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Low Vision Rehabilitation

Glaucoma Rehabilitation Using ElectricAI Transcranial Stimulation (GREAT)–Optimizing Stimulation Protocol for Vision Enhancement Using an RCT

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Purpose: We compared the effect of three different transcranial electrical stimulation (tES) protocols delivered to the occipital lobe on peripheral vision in patients with glaucoma.

Methods: A double-masked, placebo-controlled study was conducted with 35 patients with glaucoma. We compared three different tES protocols: anodal transcranial direct current stimulation (a-tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS) against sham stimulation. Each patient attended four stimulation sessions (a-tDCS, tACS, tRNS, and sham) in a random order with at least 48 hours between visits. Stimulation involved placing an anodal electrode over the occipital lobe (Oz) and cathodal electrode on the cheek for 20 minutes. High-resolution perimetry (HRP) and multifocal visual evoked potential (mfVEP) measurements were made before and immediately after stimulation. Changes in HRP detection accuracy/reaction time and mfVEP signal-to-noise ratio (SNR)/latency were analyzed using linear mixed models.

Results: Compared to sham, HRP detection accuracy was significantly improved after a-tDCS in both the central 20-degree ($b = 0.032$, $P = 0.018$) and peripheral analysis ($b = 0.051$, $P = 0.002$). Additionally, mfVEP SNR was significantly increased ($b = 0.016$, $P = 0.017$) and the latency was shortened ($b = -1.405$, $P = 0.04$) by the a-tDCS in the central 20-degree analysis. In the peripheral analysis, there was a trend toward an enhancement of SNR after a-tDCS stimulation ($b = 0.014$, $P = 0.052$), but it did not reach statistical significance; latency was increased after tACS ($b = 1.623$, $P = 0.041$). No significant effects were found in comparison to other active tES protocols.

Conclusions: A single session of a-tDCS enhances perceptual and electrophysiologic measures of vision in patients with glaucoma. However, the small magnitude of changes observed in HRP (3.2% for accuracy in central and 5.1% in peripheral) did not exceed previous test variability and may not be clinically meaningful.

Translational Relevance: a-tDCS holds promise as a potential treatment for enhancing visual function. However, future studies are needed to evaluate the long-term effects and clinical relevance of this intervention using validated measures of perimetric changes in the visual field.

Introduction

Glaucoma is a complex neurodegenerative disease. The primary symptom is vision loss caused by degeneration of retinal ganglion cells. However, the neurodegenerative effects of glaucoma extend to the thalamus and cortex.[1,2] Despite advancements in glaucoma treatment, a portion (3%–17%) of patients may still experience disease progression.[3]

Noninvasive transcranial electrical stimulation (tES) involves the delivery of a mild electrical current to targeted brain areas via electrodes placed on the head. tES modulates neuronal firing and has been used extensively to study the neural mechanisms of cognition and explored as a rehabilitation tool for a range of neurologic conditions.[4–6] tES can be delivered as a direct current (transcranial direct current stimulation [tDCS]), alternating current with a fixed sinusoidal waveform (alternating current stimulation [tACS]), or a randomly modulated waveform (transcranial random noise stimulation [tRNS]). tDCS is referred to as anodal (a-tDCS) or cathodal (c-tDCS) depending on which electrode is positioned above the targeted cortical area. A recent meta-analysis indicated beneficial and consistent effects of occipital lobe a-tDCS on normal vision (refer to Bello et al.[7] for a recent systematic review).[7]

Most important, there is accumulating evidence that tES has therapeutic and rehabilitative benefits in vision rehabilitation.[8,9] Previous human neuroimaging studies have suggested that tES may modulate the excitatory–inhibitory balance within the stimulated area by altering the local concentration of neurotransmitters. Changes in regional connectivity may also occur. Reported effects include a decrease in γ-aminobutyric acid (GABA) concentrations,[10] an increase in glutamate and glutamine (Glx) concentrations,[11] and altered functional connectivity in the targeted area.[12,13] Despite the application of various tES protocols to a wide range of visual conditions, such as age-related macular degeneration (AMD),[14,15] retinitis pigmentosa,[16] amblyopia,[9,17] and hemianopia,[8,18] no study has systematically compared the effectiveness and underlying mechanisms of different tES protocols for improving visual functions in visually impaired patients. Here, we used tES to enhance visual cortex activity in patients with glaucoma to study if—and to what extent—different tES protocols (a-tDCS versus tACS versus tRNS against sham) can enhance visual field function and obtain insight into the possible role of known brain degenerative events in glaucomatous visual field dysfunction.

Methods

Standard Protocol Approvals, Registration, and Patient Consent

All procedures adhered to the principles of the Declaration of Helsinki, and the study protocol was approved by The Hong Kong Polytechnic University Research Ethics Boards and preregistered at ClinicalTrials.gov (ID: NCT04846140). All patients provided written consent before commencing the experiment. The recruitment flowchart can be seen in Figure 1.

Patients and Study Design

A within-patient, randomized, double-masked, and sham-controlled design was employed. Patients were recruited based on the following inclusion criteria: (a) age range from 18 to 80 years, (b) diagnosis of primary open-angle or normal-tension glaucoma with relative scotoma defined as a Humphrey field analyzer (HFA) threshold perimetry loss (mean deviation [MD] of −6 dB or lower) within the central 30 degrees of the visual field for at least one eye, (c) best-corrected distance visual acuity of 6/12 or better (equivalent to 0.3 logarithm of the minimum angle of resolution acuity or better), (d) self-reported stable vision in the past 3 months, and (e) intact cognitive function with a score of 22 or above in the Montreal Cognitive Assessment–Hong Kong version. Exclusion criteria were ocular diseases other than glaucoma (e.g., age-related macular degeneration, moderate to severe cataract), severe hearing impairment, severe medical problems or self-reported neurologic or cognitive disorders, and medications for any neurologic or psychiatric conditions that might interfere with motor control.

Best-corrected distance visual acuity was measured with an early treatment of diabetic retinopathy study (ETDRS) chart and the visual field was examined with an HFA (30-2 and 10-2 SITA-Standard) for each eye. The eye with the worse visual field MD for the 30-2 visual field was chosen as the test eye. Each patient attended four different stimulation sessions (active a-tDCS, active tRNS, active tACS, and sham) in a random order with at least 48 hours between visits (mean 8.45 days, range from 2 to 89 days due to the COVID-19 lockdown). Behavioral and then electrophysiologic tests were conducted before and after each stimulation. Each visit comprised a pretest, stimulation, and posttest and typically lasted for approximately 3 hours.

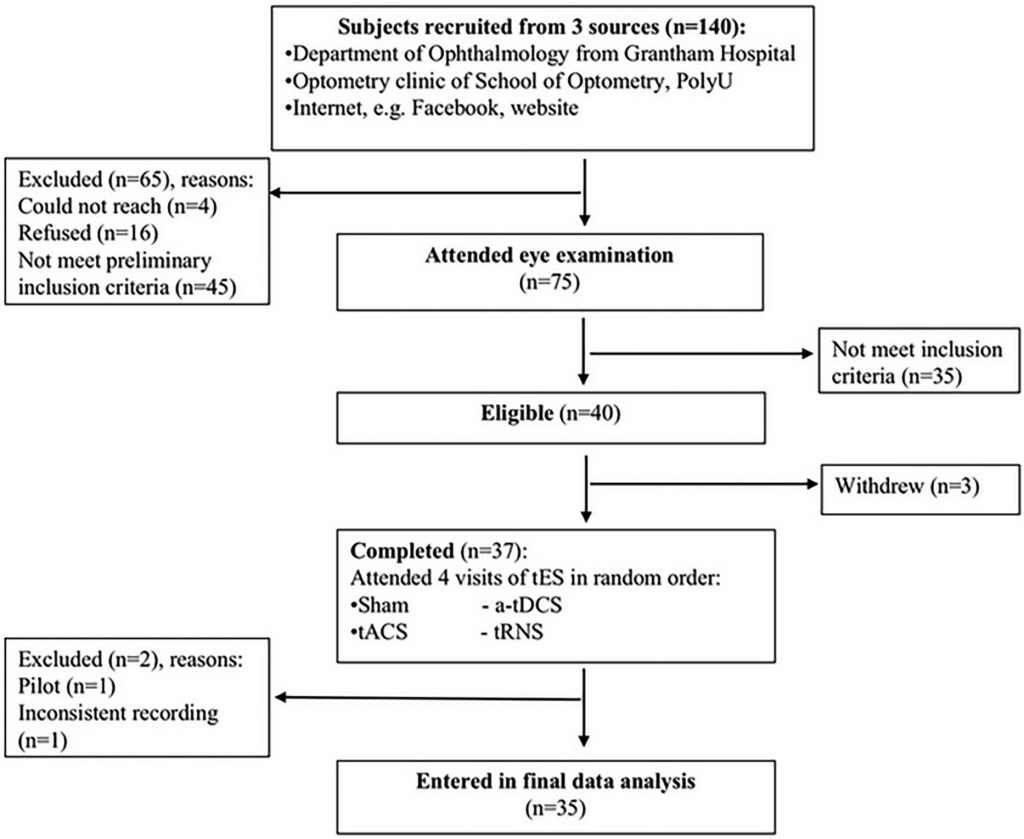

Figure 1. Recruitment flowchart.

Noninvasive Transcranial Electrical Stimulation

Stimulation was administered using a Nurostym tES device (Neuro Device Group SA, Warsaw, Poland) and followed a well-established protocol.[19] Stimulation was delivered by two 5-cm × 5-cm rubber electrodes placed inside saline-soaked sponges. The current intensity for each stimulation was set to 2 mA based on effectiveness and safety reported in previous studies.[20,21] Patients received active a-tDCS, tACS (10 Hz), tRNS (high frequency: 100–640 Hz), or sham a-tDCS for 20 minutes with a 20-second ramp up and ramp down (to mimic the sensation of a real stimulation) during each visit. The anodal electrode was positioned at Oz (visual cortex), while the cathodal electrode was placed on the left cheek. Both the patients and the experimenter were masked to the type of stimulation with the assistance of an independent researcher. This researcher helped to create a stimulation sequence table and set up the tES program. The experimenters administering the stimulation were unaware of the actual stimulation types but only knew the assigned sequence numbers. The real relationship between the sequence order and the stimulation types was revealed only after the last session of data collection for the last patient. After each stimulation, patients were asked to record their subjective sensation during the stimulation using a 5-point scale questionnaire (1 indicates no sensation at all, 5 indicates a very strong sensation). These experiences encompassed sensations such as headache, itching, pain, and others. Furthermore, patients were asked to indicate whether they were able to determine if the stimulation received was real or sham.

Outcome Measures

Behavioral Testing

The behavioral measurement was a visual field test using high-resolution perimetry (HRP), which is a computer-based perimetry (±27° each horizontal and vertical direction).[22] HRP was chosen as the outcome measure due to its high resolution (3-degree gap) and use in previous studies.[23,24] Furthermore, the flexibility in raw data extraction from HRP offers an advantage in identifying potential defect areas in the glaucoma eyes and in detecting subtle localized visual field defects with high sensitivity that can be targeted with perceptual learning interventions. The

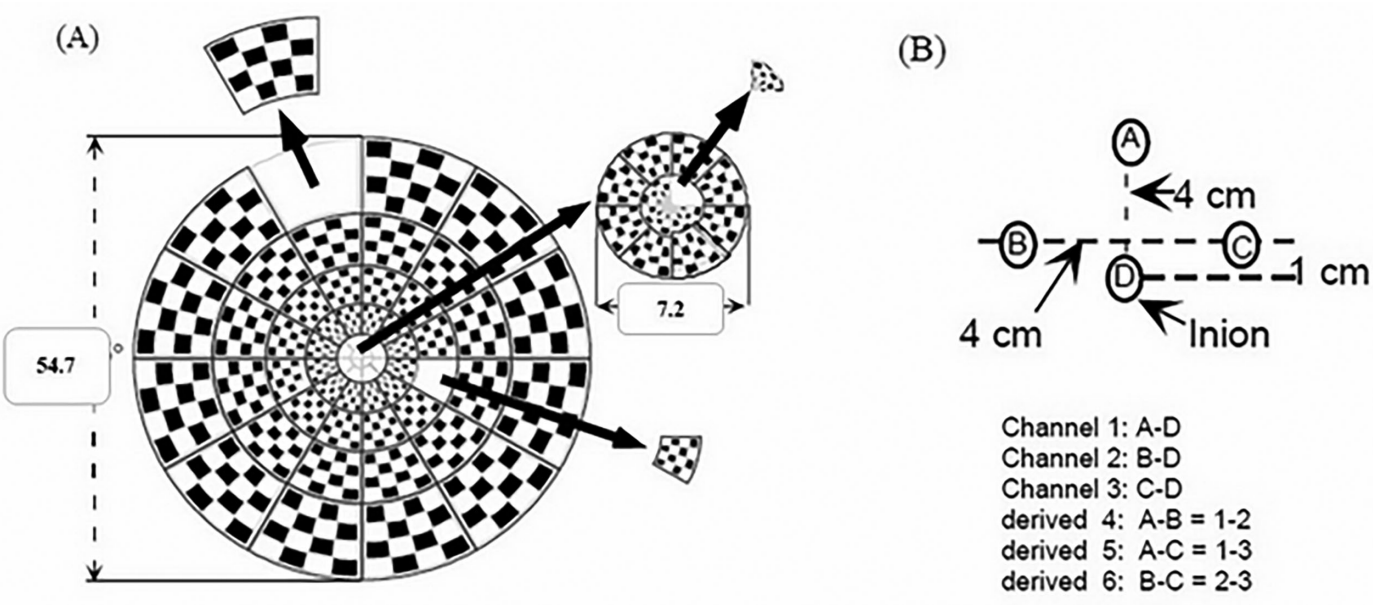

Figure 2. (**A**) The dartboard mfVEP stimulus with 60 scaled sectors, a standard option within the VERIS software. (**B**) mfVEP electrode placement, adapted from Hood et al.[25] (**A:** 5 cm vertically above inion; **B, C:** 4 cm lateral to the midline and 1 cm above inion; **D:** inion).

current HRP task was standardized across participants. Suprathreshold stimuli (a white dot extending to 0.25 degrees) were presented for 200 ms in a random order at 360 different positions to the test eye (i.e., the eye with larger field loss) and lasted about 30 minutes. Participants were instructed to press a button once they detected a white dot on the screen while fixating at the central fixation target. If a white dot appeared in an area with a visual field defect, the participant would not see it and not respond. HRP detection accuracy (ACC) was the percentage of responses for all locations, and the reaction time (RT) was the response time for the responded locations. The lower the ACC, the more severely damaged the participants' visual field. During the HRP test, fixation was monitored by using an infrared eye tracker (Eyelink Portable Duo; SR Research, Ontario, Canada). If patient's eye deviated away from the center or blinked before the trial commenced, that trial was considered invalid and was repeated later. Besides, a color fixation task was also used to monitor the fixation, where patients were instructed to press a button when the color of central fixation was changed. During the HRP test, a research assistant accompanied the patients to ensure compliance with instructions, and the HRP test always preceded the multifocal visual evoked potential (mfVEP) test. The effect of stimulation on ACC and RT was assessed by examining the post- to prestimulation changes at each visit (e.g., $\triangle$RT = PostRT – PreRT). Patients performed the HRP test three times during the eligibility visit to become familiar with the test. They also completed pre- and posttests at each stimulation visit.

Electroencephalography

An mfVEP test was used as the electrophysiologic measurement. A dartboard with 60 sectors, displaying patterns provided by VERIS software (version 6; Electro Diagnostic Imaging, San Francisco, CA, USA), was utilized. Each sector consisted of 16 checks, comprising 8 white (200 cd/m^2) and 8 black checks (<1 cd/m^2). These sectors and checks were scaled to account for cortical magnification. To match the visual field in HRP, the dartboard display subtended a diameter of 54.7 degrees and 7.2 degrees in the center ring. This display was presented on a SAMSUNG 24-inch screen (60 Hz) at 28 cm (Fig. 2A). A chinrest was employed to keep the patient's head stable, and a dimly lit environment was maintained for each session. Patients received full correction with the appropriate near addition prescribed by an optometrist for the mfVEP test. Unlike conventional visual evoked potential (VEP), each sector in mfVEP is an independent stimulus. These stimuli undergo a predefined random sequence of presentation, reversing or remaining the same with each frame change. The response associated with each sector is a mathematical abstraction, resulting from the correlation between the reversal sequence of each sector and the continuous recording. Further details regarding the mfVEP parameters are provided elsewhere.[25,26] Stimuli were presented monocularly to the test eye while the other eye was occluded. Each

mfVEP recording lasted approximately 9 minutes and was divided into 32 segments, with each segment lasting approximately 17 seconds.

During recording, three continuous visual evoked potential channels were acquired using gold cup electrodes. For the midline channel, the electrodes were placed 5 cm above the inion (active electrode), at the inion (reference electrode), and on the forehead (ground electrode). The other two channels utilized the same ground and reference electrodes, with the active electrodes placed 1 cm above and 4 cm lateral to the inion on either side (Fig. 2B). By taking the difference between pairs of channels, three additional "derived" channels were obtained, resulting in a total of six recording channels. Impedance was kept below 10 kΩ. The records were sampled at 9600 Hz and preprocessed in VERIS software with the following parameters: high-frequency cutoff set at 30 Hz and low-frequency cutoff set at 3 Hz, forced polarity, artifact removal with two iterations, and spatial averaging by one iteration with 20% overlap. The mfVEP signal-to-noise (SNR) was calculated by defining the signal window (45–150 ms) and noise window (325–430 ms) first and then dividing the root mean square (RMS) amplitude of the signal window by the RMS of the noise window.[17] SNR analyses were performed on the largest response from the six channels, referred to as the "BestSNR." The difference in mfVEP latency was determined by shifting the postresponse along the time axis for best cross-correlation with the preresponse. Smaller SNR and longer relative latency are associated with visual field defects or other eye diseases.[25,27] To increase the reliability of mfVEP recordings, electrode placement is crucial. In our study, we recorded the patient's inion position using a washable pen to mark at pre- and postmeasurements. This approach improves the consistency of mfVEP recordings. Previous studies have shown that mfVEP has reasonably good reliability across different sessions.[28]

Sample Size and Power Analysis

Our power analysis was based on data from a similar amblyopia study (within-patient Cohen's $d = 0.66$[9]). Assuming a more conservative effect size of 0.50 for our primary outcome measure of the HRP test, a sample size of 36 patients with glaucoma could provide 80% power to detect a significant difference at the two-tailed 0.05 alpha level with a 5% dropout rate.

Statistical Analysis

The analysis included HRP detection ACC and RT, as well as the mfVEP SNR and latency. To account for interindividual variability, we employed a linear mixed model with stimulation type as the fixed effect, MD from the test eye of the 30-2 VF test as the covariate, and patient as a random effect. A dummy-coding scheme with the sham condition as the reference level was utilized. Initially, a full model was fitted, and if convergence issues or overfitting arose, adjustments were made to the random intercept and slope. Model comparison was conducted using a likelihood ratio test to evaluate the adequacy of the current model relative to alternative models without the fixed effect.

We conducted two analyses, taking into account the specific geometries of both the mfVEP and HRP techniques. The 20-degree analysis focused on test points within a rectangle that deviated 20 degrees from the center in the HRP, as well as sectors within a 20-degree radius in the mfVEP (ranging from ring 1 to ring 4). The peripheral analysis excluded the central area. Considering the different geometries and data sampling between HRP and mfVEP, the central area was defined as 6 degrees in HRP and 7.2 degrees in mfVEP. The sectors falling between ring 2 and ring 4 were included in the peripheral analysis.

A mediation analysis was additionally performed to test whether the stimulation effect (e.g., tDCS, tACS, tRNS against sham) on visual field measurements was mediated by electrophysiologic responses, such as mfVEP SNR or latency. However, this mediation pathway could only be established if the initial requirement was met—the stimulation type significantly affected the proposed mediating variables of mfVEP SNR or latency. All statistical analyses were performed using R 4.1.0 with the lmerTest, lme4, and mediation packages. Unstandardized indirect effects were computed by running 1000 bootstrapped samples for estimation.

Results

Thirty-five patients (14 women, age of 62.26 ± 7.94 years) with moderate to advanced glaucoma participated. Table 1 refers to the summary of participants' demographic and clinical findings.

Subjective experiences during stimulation are detailed in Table 2. tACS induced a significantly stronger itching sensation than sham ($P < 0.001$). Sixty-three percent of patients reported at least a score of 2 for the sensation of tingling after tACS, whereas only 14% had a similar sensation after tRNS. For tDCS, the most common sensation was also tingling, about 54%. A similar proportion (56%) of patients reported tingling in the sham condition. Additionally,

Table 1. Demographic Information

Characteristic	Value
No. of patients	35
Age, y	62.26 ± 7.94 [37, 74]
Sex, male/female, *n*	21/14
Duration of glaucoma, y	5.42 ± 5.18 [0.16, 20]
Montreal Cognitive Assessment score	27.43 ± 1.96 [22, 30]
Tested eye, OD/OS, *n*	13/22
Refractive errors, in terms of spherical equivalent, D[a]	−4.70 ± 2.91 [−9.5, 0]
Best-corrected visual acuity, logMAR[a]	0.01 ± 0.17 [−0.8, 0.32]
Intraocular pressure, mm Hg[a]	14.08 ± 3.02 [7.5, 20]
Visual field results, dB	−11.98 ± 5.57 [−27.24, −6]
SITA 30-2,[a] MD	
SITA 30-2,[a] PSD	11.28 ± 2.77 [1.8, 16.81]
SITA 10-2,[a] MD	−10.94 ± 6.51 [−29.42, −1.03]
SITA 10-2,[a] PSD	9.76 ± 3.40 [−1.03, 1.39]

Values are expressed as mean ± SD [range] unless otherwise indicated. logMAR, logarithm of the minimum angle of resolution; PSD, pattern standard deviation.

[a]Clinical findings of the tested eye.

11% of patients reported feeling slightly sleepy after the sham stimulation. No other comparisons were statistically significant, suggesting successful masking to stimulation conditions.

Effects of tES on Visual Field Measurements

HRP measures showed a significant fixed effect of stimulation type on the post-to-pre changes in ACC. When comparing the change in ACC for each type of stimulation against sham, a significant effect was found for a-tDCS ($b = 0.032$, SE $= 0.013$, $t = 2.402$, $P = 0.018$) but not tACS ($b = -0.005$, SE $= 0.013$, $t = -0.362$, $P = 0.718$) or tRNS ($b = 0.005$, SE $= 0.013$, $t = 0.365$, $P = 0.715$; see Fig. 3, upper left). Despite considerable variation in visual field loss in our sample, the covariate MD did not have a significant effect on the change in ACC ($b = 0.004$, SE $= 0.001$, $t = 0.377$, $P = 0.708$). Regarding the change in RT, no significant fixed effects of stimulation type or MD were observed.

mfVEP measurements showed a significant fixed effect of stimulation type on both SNR and latency. A-tDCS significantly increased SNR compared to sham ($b = 0.016$, SE $= 0.006$, $t = 2.384$, $P = 0.017$). In contrast, neither tACS nor tRNS induced a significant change in the SNR ($P > 0.10$). The covariate MD did not have a significant effect on the change in SNR ($b < -0.001$, SE $= 0.001$, $t = -0.544$, $P = 0.59$). In addition, a-tDCS stimulation shortened the VEP latency compared to sham ($b = -1.405$, SE $= 0.684$, $t = -2.054$, $P = 0.04$), while tACS prolonged the latency ($b = 1.558$, SE $= 0.681$, $t = 2.288$, $P = 0.022$). MD did not affect the latency ($b = 0.02$, SE $= 0.077$, $t = 0.261$, $P = 0.795$).

Effects of tES on Peripheral Vision

Glaucoma primarily affects peripheral vision (although some central vision deficits also exist).[29] Therefore, we further examined the effect of tES on peripheral vision by excluding data from the central areas of the visual field. Due to the different geometries and data sampling in HRP and mfVEP, the central area was defined as 6 degrees in HRP and 7.2 degrees in mfVEP. To make the two outcome measures more compatible, the 20-degree peripheral analysis in mfVEP was defined as the sectors falling into ring 2 and ring 4.

Similar to the 20-degree visual field analysis, a-tDCS stimulation significantly enhanced ACC compared to the sham ($b = 0.051$, SE $= 0.018$, $t = 3.128$, $P = 0.002$; see Fig. 4, upper left). No significant differences in ACC were found for tACS ($b = 0.002$, SE $= 0.017$, $t = 0.131$, $P = 0.896$) or tRNS ($b = 0.019$, SE $= 0.018$, $t = 1.100$, $P = 0.274$). The covariate MD did not have a significant effect on the change in ACC ($b = 0.001$, SE $= 0.001$, $t = 0.113$, $P = 0.910$). In addition, we found no significant effects of stimulation type regarding RT but a significant effect of MD ($b = 0.003$, SE $= 0.001$, $t = 2.26$, $P = 0.031$), indicating that RT increased as MD became more severe.

Electrophysiologically, there was a trend for a-tDCS stimulation to enhance SNR compared to sham, but it did not quite reach statistical significance ($b = 0.014$, SE $= 0.007$, $t = 1.95$, $P = 0.052$). No significant differences in the SNR were found for tACS ($b = 0.006$, SE $= 0.007$, $t = 0.854$, $P = 0.393$) or tRNS ($b = -0.002$, SE $= 0.007$, $t = -0.286$, $P = 0.775$). The covariate MD did not have a significant effect on the change in SNR ($b < -0.001$, SE $= 0.001$, $t = -0.477$, $P = 0.636$). Interestingly, different results were found for latency. The fixed effect of stimulation was statistically significant with tACS, in which the poststimulation latency was prolonged compared to sham ($b = 1.623$, SE $= 0.796$, $t = 2.039$, $P = 0.041$). No other effects were significant. Examples of individual patient data demonstrating the impact of tES on visual field and electrophysiologic measurements, including HRP and mfVEP, are

Table 2. Subjective Feelings about the Stimulation

	Stimulation			
Sensation	Sham	a-tDCS	tACS	tRNS
Headache	1.06 ± 0.24	1.03± 0.17	1.03 ± 0.17	1.03 ± 0.17
Neck pain	1.03 ± 0.17	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
Scalp pain	1.09 ± 0.28	1.20 ± 0.58	1.03 ± 0.17	1.03 ± 0.17
Tingling	1.57 ± 0.56	1.69 ± 0.68	1.71 ± 0.62	1.71 ± 0.38
Itching	1.11 ± 0.32	1.20 ± 0.41	**1.54 ± 0.66**	1.14 ± 0.36
Burning	1.11 ± 0.40	1.14 ± 0.43	1.14 ± 0.43	1.00 ± 0.00
Skin redness	1.03 ± 0.17	1.03 ± 0.17	1.00 ± 0.00	1.00 ± 0.00
Sleepiness	1.11 ± 0.32	1.03 ± 0.17	1.00 ± 0.00	1.06 ± 0.24
Trouble concentrating	1.00 ± 0.00	1.00 ± 0.00	1.03 ± 0.17	1.00 ± 0.00
Acute mood change	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
Believe it is a real stimulation	25/35	26/35	31/35	19/35

Bold indicates a statistically significant difference from sham.

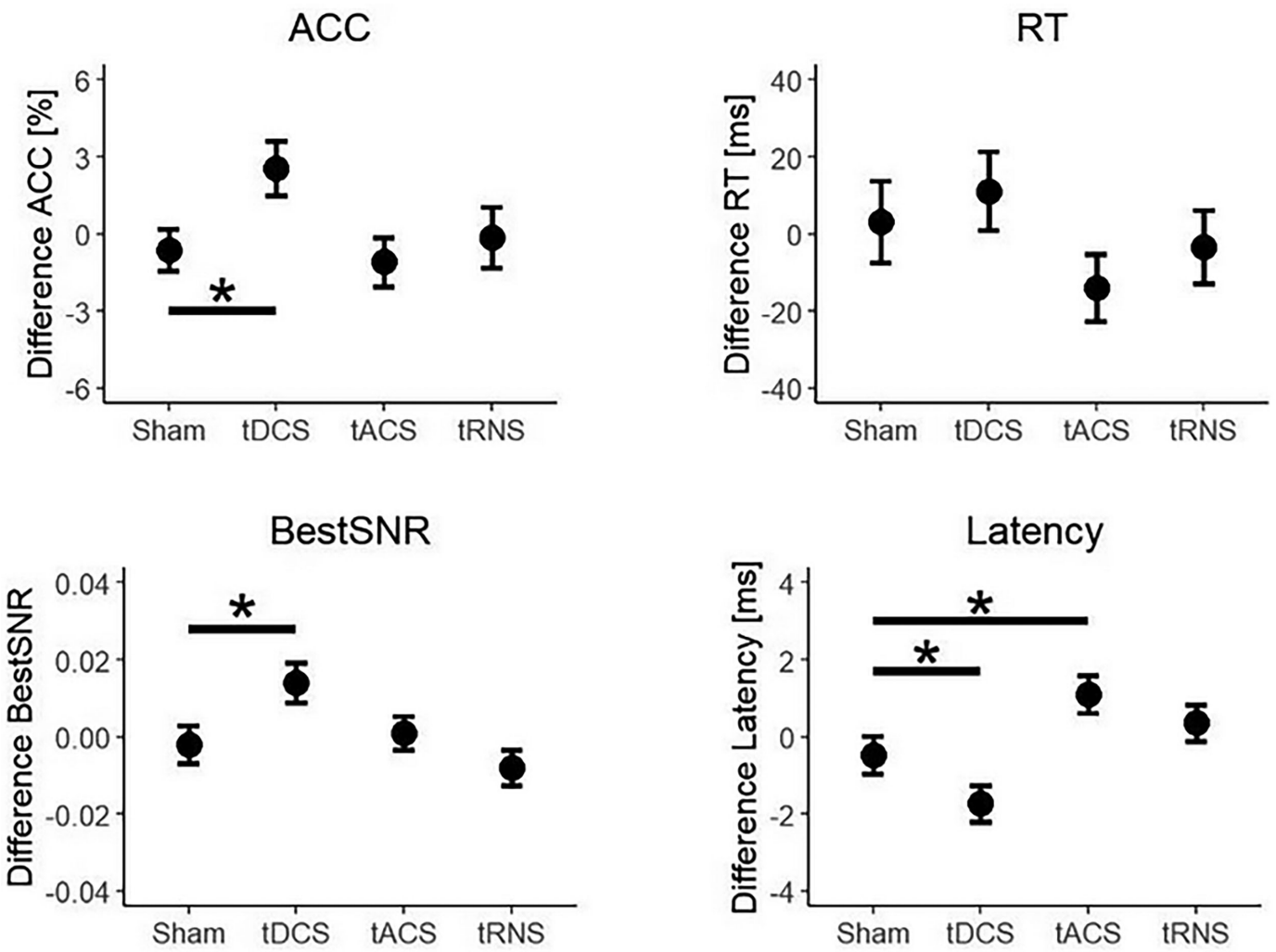

Figure 3. Stimulation induced changes in HRP (*upper panel*: differences in detection ACC, RT) and mfVEP (*lower panel*: differences in SNR and latency) for four types of stimulation in the 20-degree visual field analysis (mean ± standard error). *Asterisk* indicates the significant difference between stimulation types ($P < 0.05$).

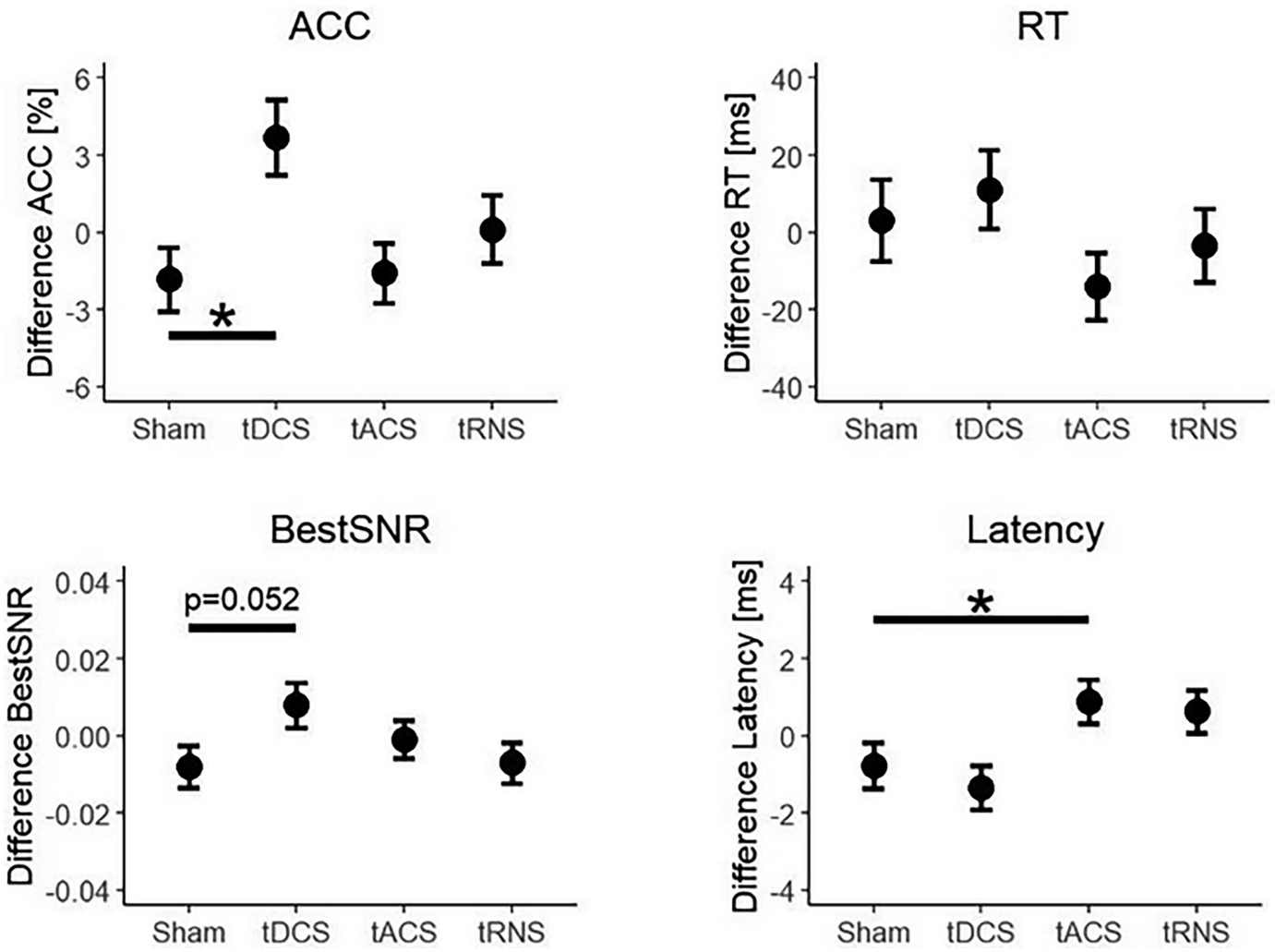

Figure 4. Stimulation induced changes in HRP (*upper panel*: differences in detection ACC, RT) and mfVEP (*lower panel*: differences in SNR and latency) for four types of stimulation for peripheral visual field measures (20 degrees without the central areas) (mean ± standard error). *Asterisks* indicate a significant difference between stimulation types ($P < 0.05$).

provided in the supplementary materials (see S1 and S2). The patient example shows increased responsiveness in mfVEP and improved detection of dots in HRP following a-tDCS. Boxplot with scatter points for both 20-degree and peripheral visual field analysis can also be found in S3 and S4.

The Mediation Effect of the Change in Electrophysiologic Response

To examine whether the improved behavioral performance (i.e., HRP ACC) after receiving tES was mediated by the electrophysiologic change in mfVEP response, mediation analyses using regression models were conducted, including both SNR and latency as potential mediators. Only SNR showed a significant effect, whereas latency did not reach statistical significance.

The effect of stimulation type on the change in ACC was mediated by the change in mfVEP SNR. As Figure 5 illustrates, the regression coefficients between stimulation type and HRP accuracy ($b = 0.028$, $t = 10.28$, $P < 0.001$) and between stimulation type and mfVEP SNR were significant ($b = 0.016$, $t = 2.43$, $P < 0.05$). Although all types of stimulation were included in the mediation analysis, a significant mediation effect was only found in the a-tDCS condition. After controlling for stimulation type, the mediation effect of mfVEP SNR on the change in accuracy remained significant ($b = 0.014$, $t = 2.27$, $P < 0.05$). We tested the significance of this indirect effect using bootstrapping procedures. The result of the bootstrapped unstandardized indirect effect was

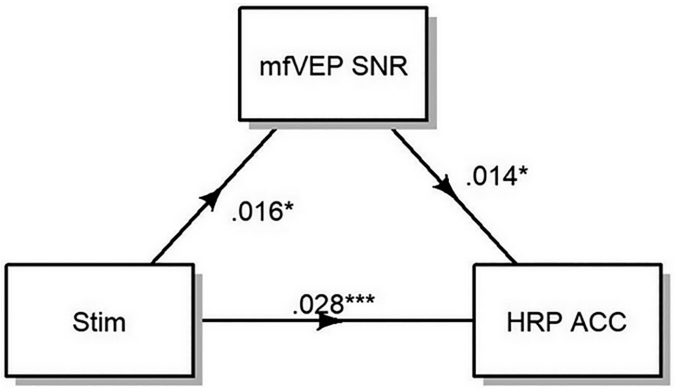

Figure 5. Mediation analysis. The results indicate that stimulation type (Stim) significantly affected the change of HRP accuracy (ACC) ($b = 0.028$, $P < 0.001$), which means on average, the stimulation from sham to a-tDCS was associated with an increase in HRP ACC by 0.028 ($P < 0.05$). Additionally, the stim type also significantly affected mfVEP response, with a-tDCS leading to a 0.016 increase in mfVEP SNR ($P < 0.05$). Importantly, there was a significant mediation effect of mfVEP SNR on HRP ACC ($b = 0.014$, $P < 0.05$), indicating that as the SNR increased, the HRP ACC also increased. Significance levels are denoted by *asterisks*, with * indicating $P < 0.05$ and *** indicating $P < 0.001$.

0.002 ($P < 0.05$), indicating that mfVEP SNR partially mediated the effect of a-tDCS on the change in HRP ACC.

Discussion

The objective of our study was to compare the effectiveness of different noninvasive tES techniques targeting the visual cortical region to improve visual function in glaucoma. Our study design included a single session of each type of tES in randomized order. Despite this short exposure, statistically significant improvements in visual behavioral assessment and related electrophysiologic changes were observed following a-tDCS compared to the sham condition. Mediation analysis further revealed that a-tDCS improved HRP accuracy by enhancing the visual cortical response to the stimuli, as evidenced by an increase in mfVEP SNR. These results reveal a potential mechanism for glaucoma rehabilitation and highlight the therapeutic potential of brain stimulation techniques for modulating visual processing.

In addition to the acute benefits observed in our study, the results shed light on the potential for neural plasticity in glaucoma, an irreversible eye disease primarily associated with retinal ganglion cellular defects. Traditionally, visual impairments in glaucoma have been attributed largely to the damage at the retinal level,[30,31] and interventions have primarily focused on managing intraocular pressure by medications, laser, surgery, or combinations thereof.[32,33] However, our study demonstrated a remarkable capacity of the brain to compensate for retinal-level deficits when neural circuits are altered by visual cortex a-tDCS. While our study incorporated a separation of 48 hours between each stimulation session to minimize the carryover effects from one experimental condition to the next, it is possible that multiple sessions of a-tDCS could further promote physiologic plasticity, leading to cumulative and lasting benefits in vision enhancement.

A-tDCS may increase neuronal resting membrane potentials, thereby increasing the likelihood of action potentials and inducing alterations in neural excitability and synaptic plasticity.[34,35] In contrast, the effect of tACS is based on the entrainment of cortical oscillations, while tRNS, a specific form of tACS, may affect the signal-to-noise ratio in the brain.[36] The effects of tACS are highly dependent on the state of the brain, including individual endogenous factors such as alpha power,[37,38] resulting in greater variability in its effects. Personalized tACS has shown therapeutic effects in disorders characterized by disrupted brain oscillations, such as Parkinson disease.[39] Additionally, personalized tACS increased sleep quality compared to fixed tACS stimulation.[40] Thus, the fixed tACS utilized in our current study may be less efficient in improving visual function compared to a-tDCS. On the other hand, tRNS, which desynchronizes pathologic cortical rhythms with a broad band of frequency noise, has induced larger improvements in perceptual learning tasks compared to a-tDCS in certain studies.[41–43] Notably, most visual cortex tRNS studies reporting an effect involved multiple stimulation sessions. It has also been suggested that tRNS facilitates task performance specifically when administered during the task.[44] Therefore, the timing of the visual task (online versus offline) and repetition rate might account for the different findings between the current study and previous ones. Nevertheless, we demonstrated that a-tDCS outperformed the other tES protocols in the present setting of cortical stimulation for vision enhancement in glaucoma.

The therapeutic effects of a-tDCS have been extensively studied in neuropsychiatric diseases. An increasing body of evidence from open-label studies and randomized clinical trials indicates that a-tDCS produces antidepressant effects in patients.[45–47] Depression is associated with interhemispheric imbalance. By stimulating the left dorsal prefrontal cortex (DLPFC), a-tDCS helps to normalize the balance of neuronal activity between hemispheres. In addition to depression, a-tDCS has shown promising effects

in the treatment of addiction by stimulating the right DLPFC, an area that plays an important role in inhibitory control and reward processing. A-tDCS applied to the left primary motor cortex (M1) and DLPFC has been found to reduce neuropathic pain,[48,49] although mixed effects were found in patients with peripheral nervous system pain secondary to lesions.[50,51] Further discussion on the therapeutic potential of a-tDCS across various disorders can be found in a comprehensive review by Lefaucheur et al.[6]

Recently, there has been more interest in the effects of noninvasive electrical stimulation on visual restoration or enhancement. A growing number of studies have reported beneficial effects of a-tDCS in individuals with hemianopia compared to controls, and these effects are further enhanced when combined with perceptual training.[8,52] Moreover, a-tDCS can induce transient improvement in contrast sensitivity through normalizing visual cortex activation in adults with amblyopia,[9,17] and this effect can be further augmented by incorporating dichoptic treatment.[17]

We tested the assumption that our electrode configuration preferentially stimulated the left visual cortex by separating data from the right and left hemifields. In the HRP 20-degree analysis, the effect size for the right hemifield by a-tDCS was 0.24, and the effect size for the left hemifield was slightly smaller at 0.23. This indicates that while the left side was preferentially stimulated, no significant side-specific effects regarding the hemifield were observed. However, to maximize the stimulation effect, it may be beneficial to tailor the decision of the cheek's side based on the patient's residual visual field.

Our study has several limitations. First, this study was designed to investigate the acute effects of tES on improving visual function and did not assess the long-term sustainability of the observed improvements. Second, our study design only included a single session of each tES protocol, and it is possible that multiple sessions of tRNS or tACS may generate larger benefits than multiple sessions of a-tDCS. Third, mfVEP was originally selected to detect regional visual defects. However, there were concerns about the SNR for analyzing data from a single sector of the visual field, and we had to average across sectors. This limitation reduced the effectiveness of using mfVEP as an outcome measure in our study and highlights the importance of selecting appropriate measures for future research. Additionally, while statistically significant improvements with a-tDCS compared to the sham condition were found, the magnitude of these improvements was relatively modest. Specifically, the difference in the HRP ACC was 0.032, which translates to a 3.2% increase in the detection of test points. In the analysis of the peripheral visual field, the improvement was slightly larger at 5.1%. Since the overall improvements did not greatly exceed the previous reported test variability of 4.5% in HRP,[23] these effect sizes may not be large enough to be considered clinically significant. This underscores the need for further research to determine their clinical utility. Importantly, our study design, which encompassed a randomized, within-patient, and double-masked approach, mitigated the potential influence of confounding factors such as learning effects. Furthermore, there were also physiologic improvements as assessed by mfVEP after a-tDCS, suggesting that the HRP improvement is unlikely to be a mere artifact. In light of these limitations, we have now initiated a larger sample clinical trial (ClinicalTrials.gov ID: NCT05874258) to investigate the time course and aftereffects of a-tDCS in glaucoma rehabilitation. The trial involves a 3-month training period with multiple interval and postmeasurements to determine the optimal timing of the observed effects (effect curve) and to evaluate the long-term sustainability of improvements.

Overall, our study contributes to the growing body of evidence supporting the therapeutic potential of noninvasive tES, here a-tDCS, in improving visual function in glaucoma. The insights gained from this study, combined with the upcoming clinical trial, will further substantiate a role for visual cortex neuroplasticity in the treatment of vision disorders and guide future development of optimal vision rehabilitation for patients with glaucoma, improving their functional performance and quality of life.

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