Repeated Photobiomodulation Induced Reduction of Bilateral Cortical Hemodynamic Activation During a Working Memory Task in Healthy Older Adults

Zhishan Hu, Xiujuan Qu, Lexuan Li, Xiaohan Zhou, Qin Yang, Qi Dong, Hesheng Liu, Xiaobo Li, Ying Han, and Haijing Niu

***Abstract*—Transcranial photobiomodulation (tPBM) is an emerging non-invasive light-based neuromodulation technique that shows promising potential for improving working memory (WM) performance in older adults. However, the neurophysiological mechanisms associated with tPBM that underlie the improvement of WM and the persistence of such improvement have not been investigated. Sixty-one healthy older adults were recruited to receive a baseline sham stimulation, followed by one-week active tPBM (12 min daily, 1064-nm laser, 250 mW/cm^2) and three-week follow-ups. N-back WM task was conducted on post-stimulation of the baseline, the first (Day 1) and seventh (Day 7) days of the active treatment, and at the follow-ups. During the task, functional near-infrared spectroscopy (fNIRS) imaging was employed to record the cortical hemodynamic changes. Brain activations during the active and follow-up sessions were compared with the baseline to determine how tPBM had changed cortical hemodynamic activity and how long these changes persisted. We found that tPBM stimulation on Day 1 induced significantly decreased activation in the right hemisphere during the 3-back. The decreased activation expanded from only the right hemisphere on Day 1 to both hemispheres on Day 7. The decreased activation persisted for one week in the right supramarginal gyrus and the left angular gyrus and two weeks in the left somatosensory association cortex. These activation changes were accompanied by significantly improved task accuracy during the N-back. These findings provide important evidence for understanding neural mechanisms underlying cognitive enhancement after tPBM.**

***Index Terms*—Functional near-infrared spectroscopy (fNIRS), older adults, n-back, photobiomodulation, working memory.**

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I. Introduction

In THE past few decades, there has been a dramatic increase in the number of older people suffering from cognitive decline and/or dementia, resulting in large social and economic burdens [1], [2], [3]. Therefore, identifying new strategies to maintain (or even improve) brain function in older individuals is of great importance. Transcranial photobiomodulation (tPBM), an emergent non-invasive brain stimulation technique, has attracted increasing interest from researchers for its potential to improve cognitive function in healthy older adults and patients with cognitive impairments [4], [5].

During tPBM, low-power, high-fluence (620 nm–1100 nm) lasers or LEDs are applied to the scalp. The photons penetrate through the scalp and skull and reach cortical tissue. The photons are primarily absorbed by cytochrome c oxidase (CCO), a terminal enzyme in the mitochondrial respiratory chain that plays a critical role in neuronal oxygen utilization for energy

metabolism [6], [7]. Absorption of photons is assumed to up-regulate CCO activity and increase the production of adenosine triphosphate (ATP) [6], [8], [9], which supports neural activity [4] and ultimately enhances cognitive function [10], [11], [12], [13].

Behavioral evidence has indicated that the utilization of single or repeated tPBM stimulation leads to beneficial effects on the cognitive abilities of healthy older adults, such as mental flexibility, lexical access, and inhibitory control [14], as well as attention and memory [15]. One of our recent studies also showed that repeated tPBM stimulation improved the accuracy rate and response time of a working memory task in healthy older adults [16]. However, the neural impacts of tPBM on cognitive tasks remain largely unknown. Although it has been demonstrated that tPBM stimulation could alter spontaneous neurophysiological activity in the cerebral cortex. For example, studies that have recorded cerebral blood oxygenation or electrophysiology signals found that tPBM increased oxygenated hemoglobin (HbO) concentrations [6], [8], [9], enhanced spectral powers of electronic activity [15], [17], and elevated cerebral concentrations of oxidized CCO [6]. However, to date, little is known about the neural mechanism underlying the effects of tPBM on task-related brain activity. Specifically, it remains unclear how tPBM influences neural activity during a cognitive task, particularly with varying task difficulty.

Neurophysiological evidence of the long-term effects of tPBM on older adults is also necessary for evaluating its potential therapeutic benefits. To date, relevant data are mostly from experiments on animals [18], [19], healthy younger adults [10], [20], or patients [21]. For example, a recent study on mice indicated that one session of tPBM led to improved recovery from brain lesions and an antidepressant effect that lasted for 4 weeks [19]. Nevertheless, data demonstrating the long-term effects of repeated tPBM on older individuals is lacking.

To address these critical gaps in the field, the current study proposed a longitudinal design that included one week of daily active tPBM and three weeks of weekly follow-ups. The N-back task was carried out on post-stimulation during the baseline, the first day (i.e., Day 1), and the seventh day (i.e., Day 7) as well as at each of the three weekly follow-ups. While participants performed the N-back tasks, their brain activity was recorded using functional near-infrared spectroscopy (fNIRS) imaging. To comprehensively investigate the impact of one week of active tPBM on WM performance and brain activation, the results from Day 1 and Day 7 were compared with those from the baseline (sham stimulation).

Given that active tPBM increases HbO concentrations in spontaneous states [6], [8], [9], we hypothesized that tPBM would induce a significant decrease in task-induced brain activation patterns, dependent on task difficulty.

II. Methods

A. Participants

A total of 61 healthy older adults, including 51 females and 10 males (age = 64.74 ± 5.73 years), were enrolled in this study. They completed an online screening assessment and a standardized clinical evaluation at Xuan Wu Hospital, Beijing, China, which included a medical history interview, a neurological examination, a battery of neuropsychological tests, and routine laboratory tests [22]. The inclusion criteria for this study were as follows: 1) participants between the ages of 55 and 79 years old; 2) participants who spoke Mandarin; and 3) participants who were strongly right-handed. The exclusion criteria were as follows: 1) participants diagnosed with mild cognitive impairment, dementia, or other major psychiatric disorders or neurological conditions and 2) participants diagnosed with other diseases that might cause cognitive decline. Four of the 61 participants were excluded from further analysis because of the poor quality of the fNIRS signal in multiple measurement channels (the detailed quality control criteria are described in the preprocessing section). Written informed consents were obtained prior to the experiment. The study protocol was approved by the Institutional Review Board of Xuanwu Hospital, Capital Medical University on November 12, 2019 (the IRB protocol number: [2019]088).

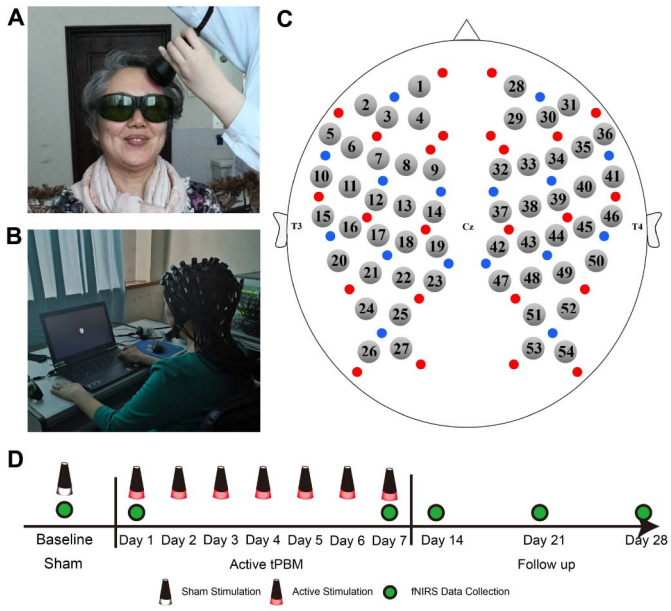

Fig. 1. Experimental procedures and settings. (a) Image of one participant receiving tPBM stimulation over the left dorsolateral prefrontal cortex (DLPFC). (b) Example of fNIRS recording during a participant performing an N-back task. (c) Layout of the sources (red dots), detectors (blue dots), and measurement channels (gray dots). (d) Timeline of the experimental procedure. Three sessions (i.e., baseline sham, active tPBM, and follow-up) were included in this experiment. After active tPBM, fNIRS was used to record brain activation during the N-back task (green dots).

B. Experimental Procedures

This was a randomized, single-blind, sham-controlled study. This study included three experimental sessions, i.e., baseline, one-week active tPBM, and weekly follow-up tests for three weeks (Fig. 1(a)). Of note, the choice of one-week stimulation period was based on previous clinical evidence and safety [23], [24], [15]. In the baseline session, participants received a sham

stimulation in which the laser was on for only the first 5 seconds and then turned off. The participants were not aware of whether this tPBM was active or a sham. They then completed an 8-minute N-back task during which their brain activity was concurrently recorded via fNIRS (Fig. 1(b)). In the active session, daily active tPBM stimulation was administered to each participant from Day 1 to Day 7. Task-related fNIRS were carried out on both Day 1 and Day 7 after the participants received active tPBM stimulation. The follow-up session involved three days separated by a one-week interval (i.e., Days 14, 21, and 28), during which participants were examined by task-related fNIRS but did not receive tPBM stimulation.

1) TPBM Stimulation Over the Left DLPFC: Participants sat in a comfortable chair and wore dark goggles during the sham/active sessions. In accordance with previous studies [6], [16], [17], we used a 1064 nm laser (CNI laser-MIL-N-1064, China) to stimulate the participants' left dorsolateral prefrontal cortex (DLPFC) (Fig. 1(c)). The circular laser beam had a diameter of 4.16 cm and covered an area of 13.6 cm^2. The midpoint of this circular laser beam was placed over F3 according to the 10–20 international system. This protocol of DLPFC localization has been validated by the previous study [25]. The measured output was constant at 3.4 W and lasted for 12 minutes. The irradiance (or power density) of the laser was 250 mW/cm^2, which generated negligible heat and was safe for the participants [16].

2) N-Back Working Memory Task: A block-designed digit N-back task was used to measure the working memory performance, as in our previous study [16]. Participants were required to press a button when the current stimulus was identical to the one presented n (here, $n = 1, 2, 3$) trials previously, which formed three N-back conditions. Each task block contained 20 trials of the same N-back condition with six of them requiring a response, and each condition was randomly presented for 3 blocks. For each trial, the stimulus (a number randomly selected between 0 and 9) was presented for 500 ms, followed by a 1500 ms intertrial interval. Between the blocks, participants were allowed to rest for 15 s and were instructed as to the condition of the next block. Participants were administered a practice run of this task before the tPBM stimulation to ensure that they fully understood the instructions.

3) FNIRS Data Acquisition: FNIRS is an optical brain imaging method with a high tolerance to motion artifacts and can be operated quietly and comfortably for older adults [26], [27], [28]. The feasibility, reliability, and reproducibility of fNIRS have been widely validated in previous studies [29], [30], [31], [32], [33]. Here, a multichannel continuous wave near-infrared imaging system (Hui Chuang, China) was used to record the brain activation of each participant during the N-back task. This machine comprised 24 laser sources and 16 detectors, which formed 54 measurement channels (Fig. 1(d)) covering the bilateral frontal, temporal, parietal, and occipital lobes of the participants. The fNIRS recording during the N-back task lasted for approximately 8 minutes and had a sampling rate of 17 Hz. To measure the positions of the probes, we acquired a structural magnetic resonance image (MRI) from one arbitrarily selected subject using Siemens 3.0 Tesla scanner. Similar to our previous studies [28], [34], [35], the participant laid supine while wearing the probe arrays in an MRI scanner during data acquisition. Vitamin E capsules were attached to each of the optode locations in the probe arrays and were used as landmarks for coregistration.

4) FNIRS Data Preprocessing: We used an in-house MATLAB package, FC-NIRS, to check the quality of the fNIRS data [36]. Specifically, the fNIRS data from each channel were first transformed into changes in optical density and then into the changes in the concentrations of HbO and deoxyhemoglobin (HbR) according to the Beer-Lambert Law, with a default differential pathlength factor of 6 for the wavelengths of 730 nm and 850 nm. Next, the power spectrum of the hemoglobin signal was calculated to check whether a heartbeat frequency was detectable. Channels lacking a detectable heartbeat frequency were considered "poor channels" and then were manually removed from further analysis. If a participant had more than five poor channels in one of these three sessions, the participant was excluded from further analysis in that session. Moreover, those excluded from the baseline stage should be excluded from the other stages. Following these criteria, four subjects were excluded from three sessions.

After the quality control, the fNIRS data were preprocessed using the Homer2 MATLAB toolbox [37]. The raw data were first converted to changes in optical density. The global noise was removed by using principal component analysis (80% of variance removed) [38]. Motion artifacts were detected by Homer2 function hmrMotionArtifactByChannel (Parameters: tMotion = 0.5; tMask = 1; STDEVthresh = 20; AMPthresh = 5) and were removed by the spline method ($p = 0.99$) [39]. Subsequently, a bandpass filter (0.01–0.1 Hz) was applied to the data to filter out high-frequency and low-frequency physical noise. Finally, the data were transformed into changes in hemoglobin concentration, in which HbO was considered to have a higher signal-to-noise ratio than HbR [40]. The results were primarily presented based on the HbO signal. As a complement, HbR results were also presented in Supplementary materials. Of note, the baseline for each block was calculated as the average of the five seconds before the start of each block (the last 5 seconds of the resting period). Thus, the block-averaged time series ranged from −5 to 50 seconds, with a 5 s baseline, a 40 s task period, and a 10 s rest.

C. Statistical Analyses

1) N-Back Brain Activation During the Baseline Sessions: We obtained brain activation patterns during the N-back task in the baseline session to show that fNIRS could identify functional activation in WM-related regions consistently reported in previous fMRI studies [41], [42], [43], [44]. Specifically, a general linear model (GLM), with canonical hemodynamic response function (i.e., double gamma function) as the basis function, was used to estimate the task-induced response in each channel for each subject, with a beta value for each N-back condition. Furthermore, we performed a two-way analysis of variance (ANOVA) on the beta values, with the three N-back conditions as the within-subject factors and groups as the between-subject

factors. The p values were FDR-corrected for multiple comparisons, with the corrected significance level set at $p < 0.05$.

2) Temporal-Spatial Changes in Brain Activation During the Active tPBM and Follow-Up Session: We adopted a model-free, cluster-based permutation method to quantify the temporal-spatial changes in brain activation of each time bin between the active tPBM and the baseline. This method was implemented in the Fieldtrip MATLAB toolbox [45] and was also used in previous fNIRS studies [46], [47]. The cluster-based permutation began with paired t-tests comparing Day 1/Day 7 with the baseline session for each channel at each time point in 10–40 s. Channels and time points with significant changes ($p < 0.05$, one-tailed) were clustered according to their spatial and temporal proximity. The sum of the channel-time point t values in each cluster was set to the cluster value. Then, a permutation test with 1000 iterations was conducted on each cluster to determine whether the observed cluster value was significant ($p < 0.05$ with the Monte-Carlo method) in the randomization null distribution. The cluster-based permutation method was also repeated to obtain the temporal-spatial changes in brain activation during the follow-up sessions.

For each channel in the significant clusters identified during the tPBM session, the t-tests used a set threshold including one-tailed p values and an FDR correction. Additionally, the corrected significance level was set at $p < 0.05$. The resulting channels with significant results were subjected to the same thresholding procedure with the follow-up data.

3) Behavioral Analysis During the Stimulation and Follow-Up Session: We further investigated the behavioral performance of the participants during the stimulation and the follow-up sessions. The overall index of task accuracy, d-prime [48], was used to measure the behavioral outcome of the participants. Unlike the percent accuracy used in our previous study [16], the d-prime is a high sensitivity index that reflects signal detection while controlling for biases in responding. The d-prime was calculated using the formula: d-prime = Z(HIT) − Z(FA), where HIT represents (hits/(hits + misses)), and FA represents (false alarms/(false alarms + correct rejections)) [48]. For the stimulation session, paired t-tests were carried out to demonstrate the behavioral outcome on Day 1 and Day 7. The d-prime was compared between Day 1 and the baseline as well as between Day 7 and the baseline, respectively. Similarly, for the follow-up session, paired t-tests between each follow-up and baseline were also conducted to examine the behavioral outcome.

III. Results

A. Identification of WM-Related Brain Regions

Fig. 2 shows the interaction effect of group on N-back task-related brain activation in the baseline session. Significant interaction was found in the bilateral DLPFC, bilateral frontal eye field (FEF), bilateral premotor cortex (PMA) and supplementary motor area, bilateral supramarginal gyrus (SMG), bilateral angular gyrus (AG), bilateral somatosensory association cortex (SAC) and right visual cortex 3 (V3). The detailed statistical results are listed in Supplementary Table S1. The fNIRS findings are approximately consistent with a recent meta-analysis of fMRI imaging [49] and demonstrate the capability of fNIRS in identifying working memory activation.

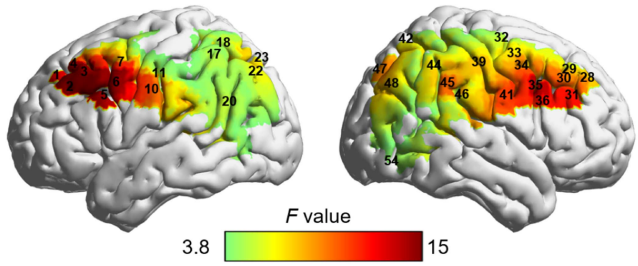

Fig. 2. Brain activation map of the significant interaction effect of HbO signal during the working memory task ($p < 0.05$). Darker red colors indicated larger F values.

B. Decreased Brain Activation After a Single tPBM Stimulation

Cluster-based permutation analysis was used to identify significant temporal-spatial changes in brain activation after a single tPBM compared to those at baseline. For the 1- and 2-back WM tasks, no significant clusters were found. For the 3-back condition, one significant cluster was identified in Fig. 3(a), in which the color bar indicated the t values included in the clusters, and the darker color represents lower activation on Day 1 compared to the baseline session. The digits represented the channel located in the clustered regions. This cluster showed significantly decreased activation in most regions of the right hemisphere ($t = -477.33$, $p = 0.028$). These regions primarily included the right FEF, SMG, and V3. The dynamic changes in brain activation during the 3-back condition over a temporal-spatial scale are shown in Supplementary Movie S1, accompanied by Supplementary Movie S2 and S3 for the changes during 1-back and 2-back conditions, respectively. Further, the temporal response of HbO changes in channels surviving the FDR correction was shown in Fig. 3(b), with the channel labeled in the form of "channel ID-hemisphere-region". It was observed that the increased HbO concentration during the 3-back task was significantly decreased in right FEF, SMG, and V3 after single tPBM (i.e., Day 1) compared to the baseline.

C. Widely Decreased Brain Activation After Repeated tPBM Stimulation

After seven days of stimulation, no significant clusters were found for the 1- and 2-back WM tasks. However, for the 3-back condition, two significant clusters were identified using cluster-based permutation analysis in repeated tPBM compared to that in baseline (Fig. 4(a) and (c). Similar to the single tPBM, an obvious decrease in HbO activation was observed after repeated stimulation in the 3-back condition; unlike the single tPBM, this activation was found in broader brain regions (Fig. 4(a), (c), and Movie S1). These regions involved both hemispheres (left: $t = -367.18$, $p = 0.044$, right: $t = -528.53$, $p = 0.014$). These results indicate that the repeated tPBM stimulation induced a significant reduction of brain activation in broad cortical regions

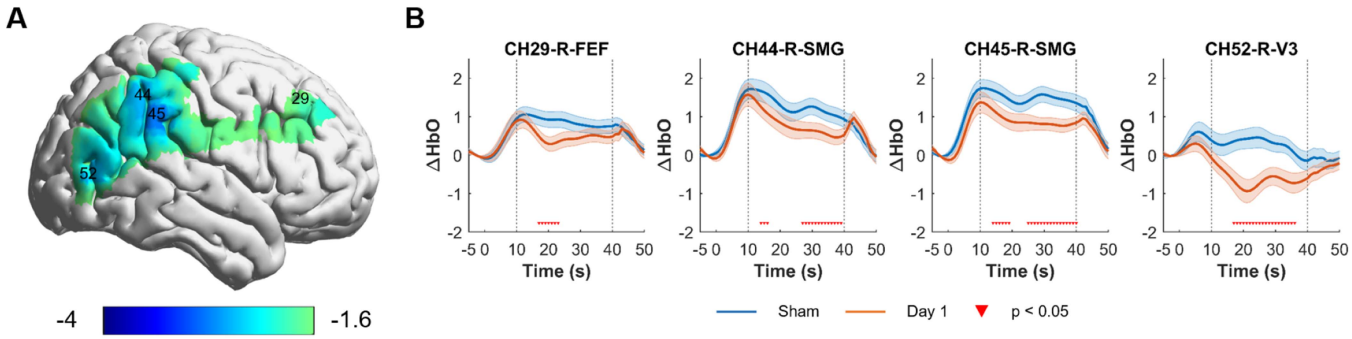

Fig. 3. A single tPBM-stimulation-induced HbO change. (a) Topographic map, at the peak of the hemodynamic response, showing significant decrease in HbO relative to baseline on Day 1. The color bar indicated the t values included in the clusters, and the darker colors represented lower activation on Day 1 compared to the sham session. Channels surviving the FDR correction were labeled on the brain map. (b) Display of HbO changes in the channels that exhibited significant decreases compared with that of the sham stimulation (blue curves) on Day 1 (red curves, one-tailed, FDR corrected, $p < 0.05$). The triangles represented the significant HbO decreases on Day 1. Abbreviations: FEF - Frontal Eye Field; SMG - Supramarginal Gyrus; V3 - Visual Cortex 3; R - Right hemisphere.

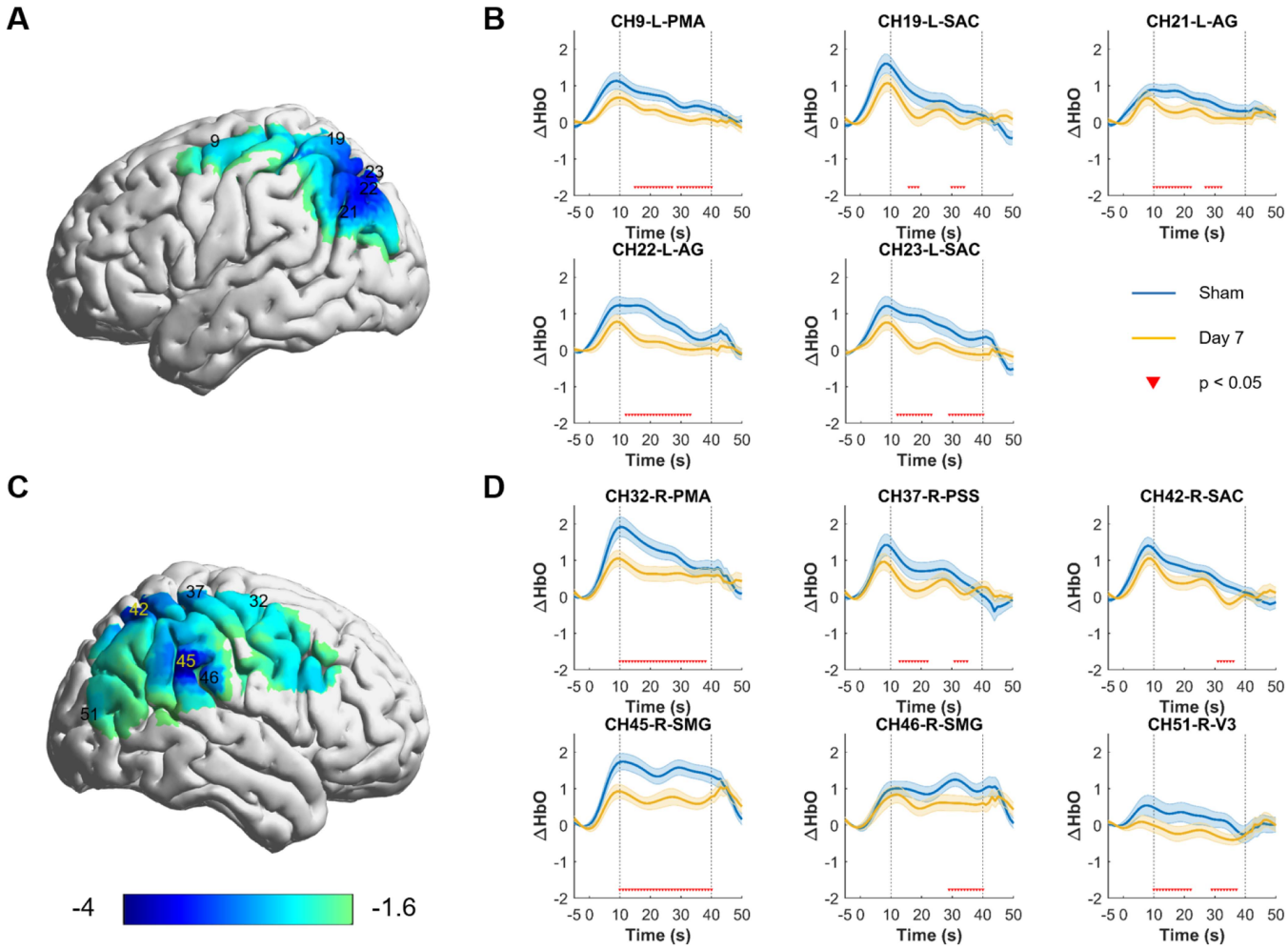

Fig. 4. One-week repeated tPBM-stimulation-induced HbO change. A&C) Topographic maps, at the peak of the hemodynamic response, showing significant decrease in HbO relative to baseline on Day 7. The color bar indicated the t values included in the clusters, and the darker color represented lower activation on Day 7 compared to the sham session. Channels surviving the FDR correction were labeled on the brain maps. B&D) Display of HbO changes in different channels that exhibited significant decreases compared with that of the sham stimulation (blue curves) on Day 7 (orange curves, one-tailed, FDR corrected, $p < 0.05$). The triangles represented the significant HbO decreases on Day 7. Abbreviations: PMA - Premotor Cortex and Supplementary Motor Area; SAC - Somatosensory Association Cortex; AG - Angular Gyrus; PSS - Primary Somatosensory Cortex; SMG - Supramarginal Gyrus; V3 - Visual Cortex 3; L - Left hemisphere; R - Right hemisphere.

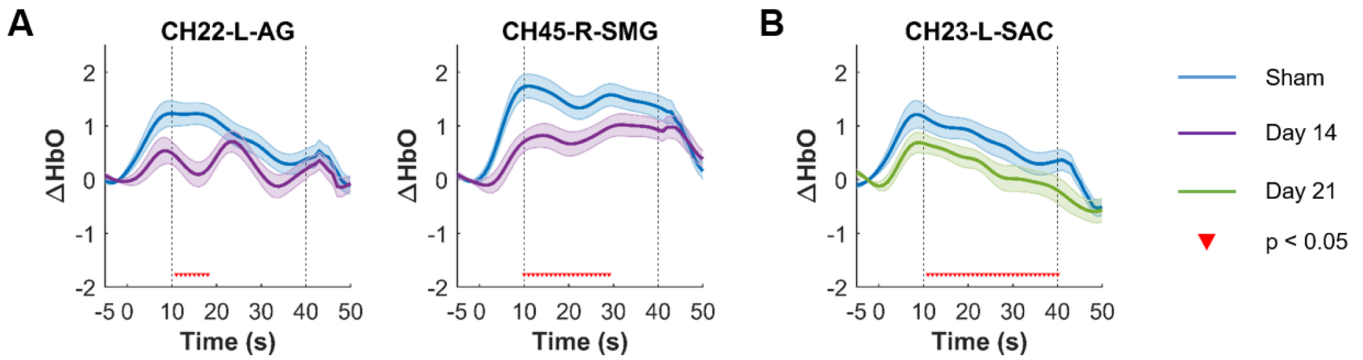

Fig. 5. HbO changes during the follow-ups. (a) for the HbO comparison between follow-up Day 14 (purple curves) and sham (blue curves) and B) for the HbO comparison between follow-up Day 21 (green curves) and sham. Three regions were found to show a significant HbO decrease compared with that of the sham stimulation (one-tailed, FDR corrected, $p < 0.05$). The triangles represented significant HbO decreases during the follow-up sessions. Abbreviations: AG - Angular Gyrus; SMG - Supramarginal Gyrus; SAC - Somatosensory Association Cortex; L - Left hemisphere; R - Right hemisphere.

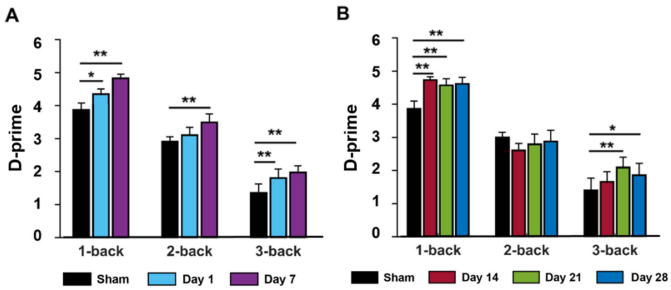

Fig. 6. N-back performance on task accuracy. (a) for the comparisons between Day 1/ Day 7 and sham. (b) for the comparisons between each follow-up and baseline sham. The error bars indicated the standard error of the mean. $^{*}p < 0.05$; $^{**}p < 0.01$.

as conducting difficult tasks. After FDR correction, channels in bilateral PMA, bilateral SAC, left AG, right PSS, SMG and V3 (Fig. 4(b) and (d)) still exhibited an obvious decrease of the increased hemoglobin concentration after repeated tPBM (i.e., Day 7) compared to the baseline.

D. Long-Term Brain Activation Decreased During the Follow-Up

No significant cluster was identified when the follow-up session was compared to the baseline. However, a comparison of the time series on each time point between the two sessions revealed a significant HbO decrease (one-tailed, FDR corrected, $p < 0.05$) in the left AG and the right SMG on one-week post-stimulation (i.e., Day 14, Fig. 5(a)) and in the left SAC two- week post-stimulation (i.e., Day 21, Fig. 5(b)). Notably, the right SMG showed consistent HbO decreases on both Day 1 and Day 7.

E. Improvement of WM-Related Behavioral Performance

The paired t-test results showed that both single and repeated tPBM improved the accuracy of working memory task at various conditions (Fig. 6(a)), e.g., 1-back (Day 1 vs. Baseline: $t(40) = -2.12$, $p = 0.041$; Day 7 vs. Baseline: $t(33) = -4.93$, $p = 0.001$), 2-back (Day 7 vs. Baseline: $t(41) = -41$, $p < 0.001$), and 3-back (Day 1 vs. Baseline: $t(49) = -3.98$, $p < 0.001$; Day 7 vs. Baseline: $t(45) = -4.16$, $p < 0.001$). For the follow-up session, when comparing these three follow-ups with the baseline, the task accuracy also exhibited a significant increase for 1-back on Day 14 ($t(37) = 3.502$, $p = 0.001$), Day 21 ($t(38) = 0.541$, $p = 0.007$) and Day 28 ($t(34) = -0.23$, $p = 0.009$), as well as for 3-back on Day 21 ($t(47) = 0.31$, $p = 0.005$) and Day 28 ($t(41) = 1.02$, $p = 0.043$).

F. tPBM-Induced Brain Changes on HbR Signal

To enhance our understanding of the tPBM-induced hemodynamic changes, we repeated the above analyses with the HbR signals. For the identification of WM-related brain regions, we found that the regions in the left DLPFC and PMA showed significant interactions (Fig. S1). The detailed statistical results are listed in Supplementary Table S1.

For a single tPBM stimulation, no significant clusters were identified for the three N-back conditions (N = 1, 2, and 3). For the one-week repeated tPBM stimulation, there were also no significant clusters identified in the 1- and 2-back conditions, but one significant cluster was identified in the 3-back condition ($t = 404.01$, $p = 0.036$, Fig. S2A). The temporal response of HbR changes in channels surviving the FDR correction was shown in Fig. S2B. It was observed that the hemoglobin concentration during the 3-back task was significantly increased in the right PMA and V3 after seven days of tPBM compared to the baseline. Of note, the dynamic changes in brain activation during the 3-back condition over a temporal-spatial scale are shown in Supplementary Movie S4, accompanied by Supplementary Movie S5 and S6 for the changes during 1-back and 2-back conditions. Similar to the HbO signal, no significant cluster was identified when the follow-up session was compared to the baseline. The comparison of time series between the two sessions revealed a significant HbR increase in right V3 on one-week post-stimulation (Fig. S2C).

IV. Discussion

The present study explored neurophysiological changes induced by one week of repeated tPBM stimulation and investigated the persistent efficacy of such effect on brain hemodynamic changes. The results showed that whereas a single tPBM

stimulation significantly decreased brain activation in only the contralateral brain regions of the target position, repeated tPBM caused decreased brain activation across both the ipsilateral and contralateral hemispheres, and this decrease lasted for at least one week after repeated stimulation had ceased. These findings provide important neurophysiological evidence for the tPBM-induced changes in brain activation at specific cognitive task conditions.

TPBM, as an emerging neuromodulation technique, exhibits the advantages of being non-invasive and easy to use, which makes it quickly an appealing tool for improving cognitive functions in older adults. Although previous studies have demonstrated that both single and repeated tPBM stimulation in elderly individuals can lead to improved behavioral performance [14], [16] and optimized resting-state network organizations [50], whether and how the tPBM brings about effect at the neurophysiological level during specific cognitive tasks remains largely unknown. Here, we provided experimental evidence through a longitudinal design with the older adults receiving one-week tPBM stimulation and then investigated the hemodynamic response during a WM task after immediate tPBM and 3-week follow-ups.

We first observed that one-week tPBM stimulation resulted in significantly decreased brain activation on Day 1 during the 3-back task. The regions with decreased brain activation were primarily located in the right FEF, SMG, and V3. Such a decrease in HbO brain activation reflected that the participants paid less effort in terms of HbO in completing such a difficult task (i.e., 3-back task) after tPBM. Similar findings were also reported in previous studies [15], [51], [52]. For example, in a study on 18 older adults with mild cognitive impairment, Chan et al. found that those who received active tPBM, compared to sham stimulation, exhibited reduced hemodynamic responses and meantime improved behavioral performance during a visual memory task [52]. Furthermore, during a verbal 3-back task, Chan et al. investigated frontal brain activity in healthy young adults and found significantly decreased frontal activation after tPBM [51]. As such, these combined studies support that the tPBM treatment could lead to improved neural function that thereby reduces the cognitive effort required to complete difficult tasks.

We further observed that the tPBM-induced decrease in HbO brain activation showed dynamic changes over the course of one-week tPBM stimulation (i.e., on Day 1 and Day 7). The significant decrease in brain activation expanded from only the right hemisphere on Day 1 to both hemispheres on Day 7. It is known that older individuals have thicker extracerebral tissue, which is negatively correlated with tPBM energy deposition [53]. The one-week repeated stimulation could increase the energy deposition and lead to a larger number of photons interacting with the cerebral tissue, which ultimately make the brain be activated from local regions to both hemispheres. Several previous studies from both animal and human subjects demonstrated that repeated tPBM treatment has a positive effect on cognitive function. For instance, Tanaka et al. conducted an animal experiment in which they administered chronic tPBM treatment to the heads of rats for ten days, with a 3-minute daily exposure, and found an improvement in anxiety and depression-related behaviors compared to those with a single exposure [54]. Moreover, in a human study, Vargas et al. found that chronic tPBM treatment (5 weekly sessions, 8 minutes each) improved working memory and attention performance better than a single stimulation (8 minutes) [15]. However, whether one-week repeated tPBM stimulation leads to optimal improvement in both brain function and cognitive outcomes of older adults, deserves further investigation in the future.

Intriguingly, recent studies have also found that the promising effect of tPBM on brain function is still observed in the large-scale functional connectivity network [55], [56]. For instance, in a study employing functional magnetic resonance imaging (fMRI), Dmochowski et al. stimulated the right frontal lobe with tPBM and observed brain-wide functional connectivity (FC) increases during the stimulation, with a quarter of all connections showing such a significant increase [55]. Consistently, an fNIRS study evaluated the cerebral changes across the whole brain brought by tPBM to the right forehead and discovered increases in the global small-world efficiency [56]. Similar results were found in studies adopting other neuromodulation techniques. For example, Reinhart et al. pointed out that 25-min transcranial direct current stimulation (tDCS) treatment increased the integration of large-scale cortical networks in older adults, which greatly improved working memory performance [57]. Furthermore, Meinzer et al. also found that 20 min of tDCS stimulation could reverse age-associated cognitive declines, ultimately resulting in a significant reduction of task-related hyperactivity and a more "youth-like" organization of the cortical network [58]. Therefore, it is plausible to speculate that the tPBM-induced HbO decrease observed in the current study could be a reflection of optimized brain functional organization after tPBM treatment, which further helps to improve information processing efficiency and the following cognitive outcomes during working memory in older adults.

It is worth noting that the regions with significantly decreased activation on Day 1 were primarily found in the contralateral hemisphere to the site of stimulation, i.e., the right dorsolateral prefrontal cortex (when tPBM was applied to the left DLPFC). During working-memory tasks, younger participants typically have more activation in the left hemisphere [59], whereas additional activation in the right homologous regions was observed in older adults [60]. After administering a single tPBM stimulation, there was a significant decrease in the strong activation in the right hemisphere, which led to a more youth-like brain activation pattern in the older participants. In fact, tPBM-induced changes in the contralateral hemisphere are not unexpected, as a previous tPBM study also found the same pattern [61]. In a study of 68 healthy adults (age: 18–85 years), Saucedo et al. found significant HbO differences in the left hemisphere between the active tPBM and placebo groups, yet tPBM was administered to the right prefrontal cortex [61]. Likewise, in a study using repetitive transcranial magnetic stimulation (rTMS) over the left motor and prefrontal cortex, the authors found that the rTMS-induced reduction in HbO appeared to be more significant for contralateral, rather than ipsilateral, brain regions [62]. Despite the above evidence supporting the reduction in activation

of the right hemisphere in older adults, future work should include a right-hemisphere stimulation condition to elucidate the potential mechanisms and differences underlying these findings.

To date, studies investigating the persistent effect of repeated tPBM on neural activity and behavioral performance are scarce. The current study aimed to shed light on this effect via a three-week follow-up design. We found that the decrease in brain activation did not disappear immediately after repeated tPBM. Specifically, the significant decrease in activation of the left AG and right SMG, induced by repeated stimulation, persisted for one week. Notably, these regions are highly associated with word processing [63], [64]. This phenomenon indicates a possible role of tPBM in enhancing word processing, thereby improving working memory. Furthermore, we found that the left SAC showed an unstable, inverted bell-shaped activation pattern. The activation decreased after 7 days of repeated stimulation, returned to baseline at the first follow-up test, and decreased again at the second follow-up test. The long-lasting effect of tPBM found in the current study is in line with previous evidence [10], [18], [20]. For instance, a two-week follow-up study on healthy adults (18 to 35 years old) found that overall emotions improved significantly in the treated group (which received 8 min of tPBM stimulation in total), as more sustained positive emotional states were reported in this group compared to those of the placebo control group; this indicated the protective effect of tPBM on mood lasted at least 2 weeks after a single intervention [10]. The long-lasting effect of tPBM can be attributed to the activation of signaling pathways and transcription factors, which strengthen and prolong protein expression [65], [66]. A recent review has also pointed out that more than fourteen different transcription factors and signaling mediators were found to be activated after tPBM [67]. Although the current study suggests that one week of repeated tPBM can generate lasting effects on neural activity and behavioral performance, further investigation is needed in the future on the effects of other stimulation durations on working memory in older adults.

It should also be noted that different power densities and doses of tPBM stimulation may lead to various results with the current study. It has been well documented in both in vitro and in vivo experiments that the tPBM dose has a biphasic effect [68], [69], [70]. To illustrate this effect, when irradiating cultured neurons with different fluences (0.03, 0.3, 3, 10, or 30 J/cm^2), researchers found that low-level light at lower fluences induced a significant increase in ATP and mitochondrial membrane potential (MMP) in neurons compared to that of the higher fluences [68]. The power density in the current study was 250 mW/cm^2. However, the effect of tPBM at various power densities should be investigated. In addition, mice with traumatic brain injury benefited the most from a four-day tPBM treatment but showed no improvement from receiving a consecutive tPBM on the fifth day [68]. Therefore, although the current study demonstrated the cumulative effect of one week of tPBM, the turning point of tPBM efficacy remains unknown. Further studies are needed to reveal whether the benefits of tPBM will continue to accumulate for stimulation sessions longer than 7 days.

Several limitations to this study should be mentioned. First, the current study lacks a brain control group for the exclusion of habituation and practice effects possibly included in the current brain findings. Actually, our previous behavioral investigation with a sham control group [16] has suggested that the repeated working-memory task (under the sham tPBM condition) did not bring about significant changes of behavioral performance, and hence excluded the effect of habituation and practice effects on the experimental design. However, whether repeated exposure to the working-memory task had not also led to habituation and practice effects on the brain needs additional evidence in the future. Second, we considered the left DLPFC of the participants as the stimulation target and observed significant changes in cerebral hemodynamic activity and task accuracy in older adults. However, it remains largely unknown whether the left DLPFC is an optimal stimulating target for cognitive improvement in older adults. Third, a fixed DPF value of 6 was used during the calculation of hemoglobin concentration in this study. Nevertheless, it is known that DPF is highly dependent on the populations' ages, wavelengths used, and anatomical regions measured. Therefore, it is important to develop a general equation of DPF (like the work from Scholkmann and Wolf [71]) and further validate the current findings in the future. Finally, we point out that the tPBM-induced brain changes identified from the HbO signal were partially replicated by the HbR signal in the current study. We speculate that the neuromodulation techniques (e.g., tPBM stimulation) may cause changes in neurovascular coupling and further bring larger changes in the HbO signal compared to that in HbR. For example, a previous study from rTMS stimulation also found significant changes (i.e., decreased activation) in the HbO signal but no significant change in the HbR signal during stimulation [62]. However, the exact reasons underlying the difference between HbO and HbR results deserve further exploration in the future.

V. Conclusion

This study on healthy older adults investigated how single and repeated tPBM induced neurophysiological changes during N-back tasks and evaluated how long the effects persisted after tPBM. The results showed that a single tPBM stimulation over the left DLPFC caused a significant task-related decrease in the contralateral regions that had exhibited compensatory hyperactivation at baseline. With repeated tPBM stimulation, the decreased activation in the right hemisphere was expanded to both hemispheres. This effect persisted for at least a week. In summary, our findings provided important evidence for a better understanding of the neural mechanism underlying tPBM-induced cognitive enhancement.

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