or mTBI, could progress to traumatic encephalopathy syndrome (TES), a clinical disorder associated with chronic traumatic encephalopathy (CTE).[4] An athlete may experience over 100 RHAEs per season.[5–7] Although the athlete may be asymptomatic, RHAEs result in microstructural and functional changes in the brain similar to that seen in concussion or mTBI,[8–10] leading to altered motor unit recruitment strategies, increased acute corticomotor inhibition,[11] and other neuromuscular impairments, such as reduced dynamic balance or reaction time, in the long-term.[12–16]

Photobiomodulation (PBM), more specifically simultaneous intranasal and transcranial PBM (itPBM), is emerging as a candidate for therapy in addressing the cognitive and psychological sequelae resulting from brain injury.[17,18] In transcranial PBM (tPBM), a headset is worn with light-emitting diodes (LEDs) positioned on the scalp to target cortical brain regions with primarily near-infrared (NIR) light (810 nm). In intranasal PBM (iPBM), an LED nasal applicator is positioned in a nostril where NIR photons can be absorbed by the capillaries in the nasal epithelium.

Mechanisms of PBM

Theories and evidence describing the mechanism of action of PBM for both brain and other tissues and are well documented.[17–30] The prevailing hypothesis is that itPBM alleviates mitochondrial dysfunction related to the head insults.[17,31] Specifically, emitted photons are absorbed by the cytochrome c oxidase (CCO) enzyme in the mitochondrial electron transport chain,[20,22,32] which leads to a cascade of biochemical events along several pathways. The end results include enhanced energy production, increased cerebral blood and lymphatic flow,[30,33] the promotion of cell survival,[32] reduced excitotoxity and inflammation, and potentially increased angiogenesis, neurogenesis, and synaptogenesis.[25,29] PBM also stimulates the proliferation and mobilization of stem cells that release trophic factors that protect and repair neural tissue.[34–36] Another theorized mechanism is the entrainment of neuro-oscillatory waves disrupted by concussion[37–39] because of the pulsation of the light.[40]

Some of these mechanisms may exhibit effects beyond the target organs, implying that PBM may affect nontargeted body systems. Studies employing remote PBM resulted in increased mobility, cognition, dynamic balance, and sense of smell in patients with Parkinson's disease,[41] and cognitive capacity, changes in depression, weight, and blood pressure in mouse models.[42] To date, literature on itPBM affecting other systems in a population with RHAE exposure is sparse. However, a case study including a former professional football player exhibiting TES not only showed brain functional improvements,[43] but also reported gains in physical strength (Personal Communication, L. Carr, Aug. 2019), implying that mechanisms of itPBM may demonstrate a systemic effect resulting in improved or preserved neuromuscular health.

The purpose of this study was to examine effects of itPBM on neuromuscular health. As part of a larger proof-of-concept study to investigate the relationship of itPBM on brain connectivity, cognitive function, and psychological health in individuals exposed to RHAE, measures of neuromuscular health, including reaction time, dexterity, grip strength, and balance, were collected in former athletes with a self-reported history of RHAE. Grip strength, reaction time, and postural control are functional biomarkers of health and tend to decline with age.[44–48] Regardless of participant age, we hypothesized that the light-stimulated processes provide additional benefits to systems subserving physical performance measures.

Methods

Participants

We enrolled 49 participants (45 males). Six did not complete the study for various reasons (e.g., unable to travel or loss of interest), leaving 43 (39 male) participants between the age of 18 and 69 years old (M = 49.5, SD = 14.45). All participants self-reported a history of mTBI and/or RHAEs, most because of participation in sports (recreational, high school, collegiate, and/or professional), and one as a result of intimate partner violence. Participants also reported at least one complaint commonly associated with effects of head impacts, for example, difficulty with mood regulation, memory, or sleep. Exclusion criteria included a history of neurological disease (i.e., dementia, stroke, epilepsy, tumor), history of severe psychiatric disorder (i.e., bipolar, schizophrenia, psychosis), and/or MRI contraindications. All enrollees signed informed consent documents approved by the Institutional Review Boards at the University of Utah and Wahlen VA Salt Lake City Healthcare System.

We administered the Ohio State University Traumatic Brain Injury Identification (OSU-TBI),[49] survey, during which participants self-reported the duration of participation in the activity that exposed them to RHAEs and the severity and number of head hits. All participants reported head impacts with at least momentary (5–30 sec) loss of consciousness and/or posttraumatic amnesia. No participants disclosed a history of mild complicated, moderate, or severe TBI; however, most described experiencing head impacts such as "stingers" or "getting their bell rung," which may have been considered concussions had they been diagnosed (see Table 1 for a summary).

Study design

This study was a nonrandomized proof-of-concept design that used active treatment only. Participants were assessed at two time points, prior to and 8–10 weeks after starting at-home itPBM treatments. The participants were instructed to maintain their normal routines and not start any new activities (e.g., resistance and/or balance training or brain training) during this time period.

Table 1. Participant Information

	N	*M*	*SD*	*Min*	*Max*
Biological sex					
Male	39				
Female	4				
Age at baseline		45.90	14.45	22	69
Years of education		15.90	2.04	12	22
Follow-up interval (days)	43	61.95	7.78	55	97
Age at first head impact/acceleration event		14.50	8.57	2[a]	45
Number of head impacts/acceleration events		7.20	6.04	0	25
Duration of exposure to head acceleration events (years)		12.39	6.14	4	30
Complaints of mood regulation	17				
Complaints of difficulty with memory and/or cognition	28				
Complaints of poor sleep quality	43				

[a]Not a personal memory; based on a family story of the participant being hit by a truck as a toddler. No other details are known.

Treatment protocol

For this study, participants self-administered itPBM with the Vielight Neuro Gamma PBM headset (Toronto, Canada) worn over the scalp and/or hair. The device has four LEDs, each emitting NIR light (810 nm), pulsating at 40 Hz (50% duty cycle) over a beam spot of 1 cm^2, three with irradiance of 100 mW/cm^2, and the fourth at 75 mW/cm^2. The LEDs are placed to target cortical nodes of the default mode network: the midline bilateral medial prefrontal cortex, left and right angular gyrus areas, and midline bilateral precuneus (see Fig. 1). In addition, the device includes an intranasal probe with one LED emitting pulsed NIR light with irradiance of 25 mW/cm^2 inside the nasal cavity targeting the olfactory bulbs and orbitofrontal cortex (see Table 2). Participants were instructed to administer a 20-min treatment every other day for 8 weeks and given a log sheet to track usage.

Clinical performance tests

The clinical performance tests included four assessments: clinical reaction time, grooved pegboard, grip strength, and the Mini Balance Evaluation Systems Test (MiniBEST). As previously noted, this study is part of a larger study; therefore, these assessments occurred in the same visit with cognitive and neuropsychological assessments and a brain MRI scan.

Clinical reaction time

The clinical reaction time test was administered according to the protocol described by Eckner et al.,[50] Briefly, participants sat with the forearm of their dominant hand resting comfortably on a table and their hand extended past the edge of the surface with their thumb and fingers forming a "C," similar to holding a cup. The examiner pinched one end of a 1.3-m-long marked stick embedded in a weighted rubber disk and suspended the disk between the fingers and thumb of the participant's hand. The examiner released the stick and participant closed their hand to catch it as quickly as possible. The participant performed 10 total trials, with the first 2 used as practice. The distance the stick dropped was converted into a reaction time (in milliseconds) using the formula for a body falling under the influence of gravity ($d = {}^1/_2 g t^2$), where d is the distance, g is the acceleration due to gravity, and t is the time.

Grooved Pegboard Test

Manipulative dexterity was assessed using the Grooved Pegboard Test.,[51] The metal board consists of 25 keyhole shaped slots with varying orientations, arranged in a 5×5 grid (Lafeyette Instruments, Lafayette, IN). Each peg has a 3-mm-diameter cylindrical shape, save for a ridge that runs along the length of the peg, such that the peg will only fit in the board if the ridge is aligned with the notch of a slot. Participants inserted pegs into the holes as quickly as possible in a row-by-row manner, completing the exercise once with each hand, starting with their dominant hand. We recorded the time the participants took to complete the task.

Grip strength

Grip strength was measured using a Jamar Plus Dynamometer (Performance Health, Chicago, IL). After adjusting the handle for proper grip, the participant held the dynamometer down at their side and squeezed the handle as hard as possible for 3 sec, completing three trials for each hand. We recorded the average force.

Mini Balance Evaluation Systems Test

The MiniBEST,[52] assessment includes 14 tasks across four domains: anticipatory postural adjustments, reactive postural control, sensory orientation, and dynamic gait.,[53] Each task used a three-level ordinal scale to score, with a maximum total score of 28. Outcome measures included the overall miniBEST score and individual subscores for each domain.

Statistical analysis

Motor tests were scored per their respective standards. Data from some participants were excluded because of limb injuries that would affect test results (e.g., lacerations on fingertips). Shapiro–Wilk tests were used to evaluate normality of measurements for all continuous variables. Separate linear mixed-effect analyses were performed using the maximum likelihood method for parameter estimations. The response variables were the motor outcome measures, the fixed effects terms were "age" and "visit time" (with no interaction term), and random effects using random intercepts by "participant." Normality was

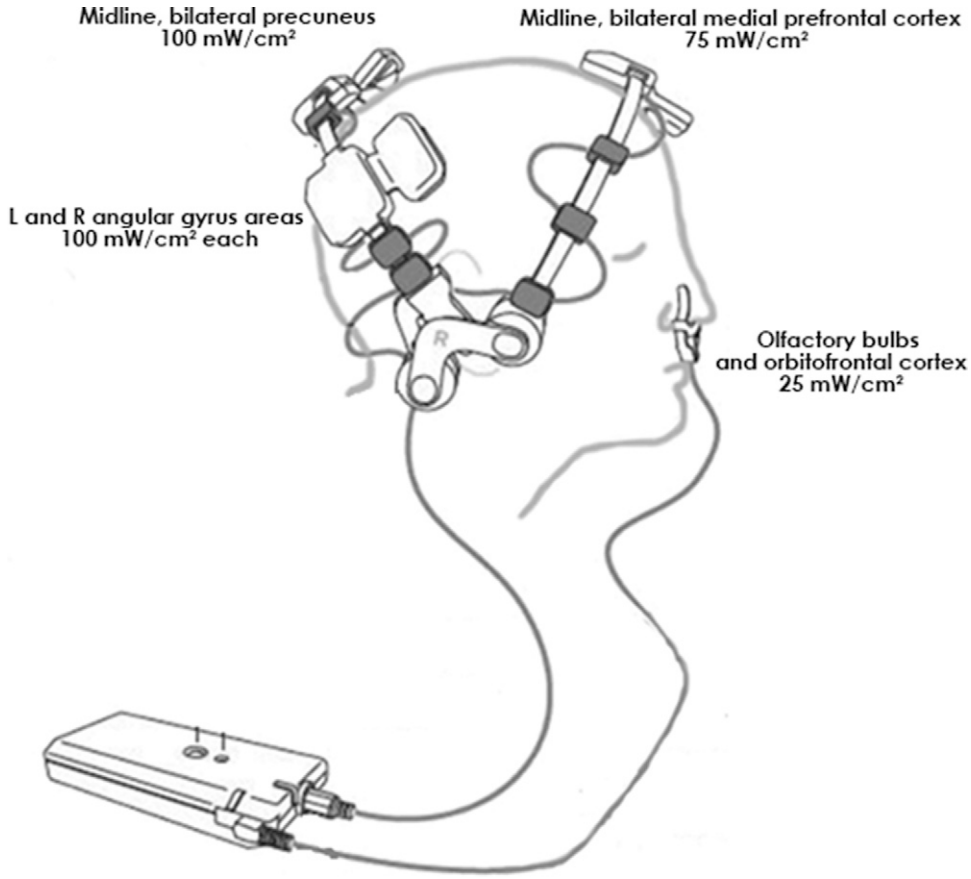

FIG. 1. Placement of the itPBM device. The Vielight Neuro Gamma PBM headset fits over the scalp with the four near-infrared LEDs targeting cortical nodes of the default mode network: the medial prefrontal cortex, located high on the center front forehead area at the center front hairline; the bilateral parietal cortices located in the left and right angular gyrus areas; and the precuneus, located at the junction of the sagittal suture line with the left and right lambdoid suture lines. An intranasal applicator is positioned over capillaries in the nasal epithelium targeting olfactory bulbs and the orbitofrontal cortex. The headset's four LEDs emit pulsed NIR light (810 nm), over a beam spot size of 1 cm^2, three at an irradiance of 100 mW/cm^2, and the fourth at 75 mW/cm^2. The nasal applicator consists of one LED emitting pulsed NIR light at an irradiance of 25 mW/cm^2. Image source: Vielight Neuro Gamma Operational Manual version 1.1; 17 April 2019, pg 8. Used with the permission from Vielight Inc. itPBM, intranasal and transcranial photobiomodulation; LED, light-emitting diode; NIR, near infrared

confirmed through examination of the residuals of each model. A Wilcoxon's signed-rank test was used to evaluate change in performance on measures for non-normal variables. To control for multiple comparisons, the Benjamini–Hochberg false discovery rate procedure was employed for all null hypothesis tests, with the statistical significance threshold kept at $\alpha = 0.05$. All p values are reported with 95% confidence intervals (CIs), and exact p values are reported for all nonparametric comparisons. For all comparisons, Hedges g is provided as a measure of effect size, where $|g| \geq 0.20$, 0.50, and 0.80 are considered small, moderate, and large effects, respectively.[54,55] Statistical analyses were performed using Matlab R2021a (2021; College Station, TX: MathWorks).

Results

The protocol for itPBM intervention was 8 weeks; however, because of travel constraints or personal conflicts, some participants were unable to return for posttreatment testing until 10–12 weeks, during which time they continued the treatment. Reported compliance rate for itPBM usage was 92%. A summary of pre- and posttreatment assessment results is provided in Table 3. Pretreatment times for each hand on the grooved pegboard test, but not other measures, were associated with age. The fitted regression models were as follows: dominant hand time = 53.2 + 0.53 *age; nondominant hand time = 54.2 + 0.64*age. The overall regressions were statically significant [$R^2 = 0.27$, $F(1,40) = 14.9$, $p = 0.0004$; $R^2 = 0.27$, $F(1,40) = 14.7$, $p = 0.0004$, respectively.] Significant improvements related to treatment visits were seen in three of the four test domains (Table 4). Average reaction time improved by 19.39 ms (95% CI [12.24,26.54], $p < 0.001$) from pre- to posttreatment visits, with an effect size of 0.75, and was not influenced by age. Average dominant-hand grip strength increased from baseline by 2.70 kg (95% CI [0.89, 4.52], $p = 0.003$), whereas nondominant hand grip strength increased by 3.73 kg (95% [2.10, 5.36], $p < 0.001$) with small effect sizes ($g = 0.22$ and $g = 0.35$, respectively). These measures were unaffected by age. Also unaffected by age were the overall MiniBEST scores, which improved by an average of 1.32 points (95% CI [0.767, 1.88]) with a moderate effect ($g = 0.51$). A breakdown of MiniBEST subscores showed improvement

Table 2. itPBM Specifications

Manufacturer	*Vielight (Montreal, Canada)*
Model	Neuro Gamma v3 (2020)
Number of emitters	5
Emitter type	Light-emitting diode (LED)
Center wavelength	810 nm
Spectral bandwidth	Full width half max: ±20.2 nm
Operating mode	Pulsed
Frequency	40 Hz
Duty cycle	50%
Pulse on duration	25 ms
Aperture diameter	1 cm^2
Beam shape	Circular
Beam divergence	0 degrees on contact
Exposure duration	1200 s * 0.5 (duty cycle) = 600 s
Number and frequency of treatment sessions	Every other day (3–4x/week) for 8 weeks

Emitter distribution, irradiance, and energy delivered

Emitter location	*Target*	*Irradiance*	*Energy delivered*
Anterior head band	Midline, bilateral medial prefrontal cortex	75 mW/cm^2	45 J
Posterior head band	Bilateral angular gyrus areas	2 × 100 mW/cm^2	2 × 60 J
Posterior head band	Precuneus	100 mW/cm^2	60 J
Nasal applicator	Olfactory bulbs and orbitofrontal cortex	25 mW/cm^2	15 J
Energy per session (at 50% duty)			120 J
Total energy over 8 weeks (3–4 sessions/week)			3360 J

itPBM, intranasal and transcranial photobiomodulation.

and moderate effect in the reactive postural control domain ($g = 0.63$). Grooved pegboard times for each hand improved after treatment; however, the improvements were not statistically significant and time difference was affected by age ($p < 0.001$, bilaterally).

Discussion

After 8–12 weeks of itPBM treatments, participants experienced small to moderate effects in bilateral grip strength, reaction time, and reactive postural balance, but not dexterity.

Table 3. Summary Statistics for Motor Assessments

Measure	N	*Baseline mean (SD) [95% CI]*	*Post-Tx mean (SD) [95% CI]*	*Diff mean (SD) [95% CI]*	*Hedge's g*
Clinical Reaction Time (ms)	43	223.0 (27.3) [214.6, 231.4]	203 (23.3) [196.5, 210.8]	−19.3 (23.8) [−26.7,−12.1]	0.75
Dom Grip (kg)	43	46.9 (12.1) [43.2, 50.6]	49.6 (11.8) [46.0, 53.3]	2.71 (6.05) [0.84, 4.57]	0.12
Non-Dom Grip (kg)	43	44.0 (11.1) [40.6, 47.5]	48.1 (11.4) [44.5, 51.6]	3.70 (5.37) [2.03, 5.37]	0.16
Dom GPB (s)	42	77.5 (15.3) [72.7, 82.2]	75.4 (18.1) [69.8, 80.9]	−2.09 (10.6) [1.24, 1.64]	0.22
Non-Dom GPB (s)	43	83.6 (18.6) [77.7, 89.4]	80.3 (21.1) [73.8, 86.8]	−3.33 (11.6) [−6.97, 0.237]	0.35
MiniBEST	43	24.7 (2.95) [23.8, 25.7]	26.1 (2.19) [25.4, 26.7]	1.33 (1.86) [0.753, 1.89]	0.51
Anticipatory postural adjustment	43	5.21 (1.21) [4.84, 5.58]	5.39 (0.955) [5.10, 5.69]	0.186 (0.699) [−0.029, 0.401]	
Reactive postural control	43	4.65 (1.42) [4.21, 5.09]	5.47 (1.10) [5.12, 5.80]	.814 (1.22) [0.438, 1.19]	
Sensory orientation	43	5.93 (0.258) [5.85, 9.01]	5.98 (0.152) [5.93, 6.02]	0.0465 (0.213) [−0.019, 0.112]	
Dynamic gait	43	8.95 (1.11) [8.61, 9.29]	9.23 (0.750) [9.00, 9.46]	0.279 (1.03) [−0.038, 0.596]	

GPB, Grooved Pegboard Test.

Table 4. Mixed-Effects Linear Model Results

Response variable	*Fixed effect*	*Fixed estimate*	*95% CI*	*AIC; BIC*	p *value*
Reaction Time	Age	–0.049	[–0.495, 0.396]	792; 804	0.825
	Pre/Post Visit	–19.38	[–26.54,–12.24]		<0.001
Dom GPB	Age	0.642	[0.395, 0.889]	664;676	<0.001
	Pre/Post Visit	–2.02	[–5.24, 1.19]		0.215
NonDom GPB	Age	0.720	[0.412, 1.02]	690; 703	<0.001
	Pre/Post Visit	–3.27	[–6.79. 0.25]		0.068
Dom Grip	Age	–0.098	[–0.326, 0.129]	616; 628	0.39
	Pre/Post Visit	2.70	[0.892, 4.52]		0.003
NonDom Grip	Age	–0.075	[–0.292, 0.141]	595; 608	0.49
	Pre/Post Visit	3.73	[2.10, 5.36]		<0.001
MiniBEST Score	Age	–0.066	[–0.109,–0.022]	373; 385	<0.001
	Pre/Post Visit	1.32	[0.767, 1.88]		<0.001

These results are consistent with existing studies reporting improvements on motor measures after tPBM. For example, balance, gait, and grip performance improved in animal models of acute severe TBI.[56,57] In healthy young adults, finger tapping frequency improved in treatment groups after 5 min of laser tPBM (with total energy of 60 J/cm^2) compared with sham groups.[58,59] Improvement in these biomarkers of health imply that PBM may address the pathology associated with RHAE-induced neuromuscular issues through its proposed mechanisms.

Head impacts decrease motor unit synchronization and recruitment because of increased excitotoxity[11] which may still be present in slowly progressing CTE resulting from RHEA.[60] PBM decreases excitotoxicity in in vitro animal models[61–63] and if the same mechanism translates to human itPBM then we might attribute improvements in grip strength and balance to increased ability of the neuromuscular system to recruit and synchronize motor units.

Cortical electrophysiology associated with neural oscillations is disrupted by concussion[64,65] and can persist, likely because of damaged white matter circuitry.[39,66–68] This disruption affects the synchronicity of the neural oscillations of the central nervous system, which modulate descending motor pathways.[69,70] itPBM delivery of pulsed light at 40 Hz possibly entrains gamma brain waves, a frequency involved in motor control.[67,69,70]

Connectivity of cortical networks, which are disturbed in concussion, is vital for optimal motor control. PBM-related reductions in inflammation, along with increased energy production, cerebral blood flow, neurogenesis, and synaptogenesis, may contribute to neuroplastic changes to the structural and functional connectivity of the motor network, and thus recovered neuromuscular control. Some have suggested that tPBM and/or iPBM could improve motor performance in populations with Parkinson's disease and Alzheimer's disease by affecting these mechanisms.[27,71–73] Although the itPBM treatments in the current study did not directly target regions in the motor cortex in the brain, results from remote PBM research studies where PBM was applied to an area distant from the cortical target (e.g., the abdomen), where significant beneficial results were observed[35,36,41] provide a plausible explanation for observed motor improvements.

Table 5. Wilcoxson's Sign-Ranked Analysis of MiniBEST Subscores

Test	*z-value*	p	*g*
MiniBEST Anticipatory Control		0.10	0.17
MiniBEST Reactive Postural Control	–3.52	>0.001	0.63
MiniBEST Static Balance		0.50	–0.23
MiniBEST Dynamic Balance	–1.64	0.10	–0.29

Cognition, mood, and sleep positively correlate with measures of clinical motor outcomes.[74–79] Thus, as itPBM-related recovery occur in these domains,[80,81] positive motor changes are likely to follow. Such changes were observed in this cohort in another arm of this study,[82] likely contributing to improvements in balance, grip strength, and reaction time.

It is important to note that although statistically significant, a 1.3-point improvement in MiniBEST scores are not necessarily clinically significant. However, 23% of participants in our study improved their scores by three or more points, with half of those improving by four or more points. Changes of 3.5 points on the MiniBEST constitute the detectable difference in a comparable population.[52] In addition, six of nine participants originally classified as moderately impaired were re-classified to normal-to-mild impairment. Similarly, improvements in grip strength of 2.7 and 3.7 kg in dominant and nondominant hands, respectively, were lower than estimates of meaningful changes of 5.0–6.5 kg.[83] However, in a cross-sectional study with almost 14,000 adults between the ages 50 and 70 years across 150 countries, an increase of 1 kg in grip strength was associated with a 6% higher score on a cognitive battery that assessed visuospatial abilities, episodic memory, and attention.[48]

Although many of the significant results fall near, or just below, the threshold for clinically important change, the uniformly positive change toward better performance suggests these changes are not random. Further, these results may or may not be clinically meaningful given the 8-week duration and dosage, but longer interventions may demonstrate greater improvements. The low-risk, ease of use, and low cost indicate that longer itPBM interventions would be very feasible.

Limitations

This proof-of-concept study had a relatively small sample of predominantly male (39 of 43) participants. The design proved the feasibility of measuring changes before and after itPBM treatments; however, to attribute such changes

definitively to the treatment, future studies with a larger sample size and a healthy control and/or sham group is necessary. An equitable male–female distribution is also necessary to investigate the influence of sex on treatment effect. The history of RHIs/acceleration events was self-reported; however, we remain confident in the reliability of the reports based on the information from Kerr et al. (2022) that indicates the stability of self-reported concussion.[84]

itPBM treatments were self-administered. There was 92% compliance with the given treatment schedule, with several reported short periods of inconsistent use. In addition, all participants administered the itPBM treatment for an 8-week period; however, because of unforeseen events and/or the difficult timing of travel, some used the itPBM devices for up to 12 weeks. Participants were also instructed to maintain current routines; however, we did not strictly monitor or control for any modifications in fitness or reactional activities related to the motor outcomes of this study.

Conclusions

This study, which is a part of a larger study that included assessments of cognitive, psychological, and structural brain health, as well as neuromuscular health, supports our hypothesis that itPBM applied to the brain of individuals with chronic symptoms of RHAE has downstream effects on the neuromuscular system. Our results indicate that itPBM has small to moderate effects on grip strength, balance, and reaction time. It is not within the scope of this study to determine how PBM applied on the head acts on the distal parts of the neuromuscular system; however, motor unit recruitment resulting from reduction of excitotoxity, entrainment of disrupted neural oscillations that control descending pathways, and improved connectivity in the motor and cerebellar networks may be possible points of scrutiny in future work. Such work will also require more robust research designs to support this proof-of-concept study.

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Authorship Confirmation/Contribution Statement

P.J.: Conceptualization, methodology, validation, formal analysis, investigation, data curation, writing—original draft, writing—review and editing, visualization, supervision, and project administration. P.F.: Conceptualization, methodology, software, formal analysis, resources, validation, data curation, and writing—review and editing. E.W.: Conceptualization, methodology, validation, investigation, resources, writing—review and editing, visualization, supervision, project administration, and funding acquisition. E.H.: Investigation, writing—original draft, writing—review and editing, visualization, and project Administration. H.R.: Investigation. C.V.: Investigation. R.P.: Investigation, writing—review and editing. A.M.: Investigation, software, writing—review and editing. N.K.: Investigation, writing—review and editing. E.R.: Investigation, writing—original draft, writing—review and editing. F.K.: Investigation. C.E.: Writing—review and editing. H.L.: Validation, writing—review and editing. M.N.: Writing—review and editing. D.T.: Investigation, writing—review and editing, project administration. C.M.: Editing. C.M.: Writing—review and editing. L.D.: Writing—review and editing. S.L.: Writing—review and editing. L.C.: Investigation, resources, project administration, and funding acquisition. D.F.T.: Conceptualization, methodology, validation, investigation, resources, visualization, supervision, project administration, and funding acquisition.

Author Disclosure Statement

L.C. serves as a consultant for Vielight, Inc. All other authors declare no direct conflicts of interest.

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References

1. Harmon KG, Clugston JR, Dec K, et al. American medical society for sports medicine position statement on concussion in sport. Clin J Sport Med 2019;29(2):87–100; doi: 10.1097/JSM.0000000000000720
2. Guskiewicz KM, Mihalik JP, Shankar V, et al. Measurement of head impacts in collegiate football players: Relationship between head impact biomechanics and acute clinical outcome after concussion. Neurosurgery 2007;61(6):1244–1252; doi: 10.1227/01.neu.0000306103.68635.1adiscussion 1252-3,
3. Prevention CfDCa. Report to Congress on Traumatic Brain Injury in the United States: Epidemiology and Rehabilitation. Atlanta, GA; 2015.
4. Katz DI, Bernick C, Dodick DW, et al. National institute of neurological disorders and stroke consensus diagnostic criteria for traumatic encephalopathy syndrome. Neurology 2021;96(18):848–863; doi: 10.1212/WNL.0000000000011850
5. Broglio SP, Eckner JT, Martini D, et al. Cumulative head impact burden in high school football. J Neurotrauma 2011;28(10):2069–2078; doi: 10.1089/neu.2011.1825
6. Stemper BD, Shah AS, Harezlak J, et al. Repetitive head impact exposure in college football following an NCAA rule change to eliminate two-a-day preseason practices: A study from the NCAA-DoD CARE consortium. Ann Biomed Eng 2019;47(10):2073–2085; doi: 10.1007/s10439-019-02335-9
7. Savino AK, Huang L, Yang J, et al. Head impact burden differs between seasons in youth and high school US football players. Ann Biomed Eng 2020;48(12):2763–2771; doi: 10.1007/s10439-020-02548-3
8. Dioso E, Cerillo J, Azab M, et al. Subconcussion, concussion, and cognitive decline: The impact of sports related collisions. J Med Res Surg 2022;3(4):54–63; doi: 10.52916/jmrs224081
9. Lust CAC, Mountjoy M, Robinson LE, et al. Sports-related concussions and subconcussive impacts in athletes: Incidence, diagnosis, and the emerging role of EPA and DHA.

Appl Physiol Nutr Metab 2020;45(8):886–892; doi: 10.1139/apnm-2019-0555
10. Bari S, Svaldi DO, Jang I, et al. Dependence on subconcussive impacts of brain metabolism in collision sport athletes: An MR spectroscopic study. Brain Imaging Behav 2019; 13(3):735–749; doi: 10.1007/s11682-018-9861-9
11. Di Virgilio TG, Ietswaart M, Wilson L, et al. Understanding the consequences of repetitive subconcussive head impacts in sport: Brain changes and dampened motor control are seen after boxing practice. Front Hum Neurosci 2019;13: 294; doi: 10.3389/fnhum.2019.00294
12. Lavender AP, Rawlings S, Warnock A, et al. Repeated long-term sub-concussion impacts induce motor dysfunction in rats: A Potential Rodent Model. Front Neurol 2020;11:491; doi: 10.3389/fneur.2020.00491
13. Bellomo G, Piscopo P, Corbo M, et al. A systematic review on the risk of neurodegenerative diseases and neurocognitive disorders in professional and varsity athletes. Neurol Sci 2022;43(12):6667–6691; doi: 10.1007/s10072-022-06319-x
14. Morales JS, Valenzuela PL, Saco-Ledo G, et al. Mortality risk from neurodegenerative disease in sports associated with repetitive head impacts: Preliminary findings from a systematic review and meta-analysis. Sports Med 2022; 52(4):835–846; doi: 10.1007/s40279-021-01580-0
15. Pearce N, Gallo V, McElvenny D. Head trauma in sport and neurodegenerative disease: An issue whose time has come? Neurobiol Aging 2015;36(3):1383–1389; doi: 10.1016/j.neurobiolaging.2014.12.024
16. Caccese JB, Best C, Lamond LC, et al. Effects of repetitive head impacts on a concussion assessment battery. Med Sci Sports Exerc 2019;51(7):1355–1361; doi: 10.1249/MSS.0000000000001905
17. Salehpour F, Mahmoudi J, Kamari F, et al. Brain photobiomodulation therapy: A narrative review. Mol Neurobiol 2018;55(8):6601–6636; doi: 10.1007/s12035-017-0852-4
18. Naeser MA, Hamblin MR. Traumatic brain injury: A major medical problem that could be treated using transcranial, red/near-infrared LED photobiomodulation. Photomed Laser Surg 2015;33(9):443–446; doi: 10.1089/pho.2015.3986
19. Chen AC, Arany PR, Huang YY, et al. Low-level laser therapy activates NF-kB via generation of reactive oxygen species in mouse embryonic fibroblasts. PLoS One 2011;6(7): e22453; doi: 10.1371/journal.pone.0022453
20. de Freitas LF, Hamblin MR. Proposed mechanisms of photobiomodulation or low-level light therapy. IEEE J Select Topics Quantum Electron 2016;22(3):348–364; doi: Artn7000417; doi: 10.1109/Jstqe.2016.2561201
21. Hamblin MR. Photobiomodulation or low-level laser therapy. J Biophotonics 2016;9(11–12):1122–1124; doi: 10.1002/jbio.201670113
22. Hamblin MR. Shining light on the head: Photobiomodulation for brain disorders. BBA Clin 2016;6:113–124; doi: 10.1016/j.bbacli.2016.09.002
23. Hamblin MR, Huang Y-Y. Photobiomodulation in the brain: low-level laser (light) therapy in neurology and neuroscience. Elsevier: Waltham; 2019.
24. Hamblin MR, Liebert A. Photobiomodulation therapy mechanisms beyond cytochrome c oxidase. Photobiomodul Photomed Laser Surg 2022;40(2):75–77; doi: 10.1089/photob.2021.0119
25. Huang YY, Gupta A, Vecchio D, et al. Transcranial low level laser (light) therapy for traumatic brain injury. J Biophotonics 2012;5(11-12):827–837; doi: 10.1002/jbio.201200077
26. Martin PI, Chao L, Krengel MH, et al. Transcranial photobiomodulation to improve cognition in gulf war illness. Front Neurol 2020;11:574386; doi: 10.3389/fneur.2020.574386
27. Salehpour F, Khademi M, Hamblin MR. Photobiomodulation therapy for dementia: A systematic review of preclinical and clinical studies. J Alzheimers Dis 2021;83(4): 1431–1452; doi: 10.3233/JAD-210029
28. Salehpour F, Majdi A, Pazhuhi M, et al. Transcranial photobiomodulation improves cognitive performance in young healthy adults: A systematic review and meta-analysis. Photobiomodul Photomed Laser Surg 2019;37(10):635–643; doi: 10.1089/photob.2019.4673
29. Xuan WJ, Agrawal T, Huang LY, et al. Low-level laser therapy for traumatic brain injury in mice increases brain derived neurotrophic factor (BDNF) and synaptogenesis. J Biophotonics 2015;8(6):502–511; doi: 10.1002/jbio.201400069
30. Hennessy M, Hamblin MR. Photobiomodulation and the brain: A new paradigm. J Opt 2017;19(1):013003; doi: 10.1088/2040-8986/19/1/013003
31. Demers-Marcil S, Coles JP. Cerebral metabolic derangements following traumatic brain injury. Curr Opin Anaesthesiol 2022;35(5):562–569; doi: 10.1097/ACO.0000000000001183
32. Bathini M, Raghushaker CR, Mahato KK. The molecular mechanisms of action of photobiomodulation against neurodegenerative diseases: A systematic review. Cell Mol Neurobiol 2022;42(4):955–971; doi: 10.1007/s10571-020-01016-9
33. Mitchell UH, Mack GL. Low-level laser treatment with near-infrared light increases venous nitric oxide levels acutely: A single-blind, randomized clinical trial of efficacy. Am J Phys Med Rehabil 2013;92(2):151–156; doi: 10.1097/PHM.0b013e318269d70a
34. Tuby H, Maltz L, Oron U. Low-level laser irradiation (LLLI) promotes proliferation of mesenchymal and cardiac stem cells in culture. Lasers Surg Med 2007;39(4):373–378; doi: 10.1002/lsm.20492
35. Gordon LC, Johnstone DM. Remote photobiomodulation: An emerging strategy for neuroprotection. Neural Regen Res 2019;14(12):2086–2087; doi: 10.4103/1673-5374.262573
36. Johnstone DM, Hamilton C, Gordon LC, et al. Exploring the use of intracranial and extracranial (remote) photobiomodulation devices in parkinson's disease: A comparison of direct and indirect systemic stimulations. J Alzheimers Dis 2021;83(4):1399–1413; doi: 10.3233/JAD-210052
37. Sponheim SR, McGuire KA, Kang SS, et al. Evidence of disrupted functional connectivity in the brain after combat-related blast injury. Neuroimage 2011;54 Suppl 1(Suppl 1): S21–9; doi: 10.1016/j.neuroimage.2010.09.007
38. Prichep LS, McCrea M, Barr W, et al. Time course of clinical and electrophysiological recovery after sport-related concussion. J Head Trauma Rehabil 2013;28(4):266–273; doi: 10.1097/HTR.0b013e318247b54e
39. Wang C, Costanzo ME, Rapp PE, et al. Disrupted gamma synchrony after mild traumatic brain injury and its correlation with white matter abnormality. Front Neurol 2017;8: 571; doi: 10.3389/fneur.2017.00571
40. Zomorrodi R, Loheswaran G, Pushparaj A, et al. Pulsed near infrared transcranial and intranasal photobiomodulation significantly modulates neural oscillations: A pilot exploratory study. Sci Rep 2019;9(1):6309; doi: 10.1038/s41598-019-42693-x

41. Liebert A, Bicknell B, Laakso EL, et al. Remote photobiomodulation treatment for the clinical signs of parkinson's disease: A case series conducted during COVID-19. Photobiomodul Photomed Laser Surg 2022;40(2):112–122; doi: 10.1089/photob.2021.0056
42. Cassano P, Caldieraro MA, Norton R, et al. Reported side effects, weight and blood pressure, after repeated sessions of transcranial photobiomodulation. Photobiomodul Photomed Laser Surg 2019;37(10):651–656; doi: 10.1089/photob.2019.4678
43. Naeser MA, Martin PI, Ho MD, et al. Transcranial photobiomodulation treatment: significant improvements in four ex-football players with possible chronic traumatic encephalopathy. J Alzheimers Dis Rep 2023;7(1):77–105; doi: 10.3233/ADR-220022
44. Bohannon RW. Grip strength: An indispensable biomarker for older adults. Clin Interv Aging 2019;14:1681–1691; doi: 10.2147/CIA.S194543
45. Anstey KJ, Dear K, Christensen H, et al. Biomarkers, health, lifestyle, and demographic variables as correlates of reaction time performance in early, middle, and late adulthood. Q J Exp Psychol A 2005;58(1):5–21; doi: 10.1080/02724980443000232
46. Deary IJ, Johnson W, Starr JM. Are processing speed tasks biomarkers of cognitive aging? Psychol Aging 2010;25(1):219–228; doi: 10.1037/a0017750
47. Ledreux A, Pryhoda MK, Gorgens K, et al. Assessment of long-term effects of sports-related concussions: Biological mechanisms and exosomal biomarkers. Front Neurosci 2020;14:761; doi: 10.3389/fnins.2020.00761
48. Zuo M, Gan C, Liu T, et al. Physical predictors of cognitive function in individuals with hypertension: Evidence from the CHARLS baseline survey. West J Nurs Res 2019;41(4):592–614; doi: 10.1177/0193945918770794
49. Bogner J, Corrigan JD. Reliability and predictive validity of the Ohio State University TBI identification method with prisoners. J Head Trauma Rehabil 2009;24(4):279–291; doi: 10.1097/HTR.0b013e3181a66356
50. Eckner JT, Kutcher JS, Richardson JK. Pilot evaluation of a novel clinical test of reaction time in national collegiate athletic association division I football players. J Athl Train 2010;45(4):327–332; doi: 10.4085/1062-6050-45.4.327
51. Strauss E, Sherman EMS, Spreen O. A. Compendium of Neuropsychologial Tests: Administration, Norms, and Commentary. Oxford University Press: New York, NY; 2006.
52. Franchignoni F, Horak F, Godi M, et al. Using psychometric techniques to improve the balance evaluation systems test: The mini-BESTest. J Rehabil Med 2010;42(4):323–331; doi: 10.2340/16501977-0537
53. King L, Horak F. On the mini-BESTest: Scoring and the reporting of total scores. Phys Ther 2013;93(4):571–575; doi: 10.2522/ptj.2013.93.4.571
54. Brydges CR. Effect size guidelines, sample size calculations, and statistical power in gerontology. Innov Aging 2019;3(4):igz036; doi: 10.1093/geroni/igz036
55. Taylor JM, Alanazi S. Cohen's and hedges' g. J Nurs Educ 2023;62(5):316–317; doi: 10.3928/01484834-20230415-02
56. Hamblin M, Xuan WJ, Huang LY, et al. Transcranial low-level laser (Light) therapy in mice: Tramautic brain injury and beyond. Laser Surg Med 2013;45:50–51.
57. Oron A, Oron U, Streeter J, et al. Near infrared transcranial laser therapy applied at various modes to mice following traumatic brain injury significantly reduces long-term neurological deficits. J Neurotrauma 2012;29(2):401–407; doi: 10.1089/neu.2011.2062
58. Bernick C, Shan G, Bennett L, et al. Assessing clinical change in individuals exposed to repetitive head impacts: The repetitive head impact composite index. Front Neurol 2021;12:605318; doi: 10.3389/fneur.2021.605318
59. Fekri A, Jahan A, Moghadam Salimi M, et al. Short-term effects of transcranial near-infrared photobiomodulation on motor performance in healthy human subjects: An experimental singleblind randomized clinical trial. J Lasers Med Sci 2019;10(4):317–323; doi: 10.15171/jlms.2019.51
60. Blaylock RL, Maroon M, Joseph C. Immunoexcitotoxicity as a Central Mechanism of Chronic Traumatic Encephalopathy – A Unifying Hypothesis. In: Biomarkers for Traumatic Brain Injury. (Dambinova S, Hayes RL, Wang KKW. eds.) The Royal Society of Chemistry: 2012.
61. Zhang D, Shen Q, Wu X, et al. Photobiomodulation therapy ameliorates glutamatergic dysfunction in mice with chronic unpredictable mild stress-induced depression. Oxid Med Cell Longev 2021;2021:6678276; doi: 10.1155/2021/6678276
62. Huang YY, Nagata K, Tedford CE, et al. Low-level laser therapy (810 nm) protects primary cortical neurons against excitotoxicity in vitro. J Biophotonics 2014;7(8):656–664; doi: 10.1002/jbio.201300125
63. Hong N, Kim HJ, Kang K, et al. Photobiomodulation improves the synapses and cognitive function and ameliorates epileptic seizure by inhibiting downregulation of Nlgn3. Cell Biosci 2023;13(1):8.
64. Dunkley BT, Urban K, Da Costa L, et al. Default mode network oscillatory coupling is increased following concussion. Front Neurol 2018;9:280; doi: 10.3389/fneur.2018.00280
65. Zhang J, Safar K, Emami Z, et al. Local and large-scale beta oscillatory dysfunction in males with mild traumatic brain injury. J Neurophysiol 2020;124(6):1948–1958; doi: 10.1152/jn.00333.2020
66. Allen CM, Halsey L, Topcu G, et al. Magnetoencephalography abnormalities in adult mild traumatic brain injury: A systematic review. Neuroimage Clin 2021;31:102697; doi: 10.1016/j.nicl.2021.102697
67. Lewine JD, Plis S, Ulloa A, et al. Quantitative EEG biomarkers for mild traumatic brain injury. J Clin Neurophysiol 2019;36(4):298–305; doi: 10.1097/WNP.0000000000000588
68. Huang MX, Theilmann RJ, Robb A, et al. Integrated imaging approach with MEG and DTI to detect mild traumatic brain injury in military and civilian patients. J Neurotrauma 2009;26(8):1213–1226; doi: 10.1089/neu.2008.0672
69. Cheyne D, Ferrari P. MEG studies of motor cortex gamma oscillations: Evidence for a gamma "fingerprint" in the brain? Front Hum Neurosci 2013;7:575; doi: 10.3389/fnhum.2013.00575
70. van Wijk BC, Beek PJ, Daffertshofer A. Neural synchrony within the motor system: What have we learned so far? Front Hum Neurosci 2012;6:252; doi: 10.3389/fnhum.2012.00252
71. Hamblin MR, Salehpour F. Photobiomodulation of the brain: Shining light on Alzheimer's and other neuropathological diseases. J Alzheimers Dis 2021;83(4):1395–1397; doi: 10.3233/JAD-210743

72. Salehpour F, Hamblin MR. Photobiomodulation for parkinson's disease in animal models: A systematic review. Biomolecules 2020;10(4); doi: 10.3390/biom10040610
73. Hong N. Photobiomodulation as a treatment for neurodegenerative disorders: Current and future trends. Biomed Eng Lett 2019;9(3):359–366; doi: 10.1007/s13534-019-00115-x
74. Topp R, Estes PK, Dayhoff N, et al. Postural control and strength and mood among older adults. Appl Nurs Res 1997;10(1):11–18; doi: 10.1016/s0897-1897(97)80034-1
75. Kitaoka K, Ito R, Araki H, et al. Effect of mood state on anticipatory postural adjustments. Neurosci Lett 2004; 370(1):65–68; doi: 10.1016/j.neulet.2004.07.088
76. Bolmont B, Gangloff P, Vouriot A, et al. Mood states and anxiety influence abilities to maintain balance control in healthy human subjects. Neurosci Lett 2002;329(1):96–100; doi: 10.1016/s0304-3940(02)00578-5
77. Fleming MK, Smejka T, Henderson Slater D, et al. Sleep disruption after brain injury is associated with worse motor outcomes and slower functional recovery. Neurorehabil Neural Repair 2020;34(7):661–671; doi: 10.1177/1545968320929669
78. Kirshner D, Spiegelhalder K, Shahar RT, et al. The association between objective measurements of sleep quality and postural control in adults: A systematic review. Sleep Med Rev 2022;63:101633; doi: 10.1016/j.smrv.2022.101633
79. Neipert L, Pastorek NJ, Troyanskaya M, et al. Effect of clinical characteristics on cognitive performance in service members and veterans with histories of blast-related mild traumatic brain injury. Brain Inj 2014;28(13–14):1667–1674; doi: 10.3109/02699052.2014.947623
80. Naeser MA, Martin PI, Ho MD. Transcranial, Red/Near-Infrared Light-Emitting Diode Therapy to Improve Cognition in Chronic Traumatic Brain Injury. Photomedicine and Laser Surgery 2016;34(12):610–626; doi: 10.1089/pho.2015.4037
81. Zhao X, Du W, Jiang J, Han Y. Brain Photobiomodulation Improves Sleep Quality in Subjective Cognitive Decline: A Randomized, Sham-Controlled Study. JAD 2022;87(4): 1581–1589; doi: 10.3233/JAD-215715
82. Liebel SW, Johnson PK, Lindsey HM, et al. Abstracts Presented at the Fifty First Annual Virtual Meeting International Neuropsychological Society February, 2023. Cambridge University Press: 2023.
83. Bohannon RW. Minimal clinically important difference for grip strength: A systematic review. J Phys Ther Sci 2019; 31(1):75–78; doi: 10.1589/jpts.31.75
84. Kerr ZY, Chandran A, Brett BL, et al. The stability of self-reported professional football concussion history among former players: A longitudinal NFL-LONG study. Brain Inj 2022;36(8):968–976; doi: 10.1080/02699052.2022.2109739

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