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Origin of facilitation in repetitive, 1.5 ms interval, paired pulse transcranial magnetic stimulation (rPPS) of the human motor cortex

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Abstract

Objective: Repetitive paired-pulse TMS (rPPS) given at an interstimulus interval (ISI) of 1.5 ms has been reported to induce a lasting motor evoked potential (MEP) facilitation. This after-effect was considered to be a cortical event because F-waves were not affected by the same rPPS. To confirm its cortical facilitation, we compared the after-effects of rPPS on MEPs to single pulse TMS over the motor cortex (motor cortical MEPs) with those to brainstem stimulation (brainstem MEPs).
Methods: Subjects were 10 healthy volunteers. Suprathreshold paired-pulse TMS at an ISI of 1.5 ms was applied to the motor cortex for 30 min at a rate of 0.2 Hz. After intervention, we measured motor cortical MEPs for 30 min. We also studied brainstem MEPs in five subjects.
Results: Motor cortical MEPs were facilitated to about 190% of baseline ($p < 0.001$) for 10 min post rPPS intervention and returned to the baseline at 10–15 min post intervention. Brainstem MEPs were not affected by the intervention.
Conclusions: The facilitation of MEPs after rPPS at an interval of 1.5 ms occurs at the motor cortex.
Significance: rPPS at an interval of 1.5 ms is an effective method for increasing motor cortical excitability.

Keywords: Repetitive transcranial magnetic stimulation (rTMS); Paired pulse stimulation; Motor cortex; Monophasic pulse; I wave periodicity

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) protocols have been reported to be a potential tool to modify human motor cortical excitability. High frequency rTMS tends to induce facilitatory after-effects and low frequency rTMS inhibitory effects (Chen et al., 1997; Maeda et al., 2000a,b; Sommer et al., 2002), although there is a moderate interindividual variability in the direction of effect (Maeda et al., 2000a). So far, most of the studies have used biphasic rTMS (Berardelli et al., 1998, 1999; Chen et al., 1997; Di Lazzaro et al., 2002; Huang et al., 2005; Maeda et al., 2000a,b; Pascual-Leone et al., 1994; Romeo et al., 2000).

We have previously shown that monophasic TMS has a stronger short-term effect during repetitive stimulation than biphasic TMS (Arai et al., 2005). This finding suggests that monophasic pulses preferentially activate population of neurons oriented in the same direction so that their effects readily summate. In the same way, it is possible that monophasic rTMS would result in a more powerful after-effect than biphasic rTMS. Indeed, Thickbroom and coworkers (2006) produced a powerful after-effect by repet-

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itive, monophasic, paired pulses TMS delivered at an I-wave periodicity (the rPPS protocol). rPPS with TMS pulses paired at 1.5 ms for 30 min facilitated motor evoked potentials (MEPs) to a single TMS delivered over the motor cortex (motor cortical MEPs), which lasted up to 10 min after the cessation of the intervention. This facilitation was proposed to occur at the cortical level because F-waves were not affected by the same protocol. However, since F-waves can reflect the activity of only a small portion of spinal motor neurons, we cannot be sure whether the whole spinal cord excitability was indeed unchanged. In contrast, MEPs to brainstem stimulation (brainstem MEPs) are considered to reflect the excitability of a larger population of spinal motor neurons than do F-waves, because it can activate most of the motor neurons in the spinal cord. In this communication, we aimed to differentiate between the cortical and subcortical loci of facilitation by comparing the after-effects of rPPS between motor cortical and brainstem MEPs. Determination of the site of action would have an important implication for the future application of this novel protocol for treating neurological disorders.

2. Subjects and methods

2.1. Subjects

Subjects were 10 healthy volunteers (2 women, 8 men, mean age ± SD: 38.0 ± 5.3 years) who gave their informed consent to participate in the experiments. None of the subjects had neurological, psychiatric or other medical problems or had any contraindication to TMS (Wassermann, 1998). The protocol was approved by the Ethics Committee of the University of Tokyo and was carried out in accordance with the ethical standards of the Declaration of Helsinki.

2.2. Stimulation and recordings

Subjects were seated on a reclining chair and motor evoked potentials (MEPs) were recorded from the right first dorsal interosseus muscle (FDI) (dominant hand in all subjects). Pairs of Ag/AgCl surface cup electrodes (9 mm in diameter) were placed over the muscle belly (active electrode) and the metacarpophalangeal joint of the index finger (reference electrode). Responses were amplified with an amplifier (Biotop, GE Marquette Medical Systems, Japan) through filters set at 100 Hz and 3 kHz, digitized with A/D converter at a sampling rate of 20 kHz and stored in a computer (TMS bistim tester, Medical Try System, Japan) for later offline analysis.

Transcranial magnetic stimulation (TMS) was given over the hand area of the left primary motor cortex (M1) at a position optimal for eliciting MEPs in the right FDI with a figure of eight coil (external diameter at each wing 9 cm, Magstim Co., Whitland, Dyfed, UK). The coil was held tangential to the scalp with the handle pointing backwards at about 45° laterally, that is perpendicular to the central sulcus. According to the previous study (Sakai et al., 1997), this is the optimal orientation for activating the corticospinal system transsynaptically via horizontal cortical connections. To determine the optimal site for FDI, we stimulated several positions separated by 1 cm with the same intensity and defined the hot spot as the site where the largest responses were elicited. The position was marked with a red pen on the scalp for repositioning the coil at the same site throughout the experiments.

Single pulse TMS was delivered by a Magstim 200 magnetic stimulator (Magstim Co., Whitland, Dyfed, UK), and paired pulse stimuli were delivered by two Magstim 200 stimulators connected with a Bistim module (Magstim Co., Whitland, Dyfed, UK).

For sham stimulation (see below), surface cup electrodes were placed over the vertex (Cz of international 10–20 system) and the left-hand motor area in each subject. An electric pulse of 0.2 ms duration was delivered through those electrodes with a conventional electric stimulator. The intensity was fixed at two times the sensory threshold for skin sensation.

Brainstem (BST) electrical stimulation was performed to evaluate spinal motoneuronal excitability changes because MEPs to this stimulation must reflect activity of most of spinal motor neurons (Ugawa et al., 1991). Anode (right) and cathode (left) were attached over the mastoid processes. Stimulation was given with a high voltage electric stimulator (D180A: 0.1 ms duration, maximal output 1.2 A, 1200 V; Digitimer, Welwyn Garden City, UK).

2.3. Interventions

2.3.1. rPPS intervention

For rPPS intervention (rPPS 30 in Fig. 1), we used the same protocol as that reported by Thickbroom et al. (2006). Paired stimuli of equal strength were delivered at an interval of 1.5 ms. The stimulus intensity was set to elicit MEPs of 0.3–0.5 mV when delivered as a pair. Paired stimuli were applied over the left hand motor area every 5 s, and 360 paired stimuli were administered in total for 30 min. During intervention, 360 MEPs (each one MEP elicited by one paired TMS) were obtained and a series of 60 MEP amplitudes were averaged to obtain the mean MEP amplitudes at 5 min intervals. Even in real rPPS, two electrodes were fixed at the same positions over the scalp as those in the sham stimulation (see the next paragraph). No currents were in real rPPS.

2.3.2. Realistic sham intervention

In sham intervention (sham 30 in Fig. 1), we performed realistic sham stimulation described previously (Okabe et al., 2003). Paired electric stimuli were given every 5 s for 30 min. The coil was not connected to a stimulator and placed over left M1. Another coil was placed near the subject. This coil was connected to Bistim module combining two Magstim 200 stimulators. These stimulators

were discharged simultaneously with the electric stimuli to produce the same sound as that associated with real rPPS intervention. The simulation parameters of paired stimuli were the same as those used in a real rPPS intervention.

2.4. Motor cortical MEPs

Motor cortical excitability was assessed by measuring the peak-to-peak amplitude of MEPs from the right FDI to single pulse TMS (motor cortical MEPs). During the experiments, subjects were encouraged to be fully relaxed with the aid of an oscilloscope monitor of the target EMG. The stimulus intensity of single pulse TMS was adjusted to elicit MEPs approximately 0.3 mV in the baseline condition. Trials contaminated with voluntary EMG activities were discarded from analysis.

2.5. Brainstem MEPs

For BST electrical stimulation, the intensity was set to produce brainstem MEPs of 0.2–0.3 mV similar sized to motor cortical MEPs. Relaxation of FDI was monitored with the aid of an oscilloscope monitor. The used intensity was 30–45% of the maximal electrical stimulator output (the highest used stimulus intensity: 0.1 ms duration, 45% of 1.2 A, 1200 V).

2.6. Timelines of experiments (Fig. 1)

Four different experiments were performed. In the same subject, two successive experiments were separated by at shortest one week interval. The order of experiments was randomized between subjects. Timelines of all the experiment are shown in Fig. 1.

Experiment (1) rPPS-TMS. Ten subjects participated in this experiment. Before and after rPPS intervention (rPPS 30), motor cortical excitability was measured by single pulse TMS. The time points of motor cortical MEP measurements are shown in Fig. 1(b, P1–6). At time point B, to evaluate the baseline motor cortical excitability, 20 motor cortical MEPs were collected every 15 s. After rPPS intervention, 120 motor cortical MEPs were collected in total for 30 min (P1–6). TMS were applied every 15 s, and mean MEP amplitudes were obtained from 20 motor cortical MEPs every 5 min.

Experiment (2) sham-TMS. Four subjects participated in this study. Before and after sham intervention (sham 30), motor cortical MEPs were measured. The time points were the same as those in experiment 1.

Experiment (3) rPPS-BST. To clarify the origins of facilitation after rPPS intervention, we performed BST electrical stimulation (Ugawa et al., 1991) in five subjects. Before rPPS intervention, 8 brainstem MEPs were obtained every 15 s to measure the baseline size of brainstem MEP. The protocol of rPPS intervention was the same as that of experiment 1 (rPPS 30). After rPPS intervention, at each time point (P1–6), BST stimuli were given every 15 s and 8 brainstem MEPs were collected. Thus, 48 brainstem MEPs were collected in total for 30 min (P1–6). Mean MEP amplitudes were obtained from 8 brainstem MEPs at each time point.

Experiment (4) rPPS-random. To exclude the effect of prediction of uncomfortable stimulation, we also performed another experiment in 3 subjects. Before rPPS intervention (B random in Fig. 1), 8 motor cortical MEPs and 8 brainstem MEPs were obtained in a random order (i.e., 16 stimuli were given every 15 s in a random order). The protocol of rPPS intervention was the same as that of experiment 1. After 5 min post intervention (P2 random in Fig. 1), 8 motor cortical MEPs and 8 brainstem MEPs were obtained in a random order.

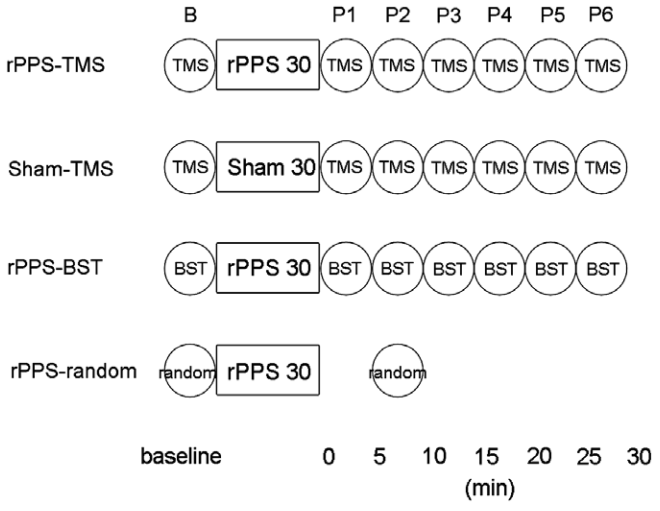

Fig. 1. Timelines of our experiments (see Section 2).

2.7. Data analysis and statistics

The effect of different conditions (rPPS-TMS, rPPS-BST) on the MEP size during rPPS intervention was studied using two way repeated measures analysis of variance (rANOVA) (between group factor; condition, within subject factor; time). The effect of different conditions (rPPS-TMS, rPPS-BST, Sham-TMS) on the time course of MEP size after intervention was evaluated with two way rANOVA (between group factor; condition, within subject factor; time). For each condition, the effect of the intervention on the time course of MEP size was analyzed using one-way factorial ANOVA. The Greenhouse–Geisser correction was used if necessary to correct for nonsphericity. Post hoc Bonferroni method was employed for further analysis. For experiment 4 (rPPS-random), MEP amplitudes were compared using paired t test. P values less than 0.05 were considered to be significant. All figures represent group data. Data are expressed as means $\pm$ SE except Fig. 4 (see Section 3). Data were analyzed using SPSS for Windows version 13.0.

3. Results

None of the subjects reported any adverse effects during and after any interventions.

3.1. rPPS intervention

Fig. 2a shows typical example of MEPs during rPPS intervention in one subject. During rPPS intervention, each response is an average MEP made from 60 raw MEPs for 5 min. Fig. 2b shows the mean MEP amplitude at 5 min interval during 30 min of rPPS intervention. In both experiments (rPPS-TMS and rPPS-BST), MEPs were increased similarly. Two way rANOVA revealed neither significant effect of the condition ($F[1,13] = 0.034$, $p > 0.05$), the time ($F[2.335, 30.354] = 1.233$, $p > 0.05$) nor significant interaction between the condition and time ($F[2.335, 30.354] = 0.159$, $p > 0.05$). For rPPS-TMS or rPPS-BST, one way factorial ANOVA revealed no significant effects of the time ($F[5,45] = 0.525$, $p > 0.05$ for rPPS-TMS, and $F[5,20] = 2.081$, $p > 0.05$ for rPPS-BST).

3.2. After-effect of rPPS or sham intervention

The upper trace of Fig. 3a shows typical motor cortical MEPs before and after rPPS intervention. Average MEPs every 5 min are depicted. The robust motor cortical MEP facilitation was seen for 10 min after intervention, and they returned to the baseline at 10–15 min post intervention. The lower trace of Fig. 3a shows typical brainstem MEPs. No facilitation was elicited in brainstem MEPs after intervention.

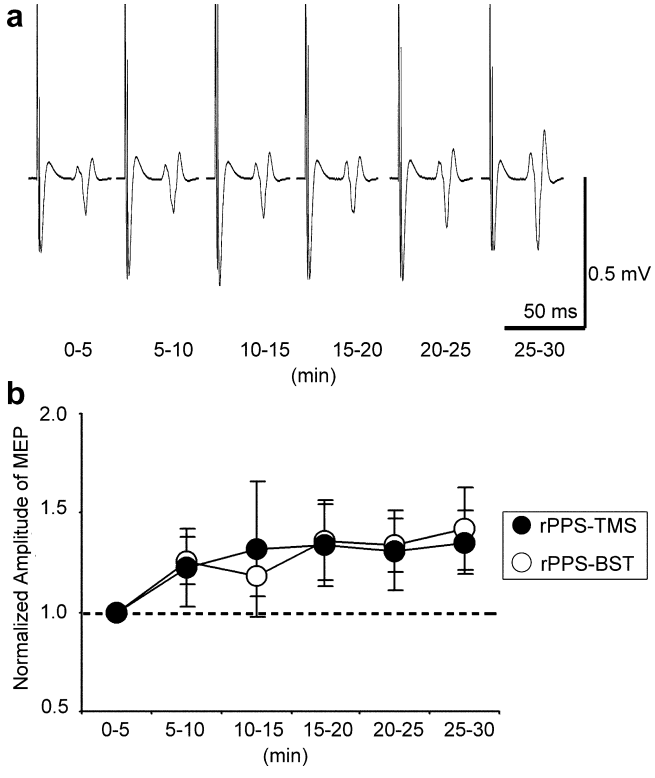

Fig. 2. MEPs during rPPS intervention. (a) Typical example of MEP waveforms from one subject. (b) Group mean MEP amplitude during rPPS intervention. MEPs are normalized to the mean of MEP amplitudes measured 5 min after the intervention. We observed similar MEP facilitation during rPPS intervention in both rPPS-TMS and rPPS-BST experiments. All data are means ± SEs.

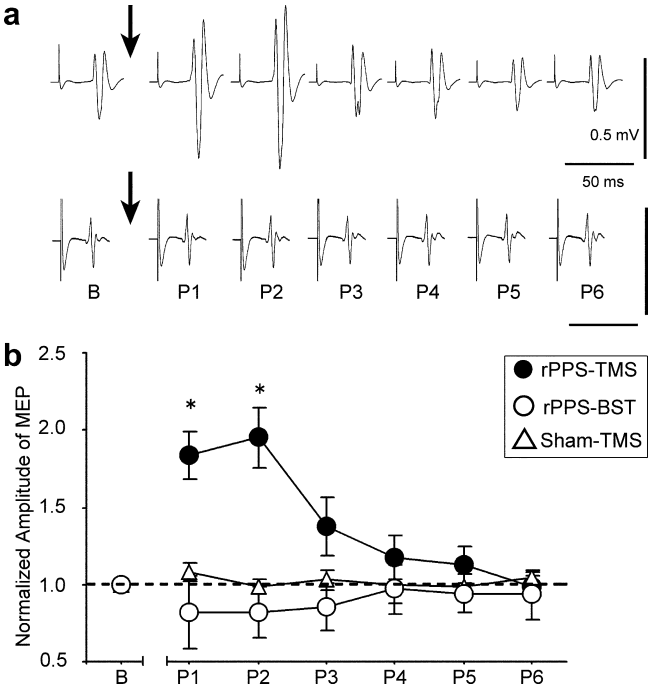

Fig. 3. After-effects of rPPS and sham intervention. (a) Representative example of MEPs before and after rPPS intervention. The arrows show the timing of rPPS intervention. Upper trace shows motor cortical MEPs (elicited by TMS) before and after rPPS intervention. Lower trace shows brainstem MEPs (elicited by BST stimulation). Only MEPs to TMS (motor cortical MEPs) were facilitated after rPPS intervention. (b) Time courses of the MEP amplitude following rPPS or sham intervention. MEPs were normalized to mean MEP amplitude measured at baseline. The facilitation was seen at P1 and P2 period in motor cortical MEPs after the real rPPS. Asterisks, $p < 0.001$.

Fig. 3b shows time courses of the MEP amplitude for three different conditions (rPPS-TMS, rPPS-BST, Sham-TMS). Two way rANOVA revealed a significant effect of the condition ($F[2,16] = 5.610$, $p = 0.014$) and a significant interaction between the condition and time ($F[5.954, 47.630] = 4.765$, $p = 0.001$), but no significant effect of the time ($F[2.977, 47.630] = 1.700$, $p = 0.129$). For rPPS-TMS, subsequent one way factorial ANOVA revealed a significant effect of the time ($F[6,54] = 9.925$, $p < 0.001$). Post hoc analysis revealed that the motor cortical MEPs were significantly larger than the baseline (B) for 10 min after the end of the intervention (at time point P1; $p < 0.001$, P2; $p < 0.001$, P3–P6; $p > 0.05$). For rPPS-BST and Sham-TMS, one way factorial ANOVA did not reveal significant effects of the time ($F[6,24] = 0.586$, $p > 0.05$, and $F[6,18] = 0.394$, $p > 0.05$).

Fig. 4 shows mean ± SD MEP sizes before and 5 min after the intervention. Following rPPS intervention, MEP amplitudes to TMS were enhanced (mean ± SD; baseline:

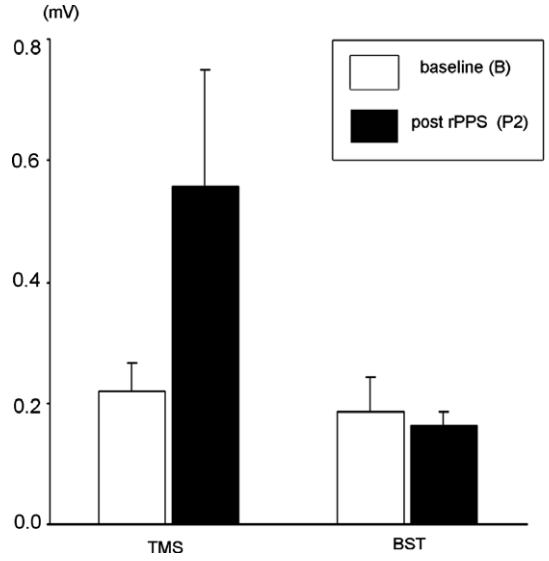

Fig. 4. Bars show mean amplitudes of cortical and brainstem MEPs. The timing of evaluation was 5 min post intervention. All data are means ± SDs. The facilitation was elicited on the motor cortical MEPs whereas brainstem MEPs were unaffected.

0.22 ± 0.05 mV, post 5 min: 0.56 ± 0.19 mV; $p < 0.05$, paired t test), while those to BST stimulation did not change significantly (baseline: 0.19 ± 0.05 mV, post 5 min: 0.16 ± 0.02 mV; $p > 0.05$, paired t test).

4. Discussion

Our main finding of the present study is that motor cortical MEPs were enhanced for 10 min after the cessation of rPPS intervention whereas there were no changes in brainstem MEPs. Whereas the size of responses to TMS reflects the excitability of the motor system as a whole, brainstem MEPs chiefly reflect the excitability of the motor system caudal to the brainstem including the spinal cord. Therefore, the facilitation should occur at the cortical level in agreement with the results of Thickbroom and colleagues (2006). We not only replicated their results but also provided robust support for the cortical site of action, an important information for the newly developed intervention protocol if it is to be used in the future for the treatment of neurological disorders.

Our results are at variance with those by Thickbroom et al. (2006) in that we did not observe marked facilitation of MEPs to paired TMS during rPPS intervention, although considerable facilitatory after-effects of MEPs to single pulse TMS were seen. A possible explanation for this discrepancy is that different populations of descending volleys contribute to MEP generation in single and paired pulse TMS. Thus, even though the same sizes of MEP are induced by the two methods, the volleys elicited by paired stimulation may not be enhanced but those by single pulse TMS are. In any case, single pulse TMS should be used for probing motor cortical excitability correctly.

Although the duration of motor cortical MEP facilitation after rPPS intervention was similar to those of Thickbroom et al. (2006), there was some difference in the magnitude of facilitation between two studies. There are at least two possible reasons for this discrepancy. The first is the interindividual variability. In our results, the standard deviation (variability) of MEP size at 5–10 min post rPPS intervention was 61.8% (mean percentage changes of MEP size = 195.40%), comparable with the variability previously reported by Maeda et al. (mean = 137.87%, SD = 53.59% after 10 Hz rTMS) (Maeda et al., 2000a). In contrast, the previous report by Thickbroom et al. (2006) showed a larger variability (mean = 476%, SD = 381% at 6 min post intervention). These data indicate that our effect was steadier even though the amount of MEP facilitation was smaller. In addition, the difference in studied subjects, perhaps in race, may explain the different magnitude of facilitation after rPPS intervention.

In contrast to its magnitude, the time course of after-effect by rPPS was very similar to what has been described previously (Thickbroom et al., 2006). The present result indicates that the after-effect of rPPS intervention is quite consistent in duration. This message is an important point when using it as a treatment of neurological disorders, because it is the lasting after-effect of rTMS that mainly produces the therapeutic effect.

4.1. Possible mechanisms of facilitation induced by rPPS

The fact that the resting motor threshold (RMT) did not change after rPPS (Thickbroom et al., 2006) suggests that the membrane excitability of pyramidal output cells was not affected by rPPS (Ziemann et al., 1996). As well as membrane excitability, the excitability of a part of synapses between interneurons and cortico-spinal cells has an influence on RMT (Di Lazzaro et al., 2003). Such parts of synapses may also not be affected by rPPS. In spite of no influence on RMT, rPPS intervention made the recruitment curves steeper after intervention (Thickbroom et al., 2006). This suggests an enhancement of efficacy of some synapses which contribute to generation of MEPs to single pulse TMS but do not much contribute to determine the threshold (mainly contribute to small sized MEPs). The previous authors speculated that repeated activation of facilitatory I wave interaction (Tokimura et al., 1996; Hanajima et al., 2002; Ziemann et al., 1998) may reinforce synaptic efficacy and the facilitation induced by rPPS may be a consequence of modulation of the trans-synaptic events. Alternatively, single pulse TMS not only activates neurons oriented in a single direction preferentially but may also activate other neurons oriented in other directions subliminally. These subliminally activated neurons might get more responsive to single pulse TMS after rPPS intervention, leading to the facilitation of MEPs.

Although further studies are needed to clarify the precise mechanism for the facilitatory effect induced by rPPS intervention, rPPS intervention protocol is one of promising

stimulation methods for increasing motor cortical excitability.

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References

Arai N, Okabe S, Furubayashi T, Terao Y, Yuasa K, Ugawa Y. Comparison between short train, monophasic and biphasic repetitive transcranial magnetic stimulation (rTMS) of the human motor cortex. Clin Neurophysiol 2005;116:605–13.

Berardelli A, Inghilleri M, Rothwell JC, Romeo S, Currà A, Gilio F, et al. Facilitation of muscle evoked responses after repetitive cortical stimulation in man. Exp Brain Res 1998;122:79–84.

Berardelli A, Inghilleri M, Gilio F, Romeo S, Pedace F, Currà A, et al. Effects of repetitive cortical stimulation on the silent period evoked by magnetic stimulation. Exp Brain Res 1999;125:82–6.

Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 1997;48:1398–403.

Di Lazzaro V, Oliviero A, Berardelli A, Mazzone P, Insola A, Pilato F, et al. Direct demonstration of the effects of repetitive transcranial magnetic stimulation on the excitability of the human motor cortex. Exp Brain Res 2002;144:549–53.

Di Lazzaro V, Oliviero A, Profice P, Pennisi MA, Pilato F, Zito G, et al. Ketamine increases human motor cortex excitability to transcranial magnetic stimulation. J Physiol 2003;547:485–96.

Hanajima R, Ugawa Y, Terao Y, Enomoto H, Shiio Y, Mochizuki H, et al. Mechanisms of intracortical I-wave facilitation elicited with paired-pulse magnetic stimulation in humans. J Physiol 2002;538:253–61.

Huang Y-Z, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron 2005;45:201–6.

Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A. Interindividual variability of the modulatory effects of repetitive transcranial magnetic stimulation on cortical excitability. Exp Brain Res 2000a;133:425–30.

Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A. Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. Clin Neurophysiol 2000b;111:800–5.

Okabe S, Ugawa Y, Kanazawa I. 0.2-Hz Repetitive transcranial magnetic stimulation has no add-on effects as compared to a realistic sham stimulation in Parkinson's Disease. Movement Disord 2003;18:382–8.

Pascual-Leone A, Valls-Sole J, Wassermann EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain 1994;117:847–58.

Romeo S, Gilio F, Pedace F, Ozkaynak S, Inghilleri M, Manfredi M, et al. Changes in the cortical silent period after repetitive magnetic stimulation of cortical motor areas. Exp Brain Res 2000;135:504–10.

Sakai K, Ugawa Y, Terao Y, Hanajima R, Furubayashi T, Kanazawa I. Preferential activation of different I waves by transcranial magnetic stimulation with a figure-of-eight-shaped coil. Exp Brain Res 1997;113:24–32.

Sommer M, Wu T, Tergau F, Paulus W. Intra- and interindividual variability of motor responses to repetitive transcranial magnetic stimulation. Clin Neurophysiol 2002;113:265–9.

Thickbroom GW, Byrnes ML, Edwards DJ, Mastaglia FL. Repetitive paired-pulse TMS at I-wave periodicity markedly increases corticospinal excitability: a new technique for modulating synaptic plasticity. Clin Neurophysiol 2006;117:61–6.

Tokimura H, Ridding MC, Tokimura Y, Amassian VE, Rothwell JC. Short latency facilitation between pairs of threshold magnetic stimuli applied to human motor cortex. Electroencephalogr Clin Neurophysiol 1996;101:263–72.

Ugawa Y, Rothwell JC, Day BL, Thompson PD, Marsden CD. Percutaneous electrical stimulation of corticospinal pathways at the level of the pyramidal decussation in humans. Ann Neurol 1991;29:418–27.

Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. Electroencephalogr Clin Neurophysiol 1998;108:1–16.

Ziemann U, Lonnecker S, Steinhoff BJ, Paulus W. Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. Ann Neurol 1996;40:367–78.

Ziemann U, Tergau F, Wassermann EM, Wischer S, Hildebrandt J, Paulus W. Demonstration of facilitatory I wave interaction in the human motor cortex by paired transcranial magnetic stimulation. J Physiol 1998;511:181–90.