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A Proof-of-Concept Study Investigating the Effects of Transcranial Plus Intranasal Photobiomodulation on Cognitive Function after Repetitive Head Acceleration Events

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Abstract

Objective: Investigate the effects of transcranial plus intranasal photobiomodulation (PBM) treatment on cognitive function, using an 810 nm light emitting diode headset and intranasal applicator every other day for 8–10 weeks.
Background Data: An effective gold standard for the rehabilitation of repetitive head acceleration events (RHAEs) does not yet exist.
Methods: Forty-four participants with a history of RHAEs completed a battery of cognitive tests before and after PBM treatment. Data were analyzed at the group level (paired samples *t*-tests, controlling for multiple comparisons) and on the individual-person level (reliable change indices).
Results: On a group level, participants demonstrated statistically significant improvements with moderate-to-large effect sizes in fluid cognition, verbal learning and memory, attention and working memory, and aspects of executive function following PBM treatment. Specific improvements were observed in verbal learning/encoding and delayed recall, sustained attention, errors of omission and commission, working memory, inhibition, and cognitive switching. On the individual level, 0–36% of participants showed reliable improvement across cognitive measures, depending on the subtest; changes were greatest on measures of attention and memory.
Conclusions: Results suggest that PBM treatment may be a promising intervention for improving cognitive function in individuals with a history of RHAEs. Observed improvements in cognitive function following PBM treatment may have important implications for the prevention and treatment of cognitive impairments associated with RHAEs. Further studies with more robust research designs that utilize clinical trial methodologies are needed to confirm and extend these findings.

Keywords: repetitive head impacts, treatment, photobiomodulation, cognition, reliable change, concussion

Introduction

Awareness and concern regarding repetitive head acceleration events (RHAEs) by the public and medical community have increased over the previous decade, leading to advances in research that have been translated to improved injury identification, diagnosis, and management.[1] However, no objective gold standard exists for the treatment of brain injuries or the long-term effects of RHAEs, leaving primary guidance up to clinical expertise and judgment. The consequences of RHAEs are highly heterogenous, often manifesting as subtle yet persistent changes in cognitive function, emotional regulation, and neurological health.[2–4] Medical management of these postinjury consequences typically involves a combination of outpatient medical treatment and psychiatric and/or behavioral interventions for specific symptoms, rather than direct interventions targeting the underlying brain injury.

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For most athletes, cognitive function changes after sport-related concussion (SRC) typically resolve within days to several weeks.[5,6] But these injuries may also result in long-term disruptions for a subset of athletes,[7] particularly in the domains of attention, memory, and executive function.[8] Recent meta-analytic research showed that retired athletes with SRC, in comparison with individuals without concussion, demonstrated significantly weaker verbal learning/encoding, verbal delayed recall, and attention.[9] Still other research has reported that, when compared with control participants or normative data, retired contact sport athletes displayed worse performance in memory, executive function, and psychomotor function.[2] Yet, there is a paucity of interventions to reduce or ameliorate cognitive function deficits in this population.[10]

The potential long-term effects of, and lack of effective treatments for, RHAEs parallel that of SRC and may increase vulnerability to cognitive, psychiatric, and psychosocial dysfunction as these individuals age.[11] For example, former professional American football players who were exposed to RHAEs at an earlier age than other professionals show worse performance on tasks of memory and executive function later in life.[12] RHAEs may even be associated with increased risk of mortality from motor neuron disease[13] and other neurodegenerative disease processes, possibly including chronic traumatic encephalopathy (CTE).[14–17]

To fully grasp the broad and often underrecognized impact of RHAEs, it is necessary to distinguish RHAEs from repetitive head impacts (RHIs). The recent Consensus Head Acceleration Measurement Practices guidelines emphasize the distinction, defining RHAE as any external, short-duration collision force that accelerates the head, whether applied directly to the skull or indirectly via the body.[18] In contrast, RHIs refer to specifically direct impacts to the head. The distinction is critical, as RHAEs capture a much wider range of events that can affect brain health, including those that occur in contact sports, as well as those resulting from whiplash, blast exposure, physical violence, or any mechanical force that directly or indirectly transmits acceleration to the brain. This broader classification acknowledges that even indirect impacts can contribute to cumulative stress on the brain and long-term neurological consequences, reinforcing the need for greater awareness and refined assessment strategies. Accordingly, RHAE is preferred over RHI when discussing the diverse mechanisms by which external forces may compromise brain function over time. As there exist few, if any, treatments for the underlying brain injury sustained in RHAEs, efforts to prevent such injuries remain the primary intervention strategy.[19]

Transcranial plus intranasal photobiomodulation (PBM) has been proposed as a noninvasive, relatively inexpensive, well-tolerated, and easy-to-use at-home treatment for individuals with traumatic brain injury (TBI), possibly including RHAEs.[20,21] Although the exact mechanisms of action for PBM are not fully established, red and near-infrared light is thought to be absorbed by cytochrome C oxidase,[22] which is associated with downstream modulation of reactive oxygen species production via effects on mitochondrial membrane potential, an increase in nitric oxide dissociation, and raised adenosine triphosphate production.[23] In addition to several other molecular interactions,[24] PBM may lead to various reported effects, including anti-inflammatory response and promotion of neuronal proliferation.[20,21]

Early case studies in former athletes[25,26] and other individuals with exposure to multiple mild TBIs and possible secondary CTE[27–30] have demonstrated promising treatment effects of PBM on cognitive function, including improved memory, attention, and executive function. In addition, some studies in head injury populations have suggested treatment-related changes apparent on neuroimaging, including improvements in standard diffusion magnetic resonance imaging (MRI) metrics,[31] altered functional connectivity on functional MRI,[26] increases in cerebral blood flow on single photon emission computed tomography (SPECT) imaging,[30] and changes in SPECT imaging that occurred along with improvements in cognitive function.[32] A recent systematic review and meta-analysis suggests several beneficial functional and histological outcomes of PBM in humans with TBI,[21] and still other research posits that PBM may positively affect cognitive function.[33,34] In addition to the literature supporting the use of PBM to remedy cognitive function in TBI, we recently published our findings regarding the effects of PBM on neuromuscular control in a subset of the present sample of individuals with a history of RHAEs.[35] The results demonstrated significant improvements across measures of reaction time, dexterity, grip strength, and balance following 8–10 weeks of PBM treatment. Given these findings, along with those of previous case studies of former athletes and of larger TBI studies, it follows that PBM may have similar positive effects on cognitive function in individuals with a history of RHAEs; however, additional research is needed.

This proof-of-concept study sought to address important gaps in the neurorehabilitation of RHAEs in adults by assessing the effects of PBM on cognitive function. Based on previous work with individuals with RHAE exposure[35] and TBI,[21] we hypothesized that, following multiple administrations of PBM, individuals with a history of RHAEs would demonstrate improved cognitive function across multiple domains, relative to their performance before PBM treatment.

Materials and Methods

Participants

Forty-nine participants with a history of RHAEs were recruited by referral, word of mouth, and posted flyers for the present study. Of the original sample, 5 participants did not complete the post-intervention assessment, resulting in a total of 44 participants (90% male, mean age = 46.05 ± 14.85) included in the current analysis. Demographic information for the final sample is provided in Table 1. Inclusion criteria included the following: age 18–69 years and a self-reported history of RHAEs (mean = 12.39 ± 6.14 years). Exclusion criteria included the following: history of neurological disease (e.g., dementia, stroke, epilepsy, brain tumor) and/or history of psychiatric disorder (e.g., bipolar, schizophrenia, psychosis). Participants were also excluded for MRI contraindications (e.g., metal in or around the body, report claustrophobia, pregnancy), as the pre- and post-intervention evaluations included a neuroimaging component as part of the larger study; however, those data are not the focus of the present analysis and will be included in future work. The Institutional Review Boards of Brigham Young University and the University of Utah approved all study procedures. Participants provided written informed consent. This study was performed in

Table 1. Sample Demographic and Injury Characteristics

Characteristic	n	*%*
Biological sex		
Male	40	90.91
Female	4	9.09
Ethnicity		
Not Hispanic	43	100.00
Racial group		
White/Caucasian	40	90.91
Asian/Asian-American	1	2.27
Native American/Alaskan Native	1	2.27
Native Hawaiian/Pacific Islander	2	4.55
Highest level of education		
High school graduate/GED	2	4.55
Some college, no degree	10	22.73
Associate's degree	6	13.64
Bachelor's degree	15	34.09
Post-bachelor's degree	1	2.27
Master's degree	9	20.45
Doctorate/professional degree	1	2.27
Dominant hand		
Right	39	88.60
Left	5	11.40
Marital status		
Never married	8	18.60
Domestic partnership	2	4.65
Married	29	67.44
Separated	1	2.33
Divorced	3	6.98
Employment status		
Employed	35	83.33
Retired	3	7.14
Disabled	3	7.14
Other: unable to work	1	2.38

	n	*M*	*SD*	*Min*	*Max*
Age at baseline	44	46.05	14.85	22	69
Total years of education	44	15.66	1.90	12	20
Follow-up interval (days)	44	62.02	7.61	55	97
PBM sessions completed	39	29.40	4.59	21	51
Pretesting to first PBM session (days)[a]	29	1.62	0.91	0	4
Final PBM session to post-testing (days)[a]	29	3.24	5.17	0	21
Total number of TBIs	44	6.68	5.79	0	25
Age at first TBI	43	14.42	8.60	2	45
RHAE exposure (years)	38	12.39	6.14	4	30

$n = 44$. TBI refers to the number of self-reported, but physician-confirmed brain injury events that were experienced by a participant independent of their exposure to RHAEs.

[a]Sessions were only logged by a subset of participants ($n = 29$).

GED, general education development; PBM, transcranial plus intranasal photobiomodulation; RHAE, repetitive head acceleration event; SD, standard deviation; TBI, traumatic brain injury.

accordance with the standards of ethics outlined in the Declaration of Helsinki.

Study design and PBM intervention

This study was a nonrandomized, proof-of-concept, pre-/post-intervention design that used active treatment only over the course of 8–10 weeks. A Vielight (Montréal, Québec, Canada) Neuro gamma (v3) at-home brain PBM device was distributed to each participant following baseline assessment, and they were instructed in its proper use and maintenance. The device has four 1 cm^2 light emitting diodes (LEDs) that deliver the following to the scalp: 75 mW of 810 nm light to the midline dorsomedial prefrontal cortex and 100 mW to each of the left and right lateral parietal areas and the midline precuneus. There is also a 1 cm^2 intranasal LED applicator that delivers 25 mW to the olfactory bulbs inside the nasal cavity, directing the light to the ipsilateral, midline, and likely contralateral orbitofrontal cortex and subcortical structures, including the indirect connections between the olfactory bulbs and entorhinal cortices.[26] Additional details and device specifications are

provided in Table 2. The treatment protocol was developed in accordance with device manufacturer recommendations and included a single 20-min treatment every other day for the duration of the 8–10-week study participation period. The total number of PBM sessions completed and the time intervals between pre-/post-intervention testing and the start/end of PBM usage are reported in Table 1.

Measures

For each participant, standard demographic information (e.g., age, education) was obtained (Table 1). Participants also completed standardized measures of cognitive function aimed to objectively assess verbal learning and memory (California Verbal Learning Test, 3rd Edition; CVLT-3), aspects of executive function (Delis–Kaplan Executive Function System; D-KEFS), and attention (Conners Continuous Performance Test, 3rd Edition; CPT-3). The NIH Toolbox Cognition Battery (NIHTB-CB) was also administered to measure additional cognitive domains, including inhibitory control, fluid cognition (i.e., the ability to solve novel problems, reason abstractly, and adapt to changing situations without relying on prior knowledge), and crystallized abilities (i.e., the ability to use accumulated knowledge, experience, and skills to solve problems). Cognitive assessments were collected prior to and following PBM treatment. The cognitive measures were administered and scored by trained personnel under the supervision of a licensed clinical neuropsychologist.

Statistical analyses

Cognitive tests were scored in accordance with their published standardized protocols, and raw scores were converted into demographically corrected standardized scores using the normative data provided in the respective testing manual. Due to unusually high base rates on demographically corrected standardized scores from NIHTB-CB measures,[36] raw NIHTB-CB subtest scores and uncorrected scaled scores for composite measures were used in the present analysis.[37] For

Table 2. Transcranial PBM Intervention Device Specifications and Settings

Specifications	
Manufacturer	Vielight (Montréal, Québec, 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
Total intervention exposure	Every other day (3–4 days/week) for 8 weeks (∼28 sessions)

Emitter distribution, irradiance, and energy delivered				
		Headset		
Energy source	*Nasal Applicator*	*Anterior*	*Lateral*	*Posterior*
LEDs	1	1	2	1
Wavelength (nm)	810	810	810	810
Pulse rate (Hz, 50% duty cycle)	40	40	40	40
Beam spot (cm^2)	1	1	1	1
Power output density (mW/cm^2)	25	75	100	100
Energy dose density (J/cm^2)	15	45	60	60
Tissue penetrated	Mucosa	Scalp	Scalp	Scalp
Target (s)	Ipsilateral, midline, and likely contralateral orbitofrontal cortex, ipsilateral and likely contralateral olfactory bulbs, with indirect connections to entorhinal cortices	Midline dorsomedial prefrontal cortex	Left and right lateral parietal lobes	Midline precuneus, posterior cingulate cortex
Total energy dose delivered to target surfaces				
Per session		15 J/cm^2 + (3 × 60 J/cm^2) + 45 J/cm^2 = 240 J/cm^2		
Total intervention		240 J/cm^2 × 28 sessions = 6720 J/cm^2		

comparison, the same analyses were also performed on age-corrected standard scores and fully corrected T-scores. All variables were initially screened for missing data, and those with greater than 5% of data missing were assessed for systematic patterns of missing data relating to the dependent variables. All missing data were found to be missing at random. Shapiro–Wilk tests were used to evaluate normality of all continuous variables, and appropriate correlational analyses were used to determine if any demographic or injury variables covaried with the outcome measures. Years of exposure to RHAEs was the only covariate found to have a meaningful impact on measures of cognitive function; however, for purposes of conserving power in our primary analyses, paired *t*-tests and Wilcoxon's signed-rank tests were used to evaluate change in performance on measures of cognitive function for normal and non-normal variables, respectively. To control multiple comparisons, the Benjamini–Hochberg False Discovery Rate procedure[38] was used for all null hypothesis tests, and statistical significance was thresholded at $\mathcal{T} = 0.05$. All *p*-values are reported with 95% confidence intervals, and exact *p*-values are reported for all nonparametric comparisons. Cohen's *d* is provided as a measure of effect size, where $|d| \geq 0.20, 0.50$, and 0.80 are considered small, moderate, and large effects, respectively.[39] All statistical analyses were performed using STATA 17.0 (2021; College Station, TX: StataCorp LP).

Reliable change indices (RCIs) were calculated for each cognitive test using the RCI formula provided by Duff,[40] where the difference between time 1 and time 2 scores is divided by the standard error of the difference (SED). Test–retest reliability (*r*) and standard error of measurement (SEM) values, which are used in the calculation of the SED, were obtained from the respective test manuals for the CVLT-3, D-KEFS, and CPT-3 scores. Intraclass correlations (ICCs) were the only test–retest reliability metrics available for NIH Toolbox scores, and these have been shown to be suitable alternatives to Pearson's *r* when calculating RCIs.[41,42] SEM and ICCs for NIH Toolbox subtest raw scores were obtained from Weintraub et al.,[37] and ICCs for NIH Toolbox composite scores (unadjusted scaled scores) were obtained from Heaton et al.[43] RCIs were calculated using a *z*-score of ±1.645 such that only 5% of cases will fall above or below reliable change.[40]

Results

Performance on cognitive testing pre- and post-PBM treatment are presented in Table 3 (CVLT-3, D-KEFS, CPT-3) and Table 4 (NIHTB-CB).

Verbal learning and memory

In the domain of verbal learning and memory, participants demonstrated statistically significant increases with moderate effect sizes in learning/encoding ($t = 3.27$; $p = 0.002$; $d = 0.49$) and delayed free recall (short-delay: $t = 4.13$; $p < 0.001$; $d = 0.62$; long-delay: $t = 3.84$; $p < 0.001$; $d = 0.58$) performances following PBM treatment.

Executive function

While no changes were observed across measures of phonemic or semantic verbal fluency following treatment, significant improvements with moderate effect sizes were observed across measures of response inhibition ($z = 3.18$; $p = 0.001$; $d = 0.54$) and cognitive switching ($z = 3.96$; $p < 0.001$; $d = 0.67$).

Sustained Attention

Participants demonstrated significant post-treatment improvements with moderate effect sizes in sustained attention ($t = -3.51$; $p < 0.001$; $d = -0.67$), as well as significantly fewer

Table 3. Pre- to Post-PBM Treatment Effects on Cognitive Measures

Measure	n	M_D	SD_D	t *or* z	df	p	*95% CI* *LL*	*95% CI* *UL*	d
CVLT-3									
Trials 1–5	44	5.93	12.02	3.27	43	0.002*	2.28	9.59	0.49
SDFR	44	1.50	2.41	4.13	43	0.000*	0.77	2.23	0.62
LDFR	44	1.43	2.47	3.84	43	0.000*	0.68	2.18	0.58
Delayed recall total	44	6.52	11.58	3.74	43	0.001*	3.00	10.04	0.56
Total recall	44	6.02	11.59	3.45	43	0.001*	2.50	9.55	0.52
D-KEFS									
CWI inhibition[a]	43	0.98	1.82	3.18		0.001*	0.42	1.54	0.54
CWI switching[a]	43	1.40	2.09	3.96		0.000*	0.75	2.04	0.67
VF letter	43	0.65	2.36	1.81	42	0.078	–0.07	1.38	0.28
VF category	43	–0.33	3.47	–0.62	42	0.542	–1.39	0.74	–0.09
VF category switching	43	0.93	3.35	1.82	42	0.076	–0.10	1.96	0.28
CPT-3									
d′	38	–4.63	6.93	–3.51		0.000*	–6.91	–2.35	–0.67
Omissions[a]	38	–1.42	4.16	–1.98		0.048*	–2.79	–0.05	–0.34
Commissions[a]	38	–4.61	7.59	–3.17		0.001*	–7.10	–2.11	–0.61
HRT SD	38	–2.37	5.37	–2.92		0.003*	–4.13	–0.60	–0.44

*Significant values are indicated by an asterisk if they survived the multiple comparison correction ($p < 0.05 <$ FDR).

[a]Wilcoxon signed-rank test was used in place of paired *t*-test due to violation of normality. Reported *p*-values are exact statistics.

CI, confidence interval; CPT-3, Conners Continuous Performance Test, 3rd Edition; CVLT-3, California Verbal Learning Test, 3rd Edition; CWI, Color-Word Interference Test; *d′*, detectability; D-KEFS, Delis–Kaplan Executive Function System; HRT SD, hit reaction time standard deviation; LDFR, long-delay free recall; LL, lower limit; M_D, mean difference; SD_D, standard deviation of the difference; SDFR, short-delay free recall; UL, upper limit; VF, verbal fluency test.

Table 4. Pre- and Post-PBM Treatment Effects on the NIH Toolbox Cognition Battery

NIHTB-CB	M_D	SD_D	t *or* z	df	p	*95% CI* *LL*	*UL*	d
Raw score								
Picture vocabulary	–0.01	0.91	–0.07	43	0.948	–0.28	0.27	–0.01
Flanker[a]	0.29	0.56	2.95		0.003*	0.12	0.46	0.51
List sorting	1.14	2.12	3.56	43	0.001*	0.49	1.78	0.54
DCCS	0.23	0.85	1.79	43	0.080	–0.03	0.49	0.27
Pattern comparison	4.25	9.40	3.00	43	0.005*	1.39	7.11	0.45
Picture sequence memory[a]	0.56	0.84	3.86		0.000*	0.31	0.82	0.67
Oral reading[a]	0.32	1.72	1.09		0.283	–0.20	0.85	0.19
Fluid composite[b]	4.72	5.01	6.25	43	0.000*	3.20	6.25	0.94
Crystallized composite[b]	0.44	3.60	0.82	43	0.418	–0.65	1.54	0.12
Total composite[b]	3.23	4.09	5.25	43	0.000*	1.99	4.47	0.79
Age-corrected SS								
Picture vocabulary	–0.34	7.18	–0.32	43	0.754	–2.52	1.84	–0.05
Flanker	6.82	11.50	3.93	43	0.000*	3.32	10.32	0.59
List sorting	5.84	10.74	3.61	43	0.001*	2.58	9.11	0.54
DCCS	4.23	15.93	1.76	43	0.086	–0.62	9.07	0.27
Pattern comparison	7.30	15.44	3.13	43	0.003*	2.60	11.99	0.47
Picture sequence memory	11.30	16.05	4.67	43	0.000*	6.41	16.18	0.70
Oral reading	2.59	11.25	0.89		0.378	–0.83	6.01	0.23
Fluid composite	10.52	11.71	5.96	43	0.000*	6.96	14.08	0.90
Crystallized composite	1.20	8.21	0.97	43	0.336	–1.29	3.70	0.15
Total composite	6.89	9.41	4.86	43	0.000*	4.03	9.75	0.73
Fully-corrected T-score								
Picture vocabulary[a]	0.07	4.85	0.14		0.895	–1.41	1.54	0.01
Flanker	3.93	7.03	3.71	43	0.001*	1.80	6.07	0.56
List sorting	3.86	7.31	3.50	43	0.001*	1.64	6.09	0.53
DCCS	2.86	9.65	1.97	43	0.056	–0.07	5.80	0.30
Pattern comparison	4.43	9.64	3.05	43	0.004*	1.50	7.36	0.46
Picture sequence memory	7.75	11.06	4.65	43	0.000*	4.39	11.11	0.70
Oral reading	1.89	8.39	1.49	43	0.143	–0.66	4.44	0.22
Fluid composite	6.89	7.70	5.94	43	0.000*	4.55	9.23	0.89
Crystallized composite[a]	1.20	6.28	1.07		0.289	–0.71	3.11	0.19
Total composite	4.86	6.66	4.17		0.000*	2.84	6.89	0.73

$n = 44$.

*Significant values are indicated by an asterisk if they survived the multiple comparison correction ($p < 0.05 <$ FDR).

[a]Wilcoxon signed-rank test was used in place of paired *t*-test due to violation of normality. Reported *p*-values are exact statistics.

[b]Uncorrected scaled scores.

CI, confidence interval; DCCS, dimensional change card sort; LL, lower limit; M_D, mean difference; NIHTB-CB, National Institute of Health Toolbox Cognition Battery; SD_D, standard deviation of the difference; SS, standard score; UL, upper limit.

errors of omission ($z = -1.98$; $p = 0.048$; $d = -0.34$) and commission ($z = -3.17$; $p = 0.001$; $d = -0.61$), with small and moderate effect sizes, respectively.

NIH toolbox cognition battery

Overall, participants demonstrated significant improvements, with moderate-to-large effect sizes, on measures of fluid cognition ($t = 6.25$; $p < 0.001$; $d = 0.94$), processing speed ($t = 3.00$; $p = 0.005$; $d = 0.45$), inhibitory control and attention ($t = 2.95$; $p = 0.003$; $d = 0.51$), working memory ($t = 3.56$; $p = 0.001$; $d = 0.54$), and sequential memory ($t = 3.86$; $p < 0.001$; $d = 0.67$). As expected, crystallized abilities, including word reading, vocabulary, and crystallized intelligence, were unchanged following PBM treatment.

Reliable change

Reliable change indices were used to test whether individual participants responded to the PBM treatment beyond that which can be expected due to measurement error, and these data are reported in Table 5. Briefly, reliable increases were observed in 14–23% of the sample across all CVLT-3 measures, whereas one participant (3% of sample) showed reliable decline on the Total Recall score. On the D-KEFS Color-Word Interference Test, 5–14% of the sample reliably improved, whereas 0% reliably declined, on both inhibition and switching conditions. Similar rates of reliable improvement (5–14%) and reliable decline (5–21%) were observed overall across D-KEFS verbal fluency conditions, which explain the lack of change in performance observed in our sample for this measure. Reliable improvements were observed across all CPT-3 measures, with a minimum of 5% improving on hit reaction time standard deviation (HRT SD) and a maximum of 26% improving on the number of commission errors made. Only one participant (3% of sample) reliably declined on CPT-3 HRT SD. Finally, reliable improvements were observed in a minimum of 7% (List Sorting Working Memory and Total Composite) to a maximum of 36% (Picture

Table 5. Reliable Change from Pre- to Post-PBM Treatment

		Improved		Declined	
Measure	n	n	%	n	%
CVLT-3					
Trials 1–5	44	10	22.73	0	0.00
SDFR	44	7	15.91	0	0.00
LDFR	44	6	13.64	0	0.00
Delayed recall total	44	6	13.64	0	0.00
Total recall	44	7	15.91	1	2.27
D-KEFS					
CWI inhibition	43	2	4.65	0	0.00
CWI switching	43	6	13.95	0	0.00
VF letter	43	5	11.63	2	4.65
VF category	43	4	9.30	9	20.93
VF category switching	43	3	6.98	2	4.65
CPT-3					
d′	38	7	18.42	0	0.00
Omissions	38	3	7.89	0	0.00
Commissions	38	10	26.32	0	0.00
HRT SD	38	2	5.26	1	2.63
NIHTB-CB					
Picture vocabulary	44	0	0.00	0	0.00
Flanker	44	11	25.00	0	0.00
List sorting	44	3	6.82	1	2.27
DCCS	44	7	15.91	4	9.09
Pattern comparison	44	9	20.45	1	2.27
Picture sequence memory	44	16	36.36	3	6.82
Oral reading	44	9	20.45	3	6.82
Fluid composite	44	4	9.09	0	0.00
Crystallized composite	44	7	15.91	3	6.82
Total composite	44	3	6.82	0	0.00

Reliable change was determined with a threshold of ±1.645. CPT-3, Conners Continuous Performance Test, 3rd edition; CVLT-3, California Verbal Learning Test, 3rd edition; CWI, Color-Word Interference Test; *d′*, detectability; DCCS, Dimensional Change Card Sort; D-KEFS, Delis Kaplan Executive Function System; NIHTB-CB, National Institute of Health Toolbox Cognition Battery; HRT SD, hit reaction time standard deviation; LDFR, long-delay free recall; SDFR, short-delay free recall; VF, Verbal Fluency Test.

Sequence Memory) of the sample across all NIHTB-CB measures, with the exception of the picture vocabulary performance (0% reliable improvement and decline), which measures a crystallized function that is not expected to change in the presence of injury or recovery. Reliable decline was observed in 3–9% of the sample on individual NIHTB-CB subtests and on the Crystallized Composite score. Overall, patterns of reliable change were consistently in favor of improvement across cognitive domains, whereas, excluding verbal fluency performance, no to few (max 4) participants declined on individual cognitive measures.

Discussion

Exposure to RHAEs is a significant public health concern, yet most research to date has focused on identifying the chronic and long-term effects of exposure to RHAEs during aging, particularly the link to neurodegenerative disease.[16,44,45] Less work, however, has focused on the treatment and rehabilitation of RHAE-related cognitive impairments; thus, an effective gold standard treatment available to medical providers for such injuries does not exist. Rather, available interventions are typically aimed at treating specific symptoms instead of the underlying pathology caused by exposure to repetitive neurotrauma. Changes in cognitive function are common both following acute RHAEs and in the years postinjury, significantly impacting the affected individual's quality of life. PBM has been proposed as a potential treatment for RHAEs, as it works mechanistically at the cellular level to ameliorate the myriad consequences of RHAEs, including cognitive decline. PBM is thought to reduce inflammation of brain tissue and encourage neuronal proliferation,[46] although the exact mechanisms of action following TBI remain unverified in humans.

The results of the current pilot study show that, following 8–10 weeks of active PBM treatment, adults with a history of RHAEs experienced statistically significant improvements across measures of fluid cognition, processing speed, learning and memory, attention, working memory, and certain aspects of executive function. With a few exceptions (see Table 3), the effect sizes ranged from moderate to large, suggesting that PBM potentially provides both clinically meaningful and statistically significant improvements in cognitive function across a number of domains. Further, these wide-ranging improvements occurred specifically across domains that are commonly affected by neurotrauma, whereas stable premorbid abilities that are not as susceptible to injury,[47,48] such as performance on the NIHTB-CB Oral Reading Recognition test and Crystallized Composite, were unaffected by PBM. This supports previous literature suggesting that PBM targets neuroplastic mechanisms relevant to recovery[49–51] rather than producing broad, nonspecific cognitive enhancement, reinforcing its potential as a therapeutic intervention for individuals with a history of RHAE exposure.

It is important to note that the improvements observed across cognitive domains were identified using gold-standard neuropsychological assessments that represent objective measures of cognitive function rather than limited to subjective improvements in function typically assessed with self-report measures. Thus, even with the limitations of the current study discussed below, this is one of the first studies to show objective improvements in cognitive function in adult individuals with exposure to RHAEs. Further, our results support those of previous case studies of former athletes with RHAE exposure, where performance on objective measures of cognitive function was also shown to be improved following PBM treatment in a small number of individuals.[25,26]

Results on the individual-subject level (reliable change) were consistent across measures of verbal learning and memory, executive function, attention, working memory, and fluid ability, with reliable improvement occurring in a larger proportion of the sample than reliable decline. The number of participants who showed reliable improvement was relatively small to moderate, ranging from 5% to 36%, whereas declines were observed in 0–9% of the sample across all measures, with the exception of the verbal fluency test, where 5–20% of the sample declined in phonemic and semantic fluency abilities. The variability in performance changes in verbal fluency may be explained by individual variability in baseline verbal ability or cognitive strategy, suggesting that individual differences are at least partially unrelated to PBM efficacy. It is also possible that verbal fluency abilities, which rely on strategic retrieval from long-term memory, require a longer duration of

neuroplastic adaptation than other abilities that may be improved by enhanced cellular metabolism, which occurs more rapidly upon exposure to PBM treatment.[52–54] There are also several possible reasons why individual reliable change is relatively lower than expected based on pre- to post-testing group average scores (e.g., individual differences in treatment response and cognitive performance) and effect sizes for improvements in performance. Meeting the criteria for reliable change is stringent and depends on psychometrically reliable measures. The measures chosen for this study generally had test–retest reliability of $r \geq 0.70$, but they were variable. For example, the retest coefficients for the NIHTB-CB tests range from ICCs of 0.73 to 0.92, contributing to variability in the reliable change intervals. Moreover, cognitive abilities are generally stable over time, and the dose of PBM needed to alter cognitive function is currently being examined.[33,55] Knowing percent with reliable change at the individual-subject level is useful and important when considering developing technology such as PBM, but it should not diminish the promising improvements seen at the group level in these early studies of PBM.

The current results are consistent with studies of adults without current dementia symptoms. Specifically, Chan and colleagues[56] demonstrated improvements in inhibitory control and flexibility after a single 7.5-min PBM session compared with a group that received placebo treatment. Their findings suggest that even after a single PBM treatment session, improvements in cognitive function occur in older adults, which may be related to increased tissue oxygenation due to increased cerebral blood flow in response to PBM.[56] Similarly, improvements in performance on cognitive tests and self-reported enhanced functional abilities, such as increased mobility and decreased incontinence, have been shown in individuals diagnosed with dementia and Alzheimer's disease after a 12-week at-home tPBM treatment protocol.[57] Other studies have found no improvement in cognitive function in patients with mild-to-moderate dementia at the 6-week interval, but significant improvement at the 12-week interval, suggesting that length of treatment is important.[58] When considered together, PBM may be effective in improving cognitive function in healthy older adults, those with dementia, as well as individuals with RHAE across the lifespan. As evidence exists for a causal relationship between repetitive TBI and traditional biomarkers of neurodegenerative diseases, such as brain atrophy and memory loss, it is imperative to examine potential benefits of PBM in treatment of brain injury.[59]

Limitations and future directions

This study represents one of the first to examine the impact of PBM on individuals with exposure to RHAEs and, to our knowledge, includes the largest sample of research participants with exposure to repetitive neurotrauma to complete a multi-week intervention of PBM to date. Strengths include measurement of objective performance on cognitive tests as opposed to only self-reported cognitive function, good treatment compliance in the cohort, and determination of both clinically meaningful and statistically significant differences at pre- versus post-treatment timepoints. However, the findings of this study should be considered within the context of several limitations. First, our study design included only an active treatment group and no control group against which to compare cognitive function pre- and post-PBM. While this limits direct comparisons, the findings support the need for future rigorous studies, and reliable change results are provided at the individual-subject level. Second, our sample size was limited and primarily composed of White male participants with varying levels of exposure to RHAEs. In addition, the wide age range contributed to considerable variability in the time since last RHAE exposure. Unfortunately, with the limited sample size, we were not powered to control for age, time since injury, or variability in the amount of exposure to neurotrauma. Third, study participants self-reported their history of RHAEs, which is potentially subject to several forms of bias. Fourth, the possible influence of practice effects on participants' cognitive function following PBM treatment is unknown. Finally, as most participants were White, we were not able to control for the possible effect of skin pigmentation regarding relative penetration of light from the LEDs.[60]

To address these limitations, future studies should incorporate a well-matched control group with double blinding to strengthen causal interpretations of PBM's effectiveness. Expanding sample diversity—including greater representation of females and individuals with varying skin pigmentation, age ranges, and exposure histories—will be crucial for understanding how individual differences influence PBM's penetration and neurobiological effects across individuals that more accurately represent the greater population. Finally, additional intervention designs, such as a combination of in-office PBM with at-home treatments targeting specific functional or structural networks, or the effectiveness of whole-body PBM on cognition could be explored to optimize treatment protocols. By addressing these research gaps, future studies can enhance the generalizability of PBM as a therapeutic intervention and refine its application for individuals with RHAEs and other neurotrauma populations.

Although this study represents an important step in understanding the effects of PBM on individuals with exposure to RHAEs, more refined analyses are needed to advance our understanding of its potential cognitive benefits. One key area for future investigation is the heterogeneity in cognitive function among individuals with RHAEs. As not all participants exhibited deficits across all cognitive domains at baseline, future subgroup analyses from larger samples should be performed to determine whether those with greater initial impairment exhibit greater cognitive improvement post-PBM. In addition, exploratory analyses could be used to identify participant clusters with varying patterns of PBM-related improvement across cognitive domains, which may provide insight into individual differences that predict treatment effectiveness. Finally, it is essential that future research assesses whether the beneficial effects of PBM are maintained over time. Our ongoing longitudinal follow-up of this cohort at multiple post-treatment timepoints will allow us to assess the persistence of cognitive improvements and examine potential delayed effects of PBM. These data will also help mitigate concerns regarding transient effects on cognitive performance, such as sleepiness, when tested immediately following the completion of treatment sessions.

Conclusions

This proof-of-concept study provides preliminary evidence supporting the use of PBM in addressing RHAE-related

cognitive difficulties. Our findings suggest that PBM may improve cognitive function across multiple critical domains, including attention, verbal learning and memory, and aspects of executive function, with moderate-to-large effect sizes. However, some domains also showed reliable declines, likely reflecting normal intraindividual cognitive variability. Future research with more robust research designs and more refined analysis is needed to further elucidate these findings and evaluate the therapeutic potential of PBM for individuals with RHAEs.

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Authors' Contributions

The following have made contributions to this work as indicated. S.W.L.: Conceptualization, methodology, validation, investigation, writing—original draft, writing—review and editing, visualization, supervision, and project administration. P.K.J.: Conceptualization, methodology, validation, data curation, and writing—review and editing. H.M.L.: Conceptualization, data curation, formal analysis, methodology, software, validation, visualization, writing—original draft, and writing—review and editing. M.J.L.: Formal analysis, methodology, software, validation, writing—original draft, and writing—review and editing. C.E.: Methodology and writing—review and editing. E.S.H.: Investigation, project administration, and writing—review and editing. H.A.R.: Investigation. C.V.: Investigation. C.M.M.: Writing—review and editing. L.S.C.: Resources, project administration, and funding acquisition. E.A.W.: Conceptualization, investigation, methodology, validation, investigation, resources, writing—review and editing, supervision, project administration, and funding acquisition. D.F.T.: Conceptualization, methodology, validation, investigation, resources, writing—review and editing, supervision, project administration, and funding acquisition.

Author Disclosure Statement

L.S.C. serves as a consultant for Vielight, Inc. All authors declare no additional competing interests relevant to this study.

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