

Motor and phosphene thresholds to transcranial magnetic stimuli : a reproducibility study

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Abstract

Objectives : as repetitive transcranial magnetic stimulation (rTMS) is often applied on different days, it is of interest to know whether motor (MT) and phosphene (PT) thresholds are reproducible across time and whether the intensity determined on the first day can be used in subsequent sessions.

Methods : we studied MT and PT over 5 separate recordings in 10 healthy volunteers using a focal coil and a Magstim (Rapid stimulator). After the initial recording (session 1), the others (2 to 5) were performed respectively after 1 day, 7 days, 1 month and 4 months.

Results : mean MT at rest were $65.30 \pm 5.54\%$, $65.7 \pm 7.18\%$, $60.4 \pm 4.27\%$, $61.8 \pm 4.34\%$, and $63 \pm 9.1\%$ at sessions 1 to 5. Mean PT were $71.43 \pm 6.68\%$, $66.29 \pm 10.67\%$, $60.71 \pm 8.64\%$, $60.57 \pm 8.08\%$, and $68.71 \pm 15.48\%$ at sessions 1 to 5. MT and PT were reproducible (ANOVA analysis), however, as shown by coefficients of variation, variability between the first 3 sessions exceeded 10% for MT in 3 subjects and in 4 subjects for PT.

Conclusions : it seems preferable to determine thresholds and adapt output intensity of the stimulator at each rTMS session.

Key words : Transcranial magnetic stimulation ; rTMS ; motor threshold ; phosphene threshold – reproducibility.

Introduction

Transcranial magnetic stimulation (TMS) is a powerful tool to investigate cortical functions. Since its first application in humans (Barker *et al.*, 1985), TMS of the motor cortex has been extensively studied as the peripheral electromyographic response offers an objective measure of cortical activation and allows to determine motor thresholds accurately. TMS studies of the visual cortex, by contrast, have to rely on subjective assessments such as phosphenes (Barker *et al.*, 1985 ; Meyer *et al.*, 1991) or visual imagery tasks (Kosslyn *et al.*, 1999), which probably explains why they are less numerous and reproducible.

Repetitive transcranial magnetic stimulation (rTMS) is nowadays tested to treat various brain disorders, especially depression but also obsessive-

compulsive disorder, schizophrenia, motor disorders like Parkinson's disease, task-related dystonia (writer's cramp) or tics, and epilepsy (for a review, see Wassermann *et al.*, 2001). Stimulation frequency is considered to be the crucial rTMS parameter which determines whether the effect on the cerebral cortex is facilitatory or inhibitory. For instance in normal subjects, low-frequency rTMS (1 Hz) decreases (Chen *et al.*, 1997a), whereas high-frequency rTMS (5-20 Hz) enhances motor cortex excitability (Pascual-Leone *et al.*, 1994). A recent study, however, shows that the after-effects of rTMS on the motor cortex depend on its frequency, but also its duration and intensity (Modugno *et al.*, 2001). For both clinical and research trials using rTMS, the stimulation intensity is most often expressed as a percentage of each subject's motor (MT) or phosphene (PT) threshold determined at baseline. Several rTMS sessions are performed on different days, which implies that these thresholds are reproducible across time. If this is not the case, they should be measured at each session and the stimulation intensity adjusted accordingly.

Only four studies have examined the reproducibility of TMS thresholds. In the first one (Mills *et al.*, 1997) reproducibility of MT was studied at a median interval of 42 days. The second study (Kammer *et al.*, 2001) determined PT three times within a single session with two different devices. The third one (Stewart *et al.*, 2001) studied reproducibility of both MT and PT at an interval of one week as in the last study (Boroojerdi *et al.*, 2002) but with an interval of at least 3 days before the 2 sessions.

In the present study, we have examined the reproducibility of motor and phosphene thresholds in 10 healthy volunteers at various delays up to 4 months.

Methods

SUBJECTS

Ten healthy volunteers (4 women, 6 men ; mean age : 24.6 ± 1.5 yrs), free of any medical condition

and without personal or family history of epilepsy, which is recommended for rTMS studies (Chen *et al.*, 1997b), were recruited among medical students to participate in the study. They were all right-handed. To avoid interference with changes of cortical excitability due to hormonal variations (Smith *et al.*, 1999), females were recorded at mid-cycle, i.e. 12 to 18 days after the 1st day of menses. Written informed consent was obtained from all participants. The study was approved by the Ethics Committee of the Faculty of Medicine, University of Liège, Belgium. Volunteers were examined on five different sessions: day 0 (session 1), after 1 day (session 2), 7 days (session 3), 1 month (session 4) and 4 months (session 5). For each session, the same conditions were observed: no sleep deprivation, no drug or alcohol intake the day before or on the day of testing, and recording at the same hour of the day. A training session was performed some days before the first session to educate subjects in the detection of phosphenes. In this training session, they got information about the technique, filled in the written informed consent and they experimented magnetic shocks and learned to discern phosphenes.

TRANSCRANIAL MAGNETIC STIMULATION

Transcranial magnetic stimulations were performed with a Magstim Rapid® stimulator (Magstim Co Ltd, Whitland, Dyfed, UK) connected to a double 7.0 cm figure-of-eight-shaped coil, with a maximal stimulator output of 1.2 Tesla. We determined phosphene and motor thresholds, using single TMS pulses of 100 s duration. The phosphene threshold (PT) was defined as the lowest stimulation intensity (expressed as a percentage of the maximal stimulator output) able to evoke phosphenes in at least three out of five trials. The coil was placed in a vertical position (its handle pointing upward) on theinion-nasion line, with its inferior limit 1 cm above theinion. The subjects were seated in an armchair in a dark room and blindfolded. As 40-45 minutes of blindfolding can change visual cortex excitability (Boroojerdi *et al.*, 2000a), its total duration was limited to 10-15 minutes. Stimulation was initially applied at 40% of stimulator output. The intensity of the stimulation was then increased by 5%-steps until the subject reported phosphenes. The threshold was thereafter finely determined by increasing and decreasing the intensity by 1%-steps. In patients who did not report phosphenes at the 100% intensity level, the procedure was repeated with the coil placed 1 or 2 cm higher or lower, and, if necessary, more to the right and to the left, before accepting the absence of phosphenes.

With the coil placed at the optimal position over the left motor area (motor hot spot, i.e. the scalp region producing the largest motor evoked poten-

tial with the shortest latency), the motor threshold (MT) was defined as the lowest stimulation intensity able to produce at rest in the first dorsal interosseus (FDI) muscle of the right hand an electromyographic response (Motor Evoked Response or MEP) of at least 50 (V peak-to-peak amplitude in at least five out of ten trials (Rossini *et al.*, 1994). Stimulation intensity was set at 40% of stimulator output initially and increased by 1%-steps. Motor evoked potentials (MEP) were recorded with Ag-AgCl surface electrodes over the right FDI muscle using a belly-tendon montage. Signals were filtered (bandpass: 30 Hz - 3 kHz) and amplified with a Digitimer® D200 amplifier (Digitimer Ltd, Hertfordshire, UK). All stimulations were performed by the same investigator (AF).

STATISTICAL ANALYSIS

We calculated means \pm SD for MT and PT at each session. The temporal evolution of thresholds was studied with an ANOVA-2 model. We searched for a possible correlation between MT and PT at each session with a Pearson's correlation test. Differences were considered significant at the alpha level 0.05. We also determined the coefficients of variation ($Cv = SD/mean$) for each subject and for both thresholds.

Results

MOTOR THRESHOLDS (table 1 & figure 1)

Stimulation over the right motor hot spot elicited MEP from the FDI muscle in all 10 subjects. The average threshold intensity able to activate the FDI muscle at rest was $65.30 \pm 5.54\%$ on day 0 (session 1), $65.7 \pm 7.18\%$ at session 2, $60.4 \pm 4.27\%$ at session 3, $61.8 \pm 4.34\%$ at session 4 and $63 \pm 9.1\%$ at session 5. ANOVA type 2 showed that MT was reproducible even when the time parameter (number of session) was integrated in the statistical model. Looking at individual values, there was a difference of more than 10% in MT between the first 3 sessions in subjects 1, 2 and 9. This was confirmed by the coefficients of variation which were 13, 15 and 11% for these 3 subjects, but below 10% for all the other subjects.

PHOSPHENE THRESHOLDS (table 1 & figure 2)

Single transcranial magnetic stimuli over the occipital cortex elicited phosphenes in all 5 sessions in 7 out of 10 subjects (70%). One subject (n 7) had phosphenes only twice at sessions 4 and 5 with similar thresholds of 75% and 79%. Phosphenes were reported as short-lasting flashes or lines. The perceived phosphene type tended to be reproducible over time in the same subject. The mean threshold intensity able to elicit phosphenes

Table 1

Motor (MT) and phosphene thresholds (PT) in the 10 healthy volunteers (no = no phosphenes visualised)

	Motor Threshold					Phosphene Threshold				
	<i>day 0</i>	<i>after 1 day</i>	<i>after 7 days</i>	<i>after 1 month</i>	<i>after 4 months</i>	<i>day 0</i>	<i>after 1 day</i>	<i>after 7 days</i>	<i>after 1 month</i>	<i>after 4 months</i>
Subject 1	66	77	60	69	59	67	47	47	47	65
Subject 2	74	73	56	60	82	72	76	58	60	72
Subject 3	68	71	65	60	65	86	71	70	70	60
Subject 4	62	67	57	57	64	no	no	no	no	no
Subject 5	60	61	62	65	51	67	60	65	60	40
Subject 6	60	54	55	55	62	70	77	68	65	86
Subject 7	63	62	62	65	58	no	no	no	75*	79*
Subject 8	58	58	59	60	55	no	no	no	no	no
Subject 9	72	70	59	61	60	68	62	52	54	80
Subject 10	70	64	69	66	74	70	71	65	68	78
Mean without (*)	65.30	65.70	60.40	61.80	63.00	71.43	66.29	60.71	60.57	68.71
SD	5.54	7.18	4.27	4.34	9.10	6.68	10.67	8.64	8.08	15.48

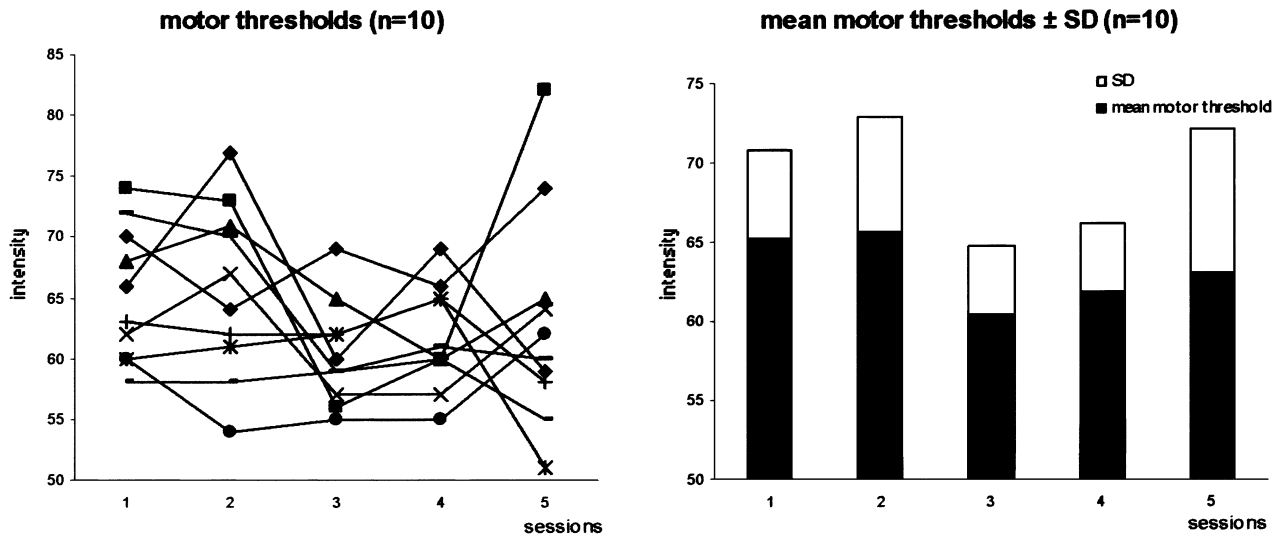


FIG. 1. — Motor thresholds in the 10 subjects over the 5 sessions

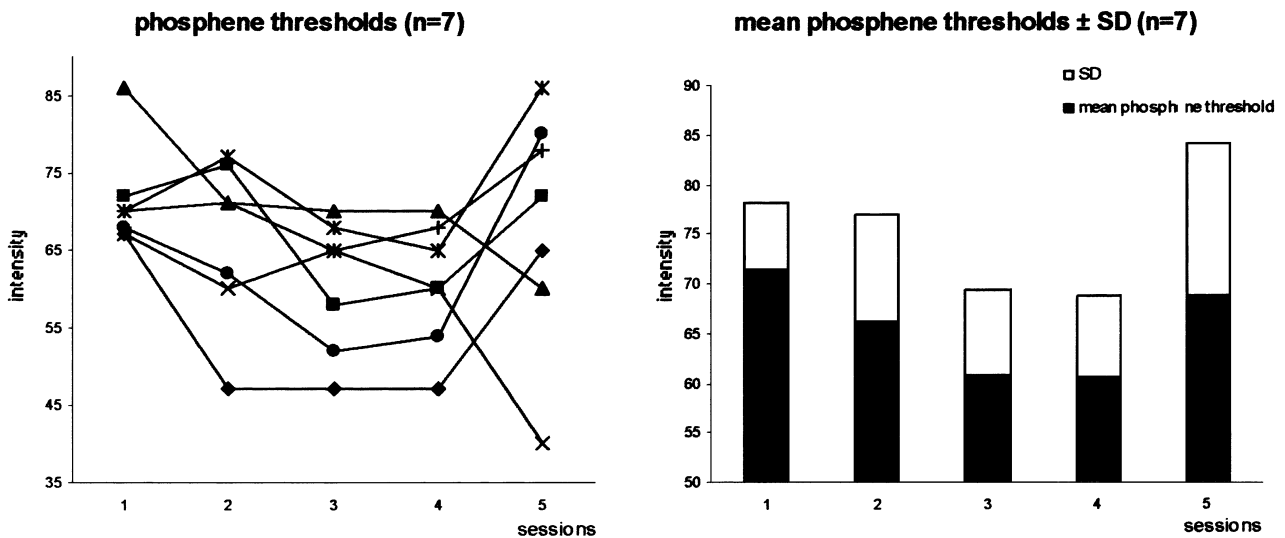


FIG. 2. — Phosphene thresholds in the 7 subjects who visualized phosphenes over the 5 sessions

in 7 subjects was $71.43 \pm 6.68\%$ on day 0 (session 1), $66.29 \pm 10.67\%$, $60.71 \pm 8.64\%$, $60.57 \pm 8.08\%$, and $68.71 \pm 15.48\%$ respectively on sessions 2, 3, 4 and 5. ANOVA type 2 showed that PT were reproducible across the 5 sessions ($p > 0.05$), but not when the time parameter (number of session) was integrated in the statistical model, PT adopting a quadratic evolution (parabola, $p = 0.038$). Looking at individual values, there was a variability greater than 10% of PT in 4 subjects ($n^{\circ}1, 2, 3$ and 9) over the first 3 sessions; this was confirmed by coefficients of variation which reached 22, 14, 12 and 13% for these 4 subjects, while they were less than 10% for the other subjects.

CORRELATION BETWEEN MOTOR AND PHOSPHENE THRESHOLDS

There was no significant correlation between MT and PT at any session. Pearson's correlation coefficients were 0.68, 0.27, 0.51, 0.27 and 0.28 in the five consecutive sessions.

Discussion

To the best of our knowledge, this is the first time that reproducibility of phosphene (PT) and motor thresholds (MT) to transcranial magnetic stimulation was assessed several times for up to 4 months. The main finding is that both thresholds are statistically reproducible in healthy volunteers over several months (and this is even the case when the time effect is included in the ANOVA-2 statistical model for MT). Only four studies have previously examined the reproducibility of TMS thresholds. Mills *et al.* (1997) studied in twenty-two subjects the reproducibility of MT defined as the minimum intensity at which 10 stimuli all produce an EMG response of at least 20mV amplitude which is at variance with International Standard Guidelines (Rossini *et al.*, 1994). They found a mean variability superior to 10% at a median interval of 42 days. Using two different stimulators, the Medtronic-Dantec Magpro® (Skovlunde, Denmark) and the Magstim® 200 (Whitland, Dyfed, UK), Kammer *et al.* (2001) determined PT three times within a single session in six subjects and found a high reproducibility for both devices. In another study (Stewart *et al.*, 2001) of MT and PT assessed in seven subjects across two sessions separated by one week, both thresholds were found stable, but PT was more variable than MT. In the fourth one (Boroojerdi *et al.*, 2002), MT and PT were tested twice with a minimum interval of three days in eight subjects. They found a highly reproducibility for both thresholds (but a better correlation coefficient for MT) without any correlation between MT and PT for the two sessions. Our results are in accordance with those of the two latter studies.

However, an analysis of results in each individual shows that over the first 3 sessions the variabilities of MT and PT exceed 10%, respectively in 3 out of 10 and 4 out of 7 subjects.

The possible reasons for the variability of TMS thresholds are multiple. It could be due to technical factors such as slight changes in scalp positioning of the coil, but variability was similar in a study using MRI-guided TMS (Gugino *et al.*, 2001). Nonetheless, all recordings were performed by the same investigator (AF) in order to minimize variations in coil position. Besides undetermined internal changes, external factors may modify thresholds. For instance, MT are increased by drugs that block voltage-gated sodium (Ziemann *et al.*, 1996; Chen *et al.*, 1997c) or calcium-channels (Ziemann *et al.*, 1996), while they are not affected by drugs altering GABA (Ziemann *et al.*, 1996) or glutamate transmission (Liepert *et al.*, 1997; Ziemann *et al.*, 1998), suggesting that they reflect neuronal membrane excitability (Chen *et al.*, 2000). Ethanol does not modify MT, but it is able to influence intracortical inhibition and facilitation (Ziemann *et al.*, 1995). Sleep deprivation increases MT and decreases excitability of the motor cortex in humans as assessed by paired-pulse TMS (Manganotti *et al.*, 2001). To avoid such factors, we selected subjects without drug treatment or alcohol consumption during the preceding 24 hours and stimulated them at the same hour of the day after a night with a normal sleep duration. Light intensity was kept constant in the laboratory in order to avoid excitability changes of the visual cortex (Boroojerdi *et al.*, 2000a).

Because of the wide range of absolute TMS intensities needed to produce comparable EMG responses across individuals, most studies of the motor cortex have expressed the stimulation intensity used as a percentage of each individual's MT. As there is no such objective measure of visual cortex activation, MT are often used to define the intensity of occipital TMS. However, as shown by Stewart *et al.* (2001) and Boroojerdi *et al.* (2002), we have confirmed that PT are not correlated to MT and that they are reproducible, though with a larger variability than MT. It seems therefore preferable to express the TMS intensity of the visual cortex by directly relating it to PT.

To conclude, since stimulation intensity cannot be neglected as a variable that conditions the effect of TMS on the underlying cortex (Modugno *et al.*, 2001), it should be recommended to measure both MT and PT at each session and to adapt rTMS intensity accordingly. Up to now, this was not done in therapeutic trials using daily rTMS like in psychiatric disorders where it may be of critical importance. Besides other factors, large variations in stimulation intensities could indeed explain the contradictory results obtained in these studies (Wassermann *et al.*, 2001).

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