

# Precise oculocentric mapping of transcranial magnetic stimulation-evoked phosphenes

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**Objective** Transcranial magnetic stimulation (TMS)-evoked phosphenes are oculocentric; their perceived location depends upon eye position. We investigated the accuracy and precision of TMS-evoked phosphene oculocentric mapping.

**Methods** We evoked central phosphenes by stimulating early visual cortical areas with TMS, systematically examining the effect of eye position by asking participants to report the location of the evoked phosphene. We tested whether any systematic differences in the precision or accuracy of responses occurred as a function of eye position.

**Results** Perceived phosphene locations map veridically to eye position, although there are considerable individual differences in the reliability of this mapping.

## Introduction

Transcranial magnetic stimulation (TMS) is a noninvasive neurostimulation technique that involves magnetic induction of an electrical current within a relatively localized area of superficial neural tissue. When an individual pulse, or a train of individual pulses, is applied to the visual cortex, an illusory light percept known as a phosphene is often experienced [1]. While there may be some systematic variation in the subjective appearance of evoked phosphenes in different early visual areas, the phosphene threshold, or the minimum stimulation output power required to evoke a phosphene response, is similar across the early visual cortex [2]. Stimulating early cortical areas can elicit phosphenes somewhat reliably, but it is more difficult to elicit phosphenes from later visual areas, such as V5 and LOC [3].

While it is vital to carefully account for the reliability and limitations inherent in the subjective reporting of phosphenes [4], phosphene thresholds and subjective judgments about phosphene characteristics have proven to be useful probes into the function and the excitability of the visual cortex. Blind participants were demonstrated to perceive phosphenes, though at a reduced rate relative

**Conclusions** Our results emphasize the need to carefully control eye movements when carrying out phosphene localization studies and suggest that individual differences in the reliability of the reported position of individual phosphenes must be considered. *NeuroReport* 32: 913–917 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

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to normal control participants, depending on the level of function of the primary visual cortex [5,6]. Additionally, reduced phosphene thresholds were observed in normal-vision participants after short-term light deprivation, indicating increased cortical excitability [7]. Cueing spatial attention toward the anticipated location of the phosphene was similarly suggested to increase cortical excitability [8].

Phosphenes evoked through direct, invasive cortical stimulation are oculocentric, moving with self-generated eye movements [9]. This is perhaps expected, as primary visual cortex is a retinotopically-defined area with adjacent cortical areas encoding adjacent retinal locations. As a result, researchers have been continuously developing visual prostheses that employ electrical cortical stimulation to evoke phosphenes, providing blind individuals with some baseline level of visual information [10–13]. These visual prostheses allow recovery of some light discrimination, but spatial and temporal information remains coarse [14]. Similarly, non-invasive TMS also evokes oculocentric phosphenes [15], though TMS must penetrate the scalp and skull and may therefore elicit a noisier oculocentric mapping.

Studies involving TMS-evoked phosphenes often require that participants fixate a point, taking for granted that participants comply with fixation and that all evoked phosphenes will be positioned identically relative to fixation if TMS-coil position remains constant. However, the precision of a phosphene's location with repeated trials,

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and the precision of the oculocentric mapping of TMS-evoked phosphenes, has not been thoroughly investigated. In the current study, we carry out a systematic investigation of the relationship between eye position and TMS-evoked phosphenes. Participants were directed to fixate individual points arranged in a grid while TMS was delivered to a fixed scalp location to induce phosphenes. Phosphene location was reported for each fixation point. We found that overall, TMS-evoked phosphenes mapped accurately to the point of fixation, though inter-participant variability was observed that could not be explained by eye movements or TMS-coil position alone.

## Methods

### Participants

Twenty-one participants with self-reported normal vision were recruited and tested for reliable phosphenes and stable eye tracking. Nine participants (6 women, 3 men, ages: 21–41, median: 24) completed the study. Informed consent was obtained from all recruited participants, and all participants were treated in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Participants received CAN\$30.

### Transcranial magnetic stimulation

Biphasic Triple-pulse TMS with an interpulse interval of 100 ms was delivered using a MagPro X100 (MagVenture Farum, Denmark) stimulator with the MCF-B65 coil guided by the Brainsight frameless stereotaxic neuronavigation system (Rogue Research, Inc., Montreal, Canada). Coil placement errors were carefully monitored during every stimulation trial. Trials were repeated if the position error exceeded 2 mm or if the angle or twist error was greater than 5°. In total, 11 trials across 9 participants were repeated due to poor coil placement. Every individual triple-pulse TMS train was preceded by a verbal 3 s countdown.

### Procedure

#### Phosphene thresholding

Individual participants' stimulation intensity was determined using a phosphene thresholding procedure to find the minimum intensity for which triple-pulse TMS evoked a phosphene five consecutive times. Participants were dark-adapted for 20 min with eyes open and all room lights off. They were then instructed to fixate a dim point ( $2.50 \text{ cd/m}^2$ ) on a solid dark background ( $1.75 \text{ cd/m}^2$ ) presented on a computer monitor with all other lights turned off. The TMS coil was placed 2 cm above the inion and the participant was stimulated with triple-pulse TMS at 40% maximum stimulator output, after which participants indicated whether they perceived a phosphene. If no phosphene was perceived after two attempts, the intensity was increased in 10% steps, to a maximum of 80%, and if the initial position failed to evoke any phosphenes, the coil was moved in increments

of 2 cm, gradually testing points further from the original stimulation point. After a phosphene was perceived, participants used a computer mouse to indicate the location of the phosphene while maintaining fixation. Participants were instructed to click on the center of their perceived phosphene. The stimulation point was adjusted until the reported phosphene was no more than  $2.62^\circ$  (100 pixels) away from fixation. The intensity of the stimulation was then changed in increments of 5% until the minimum intensity required for the participant to report seeing 5/5 phosphenes was found. The resulting coil position and stimulation intensity were saved and used in the main experiment.

#### Behavioral apparatus, task and stimuli

The stimulus software was programmed using the Python package Psychopy [16,17]. Stimuli were presented on a computer monitor of height 34 cm and width 60 cm, with  $1920 \times 1080$  pixel resolution. Participants were seated and used a chin and headrest for head stabilization. The viewing distance was 67 cm, and each pixel subtended roughly  $0.027^\circ$ .

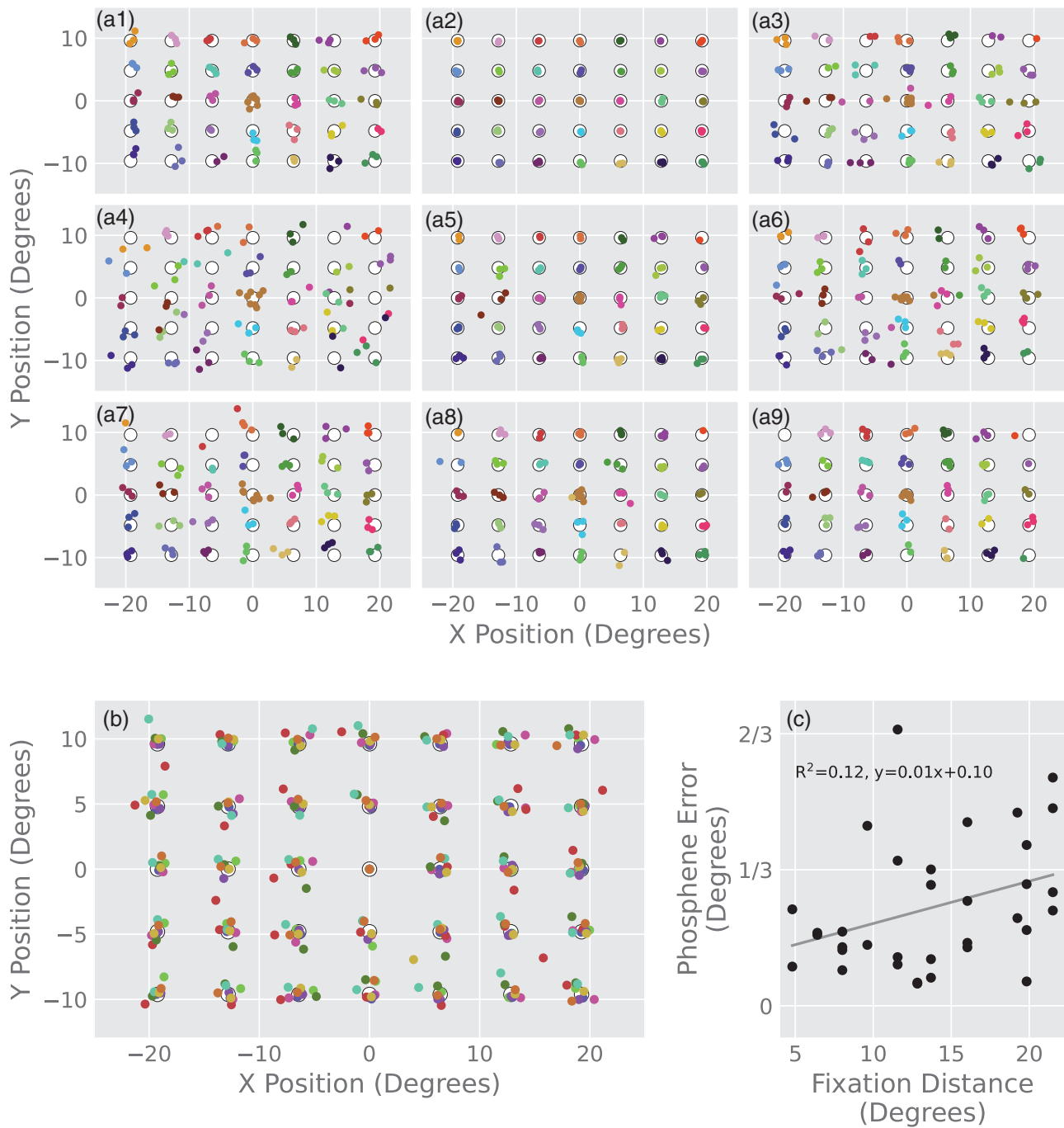
To begin each trial, participants fixated a dim gray dot. Possible locations for fixation were defined using a  $38.5^\circ$  by  $19.2^\circ$  grid of points, with seven equally-spaced points distributed horizontally and five equally-spaced points distributed vertically. Therefore, 35 total fixation locations were tested. On any given stimulation trial, only one randomly sampled fixation dot was visible. The appropriate fixation dot was visible for the entire duration of the verbal 3 s countdown, allowing participants to fixate comfortably before each stimulation.

After TMS stimulation, participants used the mouse to indicate the center of the perceived phosphene while maintaining fixation. If no phosphene was perceived, the stimulation was repeated before the mouse click. The stimulus intensity was increased by 2% of the maximum stimulator output if a phosphene was not evoked after two concurrent attempts during the experimental task.

Participants always fixated on the middle location during the first five stimulation trials. After these initial trials, all fixation locations, including the middle location, were tested three times. In all,  $35$  (fixation locations)  $\times$   $3$  (# trials)  $+ 5$  (initial middle trials) = 110 trials were presented. A Gazepoint GP3 eyetracker was used to monitor eye movements, and any trials exhibiting a saccade, defined as an eye movement with a velocity greater than  $40^\circ/\text{s}$ , were removed from the analysis.

Before performing the main stimulation task, participants underwent a brief training procedure without TMS-evoked phosphenes. Instead, brief dim circular flashes ( $2.5 \text{ cm/m}^2$ ) were presented to participants, located randomly within a square of side length 400 pixels, or  $10.7^\circ$

Fig. 1



Oculocentric phosphene mapping results. All phosphene reports were centered relative to the arithmetic mean of the individual within-subject phosphene locations at the center-most fixation location. (a) Individual-subject results. Identically colored dots represent individual phosphene reports evoked when fixating the same location. (b) Average reported phosphene locations at each oculocentric position, calculated as the arithmetic mean of all evoked phosphenes at the given position per participant. Identically colored dots represent data from the same participant. (c) Scatterplot illustrating the relationship between phosphene position error and eccentricity of the fixation point for the high precision dataset (a1, a2, a5, a8, a9).

and centered on the fixation point. Therefore, the circular flash could be as far as 7.6° from fixation. Participants were required to indicate the central position of the flash with a mouse click. Training ended when participants

were within 100 pixels or 2.7° of the flash location five consecutive times while maintaining fixation. Six participants required 10 or fewer trials, two participants required fewer than 20 trials, and one participant required

26 trials. Training was always completed within 3 min. The fixation point was randomly selected as in the main task. Participants were not informed that the precision of phosphene localization was of interest in the current study to avoid biasing the results.

## Results and discussion

During the main experiment, 52 total stimulation trials failed to evoke a phosphene out of 110 (trials)  $\times$  9 (participants) = 990 total trials. Of these, 29 trials originated from participant A5. All failed trials were repeated successfully, and all participants reported seeing the 110 phosphenes required to complete the study. Fig. 1a,b present single-subject and group results, respectively. Before any processing, all data were centered by the arithmetic average position of the phosphenes corresponding to the central fixation point. Aside from this centering procedure, the central data points were not used in any analysis.

To quantify the accuracy of phosphene reports, phosphene error was defined as the Euclidean distance between the fixation point and the arithmetic average phosphene location elicited when fixating the given point. The average phosphene error across all participants and fixations was  $0.32^\circ$  (SD:  $0.26^\circ$ ). Phosphene precision was defined as the arithmetic mean of the Euclidean distances between each of the three evoked phosphenes for a given fixation point. The average phosphene variability was  $1.43^\circ$  (SD:  $0.55^\circ$ ).

Fig. 1a,b reveal relatively veridical oculocentric mapping of perceived phosphene location to the fixation position. Average phosphene error was calculated separately for each of the 35 fixation points and the data were analyzed with a simple linear regression to examine the relationship between phosphene error and fixation eccentricity. No significant relationship between phosphene error and fixation position was found,  $R^2 = 0.02$ ,  $P = 0.44$ .

Fig. 1a demonstrates notable between-subject variability of phosphene precision. Therefore, a mean split on phosphene variability was carried out such that participants A3 ( $1.6^\circ$ ), A4 ( $3.7^\circ$ ), A6 ( $1.7^\circ$ ) and A7 ( $1.6^\circ$ ) composed a low precision group, and participants A1 ( $1.2^\circ$ ), A2 ( $0.2^\circ$ ), A5 ( $0.6^\circ$ ), A8 ( $1.1^\circ$ ) and A9 ( $1.0^\circ$ ) composed a high precision group. The simple linear regression was repeated for each group separately as exploratory analyses. No significant relationship was found in the Low Precision data,  $R^2 = 0.01$ ,  $P = 0.54$ . However, the relationship between fixation location and phosphene error was statistically significant in the high precision dataset,  $R^2 = 0.12$ ,  $F(1,32) = 4.4$ ,  $P = 0.045$ . The unstandardized regression coefficient was 0.01 and the intercept was 0.99. Therefore, the model predicts a phosphene error of  $0.15^\circ$ , or  $8.9'$ , when fixating the points nearest to center ( $4.8^\circ$  eccentricity) and a phosphene error of  $0.32^\circ$ , or  $19.3'$ , when fixating the farthest points ( $21.5^\circ$  eccentricity). Fig. 1c illustrates this analysis. No significant relationship

was found between phosphene position variability and fixation distance.

These results confirm that on average, TMS-evoked phosphenes are oculocentric [9,15]. In addition, a small but significant association was found in the post hoc analysis of the five most precise participants. This effect may arise from inexperience with making position judgments at extreme eye positions that normally induce a head turn. However, the effect was not detected in the larger and noisier dataset. Further testing is warranted to examine whether this effect is generalizable.

Furthermore, these results demonstrate the presence of individual differences with respect to the precision of oculocentric mapping. These differences may arise from external factors such as eye movements and TMS coil position errors. While the current study attempted to minimize these factors, it should be noted that due to the technical failure of our eyetracker, only the presence of saccades could be checked within the collected eye data, and not the absolute fixation location. Even so, the fixation point was presented clearly and in isolation; participants had no reason or incentive to fixate a different location. Due to the evident oculocentric nature of phosphenes, future work may also benefit from correlating measures of fixation instability with the precision of phosphene location judgments.

TMS-induced phosphenes are inherently variable and idiosyncratic across individuals. Phosphenes are known to vary in size, geometric shape and visibility [2,18]. Therefore, a participant's phosphene precision may depend on the ease of identifying their individual phosphene's center of mass. Finally, differences in the variability of the motor response may contribute to the variability of the phosphene localization. We examined this possibility using our training data, calculating the SD of the distances between the training flash and the associated mouse click response. We correlated this measure of motor variability with phosphene variability and found no association,  $r = 0.04$ ,  $P = 0.9$ . However, a study designed specifically to parse out motor variability from the overall variability of phosphene localization is required.

Ultimately, our results reinforce the need to be aware of the oculocentric nature of TMS-evoked phosphenes, as fixating an incorrect location will skew the reported localization. In addition, researchers should be mindful of inter-subject differences in the precision of phosphene localization.

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## Conflicts of interest

There are no conflicts of interest.

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