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RESEARCH

Effectiveness assessment of repetitive transcranial alternating current stimulation with concurrent EEG and fNIRS measurement

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Abstract

Transcranial alternating current stimulation (tACS) exhibits the capability to interact with endogenous brain oscillations using an external low-intensity sinusoidal current and influences cerebral function. Despite its potential benefits, the physiological mechanisms and effectiveness of tACS are currently a subject of debate and disagreement. The aims of our study are to (i) evaluate the neurological and behavioral impact of tACS by conducting repetitive sham-controlled experiments and (ii) propose criteria to evaluate effectiveness, which can serve as a benchmark to determine optimal individual-based tACS protocols. In this study, 15 healthy adults participated in the experiment over two visiting: sham and tACS (i.e., 5 Hz, 1 mA). During each visit, we used multimodal recordings of the participants' brain, including simultaneous electroencephalography (EEG) and functional near-infrared spectroscopy (fNIRS), along with a working memory (WM) score to quantify neurological effects and cognitive changes immediately after each repetitive sham/tACS session. Our results indicate increased WM scores, hemodynamic response strength, and EEG power in theta and delta bands both during and after the tACS period. Additionally, the observed effects do not increase with prolonged stimulation time, as the effects plateau towards the end of the experiment. In conclusion, our proposed closed-loop scheme offers a promising advance for evaluating the effectiveness of tACS during the stimulation session. Specifically, the assessment criteria use participant-specific brain-based signals along with a behavioral output. Moreover, we propose a feedback efficacy score that can aid in determining the optimal stimulation duration based on a participant-specific brain state, thereby preventing the risk of overstimulation.

Keywords: Brain stimulation, Electroencephalography (EEG), Functional near-infrared spectroscopy (fNIRS), Hemodynamic response (HR), Transcranial alternating current stimulation (tACS), Working memory (WM)

Background

Non-invasive brain stimulation (NIBS) has gained popularity over the last two decades in research and clinical practices as a novel neural rehabilitation therapy for patients suffering from neurological impairment such as cognition decline, depression, stroke, Parkinson's disease, etc., via modulating the excitability of neuronal circuits using external physical stimuli (e.g., electrical, magnetic, and ultrasound) [1, 2]. Additionally, abundant basic and clinical research has shown that NIBS techniques can enhance cognitive function by adjusting brain dynamics and neuronal plasticity for regaining lost or compensating the cognitive decline/impairment [3–5]. In general, transcranial electrical stimulation (tES) and transcranial magnetic stimulation (TMS) are two common safe NIBS approaches to treat human brain disorders in a clinical setting [6, 7]. One advantage of tES over TMS is that it is generally less expensive and more widely available. Broadly, tES includes transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS). In these techniques, surface electrodes on the scalp provide low-intensity constant or alternating electrical currents (usually 1–2 mA) to modulate cerebral excitability. These stimulation approaches have been

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widely applied in clinical and cognitive sciences to investigate causal links between neural activity and behavioral performance [8–10].

Depending on the type of stimulation, tDCS is thought to change neuronal activity by causing the resting membrane potential to either depolarize or hyperpolarize [11]. Anodal stimulation, a form of tDCS, stimulates neuronal activation under a specific stimulation electrode, often improves task performance, depending on the location of the electrode [12–14]. Conversely, cathode stimulation can inhibit neuronal activity and result in degraded task performance [15–20]. On the other hand, tACS, which uses an oscillating current delivered at a specific frequency and amplitude, can interact with and modulate cerebral network communication and thereby regulate cognitive function [21, 22]. Research has demonstrated that irregularities in cortical oscillations are associated with neuropsychiatric conditions [22, 23]. Recent advancements in tACS technology have made it possible to manipulate cortical oscillations at specific bandwidths by transmitting tuned electric fields through the scalp [24–27]. Therefore, tACS approaches hold promise as potential interventions for treating brain diseases [28, 29].

Obtaining an optimal stimulation effect requires consideration of multiple parameters, such as the location, intensity, frequency, and dose of stimulation. However, there currently exists no standardized protocol for defining these parameters. Theoretically, the prefrontal cortex (PFC) is a common target for tES in clinical and cognition investigations. For example, modulation of dorsolateral PFC has been shown to improve memory, attention, and multi-demand performance, and has been used in the treatment of psychiatric diseases (e.g., severe depressive disorders and autism spectrum disorder) [30–34]. Moreover, the effects of tACS within the PFC on perception, motor control, and learning have been studied extensively [35–42], as well as effects on resting state functional connectivity [37, 43, 44]. With regard to stimulation frequency, several studies have demonstrated electrophysiological and behavioral effects from tACS modulation within the theta-band (4–8 Hz) [39]. For example, Vosskuhl et al. [35] found high theta band tACS enhanced working memory performance. Additionally, Wischnewski and Schutter [45] used tACS to improve evoked cerebral theta band oscillation. A similar study indicated that tACS-induced theta oscillations modulate cortical excitability in a phase-dependent manner in a concurrent tACS-TMS-EEG study [46]. Furthermore, this pattern of tACS modulating cortical oscillations is consistent in studies using functional magnetic resonance imaging (fMRI): Theta band tACS modulates cerebral blood-oxygen-level-dependent (BOLD) signals [47–49]. With regard to stimulation duration, most studies typically administer tACS or tDCS for approximately 16–20 min [10]. Late-phase long-term potentiation (l-LTP) [50] is one possible explainable theory for this phenomenon, as l-LTP involves enhanced synaptic connections and structural alterations in neurons associated with forming and consolidation of memory [51]. Similarly, the effects of repetitive tACS have been explored in [30], which showed that tACS with a 1-min intersession interval (i.e., duration of two adjacent tACS) improved multitasking performance.

To more directly investigate neuromodulatory effects of tACS given the observed variations in stimulation parameters across studies (e.g., stimulation frequency and duration), it is crucial to integrate functional imaging techniques along with behavioral assessments [52, 53]. Broadly, two types of brain measurements have been used to determine the impact of NIBS: i) EEG, which measures neuronal population activity, and ii) functional near-infrared spectroscopy (fNIRS) and fMRI that measure the hemodynamic response, an indirect measurement of neuronal population activity. Each modality presents its own set of advantages and disadvantages. First, EEG measures electrical potential differences on the scalp generated by the firing of thousands of pyramidal cells in the cortex [54]. Measurements of EEG can provide high temporal resolution, allowing studies of changes in brain activity in real time. EEG is beneficial when combined with tES or TMS, as it allows researchers to investigate how these non-invasive brain stimulation techniques affect brain activity. However, due to electrical interference of the stimulation, the accuracy of EEG data is compromised during stimulation, in which tES modulates the electric field within the cortex and leads to changes in neuronal activity [55, 56]. Thus, it is crucial to provide a decomposition algorithm to separate the stimulation interference from EEG measurements. Similarly, for fMRI-NIBS studies, electromagnetic noise produced by the tES or TMS device can interfere with the fMRI signal that then leads to inaccuracies in the measurement of hemodynamic activity.

Compared to fMRI, fNIRS is a portable, non-invasive, and clinically deployable tool that can be readily combined with EEG [57, 58]. The fNIRS modality uses near-infrared light within a spectral window (typically between 600 nm and 1000 nm) to penetrate the scalp and measure dynamic relative changes oxygenated (HbO) and deoxygenated hemoglobin (HbR) in the outer two centimeters of the head [59]. Researchers can obtain high temporal and spatial resolution data by combining EEG and fNIRS modalities, allowing for a more comprehensive understanding of brain function. This dual-modality approach can thus help identify specific brain regions involved in

cognitive processes and even inform how brain regions interact. Moreover, the combination of EEG and fNIRS may also provide more reliable results, as each modality can provide complementary information that can be used to cross-validate the results obtained from the other modality [60].

Herein, this study aims to: (i) determine whether the combination of EEG and fNIRS can be used to accurately assess the effectiveness of tACS, and (ii) determine the participant-specific optimal stimulation protocol (e.g., stimulation duration). This study addresses gaps in the field, such as (i) currently unknown direct effects of tACS on cortical oscillations as extant studies evaluated efficacy of tACS offline after stimulation, (ii) currently unknown direct effects on hemodynamics during tACS, and (iii) a lack of quantitative assessment criteria to determine optimal stimulation parameters to prevent overstimulation. In this study, we investigate the effectiveness of the tACS during and after stimulation periods with pseudo-real-time multimodal measurements, including EEG power in multiple frequency bands, fNIRS-measured hemodynamic signals, and behavioral scores. We hypothesize that (1) the combination of behavioral scores, EEG band powers, and hemodynamic responses can be used to assess the effectiveness of tACS; and (2) the proposed brain-behavior based effectiveness criteria can be used to determine the customized stimulation protocol (e.g., stimulation duration).

Methods

Participants

In this study, we recruited fifteen healthy volunteers from Pusan National University (eleven males, four females, average age: 25.2 years ± 5.4). The Human Research Ethics Committee of Pusan National University approved the research paradigm in compliance with the latest Declaration of Helsinki [61]. The study consisted of two visits to conduct a tACS session and a separate sham experiments on two separate visits on different days (at least two months apart). All participants were right-handed, with normal or corrected-to-normal vision. This study excluded participants with self-reported metal implants or implanted electronic devices in the body, and participants with neurological illness, psychiatric impairments, pregnancy, brain injury, and/or psychoactive medication usage. The experimental procedure and associated risks were explained to all participants before starting the experiment. Participants provided written informed consent before the study. Each participant was compensated, according to university guidelines, after participants completed the experiment.

Transcranial alternating current stimulation

A non-invasive wireless battery-driven brain stimulation device (Starstim tES, Neuroelectrics®, Spain) was used to administer both tACS and sham stimulation, as illustrated in Fig. 1. This study used five Ag/AgCl electrodes (1 cm in diameter) for stimulation (4 electrodes) and return (1 electrode) electrodes in high-definition transcranial alternating current stimulation (HD-tACS) configuration. A previous investigation has shown that the high-definition stimulation paradigm can maintain neuroplasticity (e.g., motor learning enhancement) longer than conventional stimulation [62]. In the present study, one mA (zero-to-peak) alternating current at theta band (i.e., 5 Hz) was delivered from the FpZ location and returned via the nearby electrodes (FP1, FP2, AF3, and AF4). The Neuroelectrics Instrument Controller 2.0 software (Neuroelectrics®, Spain) controlled the tACS system via Bluetooth, allowing for visualization of the

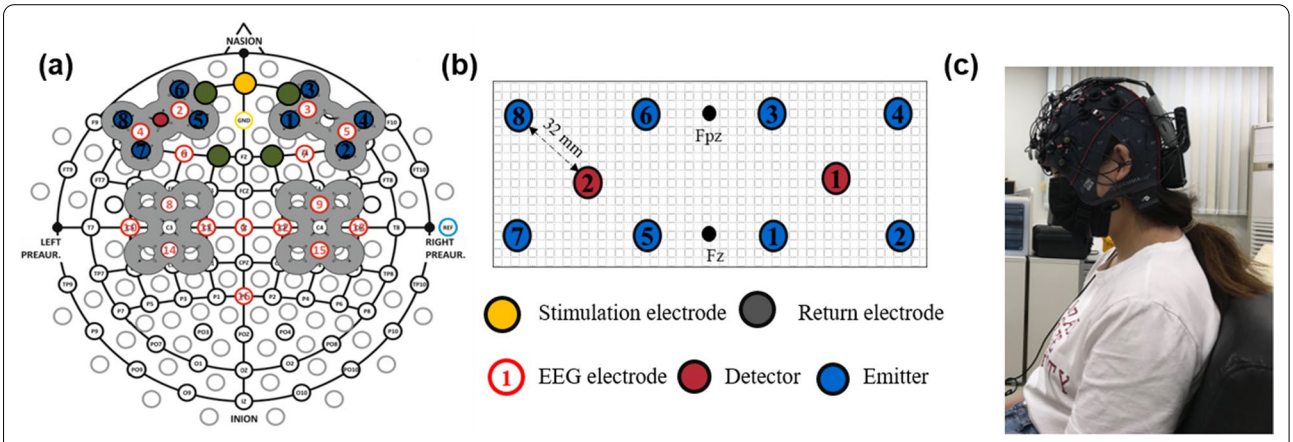

Fig. 1 **a** Channel configuration of EEG, fNIRS, and tACS: The numbers refer to the channel numbers for each modality, **b** fNIRS emitters (LEDs) and detectors (photodiodes), and **c** a subject wearing the g.Nautilus cap

electrode placement and the current distribution stimulation protocol before the experiment. The impendence remained below 10 kΩ for each trial. Eight repetitions of stimulations (2 min × 8 = 16 min) were administered to all the participants for each visit, either 16 min of tACS or Sham. Each tACS stimulation started with a ramp-up period of 5 s and ended with a ramp-down period of 5 s.

Experimental paradigm

Each stimulation-based experiment was comprised of four sections: (i) three minutes of resting, followed by (ii) three minutes of pre-stimulation, followed by (iii) 24 min of stimulation, and finally (iv) three minutes of post-stimulation, as shown in Fig. 2. Before the experiment, participants were asked to relax for three minutes in a comfortable chair. Next, the participants completed three dual 2-back tasks before the stimulation section, each with a 35-s task and a 25-s rest period (total 1 min). The during-stimulation section included eight repetitions of tACS/sham (i.e., 2 min for each sub-tACS/sham, 2 min × 8 = 16 min) and a dual 2-back task within the 1-min intersession interval. In the post-stimulation section, the participants completed three trials of a dual 2-back task, similar to the pre-stimulation task.

Dual 2-back tasks are widely used for assessing memory in healthy adults [64, 65]. In this experiment, a working memory task was designed to evaluate participants' memory capability. During the dual 2-back task, the participant must remember two independent sequences (i.e., position and color) presented simultaneously. Herein, 14 stimuli were presented, each for 2.5 s. Participants were instructed to decide whether the position and or color of the current stimulus matched the stimulus presented two items earlier. The participants were instructed to click on the left mouse button when the positions matched, and click on the right mouse button when the color matched. If both position and color matched, the participants were directed to click both sides. If neither matched, participants were advised to not click.

Signal acquisition and processing

This study acquired the EEG and fNIRS signals at a sampling rate of 250 Hz using a hybrid g.Nautilus fNIRS-8 (i.e., g.tec, Schiedlberg, Austria). A g.HIsys professional system was used to simultaneously record EEG-fNIRS data from the MATLAB platform. Before each experiment, the EEG and fNIRS channel states were calibrated to ensure suitable optical coupling between the electrodes/optodes and the scalp. A total of eight emitters (760 nm and 850 nm) and two detectors, forming eight source-detector pairs, were arranged with 32 mm separations. To ensure reproducibility, 16 EEG channels were assigned to the headset, according to the International 10–20 System. An electroconductive gel (i.e., g.GAMMAgel, Schiedlberg, Austria) was used to guarantee low impedance (i.e., < 10 kΩ) and good electrical contact between the EEG sensors and scalp.

The recorded fNIRS and EEG signals were analyzed offline using customized analyses written in MATLAB™ (MathWorks, Massachusetts, version: R2020a). For the fNIRS data, the modified Beer-Lambert law [63] was used to convert optical density data to the concentration changes of HbO and HbR. Butterworth 3rd-order filters with a low-pass frequency (i.e., 0.18 Hz) and a high-pass frequency (i.e., 0.0018 Hz) were applied to remove cardiac (i.e., approximately 1.1 Hz), respiration (i.e., around 0.25 Hz), and other extra-cortical physiological signals of non-interest from the acquired fNIRS signals. Additionally, channels of interest were selected using the MATLAB function (*robustfit*), with a hemodynamic response function (HRF) with a critical value of 0.05. Further analysis of the temporal features of the HbO and HbR to quantified hemodynamic response effects of the tACS included: Mean 1 (i.e.,, averaged HbO from 1 to 10 s), Mean 2 (i.e.,, averaged HbO from 1 to 15 s), Mean 3 (i.e.,, averaged from

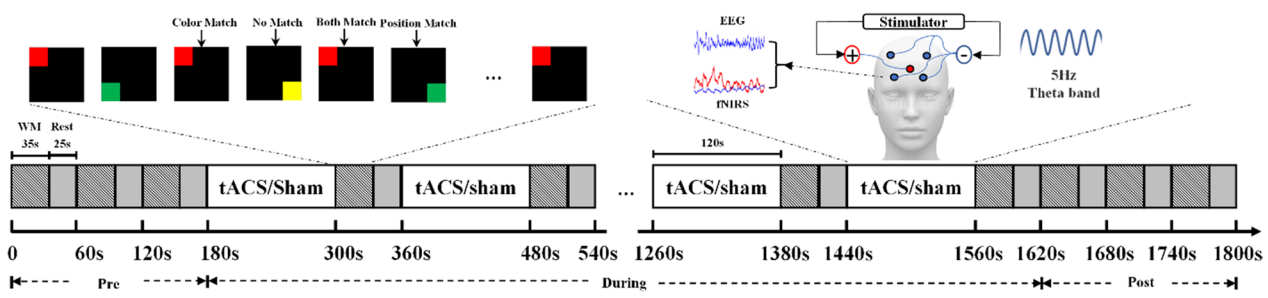

Fig. 2 One experiment includes a pre-, during-, and post-stimulation session: The pre- and post-stimulation sessions consist of three trials of dual 2-back tasks (i.e., 35 s) and resting state (i.e., 25 s); each stimulation trial includes a 2 min stimulation (tACS or sham), one dual 2-back task, and then a resting period; and eight trials of during-stimulation were conducted for each experiment

HbO 1–20 s), Slope 1 (i.e.,, slope from 1 to 8 s), Slope 2 (i.e.,, slope from 1 to 10 s), and Slope 3 (i.e.,, slope from 10 to 20 s), using the MATLAB functions (i.e., *mean* and *polyfit*). For the EEG signals, a band-pass Butterworth filter was used to focus the frequency range to 1–50 Hz. Independent component analysis (ICA) was used to identify and eliminate noise due to eye blinks [64]. In addition, a wavelet signal de-noising algorithm was used to remove the artificial noise in the EEG signals with a Bayesian approach and a Cauchy prior. The power spectral density of the EEG measurement was calculated using the Morlet wavelet algorithm with a 0.5 Hz frequency step. To compare the effect in various frequency bands, six different EEG waveforms were extracted including 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), frequency ranges, respectively [65].

tACS assessment criterion protocol

The assessment protocol proposed uses a closed-loop strategy and a pseudo-real-time analysis, as shown in Fig. 3. The brain state is assessed during tACS/sham stimulation via quantified brain measurements of neuronal activation (i.e., EEG signals, $x(t)$), hemodynamic activity (i.e., fNIRS signals, $y(t)$), and cognitive function (i.e., WM score, $z(t)$). Threshold values, x_r, y_r, and z_r are calculated individually based on the brain state of the pre-stimulation period as shown in Eqs. (1)-(3).

$$x_r^i = \frac{\sum_1^{trp} PSD^i}{num(trp)}, \tag{1}$$

$$y_r^j = \frac{\sum_1^{trp} HR^j}{num(trp)}, \tag{2}$$

$$z_r = \frac{\sum_1^{trp} WM}{num(trp)}, \tag{3}$$

where i represents a specific EEG band power including delta, theta, and alpha rhythms, respectively, and trp refers to the trial number of the pre-stimulation. The ΔHbO/ΔHbR features (i.e., hemodynamic response, *HR*), EEG power spectral density (*PSD*), and working memory (*WM*) scores were calculated based on the measurements after each tACS. The conditioning feature was selected based on our initial investigation [53], which can identify the effect of the stimulation on the brain state. In this study, two criteria were selected to compare the assessment efficacy (i.e., sets of seven or seventeen parameters), as shown in Tables 1 and 2, respectively. The effective score (*ES*) was calculated based on the individual decision matrix (*IDM*) calculated based on Eqs. (4) and (5). Herein, tr refers to the trial number of stimulation, N presents the number of the selected parameters, and d is the individual decision for each parameter and trail. The total effectiveness score is 100% if all the conditions are accepted. Conversely, the effectiveness score equals 0% if all the conditions are rejected.

$$ES(tr) = \frac{\sum_{n=1}^{N} IDM(n,tr)}{N} \times 100\%, \tag{4}$$

$$IDM = \begin{bmatrix} d(1,tr_1) & \cdots & d(1,tr_m) \\ \vdots & \ddots & \vdots \\ d(n,tr_1) & \cdots & d(n,tr_m) \end{bmatrix}. \tag{5}$$

Results

Working memory performance during and post-tACS

Participants performed 14 trials of the dual 2-back task to assess their WM capability over three different sections: pre-tACS (Trials 1 to 3), during tACS (Trials 4 to 11), and post-tACS (Trials 12 to 14). In the tACS group (Fig. 4a), the WM score did not improve during

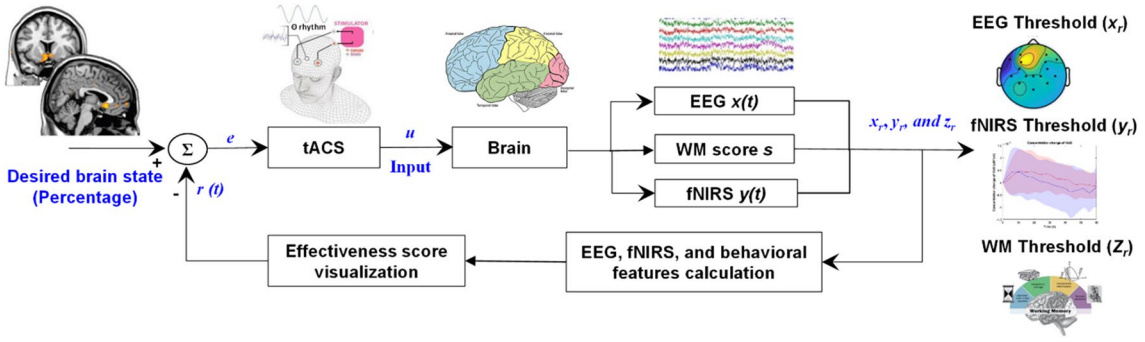

Fig. 3 Concept for tACS-effect assessment (i.e., EEG, fNIRS, and working memory scores are used to quantify the effectiveness): The brain state is monitored for comparing it with the desired brain state

Table 1 tACS assessment criterion with 17 parameters

Conditions	Individual decision	
	Accept	Reject
Mean ΔHbO(1–10 s) ≥ Mean ΔHbO threshold (1–10 s)	1	0
Mean ΔHbO(1–15 s) ≥ Mean ΔHbO threshold (1–15 s)	1	0
Mean ΔHbO(1–20 s) ≥ Mean ΔHbO threshold (1–20 s)	1	0
Mean ΔHbR(1–10 s) ≤ Mean ΔHbR threshold (1–10 s)	1	0
Mean ΔHbR(1–15 s) ≤ Mean ΔHbR threshold (1–15 s)	1	0
Mean ΔHbR(1–20 s) ≤ Mean ΔHbR threshold (1–20 s)	1	0
Slope ΔHbO(1–8 s) ≥ Slope ΔHbO threshold (1–8 s)	1	0
Slope ΔHbO(1–10 s) ≥ Slope ΔHbO threshold (1–10 s)	1	0
Slope ΔHbR(1–8 s) ≤ Slope ΔHbR threshold (1–8 s)	1	0
Slope ΔHbR(1–10 s) ≤ Slope ΔHbR threshold (1–10 s)	1	0
Frontal δ band power ≥ Frontal δ band power threshold	1	0
Frontal θ band power ≥ Frontal θ band power threshold	1	0
Frontal α band power ≥ Frontal α band power threshold	1	0
Parietal δ band power ≥ Parietal δ band power threshold	1	0
Parietal θ band power ≥ Parietal θ band power threshold	1	0
Parietal α band power ≥ Parietal α band power threshold	1	0
Working memory score > Working memory score threshold	1	0

Table 2 tACS assessment criterion with 7 parameters

Conditions	Individual decision	
	Accept	Reject
Mean ΔHbO(1–10 s) ≥ Mean ΔHbO threshold (1–10 s)	1	0
Mean ΔHbR(1–10 s) ≤ Mean ΔHbR threshold (1–10 s)	1	0
Slope ΔHbO(1–8 s) ≥ Slope ΔHbO threshold (1–8 s)	1	0
Slope ΔHbR(1–8 s) ≤ Slope ΔHbR threshold (1–8 s)	1	0
Frontal θ band power ≥ Frontal θ band power threshold	1	0
Parietal θ band power ≥ Parietal θ band power threshold	1	0
Working memory score ≥ Working memory score threshold	1	0

stimulation in the first two trials but increased from trial 5 to trial 8 (reaching the peak score). It was interesting to note that the higher level of WM score was not sustained after the 8th trial and instead showed a slight decline to a lower, constant level. This trend of improvement was not observed in the sham group, where the WM score fluctuated within a range of 45—60. Given the behavioral scores of the two groups, as shown in Fig. 4, it is evident that tACS enhances memory capability, in line with our earlier research findings.

Hemodynamic response during and post-tACS

Prior studies on tACS have primarily concentrated on the outcomes before and after the stimulation sessions, with inadequate consideration given to the influence of altering brain states during the stimulation period. Moreover, there are no standardized criteria for determining the optimal stimulation duration to achieve sufficient stimulation based on either brain activity or behavioral performance. The finding of this study demonstrated that the hemodynamic response occurs faster in the tACS group than in the sham group (Fig. 5). Notably, this phenomenon appeared after six repetitions of tACS (i.e., Trial 9, around 12 min of tACS, $p < 0.01$, Cohen's $D > 0.6$) and until the completion of the experiment. Herein, the right-tailed *t*-test and Cohen's D to quantify the significant difference and effect size between the time traces of hemodynamic response on tACS and Sham condition. Further, metrics of HbO activity reach their peak values around Trial 6 (approximately 12 min of tACS) and continues until Trial 14, including features Mean 1, Mean 2, Mean 3, Slope 1, and Slope 2 (Fig. 6), consistent with the results shown in Fig. 5. These outcomes indicated that tACS enhances the hemodynamic response. In addition, the tACS impact on the response does not increase throughout the entire stimulation time extends; rather, the effect on the hemodynamic response maintains a stable level after a participant-specific stimulation duration.

EEG power spectral density change during and post-tACS

We evaluated EEG power spectral density in the frontal and parietal cortex as a candidate to assess tACS effectiveness. Both frontal and parietal brain regions started to surpass the threshold value after Trial 7 (approximately 14 min of tACS) in the delta band. The trend in these regions was maintained until the last WM task (Fig. 7). The power amplitude of the theta band also showed a similar trend. Conversely, the alpha, beta, and gamma bands did not exhibit a consistent pattern. One possible explanation is that theta band stimulation only affects the delta and theta bands. In contrast, previous studies have indicated that alternating current stimulation could induce changes in power in neighboring bands [53].

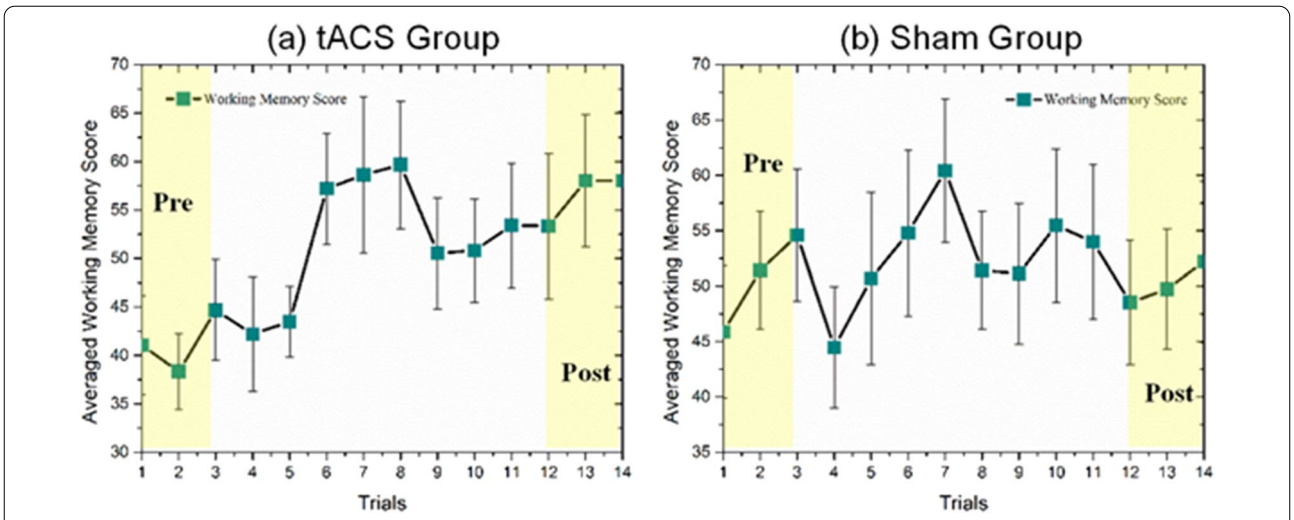

Fig. 4 Trial-wise working memory scores of all participants: **a** Averaged working memory score for tACS group, and **b** averaged working memory score for sham groups. The error bar indicates the standard variation among the WM scores of all subjects. The yellow shadow refers to the pre- and post-stimulation period

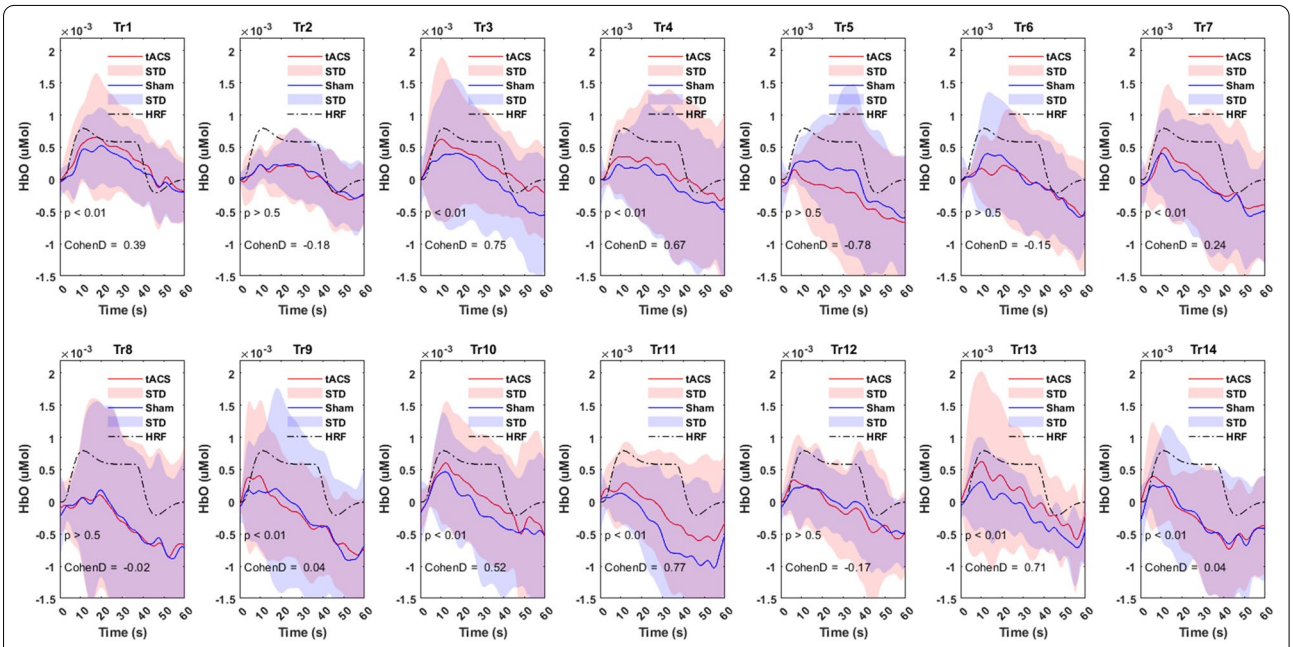

Fig. 5 Hemodynamic responses of working memory tasks for tACS and sham stimulation: The solid red line refers to the HbO fluctuation after tACS, the solid blue line presents the hemodynamic response after sham stimulation, the black dashdot line indicates the hemodynamic response function (HRF), and the standard deviations of hemodynamic responses among all participants are plotted by the shaded area

Assessment criteria of tACS effectiveness during and post-tACS

The assessment strategy utilizing EEG, fNIRS, and behavioral performance (WM score) to calculate the effectiveness score is presented in Fig. 8. The stimulation time was constrained within 15 trials (i.e., 30 min of alternating current simulation). If the effectiveness score was equal to 100%, supporting sufficient brain stimulation, then the stimulation may be discontinued. If the effectiveness score is beyond 80%, then 80% of the individual

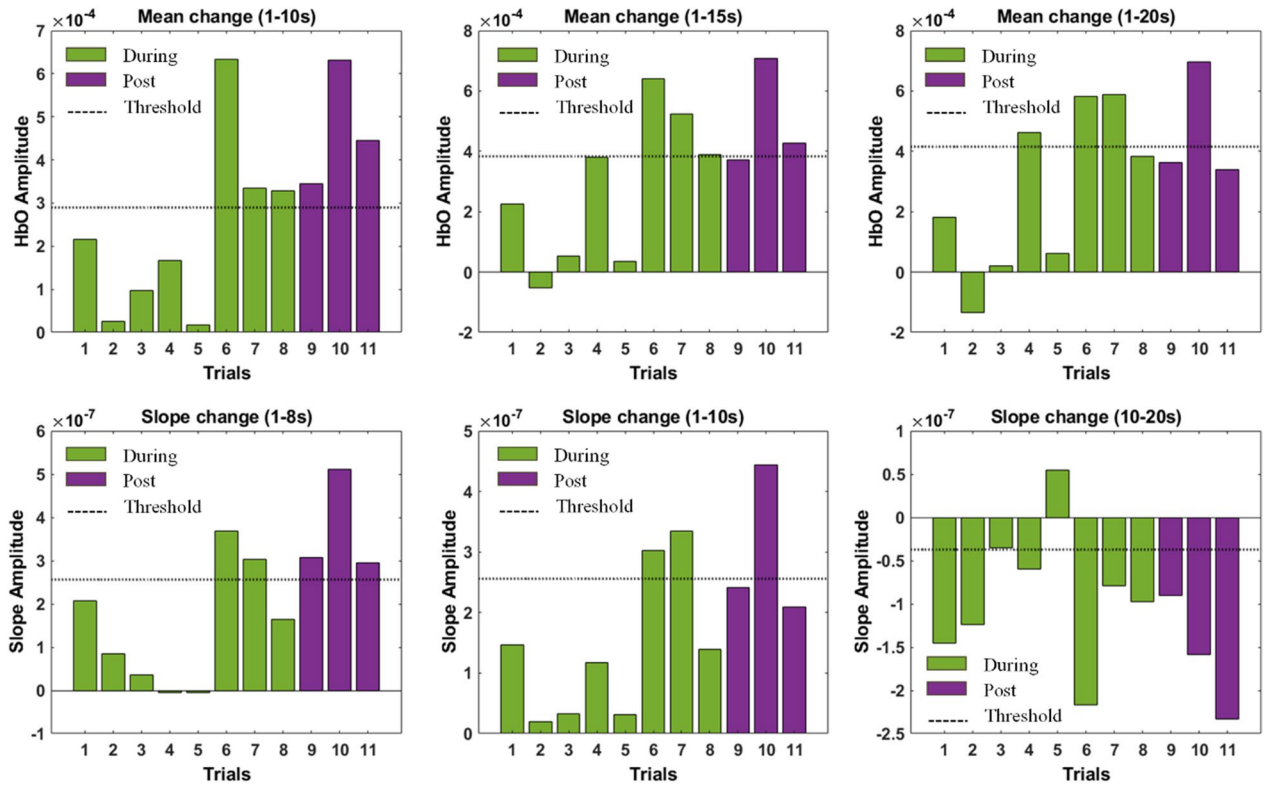

Fig. 6 Variation of temporal features over trials: The green and purple columns represent the measurement of during-tACS and post-tACS, and the black dotted line (i.e., threshold) refers to the average value of the corresponding feature in the pre-stimulation session

conditions are accepted. If two trials showed effectiveness scores beyond 80%, this also reflected maximum enhancement due to the stimulation. Table 3 illustrates the stimulation stop times for each participant using this assessment criteria. The results show that 73.3% (i.e., 11/15) of participants in the tACS group and 26.7% (i.e., 4/15) in the sham group determined the stop trials when considering the criteria with seven parameters. By contrast, with the 17 parameter assessment strategy, 66.7% (i.e., 10/15) of the tACS and 13.3% (i.e., 2/15) of the sham participants met the criteria for the stop trials. Notably, these brain-based assessments are consistent with behavioral performance: in the tACS experiment, Subjects #5, #6, #8, and #9 show a poor WM score, i.e., the average WM scores of Subjects #6 (28.29), #8 (28.21), and #9 (39.57) are much lower than the overall average WM score (i.e., 50.66). Further, in the sham group, Subjects #4 and #12 exhibit better performance than the overall subjects (average score = 51.76); i.e., the WM score in Subject # 12 is 84.21. For this subject with a poor behavioral score, the maximum stimulation effect was not reached, leading to a non-determined stop trial number in the tACS group. Thus, for this participant, additional stimulation may have been required.

Discussion

This study used a pseudo-real-time repetitive brain stimulation protocol to assess brain stimulation effectiveness during and post-tACS as measured via metrics of neurophysiology, including EEG and fNIRS, as well as behavioral performance. Additionally, we investigated the optimal stimulation duration and possible assessment features for tACS effectiveness. This work is the first study to assess the effectiveness during and post repetitive short-duration tACS based on multiple measurements. Overall, the proposed assessment criteria based on non-invasive neuroimaging modalities demonstrated the feasibility of closed-loop stimulation. Moreover, the present stimulation protocol with a calculated optimal stimulation time may provide novel insights into the future stimulation control paradigm.

The first hypothesis of this study is that the stimulation time can be determined using the proposed criteria, more specifically the combination of behavioral scores, EEG band powers, and hemodynamic responses can be used to assess the effectiveness of tACS. The study demonstrated the feasibility of combining customized repetitive short-duration tACS with multiple neuroimaging modalities to monitor brain states online. Accurate and

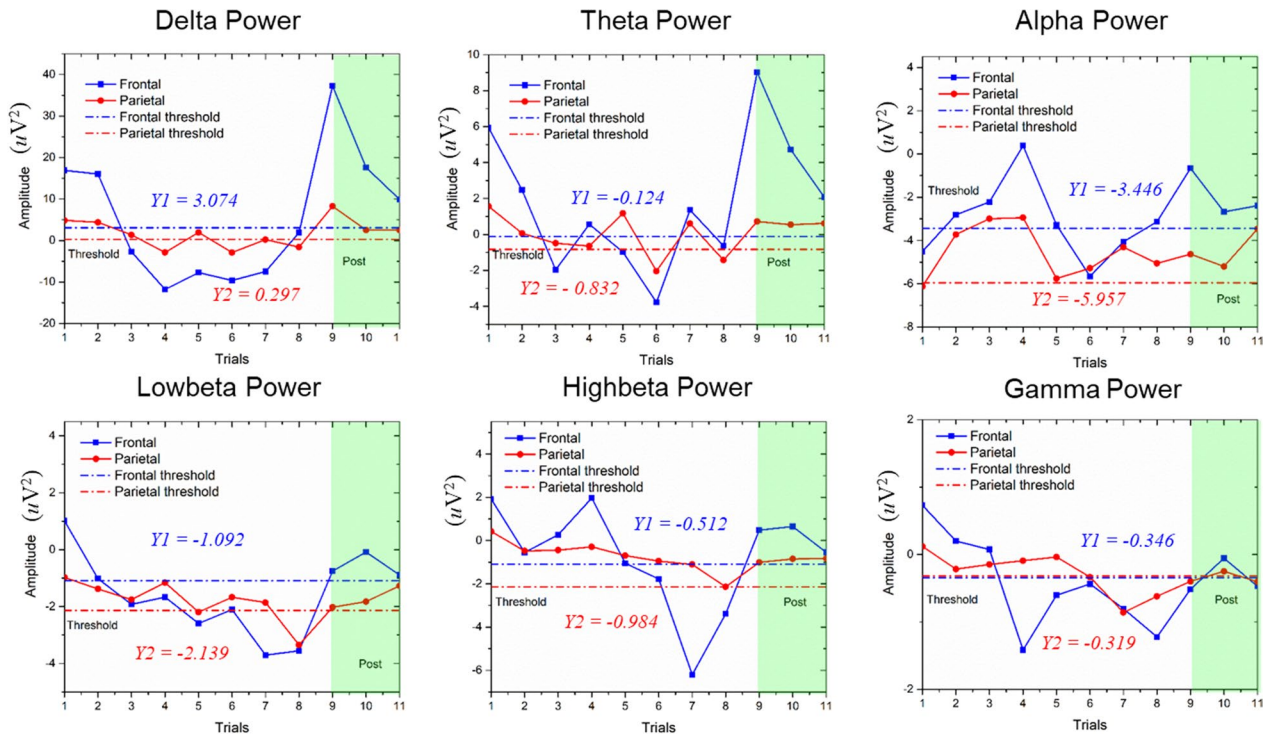

Fig. 7 EEG band-power change among the dual 2-back task at the frontal and parietal cortex: Six EEG bands are analyzed; delta, theta, alpha, low-beta, high-beta, and gamma. The solid red and blue lines represent the power change on the frontal and parietal brain regions, respectively. The blue and red dot lines represent the threshold calculated by the averaged power (i.e., Y1 and Y2) from the pre-stimulation session. The green shaded area refers to the post-stimulation session

reliable measures of the brain state are crucial for closed-loop stimulation systems. The assessment variables and selection criteria play a vital role in this regard [66–68]. Functional brain imaging can establish the correlation between brain state and concurrent behavioral performance [69]. This study employed simultaneous EEG and fNIRS neuroimaging to explore candidate indicators to study neuroplasticity effects of repetitive short-duration tACS. A general tendency of tDCS/tACS to increase the fNIRS-measured hemodynamic response (i.e., HbO) was previously observed in the resting state post-stimulation [70]. In contrast, other tACS/tDCS studies reported reduced cortical activation in the post-stimulation section [71], which is consistent with the results shown in Fig. 5, wherein the concentration changes of HbO decline after the first few trials of tACS stimulation (Trials 4–8). Nevertheless, the hemodynamic response was augmented after Trial 9 until Trial 14. A possible explanation for the reduction in hemodynamic activity is due to insufficient stimulation duration (i.e., less than 10 min), since the improvement occur after 12 min repetitive brain stimulation. Similarly, the selected temporal features of the fNIRS signals (see Fig. 6) display the same phenomenon, in which the mean/slope value starts beyond the threshold after 12 min of tACS. Meanwhile, the EEG power in the theta band in frontal cortex (i.e., Fig. 7) exhibited a high correlation for this trend that appeared in the fNIRS signals. This may reflect neurovascular coupling mechanisms among electrophysiological and hemodynamic measurements [72]. Additionally, as shown in Fig. 7, the brain oscillation enhancement occurs after 12 min of tACS stimulation within the theta band power in parietal and alpha power in both frontal and parietal regions. One possible explanation is that the theta band modulates the cortico-hippocampal pathway that subserves the WM-associated alpha band to coordinate the assigned cognitive function. Extant studies support the hypothesis that alpha and theta oscillations reflect the cognitive and memory processes of the human brain [73]. Furthermore, the endogenic theta rhythm implicates a communication between the cortical system and the hippocampus, which plays a key role in short-term memory function [74].

The use of neuromodulation with electric stimulation shows promise in helping people recover a variety of behaviors that have been lost or compromised. However, optimizing the length of stimulation is challenging and dependent on a number of subject-specific

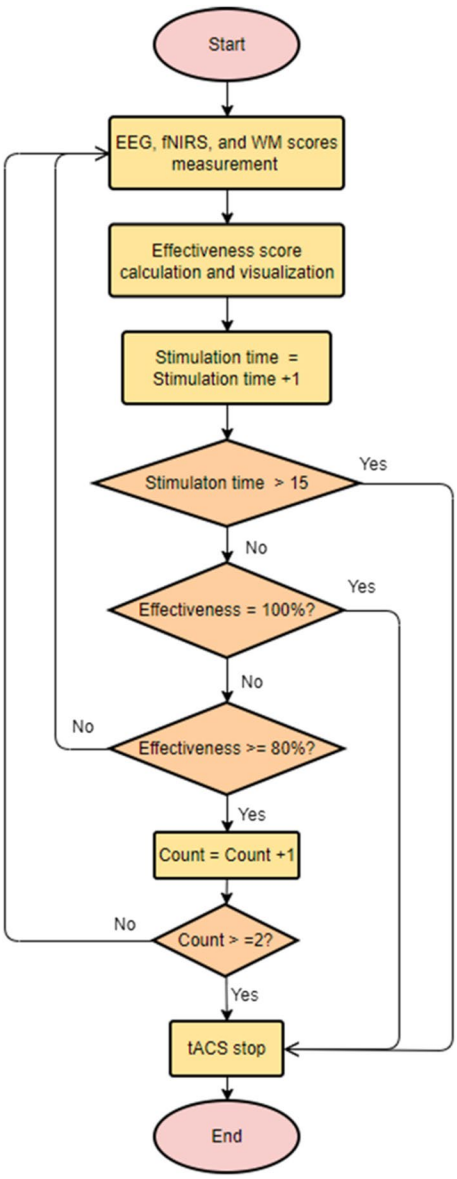

Fig. 8 tACS assessment strategy for the proposed closed-loop efficacy assessment using the quantified brain state features (i.e., EEG and fNIRS features) and behavioral performance (i.e., working memory score)

characteristics [75]. However, brain-based assessments provide reason for optimism. For example, the duration of tDCS for a specific brain area was determined using functional connectivity and graph theoretical parameters [76]. In this study, working memory enhancement was evaluated with simultaneous EEG and fNIRS modalities along with the behavioral scores. Indeed, an analysis with thresholds on multiple parameters may provide better criteria for limiting the stimulation time. Instead of continuous stimulation, repetitive short interval stimulations [30] may be more useful to enhance working memory capacity, especially when paired with imaging and behavioral criteria.

Some limitations in the current study must be addressed in future research. While we only used the theta frequency for tACS, future research should explore other frequency bands and hybrid combinations. We confined our fNIRS based analysis to the pre-frontal cortex due to the limited number of fNIRS channels. Simultaneous measurements across the head, facilitated by the addition of more fNIRS channels, may be undertaken in the future to provide more comprehensive functional assessments [77, 78]. Another limitation is the absence of computational modeling of the electric field distribution for tACS [79–82]. Additionally, we only used 1 mA of brain stimulation and did not investigate the effects of different current intensities. Further, fNIRS has a lower spatial resolution than fMRI, and so limits the spatial specificity of interpretations of the results. In the future, better data-anatomy specificity may be realized via dense optode arrangements for measurements [83–85]. Although the sample size of this study is small, it is equivalent to that of other neuroimaging studies [53, 86]. Additionally, including performance measures such as accuracy, sensitivity, specificity, false alarm, ROC curve rate and other relevant metrics for both EEG and fNIRS data will provide a more comprehensive evaluation of the proposed method and will further support the validity of these findings.

Conclusions

This study discussed assessment criteria to evaluate the efficacy of 5 Hz repetitive short-duration tACS to improve cognitive function and neuroplasticity. We developed an effectiveness evaluation strategy utilizing EEG and fNIRS signals as a brain state monitoring index for a closed loop tACS stimulation protocol, which included measures of the mean and slope of HbO activity and theta band EEG power in the frontal and parietal cortex. The combined behavioral and neurological features were also used to calculate an effectiveness score to determine optimal stimulation duration. Our findings indicated that the combination of behavioral scores, EEG band powers, and hemodynamic response signals was shown to reliably assess the effectiveness of tACS. We could find the customized stimulation duration by applying the proposed assessment criteria for each participant. Overall, this study provides a strategy to gauge the effectiveness of during- and post-stimulation, and addresses a gap in the field by illuminating the impact in different stages (pre, during, and post) of brain stimulation using repetitive tACS and validates the effectiveness using a metric of features of functional

Table 3 Determination of stimulation stop time for each participant using different assessment criteria (7 parameters vs. 17 parameters)

Subject	7 parameters		17 parameters	
	tACS (stop trial)	Sham (stop trial)	tACS (stop trial)	Sham (stop trial)
Sub 1	5 times stimulation	None stop tACS	7 times stimulation	None stop tACS
Sub 2	8 times stimulation	None stop tACS	8 times stimulation	None stop tACS
Sub 3	8 times stimulation	None stop tACS	8 times stimulation	None stop tACS
Sub 4	8 times stimulation	None stop tACS	8 times stimulation	8 times stimulation
Sub 5	None stop tACS	None stop tACS	None stop tACS	None stop tACS
Sub 6	None stop tACS	None stop tACS	None stop tACS	None stop tACS
Sub 7	2 times stimulation	None stop tACS	8 times stimulation	None stop tACS
Sub 8	None stop tACS	5 times stimulation	None stop tACS	None stop tACS
Sub 9	7 times stimulation	None stop tACS	None stop tACS	None stop tACS
Sub 10	8 times stimulation	4 times stimulation	7 times stimulation	None stop tACS
Sub 11	8 times stimulation	None stop tACS	None stop tACS	None stop tACS
Sub 12	8 times stimulation	3 times stimulation	7 times stimulation	3 times stimulation
Sub 13	8 times stimulation	8 times stimulation	8 times stimulation	None stop tACS
Sub 14	2 times stimulation	None stop tACS	7 times stimulation	None stop tACS
Sub 15	None stop tACS	None stop tACS	8 times stimulation	None stop tACS

imaging and behavioral performance to ensure reproducibility. This work is the first study to propose customized assessment criteria to assess the effectiveness to avoid the risk of overstimulation.

Abbreviations

EEG: Electroencephalography; fNIRS: Functional near-infrared spectroscopy; HbO: Concentration changes of oxyhemoglobin; HbR: Concentration changes of de-oxyhemoglobin; HD-tACS: High-definition transcranial alternating current stimulation; NIBS: Non-invasive brain stimulation; PFC: Prefrontal cortex; tACS: Transcranial alternating current stimulation; tDCS: Transcranial direct current stimulation; tES: Transcranial electrical stimulation; TMS: Transcranial magnetic stimulation; tRNS: Transcranial random noise stimulation; WM: Working memory.

Author contributions

DY—Designed the study, supervised its execution, analyzed the data and drafted the manuscript; UG—participated in designing the study and drafting the manuscript; AE—provided iterative critical commenting on the drafts of the manuscript. K-SH—suggested the theoretical aspects of the current study, corrected the manuscript, and supervised the entire process leading to the manuscript generation. All authors read and approved the final manuscript.

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Data availability

The dataset and materials used for current study are available from the corresponding author on reasonable request.

Declarations

Competing interests

The authors declare that they have no competing interests.

Ethical approval

The research paradigm was approved by the Human Research Ethics Committee of Pusan National University in compliance with the latest Declaration of Helsink.

Consent to participate

All participants in this study provided their informed consent for participation.

Consent for publication

Not applicable.

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