tACS facilitates flickering driving by boosting steady-state visual evoked potentials

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Abstract
Objective. There has become of increasing interest in transcranial alternating current stimulation (tACS) since its inception nearly a decade ago. tACS in modulating brain state is an active area of research and has been demonstrated effective in various neuropsychological and clinical domains. In the visual domain, much effort has been dedicated to brain rhythms and rhythmic stimulation, i.e. tACS. However, less is known about the interplay between the rhythmic stimulation and visual stimulation. Approach. Here, we used steady-state visual evoked potential (SSVEP), induced by flickering driving as a widely used technique for frequency-tagging, to investigate the aftereffect of tACS in healthy human subjects. Seven blocks of 64-channel electroencephalogram were recorded before and after the administration of 20min 10Hz tACS, while subjects performed several blocks of SSVEP tasks. We characterized the physiological properties of tACS aftereffect by comparing and validating the temporal, spatial, spatiotemporal and signal-to-noise ratio (SNR) patterns between and within blocks in real tACS and sham tACS. Main results. Our result revealed that tACS boosted the 10Hz SSVEP significantly. Besides, the aftereffect on SSVEP was mitigated with time and lasted up to 5 min. Significance. Our results demonstrate the feasibility of facilitating the flickering driving by external rhythmic stimulation and open a new possibility to alter the brain state in a direction by noninvasive transcranial brain stimulation.

1. Introduction

Over the last few decades, noninvasive transcranial brain stimulation gains increasing attention in the field of human neuroscience, because its emergence provides the possibility to modulate cortical excitability of brain by external methods. Among all noninvasive stimulation methods, transcranial alternating current stimulation (tACS), is a novel neuromodulation technique by applying sinusoidal stimulations on the scalp and thereby contributes to the alteration of brain oscillation [1]. Previous studies have demonstrated that tACS has the capacity to entrain endogenous oscillations in a frequency-dependent manner [2–7]. For example, in the alpha band, Zaehle et al observed that the real tACS increased the endogenous alpha oscillation power in human occipital cortex for the first time [3]. The modulatory effect of tACS was explained by computational modelling [4, 8] and recently validated by in vivo studies in awake nonhuman primates [9, 10] and nonprimate animals [11]. Besides electrophysiological methods, by using functional imaging such as fMRI, a few studies found that tACS influenced BOLD signals as a function of stimulation frequency, intensity and task condition [12, 13]. Some studies found that the duration of the aftereffect of tACS ranging from 1 to 70 min varied with the duration of stimulation [14–17]. Furthermore, it seems that the effect of tACS is also influenced by the brain state [5, 18, 19].
The rhythmic nature of tACS makes it become an ideal tool to study the causal link between brain oscillations and cognitive functions. Plenty of neuroimaging and behavioral studies found that appropriate tACS protocol would influence the cognitive processes and performance of tasks, including memory [20–26], learning and decision making [19, 27–34], speech perception [35–38], and motor functions [39–41], etc. For instance, theta-tACS was found to modulate the memory processing [20, 21, 23, 24, 26] and enhance the working-memory performance [20, 21], especially for the elder adults [20]. Protocols of tACS from various frequency bands (theta [19, 30, 31, 34], alpha [29, 33], beta [28] and gamma [32]) showed promise in facilitating the learning process [19, 28–32] and improving the decision-making [33, 34]. Due to its capacity to modulate cognitive processes, tACS is a promising new method for the treatment of cognitive disorders in clinical domains [42], e.g. obsessive-compulsive disorder, Alzheimer’s disease, Parkinson’s disease, epilepsy, and schizophrenia [43–47].

The effect of tACS on visual system has received increasing attention. Kanai and co-workers firstly finished a series of researches about the impact of occipital tACS on phosphene and demonstrated that the effect was influenced by the external environment, e.g. illuminated condition [2, 48]. Followed-up researches have reported various modulatory effects of tACS on visual cortex [49–56]. For instance, the administration of tACS in the visual tasks has been shown to influence visual discrimination [48, 49, 51, 56], spatial attention [50, 53], face and object perception [52], and inattentional blindness [54]. However, the modulatory effect of tACS on visual evoked potentials (VEPs), especially steady-state visual evoked potentials (SSVEPs), is less reported [57, 58]. Philipp et al investigated the concurrent effects of 7 and 11 Hz tACS on matched steady-state responses (SSR) by removing the artifacts in MEG recordings and suggested frequency-specific effects of tACS [57]. Recently, Fiene et al assessed the effect of intermittent tACS on SSVEPs with six different phase shifts and found the phase-specific attribute of the tACS effect [58].

Evoked potentials in the visual system, especially steady-state visual evoked potentials (SSVEPs), are widely utilized in the scientific study of visual attention [59–61] and applied settings of clinical diagnosis [62, 63]. SSVEPs are periodic signals that are neural responses to flickering visual stimulations at specific frequencies, generally ranging from 3 Hz to 60 Hz [64, 65]. The distribution of SSVEPs is predominantly located at V1 or the Oz electrode [66, 67]. Some properties of SSVEP, such as high signal-to-noise ratio (SNR) [68], make SSVEP a prime candidate for engineering applications, for instance, brain–computer interface (BCI) [69, 70].

In the present study, we focus on the interaction between tACS and periodic visual stimulation, specifically the effect of tACS on SSVEP. First, we suppose that weak tACS is able to penetrate the skull and stimulate the visual cortex, as is evidenced by previous study [71]. This assumption constitutes the basis for the common findings that tACS can modulate visual cortex [2, 48, 57, 72]. Second, SSVEP is a special type of oscillatory brain response, and its derivation might be related to the brain rhythms [73, 74]. Since tACS has the capacity to modulate brain rhythms [3, 14, 17] and the frequency-specific property characterizes both tACS and SSVEP, we assume that tACS might influence SSVEP. Because of the fact that the power of SSVEP is highest in the alpha band (8–12 Hz), we chose the central frequency of the band, 10 Hz, as the stimulus frequency of SSVEP. As recommended by [75] to choose the match frequency, 10 Hz is chosen both for tACS and SSVEP in this study. This is in line with the previous studies [3, 4] that matched frequency of tACS with brain oscillation might lead to resonance and the modulated effect is most obvious. In sum, we hypothesize that appropriate 10 Hz tACS might influence 10 Hz SSVEP.

2. Materials and methods

2.1. Participants

Twelve healthy subjects (age: 20.5 ± 2.2 years, six males and six females) participated in this study. They were all paid volunteers randomly recruited from Tsinghua University. All the participants met the following requirements (1) right-handedness (2) normal or corrected-to-normal vision (3) no attention-deficit or hyperactivity disorder (4) no history of epileptic seizures or other neuropsychiatric disorders (5) no intake of caffeine, alcohol or medication (6) no fatigue prior to the experiment (7) no history of brain injury or intracranial implantation. Full written informed consent was given by the subjects at the beginning of the experiment. This study was approved by institutional review board of Tsinghua University (No. 20 190 021) and was under the declaration of Helsinki.

2.2. Stimuli

In this study, we adopted a flickering square to evoke SSVEP and the visual flicker was generated by PsychoToolbox [76] at a frequency of 10 Hz. The size of the flicker was 250 × 250 pixels (visual angle: 6.5°) and lay at the center of a 27-inch LCD screen (LG 27GK750F, refresh rate: 60 Hz, resolution: 1920 × 1080 pixels). Initially, a photocell test
was conducted to measure photoelectric responses elicited by theticker. Besides, a frame stability test was performed to record the frame interval of each trial. Both tests were passed to ensure the preciseness of visual presentation before carrying out the experiment.

2.3. Procedure

We chose a within-subject design to exclude confounding variables for this study. All subjects took part in two experiments, i.e. real tACS and sham tACS in a counterbalanced order on different days. For each subject, the start time of experiments was fixed at either 9 a.m. or 7 p.m. to ensure the participants to have a clear and comparable mental state for both experiments.

For each experiment, subjects underwent a pre-tACS session, a tACS session, and a post-tACS session (figure 1(a)). In the pre-tACS session, subjects performed a practice block (Pre-0) and subsequent baseline block (Pre), each of which consisted of a block of SSVEP task. The practice block was set for participants to be familiar with the experiment and data collected from this session were not used for analysis. The baseline block provided us the data as a baseline prior to tACS stimulation. In the tACS session, participants received real tACS or sham tACS depending on the type of experiment and no blocks of the task were performed. The post-tACS session came instantly after the tACS session and consisted of 5 blocks of tasks.

The timeline of the visual stimuli was illustrated in figure 1(c). In a block of SSVEP task, there were 80 trials, each of which comprised 2-s flickering and 1-s black screen interval for rest. To avoid artifacts and alpha oscillation from eye blink [77], subjects were required to stare at the center of the flicker without blinking. Meanwhile, 12 Go/No-Go tasks were randomly inserted in the SSVEP tasks to measure behavioral performance. Each task block lasted approximate 5min in total, including the SSVEP task and Go/No-Go task. During the task block, participants were advised to sit calmly and not to move. Participants have a 2min break between two adjacent blocks. During the 2min break, participants were instructed to rest calmly with eyes open. The whole procedure was carefully timed.

2.4. Transcranial alternating current stimulation

To achieve spatially high-definition recording and stimulation, we combined a tACS device (StarStim, Neuroelectrics, Inc. Barcelona, Spain) with the 64-channel Electro-Cap. Transcranial alternating current was therefore delivered to two PiStim stimulating electrodes ($\pi$ cm$^2$ area, Neuroelectrics, Inc.), which lay respectively in the sagittal vicinity of Oz and Cz recording electrodes underneath the Electro-Cap (figure 1(b)). Previous work of finite-element simulation demonstrated convincing evidence that this montage ensured a maximum of current densities in occipital cortex [78]. The stimulating current was set constant at an intensity of 0.65 mA according to the previous study [79]. The frequency of tACS was at
10 Hz in a sinusoidal manner. No DC offset was added to the AC waveform.

To alleviate electrochemical sensations, the current in real tACS ramped up for 10 s at the beginning of the stimulation, maintained stable and finally ramped down for 10 s at the end of stimulation. For the purpose of blindness, the sham tACS also brought about comparable sensations by ramping up the current for 10 s and immediately ramping down for another 10 s. The duration of stimulation was 20 min [5] for both the real and sham tACS. The impedance of the stimulation electrode was kept below 2 kΩ before the start of the practice session and it was double-checked at the beginning of tACS session. During the tACS session, participants were asked to rest calmly with eyes open.

2.5. Go/No-Go task
We designed a Go/No-Go task in each block of SSVEP task to keep the subject’s alert and also measured the subject’s capacity for response control and sustained attention [80]. In the Go/No-Go task, subjects were required to press the SPACE button (Go response) as quickly as possible when presented with target stimuli and not to respond (No-Go response) when presented with distractor stimuli. The target stimuli and distractor stimuli are defined as follows. As mentioned before, there were 7 blocks of SSVEP tasks in total (2 pre-tACS blocks and 5 post-tACS blocks) and the Go/No-Go task was randomly inserted in each block. During the Go/No-Go task, one of the numbers from 1 to 12 was presented on the screen in random order. The target stimulus was the prompt of odd number in the odd blocks (1st, 3rd, 5th, 7th) whereas it was the even number in the even blocks (2nd, 4th, 6th). The prompt of number was presented for 0.5 s and responses that were later than 1.5 s after the prompt appeared were regarded as failure responses.

2.6. Visual analog scale
At the end of each session, participants were evaluated by a Visual Analog Scale (VAS) [81] to report their subjective sensation. For the pre-tACS and post-tACS sessions, a VAS of fatigue evaluation was performed. Ten scores ranging from 1 to 10 indicated the extent of fatigue. Specifically, 10 denoted no fatigue and highly focused attentiveness. Scores from 9 to 1 were split into three intervals of slight fatigue, moderate fatigue, and severe fatigue, respectively. For the tACS session, a VAS of discomfort evaluation was performed instead. At the end of stimulation, subjects rated their sensation of discomfort to scores from 2 to 10. 1 denoted no discomfort and scores from 2 to 9 were split into three intervals of slight discomfort, moderate discomfort, and severe discomfort, respectively.

2.7. Data acquisition
Three types of EEG data were recorded, including SSVEP data, 2 min rest data between two consecutive blocks and 20 min EEG data under stimulation. All these data were recorded by SynAmps2 (Neuroscan Inc., Charlotte, USA) at a sampling rate of 1000 Hz. The 64-channel recording montage was aligned according to the international 10-10 system and the vertex Cz electrode was used as the reference. The impedance of all recording electrodes were kept below 10 kΩ before the experiment and were double-checked periodically throughout the experiment. The experiment was performed in a sound-attenuated and electrically shielded room. All lights were turned off in the room during the experiment.

Five EEG data (a break after the practice session and four breaks in the post-tACS session) were also collected during the 2 min rest. Apart from the EEG data, two behavioral data, i.e. the VAS data and Go/No-Go data including response type and reaction time were collected for behavioral analysis.

2.8. Data analysis
2.8.1. EEG data
We firstly preprocessed the raw EEG data by visual inspection in EEGLAB (Salk Institute, La Jolla, CA, USA). SSVEP trials contaminated with movement artifacts were rejected, leaving 98.98 ± 0.28% of the original data for analysis. EEG were then band-pass filtered from 3.5 to 100 Hz with an infinite impulse response (IIR) filter using the standard egffilt() function in EEGLAB. For each block, 2-s SSVEP epochs were then extracted and averaged to one trial to enhance the SNR of SSVEP. The averaging procedure in the time domain before frequency-domain analysis was in accord with previous study [82]. The following procedures were implemented in MATLAB 2018b (MathWorks Inc, Natick, MA, USA).

After preprocessing, we then determined the SSVEP power for each averaged trial in the frequency domain. The SSVEP power was obtained by calculating the square of the Fourier coefficient of the 2-s trial at the stimulus frequency, i.e. 10 Hz in the study. This procedure was performed to all channels in one block, and all blocks in either real tACS or sham tACS. Considering in the SSVEP powers there existed large inter-subject variation [83], we applied a procedure of SSVEP power normalization according to the previous study [84]. For each subject, an SSVEP power normalization factor was calculated by averaging the SSVEP powers across all channels and all blocks. Since the impedance of the trials in real tACS and sham tACS could be different, we obtained the respective normalization factor in real tACS and sham tACS. The normalized SSVEP power was formed by dividing the SSVEP power in real tACS and sham tACS by its associated SSVEP power mean factor.

To measure the aftereffects induced by tACS session, the change in SSVEP power was obtained by
subtracting the SSVEP power in the baseline block from that of the post-tACS session. This procedure was applied to each subject and each channel in both real tACS and sham tACS. A planned comparison was carried out by performing Mann–Whitney U-test to the change in SSVEP power in real tACS versus sham tACS. In this manner, we could obtain a p-value at each electrode and post-tACS time level. The change in SSVEP power and its corresponding statistical significance were topographically mapped. To better illustrate the significance of the change, p-values greater than .05 in the topography were colored white.

To characterize the change in SSVEP power, we further investigated the SSVEP envelope of both conditions in the baseline and post-1 block. Since Oz electrode lay in the central occipital region where SSVEP signals were predominantly distributed [67], it was taken as the representative electrode for the analysis of SSVEP. SSVEP time series were initially normalized by their respective SSVEP power normalization factor for each subject and each tACS condition. Then narrow-band filtering (center frequency: 10 Hz, bandwidth: 0.2 Hz) with an 8-order Butterworth filter was performed to each trial. In the implementation, zero-phase forward and reverse filtering was achieved using the filtfilt() function in EEGLAB. The SSVEP envelop was formed by applying a Hilbert transform to the filtered trials and then taking the modulus of the envelop was formed by applying a Hilbert transform to the filtered trials and then taking the modulus of the

To delve into the aftereffect of tACS on SSVEP, we analyzed the ongoing change in single-trial SSVEP power within a block. We chose the remaining trials, i.e. the first 78 trials after artifact rejection (on average two trials were rejected), to calculate their respective single-trial SSVEP power for the baseline and post-1 block in both tACS and sham conditions. For comparison, SSVEP power ratio was defined as follows to characterize the change relative to its associated baseline. Values in the post-1 block were divided by the mean value of baseline block for real tACS and sham tACS, respectively, and the values in baseline block were then divided by their mean. The SSVEP power values before the division procedure were used for statistical analysis. The sequence of single-trial SSVEP power was then averaged across subjects and fitted with linear regression to quantify the dynamics of the aftereffect. To unveil the changes in SSVEP power at a global scale, all the 78 trials were divided into 3 stages, i.e. early stage (the 1–26th trial), middle stage (the 27–52nd trial) and late stage of a block (the 53–78th trial). The spatial patterns of SSVEP power were plotted for the post-1 session in the real tACS condition.

SSVEP is based on frequency coding and its available signal component can be evaluated by the metric of signal-to-noise ratio (SNR). To characterize wide-band noise and the contribution of harmonics to the signals, the SNR (in decibels, dB) is defined as follows [86]:

$$\text{SNR} = 10 \log_{10} \frac{\sum_{k=1}^{N_h} P(k \cdot f_s)}{\sum_{f=0}^{f_s/2} P(f) - \sum_{k=1}^{N_h} P(k \cdot f_s)},$$

where $P(f)$ is the power spectrum at frequency $f$, $N_h$ is the number of harmonics, $f_s$ is the stimulus frequency, and $f_s$ is the sampling rate. We calculated the mean SNR with five harmonics ($N_h = 5$) using data from nine parietal and occipital electrodes (Pz, PO3, PO4, PO5, PO6, POz, O1, Oz and O2). This procedure was applied to single trials in the three stages (initial: the 1–26th trial; middle: the 27–52nd trial; late: the 53–78th trial), yielding the mean SNR values for each stage of the baseline and post-1 block in both real and sham tACS conditions. Statistical analysis was then applied to obtain the statistical significance of the comparison between baseline block and post-1 block for real tACS and sham tACS, respectively.

Furthermore, we analyzed the 2min EEG data recorded during the break between two consecutive blocks. EEG epochs with movement artifacts and eye blinks were rejected by visual inspection. After preprocessing, two metrics, i.e. the relative alpha power
and the relative 10Hz power were then calculated. Specifically, the relative alpha power was obtained by computing the ratio of alpha band (8–12 Hz) power spectral to the whole-band power spectral and relative 10 Hz power was obtained in a similar fashion. To overcome the non-Gaussian distribution of the data, we took a logarithm of the resultant value and multiplied it by 10 (in decibels). In accordance with the SNR analysis, the nine parietal and occipital electrodes were selected for analysis and the associated metric values were then averaged by channel. This procedure was conducted for the 5 rest data (1 pre-tACS and 4 post-tACS) in both real and sham tACS. Statistical analysis was conducted to assess the change in the two metrics.

2.8.2. Behavioral data
For the Go/No-Go task, we calculated the sensitivity index $d'$ in each block for both real tACS and sham tACS. According to the signal detection theory, the $d'$ was given as follows [87]:

$$d' = Z(\text{hit rate}) - Z(\text{false alarm rate}),$$  \hfill (2)

where $Z(p)$ denoted the $z$ score of the probability. Subjects who achieved 100% false alarm rate (i.e. press button for all distractor stimuli) in one block were considered as a failure to remember the target stimuli and were removed for analysis. In addition, we further extracted the reaction time (RT) when the subject correctly hit the target. For the data of VAS, the scores of discomfort and fatigue were extracted. The metrics of $d'$, RT and the VAS score were then compared for real tACS versus sham tACS by statistical analysis.

2.9. Statistical analysis
To examine the effect of two within-subject factors, a two-way repeated measures analysis of variance (ANOVA) was conducted and the statistical significance of interaction was determined. In light of violations of sphericity, Greenhouse–Geisser correction was applied. When a significant main effect was found ($p < .05$), post-hoc pairwise comparisons of $t$-test was applied with Bonferroni adjustment. For the comparison of two groups in real tACS versus sham tACS, the normality of the difference of the data was firstly assessed by Shapiro–Wilk test on the studentized residuals. A Mann–Whitney $U$ test was employed if the assumption of normality was violated. A planned paired $t$-test was applied if the assumptions of normality and homoscedasticity were guaranteed. For the model of linear regression, the regression coefficient $k$ was determined to compare the tendency of SSVEP response with the regressor, and the $R^2$ was determined to reflect the goodness-of-fit of the model. The statistical significance of the model was assessed by ANOVA. The procedures of statistical analysis was conducted in SPSS Statistics 20 (IBM, Armonk, NY, USA).

3. Results
3.1. Changes in spatial and temporal profile of SSVEP
For each block and condition, the global changes in SSVEP power relative to the baseline block were illustrated in figure 2. In the post-1 block of the real tACS condition, we could noticeably observe a prominent increase in SSVEP power in the occipital and posterior parietal region. In contrast, a focal decrease was found in the occipital region of sham tACS condition in the post-1 block. By comparing these two conditions, the regions of central occipital and posterior temporal lobes both revealed statistical significance ($p < .05$), as indicated by the topographic map of statistical significance in figure 2. During the blocks from post-2 to post-5, the occipital SSVEP powers tended to decrease relative to the baseline block in both real and sham tACS conditions. No statistical significance was found following the post-1 block, except for the right fronto-parietal region in the post-4 block.
Specifically, a detailed version of Oz electrode was illustrated in figure 3. In accordance with the result in figure 2, the relative SSVEP power of Oz electrode showed statistically significant only in the post-1 session, \( p = .014 \).

The envelope dynamics of SSVEP on Oz electrode was illustrated in figure 4 (mean ± s.e.). As indicated by the envelope result (figure 4), the overall amplitude of envelope in the real tACS condition was elevated following tACS. This was in stark contrast with the sham tACS condition, where the amplitude of envelope exhibited a downward trend. Notice that at the start of SSVEP progression, there was no marked distinction between the real tACS and sham tACS group. However, in the later stage of the steady-state stage (1275–1700 ms), the distinction of change in SSVEP envelope (change in real tACS versus change in sham tACS) became significant (\( p < .05 \)), as indicated by the grey shaded area. This was also in line with the spatial pattern of SSVEP power (figure 4 top). Notably, we could observe a prominent increase in SSVEP power in occipital region during 1275–1700 ms, compared to its preceding stage (0–1275 ms) and subsequent stage (1700–2000 ms).

As can be seen from figure 5(a), a remarkable increase was observed in the low frequencies of the spectrogram when contrasting real tACS with sham tACS. Specifically, an evident boost was shown in 10Hz power, i.e. the fundamental frequency of SSVEP, along with the power of the second harmonic, 20 Hz. Interestingly, the vicinity of the fundamental and second harmonic also exhibited an increase in power following tACS, with a bandwidth of approximate 4 Hz. Figure 5(b) illustrated the statistical significance corresponding to figure 5(a). Despite there being scattered gray dots in the statistical map (may be false positive), two gray shaded regions were formulated, indicating powers were enhanced significantly from 7 to 13 Hz during 0.6–0.8 s, and also from 8 to 13 Hz during 1.3–1.8 s. It was noteworthy that the statistically significant regions were centered at approximately 10 Hz. Additionally, the changes in the third or fourth harmonic or even higher harmonics (not shown in figure 5(a)) were not noticeable in the result.

In terms of the temporal progression of single-trial SSVEP power, the two conditions of real tACS and sham tACS showed distinct dynamic properties, as illustrated in figure 6. The abscissa represented the normalized trial number, where \( 1/3 \) denoted the 26th trial, \( 2/3 \) denoted the 52nd trial, and so forth. Strikingly, at the early stage of the block, i.e. the first 1/3 of the trials (the 1–26th trial), the SSVEP power in real tACS was significantly greater in the post-session (10.636 ± 1.519 \( \mu V^2 \)) than its baseline block (8.324 ± 1.221 \( \mu V^2 \)), \( p = .0131 \), whereas in sham tACS no significant difference was found in post-session (7.080 ± 1.374 \( \mu V^2 \)) versus its baseline block (7.169 ± 1.007 \( \mu V^2 \)), \( p = .9350 \). For the middle stage of the block, i.e. the middle 1/3 of the trials (the 27–52nd trial), the mean SSVEP power was also greater in post-session (8.543 ± 1.225 \( \mu V^2 \)) than the baseline block (7.119 ± 0.905 \( \mu V^2 \)) of real tACS, though no significant differences were found in real tACS (\( p = .109 \)) and also in sham tACS (post: 6.561 ± 0.868 \( \mu V^2 \); baseline: 7.401 ± 1.147 \( \mu V^2 \); \( p = .286 \)). For the late stage of the block, i.e. last 1/3 of the trials (the 53–78th trial), in real tACS significant difference (\( p = .0428 \)) was found between post-session (8.230 ± 1.058 \( \mu V^2 \)) and baseline block (7.238 ± 0.976 \( \mu V^2 \)), whereas there was no significant difference in the sham tACS (post: 7.238 ± 0.976 \( \mu V^2 \); baseline: 7.764 ± 1.136 \( \mu V^2 \); \( p = .490 \)). We therefore noted that SSVEP power was the highest in the initial stage for the post block of real tACS. In other words, the intervention of tACS heightened the level of SSVEP power immediately after the end of stimulation, and then the aftereffect gradually tended to vanish, as indicated by the dashed line of linear regression. The regression coefficient was steeper in the post block of real tACS (\( k = −0.476, R^2 = .490, p < .001 \)) than the baseline block of real tACS (\( k = −0.306, R^2 = .363, p < .001 \)). Yet, the change for the sham tACS condition showed a tendency of slight decrease following tACS (post: \( k = −0.0069, R^2 = 4 \times 10^{-4}, p = .858 \); baseline: \( k = 0.1206, R^2 = .119, p = .002 \)). The spatial patterns of the post block (figure 6 right) in real tACS also confirmed the result of temporal progression, as was evident from the remarkably intense distribution of SSVEP during the early stage and its decline in the middle and late stage.

Figure 7 illustrated the change in mean SNR during the three stages (early, middle and late) for real tACS (a) and sham tACS (b). The corresponding statistical significance between SNR in baseline and the post-1 session was illustrated in the bottom panel (c: real tACS; d: sham tACS). As assessed by the Shapiro–Wilk test, the differences between the SNR data of real
Figure 4. Temporal characteristics of grand-average SSVEP epochs for real tACS and sham tACS. The lower panel illustrates the envelope of narrow-band SSVEP signals at the Oz electrode, and the upper panel illustrates spatial pattern of the changes in SSVEP power (the change in real tACS minus the change in sham tACS) during three stages (0–1275, 1275–1700, 1700–2000 ms). The baseline block (Pre) and post-1 session (Post) were analyzed for comparison. Gray shaded areas indicate statistical significance ($p < .05$, 1275–1700 ms) between the change in two conditions (change in real tACS versus change in sham tACS) and colored shaded areas indicate standard error.

Figure 5. Change in time-frequency representation following tACS and its associated statistical significance. Values in the left panel were calculated by subtracting the change in time-frequency representation (post minus pre) in sham tACS from that of real tACS. The right panel illustrates the statistical significance, where $p$ values greater than .05 are colored white and darker shades indicate greater significance. Red dashed rectangles outline the statistical significance corresponding to the left panel. EEG epochs on Oz electrode in baseline and post-1 blocks were analyzed.

Figure 6. Temporal progression of single-trial SSVEP power for both conditions in baseline (Pre) and post-1 session (Post). The abscissa denotes normalized trial number within a block, i.e. trial numbers from 1 to 78 were normalized to 0 to 1 (early stage: 1–26 trials; middle stage: 27–52 trials; late stage: 53–78 trials). The solid line indicates the mean single-trial SSVEP power and the colored shaded area indicates the standard error of the mean. The thick dashed line indicates the linear regression of SSVEP powers with its associated regression coefficients on display. The right panel illustrates SSVEP spatial patterns during early, middle and late stages in real tACS-Post. Note that SSVEP powers were highest in the early stage and then were on a gradual decline for real tACS-Post.
tACS and sham tACS were normally distributed (all $p > .05$), and the paired $t$-test was then applied. For real tACS, the SNR in the post-1 session was significantly greater than its baseline in the early stage (post-1: $-9.856 \pm 0.873$ dB; baseline: $-10.820 \pm 0.923$ dB; $p = .0056$). Similar to the single-trial SSVEP power, a tendency of decay in SNR can be observed. For the middle and late stage, the differences between SNR in post-1 session and baseline were not significant (middle: $p = .579$; late: $p = .422$). For sham tACS, no significant changes in SNR from baseline to the post-1 session could be found in the early ($p = .875$), middle ($p = .982$) and late stage ($p = .595$).

To ensure the boosted SSVEP power and SNR were independent of the change in spontaneous alpha power, we calculated the relative alpha power and relative 10 Hz power in the rest EEG. The Shapiro–Wilk test revealed that the assumption of normality was met for the relative alpha power (all $p > .05$) and the relative 10-Hz power (all $p > .05$). Mauchly’s test of sphericity indicated that the assumption of sphericity was met for the two-way interaction, $\chi = 15.741$, $p = .076$ for relative alpha power and $\chi = 10.97$, $p = .285$ for the relative 10-Hz power. There was no significant two-way interaction between tACS and time for the relative alpha power, $F(4, 44) = 2.495$, $p = .056$ and for relative 10-Hz power, $F(4, 44) = 1.619$, $p = .186$. For relative alpha power, no significant main effect of tACS ($F(1, 11) = .642$, $p = .44$) or time ($F(4, 44) = .299$, $p = .877$) was found. For relative 10 Hz power, there was also no significant main effect of tACS ($F(1, 11) = .974$, $p = .345$) or time ($F(4, 44) = .280$, $p = .899$).

### 3.2. Behavioral data

We further analyzed the VAS score to compare the participants’ actual sensations in fatigue and discomfort under the two conditions. As expected, no significant difference existed in the VAS scores of discomfort evaluation between real tACS and sham tACS, $p = .753$. With regard to the fatigue evaluation, two-way repeated measures ANOVA revealed that no significant interaction between tACS and time was found, $F(2, 761, 30.373) = .428$, $p = .827$, $\epsilon = .552$. The main effect of time showed a statistically significant difference in VAS of fatigue between blocks, $F(1.882, 20.703) = 5.350$, $p = .015$, $\epsilon = .376$. Post hoc comparisons with a Bonferroni adjustment revealed that the significance existed in post-1 versus post-4, $p = .040$, and post-2 versus post-3, $p = .028$. However, there was no statistically significant effect of tACS on VAS of fatigue between real tACS and sham tACS for each block, all $p > .05$. In other terms, as time progressed to the middle period of the experiment, subjects tended to be more fatigue. But the administration of tACS condition was imperceptible to the subjects and it did not further introduce confounds such as sensations of fatigue or discomfort, physically or psychologically. Specifically, the extent of VAS on discomfort (1.423 ± 0.643) was within the range of
slight discomfort (0–4). For fatigue, VAS evaluations (7.506 ± 1.560) were within the range of slight or moderate fatigue (5–10).

In regard to the Go/No-Go task, four subjects failed to remember the target stimuli in some blocks and accordingly were removed for analysis. There was no significant two-way interaction for the \( d^* \) data, \( F(5, 35) = 1.519, p = .209 \), and no main effect of TACS (\( p = .750 \)) or time (\( p = .541 \)) on \( d^* \). Also for the RT data, no significant interaction was found, \( F(5, 35) = 1.302, p = .286 \). The main effect of TACS or time showed no statistical significance in reaction time, \( p = .933 \) and \( p = .096 \), respectively.

**4. Discussion**

In this paper, we evaluated the effects of TACS on SSVEP both at 10 Hz in a group of healthy subjects and demonstrated the feasibility of modulating SSVEP using tACS. The current findings provide direct evidence for boosting SSVEP by a manual intervention of TACS. Since SSVEP is an indication of cortical excitability [62], this study lends support for the utility of tACS previously reported in altering the excitability of human cortex [2, 88]. Overall, the present study yielded three-fold findings. First, the administration of 10-Hz tACS significantly enhanced the 10-Hz SSVEP, as was validated by the spectral, temporal, spatial and SNR profiles of SSVEP. Second, the aftereffect of TACS on SSVEP achieved climax immediately after the termination of TACS, and gradually receded throughout trials and blocks. Third, the application of tACS did not affect the behavioral performance during the SSVEP task, as assessed by \( d^* \) and reaction time when subjects underwent the Go/No-Go task. In the following paragraphs, we discuss some issues in detail concerning the aftereffect and the study.

Most existing TACS studies adopted the approach of a pre-post stimulation comparison and consequently were unable to analyze the maximal duration of TACS aftereffect [89]. In this study, we tackled this issue and intended to determine the span of the aftereffect of tACS. The experimental design of a single flickering condition in our study ensured a decent amount of trials obtained from one block. In this fashion, the repeated measures made it possible to gauge the dynamic change of SSVEPs with time course. As such, the findings in figures 2 and 3 indicate that the significant excitatory effect on SSVEP persisted for merely the post-1 block, i.e. a period of 5 minutes following tACS. The short duration of tACS aftereffect is in line with the previous studies (5 min [14, 90], 3 min [15], 1 min [16]) and also resembles the 5-minute aftereffect by transcranial magnetic stimulation (TMS) [91], considering the physiological effects of TMS and transcranial electrical stimulation (TES) are comparable [92]. On closer examination within the post-1 block, the initial upsurge and subsequent trend of decline in single-trial SSVEP power characterize the lingering and reversible effect of TACS. Empirically, the duration of aftereffect in TACS studies depend mainly on the duration [5, 17, 93], montage [57, 94], intensity and frequency of stimulation [95], and the brain state [5]. We employed the parameters of TACS in line with previous studies (intensity [79], duration [5] and montage [17]), thus the short-lasting aftereffect in our findings may result from the task-dependent feature of tACS aftereffect [96]. Previous research in the domain of transcranial direct current stimulation (tDCS) found that the duration of aftereffect induced by visual cortical tDCS is relatively short compared with the aftereffects induced by motor cortical tDCS [97, 98]. Speculatively, the primary visual cortex may be less tunable than the primary motor cortex because of different neuronal membrane properties and cortical connections influencing neuroplasticity [97, 98]. This may provide us some insights since visual evoked potentials (VEPs) elicited by visual tasks are not well known under the intervention of tACS. It also cannot exclude the possibility that the aftereffect on cortical excitability of tACS was more reversible and susceptible to be counterbalanced by the predominantly provoked steady-state responses in the primary visual cortex.

Since SSVEP and tACS are both characterized by frequency modulation, the interplay between these two rhythmic endogenous and exogenous signals are attractive and intriguing to the researchers. However, to our knowledge, few studies have been involved in this domain. Ruhnau et al in a recent study [57] investigated the online effect of tACS in a magnetoencephalographic (MEG) setting on 7Hz and 11Hz visual SSRs (steady-state responses), a.k.a. SSVEPs. It was discovered that same-frequency tACS did not significantly affect the fundamental frequency but significantly enhanced the higher harmonics of SSVEP, which was not consistent with the result of our study. As a matter of fact, both studies utilized the tACS and SSVEP in the alpha range (8–12 Hz), i.e. 10 Hz (ours) and 11 Hz (the former), and the stimulation intensities are comparable (ours: 650 \( \mu \)A, the former: 613 ± 128 \( \mu \)A). As suggested by the verified model of the effect of tACS on spontaneous EEG [4], the frequency of 10 Hz and 11 Hz might share common tuning effects, though nuance in intensity. Therefore, the distinction in frequency might not suffice to account for the disparity of result. As such, on the one hand, we should notice that the former study employed 2-s TACS stimulation trial by trial. This very short intermittent protocol has been demonstrated too short in stimulation duration to induce tACS aftereffect [93, 99]. Thus the long span of 20 min stimulation in our study might offer an advantage to probe into the tACS aftereffect on SSVEP. On the other hand, in the former study, considerable tACS harmonics still existed in the reconstructed source.
space, and the author admitted the after-effects were out of the scope of the study. Recently, another related study [58] investigated the phase-dependent interaction between tACS and SSVEP, which differs from the current study in the tACS protocol and purpose of research. Similar to the study of Ruhnau et al [57], the recent study also utilized an intermittent tACS protocol in which stimulation lasted 6–8 s for each trial, whereas no interruption was employed during the tACS administration in our study. By leveraging the intermittent protocol, the recent study could probe into the neuromodulation under phase interaction, and the modulatory effect would be more instant, rather than the lingering aftereffect in our study. In this view, the present study is mostly orthogonal to the previous studies and provide the first informative evidence to unveil the aftereffect.

The pronounced SSVEP in our study is indicative of elevated excitability of visual cortex, which is consistent with other tACS-visual studies demonstrating tACS enhances visual cortical excitability as measured by phosphene [2, 100]. Note that as expected, all subjects in our study did not report photic perception during the administration of tACS due to the choice of stimulation intensity [79]. Apart from the elevated SSVEP in the occipital region, a noticeable statistical difference can also be observed in the left temporal and parietal region in the post-1 and the statistical difference can also be observed in the left frontal region in the post-4 (figure 2). Since our study utilizes a central flicker that was different from the stimuli with eccentricity [101], few SSVEP is evoked in the regions and the values may represent propagation of SSVEP from the occipital region [102] or background EEG during the visual task. It is interesting to note that following tACS a marked increase in power was likewise elevated in the spectral vicinity of SSVEP harmonics, which may result from the facilitation of photic driving [103] by tACS. For the finding of rest EEG, the present study reveals no significant influence of tACS on the spontaneous alpha power following tACS. The negative result on spontaneous alpha is reported in recent studies [104, 105] and may be ascribed to the difference in stimulation frequency which the majority of previous studies [3, 5, 17, 99, 106] employ at an individual alpha frequency (IAF) of each subject. In the context of the present study, the absence of tACS effect on spontaneous alpha further supports the notion of an increase in SNR of SSVEP in our finding. For the behavior findings, the result revealed that no modulatory effect of tACS was found on sensitivity index and reaction time in the Go/No-Go task. This negative report is in line with a previous study [107] of Go/No-Go task and other attention studies using 10Hz tACS [104, 108–110]. In addition, the comparable VAS ratings between real and sham tACS indicate the effective control that rules out indirect confounds such as physiological or psychological sensations.

As for the neurophysiological underpinnings of tACS aftereffect, there has been a growing debate about whether the mechanisms of neuronal entrainment [6, 111, 112] or neural plasticity [3, 99, 113] actually play the casual role. From the evidence of sinusoidal attributes of tACS and SSVEP alone, it is plausible to lend support for the theory of neuronal entrainment. As is indicated by a previous study [65], SSVEP shows resonance frequencies, i.e. strong resonance peaks around 10 Hz and weak peaks around 20 and 40 Hz, etc, a phenomenon which is in accordance with the entrainment of ongoing natural oscillation and conforms to the theory [111]. The results in the present study (figure 5(a)) clearly showcases a significant increase in 10Hz SSVEP power and also slight elevation in 20Hz SSVEP power, which may imply the resonance attribute of entrainment in the modulation of SSVEP by tACS. Moreover, it is interesting to note that the finding in the previous study [114] on tDCS manifested facilitatory effects on 10Hz SSVEP in a similar fashion though statistical significant at a smaller scale. This to some extent implies that the aftereffects in the two studies may have in common underlying mechanism, albeit the epiphenomenon of the brain might slightly vary.

From the perspective of tACS application, the finding in this study opens a new avenue for boosting SSVEP-BCI performance by transcranially potentiat- ing the SNR of visual responses. Since SNR is correlated with classification performance in BCI classification [86], the increment in SNR of SSVEP implies the possibility of facilitating classification and aiding in BCI training via tACS neuromodulation, and thereby reducing the calibration effort in the applications. The possibility of boosting BCI performance by transcranial neuromodulation is a nascent filed and it was explored in a limited number of studies, especially in motor imagery BCI (MI-BCI) [115–121]. For instance, a counterpart of tACS, i.e. tDCS has been shown potential in improving the classification performance of the MI-BCI system by transcranially enhancing the event-related desynchronization (ERD) [115, 118–121] or brain connectivity [116, 117]. However, for the system of SSVEP-BCI, it has received less attention [122]. A related pilot study [122] reported a positive effect of tACS (1 mA; 10 Hz; 10 min; PO9-PO10 protocol) on six subjects who performed a three-target (12.5, 9.37, and 8.33 Hz) BCI task. The result of our study is in line with the previous study and provides the underpinning for the integration of tACS into SSVEP-BCI task. At a pop- ulation level, the beneficial effect on SNR also proposes potential solutions for individuals of low SNR and ITR, i.e. BCI illiteracy. For instance, for the tDCS protocol, it was found that tDCS could potentially enhance the SNR of SSVEPs for electrodes with low pre-tDCS SNR [123]. Nevertheless, in the present
study, the significant improvement in SNR of SSVEP carries on at a short time-scale, i.e. the early stage of the post-1 session. This indicates the short duration of the aftereffect on SNR and also the reversible attribute of tACS effect that is favorable from the standpoint of real-world applications.

The present study has its limitations, which could be circumvented and improved by future works. First, since a large sample size is beneficial to boost the statistical power, the sample size or the number of participants could be extended in future studies. Second, since age-related differences were reported in both tACS [124–126] and SSVEP [127], in future works it is worthwhile to explore the modulatory effect of tACS among the older adults, e.g. 30 s or 40 s, or the elder. Finally, for future BCI studies, more reinforced measures, e.g. repeated sessions [128], high-definition montage [129] could be taken for the prolongation of the lingering effect.

5. Conclusion

To summarize, our study intends to explore the possibility of brain state manipulation by combing visual stimulation and rhythmic stimulation [112]. Specifically, by applying strict protocols of 10Hz tACS on 10Hz SSVEP, the current study measures the longitudinal changes of SSVEP between blocks and within a block and provides the first evidence that tACS boosts SSVEP in a short period of time. Importantly, this indicates that tACS strengthens brain excitability and facilitates flickering driving and may serve as a novel tool of neural feedback, which may provide new insight for basic neuroscience and unlock new applications.

Data availability statement

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

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