Transcranial photobiomodulation improves cognitive function, post-concussion and PTSD symptoms in mild traumatic brain injury

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Abstract

Traumatic brain injury (TBI) occurs in millions of people globally each year, with mild TBI (mTBI) representing over 90% of cases. Despite the common assumption of full recovery, significant disturbances persist in many mTBI patients, including cognitive deficit, headache, dizziness, sleep problems, and symptoms of post-traumatic stress disorder (PTSD). Given that effective treatment is still scarce, the present study investigated the efficacy of transcranial photobiomodulation (tPBM) as an intervention for improving these sequelae in patients with mTBI. In this randomized placebo-controlled trial, 17 patients with mTBI were recruited. Participants were randomized to receive both real and sham tPBM conditions with a counterbalanced order, with a 1-week washout between interventions. Assessments were conducted at baseline, after real tPBM and after sham tPBM. These included neuropsychological tests, measurements of oxygenated hemoglobin using functional near-infrared spectroscopy (fNIRS) during a visual working memory task, and self-rated questionnaires assessing sleep quality, physical post-concussion symptoms, pain intensity and PTSD symptoms. Compared to the baseline, participants demonstrated significant improvements. After receiving tPBM, patients showed enhanced cognitive efficiency, as evidenced by improved visual working memory performance, better learning in verbal memory tests, improved subjective sleep quality, fewer physical post-concussion symptoms, reduced pain intensity, and decreased PTSD symptoms. In contrast, no significant improvement was observed after patients received the sham tPBM. In addition, the statistically significant improvement in behavioral symptoms also reached the minimal clinically important difference, suggesting clinical significance. These findings support the potential of tPBM as a safe, non-invasive clinical

intervention for cognitive deficits and associated symptoms in mTBI. Further exploration is encouraged to evaluate tPBM as a rehabilitation strategy for enhancing recovery in TBI patients.

Introduction

It was estimated that 50 – 60 million people experience a traumatic brain injury (TBI) each year, resulting in a substantial global health burden of approximately US$400 billion annually [1]. TBI is a leading cause of injury-related death and disability, with over 90% of cases classified as mild TBI (mTBI) [2]. At the post-injury stage, mTBI patients may experience post-concussion symptoms, including headache, balance problems, dizziness, memory loss, trouble concentrating, forgetfulness, slowed thinking processes, and sleep disturbance. Some patients may also develop symptoms of post-traumatic stress disorder (PTSD). Both symptoms can significantly disrupt daily living [3]. Research indicates that 53% of mTBI patients experience functional limitations 12 months after injury, with common limitations including reduced work capacity, social functioning issues, and family disruptions [4]. Research on interventional TBI rehabilitation has focused primarily on severe TBI, leaving mTBI understudied despite its high prevalence and ongoing post-injury symptoms [5]. Therefore, identifying effective interventions for mTBI is essential, and recent research suggests that transcranial photobiomodulation (tPBM) may be a promising therapeutic option [6].

tPBM is a non-invasive, painless, and non-thermal brain stimulation technique that applies red and near-infrared light to the scalp [7]. tPBM has been utilized for enhancing brain function in both healthy individuals [8,9] and clinical population, including patients with stroke [10,11], mild cognitive impairment [12-14], dementia [15], and psychological disorders [16]. Previous systematic reviews have reported improvement in cognitive function in learning and memory, attention, executive function, language, and global cognitive function after tPBM [15,17,18].

The beneficial effects of tPBM on patients with TBI were initially documented in a case report involving two chronic mTBI patients [19]. One patient showed improvements in sustained attention after eight weeks of tPBM, while the other was able to return to work after four months of intervention. The latter also documented improved neuropsychological test performance in executive function and memory after nine months of intervention. After that, a case series involving 11 chronic mTBI patients reported improvements consistent with these initial findings after six weeks of tPBM [20]. In addition to improved neuropsychological test performance, these patients reported improved sleep quality and reduced post-traumatic stress symptoms. Since then, many case series have emerged, highlighting the positive effects of tPBM on cognitive function across a range of TBI severity, from mild to severe [21-25]. Furthermore, some TBI patients reported a reduction in post-injury symptoms [22,24].

Previous studies suggest that tPBM enhances the production of adenosine triphosphate [26,27] and promotes greater vasodilation and regional cerebral blood flow [28] [see [29] for a detailed explanation of the mechanism in the brain]. This process is essential for providing the energy necessary to optimize brain function. tPBM is believed to significantly counteract the reduced cerebral blood flow commonly observed in TBI patients compared to healthy controls [30,31], thereby enhancing brain function. This is supported by a previous study demonstrating that cerebral blood flow was enhanced after receiving tPBM [23]. These findings suggest the potential of tPBM as a therapeutic intervention for improving symptoms in mTBI patients.

Although the findings reviewed were encouraging, the existing support for tPBM in TBI primarily consists of case studies, which raise questions about the validity and generalizability of these findings and the potential influence of placebo or learning effects. Among the existing literature, two studies employed a control group [32,33]. Specifically, one study assessed the feasibility and safety of tPBM among patients with moderate TBI in the acute phase [33]. The results showed significant differences in the magnetic resonance imaging-derived diffusion parameters of white matter tracts between the sham and real stimulation groups in terms of radial diffusivity, mean diffusivity, and fractional anisotropy, suggesting that tPBM is feasible and safe. The other study examined the effect of tPBM on resting-state functional connectivity in patients with moderate TBI during the acute, subacute, and late-subacute phases, typically within one week to three months after injury [32]. The results showed that seven pairs of brain regions exhibited greater changes in connectivity after tPBM patients were treated with tPBM during the acute and subacute phases, whereas those who underwent sham stimulation did not, suggesting that tPBM in the acute phase may impact resting-state neuronal circuits during the early recovery phase of moderate TBI.

While the randomized controlled trials focused on the structural and functional connectivity of the brain, the effects on post-injury symptoms, such as changes in cognitive and physical post-concussion symptoms and post-traumatic stress symptoms, were not explored. In addition, since the recruited sample of these two studies primarily consisted of moderate TBI patients in the acute phase, the effects on mTBI, which is the most common type of TBI, remain uncertain.

The present study aimed to investigate the effects of tPBM on patients with mTBI. Participants with mTBI were recruited and received both sham and real tPBM in a counterbalanced design.

Their performance was compared at baseline and after both sham and real tPBM using neuropsychological assessments and self-rated questionnaires. In addition, participants' cognitive efficiency was assessed using functional near-infrared spectroscopy (fNIRS), an optical imaging tool that utilizes near-infrared light in estimating the relative concentration of oxygenated (HbO) and deoxygenated (HbR) hemoglobin in cerebral blood flow [34]. fNIRS has been found to be a reliable measure of cognitive effort [35]. Previous tPBM studies have employed fNIRS to understand the hemodynamic changes underlying tPBM, revealing reduced prefrontal activation together with unchanged or improved behavioral performance, suggesting that cognitive efficiency is enhanced by making the cognitive task less effortful to complete [13,36-38]. It was hypothesized that participants would show significant improvement only after real tPBM compared to baseline, with no significant changes observed after sham tPBM.

Materials and Methods

Participants

The study was conducted in accordance with the Declaration of Helsinki of the World Medical Association Assembly, approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (No. 2021.699), and registered in the Chinese Clinical Trial Registry on 4 April 2024 (No. ChiCTR2300070164). Informed consent was obtained from all recruited participants included in the study.

Participants were recruited from the outpatient clinic of the Department of Neurosurgery at Prince of Wales Hospital between May 2023 and April 2024. Eligible participants were required to be between 18 and 80 years old, able to understand the Chinese language and have a history of mTBI, defined by a Glasgow Coma Scale score of 13 – 15, with no loss of consciousness or loss of consciousness lasting less than 30 min, and no post-traumatic amnesia (PTA) more than 24 h after the injury. They also needed to have concerns regarding the physical, cognitive, or psychological symptoms that emerged after the injury. Interested individuals with a history of moderate to severe head injury (i.e., a Glasgow Coma Scale less than 13, loss of consciousness more than 30 min, and post-traumatic amnesia more than 24 h), a current diagnosis of cancer, hearing or speech impairments that could hinder assessment performance, or those who were pregnant were excluded from participation. Due to ethical considerations, participants are allowed to maintain, change, or initiate new treatments to manage their medical conditions. Throughout the study, participants did not report starting any new treatments for their head injuries.

The CONSORT diagram of the present study is presented in Figure 1. After screening, a total of 195 participants met the inclusion criteria, and 23 were recruited. All participants completed assessments at baseline and after the first stimulation condition. Six participants dropped out afterward due to family issues and work schedules. As a result, 17 recruited participants completed all three assessments, and their data were analyzed. Among these participants, they have already had mTBI for at least eight months, with the mean and *SD* of injury at 5.92 years and 7.03 years.

Procedures

Recruited participants first underwent a baseline assessment, which included standardized neuropsychological assessments, questionnaires, and the visual working memory span task (VWMST) with fNIRS recording. After the assessment, participants were randomly divided into two groups: one received the real tPBM first, followed by the sham tPBM (n = 12), while the other received the sham tPBM first, followed by the real tPBM (n = 11). Participants were randomly assigned to groups using a random number generator. Each intervention condition consisted of 18 sessions over six weeks. The intervention schedule was chosen based on previous studies [19-21,24]. After each intervention condition, participants completed an assessment identical to the baseline assessment. Considering that participants' improvements regressed after one week without tPBM in a previous report [19], a one-week washout period was implemented before participants began the second intervention condition. Since participants were not informed about the crossover between sham and real tPBM, they did not know the different stimulation conditions in the two phases. In this study, participants and investigators who administered tPBM were blinded to group assignment. However, the investigator who conducted outcome assessments was not blinded to group assignments because he was also responsible for managing the technical issues of the tPBM devices.

Materials

Neuropsychological assessment and self-rated questionnaires

Neuropsychological assessment was conducted to evaluate the effects of tPBM on cognitive function in various domains, including the Hong Kong List Learning Test (HKLLT) for memory

[39], the Digit Span Test (DST) for attention [40], the Five-Point Test (FPT) [41] and Shape Trail Test (STT) [42] for executive function, and the Category Fluency Test (CFT) for language [43].

In addition to neuropsychological assessment, participants were asked to complete several self-rated questionnaires evaluating changes in post-concussion symptoms and PTSD symptoms, including the Pittsburgh Sleep Quality Index (PSQI) for sleep quality [44], the Rivermead Post-Concussion Symptoms Questionnaire (RPQ) for physical post-concussion symptom [45], the Visual Analogue Scale (VAS) for pain intensity (on a scale of 0 to 10) [46]. PTSD symptoms were assessed using the PTSD Checklist for DSM-5 (PCL-5) [47].

fNIRS task

The VWMST (Figure 2a & b) was employed in this study to evaluate the effect of tPBM on cognitive efficiency [13,37,38]. In this task, participants were required to memorize a sequence of blue square blocks that changed to yellow and then recall the sequence by clicking on the square blocks in the correct order using a computer mouse. The length of the span sequence varied from two to nine square blocks, with each span level consisting of two trials. Before and after each trial, there was a control period during which participants were instructed to fixate on a central fixation cross displayed on the computer monitor and to minimize any unnecessary head and body movements. The visual span, defined as the longest correctly recalled sequence, and the average reaction time to complete each span level were calculated as measures of behavioral performance in the VWMST.

Hemodynamics measurement

A 16-channel fNIRS system (OEG-SpO2 model, Spectratech Inc., Kanagawa, Japan) was used to measure prefrontal hemodynamics during the VWMST. This system employed near-infrared light at wavelengths of 770 and 840 nm to estimate the relative concentrations of HbO and HbR in cerebral blood flow. The device consisted of six pairs of light source and detector probes arranged in a 2 × 6 matrix (Figure 2c), with a 3 cm separation between them. The bottom probe was placed at FpZ, and the sample rate was set at 12.21 Hz.

fNIRS signal preprocessing

The fNIRS signal preprocessing was performed using HomER3 [48]. Firstly, channels with a signal-to-noise ratio < 10 dB were removed from the analysis. On average, 1.84% (*SD* = 5.20%) of the channels were removed. The intensity signal was transformed into optical density changes, followed by the application of a low-pass filter at 0.1 Hz to eliminate high-frequency noise. The filtered data was then converted to HbO and HbR using the modified Beer-Lambert Law, with a differential pathlength factor of six for both wavelengths. A correlation-based signal improvement (CBSI) was applied to improve signal quality and reduce noise [49]. The corrected data was baseline-corrected using the 10 s control period prior to the main task. After the baseline correction, data were averaged across all time points within each trial and then across the two trials of each span level. Since the HbR data mirrored the HbO data after CBSI, only the HbO was analyzed.

tPBM device

The tPBM intervention was delivered using a custom device with 81 light-emitting diodes (LEDs), each emitting 810 nm light in a continuous wave. The LEDs, approximately 1 cm^2 each, were positioned over the prefrontal, parietal, and temporal regions of the participants' heads, including FpZ, Fp1, Fp2, F7, F8, T7, T8, Fz, F3, F4, Cz, C3, C4, P3, and P4. Each tPBM session lasted 12 minutes, with nine clusters of LEDs delivering 30 mW/cm^2 and 1.8 J/cm^2 of stimulation per min, resulting in a total energy delivery of 16.2 J per cluster per min. Twelve one-min stimulation sessions were conducted using one or two clusters at a time to prevent overheating, leading to a total energy delivery of 324 J per session (irradiance = 30 mW/cm^2, fluence = 21.6 J/cm^2). An identical device was used for the sham condition, differing only in that it did not emit light as the active device did. However, the sham device still produced beeping sounds at the start and end of the session, preventing participants from discerning whether they were receiving real or sham tPBM. It is noted that no participants experienced serious discomfort or aversive effects during or after the intervention.

Data analysis

Repeated measures ANOVA, along with post hoc paired *t*-tests, was performed to detect any significant differences between conditions (i.e., baseline, sham, and real). For the reaction time and HbO measurements in the VWMST, the interactions of condition × span (i.e., span levels 2 to 9) and condition × span × channel (i.e., channels 1–16) were examined. Greenhouse-Geisser correction was performed if the sphericity assumption was violated. Cohen's *d* and partial eta squared (η_p^2) were used to estimate effect sizes. To assess potential carryover effects, a linear mixed

model was conducted with participants as a random factor and condition (sham, real) and period (first, second) as fixed factors to determine if a significant condition × period interaction existed for variables that showed a significant main effect of condition. To determine whether the statistical improvement in questionnaire measures is also clinically significant, the standard error of measurement (SEM) was used in estimating the minimal clinically important difference [50]. A convention of the value of 1 SEM was used as the definition of minimal clinically important difference [50]. The test-retest reliability of the tests was based on previous studies [44,45,47,51]. In addition, Pearson's correlation coefficient (*r*) was computed to evaluate the correlation between the changes in outcome measures that showed significant improvement after tPBM, further exploring the relationship among these significant improvements. Finally, to assess possible learning effects, a paired *t*-test was performed to evaluate the changes in outcome measures between baseline and sham conditions among patients who first underwent the sham tPBM (n = 11). The statistical analyses were conducted using SPSS 28.0 (IBM Corporation), with the significance level for all tests set at 0.05 (two-tailed).

Results

The demographic characteristics of the analyzed sample are presented in Table 1, while the results of the repeated measures ANOVA are presented in Table 2.

Impact of tPBM on cognitive efficiency

In terms of visual span in the VWMST, there was a marginally significant condition difference, $F(2, 32) = 3.20$, $p = 0.05$, $\eta_p^2 = 0.17$, Figure 3a. Compared to the baseline, participants showed improved performance only after real tPBM, $t(16) = 2.95$, $p < 0.01$, $d = 0.72$. The differences between baseline and sham ($p = 0.09$) and between sham and real ($p = 0.86$) were not significant.

For the reaction time, the condition × span interaction was significant, $F(14, 224) = 1.85$, $p = 0.03$, $\eta_p^2 = 0.10$. By examining the differences at each span level, it was found that there were significant condition differences at spans 2, 4 – 7, and 9, $F = 3.35 – 14.27$, $p < 0.05$, $\eta_p^2 = 0.17 – 0.47$. Specifically, the sham condition showed significantly faster reaction time than the baseline at span 2, 4 – 6, $t(16) = 2.13 – 4.94$, $p < 0.05$, $d = 0.52 – 1.20$. Similarly, the real condition showed significantly improved reaction time than the baseline at levels 2, 4, 5, 7, 9, $t(16) = 2.03 – 3.42$, $p < 0.04$, $d = 0.55 – 0.83$. More importantly, after real tPBM, participants showed significantly faster reaction time at span 9 than baseline, $t(16) = 3.42$, $p < 0.01$, $d = 0.83$, and sham condition, $t(16) = 2.72$, $p = 0.02$, $d = 0.66$, but the significant improvement was not observed between baseline and sham condition ($p = 0.31$, Figure 3b).

For the HbO data, neither the condition × span × channel interaction ($p = 0.38$) nor the condition × channel interaction ($p = 0.23$) were significant. This suggests that the differences in stimulation conditions were unlikely related to channel effect. Therefore, the HbO data was averaged across all 16 measurement channels for further analysis. After averaging across all channels, although the real condition showed decreased HbO as compared to baseline and sham conditions (Figure 3c), neither condition × span interaction ($p = 0.80$) nor the main effect of condition ($p = 0.26$) showed a significant result, suggesting participants elicited similar cognitive effort in completing the

VWMST. Together with the improved behavioral performance, it is suggested that participants could achieve better results without much additional cognitive effort.

Impact of tPBM on cognitive function

Next, the neuropsychological assessment performance was analyzed, revealing significant results in total learning, $F(2, 32) = 7.66$, $p < 0.01$, $\eta_p^2 = 0.32$, Figure 3d. Compared to baseline, participants showed marginally significantly improved performance after sham tPBM, $t(16) = 2.17$, $p = 0.05$, $d = 0.53$, and after real tPBM, $t(16) = 3.33$, $p < 0.01$, $d = 0.81$. In addition, participants performed significantly better after real tPBM than sham, $t(16) = 2.18$, $p = 0.04$, $d = 0.53$.

Significant main effects of condition were also observed in the 10-min delayed recall ($F(2, 32) = 6.16$, $p < 0.01$, $\eta_p^2 = 0.29$), the 30-min delayed recall, ($F(2, 32) = 7.05$, $p < 0.01$, $\eta_p^2 = 0.31$), of HKLLT, and the number of unique designs in FPT, ($F(2, 32) = 5.91$, $p < 0.01$, $\eta_p^2 = 0.27$). Compared to the baseline, participants recalled more items in both the 10-min and 30-min recalls, and created more unique designs after sham tPBM, ($t(16) = 2.66 – 3.60$, $p < 0.02$, $d = 0.64 – 0.87$), and also after real tPBM, ($t(16) = 2.70 – 3.12$, $p < 0.2$, $d = 0.66 – 0.76$). However, the differences between sham and real conditions were not significant, $p = 0.56 – 0.80$. For other measures, including CFT, DST, and STT, repeated measures ANOVA did not show significant results ($p = 0.07 – 0.82$).

Impact of tPBM on sleep, physical post-concussion symptoms, and PTSD symptoms

For sleep, a significant condition difference in subjective sleep quality was found, $F(2, 32) = 7.45$, $p < 0.01$, $\eta_p^2 = 0.31$, Figure 3e. After real tPBM, participants reported significantly improved subjective sleep quality compared to baseline, $t(16) = 3.04$, $p < 0.01$, $d = 0.74$, and sham, $t(16) = 3.04$, $p < 0.01$, $d = 0.74$. No significant changes were observed between baseline and sham conditions ($p = 1.00$). The main effects of the condition on the global score and other PSQI subscale scores were not significant ($p = 0.29 – 0.89$).

For physical post-concussion symptoms measured by RPQ, a significant main effect was observed, $F(2, 32) = 3.69$, $p = 0.04$, $\eta_p^2 = 0.19$, Figure 3f. Participants showed significant improvement in post-concussion symptoms after real tPBM compared to baseline, $t(16) = 2.51$, $p = 0.02$, $d = 0.61$. However, scores did not significantly differ between baseline and sham ($p = 0.13$) or between sham and real conditions ($p = 0.21$).

A similar significant effect was found for pain intensity, measured by VAS, $F(1.15, 18.48) = 4.83$, $p = 0.04$, $\eta_p^2 = 0.23$, Figure 3g. The real condition showed significantly lower pain intensity compared to baseline, $t(16) = 2.37$, $p = 0.03$, $d = 0.57$. There was a trend toward improved pain intensity in the sham condition compared to baseline, $t(16) = 1.97$, $p = 0.07$, $d = 0.48$, and in the real condition compared to sham, $t(16) = 2.03$, $p = 0.06$, $d = 0.49$.

Lastly, regarding PTSD symptoms measured by PCL-5, a significant main effect of condition was also observed, $F(2, 32) = 4.31$, $p = 0.02$, $\eta_p^2 = 0.21$, Figure 3h. Post hoc comparisons revealed that participants showed significant improvement in PTSD symptoms only after real tPBM (t(16) =

4.25, $p < 0.01$, $d = 1.03$) but not after sham tPBM ($p = 0.19$). The difference between sham and real tPBM was not significant ($p = 0.24$).

Assessment of the carryover effect of tPBM

The above results indicated that participants showed significant improvements in visual span and reaction time at span level 9, total learning in HKLLT, subjective sleep quality, PTSD symptoms, pain intensity, and post-concussion symptoms after real tPBM compared to baseline. No improvements were observed after sham tPBM compared to baseline. To rule out the possibility of a carryover effect that performance in the second period was influenced by the first tPBM condition, the carryover effect was examined. Among the seven variables analyzed, none of the condition (real, sham) × period (first, second) interaction was significant, $F(1, 15) = 0.03 – 2.12$, $p = 0.17 – 0.86$, suggesting that the carryover effect was not significant, if not negligible.

Assessment of the clinical significance of the improvement

After assessing the carryover effect, an analysis was performed to determine whether the statistically significant improvement in sleep, post-concussion symptoms, pain intensity, and PTSD symptoms was also clinically significant. The results showed that all tests reached the minimal clinically important difference, including the subjective sleep quality of PSQI (SEM = 1.72), PCL-5 (SEM = 1.10), VAS (SEM = 2.81), and RPQ (SEM = 1.21), suggesting that the statistically significant improvement observed in self-reported questionnaires was also clinically significant.

Correlational analysis of behavioral and cognitive assessment improvements

To gain a deeper understanding of the relationship between improvements in behavioral assessments (as measured by the subjective sleep quality component of PSQI, RPQ, VAS, and PCL-5) and enhancements in cognitive assessments (including visual span, reaction time at span level 9, and total learning in HKLLT), a correlational analysis was conducted to evaluate these relationships. The analysis revealed significant correlations among the improved behavioral assessments. Specifically, there was a significant correlation between changes in RPQ and changes in PCL-5, $r = 0.57$, $p = 0.02$, as well as between changes in RPQ and changes in VAS, $r = 0.56$, $p = 0.02$. These results indicate that a greater reduction in post-concussion symptoms is associated with more improvements in both pain intensity and PTSD symptoms. Conversely, improvements in pain intensity and PTSD symptoms are associated with better post-concussion symptom outcomes. However, no significant correlations were found among other pairs of behavioral assessments, $|r| = 0.03 – 0.24$, $p = 0.34 – 0.91$. Regarding the cognitive assessments, there were no significant correlations between changes in any cognitive measures and the behavioral assessments, $|r| = 0.01 – 0.47$, $p = 0.05 – 0.96$.

Assessment of the learning effect of neuropsychological tests

From Table 2, among the neuropsychological assessments, the total learning, 10-min delayed recall, and 30-min delayed recall of HKLLT, as well as the number of unique designs of FPT, showed improved performance after sham tPBM compared to baseline. Additional analysis was

conducted for these measures to assess potential learning effects. Specifically, the baseline performance of participants who received sham tPBM first (n = 11) was compared to their post-sham performance. The results showed significant improvements in 10-min delayed recall, t = 3.09, p = 0.01, d = 0.93, and 30-min delayed recall, t = 2.24, $p < 0.05$, d = 0.68. The total learning, t = 2.03, p = 0.07, d = 0.61, and the unique designs of FPT yielded non-significant results, t = 1.82, p = 0.10, d = 0.55. The medium-to-large effect sizes, d = 0.55 – 0.93, suggest that learning effects likely influenced outcomes. Non-significant findings may reflect limited power due to the small sample size.

Discussion

Post-concussion and PTSD symptoms were commonly reported among patients experiencing mTBI, which may create a substantial burden for patients in the workplace, with family, or in social contexts. The present study investigated whether tPBM may have the potential to improve symptoms after head injury among mTBI patients. After the real tPBM, participants showed significant improvements in the VWMST and the HKLLT, as well as in self-rated questionnaires regarding subjective sleep quality, physical post-concussion symptoms, and PTSD symptoms, compared to their performance at baseline. In contrast, participants did not show significant improvement from baseline after receiving sham tPBM. Therefore, these findings suggest the potential of tPBM as an effective clinical rehabilitation tool for patients with mTBI.

Regarding the fNIRS task, improved behavioral performance was found in the visual span of the VWMST, along with improved reaction time at the highest level (i.e., span 9) after real tPBM.

However, the changes in HbO, although appeared to be decreased as compared to baseline and sham conditions, were not statistically significant. The unchanged HbO suggests that the participants could exert similar effort while achieving a higher performance level. This may imply that participants could handle more difficult tasks with a similar cognitive effort, indicating that the improved behavioral performance did not require excessive effort. Such improved cognitive efficiency aligns with previous studies using a single tPBM trial [13,36-38], where improved behavioral performance was observed without showing a higher level of HbO. The present study suggests that improved efficiency was also observed among patients with TBI. The unchanged HbO in the present study suggests there may be differences between the immediate effect of a single tPBM session and the sustained effect of a tPBM trial over six weeks, which need further investigation.

Although there was a significant improvement in visual span from baseline after real tPBM, the performance between the sham and real conditions was not significant. The non-significance between the sham and real tPBM conditions may be attributed to the sensitivity of the visual span. Considering that both conditions showed an average visual span of around five to six, it may be challenging for a group of participants with an average age of 60.25 years to improve from this level to six or seven visual spans, an average level for younger adults [52], after receiving only 18 sessions of tPBM in six weeks. Despite this, the significant difference in reaction time observed between the real and sham conditions further supports the notion that while differences in visual span may be limited, real tPBM still has an impact on processing speed.

Apart from the fNIRS measures, neuropsychological assessments were also utilized to evaluate the effect of tPBM. The results showed a significantly higher score in total learning in HKLLT

after tPBM compared to baseline and sham tPBM, consistent with previous findings that improvements in learning and memory are commonly observed after tPBM [20,22,23]. In the present study, patients after receiving tPBM also showed improvement in both the 10-min and 30-min delayed recalls. However, it is noted that the recall performance also significantly improved after participants received sham tPBM. This suggests that the observed differences may also be influenced by potential learning effects, where participants may improve their performance through repeated practice of the same test. Although this issue was addressed by using alternate test sets [20], participants may still develop skills in taking tests (e.g., by employing different memorization strategies) during baseline assessment, even if the testing set is different in the latter assessment. Therefore, caution is needed to avoid exaggerating the effects of tPBM on TBI. Furthermore, the present controlled trial also highlights the importance of employing comparison groups, especially when evaluating the effects of tPBM with neuropsychological assessments that may be prone to learning effects, which was found significant after participants received the sham tPBM.

In addition to cognitive function, the present study also examined the effects of tPBM on sleep, physical post-concussion symptoms, and PTSD symptoms, which are common complaints among patients with mTBI. From the present recruited sample, some patients expressed that their persistent symptoms prevent them from being able to work, suggesting that the post-injury symptoms could impose a substantial burden on their daily living. In the present study, the improved symptom scores provided additional support for tPBM as a non-pharmacological and effective option to treat the clinical symptoms, with consistent findings reported in previous studies on improved symptoms after six to eight weeks of tPBM [20,23,25], and some may even able to work

after the intervention [19]. In addition, one patient mentioned the reduction in medication for pain relief after receiving the real tPBM. Further in-depth investigation on improving tPBM with more objective measures may be beneficial in understanding how and what tPBM has significant effects on.

Since the items on the RPQ reflect both physical pain (e.g., headache) and psychological distress (e.g., being irritable, easily angered), it is expected that there would be a significant correlation between changes in pain intensity (VAS) and PTSD symptoms (PCL-5). The lack of significant correlations between improvements in physical symptoms and cognitive function suggests that these improvements may be independent of one another. This indicates that the effects of tPBM operate across multiple domains, highlighting the necessity of utilizing a range of assessments to evaluate its effectiveness. Furthermore, the domain-independent effects imply that the observed improvements in cognitive function are unlikely to be primarily due to symptom reduction.

The existing support for tPBM primarily consists of case series, which are prone to potential placebo and learning effects. Even with a control group, the heterogeneous nature of TBI makes it challenging to generalize findings and draw concrete conclusions. The present study included a sham control condition and allowed participants to act as their controls in evaluating the effects of tPBM, thereby minimizing the effect of heterogeneity. Furthermore, the non-significant period × condition interaction observed in the improved measures suggests that the effect of tPBM during the first period is less likely to carry over to the second period. In addition, unlike TBI in the acute stage, the studied participants were at least eight months after the injury, minimizing the effect of spontaneous recovery to the observed intervention effect.

Given those positive findings, the present study encourages future investigation from various perspectives. For instance, while the present study only focused on patients with mTBI, an investigation of patients with moderate and severe TBI may yield insights into the potential effect of tPBM on different TBI severity. Besides, within the mTBI population, the injured brain areas may differ. The relationship between the stimulated area and injured areas remains unclear in this field. Further investigations may facilitate the development of optimal tPBM protocols. In addition, the feasibility of home-based intervention may also be explored, as the tPBM device is easy to administer. This may encourage participation as patients usually decline to participate due to their schedule, which often leads to a small sample size.

Despite the positive findings, several limitations have been identified. For example, although a wide age range was selected to enhance the generalizability of the results, further investigation is needed to determine whether the observed effects are specific to certain age groups. In addition, the present study focused on the short-term effect of tPBM, whereas the long-term post-stimulation effect, including the sustained effects and side effects, was not explored. A long-term follow-up could help address this issue. Additionally, the small sample size may increase the risk of Type II errors and limit generalizability. Furthermore, given the exploratory nature of this study, corrections for multiple comparisons were not performed to avoid over-constraining preliminary findings, though this approach raises the possibility of false positives. These limitations lead to caution when interpreting results, and replication in larger cohorts with adjusted alpha levels is recommended. Finally, given that the use of the same testing set in the present study may be prone

to high potential learning effects, equivalent but content-different assessments can be employed in future studies to mitigate the effects.

Conclusions

In conclusion, the present study investigated the effects of tPBM on patients with mTBI. The results demonstrated that after 18 sessions of tPBM over six weeks, participants showed improved cognitive function in learning and cognitive efficiency, as well as improvements in post-injury-related symptoms, including subjective sleep quality, physical post-concussion symptoms, pain intensity, and PTSD symptoms. This suggests that tPBM may have the potential to be an intervention strategy for alleviating injury-related symptoms. These positive findings also encourage further investigations into different patient populations and intervention parameters.

Transparency, Rigor and Reproducibility Summary

The study was pre-registered at the Chinese Clinical Trial Registry on 4 April 2024 at https://www.chictr.org.cn (ChiCTR2300070164). The analysis plan was not formally pre-registered, but the team member with primary responsibility for the analysis certifies that the analysis plan was pre-specified. A sample size of 15 subjects per group was planned based on an expected effect size of 0.8 for the primary outcome measure(s), calculated to yield 80% power to detect significant differences between baseline and real tPBM condition using paired *t*-tests with a *p*-value 0.05 (two-tailed). A transition from a parallel to a crossover design was implemented to address recruitment challenges and clinical heterogeneity in the mTBI population. A total of 2276 participants were assessed for eligibility, with 195 meeting the inclusion criteria. Twenty-three participants agreed to participate and signed the informed consent. Twelve participants started the

real tPBM first, and 11 the sham tPBM first. Seventeen participants completed the study. Participants were randomly assigned to groups using a random number generator. Participants were blinded to group assignment by using a sham tPBM device identical to the real one, differing only in its lack of light delivery, unlike the real tPBM device. Investigators who administered the therapeutic intervention were also blinded to group assignment as they were only informed about which specific device to use on each patient without being told which condition each device corresponded to. However, the investigator who conducted outcome assessments was not blinded to group assignments because he was also responsible for managing the technical issues of the tPBM devices. The assessment materials, including the assessment tests, the fNIRS device and the software used for data collection and analysis, were widely available from commercial sources. However, the tPBM device used for the interventions is not yet commercially available. The key inclusion criteria (e.g., the definition of mTBI) are established standards in the field. The primary clinical outcome measure is an established standard in the field. Validation includes references 12, 13, 20, 33, 37. The statistical tests used were based on the assumption of normality distributions of the outcome variables. The non-independence of measurements has been addressed using repeated measures, such as ANOVA and mixed models, as reported in the text. As different correction approaches may affect the statistical significance of the results and their interpretation, only the uncorrected *p*-values were reported. However, the limitation of not performing multiple comparisons has been highlighted in the discussion section. To our knowledge, no replication or external validation studies have been performed or are planned/ongoing at this time. Only the original measures of statistical error rates have been reported in the text, given the pilot nature of this study. Data, analytic code, and materials (e.g., intervention protocol and assessment materials) used to conduct the analyses presented in this study are not available in a public repository. Instead,

they are available from the corresponding author upon reasonable request. The authors agree to provide the full content of the manuscript on request by contacting the corresponding author.

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Authors' Contributions

Tsz-lok Lee: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. **David Yuen-chung Chan:** Conceptualization, Funding acquisition, Investigation, Writing – review & editing. **Danny Tat-ming Chan:** Conceptualization, Funding acquisition, Writing – review & editing. **Mei-chun Cheung:** Conceptualization, Funding acquisition, Writing – review & editing. **David Ho-keung Shum:** Conceptualization, Funding acquisition, Writing – review & editing. **Agnes Sui-yin Chan:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

Author Disclosure Statement

All authors claim that there are no conflicts of interest.

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Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Maas AIR, Menon DK, Adelson PD, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. Lancet Neurol 2017;16(12):987-1048, doi:10.1016/S1474-4422(17)30371-X
2. Maas AIR, Menon DK, Manley GT, et al. Traumatic brain injury: progress and challenges in prevention, clinical care, and research. Lancet Neurol 2022;21(11):1004-1060, doi:10.1016/S1474-4422(22)00309-X
3. van der Naalt J, Timmerman ME, de Koning ME, et al. Early predictors of outcome after mild traumatic brain injury (UPFRONT): an observational cohort study. Lancet Neurol 2017;16(7):532-540, doi:10.1016/S1474-4422(17)30117-5
4. Nelson LD, Temkin NR, Dikmen S, et al. Recovery after mild traumatic brain injury in patients presenting to US level I trauma centers: A transforming research and clinical knowledge in traumatic brain injury (TRACK-TBI) study. JAMA Neurology 2019;76(9):1049-1059, doi:10.1001/jamaneurol.2019.1313

5. Sveen U, Guldager R, Soberg HL, et al. Rehabilitation interventions after traumatic brain injury: A scoping review. Disability and Rehabilitation 2022;44(4):653-660, doi:10.1080/09638288.2020.1773940

6. Hamblin MR. Photobiomodulation for traumatic brain injury and stroke. Journal of Neuroscience Research 2018;96(4):731-743, doi:10.1002/jnr.24190

7. Montazeri K, Farhadi M, Fekrazad R, et al. Transcranial photobiomodulation in the management of brain disorders. Journal of Photochemistry and Photobiology B: Biology 2021;221(112207, doi:10.1016/j.jphotobiol.2021.112207

8. Chan AS, Lee TL, Yeung MK, et al. Photobiomodulation improves the frontal cognitive function of older adults. International Journal of Geriatric Psychiatry 2019;34(2):369-377, doi:10.1002/gps.5039

9. 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. Journal of Lasers in Medical Sciences 2019;10(4):317-323, doi:10.15171/jlms.2019.51

10. Casalechi HL, Dumont AJL, Ferreira LAB, et al. Acute effects of photobiomodulation therapy and magnetic field on functional mobility in stroke survivors: A randomized, sham-controlled, triple-blind, crossover, clinical trial. Lasers in Medical Science 2020;35(6):1253-1262, doi:10.1007/s10103-019-02898-y

11. Naeser MA, Ho MD, Martin PI, et al. Increased functional connectivity within intrinsic neural networks in chronic stroke following treatment with red/near-infrared transcranial photobiomodulation: Case series with improved naming in aphasia. Photobiomodulation, Photomedicine, and Laser Surgery 2020;38(2):115-131, doi:10.1089/photob.2019.4630

12. Chan AS, Lee TL, Sze SL, et al. Photobiomodulation Improves Memory in Mild Cognitive Impairment: Three Case Reports. Alzheimers Disease & Dementia 2021;5(1):126-131, doi:10.36959/734/383

13. Chan AS, Lee TL, Hamblin MR, et al. Photobiomodulation enhances memory processing in older adults with mild cognitive impairment: A functional near-infrared spectroscopy study. Journal of Alzheimer's Disease 2021;83(4):1471-1480, doi:10.3233/JAD-201600

14. Cheung MC, Lee TL, Sze SL, et al. Photobiomodulation improves frontal lobe cognitive functions and mental health of older adults with non-amnestic mild cognitive impairment: Case studies. Frontiers in Psychology 2022;13(1095111, doi:10.3389/fpsyg.2022.1095111

15. Salehpour F, Khademi M, Hamblin MR. Photobiomodulation therapy for dementia: A systematic review of pre-clinical and clinical studies. Journal of Alzheimer's Disease 2021;83(4):1431-1452, doi:10.3233/JAD-210029

16. Gutierrez-Menendez A, Marcos-Nistal M, Mendez M, et al. Photobiomodulation as a promising new tool in the management of psychological disorders: A systematic review. Neuroscience & Biobehavioral Reviews 2020;119(242-254, doi:10.1016/j.neubiorev.2020.10.002

17. Gao Y, An R, Huang X, et al. Effectiveness of photobiomodulation for people with age-related cognitive impairment: A systematic review and meta-analysis. Lasers in Medical Science 2023;38(1):237, doi:10.1007/s10103-023-03899-8

18. Lee TL, Ding Z, Chan AS. Can transcranial photobiomodulation improve cognitive function? A systematic review of human studies. Ageing Research Reviews 2023;83(101786, doi:10.1016/j.arr.2022.101786

19. Naeser MA, Saltmarche A, Krengel MH, et al. Improved cognitive function after transcranial, light-emitting diode treatments in chronic, traumatic brain injury: Two case reports. Photomedicine and Laser Surgery 2011;29(5):351-358, doi:10.1089/pho.2010.2814

20. Naeser MA, Zafonte R, Krengel MH, et al. Significant improvements in cognitive performance post-transcranial, red/near-infrared light-emitting diode treatments in chronic, mild traumatic brain injury: Open-protocol study. Journal of Neurotrauma 2014;31(11):1008-1017, doi:10.1089/neu.2013.3244

21. Carneiro AMC, Poiani GC, Zaninnoto AL, et al. Transcranial photobiomodulation therapy in the cognitive rehabilitation of patients with cranioencephalic trauma. Photobiomodulation, Photomedicine, and Laser Surgery 2019;37(10):657-666, doi:10.1089/photob.2019.4683

22. Chao LL, Barlow C, Karimpoor M, et al. Changes in brain function and structure after self-administered home photobiomodulation treatment in a concussion case. Frontiers in Neurology 2020;11(952, doi:10.3389/fneur.2020.00952

23. Hipskind SG, Grover FL, Jr., Fort TR, et al. Pulsed transcranial red/near-infrared light therapy using light-emitting diodes improves cerebral blood flow and cognitive function in veterans with chronic traumatic brain injury: A case series. Photobiomodulation, Photomedicine, and Laser Surgery 2019;37(2):77-84, doi:10.1089/photob.2018.4489

24. Karr JE, Iverson GL, Boudreau N, et al. Treatment of chronic symptoms following mild traumatic brain injury with transcranial LED: A sham run-in pilot study of photobiomodulation therapy. Brain Injury 2024;38(6):425-435, doi:10.1080/02699052.2024.2309258

25. Rindner ES, Haroon JM, Jordan KG, et al. Transcranial infrared laser stimulation for the treatment of traumatic brain injury: A case series. Journal of Lasers in Medical Sciences 2022;13(e65, doi:10.34172/jlms.2022.65

26. Amaroli A, Pasquale C, Zekiy A, et al. Photobiomodulation and oxidative stress: 980 nm diode laser light regulates mitochondrial activity and reactive oxygen species production. Oxidative Medicine and Cellular Longevity 2021;2021(6626286, doi:10.1155/2021/6626286

27. Pires de Sousa MV, Ferraresi C, Kawakubo M, et al. Transcranial low-level laser therapy (810 nm) temporarily inhibits peripheral nociception: Photoneuromodulation of glutamate receptors, prostatic acid phophatase, and adenosine triphosphate. Neurophotonics 2016;3(1):015003, doi:10.1117/1.NPh.3.1.015003

28. Dole M, Auboiroux V, Langar L, et al. A systematic review of the effects of transcranial photobiomodulation on brain activity in humans. Reviews in the Neurosciences 2023;34(6):671-693, doi:10.1515/revneuro-2023-0003

29. Hamblin MR. Mechanisms of photobiomodulation in the brain. In: Photobiomodulation in the Brain. Elsevier: 2019; pp. 97-110.

30. Gaggi NL, Ware JB, Dolui S, et al. Temporal dynamics of cerebral blood flow during the first year after moderate-severe traumatic brain injury: A longitudinal perfusion MRI study. NeuroImage: Clinical 2023;37(103344, doi:10.1016/j.nicl.2023.103344

31. Ware JB, Dolui S, Duda J, et al. Relationship of cerebral blood flow to cognitive function and recovery in early chronic traumatic brain injury. Journal of Neurotrauma 2020;37(20):2180-2187, doi:10.1089/neu.2020.7031

32. Chan ST, Mercaldo N, Figueiro Longo MG, et al. Effects of low-level light therapy on resting-state connectivity following moderate traumatic brain injury: Secondary analyses of a double-blinded placebo-controlled study. Radiology 2024;311(2):e230999, doi:10.1148/radiol.230999

33. Figueiro Longo MG, Tan CO, Chan ST, et al. Effect of transcranial low-level light therapy vs sham therapy among patients with moderate traumatic brain injury: A randomized clinical trial. JAMA Network Open 2020;3(9):e2017337, doi:10.1001/jamanetworkopen.2020.17337

34. Pinti P, Tachtsidis I, Hamilton A, et al. The present and future use of functional near-infrared spectroscopy (fNIRS) for cognitive neuroscience. Annals of the New York Academy of Sciences 2020;1464(1):5-29, doi:10.1111/nyas.13948

35. Causse M, Chua ZK, Remy F. Influences of age, mental workload, and flight experience on cognitive performance and prefrontal activity in private pilots: A fNIRS study. Scientific Reports 2019;9(1):7688, doi:10.1038/s41598-019-44082-w

36. Chan AS, Lee TL, Hamblin MR, et al. Photoneuromodulation makes a difficult cognitive task less arduous. Scientific Reports 2021;11(1):13688, doi:10.1038/s41598-021-93228-2

37. Lee TL, Chan AS. Photobiomodulation may enhance cognitive efficiency in older adults: A functional near-infrared spectroscopy study. Frontiers in Aging Neuroscience 2023;15(1096361, doi:10.3389/fnagi.2023.1096361

38. Lee TL, Chan AS. Dose response of transcranial photobiomodulation on cognitive efficiency in healthy older adults: A task-related functional near-infrared spectroscopy study. Journal of Alzheimer's Disease 2024;101(1):321-335, doi:10.3233/JAD-240473

39. Chan AS. Hong Kong List Learning Test. The Chinese University of Hong Kong: Hong Kong; 2006.

40. Wechsler D. Wechsler Adult Intelligence Scale - Fourth Edition, Hong Kong version. King-may Psychological Assessment: Hong Kong; 2014.

41. Regard M, Strauss E, Knapp P. Children's production on verbal and non-verbal fluency tasks. Perceptual and Motor Skills 1982;55(3 Pt 1):839-844, doi:10.2466/pms.1982.55.3.839

42. Ding Z, Chan AS. The Shape Trail Test is sensitive in differentiating older adults with mild cognitive impairment: A culture-neutral five-minute test. The Journal of Prevention of Alzheimer's Disease 2024;11(4):1166-1176, doi:10.14283/jpad.2024.80

43. Chan AS, Poon MW. Performance of 7- to 95-year-old individuals in a Chinese version of the category fluency test. Journal of the International Neuropsychological Society 1999;5(6):525-533, doi:10.1017/s135561779956606x

44. Buysse DJ, Reynolds CF, 3rd, Monk TH, et al. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. Psychiatry Research 1989;28(2):193-213, doi:10.1016/0165-1781(89)90047-4

45. King NS, Crawford S, Wenden FJ, et al. The Rivermead Post Concussion Symptoms Questionnaire: A measure of symptoms commonly experienced after head injury and its reliability. Journal of Neurology 1995;242(9):587-592, doi:10.1007/BF00868811

46. Haefeli M, Elfering A. Pain assessment. European Spine Journal 2006;15(Suppl 1):S17-S24, doi:10.1007/s00586-005-1044-x

47. Blevins CA, Weathers FW, Davis MT, et al. The Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5): Development and initial psychometric evaluation. J Trauma Stress 2015;28(6):489-498, doi:10.1002/jts.22059

48. Huppert TJ, Diamond SG, Franceschini MA, et al. HomER: A review of time-series analysis methods for near-infrared spectroscopy of the brain. Applied Optics 2009;48(10):D280-98, doi:10.1364/ao.48.00d280

49. Cui X, Bray S, Reiss AL. Functional near infrared spectroscopy (NIRS) signal improvement based on negative correlation between oxygenated and deoxygenated hemoglobin dynamics. Neuroimage 2010;49(4):3039-3046, doi:10.1016/j.neuroimage.2009.11.050

50. Copay AG, Subach BR, Glassman SD, et al. Understanding the minimum clinically important difference: A review of concepts and methods. The Spine Journal 2007;7(5):541-546, doi:10.1016/j.spinee.2007.01.008

51. Sindhu BS, Shechtman O, Tuckey L. Validity, reliability, and responsiveness of a digital version of the visual analog scale. Journal of Hand Therapy 2011;24(4):356-363, doi:10.1016/j.jht.2011.06.003

52. Claessen MH, van der Ham IJ, van Zandvoort MJ. Computerization of the standard Corsi block-tapping task affects its underlying cognitive concepts: A pilot study. Applied Neuropsychology: Adult 2015;22(3):180-188, doi:10.1080/23279095.2014.892488

Table 1. Demographic characteristics of the sample (*n* = 17)

Characteristics	*M*	*SD*
Age	60.25	2.89
Gender (F/M)	8/9	
Education	10.71	4.37
Year of injury	5.92	7.03
GCS	14.94	0.24
Cause of head injury		
Bicycle accident	5	
Fall	5	
Assault	2	
Pedestrian accident	2	
Automobile accident	1	
Domestic accident	1	
Horse-related accident	1	

Note. GCS = Glasgow Coma Scale

Table 2. Performance of fNIRS task, neuropsychological assessments, and questionnaire scores at baseline, after sham tPBM and after real tPBM

	Baseline		Sham		Real			
Measures	*M*	*SD*	*M*	*SD*	*M*	*SD*	*F*	Post hoc
VSWMT								
Visual span	5.00	1.50	5.65	1.27	5.71	1.21	3.20†	Baseline < Real
Reaction time								
Span 2	7.35	1.81	6.32	1.81	6.12	1.35	5.49**	Baseline > Sham, Real
Span 3	7.70	1.64	7.04	1.66	7.15	1.65	2.24	
Span 4	10.26	2.72	7.85	1.55	8.48	2.52	14.27***	Baseline > Sham, Real
Span 5	11.16	2.74	9.94	2.79	9.98	2.76	3.69*	Baseline > Sham, Real
Span 6	14.71	3.79	12.22	3.57	13.12	3.58	6.06**	Baseline > Sham
Span 7	15.99	3.54	14.59	3.86	13.95	4.16	3.35*	Baseline > Real
Span 8	18.30	5.67	16.54	3.93	16.67	4.50	2.35	
Span 9	18.67	4.84	17.66	4.76	16.12	4.06	5.51**	Baseline, Sham > Real
HbO								
Span 2	0.27	0.24	0.23	0.13	0.07	0.35	2.40	
Span 3	0.50	0.33	0.40	0.33	0.26	0.37	2.25	
Span 4	0.71	0.43	0.60	0.46	0.44	0.50	2.03	
Span 5	0.80	0.34	0.76	0.53	0.62	0.51	0.73	
Span 6	1.01	0.48	1.10	0.61	0.78	0.51	1.79	
Span 7	1.14	0.47	1.14	0.56	0.91	0.63	1.15	
Span 8	1.23	0.53	1.29	0.75	1.06	0.73	0.54	
Span 9	1.32	0.57	1.31	0.71	1.19	0.66	0.27	
Neuropsychological assessment								
HKLLT								
Total learning	24.18	9.57	27.00	9.51	29.88	8.54	7.66**	Baseline < Sham < Real
10-min delayed recall	7.47	4.08	9.47	4.52	9.65	3.69	6.16**	Baseline < Sham, Real
30-min delayed recall	7.24	4.32	9.35	4.66	9.59	3.92	7.05**	Baseline < Sham, Real
CFT								
Unique items	24.88	4.83	25.88	6.57	27.35	5.97	1.72	

DST								
Forward	7.29	1.45	7.47	1.07	7.53	1.01	0.48	
Backward	4.76	1.68	4.94	1.56	4.88	1.50	0.20	
FPT								
Unique designs	17.88	6.53	21.35	8.67	22.12	8.05	5.91**	Baseline < Sham, Real
STT								
Trail A	51.19	21.86	50.05	18.75	47.11	15.82	0.62	
Trail B	124.99	46.69	112.88	36.12	113.34	35.22	3.31	
Questionnaires								
PSQI								
Global	9.59	4.74	9.88	4.72	8.82	4.65	1.00	
Quality	1.41	0.80	1.41	0.62	0.88	0.60	7.45**	Baseline, Sham > Real
Latency	1.41	1.00	1.47	0.87	1.24	0.90	0.60	
Duration	1.65	1.11	1.65	1.17	1.47	1.12	0.46	
Efficiency	1.88	1.27	1.59	1.33	1.59	1.12	0.89	
Disturbance	1.35	0.49	1.41	0.62	1.47	0.72	0.48	
Medication	0.41	0.80	0.76	1.20	0.65	1.06	1.29	
Daytime dysfunction	1.47	0.94	1.59	0.94	1.53	1.01	0.12	
PCL-5								
Total score	20.71	14.17	17.29	16.50	14.12	14.15	4.31*	Baseline > Real
VAS								
Total score	4.08	3.03	2.86	2.42	2.38	2.39	4.83*	Baseline > Real
RPQ								
Total score	19.94	12.11	17.41	12.74	14.65	12.96	3.69*	Baseline > Real

Note. CFT = Category Fluency Test; DST = Digit Span Test; FPT = Five-Point Test; HbO = Oxygenated hemoglobin; HKLLT = Hong Kong List Learning; PCL-5 = PTSD Checklist for DSM-5; PSQI = Pittsburgh Sleep Quality Index; RPQ = Rivermead Post Concussion Symptoms Questionnaire; STT = Shape Trail Test; VAS = Visual Analog Scale; VWMST = Visual Working Memory Span Task. † p = 0.05, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Figure legends

Figure 1. CONSORT diagram of the present study.

Figure 2. fNIRS task flow diagram and device setup. (a) A trial with span level 2 in the VWMST, (b) task flow of the VWMST, (c) positions of the fNIRS light sources and detectors, indicated by red and blue dots, respectively, with 16 measurement channels shown by yellow lines.

Figure 3. Assessment performance at baseline, after sham tPBM, and after real tPBM. (a) Visual span, (b) reaction time at span 9 and (c) HbO at all span levels in the VWMST, (d) total learning of the HKLLT, (e) subjective sleep quality measured by the PSQI, (f) post-concussion symptoms measured by the RPQ, (g) pain intensity measured by the VAS, and (h) PTSD symptoms measured by the PCL-5. For reaction time (panel b) and questionnaire scores (panel e – h), lower values indicate better outcomes. Error bars represent ± one standard error of the mean. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Figure 1

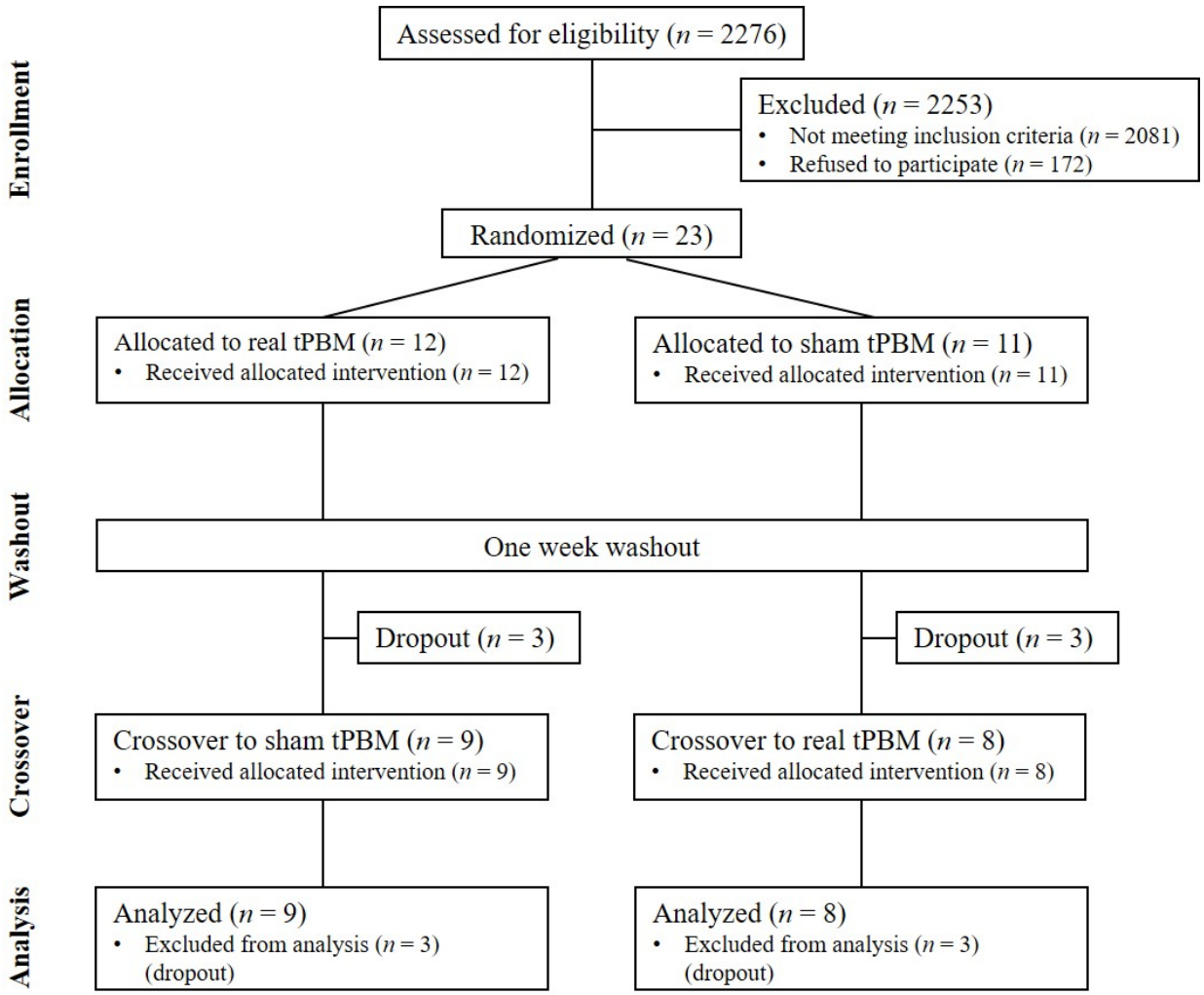
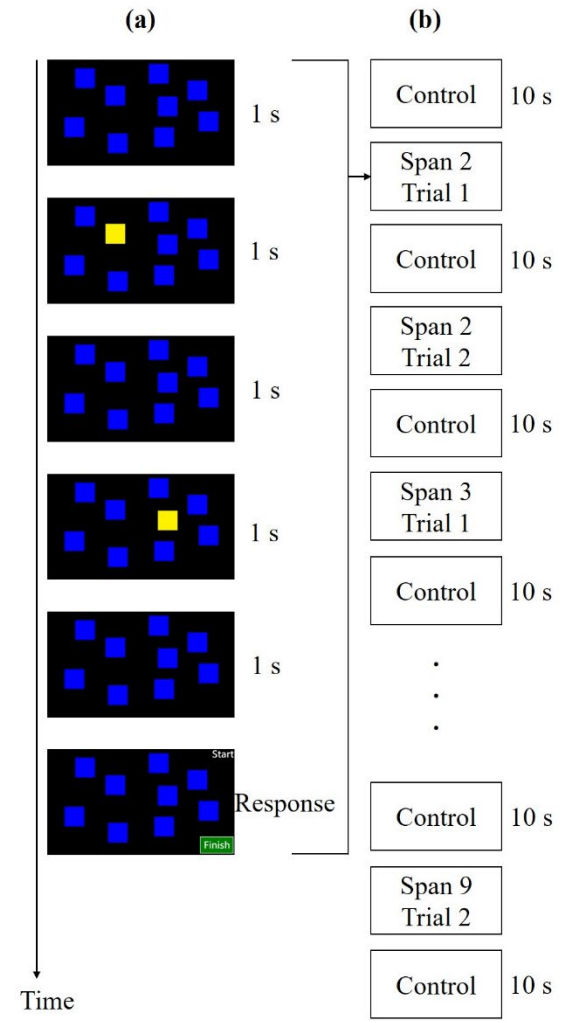

Enrollment
Assessed for eligibility (n = 2276)
Excluded (n = 2253)
• Not meeting inclusion criteria (n = 2081)
• Refused to participate (n = 172)
Randomized (n = 23)
Allocation
Allocated to real tPBM (n = 12)
• Received allocated intervention (n = 12)
Allocated to sham tPBM (n = 11)
• Received allocated intervention (n = 11)
Washout
One week washout
Dropout (n = 3)
Dropout (n = 3)
Crossover
Crossover to sham tPBM (n = 9)
• Received allocated intervention (n = 9)
Crossover to real tPBM (n = 8)
• Received allocated intervention (n = 8)
Analysis
Analyzed (n = 9)
• Excluded from analysis (n = 3) (dropout)
Analyzed (n = 8)
• Excluded from analysis (n = 3) (dropout)

Figure 2


(a)
(b)
1 s
1 s
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Start
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Time
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10 s
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Trial 1
Control
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Trial 1
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Span 9
Trial 2
Control
10 s

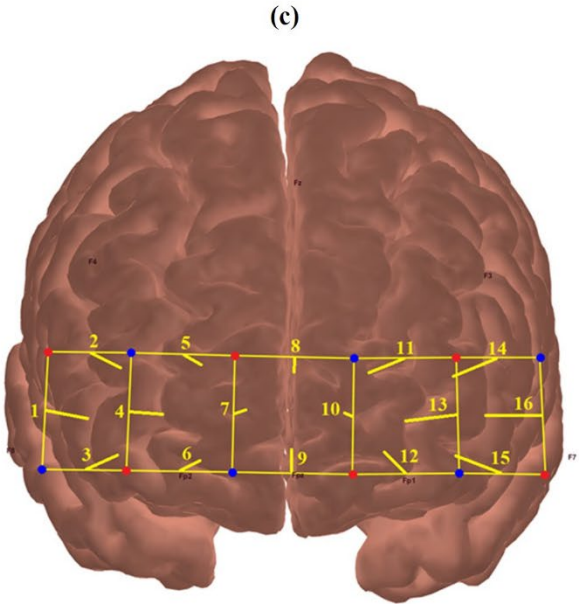
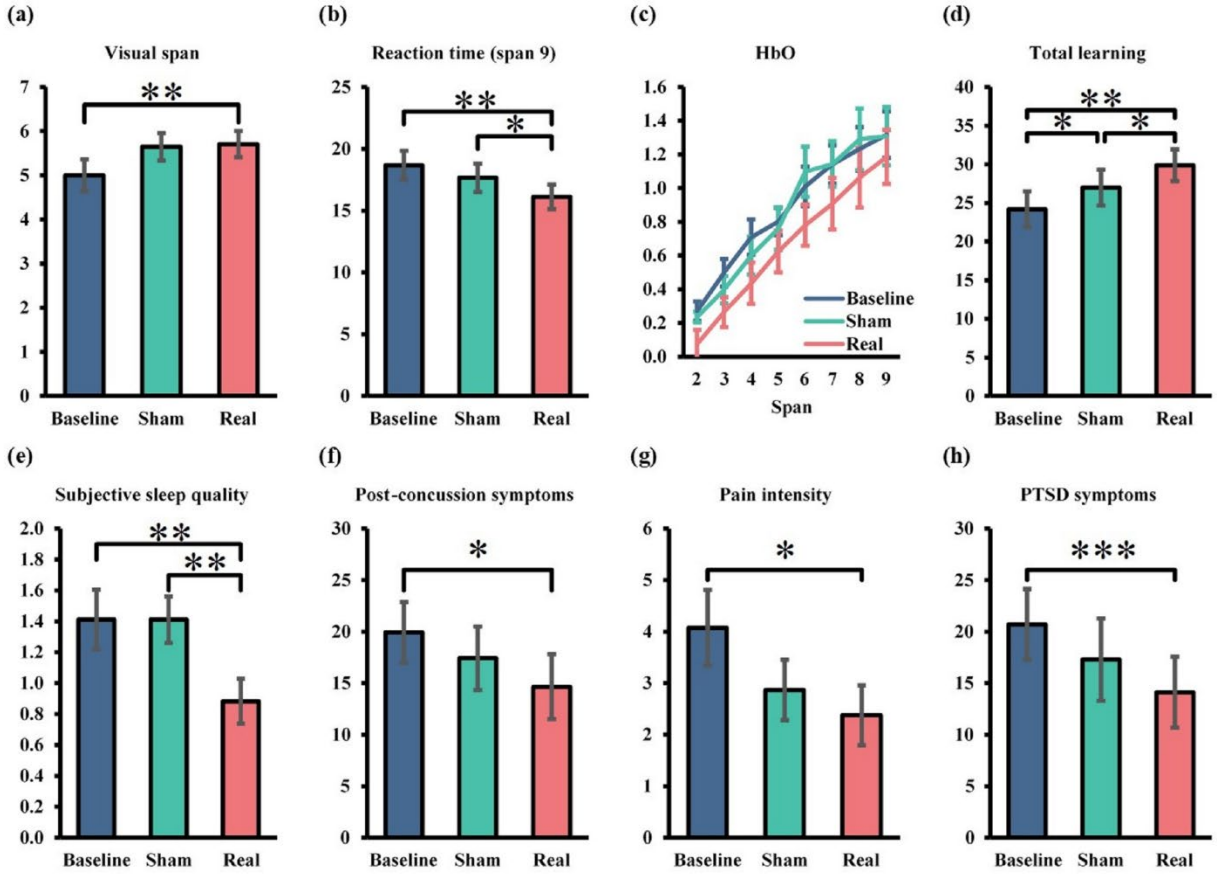

(c)
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16

Figure 3


(a)
Visual span
**
Baseline
Sham
Real
(b)
Reaction time (span 9)
**
*
Baseline
Sham
Real
(c)
HbO
Baseline
Sham
Real
Span
(d)
Total learning
**
*
*
Baseline
Sham
Real
(e)
Subjective sleep quality
**
**
Baseline
Sham
Real
(f)
Post-concussion symptoms
*
Baseline
Sham
Real
(g)
Pain intensity
*
Baseline
Sham
Real
(h)
PTSD symptoms
***
Baseline
Sham
Real