CHAPTER 19

Motor and phosphene thresholds: consequences of cortical anisotropy

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1. Introduction

Excitability of cortical areas assessed by TMS depends on the induced current direction. This has been extensively demonstrated for the motor cortex. In case of monophasic pulses currents passing the precentral gyrus from back to front are more efficient than currents in the reverse direction (Brasil-Neto et al., 1992; Mills et al., 1992; Niehaus et al., 2000; Di Lazzaro et al., 2001; Kammer et al., 2001b). The optimal current orientation is perpendicular to the central sulcus (Brasil-Neto et al., 1992; Mills et al., 1992; Nithi and Mills, 2000). In recent years, it was found that other cortical areas also show this anisotropic response behavior when stimulated with TMS. In the visual system, early reports suggested a preferential current direction from lateral to medial, both in the induction of phosphenes (Meyer et al., 1991) and for the visual extinction effect (Amassian et al., 1994). Our group confirmed this anisotropy with the first phosphene threshold study systematically varying current directions (Kammer et al., 2001a). Lowest phosphene thresholds were obtained with latero-medial currents in both hemispheres, highest threshold with medio-lateral currents. Vertical oriented currents yielded threshold values between both extremes. For a third region, the prefrontal cortex, a current direction preference has been demonstrated using a behavioral task (Hill et al., 2000).

In the present study we directly compare the current direction effect of monophasic pulses on thresholds in the visual and motor system using two different stimulator types. With a frameless stereotactic positioning system, we further demonstrate a dependency of phosphene maps from the visual cortex on current direction.

2. Methods

Six healthy subjects (age 21 to 37 years, four male, two female) participated in the study after giving their written informed consent. The study was approved by the local internal review board of the Medical Faculty, University of Tübingen.
Two stimulators were used: the Medtronic-Dantec Magpro (Skovlunde, Denmark) in the monophasic mode (maximal rate 0.33 Hz) and the Magstim 200 (Whitland, Dyfed, Wales, maximal rate 0.2 Hz). Both stimulators were fitted with their standard figure-of-8 coil. Coil position in relation to the head was monitored and registered continuously in all six degrees of freedom – three translational and three rotational – with a custom-made positioning system (Kammer et al., 2001b).

Data of phosphene thresholds presented here were taken from Kammer et al. (2001a), left hemisphere. They have been measured with the method of constant stimuli. Subjects had to report the presence or absence of a phosphene at stimulation with 10 different intensities (step size 2%) tested 10 times in a randomized order. Threshold was then calculated using a sigmoidal Boltzmann fit to the data. Three independent measurements with 100 stimuli each were averaged. For more details, see Kammer et al. (2001a).

Resting motor thresholds were measured in the right abductor pollicis brevis muscle as described in Kammer et al. (2001b). The threshold criterion was 50 µV peak-to-peak amplitude. 10 trials were performed at each stimulator intensity, varied in steps of 1%. Thresholds were calculated using a sigmoidal Boltzmann fit.

In order to compare threshold data from both stimulators, they were normalized with respect to $\sqrt{E_{\text{max}}}$, the maximal energy stored in the stimulator (cf. Barker et al., 1991; Kammer et al., 2001b). $E_{\text{max}}$ of Medtronic-Dantec is 300 J, $E_{\text{max}}$ of Magstim 200 is 720 J.

For phosphene mapping, subjects looked at a fixation point in the middle of the screen with a background intensity of 0.3 cd/m². They observed phosphenes induced by a single TMS pulse and drew the contours of the observed phosphene directly on the screen using a mechanical digitizing arm programmed as a drawing device. Traces of the drawing appeared as white lines on the screen. Subjects could freely release stimulation pulses in order to compare the drawings with the perceived phosphene and if necessary correct the drawing.

Finally the drawing was saved on the computer together with the exact stimulation site of the coil as measured by the positioning system. The drawings were off-line classified according to the visual hemifield the phosphenes appeared in right (coded in red), left (blue) or bilateral (yellow). A 3D mesh of the cortical surface was obtained with the software BrainVoyager (Brain Innovation, Maastricht, The Netherlands) based on a segmentation of the white matter in a T1-weighted anatomical scan of the subject. Stored coil positions (midpoint of the figure-of-8 coil, peak electric field) were projected on the 3D mesh of the individual subject’s cortical surface. They were colored according to the phosphene hemifield classification.

3. Results

Mean normalized threshold values from the left visual and motor cortex are shown in Fig. 1. They were subjected to a three-way analysis of variance (ANOVA) with factors of threshold type (phosphene vs. motor), stimulator type (Medtronic-Dantec vs. Magstim), and current direction (latero-medial vs. medio-lateral for phosphene threshold, antero-posterior vs. postero-anterior for motor threshold). Significant main effects of stimulator type ($F(1,5) = 144.6; p < 0.0001$) and current direction ($F(1,5) = 113.7; p < 0.0002$) were obtained. No significant difference was found for the factor threshold type ($F(1,5) = 1.54; p = 0.27$), as well as no significant interaction. Medtronic-Dantec was more efficient compared to Magstim. The ratio of Magstim/Medtronic-Dantec thresholds in the visual system was 1.26; in the motor system the ratio was 1.32. The mean threshold ratio for the different current directions was 1.19 in the visual system (medio-lateral/latero-medial) and 1.32 in the motor system (antero-posterior/postero-anterior).

Correlation of phosphene and motor thresholds for the individual subjects is depicted in Fig. 2 for each of the four measurement types (two stimulators, two current directions). Linear regressions revealed no systematic dependency of phosphene and motor thresholds in the individual subjects.
In Fig. 3 a map of perceived phosphenes in dependence of the coil position is shown. Horizontally oriented stimulation pulses at a constant stimulus intensity were applied at several sites of the occipital cortex. The pins indicate the midpoint of the coil inducing a certain phosphene coded by the color of the pin. At the lateral stimulation sites over one hemisphere the evoked phosphenes appeared in the contralateral visual hemifield (red or blue pins). More medial stimulation sites resulted in the perception of phosphenes in both visual hemifields (yellow pins) indicating the supra-threshold stimulation of both hemispheres. The borders between unilateral and bilateral stimulation depend on the induced current direction which is indicated by the arrows. They were not found in symmetry to the interhemispheric cleft but were shifted in the direction of the induced current. In the depicted example the amount of shift was 12 mm. The shift could be observed with both stimulators, Magstim 200 as well as Medtronic-Dantec in the monophasic mode. It was confirmed in four subjects investigated, ranging from 7–15 mm.

Fig. 1. Comparison of motor and phosphene thresholds (mean ± SD) measured in the left hemisphere in six subjects. Motor thresholds in the right abductor pollicis brevis muscle were measured with the coil over the left motor hot spot. The coil handle was oriented perpendicular to the central sulcus. Phosphene thresholds were measured over the left occipital pole with the coil handle oriented horizontally. Notice that thresholds were normalized with respect to the maximal energy stored in the stimulator. For ANOVA, see text.

Fig. 2. Correlation of threshold values between motor and visual cortex. The normalized individual values of six subjects × four conditions are plotted. The two different stimulator types are coded as dots (Magstim) and triangles (Medtronic-Dantec). Induced current directions are indicated by filled (optimal direction, latero-medial or postero-anterior) and open (non optimal direction: medio-lateral or antero-posterior) symbols. Linear regression lines are solid (optimal direction) or stippled (non optimal direction). None of the linear regressions was statistically significant.

Fig. 3. Phosphene map in dependence of induced current direction. The upper and lower images are two different views on the occipital pole of subject KP, showing the same measurement. Coil positions (midpoint of the figure-of-8 coil) are depicted as colored pins. The color indicates the visual hemifield where the subject perceived a phosphene. Red: right hemifield, blue: left hemifield, yellow: both visual hemifields. The induced current direction is indicated by the large arrows. Stimulation parameters: Medtronic-Dantec, monophasic, 80% intensity.
It did neither depend on the stimulation strength nor on the horizontal position of the coil but could be observed within a large area over the occipital pole.

4. Discussion

Excitability of the visual cortex depends on current direction, similar to excitability of the motor cortex. In case of monophasic pulses in both hemispheres at the occipital pole latero-medial currents are more efficient compared to medio-lateral currents (Kammer et al., 2001a). The data presented here extend our previous results by direct comparison of phosphene thresholds and motor thresholds in the same subjects. The mean of motor thresholds in six subjects confirms the pattern reported in a previous study (Kammer et al., 2001b), i.e. lower thresholds for postero-anterior oriented currents compared to antero-posterior currents. Furthermore, normalization of threshold values with respect to the maximal stored energy (Barker et al., 1991; Kammer et al., 2001b) reveals that the Medtronic-Dantec stimulator transfers stimulation energy more efficient to the brain compared to the Magstim stimulator. The main reason for this difference is the coil geometry of the two figure-of-8 coils, as shown in a modeling approach (Thielscher, 2002). In case of Medtronic-Dantec the two circular windings are bent to each other forming an angle of 140°, whereas in case of Magstim the two windings are placed in a plane thus forming an angle of 180°.

In our sample of six subjects we did not observe a significant correlation between motor and visual thresholds. This finding confirms previous observations (Stewart et al., 2001; Boroojerdi et al., 2002) that excitability of the two areas differ within a subject. However, we cannot exclude that these results are based on variations of the coil-cortex distance within a subject (Kozel et al., 2000; McConnell et al., 2001). Further studies combining careful threshold measurement and a model of field strength in dependence of the coil-cortex distance (Thielscher and Kammer, 2002) are required to clarify this important question.

Phosphene mapping revealed that stimulation sites evoking phosphenes bilaterally in the left and right visual field depend on the induced current direction. Under the assumption that the generator of an unilateral phosphene sits in the contralateral hemisphere bilateral phosphenes require a suprathreshold stimulation of both occipital lobes. The shift of the border from bilateral to unilateral stimulation can be directly explained as a consequence of threshold differences. The suprathreshold stimulation of the hemisphere stimulated in the preferred current direction still works with a coil position shifted over the non-preferred hemisphere. This explanation assumes, in addition, that the stimulus site under the coil depends on the electric field strength with its maximum at the midpoint of the coil (Amassian et al., 1992; Ilmoniemi et al., 1999), an assumption that has recently been proved for the motor cortex (Thielscher and Kammer, 2002).

Our data demonstrate that a preference in current direction does exist in the visual cortex, comparable to the motor cortex preference. It seems to be a general feature of cortical networks to have a preferred current direction since it has been demonstrated in prefrontal cortex, too (Hill et al., 2000). Studies in the motor system have demonstrated that a change in the current direction changes the response pattern of the cortical network (Day et al., 1989; Sakai et al., 1997; Di Lazzaro et al., 2001). It is still unclear whether different sites of the same population are stimulated or whether different cell populations respond with reversing current direction. Why do we find differences in the cortical responses in dependence of induced current orientation? Neurons are optimal stimulated with extracellular currents oriented in parallel to longitudinal structures, i.e. the axons of the cells (Rushton, 1927). The striking dependency on current orientation indicates an orientation preference of axons in the cortex. In an histological study of the human motor cortex, Marin-Padilla (1970) described a preferential orientation of dendritic and axonal fields of large basket cells perpendicular to the main axis of the central gyrus thus corresponding to the preferential current direction in TMS. However, using systematic sections
alternatively parallel and perpendicular to the main axis of the human precentral gyrus, Meyer (1987) failed to confirm the preferential orientation perpendicular but rather found an orientation dominance in parallel to the main gyrus’ axis. We are not aware of histological studies of other cortical areas revealing a general orientation preference in relation of the gyral architecture.

In order to explain threshold differences with polarity reversion of the currents the anatomical orientation preference has to be accomplished by a functional anisotropy implementing a diode-like rectifying response behavior. A hypothesis could be derived from the concept of virtual anodes surrounding a stimulating cathode (Rattay, 1987). It has been shown that certain geometric arrangements of electrodes lead to depolarization of axons with unidirectional propagation. (Ranck, 1975; Van den Honert and Mortimer, 1979; Ungar et al., 1986). It remains to be clarified whether the geometry of electromagnetically induced currents can mimic such a behavior.

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References


