

Boosting visual perceptual learning by transcranial alternating current stimulation over the visual cortex at alpha frequency

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ABSTRACT

Background: Transcranial alternating current stimulation (tACS) has been widely used to alter ongoing brain rhythms in a frequency-specific manner to modulate relevant cognitive functions, including visual functions. Therefore, it is a useful tool for exploring the causal role of neural oscillations in cognition. Visual functions can be improved substantially by training, which is called visual perceptual learning (VPL). However, whether and how tACS can modulate VPL is still unclear.

Objective: This work aims to explore how tACS modulates VPL and the role of neural oscillations in VPL.

Methods: A between-subjects design was adopted. Subjects were assigned to six groups and undertook five daily training sessions to execute an orientation discrimination task. During training, five groups received occipital tACS stimulation at 6, 10, 20, 40, and sham 10 Hz respectively, and one group was stimulated at the sensorimotor regions by 10 Hz tACS.

Results: Compared with the sham stimulation, occipital tACS at 10 Hz, but not at other frequencies, accelerated perceptual learning and increased the performance improvement. However, these modula-

task could induce an increase in gamma power [18]. Theta and beta oscillations were found to be involved in texture discrimination learning [19] and motion discrimination learning [20], respectively. In these studies, oscillatory neural activity was recorded before and after training, but was not manipulated during training to modulate VPL. Therefore, these studies could not reveal the causal link between neural oscillations and VPL.

Transcranial alternating current stimulation (tACS) is a neuro-modulation technique that can non-invasively alter brain activity in a frequency-specific manner by delivering weak alternating currents to the scalp [21–25]. It is a wide-used tool for establishing a causal link between neural oscillations and cognition [26,27], across a broad range of frequencies and tasks [23,28–31]. However, tACS has not been applied to modulate VPL yet. In this exploratory study, we stimulated human subjects' visual cortex using tACS at a given frequency (6, 10, 20, or 40 Hz) while they were practicing an orientation discrimination task subserved by early visual cortex [9,10]. Sensorimotor cortex was also stimulated as a control location because it is minimally involved in VPL. We hypothesize that if neural oscillations at a given frequency play a pivotal role in the orientation discrimination learning, applying tACS at that frequency to the visual cortex will modulate the learning process and performance improvement.

2. Materials and methods

2.1. Subjects

A total of 121 healthy subjects (82 females, 21.58 ± 3.51 years) participated in the present study. Subjects were assigned to one of six groups (Table 1): Groups 1–4 received occipital tACS at 6 Hz (the 6 Hz occipital stimulation group), 10 Hz (the 10 Hz occipital stimulation group), 20 Hz (the 20 Hz occipital stimulation group), and 40 Hz (the 40 Hz occipital stimulation group), respectively. Group 5 received occipital sham stimulation (the sham occipital stimulation group); Group 6 received bilateral sensorimotor tACS at 10 Hz (the 10 Hz sensorimotor stimulation group). The group sizes were determined by a power analysis ($\alpha = 0.05$, two-tailed, power = 80%) based on our pilot study. A screening questionnaire was administered before starting the study for each subject. Subjects were included if they met the following criteria: 1) right-handed, 2) aged 18–40 years, 3) normal or corrected-to-normal vision. Subjects were excluded if they met the following criteria: 1) a history of neural surgery or epileptic seizures or any psychiatric or neurological disorders, 2) sleep disorders or a total sleep time less than 8 h per night over the last two weeks, 3) during ovulation phase of the menstrual cycle or pregnancy [32,33]. The present study was approved by the Ethics Committee of School of Psychological and Cognitive Sciences, Peking University. Written consent was obtained from each subject prior to the study.

2.1.1. Apparatus and stimulation protocol

Visual stimuli were generated and controlled using MATLAB (R2015a, MathWorks, Natick, MA) and Psychtoolbox-3 extensions

Table 1
Demographic information of subjects.

Group	Sample size	Female/Male	Mean age (SD)	Age range
Group 1	20	15/5	22.05 (3.33)	18–30
Group 2	21	15/6	21.81 (4.92)	18–37
Group 3	20	13/7	21.50 (3.90)	18–34
Group 4	20	13/7	20.25 (2.05)	18–24
Group 5	20	13/7	21.15 (3.05)	18–28
Group 6	20	13/7	21.70 (3.16)	18–30

[34] and were presented on a 19-inch Sony Trinitron color monitor (spatial resolution = 1600×1200 pixels, frame rate = 85 Hz) with a grey background (mean luminance = 47.59 cd/m^2). The monitor was the only source of light in the room. A chin-and-head rest was used to stabilize the head at a viewing distance of 65 cm. Subjects' eye movements were monitored by an Eyelink1000 plus eye-tracking system (SR Research Ltd., Ontario, Canada) throughout the whole experiment. Their eye positions were stable, well within 1° from the fixation point. There was no significant difference in the eye position distribution across the six groups.

Electrical stimulation was delivered using the DC-STIMULATOR MC (neuroConn GmbH, Ilmenau, Germany) through a pair of rubber electrodes of $5 \times 5 \text{ cm}^2$. The electrodes inserted in two soaked sponges (0.9% saline solution) were attached to the subjects' scalp using elastic bandages. A sinusoidal current with a peak-to-peak intensity of 1.5 mA was administered when subjects performed the training task. Both the DC offset and the phase difference between the two stimulation electrodes were set at zero. The impedance was constantly lower than $8 \text{ k} \Omega$ during all stimulation sessions.

2.1.2. Visual stimulus and task

Oriented Gabor patches (diameter = 1.25° ; spatial frequency = 3.0 cycle/° ; Michelson contrast = 0.5; standard deviation of Gaussian envelope = 0.42° ; random spatial phase) were located 5° from fixation in the lower left quadrant of the visual field. Here, 25% of the pixels in the Gabor patch were replaced with random noise. In each trial, a small fixation point was displayed for 500 ms firstly, and then two Gabor patches with orientations of 26° and $26^\circ + \theta$ were presented successively for 100 ms each and were separated by a 500 ms blank interval (Fig. 1(A)). These two Gabor patches were presented in random order. Subjects were instructed to make a two-alternative forced-choice (2AFC) judgment of the orientation of the second Gabor patch relative to the first one (clockwise or counter-clockwise) by pressing a key. The θ varied trial by trial and was adaptively controlled by a QUEST staircase to estimate subjects' discrimination threshold with 75% accuracy [35]. Subjects were asked to have a rest after each staircase. Feedback was not provided in all test and training sessions.

2.1.3. Design

A single-blind, sham-controlled, between-subject design was adopted to explore the role of tACS in modulating orientation discrimination learning. Subjects underwent five daily training sessions of the orientation discrimination task, which was preceded by a pre-training test (Pre) and was followed by two post-training tests. One of the post-training tests was completed immediately after training (Post1), and the other one (Post2) was conducted at least two months after Post1 (Fig. 1(B)). Each participant completed six QUEST staircases of 50 trials at Pre, Post1, and Post2, and nine QUEST staircases during each training session. Each staircase lasted about 3 min.

First, to investigate which stimulation frequency is able to modulate orientation discrimination learning, we recruited four groups of subjects to take part in this study, i.e., the 6, 10, 20, and 40 Hz occipital stimulation groups. The choice of stimulation frequency of tACS was based on the controversy of underlying neural oscillatory mechanisms of VPL. Also, 6, 10, 20, and 40 Hz are representative frequencies of theta band (4–8 Hz), alpha band (8–12 Hz), beta band (13–30 Hz), and gamma band (above 30 Hz), respectively. In line with previous tACS studies (e.g., Ref. [36]), two electrodes were placed over subjects' visual cortex and the vertex (i.e., O2 and Cz in the international 10–20 EEG system), respectively (Fig. 1(C)). The stimulated hemisphere was contralateral to the visual field where the Gabor patches were presented. Subjects

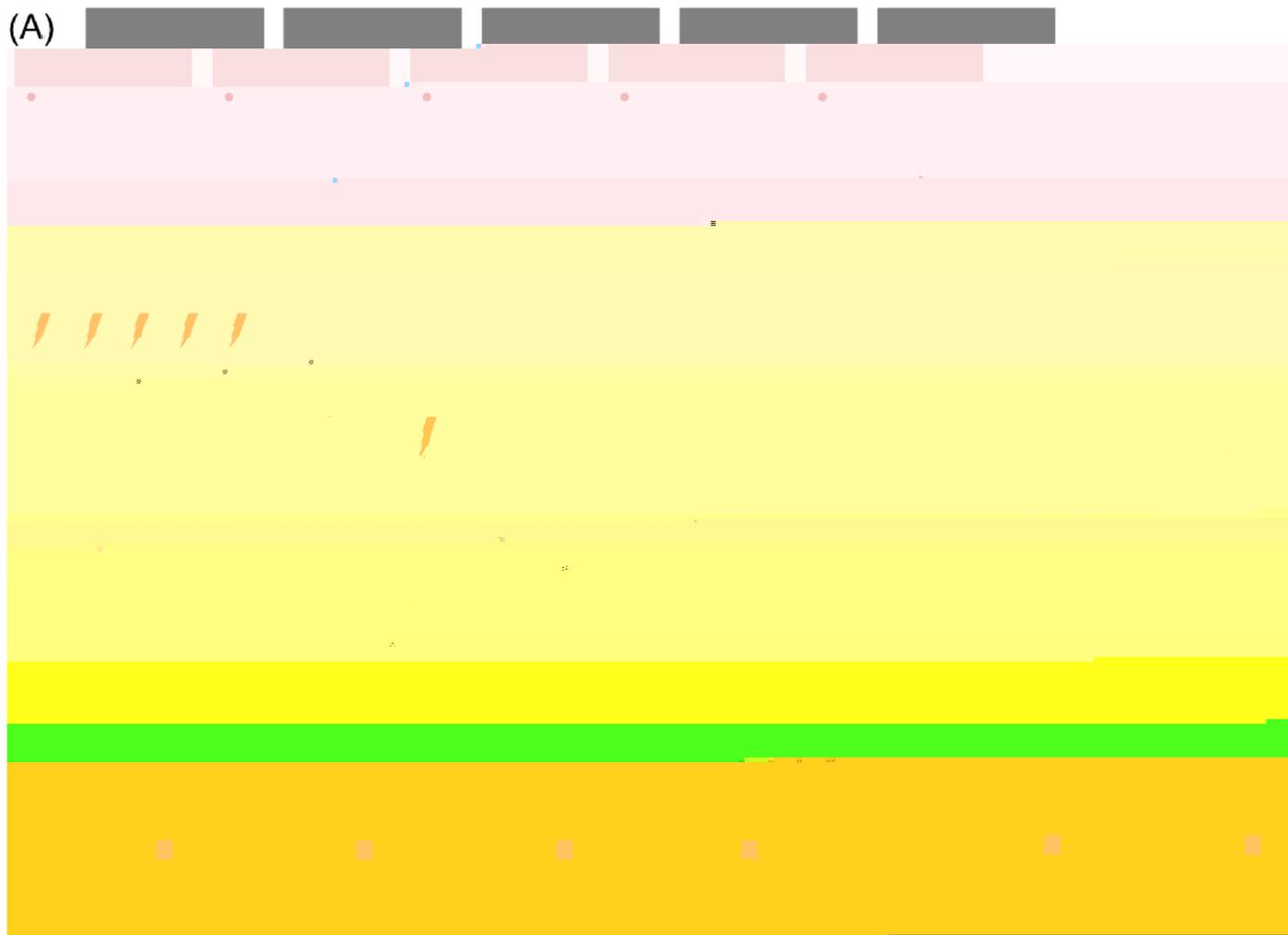


Fig. 1. Stimuli, experimental protocol, and electrical stimulation protocol. (A) Schematic description of a 2AFC trial in a QUEST staircase for measuring orientation discrimination thresholds. Subjects were instructed to make a judgment of the orientation in the second interval relative to that in the first interval (clockwise or counter-clockwise), while gazing at the central fixation point. There was no feedback after each trial. (B) Experimental protocol. Subject underwent one pre-training test, five daily training sessions, and two post-training tests. The pre-training test (Pre) and post-training test 1 (Post1) and test 2 (Post2) took place on the days before, immediately after, and two months after training. TACS was concurrently administered during each training session. (C) Electrical stimulation protocol and montage. TACS at different frequencies (6 Hz, 10 Hz, 20 Hz, and 40 Hz) were applied over different cortical regions. For occipital stimulation groups, stimulation electrodes were positioned over the occipital cortex (O2) and the vertex (Cz), while for the sensorimotor stimulation group, stimulation electrodes were positioned over the sensorimotor regions of both hemispheres. The electrode positions were identified by the international 10–20 EEG system. These heads were generated by FaceGen Modeller (version 3.4).

received electrical stimulation at a given frequency concurrent with training with a ramp-up of 30 s at the beginning of each training session. The electric field simulation of 10 Hz tACS using ROAST [37] is shown in Fig. S2 (see Supplemental Material).

Second, we asked whether the observed modulatory effects by 10 Hz tACS (see Results) were due to potential indirect effects, such as placebo effect. To this end, a fifth group of subjects were recruited, i.e., the sham occipital stimulation group. The electrical stimulation parameters were the same as those in the 10 Hz occipital stimulation group, except that subjects in the sham occipital stimulation group received 10 Hz tACS for 15 s with a ramp up/down of 30 s at the beginning of each training session.

Finally, to examine whether 10 Hz tACS modulated orientation discrimination learning in a stimulation location-specific manner, a sixth group of subjects were recruited, i.e., the 10 Hz sensorimotor stimulation group. The electrical stimulation parameters were the same as those in the 10 Hz occipital stimulation group, except that two electrodes were positioned over the bilateral sensorimotor cortical regions, i.e., C1 and C2 [38].

2.1.4. Statistical analysis

For each test or training session, the estimated threshold was defined as the geometric mean of thresholds from all QUEST staircases. Percent improvement, which describes changes in performance after training, was calculated as $(\text{pre-training threshold} - \text{post-training threshold}) / \text{pre-training threshold} \times 100\%$. To illustrate the threshold dynamics during the training course, a power function was used to fit the learning curves of orientation discrimination across all test and training sessions:

$$\text{Th}(t) = \lambda \times (t)^{-\rho} + \alpha$$

where Th is the predicted orientation discrimination threshold, t is the number of training sessions, λ is the initial threshold, ρ is the learning rate, and α denotes the minimum threshold achieved after training. A nonlinear least-square method, implemented in MATLAB, was used to minimize the sum of squared differences between model predictions and observed values.

Orientation discrimination thresholds were analyzed using a mixed-design analysis of variance (ANOVA) with a between-

subjects factor Group (occipital 6 Hz, 10 Hz, 20 Hz, 40 Hz, sham, and sensorimotor 10 Hz) and a within-subjects factor Test (Pre, Post1, and Post2). Learning rates and percent improvements were analyzed using ANOVA with a between-subjects factor of Group. For multiple comparisons, Benjamini-Hochberg method (BH) was used to control false discovery rate (FDR). η_p^2 and Cohen's d were computed as a measurement of effect size for ANOVAs and t-tests, respectively. Statistical analyses were conducted using R [39].

3. Results

3.1. Occipital tACS modulated orientation discrimination learning in a frequency-specific manner

First, subjects stimulated by occipital tACS at 6, 10, 20, and 40 Hz started with comparable performance at Pre ($F(3, 77) = 0.41, p = 0.75$). As shown in Fig. 2(A), subjects' orientation discrimination thresholds declined with training for all the training groups. For each subject, the orientation discrimination thresholds across all test and training sessions were fitted with a power function. A one-way ANOVA with Group (6, 10, 20, and 40 Hz) as a between-subjects factor revealed that there were significant group differences in learning rate, i.e., the estimated ρ -value of the power function ($F(3, 77) = 10.49, p < 0.001, \eta_p^2 = 0.29$). Post-hoc analysis showed that the learning rate of the 10 Hz occipital stimulation group was significantly greater than those of the other stimulation groups (10 Hz vs. 6 Hz: $t(39) = 3.02, p_{adj} < 0.001, \text{Cohen's } d = 0.92$; 10 Hz vs. 20 Hz:

$t(39) = 3.06, p_{adj} < 0.001, \text{Cohen's } d = 0.96$; 10 Hz vs. 40 Hz: $t(39) = 3.01, p_{adj} < 0.001, \text{Cohen's } d = 0.94$), and there was no significant difference in learning rate among other stimulation groups (all $p_s > 0.70$) (Fig. 2(B)). These results demonstrated that, relative to theta, beta, and gamma frequencies, tACS at alpha frequency accelerated the learning process.

Then subjects' orientation discrimination thresholds were submitted to a mixed-design ANOVA with Test (Pre and Post1) as a within-subjects factor and Group (6, 10, 20, and 40 Hz) as a between-subjects factor to examine differences in performance. We found a significant main effect of Test ($F(1, 77) = 98.81, p < 0.001, \eta_p^2 = 0.56$), and a significant interaction between Test and Group ($F(3, 77) = 4.70, p = 0.005, \eta_p^2 = 0.16$), but no significant main effect of Group ($F(3, 77) = 0.68, p = 0.57$). Further analysis showed that the thresholds at Post1 were lower than those at Pre for all groups (6 Hz: $t(19) = 4.21, p_{adj} < 0.001, \text{Cohen's } d = 0.81$; 10 Hz: $t(20) = 6.88, p_{adj} < 0.001, \text{Cohen's } d = 1.70$; 20 Hz: $t(19) = 3.85, p_{adj} < 0.001, \text{Cohen's } d = 0.82$; 40 Hz: $t(19) = 4.93, p_{adj} < 0.001, \text{Cohen's } d = 0.93$). At Post1, the threshold in the 10 Hz occipital stimulation group was significantly lower than those in other stimulation groups (10 Hz vs. 6 Hz: $t(39) = -3.42, p_{adj} < 0.05, \text{Cohen's } d = 1.07$; 10 Hz vs. 20 Hz: $t(39) = -2.94, p_{adj} < 0.05, \text{Cohen's } d = 0.92$; 10 Hz vs. 40 Hz: $t(39) = -3.64, p_{adj} < 0.05, \text{Cohen's } d = 1.14$). The threshold difference among other stimulation groups was not significant (all $p_s > 0.62$) (Fig. 2(C)).

The above results suggested that the performance improvement in the 10 Hz occipital stimulation group was greater than those in

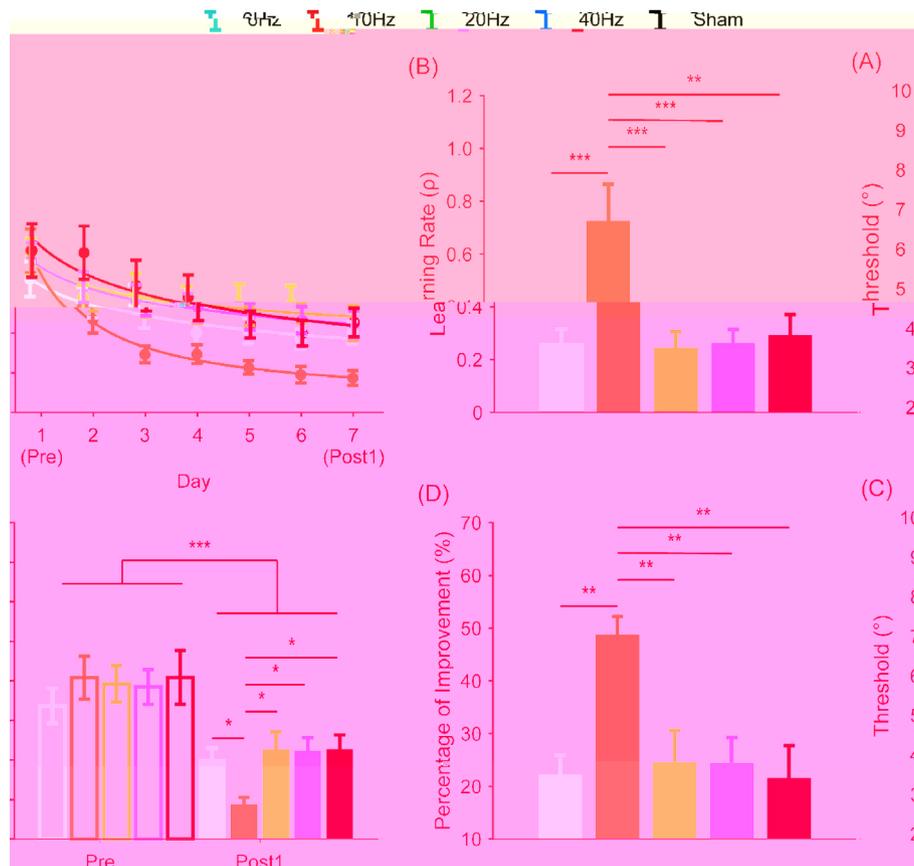


Fig. 2. Results of the main experiment in which visual cortex was stimulated using tACS at different frequencies. (A) Learning curves. Dots represent averaged thresholds across subjects at different test and training days, and lines represent fitted learning curves using a power function. (B) Learning rates. (C) Orientation discrimination thresholds at Pre and Post1. (D) Percent improvements in orientation discrimination performance at Post1, relative to Pre. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Error bars denote 1 SEM (standard error of the mean) across subjects.

other groups. To confirm this, a one-way ANOVA on percent improvement was performed. The statistical results showed that the differences in percent improvement among the four stimulation groups were significant ($F(3, 77) = 7.55, p < 0.001, \eta_p^2$

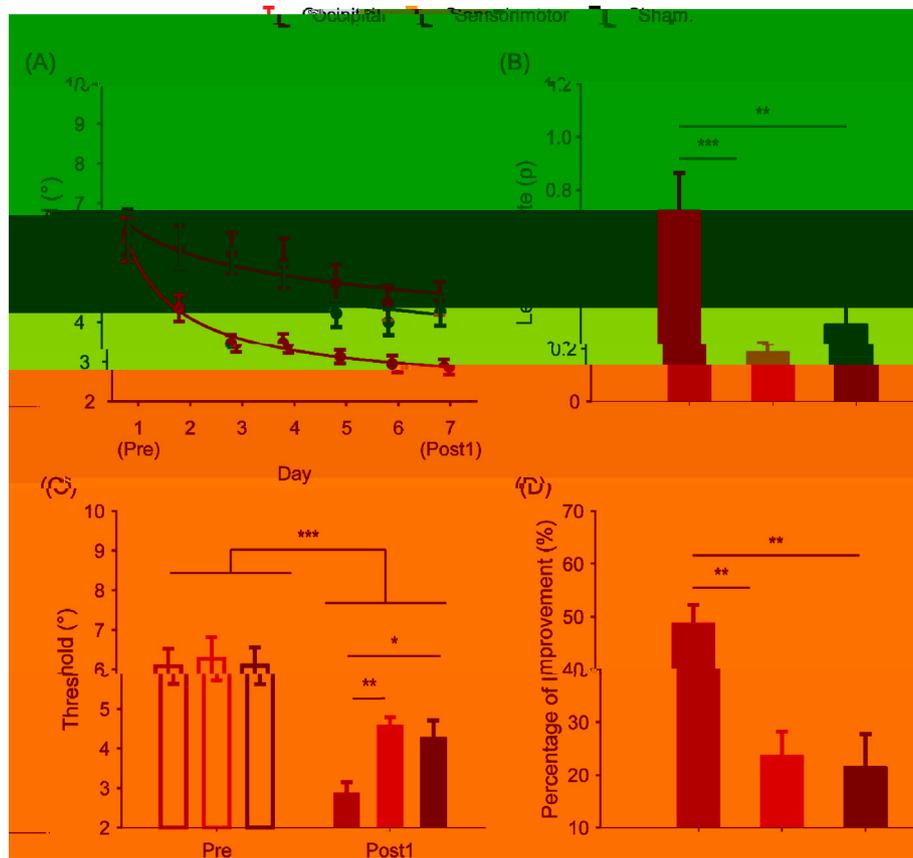


Fig. 4. Results of the control experiment in which 10 Hz tACS was applied to bilateral sensorimotor areas. (A) Learning curves. Dots represent averaged thresholds across subjects at different test and training days, and lines represent fitted learning curves using a power function. (B) Learning rates. (C) Orientation discrimination thresholds at Pre and Post1. (D) Percent improvements in orientation discrimination performance at Post1, relative to Pre. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Error bars denote 1 SEM across subjects.

difference between the 10 Hz sensorimotor stimulation group and the sham occipital stimulation group was not significant ($t(38) = 0.58, p = 0.56$) (Fig. 4(C)). Accordingly, there were significant differences in percent improvement among the three groups ($F(2, 58) = 10.16, p < 0.001, \eta_p^2 = 0.26$). Post-hoc analysis showed that the percent improvement in the 10 Hz occipital stimulation group was higher than that in the 10 Hz sensorimotor stimulation group ($t(39) = 4.45, p_{adj} < 0.01, \text{Cohen's } d = 1.39$), while there was no significant difference between the 10 Hz sensorimotor stimulation group and the sham occipital stimulation group ($t(39) = 0.31, p = 0.76$) (Fig. (D)). These results demonstrated that 10 Hz tACS delivered over sensorimotor areas did not result in more performance improvement in the orientation discrimination learning than sham stimulation.

4. Discussion

We found that, relative to sham stimulation, 10 Hz tACS applied to visual cortex accelerated learning and led to greater improvement in the orientation discrimination performance. The facilitatory effects were absent when visual cortex was stimulated by tACS at other frequencies (6, 20, and 40 Hz) or when other cortical areas (e.g., sensorimotor cortical areas) were stimulated by 10 Hz tACS, indicating that tACS modulated VPL in a frequency- and location-specific manner. To the best of our knowledge, this is the first systematic study demonstrating the modulatory effects of tACS on VPL. Our results suggest that occipital alpha oscillations play a key role in VPL, expanding the understanding of the role of alpha oscillations in neural plasticity. Moreover, it is the first reported study

that the enhanced performance by combining perceptual training with non-invasive brain stimulation could last for at least one year after training, providing a promising and feasible approach for clinical applications.

Our study demonstrated that tACS effectively boosted VPL, extending our knowledge of available tES techniques that can modulate VPL. Previous studies found that tDCS and tRNS could modulate VPL [32,38,40–44]. However, the working mechanisms of tDCS and tRNS are not well understood. Neither of them can alter brain oscillations in a frequency-specific manner, which limits our understanding of the neural oscillatory mechanisms of VPL. In contrast, tACS applied over the scalp of non-human primates and humans can produce changes in intracerebral electric fields in Refs. [21,22,25,27,45,46], thereby modifying ongoing neural oscillations in the targeted brain region [24,30,47]. TACS effects usually manifest as increased neural spectral power and/or phase synchronization [27,30,46], which is confirmed by our EEG experiment (see Supplementary Material). In this experiment, we found that subjects' resting-state alpha power in parieto-occipital areas after the tACS stimulation was significantly higher than that before the stimulation. Significantly, in our study, tACS at alpha frequency modulated VPL in a location-specific manner. Moreover, consistent with previous studies (e.g., Ref. [32]), no evident phosphene perception was reported by subjects when they were executing the training task. Thus, possible indirect effects, such as retinal stimulation, transcutaneous stimulation of peripheral nerves, and placebo effects [22,48,49], are unlikely to induce the facilitatory effect. Our results suggest that occipital tACS at 10 Hz entrained endogenous alpha oscillations in visual cortex and thereby facilitated VPL.

Our finding on the key role of occipital alpha oscillations in VPL is consistent with previous human EEG studies on different visual learning tasks [16,17,50,51], and with studies on tactile perceptual learning [52,53]. These EEG learning studies suggested that the alpha power enhancement in parietal-occipital regions is a manifestation of the neural mechanisms of perceptual learning. Furthermore, both the resting-state alpha power before learning [17,51,53] and the learning-induced alpha power change during task execution [52] correlated with individual's learning outcome, demonstrating a close association between alpha oscillations and perceptual learning. We also noticed that several human M/EEG studies found that training induced increase in neural oscillations in other frequency bands [18–20,54,55]. This discrepancy may be due to the different stimuli and tasks that engaged distinctive processing mechanisms in these learning studies.

Alpha oscillations function to gate ongoing sensory information processing [56], rather than simply reflect an idle state of the brain [57]. According to a dominant view about the function of alpha oscillations (i.e., the inhibition hypothesis), alpha oscillations are assumed to suppress the processing of irrelevant sensory information actively, and therefore direct computational neural resources to task-relevant events of higher priority [58]. Specifically, alpha power was correlated with neural excitability negatively [59], and higher alpha power was predictive of decreased visual detection and discrimination performance [60,61]. Since many studies have demonstrated that alpha tACS increases ongoing alpha power [24,30,47,62], the inhibition hypothesis cannot explain our finding here. Notably, alpha oscillations also reflect cortical feedback mechanisms in visual cortex [63–65]. For example, researchers found that neural activity in primary visual area V1 was driven by feedback signals in the alpha band from visual area V4 [63,64]. Recently, several studies proposed that VPL could be, at least partially, modulated by cortical feedback that propagated neural signals from higher to lower areas [66–68]. Under this framework, entrained alpha oscillations by 10 Hz tACS may boost VPL by strengthening cortico-cortical feedback connections, which should be investigated in the future.

Additionally, our findings offer a valuable guide for future clinical intervention to rehabilitate impaired visual functions. In clinical practice, efficacy/effectiveness, efficiency, and persistence are three of the major factors that constrain the application of perceptual enhancement methods or techniques [43]. Here, we found that applying tACS at 10 Hz over the visual cortex can help observers obtain more benefits within a shorter time. What is more, the modulatory effect of occipital 10 Hz tACS on visual performance was able to last for a very long period. Therefore, our training and stimulation protocol can be used as a potential treatment for visual impairment, such as neuro-ophthalmological disorders [69].

CRedit authorship contribution statement

Qing He: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Xin-Yue Yang:** Software, Investigation, Writing – review & editing. **Baoqi Gong:** Investigation. **Keyan Bi:** Investigation. **Fang Fang:** Conceptualization, Supervision, Funding acquisition, Resources, Validation, Data curation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing
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