The oscillatory transcranial electric stimulation and the amplitude-modulated frequency dictate the quantitative features of phosphenes

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Abstract

The study explores the crucial role of current oscillation and neural alignment to amplitude-modulation frequency in phosphene induction through various forms of transcranial electric stimulation. Previous research has shown that transcranial alternating current stimulation (tACS) can modulate phosphene perception. The application of tACS introduces rhythmic electric field changes and alternating polarity, making the oscillatory mechanism behind phosphene perception still unclear. To dissociate the effects of changing electric field vs. alternating polarity, the present study employs oscillatory transcranial direct current stimulation (otDCS) to eliminate the influence of polarity switching. We administered scalp electric stimulations using tACS and otDCS in anodal or cathodal polarities over the occipital lobe. All stimulations were conducted with sinusoidal (18 Hz) or amplitude-modulated (2 Hz AM embedded in an 18 Hz carrier) waveforms at threshold or suprathreshold intensities. The results revealed no difference between stimulation polarities, suggesting the importance of current oscillation rather than polarity alteration in phosphene induction. Furthermore, amplitude-modulated stimulation consistently produced slower phosphene flash rates, unaffected by intensity, indicating the dominance of amplitude-modulation frequency in phosphene perception. Our findings suggest (1) current oscillation, rather than polarity switching, is crucial for phosphene generation; (2) amplitude-modulation frequency effects on perception threshold, response time, and perceived flash rate are robust irrespective of the oscillatory stimulation protocols; (3) amplitude-modulation information is encoded in phosphene perception generation independently of the carrier frequency. This study provides direct evidence of the link between phosphene occurrence and oscillatory current activity, underscoring the robustness and independence of amplitude-modulation coding in visual perception.

Title page:

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Running Title: Oscillatory TES & Phosphene Traits in AM

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Introduction

Aligning neuronal activity with the content of perception is a fundamental concern in consciousness studies. This not only contributes to addressing the "what-it-is-like" problem (Nagel, 1974) but also establishes the technical foundation for developing virtual perceptions, such as bionic eyes and auditory prostheses. While the brain itself does not receive direct light stimulation, understanding the "visual code" connecting the brain and perception remains crucial. One way to investigate this process more directly is via the use of phosphene—the phenomenon of experiencing visual light without external light stimulation. Studies have demonstrated that phosphene experiences can be induced through direct electrical stimulation of the visual cortex (Brindley & Lewin, 1968; Foerster, 1929; Fox et al., 2020) or magnetic pulses applied over the visual cortex (Barker et al., 1985; Meyer & Allen, 1991). Particularly, transcranial alternating current stimulation (tACS), involving a current with a constant polarity exchange, has been shown to elicit phosphenes (Kanai et al., 2008). Phosphenes induced by tACS are commonly perceived as repetitive flickering in the visual field. Previous research has indicated that the perception of tACS-induced phosphenes can be dependent on the stimulation frequency (Evans et al., 2019, 2021; Hsu et al., 2023; Kanai et al., 2008; Turi et al., 2013). In contrast to conventional tACS, amplitude-modulated tACS (AM-tACS) has garnered attention, driven in part by efforts to minimize phosphene occurrence during stimulation while examining the impact of tACS on visual cognition performance (Thiele et al., 2021). A strategy employed to achieve this goal involves embedding the target frequency into a rapidly oscillating tACS in AM form (Thiele et al., 2021). This approach aims to prevent phosphene occurrence (Thiele et al., 2021) and contamination of neighboring ongoing neural activity (Witkowski et al., 2016) during neural entrainment. Recent studies have emphasized the crucial role of AM information in sensory encoding (Clarke et al., 2015; Juan et al., 2021; Nguyen et al., 2019; Ryu et al., 2017). Specifically, one study by Hsu et al.(2023) provided direct insights into the effects of AM-tACS on visual awareness, shedding light on the role of AM in tACS-induced phosphene perception. The study applied AM-tACS with carrier frequencies of 10, 14, 18, and 22 Hz, and AM frequencies of 0, 2, and 4 Hz. The results indicated that AM-tACS-induced phosphene perception exhibited higher thresholds and a slower flash rate, suggesting that the AM frequency exerts a more substantial influence on phosphene perception than the carrier frequency. Nevertheless, our understanding of how AM frequency influences visual perception is still in its early stages (Juan et al., 2021; Nguyen et al., 2019). In the study, we build upon our previous work and investigate the neural mechanisms underlying phosphene perception induced by transcranial electric brain stimulation. To comprehend phosphene perception, it is imperative to deconstruct the biophysiological effects induced by tACS. This technique entails the application of an alternating current, where the polarities—referred to as the "source" and "sink" of the electricity—rhythmically switch between the two electrodes. Unlike phosphene elicitation through transcranial magnetic stimulation, where magnetic pulses induce neural firing in the visual cortex, scalp electric stimulation is not potent enough to directly provoke action potentials in the cortex (Asamoah et al., 2019; Y.-Z. Huang, 2017; Vöröslakos et al., 2018). Nevertheless, the oscillations of the electric field can modulate the rhythms of spontaneous neural firing, resulting in synchronous excitation and inhibition during specific oscillatory phases (Wischnewski et al., 2023). Additionally, tACS may induce ephaptic coupling (Anastassiou et al., 2011; Han et al., 2018), a phenomenon wherein non-synaptic interneural communication occurs via extracellular potential oscillation. This is considered one of the electromagnetic foundations for the occurrence of consciousness (Hunt, 2020; Hunt et al., 2022; Hunt & Jones, 2023; McFadden, 2021). The application of tACS, therefore, brings about both rhythmic changes in the electric field and the alternating polarity (excitatory or inhibitory phase). Considering that no phosphene has been reported during monotonous transcranial direct current stimulation (tDCS), it is plausible that electric oscillation plays a pivotal role in inducing phosphene perception. One potential method to test this hypothesis is to dissociate the effects of rhythmic changes in electric field vs. alternating polarity. To do this, the present study employs oscillatory transcranial direct current stimulation (otDCS), where the current oscillation is confined to one polarity—either positive or negative—to eliminate the influence of polarity switching. Previous studies utilizing otDCS for modulating cognitive function have demonstrated that otDCS can induce changes in excitability (Antal et al., 2008; Bergmann et al., 2009; Groppa et al., 2010) and neural entrainment (Vulić et al., 2021; Živanović et al., 2022), combining characteristics of both tDCS and tACS. Evans et al. (2021) used sinusoidal direct current on the scalp, eliciting phosphenes without polarity differences, focusing only on threshold measurement. In the study, we employed various measurements, including response times (RT), ratings of perceived brightness, flash rate, and confidence, along with indices of threshold intensity and pattern drawing. This comprehensive approach allows us to thoroughly investigate the features of phosphenes induced by both otDCS and tACS, facilitating direct comparison of potential differences between them. We hypothesize that if current oscillation plays a crucial role in inducing phosphene perception, phosphenes should be observed in both anodal and cathodal otDCS. While the primary neural effect of tACS is synchronization rather than a general firing rate increase (Wischnewski et al., 2023), the polarity of otDCS may not affect the threshold intensity or interact with the AM frequency. However, ratings on other perceptual reports may be influenced by polarity if it is involved in the general firing rate. Hsu and his colleagues (2023) delved into the characterization of phosphene content by instructing participants to report on the pattern and flash rate of tACS-induced phosphenes. In terms of flash rate scoring, they demonstrated a linear effect of carrier frequency in sinusoidal tACS. Interestingly, they found that the amplitude modulation (AM) frequency could override the carrier frequency, disrupting the linear relationship and resulting in a slower flash rate. These findings suggested the intriguing possibility that AM may take precedence over carrier frequency in influencing the perception system. Numerous previous studies have indicated the ability of the visual neural system to capture envelope information at both retinal (Ryu et al., 2017) and visual cortical (Nguyen et al., 2019; Shapley, 1998) levels. Additionally, a simulation study (Negahbani et al., 2018) demonstrated that the local field potential could synchronize with the AM frequency when applying AM-tACS to simulated pyramidal cortical cells. Collectively, these studies strongly suggest that AM information could play a pivotal role in perception by exerting an overriding influence on carrier frequency. However, an alternative hypothesis could potentially explain the observed slower flash ratings. It is conceivable that the slower flash perception may result from the waveform of the AM-tACS. Specifically, the amplitude of the carrier oscillation might be modified by the AM frequency, causing it to change over time. It is plausible that the amplitude of the carrier oscillation reaches the perception threshold only when the amplitude of the AM frequency peaks at phase angles of 90 or 270 degrees. Consequently, AM-tACS may trigger a phosphene percept at the AM frequency, leading to a slower flash that is less sensitive to the carrier frequency. This concern is addressed by comparing ratings from trials with intensities above the mean threshold. The hypothesis posits that if the phosphene flash follows this pattern, participants should report a higher flash rate during suprathreshold trials, as more oscillations could exceed the phosphene threshold. A null result from the test could imply that the slower ratings support the perceptual dominance of the AM frequency or are simply a result of missing values and data variation due to not every participant having trials with the same intensity. Therefore, to better elucidate the source of the slow flash rate in AM-tACS, we introduced an additional suprathreshold condition that stimulates at 120% intensity of the threshold. We anticipate that a higher stimulation intensity will enhance neural alignments to the oscillation that determines our flash percept. If the AM frequency holds an advantage in phosphene perception, the flash rate would align with the AM frequency and remain unaffected by the stimulation intensity. In contrast, if the flash rate reflects the frequency of carrier oscillations surpassing the perception threshold, ratings for the suprathreshold condition should be faster than those for the threshold condition. The current study delves into the neural mechanisms underlying transcranial electric stimulation (tES) induced phosphene perception by investigating quantitative indicators of phosphene experiences. The specific objectives of this study are to explore (1) the essential role of neural electric field oscillation by isolating oscillation from polarity, (2) the impact of polarity in oscillatory tDCS on phosphene perception, and (3) the influence of neural alignment with AM frequency on phosphene flash rate through the implementation of suprathreshold stimulation. By incorporating multiple behavioral measurements beyond the threshold, we anticipate gaining a more comprehensive understanding of the neural mechanisms that connect neural oscillations with visual perception.

Method

2.1 Participants

Thirty-seven participants with normal or corrected-to-normal vision were recruited for the experiment. Participants who had neuronal disease or a family history of epilepsy were excluded. Among the recruited participants, eleven did not finish the task because they could not detect phosphene with the maximum intensity (2000 µA) in any of the stimulation conditions. During data analysis, data from one participant was excluded because they responded earlier than stimulation had begun. As a result, data from 25 participants (13 males aged 20 – 45) were included in the analysis. All participants were instructed on the experimental procedures and provided their signed consent on a form that received approval from the Institutional Review Board of Chang-Gung Memorial Hospital, Taiwan.

2.2 Experimental design and stimulation parameters

The current study employed a within-subject design. Each participant visited the lab three times, with a one-week gap in between each visit. During each visit, participants received stimulation of one polarity (anodal otDCS or cathodal otDCS or tACS) in four stimulation blocks: threshold-level sinusoidal wave (18 Hz), threshold-level AM wave (2 Hz amplitude-modulated 18 Hz, 2 AM 18 Hz), supra-threshold level sinusoidal, and supra-threshold AM wave (the waveforms are illustrated in Figure 1A). The carrier and AM frequencies were selected based on our previous finding in which participants reported the most phosphene responses with these frequencies (Hsu et al., 2023). The order of stimulation polarities and blocks was counterbalanced within participants.

2.3 Experimental apparatus

During the experiment, participants were seated in a dim room with a 0.25 cd/m^2 luminance level with a chin rest at 60 cm from the 24-inch LCD monitor. The task was programmed using Matlab 2021b and Psychtoolbox-3 (Brainard, 1997; Kleiner et al., 2007; Pelli, 1997), allowing precise control over stimulus presentation. otDCS and tACS were delivered with the Geodesic Transcranial Electrical Neuromodulation (GTEN) Planning Module (Magstim Electrical Geodesics, Inc., USA) through a 128-channel elastic cap. A total of 20 electrodes on the posterior sites were selected to serve the current delivery. The electrode numbers in the EGI system (corresponding 10-10 system electrode name) are 60, 66, 67(PO3), 71, 62(Pz), 72(POz), 76, 77(PO4), 84, 85(P2), and 69, 73, 70(O1), 74, 75(Oz), 81, 82, 83(O2), 88, 89). Conductive gel was applied for electrode-delivered stimulations to reduce electrode impedance, and anesthetic spray was applied to these electrodes to decrease tactile perception induced by stimulation.

2.4 Experimental procedures

Each stimulation block included 10 trials. The threshold intensities were defined by a pre-experimental test that used the modified binary search (MOBS) method (Anderson & Johnson, 2006; Tyrrell & Owens, 1988) (also see Appendix S1: Supplementary 4 of (Hsu et al., 2023) for details) with the upper and lower bound at peak-to-peak 1000 and 2000 µA respectively. The threshold intensity was verified with another 10 trials to ensure its response rate exceeded 50%; otherwise, the threshold was re-defined again with MOBS. The suprathreshold intensity was defined as 120% threshold intensity.

In every trial, participants were stimulated for 5 seconds. They were asked to press the space key when seeing phosphene for an RT recording. They then drew the phosphene pattern on the screen with a mouse. After the stimulation, participants entered a new frame to report (1) brightness, (2) flash rate, and (3) confidence level (as illustrated in Figure 1D).

2.5 Data processing and statistical methods

For the dataset of each participant, trials with RT exceedingly twice the standard deviation were excluded from further analysis. Responses to the same stimulation condition were then averaged into mean values. In cases where no trials survived in one condition, the missing values were replaced by the cross-subject mean value.

For phosphene size estimation, we adopted the "im2bw" and "bwarea" functions built in MATLAB 2021b (Pratt, 1991). These functions converted the phosphene images into grayscale and computed the brightness value for the pixels from 0 (black) to 1 (white). Pixels with brightness values greater than 0.5 were counted as 1, while others were counted as 0. The phosphene size was then calculated as the sum of the entire screen.

For each measure, we conducted a within-subject 3 × 2 × 2 ANOVAs which employed factors of stimulation polarity (anodal otDCS, cathodal otDCS, and tACS), AM condition (0 and 2 Hz, where 0 Hz AM indicates a sinusoidal waveform), and intensity (threshold: 100% and suprathreshold: 120%). Further paired contrasts were conducted when the main effects or interactions were significant.

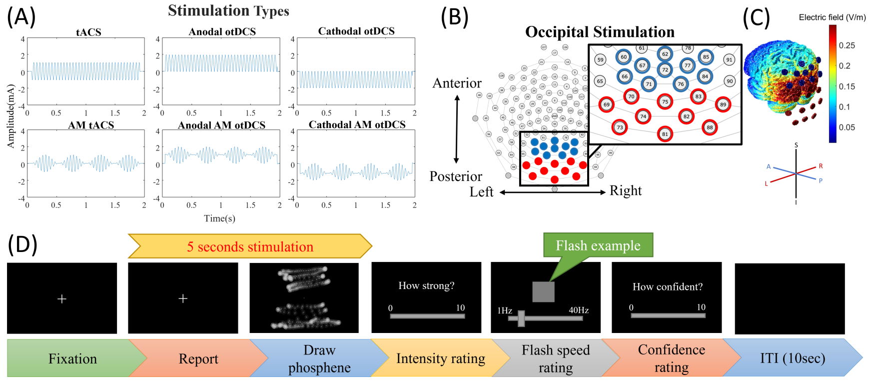

Figure 1. The general diagram of the experimental methods. (A) Illustrations of the given tACS and otDCS waveforms. Waveforms in the upper row have the same carrier frequency, and waveforms in the lower row have the same AM frequency. (B) The electrode montages that were used in the experiment. Electrodes over the occipital scalp were selected and assigned into two groups marked in different colors. In the anodal otDCS, electrodes in the red group served as the anode, while the blue group was the cathode. The assignment reversed during the cathodal otDCS. In the tACS session, the two groups of electrodes switched polarities according to the given waveform. (C) The current distribution simulation was conducted based on the electrode configuration described in Figure (1B), applying an intensity level of 2000 µA. This simulation identified the occipital stimulation montage as producing the highest current density, particularly around the primary visual cortex located in the bilateral occipital lobes. The intensity levels of the simulated current are represented through color coding on the diagrams. The modeling of the head's current flow was carried out with the ROAST software (Y. Huang et al., 2019) (D) The trial structure of the phosphene task. Participants fixated their eyes on a fixation (0.7 visual degrees) on the center of the screen for 2 to 3 seconds, followed by a 5-second current stimulation. Participants were instructed to maintain focus on the fixation point and to signal phosphene perception by pressing the space key. Subsequently, they utilized a mouse to depict the observed phosphene pattern using scattered dots, with the dot positions being captured for subsequent analysis of the pattern's size. Following this, participants advanced to a new screen to evaluate the flash's brightness by adjusting a horizontal slider located at the bottom of the display from 0 (none) to 10 (strongest). In the flash rate scoring, a square was presented at the center of the screen, which flashed

at frequencies varying from 1 Hz (left pole of the sliding bar) to 40 Hz (right pole of the sliding bar). Participants were required to move the sliding bar to adjust the flash rate, so the flashing square reproduced the flash rate of their phosphene. Finally, the participant moved the sliding bar to rate the confidence level of their response from 0 (not confident at all) to 10 (very confident).

Results

Repeated measures ANOVA analyses were conducted on various behavioral parameters, as summarized below in Table 1.

not-yet-known not-yet-known

not-yet-known

unknown

Table 1. The summary table of statistical results

Threshold intensity	SP
	AM
	SP × A
Reaction time	SP
	AM
	IT
	SP × A
	SP × IT
	AM × I
	SP × A
Flash brightness rating	SP
	AM
	IT
	SP × A
	SP × IT
	AM × I
	SP × A
Flash rate scoring	SP
	AM
	IT
	SP × A
	SP × IT
	AM × I
	SP × A
Confidence of flash rate scoring	SP
	AM
	IT
	SP × A
	SP × IT
	AM × I
	SP × A
Phosphene size	SP
	AM
	IT

SP × A
SP × IT
AM × I
SP × A

Note. Stimulation polarity (SP), AM conditions (AM), and Intensity (IT). *: $p<0.05$, **: $p<0.01$. ***: $p<0.001$

3.1 Threshold intensity

The ANOVA result indicated a significant AM main effect (F (1,24) = 26.505, $p < 0.001$, $\eta_{p}^{2} = 0.525$), showing that the phosphene threshold for AM stimulation (mean value with 95% CI: 1284.12 ± 42.10) was significantly higher than for sinusoidal stimulation (1080.96 ± 86.90). We did not observe a main effect of polarity (F (2,48) = 0.716, $p = 0.494$, $\eta_{p}^{2} = 0.029$) or the interactions between polarity and AM (F (2,48) = 0.653, $p = 0.525$, $\eta_{p}^{2} = 0.026$; Figure 2A).

3.2 Reaction time

For the reaction time of phosphene response, the ANOVA test revealed significant main effects of polarity (F (2,48) = 3.797, $p = 0.029$, $\eta_{p}^{2} = 0.137$). Post-hoc comparisons with Bonferroni corrections indicated that reaction time for tACS was significantly faster than cathodal otDCS ($p = 0.035$) but not anodal otDCS (p =1). We also found significant main effect of AM (F (1,24) = 26.715, $p < 0.001$, $\eta_{p}^{2} = 0.527$) and intensity (F (1,24) =47.562, $p < 0.001$, $\eta_{p}^{2} = 0.665$), showing that RTs were shorter for sinusoidal (1746.57 ± 232.69 ms) than AM (2051.10 ± 192.01 ms) stimulation, and for supra-threshold (1772.25 ±210.12 ms) than the threshold (2025.42 ± 205.77 ms) intensity (Figure 2B).

3.3 Flash brightness rating

ANOVA test indicated significant main effects of polarity (F (1.5,36.9) = 5.111, $p = 0.017$, $\eta_{p}^{2} = 0.176$), and intensity (F (1,24) = 18.038, $p < 0.001$, η_{p}^{2} =0.429), but not AM conditions (F (1,24) = 1.954, $p = 0.175$, $\eta_{p}^{2} = 0.075$). The flash brightness ratings were, in general, higher for the suprathreshold (3.00 ± 0.71) than threshold (2.52 ± 0.68) intensity. Paired comparison of the three polarities, however, only revealed marginal results that brightness ratings were higher for anodal otDCS (3.07 ± 0.82) than for cathodal otDCS (2.54 ± 0.63) and tACS (2.67 ± 0.69). The test did not yield any significant 2-way or 3-way interactions (polarity × AM: F (2,48) = 1.336, $p = 0.272$, $\eta_{p}^{2} = 0.053$; AM × intensity: F (1,24) = 1.567, $p = 0.223$, $\eta_{p}^{2} = 0.061$; polarity × intensity:F (2,48) = 2.278, $p = 0.113$, $\eta_{p}^{2} = 0.087$; polarity × AM × intensity: F (2,48) =0.992, $p = 0.378$, $\eta_{p}^{2} = 0.040$ (Figure 2C).

3.4 Flash rate scoring

The ANOVA revealed a significant main effect of AM (F (1,24) = 8.487, $p = 0.008$, $\eta_{p}^{2} = 0.261$) condition, indicating a higher perceived flash rate for sinusoidal (16.02 ± 3.19) than for AM (13.34 ± 3.61) stimulations. The main effect of intensity was marginally significant (F (1,24) = 3.446,$p = 0.076$, $\eta_{p}^{2} = 0.126$), with a marginal interaction between polarity and intensity (F (2,48) = 2.885, $p = 0.066$, $\eta_{p}^{2} = 0.107$). Further tests on this effect revealed that only in the anodal otDCS participants score the flash of suprathreshold stimulations as faster than threshold stimulations ($p = 0.011$). However, ANOVA did not reveal the significance of polarity (F (2,48) = 0.256, $p = 0.775$, $\eta_{p}^{2} = 0.011$), or any 2-way and 3-way interactions (polarity × AM: F (1.5,35.6) = 0.580, $p = 0.516$, $\eta_{p}^{2} = 0.024$; AM × intensity:F (1,24) = 0.508, $p = 0.483$, $\eta_{p}^{2} = 0.021$; polarity × AM × intensity: F (2,48) = 1.009, $p = 0.372$, $\eta_{p}^{2} = 0.040$; Figure 2D).

3.5 Confidence of flash rate scoring

ANOVA on the confidence levels revealed a significant main effect of intensity (F (1,24) = 11.613, $p = 0.002$, $\eta_{p}^{2} = 0.326$) and the 3-way interaction between polarity, AM, and intensities (F (2,48) = 4.224, $p = 0.020$, $\eta_{p}^{2} = 0.150$). The statistics yielded a higher confidence rating for the suprathreshold (5.74 ± 0.80) than for the threshold (5.36 ± 0.91) stimulation, and the effect was most pronounced in the AM stimulation of anodal otDCS ($p = 0.007$) and sinusoidal stimulation of tACS ($p = 0.04$). The analysis did not reveal other main effects (polarity: F (1.4,34.5) = 0.403,$p = 0.604$, $\eta_{p}^{2} = 0.017$; AM:F (1,24) = 0.011, $p = 0.919$, $\eta_{p}^{2} = 0.000$; polarity × AM:F (2,48) = 2.059, $p = 0.139$, $\eta_{p}^{2} = 0.079$; polarity × intensity:F (2,48) = 2.715, $p = 0.076$, $\eta_{p}^{2} = 0.102$; AM × intensity:F (1,24) = 0.006, $p = 0.939$, $\eta_{p}^{2} = 0.000$; Figure 2E).

3.6 phosphene size

Statistics on the phosphene area revealed a significant main effect of intensity (F (1,24) = 15.518, $p < 0.001$, $\eta_{p}^{2} = 0.393$), indicating that the phosphene was perceived larger for the suprathreshold (90489.46 ± 22043.31) than the threshold (77891.75 ± 19484.09) stimulations. We also found a marginal effect of AM (F (1,24) = 4.113, $p = 0.054$, $\eta_{p}^{2} = 0.146$) that the phosphene sizes were larger for sinusoidal (91753.79 ± 24106.19) than for AM stimulation (76627.42 ± 19522.28). We did not find the main effect of polarity (F (1.5,34.8) = 0.329, $p = 0.652$, $\eta_{p}^{2} = 0.014$) nor any 2-way (polarity × AM: F (2,48) = 0.781, $p = 0.464$, $\eta_{p}^{2} = 0.032$; polarity × intensity:F (2,48) = 2.534, $p = 0.090$, $\eta_{p}^{2} = 0.096$; AM × intensity:F (1,24) = 0.252, $p = 0.621$, $\eta_{p}^{2} = 0.010$) or 3-way (F (1.5,37.1) = 1.282, $p = 0.283$, $\eta_{p}^{2} = 0.051$) interactions (Figure 2F).

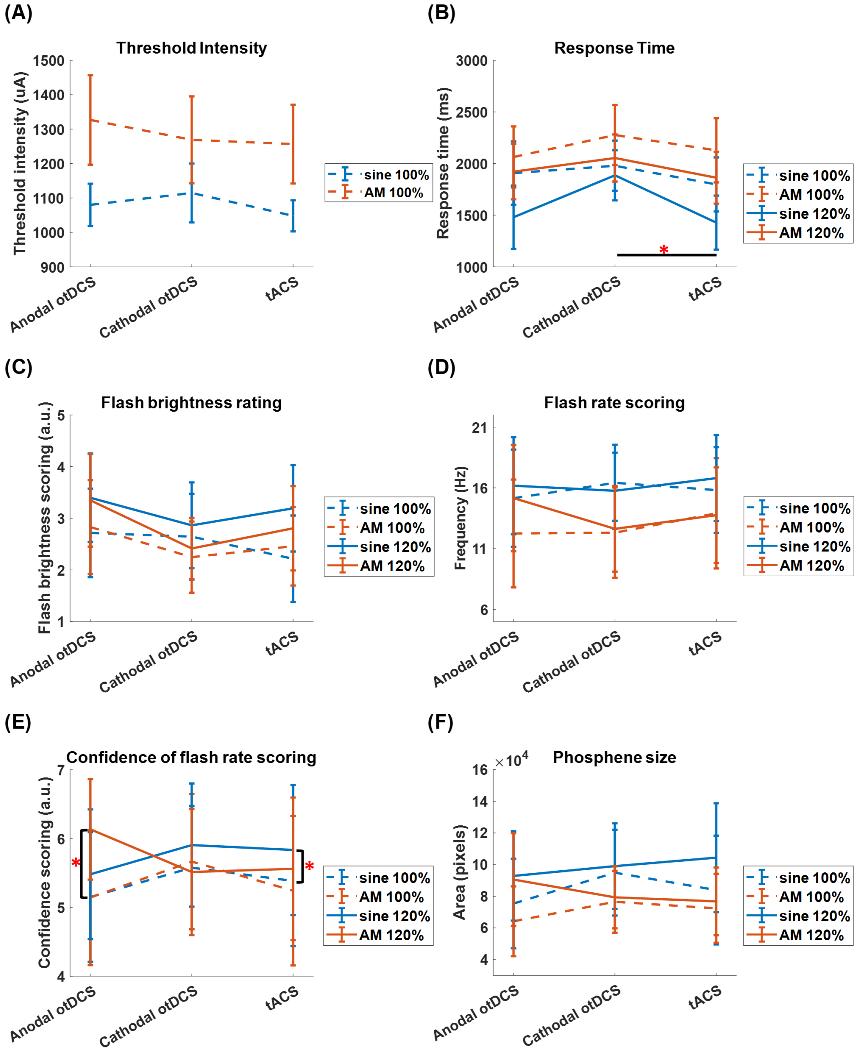

Figure 2. Comparisons of all measurement indices. (A) The phosphene threshold results were averaged across the anodal otDCS, cathodal otDCS, and tACS conditions, with the error bars representing 95% confidence intervals. Phosphene thresholds for AM stimulation were found to be higher than those for sinusoidal stimulation. (B) The graph presents the mean phosphene reaction time, with the solid line representing the threshold intensity (100%) and the dashed line indicating the suprathreshold intensity (120%). Phosphene reaction times for tACS were faster compared to those for cathodal otDCS. Additionally, reaction times in sinusoidal trials were faster than in AM trials, and they were quicker under suprathreshold conditions compared to threshold conditions. (C) The flash brightness scoring results indicated that participants perceived phosphene as being more absent at threshold intensity than at suprathreshold intensity. (D) The graph displayed the mean flash rate scoring. The results showed that AM dominated in both otDCS and tACS conditions. (E) The results showed that participants displayed greater confidence levels when responding to suprathreshold stimulation than threshold stimulation. This difference was particularly apparent in the AM stimulation during anodal otDCS and in the sinusoidal stimulation in tACS. (F) Drawings of phosphene size for sinusoidal stimulation were significantly larger than those for AM stimulation. Likewise, phosphene areas produced at suprathreshold intensities were apparently larger than those at threshold intensities. In addition to the results that both otDCS and tACS did not influence the phosphene size, exceptions were observed for both AM and intensity levels.

	Threshold	RT	Brightness	Flash Rate	Confidence
Polarity AM Intensity	X O —	O O O	O X O	X O X	X X O
Interaction	X	X	X	Polarity*Intensity (marginal)	Polarity*AM*Intensity

4.1 The current oscillation is the key to phosphene occurrence

Following our prediction and Evans et al.'s finding (Evans et al., 2021), participants reported phosphene occurrences in both anodal and cathodal otDCS, with no significant polarity effect on threshold intensity. This result suggests two key points: (1) current oscillation could be necessary for phosphene generation, and (2) the occurrence of phosphene is independent of cortical excitability, typically modulated by tDCS. In other words, the occurrence of phosphene relies on the*relative change* rather than the *absolute level* of the neural electromagnetic field.

This result is plausible as the phosphene percept essentially involves the detection of changes in brightness. By discerning spatial or temporal changes in brightness, individuals develop perceptions of contours or flashes. This perspective finds support in prosthesis research, where it has been observed that only dynamic stimulation on the visual cortex can elicit meaningful perceptions in individuals who are blind (Beauchamp et al., 2020). The importance of relative change in phosphene perception aligns with the well-established predictive coding theory (Rao & Ballard, 1999; Schultz et al., 1997). This theory posits that the system makes prior predictions about what should be perceived in a top-down manner. Within this framework, certain neurons carry information about the ”difference” between the predicted and perceived information (Koster-Hale et al., 2013). Only unexpected inputs are signaled for further processing (Koch & Poggio, 1999), or the awareness of information would be suppressed if it is ”explained away” (Seth et al., 2011).

Our results underscore the significance of neural oscillation in perception generation. As tACS applied to human participants (less than 2000 µA) is considered insufficient to induce neural spiking in the visual cortex, the source of phosphene has remained a puzzle for the past decade. While the prevailing explanation attributes tACS-induced phosphene to the activation of retinal cells through current leakage over the scalp (Laakso & Hirata, 2013), there are lines of evidence suggesting a contribution from cortical areas, as seen in (Evans et al., 2019, 2021). Despite the inherent challenges in measuring the cortical activation of phosphene perception in vivo in humans, the possibility of cortical involvement cannot be ruled out. In fact, the electromagnetic field of the neural system has been proposed as the basis of consciousness (McFadden, 2021). The global resonance theory posits that brain electromagnetic field oscillations could serve as the ”seat” of consciousness (Hunt, 2020; Hunt et al., 2022; Hunt & Jones, 2023). According to this theory, synchronous firing, or neural oscillation, signifies a shared electric field wherein local and global oscillatory couplings may represent complex information transfer across different brain areas or levels (Buzsáki, 2006). Supporting this perspective, an increasing number of studies have suggested the importance of neural oscillations and their functional connectivity in conscious function, as seen in (Engel & Fries, 2016; Modolo et al., 2020; Plosnić et al., 2023). Therefore, our results suggest the crucial role of the neural electromagnetic field in perception, as it causally induces visual perception through external current stimulations.

4.2 Response time reflects the mechanism of ephaptic coupling

Response times in our study are measured as the latency between the onset of stimulation and the keypress from participants reporting seeing a flash. Our findings reveal that multiple factors influence response time, including stimulation polarity, amplitude modulation, and intensity. Participants exhibited slower responses in cathodal otDCS compared to tACS, in 2 Hz amplitude-modulated at 18 Hz compared to sinusoidal at 18 Hz, and in threshold compared to suprathreshold stimulations.

Among these findings, the effects of both intensity and AM can be explained by the amount of delivered energy due to waveform shape and amplitude. With the same peak-to-peak amplitude, AM stimulation could deliver approximately half the energy of sinusoidal stimulation. In our experiment, the threshold amplitude for AM stimulation is about 1.3 times that of sinusoidal stimulation, with the delivered energy being approximately 65% of the threshold sinusoidal stimulation.

While the relationship between stimulation intensity and response time is commonly observed in psychophysics studies, the underlying neural mechanisms are rarely explained. Expanding on the global resonance theory, our results can be elucidated by the occurrence of ephaptic couplings in phosphene perception. Unlike typical synaptic transmission, ephaptic coupling transfers information between adjacent neurons through extracellular ion exchange or potential oscillation. It is thought to influence the synchronization of neural spiking (Anastassiou et al., 2011) and could be potent enough to elicit the firing of adjacent pyramidal cells with a single action potential (Han et al., 2018).

Computational models propose that ephaptic coupling within neural bundles may explain selective behavior (Chawla & Morgera, 2014), responses to peripheral nerve stimulation (Capllonch-Juan & Sepulveda, 2020), and the propagation of epilepsy (Shivacharan et al., 2021). A recent simulation study (Schmidt et al., 2021) demonstrated how ephaptic couplings could contribute to response time. The model showed that stronger stimulation triggers more neural spiking. While each spike could induce ephaptic coupling within the neural bundle, collections of ephaptic couplings become strong enough to elicit spiking volleys, thereby increasing the velocity of neural transmission that leads to the acceleration of response time. According to the model, not only are more neural spiking elicited by stronger stimuli, but the stimulation effect is also prolonged in the neural system.

This ephaptic coupling hypothesis could also explain the slower response time in cathodal otDCS. It is possible that cathodal direct current creates a hyper-polarized environment that makes it difficult to maintain the spiking volley. Therefore, our response time results can be explained by ephaptic coupling, which is considered the neural mechanism of the global resonance theory.

Polarity effect may imply the selective effect of stimulation

One of the primary goals of our study is to examine the polarity effect on phosphene perception. Compared to tACS, anodal otDCS induced brighter phosphene, but no significant difference was found between cathodal otDCS and tACS. However, cathodal otDCS did lead to longer response times. Interestingly, none of the otDCS conditions influenced the phosphene threshold, which is typically considered an index of neural excitability. This result indicates that while the occurrence of phosphenes is determined by electromagnetic oscillation, the perceptual quality can be influenced by cortical excitability.

TES has been observed to influence visual perception in various ways. A recent review discussed how noninvasive current stimulation over the visual cortex can affect visual perception (Bello et al., 2023). It suggested that anodal tDCS could marginally cause acute improvement in contrast perception, and offline current stimulation (including both tACS and anodal tDCS) could significantly enhance the ability of contrast detection. However, this study did not find any tES effect on response time, which contrasts our findings.

In a study that utilized the pedestal-delta-pedestal psychometric task to explore the contrast detection function of different visual pathways (Costa et al., 2015), a selective effect of tES was found. In the 4-alternate-forced-choice task, participants were asked to detect one of the four squares that increased (inferred parvocellular pathway) or decreased (inferred magnocellular pathway) its luminance in a different amount from other squares for a short period. Their results showed that during anodal tDCS, participants had a higher threshold for detecting the target of decreasing luminance than sham stimulation, indicating that anodal tDCS selectively affected the magnocellular pathway. The magnocellular pathway is associated with the processing of motion, depth, and high temporal and low spatial frequency information. In our study, the impact of polarity on brightness perception might also signify changes in the magnocellular pathway, as the perception of phosphenes inherently indicates the detection of temporal contrast of luminance.

Null result of intensity modulation on flash rate revealed independence of AM information coding in phosphene percept

Our flash rate scoring revealed a significant effect in the AM condition, consistent with our previous findings (Hsu et al., 2023). Participants perceived the flash rate as slower under AM stimulation than under sinusoidal stimulation. We observed a marginally significant interaction between intensity and polarity ($p = 0.07$), indicating that the flash rate was perceived faster under suprathreshold stimulation only in the case of anodal AM otDCS ($p = 0.01$). However, this effect was insignificant in other conditions, suggesting a limited overall impact of intensity on flash rate scoring. In essence, AM emerged as the primary determinant of the perceived flash rate, implying that the AM frequency may be encoded by the perceptual system and, at least partially, contribute to the perceived flash rate of phosphene.

The current results, therefore, suggest the constitution of the AM component in phosphene flash rate and provide strong evidence of detecting the temporal envelope despite the spatial envelope in visual perception.

5. Conclusion

The study investigated the neural mechanisms of phosphene using oscillatory transcranial electric stimulations with different polarities and amplitude modulations. Firstly, our results demonstrated that oscillatory electric stimulation can elicit phosphene irrespective of polarity. This finding underscores the importance of dynamic electromagnetic changes in the emergence of visual experiences, supporting the global resonance theory's proposition that brain oscillation could serve as the foundation of consciousness. Furthermore, we illustrated that neural alignment to AM frequency contributes to phosphene flash rate, and this effect is independent of carrier frequency. This result implies that alignment to external stimulations significantly influences the subjective perception of temporal frequency. Finally, the observation of increased brightness with anodal otDCS and prolonged RT with cathodal otDCS suggests a polarity effect on phosphene quality without interacting with threshold intensity. This discovery implies that current oscillation and polarity may be processed independently, contributing to different aspects of phosphene. In line with our research objectives, the current study provides substantial evidence elucidating the underlying mechanisms of phosphene perception. Our findings in perceptual measurements establish a connection between neural oscillation and subjective visual experiences, opening up new possibilities for future research on prosthesis vision techniques.

Credit author statement

Che-Yi Hsu : Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review and editing, Visualization.**Tzu-Ling Liu** : Conceptualization, Methodology, Validation, Formal analysis, Resources, Data curation, Writing – original draft, Writing – review and editing, Visualization. **Chi-Hung Juan** : Conceptualization, Methodology, Project administration, Funding acquisition, Writing – review and editing.

Conflict of interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics statements

The studies involving human participants were reviewed and approved by the Research Ethics Committee of Chang-Gung Memorial Hospital, Taiwan. Furthermore, the patients/participants provided their written informed consent to participate in this study.

Data availability

The raw data and analysis code supporting the findings of this article are openly available on the Open Science Framework: https://osf.io/rd4g5/.

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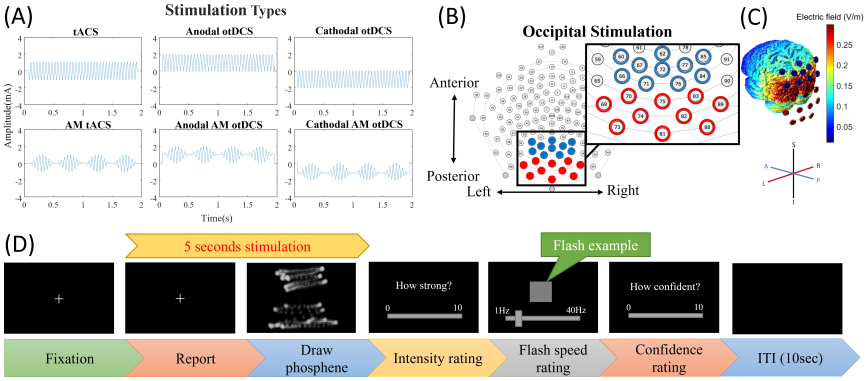
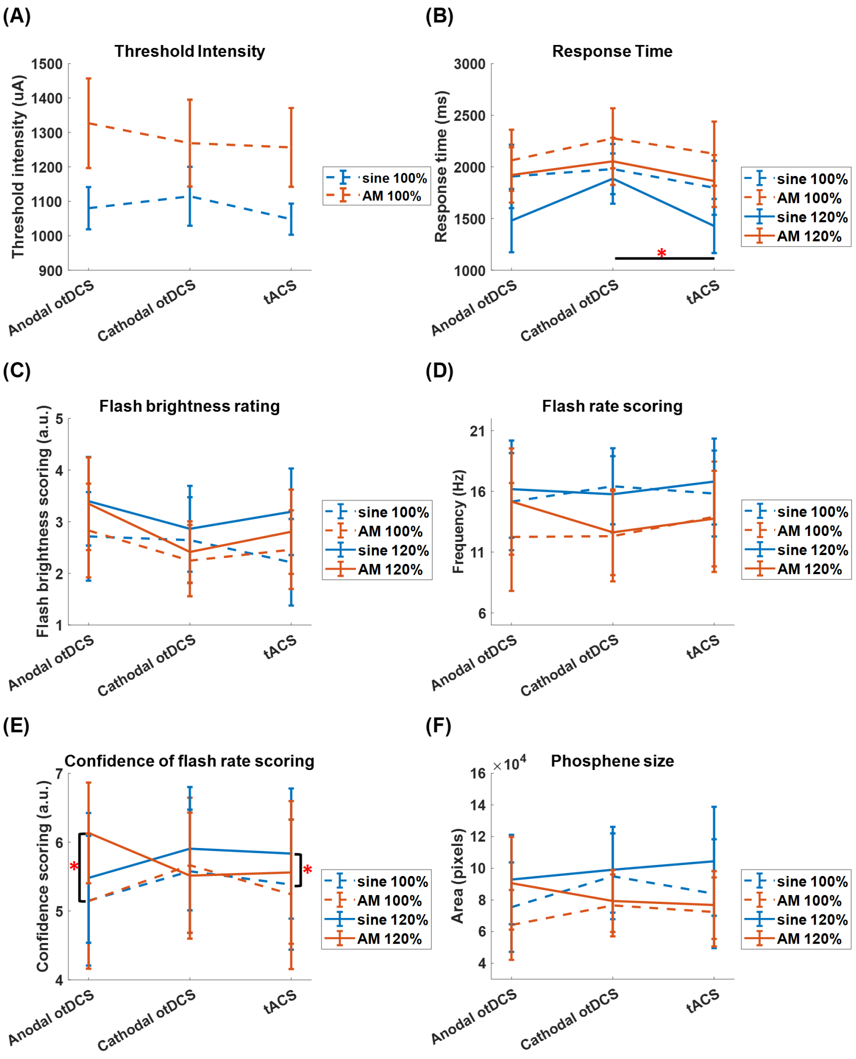

(A)
Stimulation Types
tACS
Anodal otDCS
Cathodal otDCS
AM tACS
Anodal AM otDCS
Cathodal AM otDCS
Amplitude(mA)
Time(s)
(B)
Occipital Stimulation
Anterior
Posterior
Left
Right
(C)
Electric field (V/m)
0.25
0.2
0.15
0.1
0.05
S
A
R
L
P
I
(D)
5 seconds stimulation
Flash example
How strong?
0
10
1Hz
40Hz
How confident?
0
10
Fixation
Report
Draw phosphene
Intensity rating
Flash speed rating
Confidence rating
ITI (10sec)



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