



Motor and phosphene thresholds: a transcranial magnetic stimulation correlation study

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Abstract

Objective: To investigate the stability of visual phosphene thresholds and to assess whether they correlate with motor thresholds. **Background:** Currently, motor threshold is used as an index of cortical sensitivity so that in transcranial magnetic stimulation (TMS) experiments, intensity can be set at a given percentage of this value. It is not known whether this is a reasonable index of cortical sensitivity in non-motor and hence whether it should be used in experiments where other cortical areas are targeted. Previous studies have indicated that phosphene threshold might be a suitable alternative in TMS studies of the visual system. **Method:** Using single pulse TMS visual phosphene and motor thresholds were measured in 15 subjects. Both thresholds were retested in seven of these subjects a week later. **Result:** Visual phosphene thresholds, though stable within subjects across the two sessions, showed greater variability than motor thresholds. There was no correlation between the two measures. **Conclusion:** TMS motor thresholds cannot be assumed to be a guide to visual cortex excitability and by extension are probably an inappropriate guide to the cortical excitability of other non-motor areas of the brain. Phosphene thresholds are proposed as a potential standard for inter-individual comparison in visual TMS experiments. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Transcranial magnetic stimulation; Phosphene threshold; Motor threshold

1. Introduction

The use of transcranial magnetic stimulation (TMS) in investigations of the motor system has advanced further than in studies of the visual system. One of the main reasons for this is that a muscle response elicited by TMS and measured by electromyogram (EMG) provides a reasonably objective measure of the individual subject's sensitivity to stimulation. This measure can then be used in other motor experiments to calibrate the level of stimulation across subjects by applying TMS at a given percentage of each subject's motor threshold. A standardized method of calibrating stimulation intensity to an individual subject's sensitivity is important for at least two reasons. Firstly, motor

thresholds are commonly used as a valuable guide in establishing the envelope of safety in TMS studies [16]. Secondly, a standardized method of setting stimulation level according to an individual's sensitivity allows findings from different TMS studies to be more directly comparable. Non-motor TMS experiments do not at present benefit from such a standardized procedure. Studies of visual cortex have variously used stimulator output levels ranging from 35 to 100% of stimulator output to achieve functional disruption [2,6,13] but rarely are these levels chosen on the basis of an individual's sensitivity to TMS.

Single pulse or repetitive TMS can be used to readily elicit phosphenes in healthy subjects [12]. Two studies have used TMS to elicit phosphenes in migraine sufferers in order to determine whether, as a group, the excitability of occipital cortex differs from that of non-migraine sufferers [1,4]. The present study suggests that phosphene threshold be used as a measure of occipital

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cortex excitability in healthy subjects, in the same way that motor threshold is used as an index of cortical excitability of this area. In order to investigate the potential usefulness of phosphene thresholds as an analogue of motor thresholds, it is first necessary first to establish whether phosphene thresholds correlate with motor thresholds. If this were found to be the case, experimenters would have the option of using visual or motor measures to standardize the stimulation intensity to the individual subject's sensitivity. If they were not found to correlate, one might propose that TMS studies of vision or cognition should calibrate stimulation intensity as a function of phosphene rather than motor threshold since the former is more likely to reflect the sensitivity of the areas which will be stimulated. However, in order for phosphene thresholds to be truly useful, they must be demonstrated to be as robust as motor thresholds.

2. Methods

Fifteen subjects, aged between 19 and 37 and all right handed, took part in the experiment. All 15 had visual and motor thresholds measured and seven of them returned to have these measures repeated at least 1 week later. Subjects reported absence of epilepsy, migraine, or any other neurological condition in themselves and their known family history. Ethical committee approval was granted for all procedures.

The stimulator used was a Magstim TM model 200 (Magstim, Whitland, Dyfed) connected to a figure of eight coil with external wing diameters of 9 cm and a peak magnetic field of 2.2 T. The double coil windings carry two currents in opposite directions such that, where the two loops meet, there is a localized summation of current, and stimulation is more focal compared to coils with a single winding [14]. The coils are connected such that the initial phase of the stimulating current in the junction region flows toward the coil handle.

2.1. Establishing phosphene threshold

Subjects wore a blindfold and a cap on which three points, positioned over the occipital midline and 2, 3 and 4 cm above the inion were marked. The coil was positioned such that the handle pointed upwards and was parallel to the subject's spine. Single pulse TMS was applied over one of the marked points and the subject was asked to report the presence or absence of a phosphene immediately after stimulation. Stimulation was repeated ten times at each intensity at a maximal frequency of 0.2 Hz. Stimulation was initially applied at 60% of stimulator output. If the subject reliably perceived a phosphene, reporting it five or more times out

of ten, intensity was reduced in steps of 5% and stimulation was again given ten times. Stimulation intensity was reduced until the subject no longer reliably perceived a phosphene. Stimulation intensity was then changed in blocks of 5% around this level until the minimum intensity at which the subject could perceive a phosphene five times out of ten was established and this value was taken as threshold. If the subject did not perceive a phosphene at 60% of stimulator output, intensity was increased in blocks of 5% to a maximum level of 100% of stimulator output. If the subject still failed to perceive a phosphene, the coil position was shifted to another of the points marked on the cap and the procedure was repeated at this location.

2.2. Establishing motor threshold

Surface EMG responses were recorded from the first dorsal interosseus (FDI) muscle of the left hand using 0.9 cm diameter silver/silver-chloride surface electrodes, with the active electrodes placed over the motor joint. The reference electrodes were placed over the interphalangeal joint. Responses were amplified by Digitimer D150 amplifiers (Digitimer, Welwyn Garden City, Herts) at a gain of $5000 \times$, filtered with a time constant of 3 ms and a high-pass filter set at 3 kHz. Subjects were asked to press the first finger and thumb together and to maintain a constant level of contraction in the FDI muscle throughout the procedure. Feedback was provided by the recorded EMG signal, displayed on an oscilloscope. The coil was positioned such that the junction region of the figure of eight coil was approximately perpendicular to the presumed line of the central sulcus. Single pulse TMS was given over the subject's right motor cortex at an intensity which could elicit a motor evoked potential (MEP). A motor hotspot (the area of motor cortex producing the largest MEP) was found by moving the coil in 1–2 cm steps using constant suprathreshold stimulus intensity. At this point the stimulation intensity was reduced in steps of 2%. Stimulation was applied 10 times at each intensity at a maximum frequency of 0.5 Hz. The intensity at which an MEP of over 100 μV occurred in more than 50% of trials was designated the motor threshold.

3. Results

3.1. Phosphene thresholds

Stimulation, applied over the occipital midline and between 2 and 4 cm above the inion, elicited phosphenes in all 15 subjects. Phosphene threshold ranged between 35 and 85% of stimulator output. Phosphene thresholds of the seven subjects who were retested at least 1 week later ranged between 35 and 65% stimula-

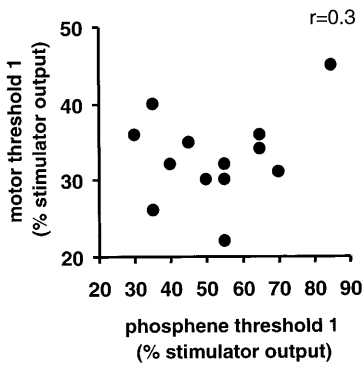


Fig. 1. Visual phosphene thresholds (in percent of maximum stimulator output) of the seven subjects who were tested at both sessions. These subjects had the same range of thresholds as the remaining subjects who were only tested once. As can be seen, their thresholds were stable over the two sessions. The solid line is the calculated regression of threshold 1 against threshold 2.

tor output. There was a significant correlation between the phosphene thresholds at the two times of testing (Fig. 1, correlation coefficient = 0.7; $P < 0.01$).

3.2. Motor thresholds

Stimulation over the right motor cortex elicited MEPs from the FDI muscle in all 15 subjects. Motor threshold ranged between 22% and 45% of stimulator output. Motor thresholds of the seven subjects who were retested at least 1 week later ranged between 22% and 38% of stimulator output. There was a significant correlation between motor thresholds at the two times of testing (Fig. 2, correlation coefficient = 0.8; $P < 0.01$).

Motor and phosphene thresholds did not correlate with each other (Fig. 3(a) and (b); correlation coefficient = 0.33 and 0.08 at the two times of testing, respectively).

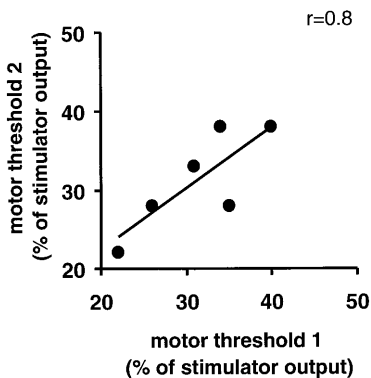


Fig. 2. Motor thresholds of the seven subjects who were tested at both sessions. These subjects had the same range of thresholds as the remaining subjects who were only tested once and, as can be seen, their thresholds were stable over the two sessions. The solid line is the calculated regression of threshold 1 against threshold 2.

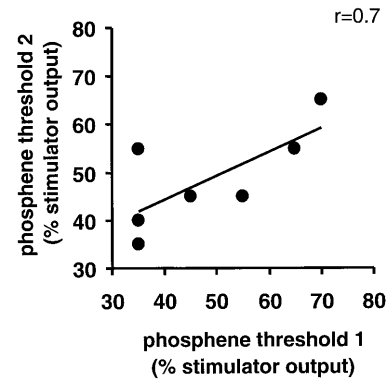


Fig. 3. (a) Relationship between visual and motor thresholds in all 15 subjects. There is no significant correlation between the two sets of values. (b) Relationship between visual and motor thresholds in the seven subjects who were retested 1 week later. There is no significant correlation between the two sets of values.

4. Discussion

The findings of this study were:

1. Phosphene and motor thresholds were robust across testing sessions held at least a week apart.
2. Phosphene and motor thresholds differed within subjects with phosphene threshold greater than motor threshold except in two cases.
3. Phosphene thresholds were more variable across subjects than motor thresholds.
4. Phosphene and motor thresholds did not correlate with each other.

The finding that visual phosphene thresholds were stable across different testing sessions held at least 1 week apart suggests that phosphene thresholds provide a stable and reliable measure of visual cortical sensitivity. Subjects do not always perceive phosphenes immediately but sometimes require a few trials of suprathreshold stimulation to get an idea of what the perception may be like. Once experienced, however, phosphenes seem to be unambiguous and reproducible phenomena. Several laboratories use phosphenes as a routine procedure [6,7,13] and these report that the perceived form of the phosphene also tends to be stable over time. For example, if TMS applied in the midline 4 cm aboveinion causes a subject to describe, say, a crescent-shaped object with fuzzy edges $\sim 2^\circ$ to the left of fixation, then it is highly likely that the subject will perceive the same, or at least, very similar phosphene when that same site is stimulated on later occasions. This is also true of phosphenes elicited by TMS of extrastriate visual area V5 which produces moving phosphenes [13] and it will be interesting to determine whether the V5 thresholds are also stable over time.

The finding that phosphene and motor thresholds differed within subjects could be due to a number of factors. We do not know if the absolute amount of cortical stimulation required to reach motor and pho-

sphene threshold is equal. Even if this were found to be the case, a different degree of skull thickness over the two cortical areas would result in different stimulation intensities required to reach threshold. In addition, differences in neuronal size and orientation of the two cortical areas will affect the intensity required to reach threshold. It is interesting to note how widely motor and phosphene thresholds varied between subjects. In some individuals ($n = 2$), phosphene threshold was below motor threshold whilst in others ($n = 13$), phosphene threshold was twice motor threshold. This may partly be explained by the fact that the motor hand area is situated on the lateral surface of the cortex while the greater part of the primary visual cortex is buried on the medial surface. Although both cortical areas show considerable variation in their location, the motor hand area is likely to vary more in the medio-lateral and antero-posterior directions between individuals whilst the primary visual cortex will tend to vary more in depth. Movement of the TMS coil can compensate to some extent for variability in location over the surface of the skull but not in depth. Thus the threshold for primary visual cortex will vary more between subjects than for the motor hand area. It should be noted that primary visual cortex is not the sole candidate site for the generation of phosphene; the optic tract or extrastriate areas abutting V1 have also been suggested, [5,8] however, regardless of the exact location from which phosphenes are elicited, the same arguments about anatomical variability would still apply.

The lack of a correlation between visual and motor thresholds is most likely due to the fact that absolute location of the motor hand area and the primary visual cortex relative to the skull will vary independently within a subject. For example, one subject's motor cortex may be relatively easy to stimulate whilst the same subject's primary visual cortex may be more buried and hence require larger amounts of stimulation before a phosphene is elicited. The primary visual cortex of another subject may be as easily stimulated as their hand area and hence will show less of a disparity between motor and phosphene threshold. It may be argued, of course, that a larger survey would have revealed some relationship between the two measures. However, as the above discussion suggests, such a relationship would require covariation of distance from scalp to cortex between motor and visual cortex as well as covariation of neuronal orientation in the two areas and such a close correspondence would be surprising.

The lack of correlation between motor and phosphene threshold means that motor thresholds cannot be assumed to be a guide to cortical sensitivity of areas other than the region directly stimulated. Hence in order to apply TMS at intensity levels normalized to an individual subject's cortical sensitivity, one may have to find a separate measure for each area stimulated. This

may even be the case for areas that are close to the motor cortex such as the posterior parietal cortex [9,10,15,17]. The problem here is that whereas TMS over the visual and motor cortices have measurable consequences (phosphenes and EMG), the same is not true for association areas such as prefrontal and parietal cortex. This problem was noted by Penfield and Rasmussen [11] who discovered that some regions of the cortex, regions they called 'elaboration areas' could not be stimulated to produce a measurable output. Other measures may be used, however. For example, in studies of parietal cortex function we find it useful to employ the disruptive effects of TMS on visual search tasks to determine sensitivity [3].

Although the present study has established that motor threshold cannot be used as a reliable indicator of sensitivity of other cortical areas and that in TMS studies of the visual system, the use of phosphene threshold can provide a reliable method of equating stimulation intensity across subjects, it is yet to be established whether phosphenes are a true analogue of surface EMGs i.e. whether the elicitation of phosphenes and EMGs require a similar amount of cortical stimulation over the respective areas. This is important to establish from a safety point of view; if phosphene thresholds are to be used as an index of visual cortical sensitivity, safety guidelines detailing maximum levels of stimulation (expressed as % phosphene threshold) must be drawn up. In order to establish what these safety levels should be, we are currently investigating the degree to which the effects of occipital stimulation on visual perception can usefully be expressed as a function of phosphene threshold.

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