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 ± 5.54%, 65.7 ± 7.18%, 60.4 ± 4.27%, 61.8 ± 4.34%, and 63 ± 9.1% at sessions 1 to 5. Mean PT were 71.43 ± 6.68%, 66.29 ± 10.67%, 60.71 ± 8.64%, 60.57 ± 8.08%, and 68.71 ± 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 the inion-nasion line, with its inferior limit 1 cm above the inion. 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 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 ± 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 ± 5.54% on day 0 (session 1), 65.7 ± 7.18% at session 2, 60.4 ± 4.27% at session 3, 61.8 ± 4.34% at session 4 and 63 ± 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.

**Phosphenes 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)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Day 0</th>
<th>After 1 day</th>
<th>After 7 days</th>
<th>After 1 month</th>
<th>After 4 months</th>
<th>Day 0</th>
<th>After 1 day</th>
<th>After 7 days</th>
<th>After 1 month</th>
<th>After 4 months</th>
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<tr>
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<td>60</td>
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<td>72</td>
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<td>58</td>
<td>60</td>
<td>72</td>
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<tr>
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<td>no</td>
<td>75*</td>
<td>79*</td>
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<td>no</td>
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<tr>
<td>Subject 9</td>
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<td>61</td>
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<td>65</td>
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</table>

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 ± 6.68% on day 0 (session 1), 66.29 ± 10.67%, 60.71 ± 8.64%, 60.57 ± 8.08%, and 68.71 ± 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=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 Phosphenes 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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