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RESEARCH ARTICLE

Fumiko Maeda · Julian P. Keenan · Jose M. Tormos
Helge Topka · Alvaro Pascual-Leone

Interindividual variability of the modulatory effects of repetitive transcranial magnetic stimulation on cortical excitability

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Abstract Repetitive transcranial magnetic stimulation (rTMS) appears to have effects on cortical excitability that extend beyond the train of rTMS itself. These effects may be inhibitory or facilitatory and appear to depend on the frequency, intensity, duration and intertrain interval of the rTMS. Many studies assume facilitatory effects of high-frequency rTMS and inhibitory effects of low-frequency rTMS. Nevertheless, the interindividual variability of this modulation of cortical excitability by rTMS has not been systematically investigated. In this study, we applied 240 pulses of rTMS at 90% of the subjects' motor threshold to their motor cortex at different frequencies (1, 10, 15 and 20 Hz) and examined the effects on motor evoked potentials (frequency tuning curve). Although the averaged group data showed a frequency-dependent increase in cortical excitability, each subject had a different pattern of frequency tuning curve, i.e. a different modulatory effect on cortical excitability at different rTMS frequencies. The interindividual variability of these modulatory effects was still high, though less so, when the number of rTMS pulses was increased to 1600. These findings illustrate the degree of variability of the rTMS effects in the human brain.

Key words Repetitive transcranial magnetic stimulation (rTMS) · Train · Frequency tuning curve · Cortical excitability · Neurophysiology

A. Pascual-Leone · F. Maeda · J.P. Keenan
Laboratory for Magnetic Brain Stimulation,
Department of Neurology, Beth Israel Deaconess Medical Center,
Harvard Medical School, 330 Brookline Ave. KS452, Boston,
MA 02215, USA

F. Maeda
Department of Neuropsychiatry,
Keio University School of Medicine, Tokyo, Japan

J.M. Tormos · A. Pascual-Leone
Institute for Bioengineering, Miguel Hernandez University,
Alicante, Spain

H. Topka
Department of Neurology, University of Tübingen, Tübingen,
Germany

Introduction

Transcranial magnetic stimulation (TMS) was developed by Barker in 1985 (Barker et al. 1995a, 1985b). Since then, it has become a useful tool for investigating various aspects of human neurophysiology. In 1987, repetitive TMS (rTMS) (regularly repeated TMS delivered to a single scalp position) was introduced (Pascual-Leone et al. 1996). Repetitive TMS appears to have effects on cortical excitability that last beyond the duration of the rTMS application itself. A growing number of studies utilize these modulatory effects of rTMS on cortical excitability (Pascual-Leone et al. 1998). The potential therapeutic application of rTMS in neuropsychiatric disorders is one example of such studies (Reid et al. 1998; George et al. 1999).

Findings to date suggest that the modulatory effects of rTMS on cortical excitability may be inhibitory or facilitatory depending on the frequency, intensity, duration and intertrain interval (Chen et al. 1997; Berardelli et al. 1998; Pascual-Leone et al. 1998). The distinction between slow or low-frequency rTMS (stimulus rates of 1 Hz or less) and fast or high-frequency rTMS (stimulus rates of more than 1 Hz) is based in part on these different physiological effects of rTMS (Wassermann 1998).

In the present study, we have systematically investigated the modulatory effect on cortical excitability of rTMS at various frequencies and at various numbers of pulses. The modulatory effects of rTMS in a given subject across stimulation frequencies are termed 'frequency tuning curves'.

Materials and methods

Subjects

We studied 36 right-handed healthy volunteers (22 subjects in experiment 1 and 14 subjects in experiment 2). The study was approved by the local Institutional Review Board (IRB) and written informed consent was obtained. None of the subjects had any psychiatric or medical history, nor any contraindications to TMS (Wassermann 1998).

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 each subject's head to mark the site for stimulation. 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). Stimulation was delivered to the optimal scalp site, i.e. the scalp position from which TMS evoked 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 the right abductor pollicis brevis (APB) muscle. A circular 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. The EMG signal was amplified using a Dantec counterpoint electromyograph with an amplification of 1.0 mV and a band pass of 20–1000 Hz (Dantec, Skovlunde, Denmark). The preamplified signal was digitized using PowerLab 16 S (AD Instruments Limited, Hastings, UK) with a sampling rate of 2 kHz per channel and stored on a Macintosh G3/300 Power PC (Apple Computers, CA, USA) for off-line analysis.

Determination of motor threshold

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 pointing in an antero-medial direction, 45° from the mid-sagittal axis of the subject's head. This coil placement was chosen based on the finding that the lowest motor threshold (MT) is achieved when the induced electric current in the brain is flowing approximately perpendicular to the orientation of the central sulcus (Brasil-Neto et al. 1992a; Mills et al. 1992). 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 six out of ten consecutive trials. Stimulation began at well above threshold intensity (generally 90% of the stimulator output) and decreased in steps of 2% of the stimulator output. For the purpose of MT determination, a TMS stimulus was applied approximately every 10 s (±1 s). This interval between each pulse was based on the data from Chen et al. (1997) who found no change in cortical excitability after an hour of 0.1 Hz (one pulse per 10 s) rTMS. The interval between pulses was randomly varied (±1 s) to avoid any priming effects that could affect the MEP size.

The threshold determination was made during complete muscle relaxation that was monitored on audio and EMG signals for 50 ms prior to the application of the TMS.

Data collection and rTMS procedure

Experiment 1

For determination of baseline corticospinal excitability, ten single-pulse TMS pulses at 120% of the subject's MT were applied to the optimal site with a random stimulus interval of approximately 10 s (±1 s).

Thereafter, rTMS was administered at 1, 10, 15 or 20 Hz. Regardless of rTMS frequency, stimulation intensity was always 90% of the subject's MT. The total number of stimuli (240 pulses) delivered and the total duration (4 min) over which the rTMS was applied were also kept constant. With an rTMS of 1 Hz, a single train of 240 pulses was applied over 4 min. With an rTMS of 10 Hz, we applied three trains (80 pulses each) with an intertrain interval of 72 s [72 s rest – 8 s rTMS – 72 s – 8 s – 72 s – 8 s]. With an rTMS of 15 Hz, we applied four trains (60 pulses each) with an intertrain interval of 56 s (56 s rest – 4 s rTMS – 56 s – 4 s – 56 s – 4 s – 56 s – 4 s). With an rTMS of 20 Hz, six trains (40 pulses each) were applied with an intertrain interval of 38 s (38 s rest – 2 s rTMS – 38 s – 2 s – 38 s – 2 s – 38 s – 2 s – 38 s – 2 s – 38 s – 2 s).

After the completion of the rTMS, corticospinal excitability was measured again. This evaluation began 30 s after completion of the rTMS and consisted of 10 MEPs to single-pulse TMS, recorded using the same methodology as described above for the baseline 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 trials of different frequencies (1, 10, 15 or 20 Hz) was counterbalanced across subjects. There was a 5–10 min-interval between each trial. One trial refers to an rTMS train of a certain frequency and 10 single-pulse TMS before and after rTMS.

Experiment 2

After the first experiment had been completed and analyzed, a second experiment was carried out on 14 additional healthy volunteers. The purpose of this second experiment was to test whether the effect of rTMS would be greater or the interindividual variability smaller when the total number of pulses was increased. The same methodology as described above was used except for the rTMS parameters. The rTMS parameters were either a single train of 1 Hz or 20 trains of 10 Hz with an intertrain interval of 52 s. In both cases, a total of 1600 pulses was applied at 90% of the subject's MT.

Data analysis

The MEPs were analyzed off-line on a Macintosh G3/300 Power PC (Apple Computers, CA, USA) using PowerLab Scope software (AD Instruments Limited, Hastings, UK). MEPs were rectified and area-under-the-curve was measured. For each subject, we averaged the ten rectified MEPs before and after each rTMS setting. Thereafter, the size of the post-rTMS MEPs was expressed as the percentage change from baseline (MEPs before rTMS). All tabulations were performed using Statistical Packages for Social Sciences (SPSS v9.0) (SPSS Inc., Chicago, Ill., USA).

Results

In regard to safety, all subjects tolerated the study well without unexpected complications. The current safety guideline only points out the maximum safe rTMS train duration for suprathreshold intensity (Wassermann 1998). Our study was conducted with multiple trains but at subthreshold intensity. We assumed that the safety margin would be wide for such lower intensity stimulation. The only side-effect of the stimulation was a mild transient headache in two subjects in experiment 1 and five subjects in experiment 2. In all cases the headache resolved promptly with mild analgesia (acetaminophen).

Experiment 1: 240 pulses

Figure 1 provides a representative example of the MEPs recorded pre- and post- rTMS across rTMS conditions.

A comparison was first made across the four rTMS settings (Fig. 2). It was found that there was a trend for significance using a single-factor repeated measures analysis of variance (ANOVA, $F_{3, 63}$=2.404, P=0.076, eta^2=0.103). Despite the fact that only a trend was found, we per-

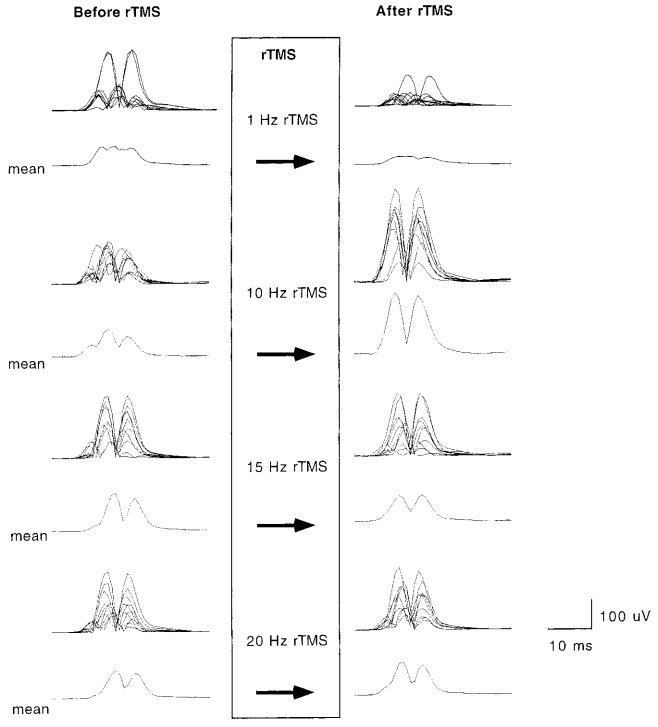

Fig. 1 An example of rectified motor evoked potentials (MEPs) at baseline and post-rTMs (Experiment 1). The *upper lines* of each frequency show all MEPs, and the *bottom lines* show the mean value. Note that all baseline MEPs have a similar size. The modulatory effect at 1 Hz is inhibitory, 10 Hz is facilitatory and there are no significant effects at 15 and 20 Hz

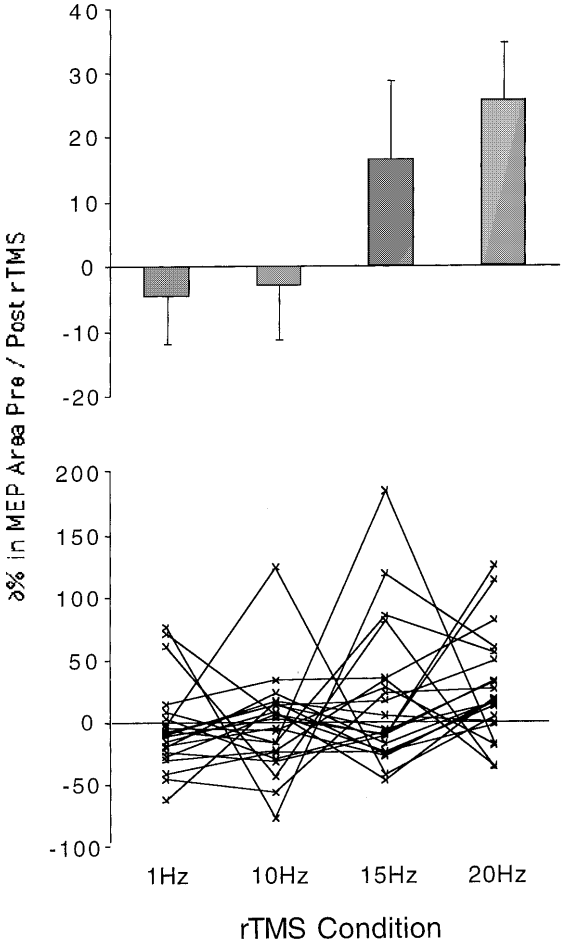

Fig. 2 Frequency tuning curve of experiment 1. The total number of pulses applied at each rTMS condition was 240. *Top* the mean percentage changes in the averaged MEP area from pre-to-post rTMS. The *bars* indicate standard error. *Bottom* frequency tuning curves of each individual. *∂%*=percentage change

formed additional comparisons to investigate potential group differences. In a first comparison, we addressed the differences between the groups. Employing Bonferroni adjusted comparisons, it was found that the only significant difference between rTMS conditions was between the 1 Hz (mean=–4.42%, SD=35.2%) and the 20 Hz group (mean=25.92%, SD=42.36%; $P<0.05$). All other possible comparisons were non-significant (10 Hz: mean=–2.81%, SD=39.47%; 15 Hz: mean=16.67%, 57.03%; $P>0.05$).

In a second comparison, we evaluated whether the percentage threshold changes differed significantly from zero for each of the rTMS conditions. To calculate this, four one-sample *t*-tests were performed using a Bonferroni adjusted procedure. It was found that only the 20 Hz condition resulted in a significant difference ($t(21)=2.871$, $P=0.009$; $\text{eta}^2=0.28$). All other comparisons were found to be non-significant ($P>0.05$). Finally, we examined the correlation across the rTMS conditions. The only significant correlation was found between 15 Hz condition and the 1 Hz condition ($r=0.46$, $P<0.05$) and the 15 Hz and the 10 Hz condition ($r=–0.47$, $P<0.05$). All other correlations were non-significant.

Experiment 2: 1600 pulses

In this experiment with the larger number of rTMS stimuli, we found a significant difference between the two rTMS conditions (Fig. 3). There was a facilitation after 10 Hz rTMS (mean=37.87%, SD=53.59%) compared to an inhibition after 1 Hz rTMS (mean=–34.03%, SD=37.87%). This differential effect of 1 versus 10 Hz rTMS was significant [$t(13)=–4.542$, $P<0.001$; $\text{eta}^2=0.61$]. The percentage change for the 10 Hz condition was significantly greater than zero [$t(13)=2.644$, $P<0.02$; $\text{eta}^2=0.35$], and the percentage change for the 1 Hz group [$t(13)=–3.470$, $P<0.004$; $\text{eta}^2=0.48$] was significantly less than zero. It was also found that there was not a significant correlation between the two conditions ($r=0.18$, $P>0.05$).

Comparison of the effects in experiments 1 and 2

The 240-pulse subjects (experiment 1) were then compared with the 1600-pulse subjects (experiment 2) for 1 and 10 Hz. There was a significant increase for the 1600-pulse subjects in the 10 Hz condition [$t(34)=2.621$, $P<0.05$; $\text{eta}^2=0.17$], and a significant decrease in the

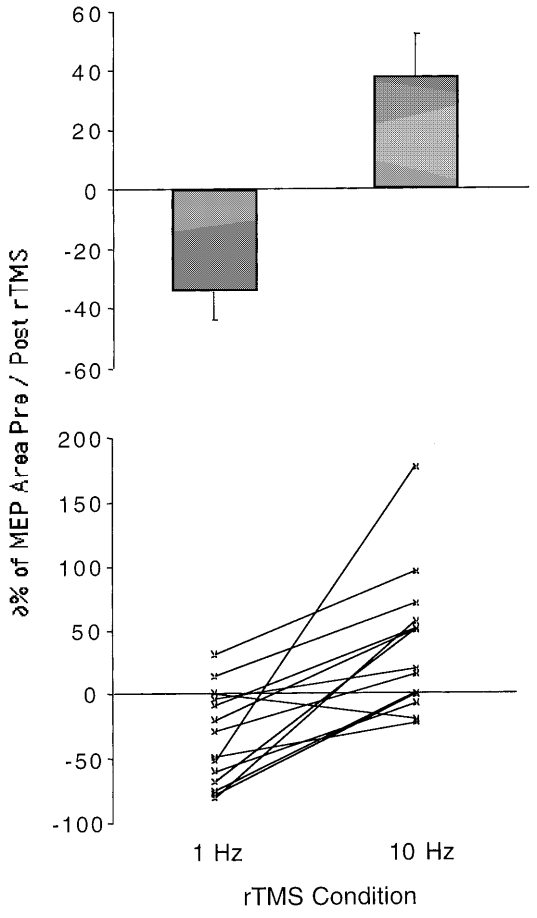

Fig. 3 Frequency tuning curve of experiment 2. The total number of pulses applied at each rTMS condition was 1600. *Top* the mean percentage changes in the averaged MEP area from pre- to-post-rTMS. *Bars* indicate standard error. *Bottom* frequency tuning curves of each individual. *∂%*=percentage change

1 Hz condition [$t(34)$=–2.421, P<0.05; eta^2=0.15]. However, these data should be interpreted with caution as the two groups were treated differently (i.e. the 240-pulse subjects received four rTMS conditions as compared to the two received by the 1600-pulse subjects) and the sample sizes were different.

Discussion

In this study, we have examined the frequency tuning curves of 36 subjects. Although measurements of MEPs include cortical as well as spinal components, previous studies have shown that the modulation in MEP size by rTMS is most likely cortical in origin (Berardelli et al. 1998, Berardelli et al. 1999). In the first experiment in which subjects were exposed to 240 pulses of rTMS, there was a trend toward an rTMS frequency-dependent increase in cortical excitability, but the only significant change was observed at 20 Hz. On the other hand, 1600 pulses of 1 Hz or 10 Hz rTMS (experiment 2) resulted in significant modulation of the cortical excitability (inhibition and facilitation respectively).

A number of previous studies have reported similar changes in cortical excitability after rTMS. For example, a long train of low-frequency rTMS (0.9 or 1 Hz) reduces the excitability in the motor cortex (Chen et al. 1997; Tergau et al. 1997; Wassermann et al. 1996, 1998; Pascual-Leone et al. 1998). Wassermann et al. (1997) and Fox et al. (1997) showed a decrease in cortical excitability by measuring the cerebral metabolic rate or cerebral blood flow, respectively. On the other hand, high-frequency rTMS (5–25 Hz) has been shown to increase cortical excitability in several studies. This was demonstrated either by an increase in MEP amplitude (Pascual-Leone et al. 1994b; Tergau et al. 1997; Berardelli et al. 1998), by paired-pulse technique (Tergau et al. 1997), or by cerebral metabolic activity (Pascual-Leone et al. 1997). These types of phenomena have been referred to as long-term depression (LTD)-like (Hess and Donoghue 1996; Linden 1994) and long-term potentiation (LTP)-like changes (Wang et al. 1996). However, the mechanisms underlying modulation of cortico-spinal excitability by rTMS remain unknown and the possible relation to LTD or LTP is uncertain.

This modulation of cortical excitability by rTMS has been advocated to be responsible for the apparent therapeutic effects of rTMS in various neuropsychiatric conditions. Preliminary data in humans showed a reduction in cortical myoclonus after low-frequency rTMS (Wedegaertner et al. 1997). A similar low-frequency rTMS protocol has also been shown to reduce writing pressure and motor disturbance in patients with dystonic writer's cramp (Siebner et al. 1999). On the other hand, high-frequency rTMS has been applied for the treatment of depression with the argument that it might aid by normalizing a suppressed cortical excitability (George et al. 1999).

Nevertheless, the most striking finding of this study is not the net modulation of cortical excitability in a group of subjects but that, at all frequencies tested, the interindividual variability was substantial and many of the subjects did not show a frequency-dependent increase in the frequency tuning curves. It is also interesting to note that most of the past literature has examined the modulatory effects of *supra*threshold rTMS on cortico-spinal excitability. In our study, we document modulatory effects of rTMS at *sub*threshold intensity.

Recent studies of TMS in animal models have also encountered evidence supporting substantial interindividual variability of the effects. For example, Fujiki and Steward (1997) applied up to 30 trains of 25 Hz rTMS at an intensity that evoked muscle twitches in the extremities of mice. These investigators examined the expression patterns of glial fibrially acidic protein (GFAP) and concluded that the variability in expression pattern was most likely due to significant biological differences between the mice. In another example, Wang et al. (1996) studied the long-term responses of neuronal ensembles in rodent auditory cortex. After rTMS (8 Hz, 1 s stimulation, 5 s pause, 30 iterations, 240 pulses), these authors found sustained decreases in evoked spike rates in some

animals but increases in others despite the same rTMS protocol. Our results most likely illustrate the equivalent large variability in human neurophysiologic responses to specific brain interventions. Functional neuroimaging studies reveal similarly great interindividual variability and support the notion of a highly dynamic and flexible nervous system (Berns et al. 1999). However, there are other factors that may have contributed to our findings.

The first concern is whether the resting period was sufficient to prevent carry-over effects. Chen et al. (1997) showed a decrease in MEP amplitude for at least 15 min after rTMS at 0.9 Hz for 15 min (810 pulses) at 115% of the MT. With high-frequency rTMS, the lasting effect was 600 to 900 ms in the study by Berardelli et al. (1998) (one train of 20 rTMS pulses at 5 Hz and 120% of MT) and 3 to 4 min in a study by Pascual-Leone et al. (1994b) (10-pulse rTMS train at 20 Hz and 150% of MT). The lasting effects on corticospinal excitability of the rTMS parameters used in our study are unknown. Carry-over effects may have resulted in the interindividual variability, since the order of frequency was randomized. However, this is unlikely since each subject's mean baseline MEPs for all frequencies did not vary significantly. This consistency in the baseline MEPs suggests that the lasting effect was short enough or at least not robust enough to significantly influence the MEP amplitude.

The second issue is that technical limitations might have contributed to the encountered variability of the rTMS effects. For example, the TMS coil was hand-held and despite the use of experienced researchers this may have conditioned the variability. However, this may also be disregarded because the baseline MEPs before each frequency were of similar size.

In experiment 1, the lack of significant and consistent modulation effects may have been due to the small number of rTMS pulses (240). Experiment 2 showed significant modulation of the cortical excitability by rTMS at 1 and 10 Hz. Therefore, it might be necessary to apply trains of nearly or more than 1000 pulses for interindividual consistent and significant effects of rTMS on cortical excitability. Nevertheless, it should be noted that in order to keep the rTMS duration constant (4 min) despite various stimulation frequencies, we had different intervals between trains and that may have affected the results. However, we felt it was important to make the total duration of the rTMS session and total number of pulses consistent across conditions when comparing various frequencies.

Furthermore, after rTMS trains of a small number of pulses, the effects may be short-lived and we might have missed consistent findings due to the fact that we started collecting data 30 s after the rTMS application.

One final concern is that averaging ten trials at a single intensity may be an unstable parameter. Brasil-Neto et al. (1992b) examined the variability of MEP amplitude at rest. They showed that with a larger number of stimuli, with a shorter distance to the optimal site, and with the use of distal muscles, the variability decreased. The result shown in their study was that a minimum of five stimuli was necessary to have at least 90% of the mean MEPs within 20% of the true MEP amplitude. Nevertheless, Thickbroom et al. (1999) applied four stimuli of 120% MT at approximately 10% of maximum root-mean-square EMG activity and demonstrated that reliable and accurate mapping studies can be carried out in the presence of an intrinsic variability in APB amplitude. Therefore, even though a greater number of data points before and after the rTMS trains should reduce variability and be desirable, we do not believe that this factor conditioned our results.

Our findings suggest that rTMS can have a different effect on cortical excitability across individuals. Further, although there was a frequency-dependent increase in the modulatory effect as a group, it is important to notice that each individual seems to have a different frequency tuning curve. However, the reproducibility of this frequency tuning curve needs further testing. This will become particularly important in studies where interpretation of the result might depend on the effect of rTMS. A good example is clinical trials of depression, where many of the studies raise the possibility that the therapeutic effect with high-frequency rTMS may be due to its facilitatory effects while low-frequency rTMS may exert antidepressant effects via inhibitory effects on cortical excitability (Klein et al. 1999). Our results suggest that studies assuming that the rTMS effects are either facilitatory or inhibitory and consistent across subjects may be misleading and that stimulation parameters may need to be tailored to each individual.

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