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Parametric effects of transcranial alternating current stimulation on multitasking performance

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Background: We have previously demonstrated that transcranial alternating current stimulation (tACS) can generate positive effects on multitasking performance and associated neurophysiological measures when it is applied with anti-phase theta band stimulation across bilateral prefrontal cortex (PFC) and a short (1-min) inter-session interval (ISI). However, it is unclear how altering the phase of stimulation and the duration of the ISI might impact positive tACS effects. Here, we investigated the role of tACS parameters in engendering performance improvements by manipulating these two stimulation parameters (i.e. phase and ISI) in two experiments.

Methods: Repetitive sessions of bilateral PFC theta-tACS were applied with in-phase stimulation + 1-min ISI (experiment 1) and anti-phase stimulation + 5-min ISI (experiment 2) while participants were engaged in a multitasking challenge accompanied by electroencephalography (EEG) data collection.

Results: Compared to the control group, in-phase stimulation + 1-min ISI showed an enhancement of multitasking performance coupled with a modulation of posterior alpha (8–12 Hz) and beta (13–30 Hz) activities. However, repetitive sessions of anti-phase tACS + 5-min ISI did not generate significant enhancement in multitasking performance, nor changes in neural oscillatory activities compared to the control group.

Conclusion: The results revealed that the previous reported positive tACS effects on multitasking performance are not affected by manipulating the phase of current polarity. Yet, changing the ISI of the stimulation protocol eliminated the previous observed performance improvements. Taken together, these results stress the importance of stimulation protocol for generating positive tACS effects on cognitive function and neural oscillations.

Introduction

Cortical oscillatory activities play a critical role in brain functions, such as sensory [1], motor [2], and cognitive processing [3]. Numerous studies have demonstrated a correlational association between brain oscillation and cognitive functions [4–6]. For instance, theta oscillations (4–7 Hz) have been linked to a variety of cognitive control abilities, such as working memory [7–9], decision making [10], retrospective monitoring [11], focused attention [12], and of current interest, multitasking [13]. To assess the causal role of this oscillatory neural activity, transcranial alternating current stimulation (tACS) has been used in interventional designs. tACS is a non-invasive electrical stimulation approach that applies weak sinusoidal currents to the brain through the scalp in a frequency-specific manner. Recently, studies have demonstrated that tACS is capable of modulating and interfering with ongoing endogenous brain oscillations [14–16], in turn affecting perception [17–19], motor [20–22], and cognitive functions [23,24]. In a previous study, we investigated the effects of frontal theta-tACS on multitasking performance and associated neurophysiological measures. Results showed that with a 1-min inter-session interval (ISI; time delay between two adjacent tACS sessions), repeated sessions of anti-phase (i.e. 180° phase offset across the electrodes) theta-tACS

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across bilateral prefrontal cortex (PFC) generates positive effects on multitasking performance, which was assessed by challenging visual discrimination ability in the context of visuomotor tracking [25] (see NeuroRacer below). These performance improvements were correlated with increased frontal theta activity and accompanied by an increase in posterior beta power.

Although tACS is capable of influencing brain function [14,19,21], the effects of tACS on neural activity and performance are dependent on the stimulation parameters [26,27]. For instance, the phase of the sinusoidal current of tACS can shape the direction of the tACS-induced effects [28–30]. Nakazono et al., 2016 showed that 20 Hz tACS modulates motor cortical excitability only when the stimulation is delivered at 90° phase offset. Similarly, other studies have revealed that the phase of the applied current is a crucial factor in the modification of target detection in human auditory [31] and visual [28] processing. Moreover, working memory performance is also affected by the phase of the applied stimulation, such that in-phase theta stimulation between left prefrontal and parietal cortices improves visual working memory, whereas anti-phase stimulation deteriorates performance [30].

In addition to the phase of the stimulation, the duration of the inter-session interval (ISI) of repeated sessions of stimulation is also a critical parameter. In transcranial direct current stimulation (tDCS) studies, an approach that has been used to prolong and stabilize stimulation after-effects is to apply repetitive sessions of stimulation [32,33], with the stimulation repetition interval being shown as critical for optimizing after-effects [32–35]. For instance, Monte-Silva et al. (2010) found that the effects of cathodal tDCS on motor evoked potentials are affected by the ISI between two sessions of 9-min stimulation where the inhibitory effects of tDCS is stronger when the second session of stimulation is employed during the after-effects of the first session of stimulation [33]. However, for tACS, it is unclear how the interval between stimulation sessions alters the stimulation effects.

Here, we aimed to discern the role of tACS parameters in engendering positive stimulation effects. Specifically, we manipulated two stimulation parameters, phase and ISI, to assess if previously observed positive effects of theta-tACS on multitasking performance [25] are phase- and ISI-dependent. We repeated the same experiment as our previous study [25] with two new groups of participants in order to manipulate the phase and ISI of the stimulation. As such, two experiments were conducted, one for each parametric manipulation. In experiment 1, participants received tACS with a 0° relative phase between bilateral PFC (in-phase) and a 1-min ISI, whereas in experiment 2, participants received repetitive sessions of tACS with a 180° relative phase between bilateral PFC (anti-phase) and a 5-min ISI. During tACS (or control tACS), participants were engaged with NeuroRacer (see below) game-play that evaluated multitasking performance by measuring perceptual discrimination in the context of simultaneous visuomotor tracking [13,25,36]. The data collected from both experimental groups were compared to the placebo control group from our previous study [25].

For experiment 1, we hypothesized that manipulating the phase of tACS across bilateral PFC would enhance multitasking performance similar to our previous observation. Although previous tACS research might predict the opposite effect of stimulation by changing the phase offset by 180°, here, we are aiming to manipulate cognitive function associated with midline frontal theta activity, which arises from medial PFC [37]. As such, oscillating a current in the theta band between bilateral PFC should affect medial PFC similarly, regardless of the phase offset. As long as the medial PFC is being targeted, a phase-lag above 0° between bilateral PFC should not be a critical factor in influencing behavior. For experiment 2, according to tDCS research, it was hypothesized that the effects of tACS would decay with a longer ISI since the timing that the stimulation is being applied may be outside of the critical time window in which the prior stimulation exhibits after-effects, and therefore, would not generate beneficial effects on multitasking performance or changes in neural activity.

Materials and methods

Participants

A total of forty healthy adults (mean age: 27.4 y/o; range 18–35 years; 17 males) took part in two experiments. Written informed consent was obtained from each participant according to procedures approved by the Committee for Human Research at the University of California at San Francisco. All participants had normal or corrected-to-normal vision, and were free from neurological/psychiatric disorders or other contra-indications for tACS exposure. Twenty of them (mean age: 28.5 y/o; 9 males) participated in experiment 1, in which they received in-phase alternating current (in-phase group) with a 1-min ISI in repetitive sessions of tACS. The remaining twenty participants (mean age: 26.2 y/o; 8 males) took part in experiment 2, where the repetitive sessions of anti-phase tACS stimulation was delivered with a 5-min ISI (long-ISI group) (see transcranial alternating current stimulation (tACS) part below). The data collected from both experimental groups were compared to the placebo control group from our previous study ($N = 20$; mean age: 25.8 y/o; 9 males) [25].

For behavioral data analyses, data from one participant in experiment 2 was excluded from the analyses because the participant could not follow the instructions appropriately. Four participants' EEG data were excluded (two from experiment 1, two from experiment 2) from the analyses due to excessive noise.

Experimental design

Fig. 1 shows the experimental procedure. Each participant had a baseline thresholding evaluation to establish the parameters of the component tasks in the multitasking condition (see NeuroRacer part below). Having individuals engage in the component tasks at their own difficulty level provided a means to normalize challenge so that the assessment of multitasking skills was not confounded by group and individual differences in abilities. The 30-min thresholding evaluation was followed by the EEG/tACS cap setup procedure and sixteen 3-min multitasking sessions with a 30-min break after the 8th session (Fig. 1). At the end of each session, all participants completed a 1-min survey to scale the perception of stimulation (headache, neck pain, scalp pain, tingling, itching, burning sensation, sleepiness, trouble concentrating, and acute mood change) from 1 (mild) to 10 (severe). For experiment 1, control and stimulation sessions were determined based on our previous research. Therefore, we utilized the same order of stimulation to ascertain whether changing the phase of stimulation would yield comparable results [25]. For experiment 2, we used the same stimulation parameters as our previous research, but alternated the control and stimulation sessions to ascertain whether changing the ISI would yield comparable results. Alternating between control and stimulation sessions enabled maximal segregation between stimulation sessions, while retaining the same total amount of stimulation across the entire experiment as our previous study [25].

Transcranial alternating current stimulation (tACS)

tACS was delivered via a pair of Ag/AgCl electrodes ($3.14\ cm^2$) at 6 Hz through a Starstim-8 system (Neuroelectrics, Spain). For

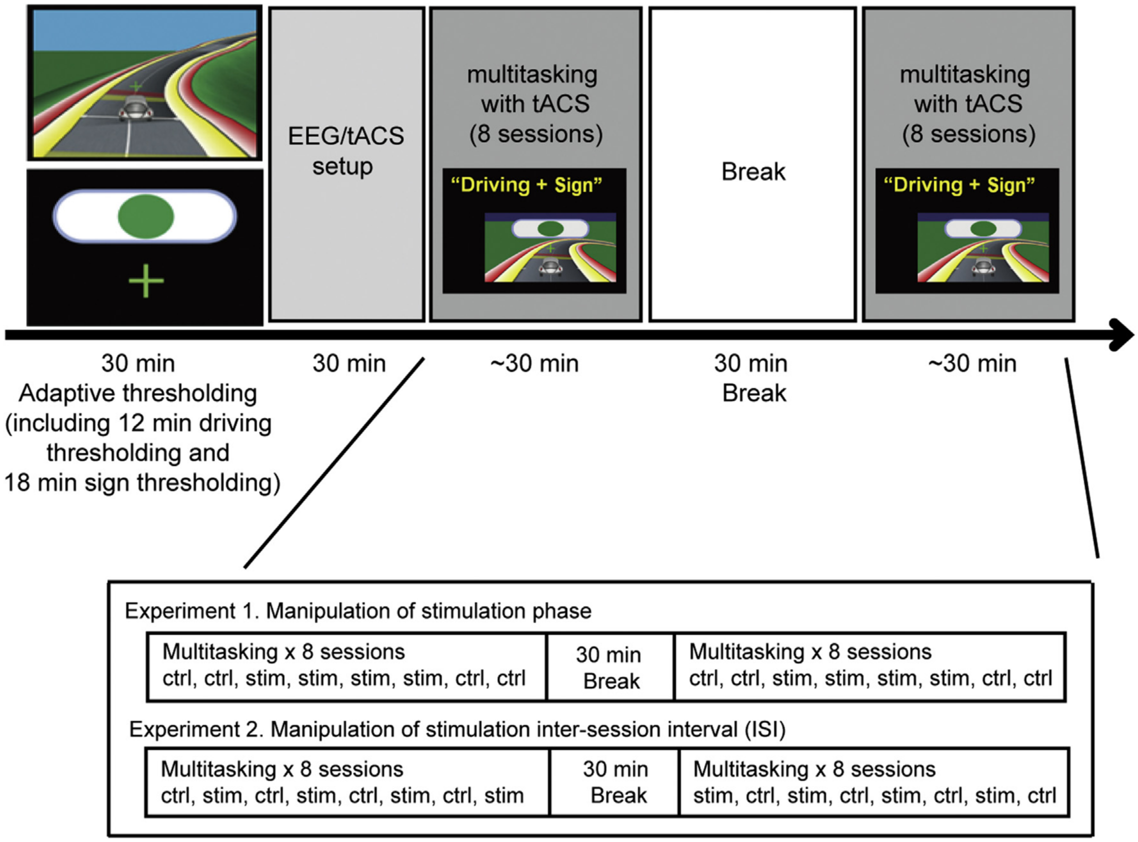

Fig. 1. NeuroRacer and experimental procedure of the two experiments. stim, tACS stimulation session; ctrl, control stimulation session.

stimulation sessions, the alternating current was delivered while participants were engaged in the NeuroRacer multitasking paradigm (see NeuroRacer part below) with 3 min of stimulation including 10-s ramp up and 10-s ramp down. For control sessions, the 10-s ramp up period was immediately followed by a 10-s ramp down period and turned off for the rest of the 3 min session.

Experiment 1: manipulation of stimulation phase

A sinusoidal alternating current of 1000μA (2000μA peak-to-peak amplitude) was applied and the impedance was kept below 10 kΩ. The stimulation electrodes were placed over bilateral PFC centered at F3 and F4 of the 10–20 electrode coordinate system with a 0° relative phase (in-phase). The return electrodes were located at AFz, Fz, FCz. Participants received stimulation during the third, fourth, fifth, sixth, eleventh, twelfth, thirteen and fourteenth sessions and control stimulation for all other sessions (Fig. 1). This experimental design led to a 1-min inter-session interval (consisting of a survey) between stimulation sessions. This stimulation protocol of experiment 1 was identical to our previous study [25], with the exception of in-phase stimulation.

Experiment 2: manipulation of stimulation inter-session interval (ISI)

A sinusoidal alternating current of 1000μA (2000μA peak-to-peak amplitude) was delivered with a 180° phase offset between stimulation electrodes that were located over bilateral PFC, centered at F3 and F4. The impedance was kept below 10 kΩ. Participants received alternating tACS and control sessions. Specifically, tACS stimulation was delivered during the second, fourth, sixth, eighth, ninth, eleventh, thirteenth, and fifteenth sessions. Control stimulation was delivered for all other sessions (Fig. 1). This experimental design led to a 5-min inter-session interval (consisting of a 3-min control stimulation session and two 1-min surveys) between tACS stimulation sessions. Again, the stimulation protocol of experiment 2 was the same as our previous study [25] except the ISI (5-min) is longer in the current experiment.

Stimulation applied to the control group

The data collected from experiment 1 and 2 were compared to a control group of our previous study [25], where the experimental design and paradigm were identical to the current study except the control group received only control stimulation, that is, 10-s ramp up period followed immediately by a 10-s ramp down period and turned off for the rest of the 3 min, for all 16 multitasking task sessions. The sinusoidal alternating current of 1000μA (2000μA peak-to-peak amplitude) was delivered at stimulation electrodes that were located over F3 and F4 (anti-phase). The impedance was kept below 10 kΩ.

NeuroRacer

NeuroRacer software was developed using the OpenGL Utility Toolkit (GLUT; http://www.opengl.org/resources/libraries/glut/) as a video game that assesses multitasking performance by challenging visual discrimination ability (sign task) in the context of visuomotor tracking (driving task) [13]. For the visual discrimination (sign task), each 3-min experimental run contained 24 targets (green circles) and 48 non-targets (green pentagons and squares; blue and red circles, pentagons, and squares). The signs were randomly presented for 400 ms every 2, 2.5, or 3 s. The participants were instructed to selectively respond to the target sign as fast as possible by pressing a button on a Logitech (Logitech, USA) gamepad controller with their right thumb and ignore the non-target signs. A white fixation cross that provided performance feedback was present on the screen at all times below the signs (and above the car during the multitasking condition): it turned green for 50 ms when the participant responded to the target sign within the proper amount time after the target showed up, or when a non-target sign was correctly ignored. When either of the aforementioned conditions was not met, it would turn red for 50 ms. The visuomotor tracking (driving task) required participants to control a car, keeping it in a specific area (center of the road, avoiding the yellow and red boundaries) by using the left thumb-stick of the game controller. The road was created by track pieces that included right and left turns, as well as uphill and downhill pieces. These pieces were presented pseudo-randomly for 2, 2.5 or 3 s, generating a path that the participant had to guide the car on. During multitasking, participants were instructed to perform driving task and sign task concurrently. Participants had to respond to the target sign as fast as possible by pressing a button on a Logitech gamepad controller (Logitech, USA) with their right thumb, while simultaneously controlling the car by using the left thumb-stick of the game controller (Fig. 1) (for more details, please see Methods section of Anguera et al., [13]).

At the beginning of the study, an adaptive thresholding procedure of both single tasks - visuomotor tracking (twelve 1-min sessions) and visual discrimination (nine 2-min sessions) ability - was conducted to determine a "driving" and "sign discrimination" difficulty level so that each participant played the game at a customized challenge level (~80% accuracy). For the visual discrimination thresholding, each participant's performance for a given session was determined by calculating a proportion correct score involving correctly avoiding non-targets, correctly responding to targets, late responses to targets, and responding to non-targets. The adaptive algorithm would make proportional level changes depending on participants' performance from ~80% accuracy, such that each 1.75% increment away from this 80% accuracy corresponded with a change in level. For instance, a 90% performance would lead to a 40-ms reduction in the time window for responses to target, while a 55% (or less) performance would lead to a 100-ms lengthening of the time window. Visuomotor tracking thresholding followed a similar pattern with each 0.58% increment away from the 80% accuracy corresponded with a change in level. These parameters were chosen following extensive pilot testing to minimize the number of trial runs until convergence was reached while maximizing sampling resolution of user performance (for more details, please see Method section and supplementary Fig. 1 of Anguera et al., [13]). The first three visuomotor tracking thresholding sessions were considered practice to familiarize participants with the driving task and were not analyzed. A regression over the nine thresholding session for each driving and sign discrimination was computed to select the ideal time window for response for sign task and road speed to promote a customized challenge level (~80% accuracy). All participants began the thresholding procedures at the same driving and sign levels.

The video game approach as a cognitive assessment tool is somewhat different from traditional tasks in cognitive neuroscience research. However, it incorporates several cognitive processes and increases participants' engagement and motivation [38] without compromising the reliability and validity of assessing multitasking abilities.

Behavioral data analysis

To delineate the role of tACS parameters in engendering stimulation effects on multitasking performance, we assessed perceptual discrimination performance during each multitasking session using a metric of discrimination performance (d') [39], which was estimated for each participant by comparing hit rate (correct responses to target signs) and false alarm rate (responses to non-targets) and calculated as d' = Z(hits) − Z(false alarms). In both experiments, data across sessions were grouped to enhance statistical power for behavioral and EEG data analyses.

Experiment 1: manipulation of stimulation phase

In experiment 1, d-prime obtained from the first two sessions were averaged to serve as baseline performance levels. D-prime evaluated in the last two sessions (i.e. sessions 15 and 16) were averaged as the measure of post-stimulation performance. The data was compared to a control group of our previous study [25], where the experimental design and paradigm were identical to experiment 1 in the current study except the control group received control stimulation over the 16 multitasking task sessions. The multitasking performances in correspondingly game sessions were compared between in-phase stimulation and control groups.

Experiment 2: manipulation of stimulation inter-session interval (ISI)

In experiment 2, d-prime assessed from sessions 1 and 3, in which participants received control stimulation, were averaged to serve as baseline multitasking performance. Averaged d-prime of sessions 14 and 16 was measured as post-stimulation performance. Again, the multitasking performances in correspondingly game sessions were compared between long-ISI stimulation group and a control group of our previous study [25]. Data from sessions 2 and 15 were not analyzed due to the tACS artifacts in the EEG signal, and so for consistency, behavioral data was assessed from the same sessions as the EEG analysis (see below).

Electroencephalography data analysis

Electrophysiological signals were recorded with a wireless, dry electrode Enobio-20 system (Neuroelectrics, Spain) with a sampling rate of 500 Hz. One of the 20 electrodes was used as an electrooculogram (EOG) channel. The remaining 19 channels were distributed over the scalp (F7, AF3, FP1, FP2, AFz, AF4, F8, P8, C4, O2, Cz, Pz, PO8, C3, C3, PO7, Fz, P7, O1). Raw EEG data were analyzed using the FieldTrip toolbox (http://fieldtrip.fcdonders.nl/ [40]). As d-prime was used as the behavioral measurement and it takes performance on every trial into account, we collapsed across all trial types (target and non-target) for subsequent EEG data analyses. Only data from the control stimulation sessions were analyzed to prevent any potential confound introduced by tACS artifacts.

Data were segmented into epochs beginning 1000 ms before to 1000 ms post sign onset and were demeaned/detrended and referenced to the average EEG signal. An independent component analysis was performed to remove components consistent with the timeseries and topographies for blinks and eye movements. Epochs that exceeded a voltage threshold of 80 μV were rejected. For experiment 1 and experiment 2, an average of 33.5% and 31.3% trials were rejected per session, respectively. For the control group data collected from our previous study [25], an average of 28.9% trials was rejected per session. As the remaining trial number per session might be underpowered for time-frequency analyses, data across sessions were grouped in the same way as behavioral data analyses for both experiments. Time frequency analyses were conducted from 500 ms before to 600 ms after the onset of the sign presentation. A fast fourier transformation was performed

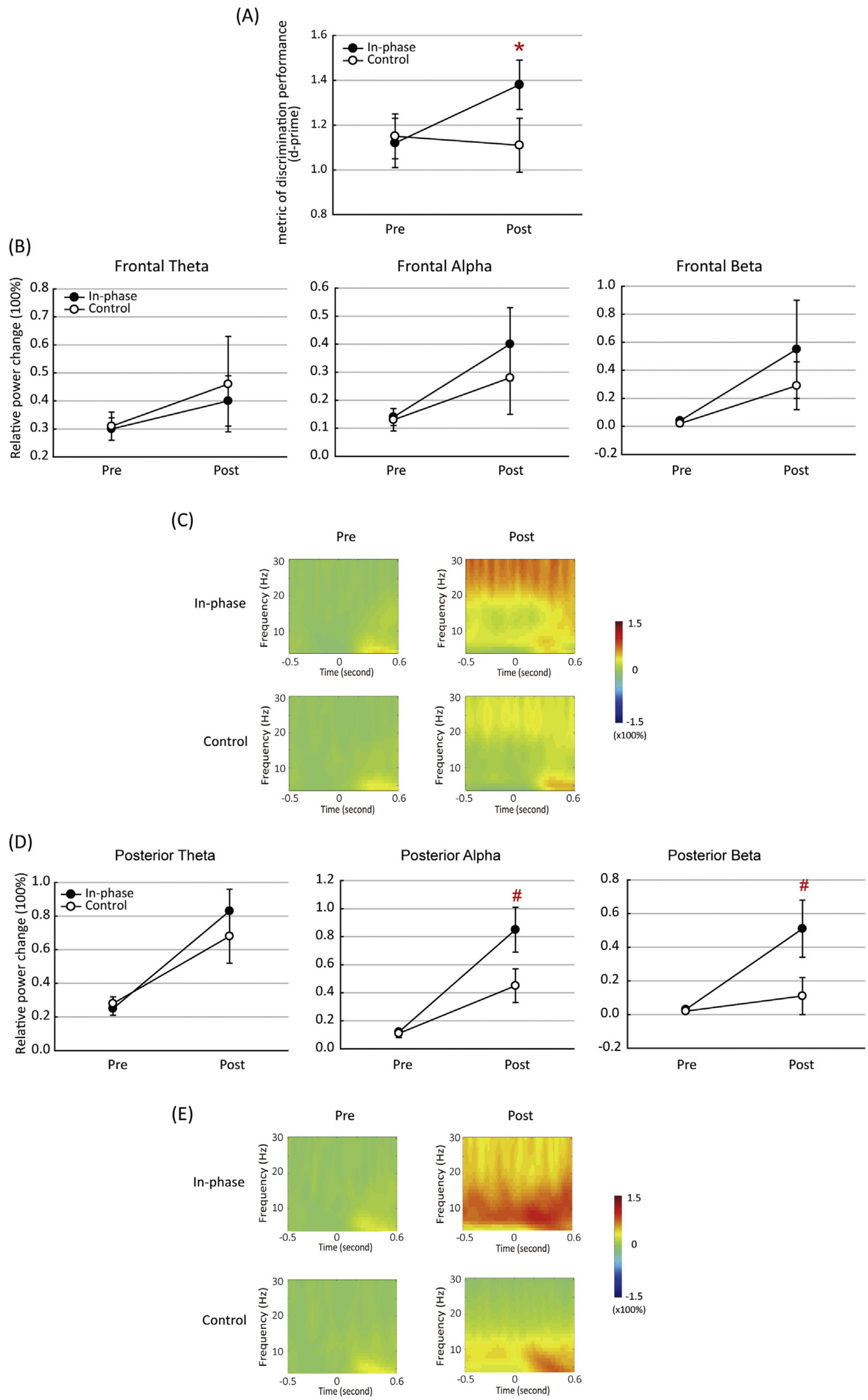

Fig. 2. Multitasking behavioral performance and electrophysiological activities of experiment 1 (manipulation of stimulation phase). (A) In-phase stimulation group showed higher d-prime compared to the control group. (B) and (D) Mean relative power change for frontal and posterior theta, alpha and beta. In-phase stimulation group demonstrated stronger post-stimulation posterior alpha and beta. (C) and (E) Grand-averaged time-frequency representation plots for frontal and posterior electrophysiological activity.
Error bars represent SEM. $^{*}p \leqq 0.05$; $^{\#}p = 0.06$.

Table 1
Behavioral and neurophysiological results for experiment 1.

	Group	Baseline	Post-stimulation	Cohen's d (95% CI)
D-prime	In-phase	1.12 (0.11)	1.38 (0.11)	0.50 (−0.12–1.14)
	Control	1.15 (0.10)	1.11 (0.12)	
Frontal theta	In-phase	0.30 (0.04)	0.40 (0.09)	−0.09 (−0.75–0.55)
	Control	0.31 (0.05)	0.46 (0.17)	
Frontal alpha	In-phase	0.14 (0.03)	0.40 (0.13)	0.21 (−0.43–0.87)
	Control	0.13 (0.04)	0.28 (0.13)	
Frontal beta	In-phase	0.04 (0.01)	0.55 (0.35)	0.21 (−0.43–0.87)
	Control	0.02 (0.02)	0.29 (0.17)	
Posterior theta	In-phase	0.25 (0.04)	0.83 (0.13)	0.24 (−0.41–0.89)
	Control	0.28 (0.04)	0.68 (0.16)	
Posterior alpha	In-phase	0.12 (0.02)	0.85 (0.16)	0.65 (−0.01–1.32)
	Control	0.11 (0.03)	0.45 (0.12)	
Posterior beta	In-phase	0.03 (0.01)	0.51 (0.17)	0.65 (−0.01–1.32)
	Control	0.02 (0.01)	0.11 (0.11)	

from 2 to 30 Hz. The data were multiplied by a hanning taper, using a sliding time window. Power changes of oscillatory activity as a function of time were calculated for theta (4–7 Hz), alpha (8–12 Hz), and beta (13–30 Hz) bands with one power value every 10 ms. To normalize the obtained oscillatory power changes, the data was referenced to a baseline period (500 ms–100 ms prior to the sign onset of the baseline measure) according to the following formula: Percent power change(k) = (A(k)-R)/R*100, where A is the power within the frequency band of interest at sample k and R is mean power of the baseline period. For statistical analysis, results from the time-frequency analysis were averaged over time (300 ms–500 ms post sign), frequencies, and electrodes, separately for 2 regions of interest (ROI): frontal (AF3, FP1, FPz, FP2, AF4) and posterior (P7, PO7, O1, O2, PO8, P8) ROI. We selected the time window between 300 ms and 500 ms post sign based on the Anguera et al., 2013 study [13] in which the maximum neuronal activity was found within this time window when participants are engaged in Neuroracer multitasking.

Statistical analyses

To evaluate differences in behavioral and neurophysiological measures between the experimental and control groups, analysis of covariate (ANCOVA) was conducted with baseline data as the covariate and post-stimulation data as the dependent measure. As the ANCOVA assesses the difference in the post-intervention measures after accounting for pre-intervention assessments, the results of the analyses reflect the effect of the stimulation, and are not affected by group differences at baseline. Since there are two separate experiments designed to investigate the role of different two parameters (phase and ISI) that would affect tACS effects, we did not directly compare the two experimental groups (in-phase stimulation vs. long-ISI stimulation). Instead, both behavioral and neural results of experimental groups were directly compared to the corresponding session in the control group. The difference between stimulation and control sessions in terms of the perception of tACS sensation (scaled from 1 to 10) was analyzed with t-tests. All numerical data are presented as the mean ± the standard error of the mean (SEM). The statistical significance threshold was set as $p \leqq 0.05$.

Results

All the participants tolerated tACS well and no one reported adverse effects. Confirming that control session was an appropriate placebo manipulation, there were no statistical differences in the perception of stimulation between stimulation and control sessions for both stimulation groups in experiment 1 and 2 (all nine measures $p > 0.10$). Importantly, there were also no statistical differences in the perception of stimulation between stimulation groups in their tACS sessions and the corresponding sessions in the control group (all $p > 0.25$).

Experiment 1: manipulation of stimulation phase

Multitasking behavioral performance

No significant baseline difference in multitasking performance was found between the in-phase stimulation and control groups ($t_{37} = 0.20$, $p = 0.84$). To assess differences between the in-phase stimulation and control groups in terms of tACS effects on multitasking performance, an ANCOVA was conducted with the baseline measurement as the covariate and the post-stimulation measurement as the dependent factor. There was a significant effect of tACS on post-stimulation multitasking performance ($F_{1,36} = 4.16$, $p = 0.04$, $\eta p^2 = 0.10$) (Fig. 2A). An effect size for d' was calculated based on the mean and the standard deviation of the post-stimulation measurement using Cohen's d [41]. The difference between the in-phase stimulation and control groups was equivalent to a moderate effect size (0.50, 95% confidence interval (CI): 0.12–1.14). Detailed behavioral results are listed in Table 1.

The behavioral results of experiment 1 indicated that in-phase theta-tACS had positive effects on multitasking performance, as revealed by the higher d-prime in the in-phase tACS than that of the control group.

Neurophysiological measures

Neurophysiological data across sessions were grouped in the same way as the behavioral data analyses. Power changes of oscillatory activity as a function of time were calculated for theta (4–7 Hz), alpha (8–12 Hz), and beta (13–30 Hz) for frontal and posterior regions. ANCOVA analyses were performed to delineate the difference of stimulation effects between in-phase stimulation and control groups. For frontal electrophysiological activity analyses, ANCOVA with the baseline measurement as the covariate and the post-stimulation measurement as the dependent factor showed no differences in frontal theta ($F_{1,33} = 0.06$, $p = 0.79$, $\eta p^2 = 0.002$), alpha ($F_{1,33} = 0.32$, $p = 0.57$, $\eta p^2 = 0.01$) and beta ($F_{1,33} = 0.38$, $p = 0.54$, $\eta p^2 = 0.01$) between the two groups (Fig. 2B). Fig. 2C illustrates grand-averaged time-frequency representation plots for frontal electrophysiological activity. ANCOVA analyses of posterior electrophysiological activity showed no group difference in posterior theta ($F_{1,33} = 0.52$, $p = 0.47$, $\eta p^2 = 0.01$). However, a strong trend towards a significant group difference was found in posterior

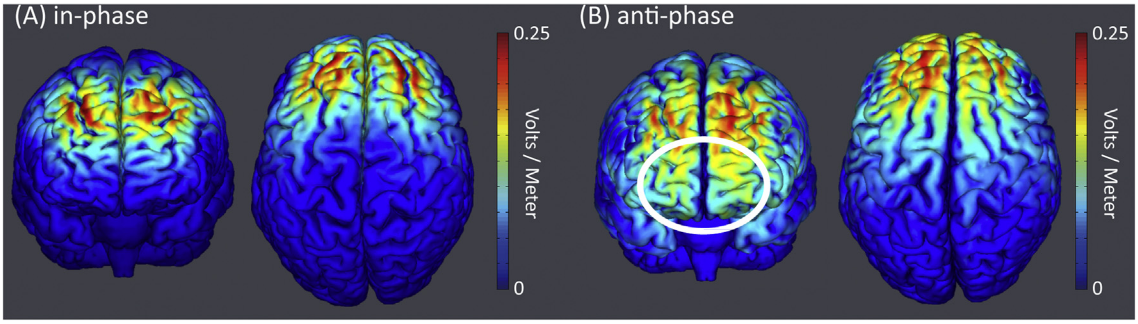

Fig. 3. Current modeling of (A) in-phase and (B) anti-phase tACS. Red-yellow colors represent increased magnitude of the total electric field caused by tACS. The modeling demonstrates greater stimulation within medial prefrontal cortex with anti-phase tACS compared to in-phase stimulation. Left panels of (A) and (B) show frontal regions, and the right panels depict top view of both hemispheres. The white circle in the frontal region of anti-phase tACS modeling denotes the difference of current distribution between in-phase and anti-phase tACS.

alpha ($F_{1,33} = 3.63$, $p = 0.06$, $\eta p^2 = 0.09$) and beta ($F_{1,33} = 3.72$, $p = 0.06$, $\eta p^2 = 0.10$) (Fig. 2D). Fig. 2E depicts grand-averaged time-frequency representation plots for posterior electrophysiological activity. Between-group effect size evaluation revealed a moderate effect size for both post-stimulation posterior alpha (0.65, 95% CI: 0.01–1.32) and beta (0.65, 95% CI: 0.01–1.32). Detailed electrophysiological results and effects sizes for each measure are listed in Table 1.

The results of neurophysiological measures of experiment 1 suggested that repetitive sessions of in-phase theta-tACS lead to marked offline neural effects as shown by greater posterior alpha and beta power in the stimulation group compared to the control group.

These current findings revealed that the effects of in-phase theta-tACS are similar to our previous finding, where the positive effects of anti-phase theta-tACS were observed [25]. However, the magnitude of group differences in behavioral and electrophysiological results of the current study (effect size: 0.50 for d-prime and 0.65 for posterior beta, respectively) are smaller than our previous study (effect size: 0.96 for both d-prime and posterior beta). One possible explanation is that the current flow of anti-phase stimulation applied in our previous study was able to more effectively target midline frontal regions, an area that is associated with multitasking [13,25], and thus resulted in stronger behavioral and neural effects. To address this possibility, we modeled the magnitude of electric fields induced by tACS with the NIC software (Neuroelectrics, Spain) for both in-phase and anti-phase electrode montages. The results of the current modeling revealed a greater electrical field within more medial prefrontal cortical regions when using the anti-phase, compared to in-phase, electrode montage (Fig. 3). In accordance with the electrode configuration, with anti-phase stimulation, the stimulation and return electrodes were placed at F3 and F4 of the 10–20 electrode coordinate system, in which case much of the current would pass through midline frontal regions. However, with in-phase stimulation, three more return electrodes were located along the midline (AFz, Fz, FCz), which may decrease the amount of current that passes through midline frontal regions because the distance between the stimulation and return electrodes are smaller, which results in more current being shunted at the scalp [42,43].

Experiment 2: manipulation of stimulation inter-session interval (ISI)

Multitasking behavioral performance

No baseline difference was found between the long-ISI stimulation and control groups in multitasking performance ($t_{36} = 0.98$, $p = 0.33$). An ANCOVA was performed to elucidate the effects long-ISI theta-tACS on multitasking performance. No significant difference between the long-ISI and control groups was observed on post-stimulation multitasking performance ($F_{1,35} = 0.10$, $p = 0.75$, $\eta p^2 = 0.003$) (Fig. 4A).

The behavioral results of experiment 2 revealed that long-ISI group did not show differentiable d-prime compared to the control group. With a 5-min inter-session interval, tACS did not induce after-effects on multitasking performance. The results suggested that inter-session interval between the repetitive sessions of tACS is a critical factor for generating positive effects.

Neurophysiological measures

Data across sessions were grouped in the same way as the behavioral data analyses. Power changes of oscillatory activity as a function of time were calculated for theta (4–7 Hz), alpha (8–12 Hz), and beta (13–30 Hz) for frontal and posterior regions. ANCOVA analyses were conducted to investigate the difference of stimulation effects on neurophysiological measurements between long-ISI stimulation and control groups. For frontal electrophysiological data analyses, ANCOVA with the baseline measurement as the covariate and the post-stimulation measurement as the dependent factor showed no differences in frontal theta ($F_{1,32} = 0.03$, $p = 0.85$, $\eta p^2 = 0.001$), alpha ($F_{1,32} = 0.10$, $p = 0.75$, $\eta p^2 = 0.003$) and beta ($F_{1,32} = 0.41$, $p = 0.52$, $\eta p^2 = 0.01$) between the two groups (Fig. 4B). Fig. 4C shows grand-averaged time-frequency representation plots for frontal electrophysiological activity. Similar to frontal activity, statistical analyses of posterior electrophysiological activity showed no difference between the two groups (posterior theta: $F_{1,32} = 0.004$, $p = 0.95$, $\eta p^2 = 0.00$; posterior alpha: $F_{1,32} = 1.01$, $p = 0.32$, $\eta p^2 = 0.03$; posterior beta: $F_{1,32} = 2.61$, $p = 0.11$, $\eta p^2 = 0.07$) (Fig. 4D). Fig. 4E illustrates grand-averaged time-frequency representation plots for posterior electrophysiological activity. Detailed electrophysiological results and effects sizes for each measure are listed in Table 2.

In line with the behavioral data, the results of neurophysiological measures indicated that, repetitive sessions of tACS with a 5-min interval did not generate significant changes in neural oscillatory activities compared to the control group.

Discussion

Here we investigated the role of tACS parameters in engendering stimulation effects by manipulating the phase and the interval between stimulation sessions in two experiments, respectively. With the in-phase stimulation (experiment 1), we replicated our previous findings where the positive effects of theta-

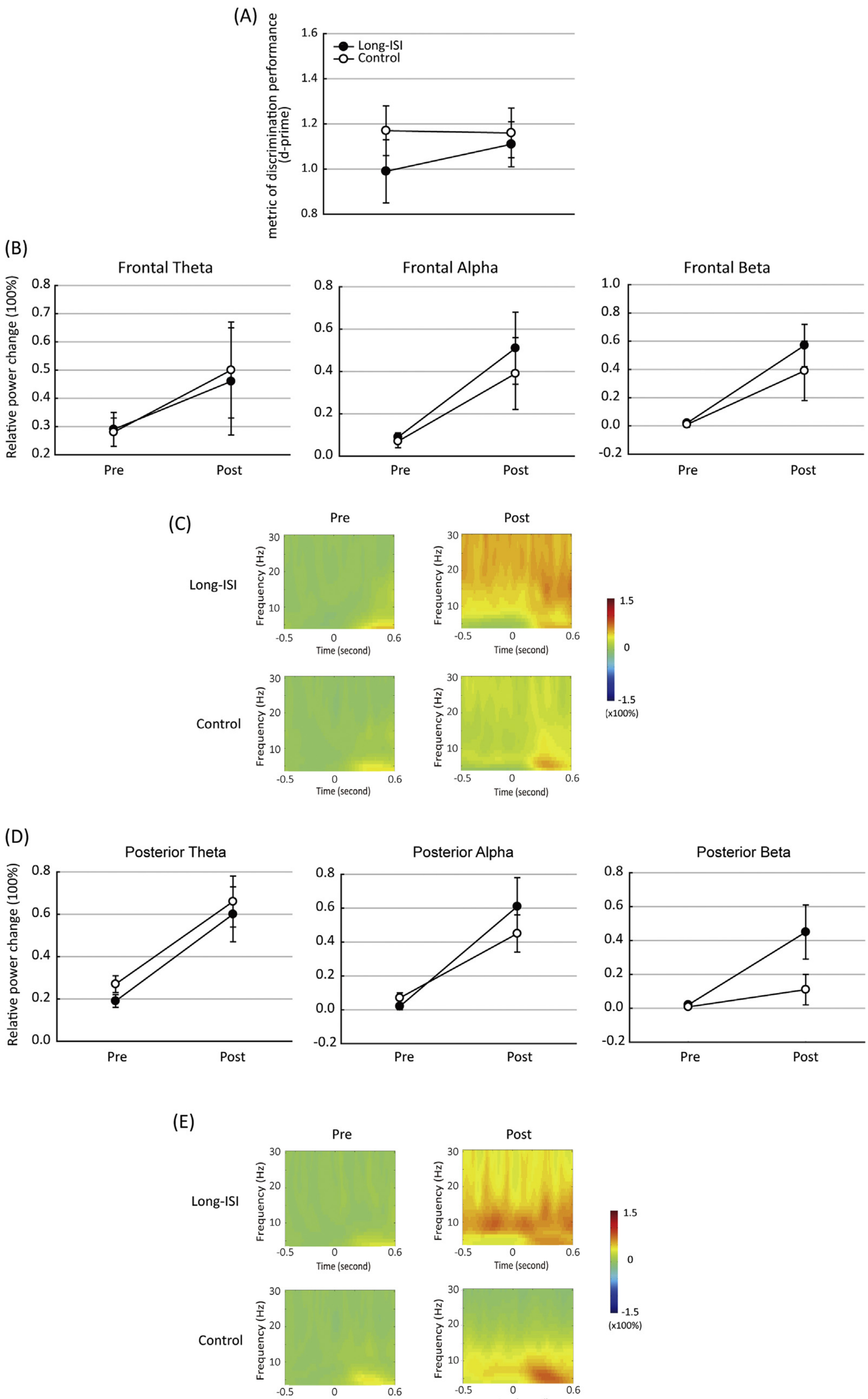

Fig. 4. Multitasking behavioral performance and electrophysiological activities of experiment 2 (manipulation of stimulation inter-session interval). (A) No significant differences in d-prime were observed between long-ISI stimulation and control groups. (B) and (D) Mean relative power change for frontal and posterior theta, alpha and beta. No differences in electrophysiological activities were found between long-ISI stimulation and control groups. (C) and (E) Grand-averaged time-frequency representation plots for frontal and posterior electrophysiological activity.
Error bars represent SEM.

Table 2
Behavioral and neurophysiological results for experiment 2.

	Group	Baseline	Post-stimulation	Cohen's d (95% CI)
D-prime	Long-ISI	0.99 (0.14)	1.11 (0.10)	−0.10 (−0.73–0.53)
	Control	1.17 (0.11)	1.16 (0.11)	
Frontal theta	Long-ISI	0.29 (0.06)	0.46 (0.19)	−0.05 (−0.71–0.61)
	Control	0.28 (0.05)	0.50 (0.17)	
Frontal alpha	Long-ISI	0.09 (0.02)	0.51 (0.17)	0.16 (−0.50–0.82)
	Control	0.07 (0.03)	0.39 (0.17)	
Frontal beta	Long-ISI	0.02 (0.01)	0.57 (0.15)	0.22 (−0.43–0.89)
	Control	0.01 (0.02)	0.39 (0.21)	
Posterior theta	Long-ISI	0.19 (0.03)	0.60 (0.13)	−0.07 (−0.73–0.58)
	Control	0.27 (0.04)	0.66 (0.12)	
Posterior alpha	Long-ISI	0.02 (0.02)	0.61 (0.17)	0.26 (−0.39–0.93)
	Control	0.07 (0.03)	0.45 (0.11)	
Posterior beta	Long-ISI	0.02 (0.01)	0.45 (0.16)	0.61 (−0.05–1.29)
	Control	0.008 (0.01)	0.11 (0.09)	

tACS were observed when the stimulation was delivered with 1-min ISI (i.e. same as in experiment 1), but with an anti-phase current polarity [25]. However, in experiment 2, by applying anti-phase stimulation with a 5-min long ISI, we did not find significant tACS effects on behavioral or neurophysiological measurements. These current findings suggest that the effects of tACS on multitasking performance and electrophysiological activity observed in our previous study [25] are dependent on the interval between stimulation sessions, but not the phase of the current polarity (i.e. phase-independent but ISI-dependent).

Phase-independent tACS effects

The results suggested that the effects of in-phase theta-tACS are similar to our previous finding, in which the positive effects of anti-phase theta-tACS were discovered [25]. As all experimental procedures and paradigm of experiment 1 were identical to the anti-phase stimulation group in our previous study with the exception of current polarity (i.e. in-phase stimulation for experiment 1 and anti-phase stimulation for the previous study), the same pattern of results corroborated our previous findings, and demonstrate that the observed effects were unspecific to phase differences.

In contrast with previous studies [28–30], we found phase-independent stimulation effects by replicating our previous findings with a tACS phase manipulation. It has been proposed that direct information transfer between two brain regions are bound to have a phase-lag above 0° due to information transmission time, whereas a zero time lag neuronal synchronization may implicate indirect communication, such that the two regions are receiving common input from other areas or a third relay assembly [44,45]. Since both in-phase and anti-phase theta stimulation showed similar effects on multitasking performance and neural oscillations, our results suggest that lateral PFC regions might not utilize theta oscillations for this particular form of multitasking. Rather, midline frontal theta activity, which arises from medial prefrontal regions, correlates with changes in multitasking performance [13,25]. Importantly, this phase-insensitvity would suggest midline frontal theta activity does not communicate task-related information to lateral prefrontal cortical regions. Therefore, as hypothesized, theta stimulation around medial PFC enhances multitask performance regardless of the stimulation-related temporal lag (or phase) between medial and lateral prefrontal regions.

Of note, a smaller between-group effect size in post-stimulation multitasking performance was found (0.50; 95% CI: 0.12–1.14) in experiment 1 compared to our previous study (0.96; 95% CI: 0.28–1.63). The magnitude of group differences in electrophysiological results (i.e. posterior beta) was also not as strong as the previous study and the previous study exhibited a correlation between improved performance and increased frontal theta activity, which was not observed here in experiment 1. While it could be argued that this is due to phase differences between cortical regions, previous tACS studies [29,30] and the communication through coherence hypothesis [46–48] would predict larger differences, such as either a null effect or perhaps detrimental multitasking performance, if communication between bilateral PFC or between medial and lateral PFC were important. The results of current modeling support the explanation that current flow of anti-phase stimulation was able to more effectively target midline frontal regions (Fig. 3), an area that is associated with multitasking [13,25], and thus had stronger behavioral and neural effects. Electric fields generated by transcranial electrical stimulation have components both parallel (i.e. current shunted at the scalp surface without reaching the brain) and perpendicular (i.e. current reaches brain) to the scalp surface [43]. Studies have shown increasing the distance between stimulation electrodes increases the electric field distributions reaching the brain and decreases the current portion shunted at scalp surface [42]. The reason less current gets into the cortex during in-phase stimulation is because there is a smaller distance between the stimulating and return electrodes, which results in greater scalp shunting of the electrical current [42,49]. As such, anti-phase stimulation likely yields larger positive effects due to greater stimulation intensity within the medial PFC cortical regions since the distance between the stimulation and return electrodes are larger, which would result in a larger portion of current getting into the brain and targeting medial PFC more effectively.

In line with our previous study, an interregional cross-frequency modulation was observed. In-phase frontal theta-tACS increased posterior neural activities as indicated by greater posterior alpha and beta power in the stimulation group compared to the control group. With an identical experimental design, our previous study [25] also showed that anti-phase stimulation increased posterior beta power and a trend for increased posterior alpha power. The results suggested a similar underlying mechanism of how in-phase and anti-phase theta-tACS affect this particular form of multitasking, which involves inhibitory control, sustained attention, task switching, and selective attention. The interregional cross frequency modulation may be the result of overall enhancement of cognitive functions that are involved in this cognitive network. Since beta and alpha activities is associated with anticipatory attention [50,51] and a top-down mechanism of inhibition [52], respectively, we speculate that increased posterior beta power may serve to maintain a sensorimotor representation of the visuotracking (i.e. driving) task [53] while increased alpha oscillations reflect inhibitory control for the visual discrimination (i.e. sign) task.

Inter-session interval-dependent tACS effects

In our previous study, repeated sessions of theta-tACS with a 1-min ISI exerted positive effects on multitasking performance along with an increase of posterior beta power. In the present study, we investigated how the ISI of a repeated stimulation protocol would affect stimulation effects by changing the ISI from 1 min to 5 min. All other stimulation parameters (i.e. current intensity, total amount of stimulation, stimulation sites, phase offset) and experimental procedures are the same as our previous study. However, such manipulation of ISI yielded no tACS facilitation effects. The null findings according to inter-session intervals revealed that specific repetition rate is critical for generating after-effects in protocols with repeated sessions of tACS.

As documented by previous studies, a substantial impact of manipulations of inter-session interval for non-invasive electrical stimulation exists in spaced stimulation protocols [32–35]. In a cathodal tDCS study, Monte-Silva et al. (2010) applied two sessions of 9-min stimulation with different inter-session intervals. The authors found that when the second stimulation is performed during the after-effects of the first, the stimulus after-effects on motor cortical excitability is prolonged and enhanced. An anodal tDCS study reported that with different intervals, the effects of two sessions of stimulation were reduced or even reversed compared to a single session of stimulation [35]. Previous studies have also proposed that a restricted inter-training interval is important for learning when multiple training sessions are spaced over time [54,55]. Our previous finding suggested that, with a rapid repetition rate (i.e. 1-min ISI), theta-tACS enhanced multitasking performance and increased posterior beta power. In contrast to our previous study, experiment 2 showed that the multitasking performance and electrophysiological activity were not differentiable between the long-ISI stimulation and control groups. Since the total amount of stimulation duration in experiment 2 was the same as it was in our previous study (8 sessions of 3-min stimulation, 24 min stimulation in total), the different results of the two studies may infer that the effects of tACS on behavioral and electrophysiological performance are ISI-dependent. With a 1-min ISI, tACS application seems to have targeted the restricted time window in which the prior stimulation exhibits after-effects. Thus, the repeated stimulation may cause subsequent stabilization and accumulation of tACS effects, and as a consequence, leads to offline behavioral and electrophysiological effects, whereas the 5-min ISI might have been too long to generate a beneficial effect.

These results accent the importance of inter-session interval for generating after-effects in protocols with repeated tACS sessions, given our finding that repeated sessions of tACS with shorter, but not longer, intervals induced behavioral and neurophysiological changes. This also raises the intriguing possibility of using the exact same stimulation parameters as a control in future research, by maintaining the electrode montage, intensity, phase, and total stimulation duration, but introduce a longer ISI to prevent tACS effects from accumulating.

General remarks

The current study replicated our previous findings and corroborated that theta-tACS can enhance multitasking performance along with increased power of neural oscillations. Furthermore, the findings delivered evidence that tACS enhances multitasking performance in a stimulation phase-independent and ISI-dependent fashion, thus stressing the importance of selection of stimulation protocol for generating tACS effects on cognitive function and neural oscillations. These findings may contribute to the development of optimal tACS protocols for research or therapeutic purposes. Due to the vast array of stimulation parameters, additional studies on the systematic manipulation of stimulation parameters are needed to determine the most favorable protocols for achieving the intended tACS effects.

Conflicts of interest

A.G. is a scientific advisor for Neuroelectrics, a company that produces a tACS device, and co-founder, shareholder, BOD member, and advisor for Akili Interactive Lab, a company that produces therapeutic video games.

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