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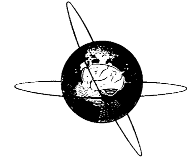

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Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation

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Abstract

Objective: Repetitive transcranial magnetic stimulation (rTMS) is able to modulate the corticospinal excitability and the effects appear to last beyond the duration of the rTMS itself. Different studies, employing different rTMS parameters, report different modulation of corticospinal excitability ranging from inhibition to facilitation. Intraindividual variability of these effects and their reproducibility are unclear.

Methods: We examined the modulatory effects of rTMS to the motor cortex at various frequencies (1, 10, 20 Hz) and at different time-points in twenty healthy volunteers.

Results: We observed significant inhibition of MEPs following 1 Hz rTMS and significant facilitation of MEPs following 20 Hz rTMS for both day1 and day 2. Interestingly, at 1 Hz and 20 Hz rTMS, the modulatory effect produced by rTMS was greater on day 2. However, there was no significant change in corticospinal excitability following 10 Hz rTMS neither on day 1 nor day 2.

Conclusion: Our findings raise questions as to how stimulation parameters should be determined when conducting studies applying rTMS on multiple days, and in particular, studies exploring rTMS as a treatment modality in neuropsychiatric disorders. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Repetitive transcranial magnetic stimulation (rTMS); Reproducibility; Modulation; Excitability; Neurophysiology; Human

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) refers to the application of regularly repeated stimuli to a single scalp position (Wassermann, 1998). The term fast or high-frequency rTMS is used when the stimulation rate is more than 1 Hz, and slow or low-frequency rTMS is used when the stimulation rate is 1 Hz or less. This is said to be partially based on the physiological effects of low- and high-frequency stimulation (Wassermann, 1998). Indeed, there are some suggestions to these differential effects of rTMS depending on stimulation frequency. Such supporting evidence comes largely from studies of rTMS of the motor cortical outputs. The frequency dependent rTMS effects on corticospinal excitability appear to be demonstrable during (Pascual-Leone et al., 1994; Jennum et al., 1995) as well as following the rTMS application (Pascual-Leone et al., 1994, 1998; Chen et al., 1997; Tergau et al., 1997). For seconds to minutes following completion of the rTMS application, rTMS at 1 Hz is reported to lead to a transient decrease in corticospinal excitability (Chen et al., 1997) while rTMS at 5 Hz (Berardelli et al., 1998) or 10 Hz (Pascual-Leone et al., 1998) is thought to lead to a transient increase in corticospinal excitability. Few studies have looked at the effects of different rTMS frequencies on the modulation of corticospinal excitability within the same subjects (Tergau et al., 1997; Pascual-Leone et al., 1998), and to date there is no systematic study of the interindividual and intraindividual variability of such modulatory effects of rTMS. Nevertheless, this is an important issue, since a growing number of studies evaluating the potential therapeutic effects of rTMS on neuropsychiatric disorders

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assume a consistent effect of rTMS on cortical excitability across patients and use the same rTMS parameters within subject groups and across 'treatment days' (for an extended review, refer to George et al., 1999).

2. Subjects and methods

2.1. Subjects

Twenty healthy volunteers (9 males, 11 females; mean age 26.3 years old; range 20–41 years old; all right-handed) were recruited. The study was reviewed by the local Institutional Review Board (IRB) and written informed consent was obtained. None of the subjects had any psychiatric or medical history, nor had any contraindications to TMS (Wassermann, 1998).

2.2. Preparation

Subjects were seated in a comfortable reclining chair so that the whole body including both arms would be at rest. They were instructed to keep their hands still and as relaxed as possible. A tightly fitting white lycra swimming cap was placed on their head to mark the site for stimulation. Stimulation was delivered to the 'optimal scalp site,' i.e. the scalp position from which TMS induced motor evoked potentials (MEPs) of maximal amplitude in the contralateral target hand muscle. Two disposable self-adhesive electrodes (Nicolet Biomedical, Wisconsin, USA) were placed on the belly and tendon of their right abductor pollicis brevis (APB) muscle. A round ground electrode with a diameter of 30 mm was placed on the wrist. All of these sites were prepared appropriately before the electrodes were attached. MEPs were amplified using a Dantec Counterpoint electromyograph with a band pass of 20–1000 Hz (Dantec, Skovlunde, Denmark). The preamplified signal (×1000) was digitized using PowerLab 16S (AD Instruments Ltd, Hastings, UK) with a sampling rate of 2 kHz per channel and stored on a Macintosh G3/300 Power PC (Apple Computers, Cuppertino, CA, USA) for off-line analysis.

2.3. Determination of motor threshold

TMS was performed with a commercially available 70 mm figure-of-eight coil and a Magstim Super Rapid Transcranial Magnetic Stimulator (Magstim Company, Dyfed, UK). Single pulse TMS was delivered to the optimal scalp position (as defined above) and the motor potentials evoked in the contralateral APB were recorded. The coil was positioned tangentially to the scalp with the handle of the coil 135 degrees from the midsagittal axis of the subject's head and the coil pointing anteriorly. This orientation was chosen based on the finding that the lowest motor threshold (MT) was achieved when the induced electric current in the brain was flowing approximately perpendicular to the line of the central sulcus (Brasil-Neto et al., 1992; Mills et al., 1992). The induced pulse was polyphasic and hence with this orientation, the first phase of the induced pulse was directed towards posterior and lateral and the second anterior and medial, both approximately perpendicular to the presumed central sulcus location. The MT was defined as the minimal intensity of stimulation capable of inducing MEPs greater than 50 μV peak-to-peak amplitude in at least 6 out of 10 trials. Stimulation was started at well suprathreshold intensity (generally 90% of the stimulator output) and decreased in steps of 2% of the stimulator output. The threshold determination was made during complete muscle relaxation that was monitored on audio and electromyogram (EMG) signals for 50 ms prior to the application of the TMS.

2.4. Data collection and rTMS procedure

For determination of baseline corticospinal excitability, 10 single-pulse TMS at 120% of the subject's MT were applied to the optimal site, each pulse being approximately 10 s apart (±1 s). The choice of the frequency of these single-pulse TMS was based on the data from Chen et al. (1997) who found no change in corticospinal excitability by an hour of 0.1 Hz (1 pulse per 10 s) rTMS. The pulses were not spaced out equally to avoid any priming effects or boredom that could affect the MEP size.

Thereafter, rTMS was administered at 1, 10 or 20 Hz. Regardless of rTMS frequency stimulation intensity was always 90% of the subject's MT. The total number of stimuli applied in these rTMS trains and the time over which the rTMS was applied were also kept constant. In the case of 1 Hz rTMS, a single train of 240 stimuli was applied over 4 min. In the case of 10 Hz rTMS, we applied 3 trains (80 pulses each, total 240 stimuli) with an intertrain interval of 72 s. In the case of 20 Hz rTMS, 6 trains (40 pulses each) were applied with an intertrain interval of 38 s.

Following the completion of the rTMS, post-rTMS corticospinal excitability was tested. This evaluation began 30 s after completion of the rTMS and consisted in the recording of 10 MEPs to single-pulse TMS using the same methodology described above for the baseline corticospinal excitability measurement. The 30 s interval was the time required to switch driving software for the magnetic stimulator and double check the EMG connections.

The order of rTMS frequency was varied across subjects. There was a 5–10 min interval between each trial (one trial implies to a set of one rTMS application and 10 single-pulse TMS before and after rTMS).

All subjects were studied on two different days using the same protocol. On each of the 2 days, the study was conducted approximately at the same time of the day. The devices, instruments and investigators (both for stimulation and analysis) were kept constant for the 2 study days on a given subject.

2.5. Data analysis

The MEPs were analyzed off-line on a Macintosh G3/300

Power PC (Apple Computers) using PowerLab software (AD Instruments). MEPs were rectified and area under the curve was calculated. The 10 MEPs before and after each rTMS application were averaged, and the percent change of averaged post- to pre-rTMS MEP were calculated for further analysis. Statistical analysis was carried out by Statistical Packages for Social Sciences (SPSS 6.0/9.0) (SPSS Inc., Chicago, IL, USA).

3. Results

In regards to safety, all subjects tolerated the study well without unexpected complications. The only side effect of the stimulation was a mild transient headache in two subjects. This results in an incidence of headache of only 1%.

3.1. Reproducibility

Pre- and post-MEPs were compared across subjects for the 3 rTMS conditions. These tests were administered across two separate testing sessions, on two different days. These two testing days were separated by at least 1 week. For each subject at each condition, a total of 10 MEPs were recorded.

Grouping the data, we compared the pre- and post-rTMS scores using percent change from pre-rTMS for each of the two days. It was found that the average percent change score for 1 Hz rTMS was −16.13% (SE = 3.99%) for day 1 and −18.50% (SE = 5.60%) for day 2 (Fig. 1). To determine if, as a group, the reduction for both days was significant, two single-group, two-tailed t-tests were run (for all comparisons, Bonferroni correction: $\alpha = 0.0083$). There was a significant decrease in MEPs for day 1 ($t(19) = -3.831$, $P < 0.001$). The size of this effect as indexed by η^2 was 0.44. For day 2, there was also a significant difference ($t(19) = -3.131$, $P < 0.005$; $\eta^2 = 0.32$).

We then compared the 10 Hz group. The average pre/post difference was −6.69% (SE = 4.71%) for day 1 and −0.22% (SE = 4.56%) for day 2. No significant difference was found for day 1 ($t(19) = -1.345$, $P > 0.008$) nor day 2 ($t(19) = -0.46$, $P > 0.008$).

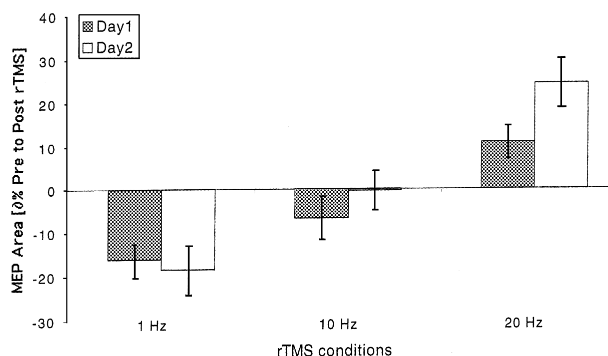

Fig. 1. Percent change in MEP area from pre- to post-rTMS application on day 1 and day 2. Results are displayed as mean and standard errors.

For the 20 Hz group on day 1, the average percent change from pre to post was 10.8% (SE = 3.93%). For day 2, the average percent change was 24.58% (SE = 5.70%). This change was significant for both day 1 ($t(19) = 2.600$, $P < 0.008$), and day 2 ($t(19) = 4.088$, $P < 0.001$; $\eta^2 = 0.47$).

Thus for the 1 Hz condition, MEPs were significantly reduced on both days, while no change was found for either day in the 10 Hz condition. For the 20 Hz group, a significant increase was observed on both days.

The correlation between the 2 days for the 1 Hz group was 0.266 ($P > 0.05$) (Fig. 2). The correlation for the 10 Hz group was 0.260 ($P > 0.05$). For the 20 Hz group, the correlation between day 1 and day 2 was 0.543 ($r^2 = 0.29$; $P < 0.013$). Comparing these correlations using Fisher's test, it was found that the correlation coefficient for the 20 Hz group was not significantly higher than the coefficient for the 1 Hz group ($Z = 0.98$, $P > 0.05$) or the coefficient for the 10 Hz group ($Z = 1.00$, $P > 0.05$).

We then compared the two days to see if there were significant changes in reduction or increase in MEPs within the conditions. There was no difference found for the 1 Hz or the 10 Hz conditions ($P > 0.05$). However, it was found that there was a difference within the 20 Hz group ($t(19) = -2.689$, $P < 0.015$; $\eta^2 = 0.28$). This indicated that increase on day 2 was significantly greater than the increase on day 1. Thus while there is a significant correlation between the MEPs in the 20 Hz condition, the change was significantly greater for the second day compared to the first.

4. Discussion

There have been some preliminary studies suggesting that the rTMS effects on corticospinal excitability may depend on the frequency, duration, intervals and intensity of stimulation. Following rTMS application to the primary motor cortex, responses to single suprathreshold TMS stimuli have been shown to be suppressed or facilitated depending on the stimulation frequency of the applied rTMS train (Chen et al., 1997; Tergau et al., 1997; Pascual-Leone et al., 1998). Wang et al. (1996) observed long-term depression (LTD)-like and long-term potentiation (LTP)-like changes in rodent auditory cortex using rTMS. They reported a frequency-dependant increase in spike-rate. Our results confirm and expand previous work in showing a frequency-dependant modulation in MEP size. However, in our study, we see a rather large degree of interindividual variability in the pattern such that some subjects do not show any frequency-dependent modulation in MEP size. In addition, the intraindividual results were not always reproducible on a different day.

How long the resulting modulation of corticospinal excitability persists with these parameters is unknown. Pascual-Leone et al. (1994) demonstrated a 3–4 min period of increased excitability after 10 pulses of 20 Hz rTMS at

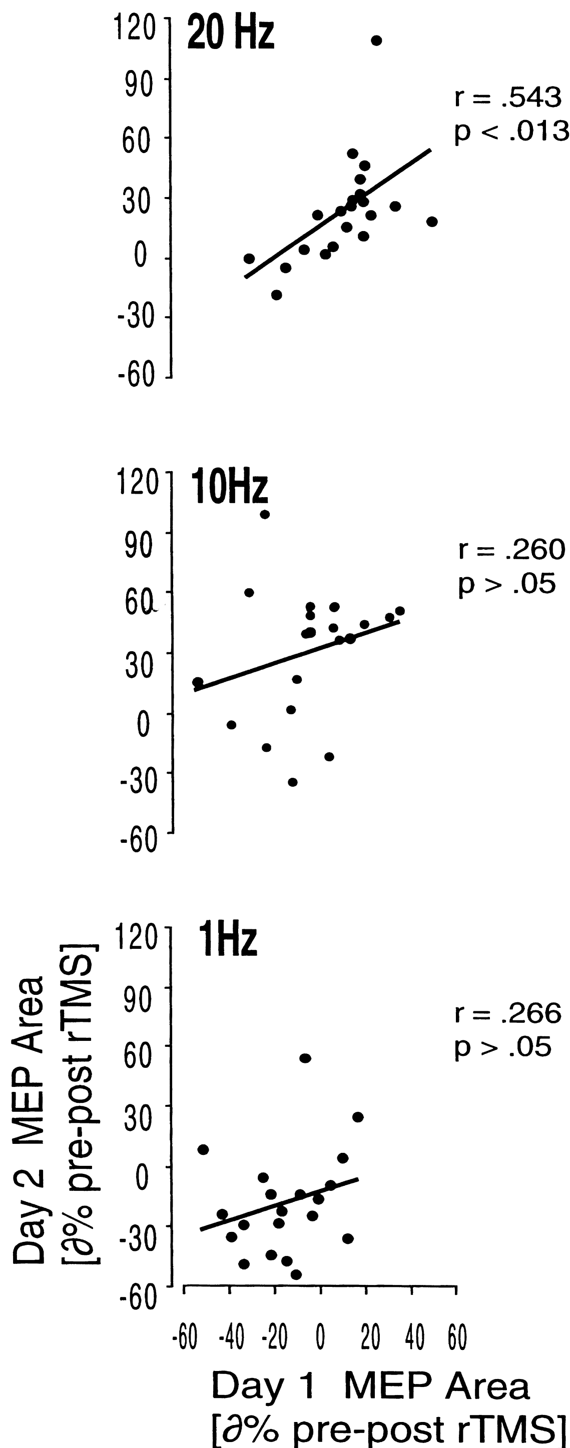

Fig. 2. Correlation of the results from day 1 and day 2 at all rTMS conditions tested. Results represent the percent change in MEP area from pre- to post-rTMS application.

150% of MT. Berardelli et al. (1998) observed an increase in corticospinal excitability of up to 900 ms after 1 train of 5 Hz rTMS at 120% of MT. An increase in cerebral blood flow was observed at 10 min after 1 Hz stimulation to the motor cortex (at an intensity of 120% of the subject's MT; total of 1800 pulses) (Fox et al., 1997). Therefore, the modulatory effects of rTMS on corticospinal excitability can vary from milliseconds to minutes, depending on frequency, stimulus intensity, intertrain interval and duration of the rTMS. Hence, with the stimulation parameters used in our study, the effect may not have lasted long enough to show a larger significance in MEP size, or may have lasted too long and have distorted the result of the following trial. However, at least the variability (either excitatory or inhibitory) in response on different days cannot be explained by this, since within the same subject, the order of frequencies and the resting period were kept constant.

So far, there is only one preliminary report by Tergau et al. (1997) that briefly mentions the variability of the results repeated on a different day. In their study, although repeated studies in single subjects over different days revealed somewhat variable results, in most cases the rTMS that led to the maximal increase in corticospinal excitability remained constant. Although the details of the methodology and the results are not described in their brief report, the results obtained in our study seem to be similar. Not only with the neurophysiological response, but also in a study that examined the upregulation of astroglial gene expression in the murine central nervous system, the variability of the rTMS effects across animals was substantial (Fujiki and Steward, 1997).

Since the early 1990s, a number of investigators have been studying TMS as a potential treatment tool in neuropsychiatric disorders. Such disorders include depression, mania, anxiety disorders, schizophrenia, movement disorders and epilepsy (George et al., 1999). The most widely studied disorder of all is major depression disorder (MDD). In most of the MDD studies, the stimulation parameters (site, frequency, intensity, train duration, intertrain interval, trains per session, number of sessions and total number of pulses) are consistent for all patients and within the patients throughout the treatment course. The hypothesis underlying the determination of stimulation parameters is that; (1) neuroimaging studies have implicated that patients with mood disorders have hypo- and/or asymmetrical brain activity in certain brain regions (Baxter et al., 1989; Bench et al., 1992; George et al., 1993; Mayberg, 1994; Mayberg et al., 1994; Gonzalez Torrecillas et al., 1997; Iidaka et al., 1997; Soares and Mann, 1997; Fernandez-Arguelles et al., 1998; Galynker et al., 1998), and that, (2) electrophysiology studies have implicated that high-frequency rTMS may result in excitatory cortical effects. However, these hypotheses are unclear since neuroimaging studies on patients (hypothesis (1)) as well as functional neuroimaging studies of the rTMS effect on normal subjects has yielded inconsistent results (Fox et al., 1997; Kimbrell et al., 1997; Paus et al., 1997, 1998; Stalling et al., 1997; Wassermann et al., 1997; Bohning et al., 1999). While neuroimaging studies have the advantage of studying the effect of rTMS on areas other than the primary motor cortex and can examine effects distant from the stimulation site, the temporal resolution is reduced and it is not known how blood-flow and

metabolic rate correlate with electrophysiological indicators of neural activity. On the other hand, studying the effect of rTMS on the primary motor cortex with TMS has the advantage of examining the direct electrophysiological neural activity with excellent temporal resolution. However, the results obtained cannot simply be extrapolated to other areas such as the dorsolateral prefrontal cortex.

In this study, we have examined (1) the interindividual difference of the modulatory effects on motor cortical excitability by rTMS, and (2) the reproducibility of these effects. Although there was a significant suppression of MEPs following 1 Hz rTMS and a significant facilitation of MEPs following 20 Hz rTMS on both day 1 and day 2, this phenomenon was not observed for 10 Hz rTMS. Hence, it may be said that the modulatory effect of 1 and 20 Hz is fairly reproducible in contrast to the effect of 10 Hz rTMS. The complex interaction between the results on the two testing days is illustrated by the correlation analysis performed (Fig. 2). Interestingly, the effect (when it was significant) was greater on day 2, which in turn may be related to the LTD and LTP-like effect as was shown by Wang et al. (1996). These investigators showed an effect by 240 pulses of rTMS at 8 Hz lasting occasionally up to the observed 24 h.

However, it should be stressed that methodological issues may account for, or at least contribute to the variability observed. For example, inconsistencies in coil positions which was hand-held by the investigator (Ellaway et al., 1998), environmental factors, or fluctuations in the subjects' alertness could all play an important role in the reproducibility of the TMS effects. Nevertheless, whether due to physiological factors or secondary to environmental or methodological limitations, the present results suggest that great care is needed in TMS studies assuming consistent effects across stimulation sessions.

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