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Reliability of TMS phosphene threshold estimation: Toward a standardized protocol

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ABSTRACT

Background: Phosphenes induced by transcranial magnetic stimulation (TMS) are a subjectively described visual phenomenon employed in basic and clinical research as index of the excitability of retinotopically organized areas in the brain.
Objective: Phosphene threshold estimation is a preliminary step in many TMS experiments in visual cognition for setting the appropriate level of TMS doses; however, the lack of a direct comparison of the available methods for phosphene threshold estimation leaves unsolved the reliability of those methods in setting TMS doses. The present work aims at fulfilling this gap.
Methods: We compared the most common methods for phosphene threshold calculation, namely the Method of Constant Stimuli (MOCS), the Modified Binary Search (MOBS) and the Rapid Estimation of Phosphene Threshold (REPT). In two experiments we tested the reliability of PT estimation under each of the three methods, considering the day of administration, participants' expertise in phosphene perception and the sensitivity of each method to the initial values used for the threshold calculation.
Results: We found that MOCS and REPT have comparable reliability when estimating phosphene thresholds, while MOBS estimations appear less stable.
Conclusions: Based on our results, researchers and clinicians can estimate phosphene threshold according to MOCS or REPT equally reliably, depending on their specific investigation goals. We suggest several important factors for consideration when calculating phosphene thresholds and describe strategies to adopt in experimental procedures.

1. Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive method for temporarily and reversibly interacting with functions of a targeted brain area. The experimental practice involves setting different parameters to define the TMS protocol (i.e., stimulation intensity, frequency duration, and pulse latency) [1]. Among those parameters, the intensity of the magnetic field (the percentage of the maximum stimulator output, MSO), has special relevance since it is used to measure and standardize the stimulus doses among individuals. Recent evidence suggests that choosing high or low TMS doses can either suppress or enhance behavioural response outcomes, respectively [2–5] thus making TMS intensity a critical parameter for data interpretation in cognitive models and for clinical applications.

There are different approaches for setting TMS intensity and one of them involves choosing a fixed value for all participants (e.g. 65%) [6], thus saving time. However, differences in cortical excitability, cortical structure and skull shape between participants require adjusting the TMS pulse individually, for example calculating psychophysical threshold on motor (motor threshold – MT) or visual (phosphene threshold – PT) cortices, respectively. While there are well-established procedures for computing MT [7–9], PT procedures are scarce. This is an important gap in experimental routine, because MT ceases to provide a reliable index for individually setting TMS intensity moving from motor cortex to other cortical areas [10]. Conversely, PT is a good candidate for establishing the effectiveness of the stimulation of the posterior brain.

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Indeed, reliable phosphenes have been reported after stimulation of retinotopic areas both in occipital and parietal cortex [11–13], making PT a cardinal parameter in investigating complex cognitive processes, like visual attention and awareness [14].

A standardized procedural definition of PT calculation is particularly challenging since phosphenes are subjective reports. Adding to complexity, PT can be affected by several other factors. For example, keeping the eyes closed or open changes the PT [15,16], as do the light level of the environment [17], instructions given to participants, participants' expectancy and expertise in phosphene perception, and the method used to calculate the threshold. Our aim is to compare psychophysical methods to calculate the PT.

Three main procedures are typically used to estimate PT: the Modified Binary Search (MOBS) [18,19], the Method of Constant Stimuli (MOCS) [20], and the Rapid Estimation of Phosphene Threshold (REPT) [21]. We conducted two experiments. In the first one three methods (i.e. MOBS, MOCS, and REPT) were compared within one session on three different days. This way, we aimed at testing the reliability of each method between and within participants in repeated sessions. We also considered participants' expertise with phosphene phenomenon comparing two groups (naïves vs. experts). In Experiment 2, we used data from Experiment 1 as prior to evaluate possible improvements in PT estimation due to the initial intensity range of two of the PT methods (MOCS and REPT) employed in Experiment 1.

2. Method

2.1. Experiment 1

2.1.1. Participants

A total of 22 healthy participants with normal or corrected to normal visual acuity were recruited for the experiment and reimbursed for their participation. They had no contraindications to TMS, as assessed by the safety screening questionnaire (adapted from Ref. [22]). Three participants were not able to perceive phosphenes and were excluded from the experiment. Moreover, two participants dropped out after the first day of testing and they did not complete the experiment. The remaining 17 participants (4 males), including two authors (C.M. and S.S.), took part in the experiment (19–39 years old; one left-handed). Ten of them were naïve to phosphene. All of them but the two authors were naïve to the goals of the study.

All the participants gave their written informed consent before participating in the study, which was conducted in accordance with the 2013 declaration of Helsinki and approved by the local Ethics Committee.

2.1.2. Apparatus and procedure

The participants were seated in a dark room at a distance of 57 cm from a 17 inch LCD monitor (LG L1753HM), with chin and forehead steadied so that eyes were aligned with the centre of the screen. The participants wore earplugs and a close-fitting cap with the 10–20 international system marked on.

To illustrate what a phosphene is, we showed participants some examples of phosphenes drawings [15]. Participants were instructed to not expect a flash of light, instead to covertly explore all the visual field and to look for a spatially circumscribed visual change (in brightness or texture) on the background.

Participants were adapted to the light conditions of the experimental room for at least 5 min prior to the experiment. They were instructed to keep the fixation steady on the central spot on a completely black screen. To confirm that participants perceived authentic phosphenes, some criteria [23] such as the dependence on the stimulated hemisphere (i.e. phosphenes in the contralateral visual field [24]), the dependence on gaze direction [24], and the visibility with eyes both open and closed [25] had to be satisfied. We further tested phosphenes reliability asking participants to describe the position, size, texture, colour and shape of perceived phosphenes. A few days before the beginning of the experiments, naive participants were invited to the laboratory and familiarized with TMS procedure and phosphenes perception. Furthermore, all the participants ran at least one threshold estimation before the beginning of the experiment as training.

At the beginning of each session, the coil was placed over O1 (we only tested the left hemisphere) and it was slightly moved in all directions in a region within a circle of 2 cm in diameter centered on O1 until bright and reliable phosphenes were induced. By means of a mechanical arm (www.manfrotto.com) the coil was then fixed over this "hotspot" (i.e. the best location where circumscribed, right hemifield-lateralized phosphenes were perceived) and this position was marked on the cap to be used throughout the experimental session. The coil was placed tangentially to the skull, parallel to the mid-line with the handle pointing upwards to avoid unspecific activation of neck and shoulder muscles. Single-pulse TMS was discharged using a Magstim Rapid^2 (Magstim Company Limited, Whitland, UK) system (MSO = 3.5 T) through a 70 mm figure-of-eight coil. Both TMS pulse trigger and response acquisition were controlled by Matlab (The MathWorks, Natick, MA) and the Psychtoolbox (ver. 3.00 [26–28]).

2.1.3. Phosphene threshold measurement

We collected data from three psychophysical methods (MOBS, MOCS, and REPT) on three days (Monday, Wednesday and Friday of the same week within participant). Each day, the order of methods was counterbalanced among participants. The experiment lasted about half an hour each day.

On each trial, participants were instructed to keep their eyes open, to maintain visual fixation on the central spot and, after each TMS pulse, to report the presence or the absence of a phosphene with a "yes/no" response by pressing two different keys. Based on the response and psychophysical method, the computer automatically adjusted the TMS intensity for the subsequent trial, thus avoiding the experimenter to manually adjust the intensity after each response. Participants had to press the spacebar to continue to the next trial, thus promoting coordination between pulse delivery and attending to phosphenes. The inter-pulse interval was longer than 3 s for all methods employed, in accordance with the safety guidelines [22].

2.1.4. Modified Binary Search (MOBS)

MOBS [18] is an adaptive non-parametric algorithm which uses the mathematical method of bisection combined with additional heuristics to estimate PT. Initially, the first TMS intensity is set to the midpoint of the available range (51% of MSO). The extreme values (1% and 100%) are called the bottom and top elements and 51% is called middle element. After participant's response, the search range for PT is updated by setting new values of each element. For example, if participant responded "no" to seeing phosphene at 51% intensity, the bottom and top elements are set to 51 and 100%, respectively, and the middle element is set to 76%. The middle element (76%) is the next stimulation intensity. If participant responds "yes" at this intensity, the new search range will be set from 51 to 76% while if the response is "no" the search range is moved from 76% to 100%. If two consecutive "yes" (or "no") are reported, the next stimulation intensity will be the bottom (or top) element of the available range. A process of "regression" is needed if the participant responds inconsistently to her/his previous response. In this case, all elements are moved up by one, losing the