Repetitive Transcranial Alternating Current Stimulation to Improve Working Memory: An EEG-fNIRS Study

Dalin Yang, Min-Kyoung Kang, Guanghao Huang, Adam T. Eggebrecht, and Keum-Shik Hong, *Fellow, IEEE*

***Abstract*— Transcranial electrical stimulation has demonstrated the potential to enhance cognitive functions such as working memory, learning capacity, and attentional allocation. Recently, it was shown that periodic stimulation within a specific duration could augment the human brain's neuroplasticity. This study investigates the effects of repetitive transcranial alternating current stimulation (tACS; 1 mA, 5 Hz, 2 min duration) on cognitive function, functional connectivity, and topographic changes using both electroencephalography (EEG) and functional near-infrared spectroscopy (fNIRS). Fifteen healthy subjects were recruited to measure brain activity in the pre-, during-, and post-stimulation sessions under tACS and sham stimulation conditions. Fourteen trials of working memory tasks and eight repetitions of tACS/sham stimulation with a 1-minute intersession interval were applied to the frontal cortex of the participants. The working memory score, EEG band-wise powers, EEG topography, concentration changes of oxygenated hemoglobin, and functional connectivity (FC) were individually analyzed to quantify the behavioral and neurophysiological effects of tACS. Our results indicate that tACS increases: i) behavioral scores (i.e., 15.08, *p* <0.001) and EEG band-wise powers (i.e., theta and beta bands) compared to the sham stimulation condition, ii) FC of both EEG-fNIRS signals, especially in the large-scale brain network communication and interhemispheric connections, and iii) the hemodynamic response in comparison to the pre-stimulation session and the sham condition. Conclusively, the repetitive theta-band tACS stimulation improves the working memory capacity regarding behavioral and neuroplasticity perspectives. Additionally, the proposed fNIRS biomarkers (mean, slope), EEG band-wise powers, and FC can be used as neuro-feedback indices for closed-loop brain stimulation.**

***Index Terms*— Brain stimulation, electroencephalography, functional near-infrared spectroscopy, hemodynamic response, neurofeedback, transcranial alternating current stimulation.**

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This work involved human subjects or animals in its research. Approval of all ethical and experimental procedures and protocols was granted by the Human Research Ethics Committee of Pusan National University, and performed in line with the Declaration of Helsinki.

Dalin Yang was with Pusan National University, Busan 46241, South Korea. She is now with the Mallinckrodt Institute of Radiology, Washington University School of Medicine in St. Louis, St. Louis, MO 63110 USA.

Min-Kyoung Kang is with the School of Mechanical Engineering, Pusan National University, Busan 46241, South Korea.

Guanghao Huang is with the Institute for Future, Qingdao University, Qingdao 266071, China.

Adam T. Eggebrecht is with the Mallinckrodt Institute of Radiology, Washington University School of Medicine in St. Louis, St. Louis, MO 63110 USA.

Keum-Shik Hong is with the School of Mechanical Engineering, Pusan National University, Busan 46241, South Korea, and also with the Institute for Future, Qingdao University, Qingdao 266071, China (e-mail: kshong@pusan.ac.kr).

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I. Introduction

WORKING memory (WM) denotes the brain's ability to temporarily retain information for future action planning [1]. It is pivotal in intelligence, information manipulation, and complex mental activities like learning, comprehension, and reasoning [2], [3]. Diverse metrics to measure WM are currently employed to assess the deterioration level of neuropsychiatric diseases (e.g., neurodegenerative, attention-deficit, and hyperactivity disorders) [4]. The underlying mechanism of the WM deficit has been hypothesized to be due to various neurobiological causes, such as the volume change of white and gray matter, alteration of cerebral blood flow, concentration changes in neurotransmitters, and abnormal interbrain neural connections [5], [6]. However, WM capacity is flexible, not fixed. Neuromodulation and WM training can expand the storage capacity of WM by increasing neural activity and enhancing brain connectivity, as indicated by accumulating evidence in neuroimaging, neurophysiological, and computational modeling studies [1], [7].

Transcranial alternating current stimulation (tACS) is emerging as a safe and relatively inexpensive means of modulating psychological and physiological processes through the non-invasive application of low-voltage alternating currents to the brain [8], [9]. The delivered sinusoidal current can synchronize with endogenous oscillations by inducing rhythmic neuron firing [9], [10]. Through spike-timing-dependent plasticity, tACS can induce long-lasting synaptic changes and neuron connectivity, a phenomenon often referred to as neuroplasticity [10], [11]. Neuroplasticity denotes the capability of the nervous system to reorganize its structure and functioning in response to various intrinsic or extrinsic stimuli [12]. There has been conclusive evidence that tACS effectively maintains cognitive function by modulating brain oscillations at a specific frequency [13]. In particular, theta band (4–8 Hz) tACS exhibits the potential to modulate cognitive functions, such as memory retrieval, fluid intelligence, visual perception, and executive functions [13], [14]. Herein, as reported in the literature, theta oscillations play an essential role in neural network communication when cognitive control is performed, and theta synchronization has been found between the frontal cortex and hippocampus during WM maintenance [15]. Consequently, tACS with a frequency band of 4–8 Hz has been commonly applied to improve WM capacity by enhancing endogenous brain rhythms in the theta band.

Advancements in neuroimaging techniques have propelled the field of brain stimulation, where the synergy between neuroimaging and neurostimulation accelerates the development of symptomatic therapies [16], [17]. The existing mainstream neuroimaging techniques used in combination with brain stimulation techniques include positron emission tomography (PET), functional magnetic resonance imaging (fMRI), functional near-infrared spectroscopy (fNIRS), and electroencephalography (EEG). However, fMRI and PET have limitations when applied routinely compared to EEG and fNIRS techniques [18]. For instance, fMRI is expensive, susceptible to magnetic interference and motion artifacts, lacks mobility, has a low temporal resolution, and precludes those who suffer from noise and claustrophobia [19], [20]. In addition, PET involves an additional concern of radiation exposure and radiotracers. Compared to fMRI and PET techniques, EEG and fNIRS are portable, safe, cost-effective, and have excellent temporal resolution [21].

Moreover, the EEG technique allows monitoring of the electrical potential differences during neural firing across different brain locations on the scalp [22], [23]. Additionally, fNIRS provides an indirect methodology to quantify the concentration change in oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HbR) [24], [25], [26]. Owing to the absence of electro-optical interference, the hybrid EEG–fNIRS neuroimaging modality is widely employed to examine the electrical potential differences on the scalp and the cerebral hemodynamic response concurrently upon neural activity [17], [27], [28]. Compared to single-modal neuroimaging, multimodal neuroimaging techniques provide a more comprehensive means to formulate a customized therapy plan in the pre-treatment stage, monitor the alteration of neuroplasticity during the stimulation period, and assess the modulation of brain circuitry in association with clinical measurements in the post-stimulation section.

As mentioned above, the success and strength of WM depend on the hippocampal–neocortical interaction [29], [30]. Theta oscillation dominates the hub of memory consolidation and hippocampal activity via the coordination of anatomically distributed nodes of the brain network. Several studies have investigated the effect of theta tACS on WM processes. These investigations demonstrated that tACS enhances ongoing processes via exogenous augmentation with specific theta band frequencies [31]. Generally, the theta band synchronization of a large-scale neuronal network generated by tACS phase manipulation leads to a positive change in the WM capacity. Desynchronization induces an inhibitory effect. In addition, the combined neuroimaging study in [32] demonstrated that the theta band tACS could alter functional connectivity, EEG power spectrum, and cerebral blood activity. This finding is consistent with invasive electrophysiological studies on rodent and primate models, where tACS reliably modulates a specific frequency of ongoing neuron spiking [10], [33], [34].

Studies have shown the positive effect of 5-Hz theta tACS on cognitive improvement, although some reported different outcomes, with neither transcranial direct current stimulation (tDCS) nor tACS significantly affecting memory performance [35], [36]. Factors influencing such inconsistency include different stimulation location distributions, insufficient stimulation durations, inadequate assessment criteria, and individual differences in susceptibility to brain stimulation [37], [38]. Recent tDCS research has indicated that extending stimulation duration is not the key to enhancing the prolongation of the effect [39], [40]. In contrast, repetitive tDCS with an appropriate interval has been proven to have a lasting effect after stimulation compared to continuous tDCS. One possible explanation for this is late-phase long-term potentiation (l-LTP) [41] via enhanced synaptic connections and structural alteration of neurons [42].

Periodic stimulation protocols can alter neuroplasticity and preserve stability for days or weeks. For instance, the effect of repetitive tACS has been investigated by Hsu et al. (2019), who demonstrated that tACS with a one-minute intersession interval (i.e., duration of two adjacent tACS) generated a positive effect on multitasking performance [43], [44]. Therefore, this study applies repetitive short-duration tACS with a one-minute intersession interval to investigate the effects on WM and neuroimaging. In addition, the electrical interference of the tACS with the EEG signals has always been the principal challenge to recording EEG data simultaneously during the stimulation period, despite using several methodologies to remove the noise from EEG recordings [45]. Our design of repetitive short-duration (RSD) tACS provides convenience for avoiding interference caused by tACS/tDCS during the EEG recording. Furthermore, neuroimaging information can reflect the brain state and determine the optimal repeated sessions to achieve closed-loop stimulation [46].

Herein, the present study aims to demonstrate the effects of RSD-tACS on neuroplasticity alternation and WM capacity modulation by performing multiple brain state measurements via electrophysiology (i.e., EEG features), hemodynamics (i.e., fNIRS features), and cognitive performance (i.e., WM scores). To address potential quantitative assessment of the stimulation effects, we further investigate hybrid EEG-fNIRS features to measure the modulatory effects of the stimulation on cognitive performance. We hypothesize that the RSD-tACS at a frequency of 5 Hz would improve the WM score and induce changes in neuroplasticity.

II. Methods

A. Subjects

Fifteen healthy volunteers (eleven males, average age: 25.2 years) were recruited from Pusan National University to participate in this study. All participants were right-handed and

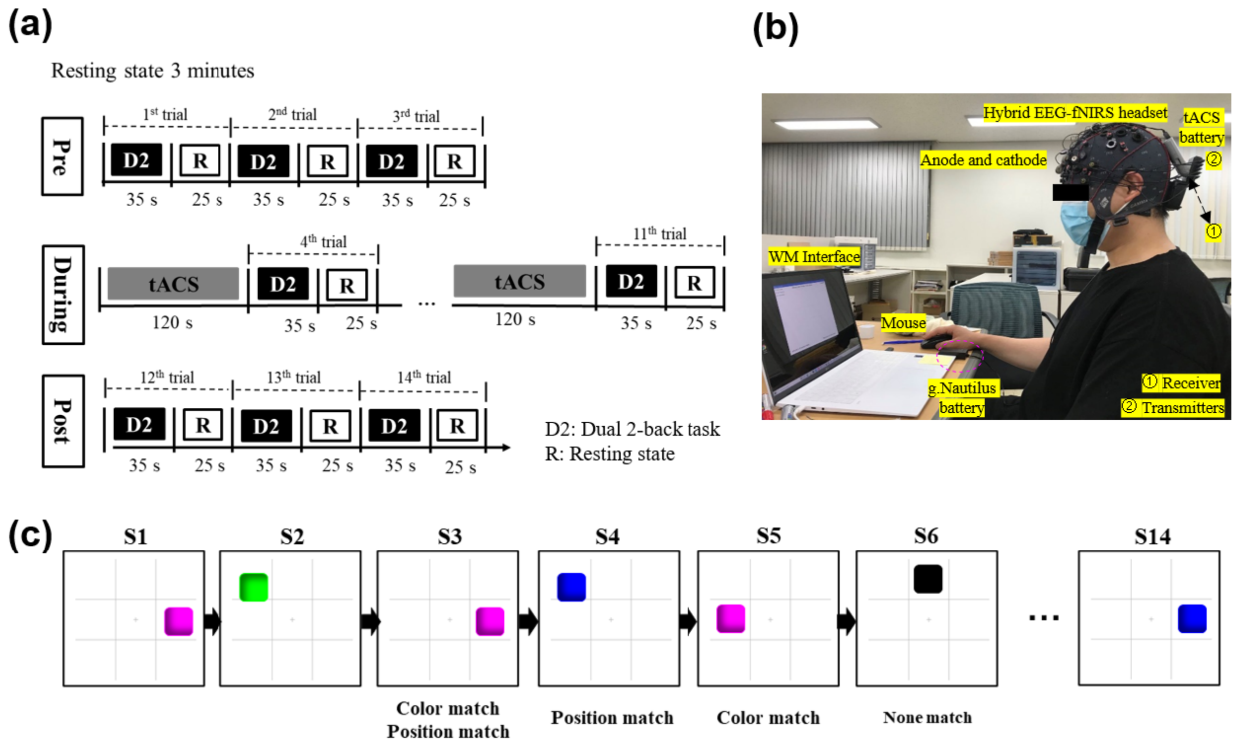

Fig. 1. Experiment design: (a) One experiment is composed of three sections (pre-, during-, and post-stimulation), the pre/post-stimulation section consists of three trials of dual 2-back tasks, and the during-stimulation section includes eight 120 s tACSs accompanied by a 35 s task and a 25 s rest; (b) the experimental setup showing a participant with equipment on the head, sitting in a comfortable chair; and (c) an illustration of the visual-spatial dual (color, position) 2-back task.

had normal or correct-to-normal vision. The exclusion criteria of this study were as follows: Self-reported metal implants or implanted electronic devices in the body, history of neurological illness, psychiatric impairment, pregnancy, brain injury, and use of psychoactive medication. Before the experiment, we informed the participants of the experimental procedure and the risk of non-invasive electrical stimulation. Participants were permitted to stop the procedure if they experienced high-level discomfort. Written informed consent was obtained from all participants after they understood the procedures and risks. After completing the study, each subject received an allowance for compensation. The entire experimental paradigm was approved by the Human Research Ethics Committee of Pusan National University and conducted following the latest Declaration of Helsinki [47].

B. Experimental Paradigm Design

Fig. 1 illustrates the experimental procedure. One experiment consists of four parts: A resting period of 3 min, a pre-stimulation period of 3 min, a stimulation period of 24 min, and a post-stimulation period of 3 min. First, all participants spent 3 min resting on a comfortable chair. The subjects were asked to perform three trials of dual (color and position) 2-back working memory tasks in the pre-stimulation section with a 35 s task and a 25 s resting period. The during-stimulation section includes eight repeated tACS or sham stimulations (2 min/stim) and eight trials of dual 2-back tasks (35s task and 25 s rest) after each repetitive stimulation. Finally, the subjects conducted three trials of dual 2-back tasks in the post-stimulation section, as shown in Fig.1 (a). Assessing the tACS effect objectively, the stimuli were randomly assigned to the subjects, either tACS or sham, for each visit (2 visits/subject).

A dual 2-back task is typically applied to assess the participants' psychology and cognitive neuroscience performance by measuring their WM capacity and WM-induced neuroplasticity [48]. In this study, the participants underwent a comprehensive training session to familiarize themselves with the task [49], then performed fourteen trials of dual 2-back tasks (3 + 8 + 3 for pre-, during-, and post-stimulation periods). Each dual 2-back task contained 14 stimuli, and each stimulus lasted for 2.5 s. The subjects were requested to decide whether the position and color of the object on the current screen were the same as those that appeared on two screens previously. If only the position matches, the subject should click the left side of the mouse. Instead, if only the color matches, click the right side of the mouse. If the position and color match, click both sides of the mouse; if none matches, click nothing. Additionally, participants completed an adverse effects questionnaire, rating feelings of itching, tingling, burning sensation, phosphene, or fatigue on a scale of 1 to 10.

C. Data Acquisition

A hybrid g.Nautilus fNIRS-8 device (g.tec, Schiedlberg, Austria) was used to acquire the EEG and fNIRS signals at a sampling rate of 250 Hz. Fig. 2 depicts the EEG, fNIRS, and tACS channel configurations. The recorded EEG–fNIRS data were simultaneously read in MATLAB using the g.HIsys professional software. A surface conductive

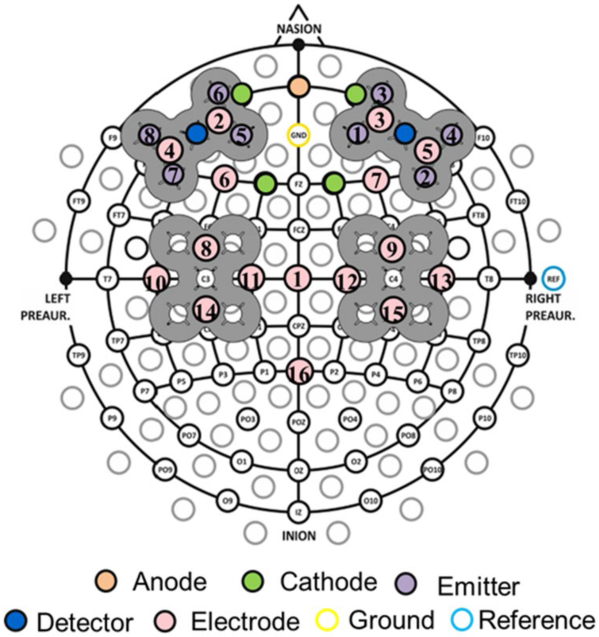

Fig. 2. Channel configuration of EEG, fNIRS, and tACS: The one orange circle refers to the tACS anode; the four green circles are the tACS cathodes; the two blue circles present the fNIRS detectors; the eight purple circles are the fNIRS emitters where the numbers refer to the fNIRS channel numbers; the sixteen pink circles the EEG electrodes; and the hollow yellow and blue circles represent the ground and reference electrodes, respectively.

gel (i.e., g.GAMMAgel, Schiedlberg, Austria) was used to ensure low impedance (i.e., < 10 kΩ) and good electrical contact between the EEG sensors and the scalp.

D. Electrical Stimulation

Repeated tACS was administered using a wireless battery-driven brain stimulation device (Starstim tCS, Neuroelectrics®, Spain). As reported in [50] and [51], a high-definition montage can induce a more extended neuroplasticity maintenance period than the conventional stimulation montage. Therefore, high-definition transcranial alternating current stimulation (HD–tACS) with five Ag/AgCl electrodes (i.e., 1 cm^2) was employed in this study: One as a stimulating electrode and four as return electrodes. A 5 Hz sinusoidal alternating current of 1,000 μA (i.e., zero to peak) was delivered to the participant's brain from the stimulation electrode (i.e., FpZ) and returned to the return electrodes (i.e., FP1, FP2, AF3, and AF4). The simulated E-field modeling using the current configuration was pre-examined to validate the current effect in the frontal cortex, as shown in Fig. 3. All participants received eight repetitive tACS/sham stimulations for each visit, each stimulation was maintained for 2 min with a 5 s ramp-up and ramp-down period. The entire stimulation protocol (e.g., electrode placement and 25% current distribution of return electrode) was configured using the Neuroelectrics Instrument Controller 2.0 software (Neuroelectrics®, Spain), which controls the tCS system using Bluetooth.

E. Data Preprocessing

MATLAB–Simulink was used to record the synchronized EEG and fNIRS data from the hybrid EEG–fNIRS device

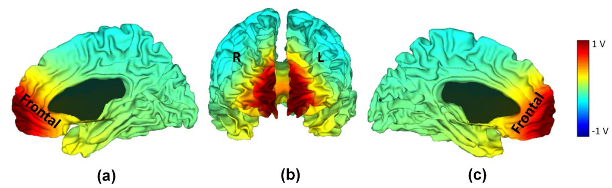

Fig. 3. Simulated electrical field visualization obtained using the present stimulation protocol: (a) The right hemisphere (the left-side view), (b) both hemispheres (the frontal view), and (c) the left hemisphere (the right view).

in real time. EEG and fNIRS data were processed/analyzed offline using our customized codes on the MATLAB™ platform (MathWorks, version: R2020a). We conducted the baseline correction to eliminate the potential drifting and the baseline shifting during the experiment. In the fNIRS case, the HbO and HbR concentration changes were obtained using the modified Beer-Lambert law [52]. A third-order Butterworth filter with a low-pass cutoff frequency (0.18 Hz) and a high-pass cutoff frequency (0.0018 Hz) was applied to remove the environmental and physiological noises, such as cardiac pulses and respiration artifacts [53]. Likewise, the EEG raw data were first processed using the independent component (IC) analysis to remove eye movement/blink artifacts [54]. Specifically, we extracted the eye-blink-related IC from EEG channels using the reference channel near the eyebrow (Fp1) and reconstructed the EEG data using the remaining ICs. Furthermore, third-order Butterworth low- and high-pass filters (1-50 Hz cutoff range) were used to remove the lower/higher interference noises. Furthermore, wavelet signal denoising was conducted to remove the artificial noise in the EEG data using an empirical Bayesian method with a Cauchy prior [55]. To reduce the susceptibility of the EEG signals, the threshold removal method (< 1,000 μV) was applied to exclude those EEG channels that might be interfered with by tACS.

F. Cerebral Hemodynamic Response

Typically, the cerebral hemodynamic response (HR) occurs owing to brain activity or external stimuli, which enable the rapid delivery of nutrients (i.e., oxygen and glucose) to active neuronal tissues [53]. The HR reflects whether the HbO (and HbR) concentration changes increase or decrease upon neuronal firing. The desired hemodynamic response function (dHRF) is widely used to determine neuronal activation (i.e., activated channels) by fitting the measured signals to the dHRF. In this study, the channels of the region of interest were identified using the MATLAB function (*robustfit*) with the input of the measured trial-wise WM task HR signals and dHRF with a critical value: i) t-value > t_{crt} and ii) p-value < 0.05. To quantify the temporal features of the HRs upon the tACS, the HbO's mean and slope were further calculated using the *mean* and *polyfit*MATLAB functions Mandrick et al. [53].

G. EEG Power Spectrum and Topography

The EEG topographic mapping provides a view of the spatial distribution of each electrode by projection with a geometrical array of evenly spaced points. In the present study,

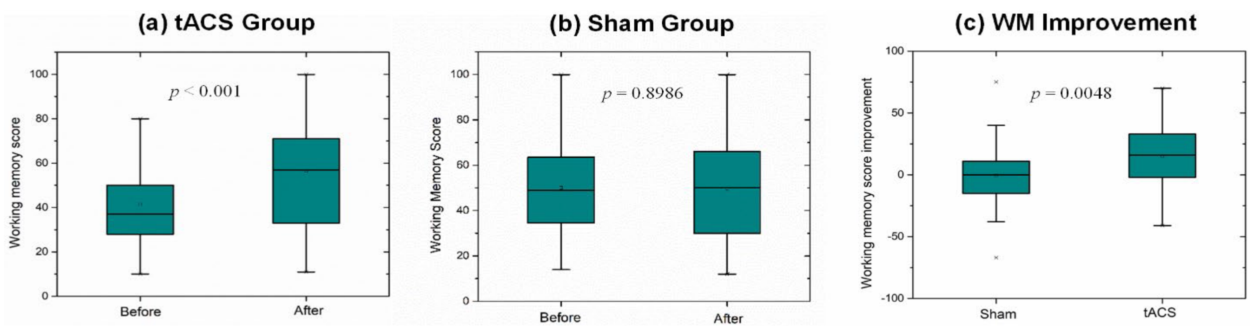

Fig. 4. Comparison of working memory test results (dual 2-back task): (a) Before and after tACS (*Cohen*'s $d = 0.568$), (b) sham condition (*Cohen*'s $d = 0.017$), and (c) the difference between sham and tACS conditions (*Cohen*'s $d = 0.472$).

the EEG power spectrum was calculated by the wavelet transform algorithm, *Morlet*, with a frequency step of 0.5 Hz. The divided EEG bands are delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), low beta (12–18 Hz), high beta (18–30 Hz), and gamma (30–50 Hz) bands. After visual inspection, we selected the task period (i.e., from 5 s to 35 s) from each trial for analyzing the EEG signal's changes to ensure no interference from the tACS. The resting period (i.e., from 40 s to 45 s for each trial) was chosen as the reference to calculate the relative EEG power (i.e., $\text{power}_{\text{task}} - \text{power}_{\text{rest}}$).

H. Functional Connectivity and Graph Theory

This study analyzed the connectivity by computing the Pearson correlation coefficients between two fNIRS channels. In the EEG case, the phase lag index (PLI) was calculated to assess the functional connectivity of individual channels since the PLI algorithm can avoid the effect of volume conduction (less sensitive) [54] [55]. A higher correlation coefficient indicates a substantial synchronization between the two brain regions. A valid connection was made based on the correlation coefficient value that exceeded the threshold value of 0.6 for generating functional brain networks based on our previous experience [56]. A low threshold value renders the results more likely to include unreliable connections, detrimental to credibility. Including these unreliable connections can overstate the results by reducing the scope of the legitimate functional network [57]. Additionally, node efficiency is an essential indicator of a node's influence on the measured network and is defined as a characteristic of communication efficiency [58] [59]. In this work, graph theory metrics of the node efficiency were calculated in different studies to examine the node influence on the brain network using the GRETNA toolbox in MATLAB [60].

I. Statistical Analyses

A Wilcoxon matched-pairs signed-rank test was conducted to evaluate the statistical difference between tACS and sham stimulation for WM capacity and brain state alternation with a confidence interval of 95%. The effect size (*Cohen's d*value) was applied to describe the effect of the standardized mean difference and the size of associations between variables. If the effect size of the two stimulation conditions is less than 0.2 standard deviations, the significant difference is negligible [61].

III. Results

A. Working Memory Performance and Safety Evaluation

All the participants performed fourteen trials of the dual 2-back task to examine the WM capability, including the pre-tACS (i.e., trials 1–3), during-tACS (is not discussed in the present study), and post-tACS (i.e., trials 12–14). As shown in Fig. 4(a), the increased WM score ($p < 0.01$, *Cohen*'s $d = 0.568$) in the post-tACS section (i.e., an average score of 56.44) was found, compared with the pre-tACS section. On the other hand, there is no positive effect in the sham-stimulation condition (i.e., $p = 0.8986$, *Cohen*'s $d = 0.017$), as shown in Fig. 4(b). Further, Fig. 4(c) depicts the WM score improvement (i.e., $\text{WMscore}_{\text{post-stimulation}} - \text{WMscore}_{\text{pre-stimulation}}$) between the sham and tACS conditions to validate the cognitive function improvement of the proposed method. It is seen that tACS increased the WM score by 15.08, whereas it did not improve in the sham stimulation case (i.e., the mean difference between before and after sham stimulations was -0.46). Moreover, no severe adverse effects were observed during the experiment. Most participants reported a medium phosphene feeling (9/15 subjects, average score: 4.94) and a slight tingling sensation (8/15 subjects, average score: 2.87) during the tACS. A few participants felt slight itching (5/15 subjects, average score: 3.60) and a burning sensation (1/15 subjects, score: 1). The phosphene effect can be attributed to the stimulation location being arranged in the frontal cortex near the eye and the theta alternating rhythm oscillation induces phosphene.

B. Hemodynamic Response

The present study delves deeper into potential biomarkers for quantifying the effects of tACS based on hemodynamic measurements. Mean and slope features of HbO were extensively employed to assess the hemodynamic response's characteristics, including initial increase, plateau, and undershooting period evoked by events [53]. Three distinct time windows were defined in this study to quantify HbO levels: Mean 1 refers to the mean value of HbO from 1 s to 10 s after the WM task onset. Similarly, Mean 2 (1∼15 s), Mean 3 (1∼20 s), Slope 1 (from 1 s to 8 s), Slope 2 (1–10 s), and Slope 3 (10–20 s) are defined. Fig. 5 compares the mean and slope values for the defined time durations of the HbOs after tACS and sham stimulations. The mean HbO values of the tACS condition are higher than the sham condition; see Fig. 5(a). In addition, the slope features (i.e., Slopes 1 and 2)

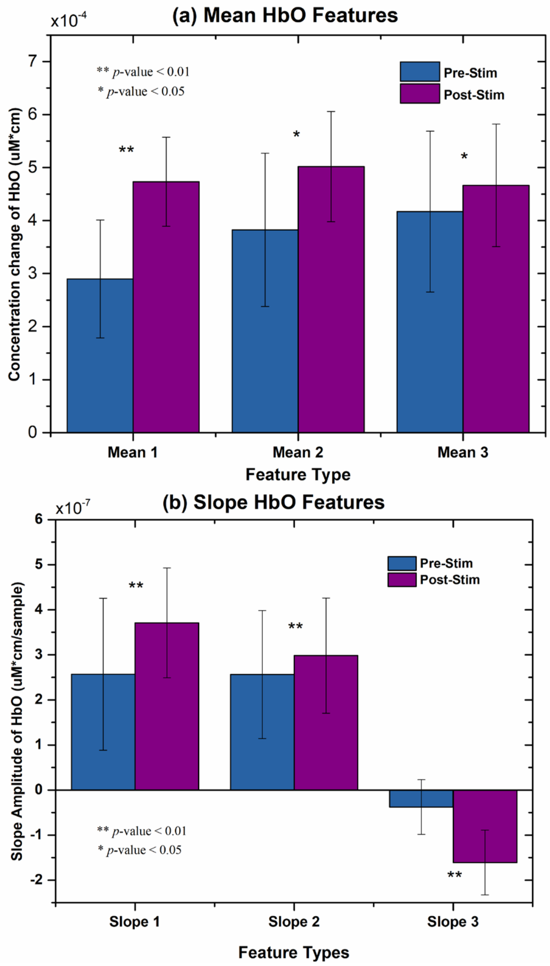

Fig. 5. Comparison of HbO means and slopes between Pre- and post-tACS stimulations.

obtained by tACS show higher increases than those obtained from the sham condition with a similar pattern. The more significant HR decrease (Slope 3) in the tACS condition than in the sham stimulation is also seen in the last bar chart in Fig. 5(b). The early increase of HbO during 1-10 s and the fast decay of HbO during 10-20 s can be used as features of tACS stimulation. The results indicate that the RSD-tACS enhances the speed (rapid increase of HbO) and amplitude of the hemodynamic response. Nonetheless, the hemodynamics difference between the two conditions' means is less than 0.2 standard deviation, except the Slope 3 (*Cohen's* $d = 0.243$).

C. EEG Band Power and Topography

Additionally, the neurophysiological effects of tACS are quantified by EEG band powers and topography in the frontal and parietal regions, as illustrated in Figs. 7 and 8. The EEG band power changes before/after the tACS and sham stimulation are shown in Fig. 6(a)-(d). Upon tACS, the powers of delta and theta bands have significantly increased ($p < 0.05$) in the frontal cortex, but a similar trend is not observed in the sham condition ($p < 0.05$). In the parietal case, a similar phenomenon occurs, in which the delta and theta powers significantly increase ($p < 0.05$, $p < 0.01$). Cohen's d values are illustrated for individual EEG bands between the pre/post stimulations. Although the beta and gamma bands of the sham condition reveal a significant difference (see Fig. 6(c)(d)), the effect sizes are relatively small (i.e., Cohen's d values $= 0.03$ (parietal) and 0.24 (frontal); therefore, the difference is negligible. However, the significant difference in the tACS condition is further confirmed by the large effect size (Cohen's d value > 0.8). The topographies in Fig. 7 reveal the comparative power distributions in specific EEG bands. In the pre-tACS session, the region of the high activation during the WM task exists in the left dorsolateral prefrontal cortex (near F3) and the right prefrontal cortex (near Fp2). Similarly, this was also observed in the post-sham stimulation condition. However, the geographical brain maps of the post-tACS condition in the overall bands are very distinct compared to the pre-tACS and sham condition, where the entire frontal region is activated when performing the WM task, including the bilateral dorsolateral and ventrolateral prefrontal regions, specifically in the theta band. These critical tACS effects may enhance the neuropsychological performance (i.e., increase specific EEG-band power).

D. Brain Connectivity

Functional brain connectivity means the strength to which activity between a pair of brain regions correlates over time. Fig. 8 illustrates the EEG and fNIRS functional connectivity. The different colors of the edges among the nodes represent the connectivity strength, ranging from 0.6 to maximum connectivity. The red line indicates a higher correlation between the two nodes than the blue line. The node efficiency determines the node's size, where a larger node indicates better communication with other nodes within the current brain network. In the EEG case, the connection in the post-stimulation section, see Fig. 8(b), is denser than that of the pre-tACS stimulation case, see Fig. 8(a); especially for large-scale connectivity (i.e., the connection between the frontal and parietal cortices). In addition, connectivity is augmented with a higher value of the phase lag index. The theta band oscillation and synchrony are related to large-scale brain network communication, enhancing cognitive function and integration, consistent with the literature [61], [62]. Likewise, the interhemispheric frontal connectivity in the fNIRS case also improves after tACS compared to the pre-tACS stimulation.

IV. Discussion

This study aims to assess the effect of repetitive short-duration tACS on WM capacity and neuroplasticity using hybrid EEG and fNIRS neuroimaging modalities. This work is the first report to assess the effect of theta band tACS on WM performance, electrophysiological activity, and hemodynamic responses. In addition, the present work investigates two quantified brain imaging features (mean, slope) to evaluate the tACS effect. Besides, the application of multiple neurophysiological readouts (i.e., EEG and fNIRS) enables a direct comparison of the tACS effect and provides complementary brain state information. Two modalities were seldom integrated for application in tDCS/tACS neuromodulation-based studies. Moreover, the proposed stimulation protocol with quantified brain imaging features may provide novel insights into future stimulation paradigms and closed-loop stimulation designs.

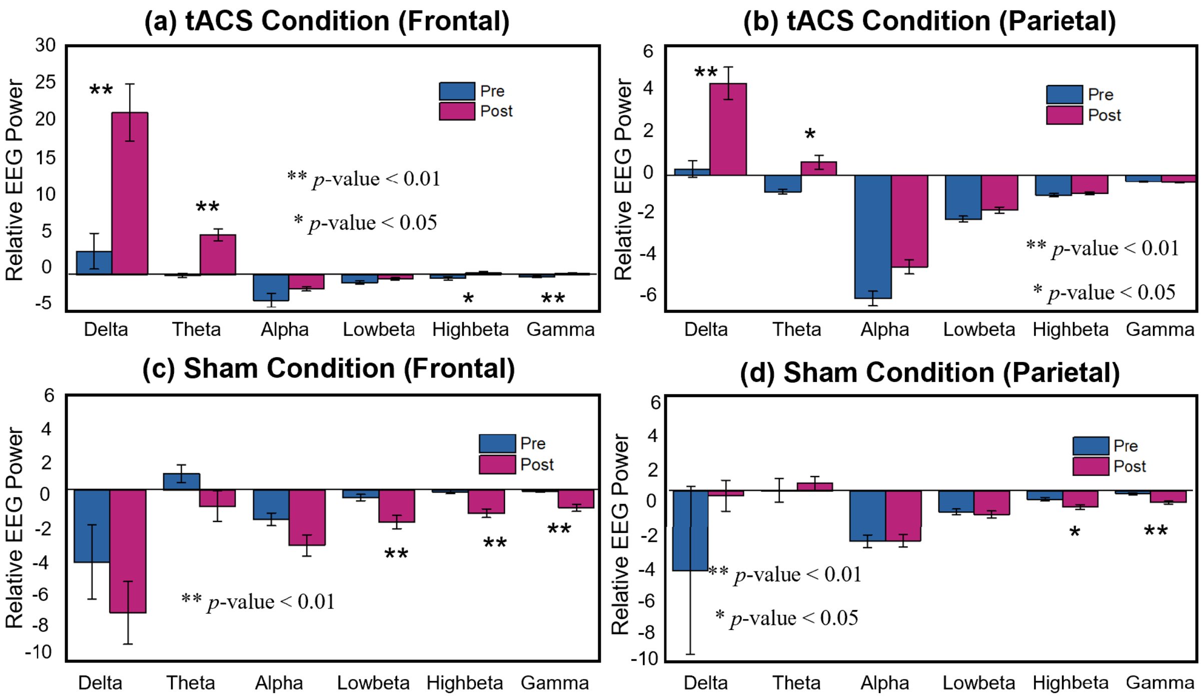

Fig. 6. Comparison of EEG band powers (pre/post stimulations): (a) The frontal cortex (tACS), (b) the parietal cortex (tACS), (c) the frontal cortex (sham), and (d) the parietal cortex (sham).

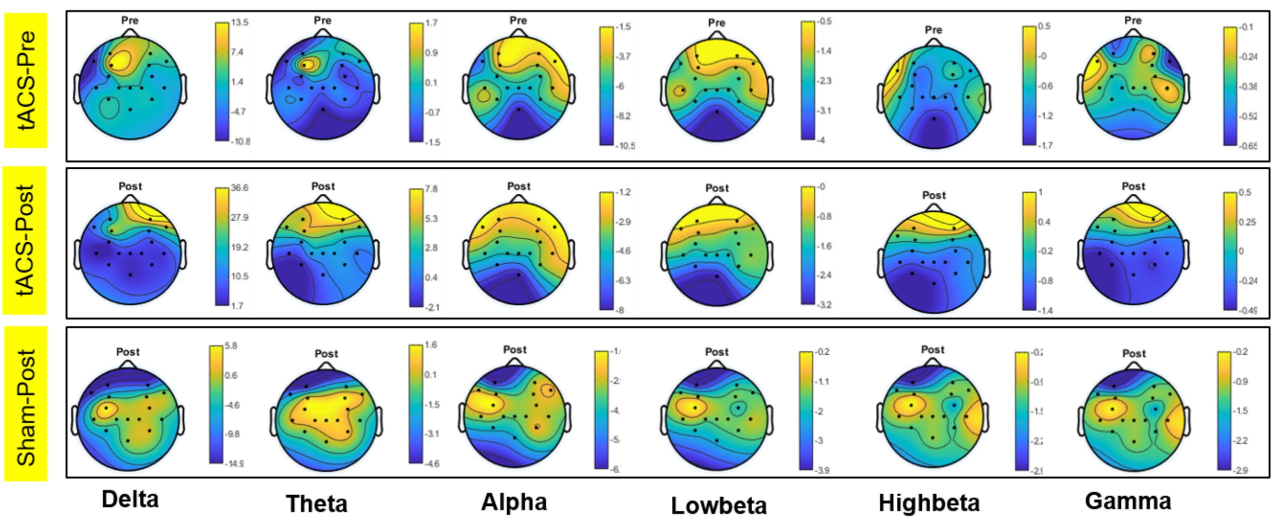

Fig. 7. EEG band topographies: Pre-tACS, post-tACS, and post-sham stimulation.

One hypothesis of this study posits that repetitive short-duration tACS positively impacts WM scores and neuroplasticity in the frontal and parietal brain regions. As anticipated, the post-stimulation WM score, see Fig. 4(a), demonstrated a positive effect compared to the pre-tACS and post-tACS stimulation sessions, aligning with findings from previous tACS studies [43], [44]. The neuroimaging results also indicate that repetitive short-duration tACS enhances the hemodynamic response speed (Fig. 5) coupled with the modulation of EEG delta and theta band activity in the frontal and parietal brain regions (Fig. 6). The present EEG results are somewhat different from those reported in [44] due to the difference of the task performed. The previous research investigated multitasking (called NeuroRacer), which examines the capabilities of visuo-motor tracking and visual discrimination [64]. These cognitive functions are highly relevant to the alpha and beta frequency bands. However, in the present study, the dual 2-back task was performed by the participants, and cerebral theta oscillations played an essential role in memory processing compared to other EEG bands [65]. The topographies of various EEG bands confirmed this statement. Before stimulation, only the left dorsolateral cortex and right frontal cortex were activated during the dual 2-back task in the theta and beta bands. The whole frontal cortex power was then enhanced in the post-stimulation session. However, this change did not appear in the alpha, beta, and gamma bands.

One of the rodent studies on hemodynamic responses illustrated that the cerebral blood flow (CBF) response peaked

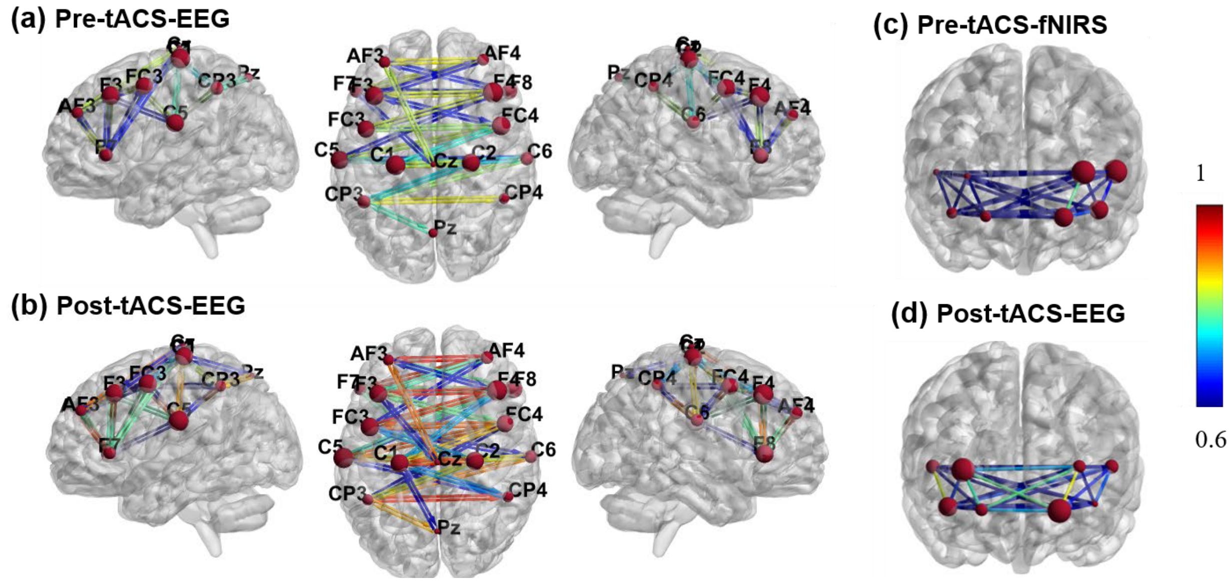

Fig. 8. Functional connectivities of EEG and fNIRS signals: (a) EEG (pre-tACS), (b) EEG (post-tACS), (c) fNIRS (pre-tACS), and (d) fNIRS (post-tACS).

more quickly at a higher stimulation intensity [66]. CBF is primarily caused by neuronal depolarization, and synaptic plasticity further affects neuronal firing [67]. Transcranial currents can indirectly affect hemodynamic responses through altered synaptic plasticity. Moreover, there is an enhancement in the functional connectivity of both EEG and fNIRS, particularly for large-scale and interhemispheric connectivity, as illustrated in Fig. 8. Accumulated evidence suggests that theta oscillations support the connection between the dorsal/ventral lateral cortex and hippocampus, forming an essential circuit in the memory process [68], [69]. The connectivity improvement provides a neurological explanation for the effect of theta band tACS on WM capacity. The altered large-scale brain network and local frontal interhemispheric connections are shown to impact human cognitive performance.

As demonstrated in a recent study [44], periodic stimulation with an intersession interval of 1 min showed an excellent ability to enhance neuroplasticity and extension of the tACS/ tDCS effect. Furthermore, a benefit of the existence of a no-stimulation interval makes the EEG measurement possible during a long-time hybrid EEG-fNIRS experiment without any interference from electrical stimulation. The measured neuronal activity and the hemodynamic signal can trigger the control system of tACS by offering complementary information available in two signals for detecting the brain states. In addition, the combination of non-invasive neurostimulation (i.e., tACS and tDCS) and portable neuroimaging modalities has the potential to advance non-pharmacological therapy applications in daily life rapidly, thanks to their economical convenience, high temporal resolution, and compact size (compared to fMRI and transcranial magnetic stimulation).

Determining proper imaging features is essential to a closed-loop stimulation system, which requires high accessibility to the actual brain state [70]. Functional brain imaging can establish the correlation between the brain state and behavioral performance by investigating the direct/indirect neuronal activity of the circumscribed brain region and brain network [71]. This study investigated the hybrid EEG and fNIRS to explore candidate indicators to express the effect of neuroplasticity on repetitive tACS. In fNIRS studies, the general tendency of tDCS/tACS in increasing HbO was observed in the resting state after stimulation [72]. As shown in Figs. 5 and 6, the mean and slope of hemodynamic responses of a segmented interval and the decline slope during the primary hemodynamic response can be the meaningful features qualified for assessing the repetitive tACS effect owing to the rapid hemodynamic response characteristics.

Meanwhile, the EEG power in the theta band in the frontal cortex (Fig. 6) exhibited a higher power than the sham condition. One possible explanation is that the theta band modulates the cortex and hippocampal system pathway, and the latter redeploys the WM-associated alpha band to coordinate the assigned cognitive function. Evidence indicates that alpha and theta oscillations reflect cognitive and memory processes in the human brain [73]. Furthermore, the endogenic theta rhythm implicates communication between the cortical system and the hippocampus, primarily responsible for short-term memory function [74].

One limitation of the present study is the restricted number of fNIRS measurement channels, and another is the confined measurement region, recording all fNIRS signals from the frontal or parietal cortices. The dorsolateral and ventrolateral prefrontal brain regions are the cortices of interest concerning visual and spatial WM tasks [75]. Future work can extend further broader brain regions to explore connectivity alternation in a large-scale brain network. Moreover, despite the imaging device incorporating multiple neuroimaging modalities such as EEG and fNIRS, there is limited space to arrange the dense fNIRS or EEG optodes. The sparse design of the fNIRS array presents challenges in establishing short separation channels for measuring extracerebral signals. Additionally, future work on systematic manipulation is required to determine the best stimulation protocol (i.e., stimulation intensity and frequency) and to enhance brain excitation [17], [76], [77].

Moreover, based on the stimulation protocol, a personalized closed-loop neuromodulation can be developed for the therapy of working memory loss for the general population (e.g., healthy adults or throughout childhood brain development) or early prodromal of Alzheimer's disease in our future work.

V. Conclusion

This study investigated the feasibility of the 5 Hz repetitive short-duration transcranial alternating current stimulation (tACS) to improve working memory (WM) and neuroplasticity. The WM capacity increased by approximately 15% after eight repetitions of tACS compared to the sham and pre-stimulation sessions. In addition, the large-scale connectivity between the frontal and parietal cortices and the interhemispheric functional connection was enhanced after tACS stimulation compared to the pre-tACS and sham stimulation conditions. Furthermore, there was a significant increase in the HbO amplitude (mean values of HbO). Also, a rapid rise in hemodynamic response was observed during the WM task compared to the pre-tACS sessions.

Moreover, three feature biomarkers in featured brain states based on the EEG and fNIRS recordings were proposed to evaluate the tACS stimulation effect, including the mean of HbO and the theta band EEG power in the frontal cortex. The present study demonstrated that repetitive short-duration tACS with 1 min intersession intervals could be used for memory-related rehabilitation. The biomarkers found can be utilized as neuro-feedback indices for a closed-loop neuromodulation therapy for memory loss-based brain disorders (i.e., Alzheimer's disease) in the clinical field.

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