



# 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 modulatory effects were absent when 10 Hz tACS was delivered to the sensorimotor areas. Moreover, the tACS-induced performance improvement lasted at least two months after the end of training.

**Conclusion:** TACS can facilitate orientation discrimination learning in a frequency- and location-specific manner. Our findings provide strong evidence for a pivotal role of alpha oscillations in boosting VPL and shed new light on the design of effective neuromodulation protocols that can facilitate rehabilitation for patients with neuro-ophthalmological disorders.

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## 1. Introduction

Repetitive visual experience or practice results in a dramatic and long-lasting improvement in perceiving visual contents, which is referred to as visual perceptual learning (VPL) [1]. VPL is usually viewed as a manifestation of experience-dependent neural plasticity in the human brain [2,3], and has been used as a rehabilitation therapy for visually impaired people, such as patients with

amblyopia [4], cortical blindness [5], and macular degeneration [6]. Numerous studies have been conducted to explore the neural substrates of VPL, primarily focusing on the cortical sites of occurrence and manifestation of VPL [7–13].

Neural oscillations, characterized by rhythmic changes in neural activity in a wide range of frequencies, play a critical role in various cognitive functions [14]. Aberrant neural oscillations have been shown to be associated with some neurological and psychiatric disorders [15]. However, to date, the neural oscillatory mechanisms of VPL have been explored by only sparse human magneto-/electroencephalography (M/EEG) studies, and the results of these studies are inconsistent. Neural oscillations in multiple frequency bands were found to be associated with VPL. Alpha power in parietal-occipital areas increased after training on visual tasks, such as visual search [16,17], while training on an object identification

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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,  $21.58 \pm 3.51$  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 =  $1600 \times 1200$  pixels, frame rate = 85 Hz) with a grey background (mean luminance =  $47.59 \text{ cd/m}^2$ ). 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  $1^\circ$  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.

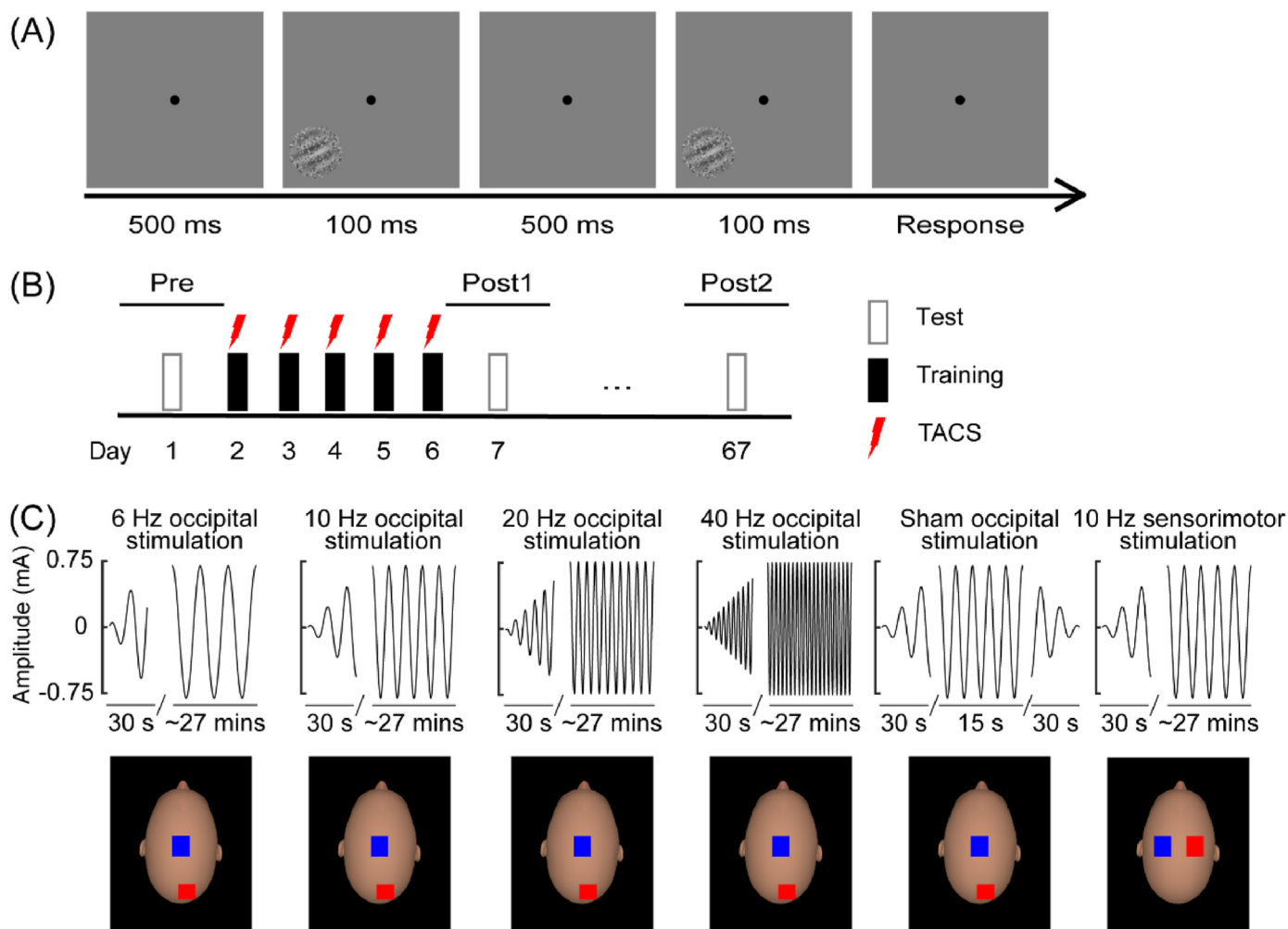
#### 2.1.2. Visual stimulus and task

Oriented Gabor patches (diameter =  $1.25^\circ$ ; spatial frequency =  $3.0 \text{ cycle/}^\circ$ ; Michelson contrast = 0.5; standard deviation of Gaussian envelope =  $0.42^\circ$ ; random spatial phase) were located  $5^\circ$  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  $26^\circ$  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  $\theta$  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 (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  $(pre\text{-}training\ threshold - post\text{-}training\ threshold) / pre\text{-}training\ threshold \times 100\%$ . 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:

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

where  $Th$  is the predicted orientation discrimination threshold,  $t$  is the number of training sessions,  $\lambda$  is the initial threshold,  $\rho$  is the learning rate, and  $\alpha$  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).  $\eta_p^2$  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

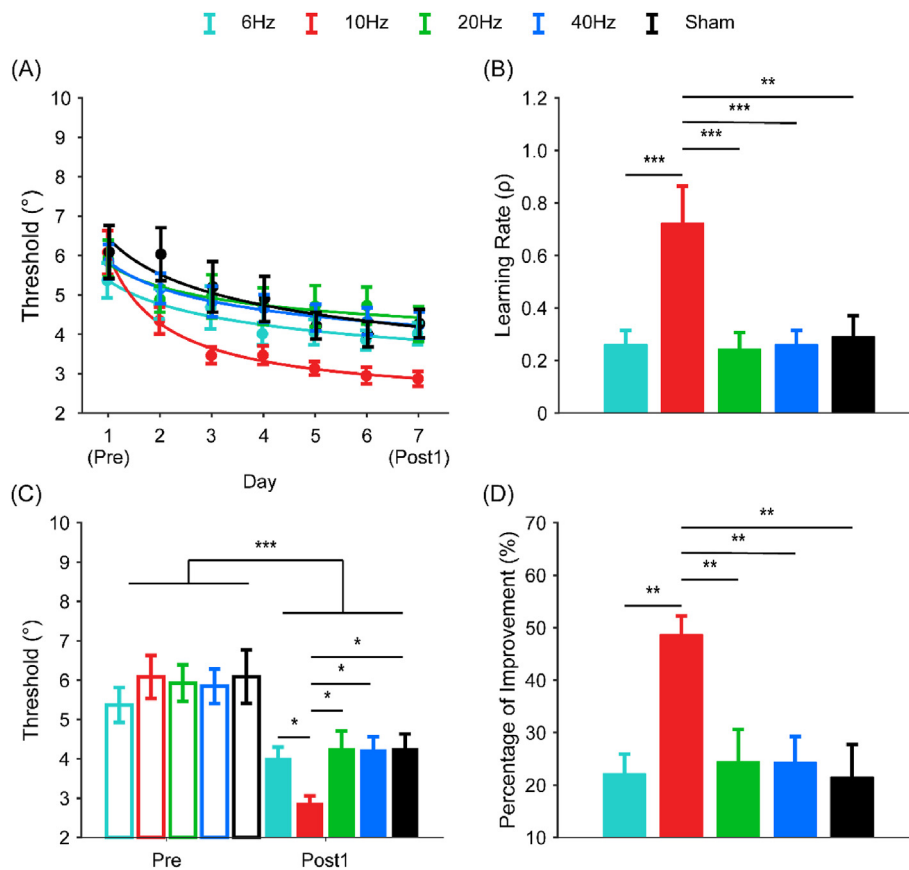
#### 3.1. Occipital tACS modulated orientation discrimination learning in a frequency-specific manner

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  $\rho$ -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 ( $F(3, 77) = 7.55, p < 0.001, \eta_p^2 = 0.23$ ). *Post-hoc* analysis revealed that the percent improvement in the 10 Hz occipital stimulation group was higher than those in the other stimulation groups (10 Hz vs. 6 Hz:  $t(39) = 5.26, p_{adj} < 0.01$ , Cohen's  $d = 1.64$ ; 10 Hz vs. 20 Hz:  $t(39) = 3.51, p_{adj} < 0.01$ , Cohen's  $d = 1.10$ ; 10 Hz vs. 40 Hz:  $t(39) = 4.09, p_{adj} < 0.01$ , Cohen's  $d = 1.28$ ), and the difference among other occipital stimulation groups was not significant (all  $ps > 0.73$ ) (Fig. 2(D)). These results demonstrated that, relative to theta, beta, and gamma frequencies, tACS at alpha frequency enabled subjects to acquire a greater improvement in the learning task.

To examine whether the observed modulatory effects from 10 Hz tACS were due to possible indirect effects (e.g., placebo effect), one more group of subjects received the sham occipital stimulation. Notably, the learning effect in the sham occipital stimulation group is presumably equivalent to the learning effect without electrical stimulation. Compared with the sham occipital stimulation group, only the 10 Hz occipital stimulation group showed a faster learning rate ( $t(39) = 2.65, p_{adj} < 0.01$ , Cohen's  $d = 0.83$ ), a lower threshold at Post1 ( $t(39) = -3.52, p_{adj} < 0.05$ , Cohen's  $d = 1.10$ ), and a greater improvement ( $t(39) = 3.92, p_{adj} < 0.01$ , Cohen's  $d = 1.22$ ), and these beneficial effects were absent in the 6, 20, and 40 Hz occipital stimulation groups (all  $ps > 0.58$ ).

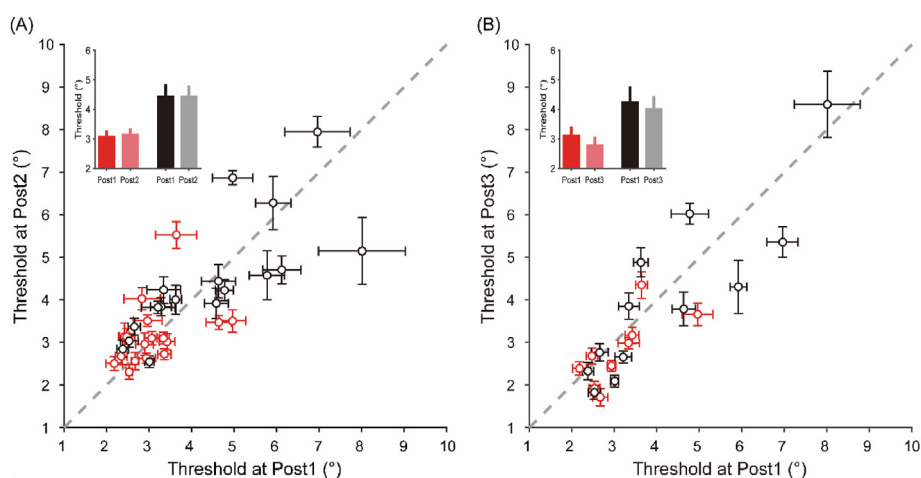
To examine whether the facilitatory effect on the orientation discrimination learning by 10 Hz tACS is long-lasting, most subjects in the 10 Hz occipital stimulation group ( $N = 17$ ) and the sham occipital stimulation group ( $N = 17$ ) were retested at least two months after Post1, i.e., Post2. For subjects in the 10 Hz occipital stimulation group, their thresholds at Post2 were not significantly different from those at Post1 ( $t(16) = -0.37, p = 0.72$ ). Similarly, there was no significant difference in threshold between Post1 and Post2 in the sham occipital stimulation group ( $t(16) = -0.005, p = 0.99$ ) (Fig. 3(A)). Additionally, some subjects ( $N = 9$  and  $N = 12$  in the 10 Hz occipital stimulation group and the sham occipital stimulation group, respectively) were retested at least 14 months after training, i.e., Post3. There was no significant difference in threshold between Post1 and Post3 (10 Hz:  $t(8) = 1.51, p = 0.17$ ;

sham:  $t(11) = 0.76, p = 0.47$ ) (Fig. 3(B)). Therefore, the modulatory effect of 10 Hz tACS on the orientation discrimination learning was remarkably long-lasting.

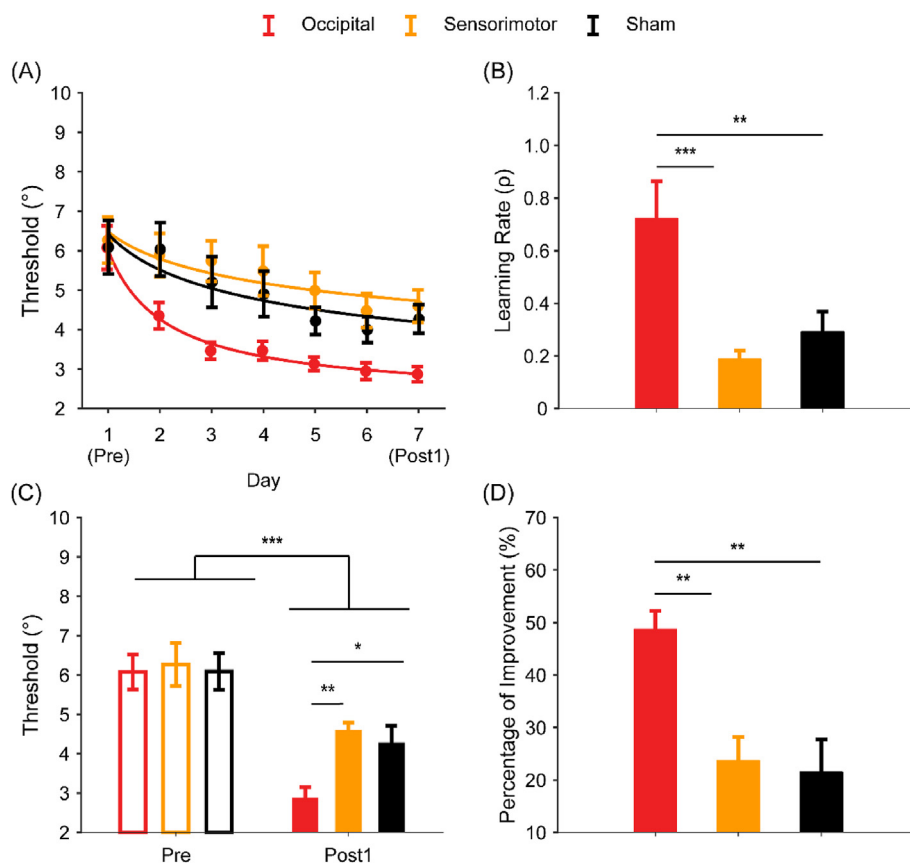
### 3.2. 10 Hz tACS modulated orientation discrimination learning in a location-specific manner

To explore whether 10 Hz tACS could modulate the orientation discrimination learning in a location-specific manner, one more group of subjects (i.e., the 10 Hz sensorimotor stimulation group) were trained on the orientation discrimination task while their bilateral sensorimotor regions were stimulated by 10 Hz tACS. For the three groups of subjects (the 10 Hz occipital stimulation group, the 10 Hz sensorimotor stimulation group, and the sham occipital stimulation group), their thresholds at Pre were roughly the same ( $F(2, 58) = 0.03, p = 0.97$ ). Extensive training reduced subjects' orientation discrimination thresholds gradually for all groups (Fig. 4(A)). Again, there were significant differences in learning rate among the three groups ( $F(2, 58) = 8.83, p < 0.001, \eta_p^2 = 0.23$ ). The learning rate of the 10 Hz occipital stimulation group was greater than that of the 10 Hz sensorimotor stimulation group ( $t(39) = 3.63, p_{adj} < 0.001$ , Cohen's  $d = 1.13$ ), but the difference in learning rate between the 10 Hz sensorimotor stimulation group and the sham occipital stimulation group was not significant ( $t(38) = -0.20, p = 0.84$ ) (Fig. 4(B)). These results on learning rate demonstrated that the orientation discrimination learning efficiency was not modulated by 10 Hz tACS applied at sensorimotor areas.

Regarding orientation discrimination thresholds, a  $2 \times 3$  mixed-design ANOVA with a within-subjects factor of *Test* (Pre and Post1) and a between-subjects factor of *Group* (occipital, sensorimotor, and sham) showed that the main effect of *Test* ( $F(1, 58) = 75.31, p < 0.001, \eta_p^2 = 0.57$ ) and the interaction between *Test* and *Group* ( $F(2, 58) = 3.69, p = 0.03, \eta_p^2 = 0.11$ ) were significant, but the main effect of *Group* ( $F(2, 58) = 1.33, p = 0.27$ ) was not. Paired *t*-test showed that the thresholds at Post1 were lower than those at Pre for all the three groups (all  $ts \leq -3.61$ , all  $p_{adj}s \leq 0.002$ , and all Cohen's  $ds \geq 0.74$ ). A simple main effect analysis revealed that, at Post1, the threshold in the 10 Hz occipital stimulation group was lower than that in the 10 Hz sensorimotor stimulation group ( $t(39) = -3.88, p_{adj} < 0.01$ , Cohen's  $d = 1.21$ ), but the threshold



**Fig. 3.** Retention of the learning effect. (A) Retest results two months after training for subjects in the 10 Hz occipital stimulation group and the sham occipital stimulation group. (B) Retest results 14 months after training for part of the subject cohort. Each red dot and black dot represent a single subject in the 10 Hz occipital stimulation group and the sham occipital stimulation group, respectively. The insets depict the mean thresholds for the 10 Hz occipital stimulation group (red and pink bars) and the sham occipital stimulation group (black and grey bars). Error bars denote 1 SEM across QUEST staircases or subjects. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)



**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. 4(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 financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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#### Appendix ASupplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2022.02.018>.

#### References

- [1] Watanabe T, Sasaki Y. Perceptual learning: toward a comprehensive theory. *Annu Rev Psychol* 2015;66:197–221. <https://doi.org/10.1146/annurev-psych-010814-015214>.
- [2] Lu J, Luo L, Wang Q, Fang F, Chen N. Cue-triggered activity replay in human early visual cortex. *Sci China Life Sci* 2021;64(1):144–51. <https://doi.org/10.1007/s11427-020-1726-5>.
- [3] Yang XY, He Q, Fang F. Transcranial direct current stimulation over the visual cortex facilitates awake consolidation of visual perceptual learning. *Brain Stimul* 2022;15(2):380–2. <https://doi.org/10.1016/j.brs.2022.01.019>.
- [4] Polat U, Ma-Naim T, Belkin M, Sagi D. Improving vision in adult amblyopia by perceptual learning. *Proc Natl Acad Sci U S A* 2004;101(17):6692–7. <https://doi.org/10.1073/pnas.0401200101>.
- [5] Barbot A, Das A, Melnick MD, Cavanaugh MR, Merriam EP, Heeger DJ, Huxlin KR. Spared perilesional V1 activity underlies training-induced recovery of luminance detection sensitivity in cortically-blind patients. *Nat Commun* 2021;12(1):6102. <https://doi.org/10.1038/s41467-021-26345-1>.
- [6] Maniglia M, Pavan A, Sato G, Contemori G, Montemurro S, Battaglini L, Casco C. Perceptual learning leads to long lasting visual improvement in patients with central vision loss. *Restor Neurol Neurosci* 2016;34(5):697–720. <https://doi.org/10.3233/RNN-150575>.
- [7] Schwartz S, Maquet P, Frith C. Neural correlates of perceptual learning: a functional MRI study of visual texture discrimination. *Proc Natl Acad Sci U S A* 2002;99(26):17137–42. <https://doi.org/10.1073/pnas.242414599>.
- [8] Law C-T, Gold JI. Neural correlates of perceptual learning in a sensory-motor, but not a sensory, cortical area. *Nat Neurosci* 2008;11(4):505–13.
- [9] Yotsumoto Y, Watanabe T, Sasaki Y. Different dynamics of performance and brain activation in the time course of perceptual learning. *Neuron* 2008;57(6):827–33. <https://doi.org/10.1016/j.neuron.2008.02.034>.
- [10] Jehee JF, Ling S, Swisher JD, van Bergen RS, Tong F. Perceptual learning selectively refines orientation representations in early visual cortex. *J Neurosci* 2012;32(47):16747–16753a. <https://doi.org/10.1523/JNEUROSCI.6112-11.2012>.
- [11] Bi T, Chen J, Zhou T, He Y, Fang F. Function and structure of human left fusiform cortex are closely associated with perceptual learning of faces. *Curr Biol* 2014;24(2):222–7. <https://doi.org/10.1016/j.cub.2013.12.028>.
- [12] Chen N, Bi T, Zhou T, Li S, Liu Z, Fang F. Sharpened cortical tuning and enhanced cortico-cortical communication contribute to the long-term neural mechanisms of visual motion perceptual learning. *Neuroimage* 2015;115:17–29. <https://doi.org/10.1016/j.neuroimage.2015.04.041>.
- [13] Chen N, Cai P, Zhou T, Thompson B, Fang F. Perceptual learning modifies the functional specializations of visual cortical areas. *Proc Natl Acad Sci U S A* 2016;113(20):5724–9. <https://doi.org/10.1073/pnas.1524160113>.
- [14] Thut G, Miniussi C, Gross J. The functional importance of rhythmic activity in the brain. *Curr Biol* 2012;22(16):R658–63. <https://doi.org/10.1016/j.cub.2012.06.061>.
- [15] Schnitzler A, Gross J. Normal and pathological oscillatory communication in the brain. *Nat Rev Neurosci* 2005;6(4):285–96. <https://doi.org/10.1038/nrn1650>.
- [16] Bays BC, Visscher KM, Le Dantec CC, Seitz AR. Alpha-band EEG activity in perceptual learning. *J Vis* 2015;15(10):1–12. <https://doi.org/10.1167/15.10.7>.
- [17] van den Berg B, Appelbaum LG, Clark K, Lorist MM, Woldorff MG. Visual search performance is predicted by both prestimulus and poststimulus electrical brain activity. *Sci Rep* 2016;6(1):37718. <https://doi.org/10.1038/srep37718>.
- [18] Gruber T, Muller MM, Keil A. Modulation of induced gamma band responses in a perceptual learning task in the human EEG. *J Cognit Neurosci* 2002;14(5):732–44. <https://doi.org/10.1162/08989290260138636>.
- [19] Tamaki M, Berard AV, Barnes-Diana T, Siegel J, Watanabe T, Sasaki Y. Reward does not facilitate visual perceptual learning until sleep occurs. *Proc Natl Acad Sci U S A* 2020;117(2):959–68. <https://doi.org/10.1073/pnas.1913079117>.
- [20] La Rocca D, Ciuciu P, Engemann DA, van Wassenhove V. Emergence of beta and gamma networks following multisensory training. *Neuroimage* 2020;206:116313. <https://doi.org/10.1016/j.neuroimage.2019.116313>.
- [21] Voroslakos M, Takeuchi Y, Brinyiczki K, Zombori T, Oliva A, Fernandez-Ruiz A, et al. Direct effects of transcranial electric stimulation on brain circuits in rats



- and humans. *Nat Commun* 2018;9(1):483. <https://doi.org/10.1038/s41467-018-02928-3>.
- [22] Liu A, Voroslakos M, Kronberg G, Henin S, Krause MR, Huang Y, et al. Immediate neurophysiological effects of transcranial electrical stimulation. *Nat Commun* 2018;9(1):5092. <https://doi.org/10.1038/s41467-018-07233-7>.
- [23] Fiene M, Radecke JO, Misselhorn J, Sengelmann M, Herrmann CS, Schneider TR, et al. tACS phase-specifically biases brightness perception of flickering light. *Brain Stimul* 2022;15(1):244–53. <https://doi.org/10.1016/j.brs.2022.01.001>.
- [24] Vossen A, Gross J, Thut G. Alpha power increase after transcranial alternating current stimulation at alpha frequency ( $\alpha$ -tACS) reflects plastic changes rather than entrainment. *Brain Stimul* 2015;8(3):499–508. <https://doi.org/10.1016/j.brs.2014.12.004>.
- [25] Krause MR, Vieira PG, Csorba BA, Pilly PK, Pack CC. Transcranial alternating current stimulation entrains single-neuron activity in the primate brain. *Proc Natl Acad Sci U S A* 2019;116(12):5747–55. <https://doi.org/10.1073/pnas.1815958116>.
- [26] Cabral-Calderin Y, Wilke M. Probing the link between perception and oscillations: lessons from transcranial alternating current stimulation. *Neuroscientist* 2019;26(1):57–73. <https://doi.org/10.1177/1073858419828646>.
- [27] Johnson L, Alekseichuk I, Krieg J, Doyle A, Yu Y, Vitek J, et al. Dose-dependent effects of transcranial alternating current stimulation on spike timing in awake nonhuman primates. *Sci Adv* 2020;6(36):eaa22747. <https://doi.org/10.1126/sciadv.aaz2747>.
- [28] Reinhart RMG, Nguyen JA. Working memory revived in older adults by synchronizing rhythmic brain circuits. *Nat Neurosci* 2019;22(5):820–7. <https://doi.org/10.1038/s41593-019-0371-x>.
- [29] Nakazono H, Ogata K, Takeda A, Yamada E, Kimura T, Tobimatsu S. Transcranial alternating current stimulation of  $\alpha$  but not  $\beta$  frequency sharpens multiple visual functions. *Brain Stimul* 2020;13(2):343–52. <https://doi.org/10.1016/j.brs.2019.10.022>.
- [30] Helfrich RF, Schneider TR, Rach S, Trautmann-Lengsfeld SA, Engel AK, Herrmann CS. Entrainment of brain oscillations by transcranial alternating current stimulation. *Curr Biol* 2014;24(3):333–9. <https://doi.org/10.1016/j.cub.2013.12.041>.
- [31] Zhang Y, Zhang Y, Cai P, Luo H, Fang F. The causal role of alpha-oscillations in feature binding. *Proc Natl Acad Sci U S A* 2019;116(34):17023–8. <https://doi.org/10.1073/pnas.1904160116>.
- [32] Fertonani A, Pirulli C, Miniussi C. Random noise stimulation improves neuroplasticity in perceptual learning. *J Neurosci* 2011;31(43):15416–23. <https://doi.org/10.1523/JNEUROSCI.2002-11.2011>.
- [33] He Q, Lin BR, Zhao J, Shi YZ, Yan FF, Huang CB. No effects of anodal transcranial direct current stimulation on contrast sensitivity function. *Restor Neurol Neurosci* 2019;37(2):109–18. <https://doi.org/10.3233/RNN-180881>.
- [34] Brainard DH. The psychophysics toolbox. *Spatial Vis* 1997;10(4):433–6. <https://doi.org/10.1163/156856897X00357>.
- [35] Watson AB, Pelli DG. QUEST: a Bayesian adaptive psychometric method. *Percept Psychophys* 1983;33(2):113–20. <https://doi.org/10.3758/BF03202828>.
- [36] de Graaf TA, Thomson A, Janssens SEW, van Bree S, Ten Oever S, Sack AT. Does alpha phase modulate visual target detection? Three experiments with tACS-phase-based stimulus presentation. *Eur J Neurosci* 2020;51(11):2299–313. <https://doi.org/10.1111/ejn.14677>.
- [37] Huang Y, Datta A, Bikson M, Parra LC. Realistic volumetric-approach to simulate transcranial electric stimulation-ROAST—a fully automated open-source pipeline. *J Neural Eng* 2019;16(5):056006. <https://doi.org/10.1088/1741-2552/ab208d>.
- [38] Cappelletti M, Gessaroli E, Hithersay R, Mitolo M, Didino D, Kanai R, et al. Transfer of cognitive training across magnitude dimensions achieved with concurrent brain stimulation of the parietal lobe. *J Neurosci* 2013;33(37):14899–907. <https://doi.org/10.1523/JNEUROSCI.1692-13.2013>.
- [39] R Core Team. R: a language and environment for statistical computing (version 4.0.3). Vienna, Austria: R Foundation for Statistical Computing; 2020. <http://www.R-project.org/>.
- [40] Campana G, Camilleri R, Pavan A, Veronese A, Lo Giudice G. Improving visual functions in adult amblyopia with combined perceptual training and transcranial random noise stimulation (tRNS): a pilot study. *Front Psychol* 2014;5:1402. <https://doi.org/10.3389/fpsyg.2014.01402>.
- [41] Pirulli C, Fertonani A, Miniussi C. The role of timing in the induction of neuro-modulation in perceptual learning by transcranial electric stimulation. *Brain Stimul* 2013;6(4):683–9. <https://doi.org/10.1016/j.brs.2012.12.005>.
- [42] Frangou P, Correia M, Kourtzi Z. GABA, not BOLD, reveals dissociable learning-dependent plasticity mechanisms in the human brain. *Elife* 2018;7:e35854. <https://doi.org/10.7554/eLife.35854>.
- [43] Herpich F, Melnick MD, Agosta S, Huxlin KR, Tadin D, Battelli L. Boosting learning efficacy with noninvasive brain stimulation in intact and brain-damaged humans. *J Neurosci* 2019;39(28):5551–61. <https://doi.org/10.1523/JNEUROSCI.3248-18.2019>.
- [44] Camilleri R, Pavan A, Ghin F, Battaglini L, Campana G. Improvement of uncorrected visual acuity and contrast sensitivity with perceptual learning and transcranial random noise stimulation in individuals with mild myopia. *Front Psychol* 2014;5:1234. <https://doi.org/10.3389/fpsyg.2014.01234>.
- [45] Louvriot S, Tyvaert L, Maillard LG, Colnat-Coulbois S, Dmochowski J, Koessler L. Transcranial Electrical Stimulation generates electric fields in deep human brain structures. *Brain Stimul* 2021;15(1):1–12. <https://doi.org/10.1016/j.brs.2021.11.001>.
- [46] Huang WA, Stitt IM, Negahbani E, Passey DJ, Ahn S, Davey M, et al. Transcranial alternating current stimulation entrains alpha oscillations by preferential phase synchronization of fast-spiking cortical neurons to stimulation waveform. *Nat Commun* 2021;12(1):3151. <https://doi.org/10.1038/s41467-021-23021-2>.
- [47] Zaehle T, Rach S, Herrmann CS. Transcranial alternating current stimulation enhances individual alpha activity in human EEG. *PLoS One* 2010;5(11):e13766. <https://doi.org/10.1371/journal.pone.0013766>.
- [48] Asamoah B, Khatoun A, Mc Laughlin M. tACS motor system effects can be caused by transcutaneous stimulation of peripheral nerves. *Nat Commun* 2019;10(1):266. <https://doi.org/10.1038/s41467-018-08183-w>.
- [49] Turi Z, Ambrus GG, Janacek K, Emmert K, Hahn L, Paulus W, Antal A. Both the cutaneous sensation and phosphene perception are modulated in a frequency-specific manner during transcranial alternating current stimulation. *Restor Neurol Neurosci* 2013;31(3):275–85. <https://doi.org/10.3233/RNN-120297>.
- [50] Nikolaev AR, Gepshtein S, van Leeuwen C. Intermittent regime of brain activity at the early, bias-guided stage of perceptual learning. *J Vis* 2016;16(14). <https://doi.org/10.1167/16.14.11>.
- [51] Muller-Gass A, Duncan M, Campbell K. Brain states predict individual differences in perceptual learning. *Pers Indiv Differ* 2017;118:29–38. <https://doi.org/10.1016/j.paid.2017.03.066>.
- [52] Brickwedde M, Kruger MC, Dinse HR. Somatosensory alpha oscillations gate perceptual learning efficiency. *Nat Commun* 2019;10(1):263. <https://doi.org/10.1038/s41467-018-08012-0>.
- [53] Freyer F, Becker R, Dinse HR, Ritter P. State-dependent perceptual learning. *J Neurosci* 2013;33(7):2900–7. <https://doi.org/10.1523/JNEUROSCI.4039-12.2013>.
- [54] Gruber T, Keil A, Muller MM. Modulation of induced gamma band responses and phase synchrony in a paired associate learning task in the human EEG. *Neurosci Lett* 2001;316(1):29–32. [https://doi.org/10.1016/S0304-3940\(01\)02361-8](https://doi.org/10.1016/S0304-3940(01)02361-8).
- [55] Theves S, Chan JS, Naumer MJ, Kaiser J. Improving audio-visual temporal perception through training enhances beta-band activity. *Neuroimage* 2020;206:116312. <https://doi.org/10.1016/j.neuroimage.2019.116312>.
- [56] Jensen O, Mazaheri A. Shaping functional architecture by oscillatory alpha activity: gating by inhibition. *Front Hum Neurosci* 2010;4(186):186. <https://doi.org/10.3389/fnhum.2010.00186>.
- [57] Clayton MS, Yeung N, Cohen Kadosh R. The many characters of visual alpha oscillations. *Eur J Neurosci* 2018;48(7):2498–508. <https://doi.org/10.1111/ejn.13747>.
- [58] Klimesch W, Sauseng P, Hanslmayr S. EEG alpha oscillations: the inhibition-timing hypothesis. *Brain Res Rev* 2007;53(1):63–88. <https://doi.org/10.1016/j.brainresrev.2006.06.003>.
- [59] Lange J, Oostenveld R, Fries P. Reduced occipital alpha power indexes enhanced excitability rather than improved visual perception. *J Neurosci* 2013;33(7):3212–20. <https://doi.org/10.1523/JNEUROSCI.3755-12.2013>.
- [60] Ergenoglu T, Demiralp T, Bayraktaroglu Z, Ergen M, Beydagi H, Uresin Y. Alpha rhythm of the EEG modulates visual detection performance in humans. *Brain Res Cogn Brain Res* 2004;20(3):376–83. <https://doi.org/10.1016/j.cogbrainres.2004.03.009>.
- [61] van Dijk H, Schoffelen JM, Oostenveld R, Jensen O. Prestimulus oscillatory activity in the alpha band predicts visual discrimination ability. *J Neurosci* 2008;28(8):1816–23. <https://doi.org/10.1523/JNEUROSCI.1853-07.2008>.
- [62] Kasten FH, Duecker K, Maack MC, Meiser A, Herrmann CS. Integrating electric field modeling and neuroimaging to explain inter-individual variability of tACS effects. *Nat Commun* 2019;10(1):5427. <https://doi.org/10.1038/s41467-019-13417-6>.
- [63] van Kerkoerle T, Self MW, Dagnino B, Gariel-Mathis MA, Poort J, van der Togt C, Roelfsema PR. Alpha and gamma oscillations characterize feedback and feedforward processing in monkey visual cortex. *Proc Natl Acad Sci U S A* 2014;111(40):14332–41. <https://doi.org/10.1073/pnas.1402773111>.
- [64] Michalareas G, Vezoli J, van Pelt S, Schoffelen JM, Kennedy H, Fries P. Alpha-beta and gamma rhythms subserve feedback and feedforward influences among human visual cortical areas. *Neuron* 2016;89(2):384–97. <https://doi.org/10.1016/j.neuron.2015.12.018>.
- [65] Mejias JF, Murray JD, Kennedy H, Wang XJ. Feedforward and feedback frequency-dependent interactions in a large-scale laminar network of the primate cortex. *Sci Adv* 2016;2(11):e1601335. <https://doi.org/10.1126/sciadv.1601335>.
- [66] Mukai I, Kim D, Fukunaga M, Japee S, Marrett S, Ungerleider LG. Activations in visual and attention-related areas predict and correlate with the degree of perceptual learning. *J Neurosci* 2007;27(42):11401–11. <https://doi.org/10.1523/JNEUROSCI.3002-07.2007>.
- [67] Crist RE, Li W, Gilbert CD. Learning to see: experience and attention in primary visual cortex. *Nat Neurosci* 2001;4(5):519–25. <https://doi.org/10.1038/87470>.
- [68] Schafer R, Vasilaki E, Senn W. Perceptual learning via modification of cortical top-down signals. *PLoS Comput Biol* 2007;3(8):e165. <https://doi.org/10.1371/journal.pcbi.0030165>.
- [69] Huang X, Xia H, Zhang Q, Blakemore C, Nan Y, Wang W, et al. New treatment for amblyopia based on rules of synaptic plasticity: a randomized clinical trial. *Sci China Life Sci* 2022. <https://doi.org/10.1007/s11427-021-2030-6>.