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Direct demonstration of the effects of repetitive paired-pulse transcranial magnetic stimulation at I-wave periodicity

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Abstract

Objective: To investigate the central nervous system level at which paired-pulse repetitive transcranial magnetic stimulation at I-wave periodicity (iTMS) produces a facilitation of motor evoked potential (MEP) amplitude.
Methods: In one conscious patient who had an electrode implanted in the cervical epidural space for the control of pain, we recorded corticospinal volleys evoked before, during and after iTMS of the motor cortex. Moreover, we compared MEPs to TMS and cervico-medullary junction stimulation before and after iTMS in a separate group of five healthy subjects.
Results: In the patient with the epidural electrode, during iTMS there was progressive increase of MEP amplitude, and by the end of the intervention period MEP increased by more than 300%. The pronounced increase in MEP amplitude was paralleled by a slight increase in the amplitude of epidural volleys. An increased MEP amplitude (more than 200%) was still evident 3 min after the end of iTMS. In the five healthy subjects, iTMS produced a facilitation of MEPs evoked by transcranial magnetic stimulation but had no effect on CMEPs evoked by cervico-medullary junction stimulation.
Conclusions: The results indicate that iTMS leads to an increase in corticomotor excitability at a supraspinal level, and that this may include circuits in addition to those involved in I-wave generation.
Significance: iTMS increases cortical excitability more widely than the I-wave networks that it targets.

Keywords: Transcranial magnetic stimulation; rTMS; Motor cortex

1. Introduction

In recent years, several authors have used repeated pulses of transcranial magnetic stimulation (TMS) to produce effects on the excitability of the corticospinal system that outlast the period of stimulation for several minutes or even hours (Pascual Leone et al., 1994, 1998; Chen et al., 1997; Tergau et al., 1997; Berardelli et al., 1998; Peinemann et al., 2000; Maeda et al., 2000; Huang et al., 2005). Thus 30 min of 1 Hz rTMS decreases the amplitude of the MEP evoked by single pulse stimulation for the next 30 min (Chen et al., 1997), whereas higher frequencies may either increase (Berardelli et al., 1998; Peinemann et al., 2000; Maeda et al., 2000; Huang et al., 2005) or decrease MEPs (Huang et al., 2005).

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In three recent studies we provided evidence for the cortical origin of the effects of rTMS by direct recording of the corticospinal volleys evoked by single pulse TMS in conscious human subjects who had received an implanted epidural stimulator for the control of pain (Di Lazzaro et al., 2002a,b; Di Lazzaro et al., 2005). We found that suprathreshold 5 Hz stimulation of motor cortex is accompanied by a gradual increase in the size and number of descending corticospinal volleys evoked by each TMS pulse that parallels the increase in the MEP (Di Lazzaro et al., 2002a). Subthreshold 5 Hz stimulation (50 total stimuli at AMT) has no effect on MEPs but reduces short interval intracortical inhibition (SICI) as evaluated with EMG measures (Di Lazzaro et al., 2002b). Continuous theta burst rTMS at an intensity of 80% active motor threshold leads to a rapid decrease in the excitability of cortical mechanisms generating the earliest I wave, suggesting that continuous TBS may reduce the responsiveness of pyramidal cells to excitatory stimuli (Di Lazzaro et al., 2005).

Recently, Thickbroom et al. (2006) have described a novel method of increasing excitability in the corticospinal system based on repetitive paired TMS at I-wave periodicity (iTMS). This uses paired TMS stimuli of equal strength with a 1.5 ms interstimulus interval delivered for several minutes at a rate of 0.2 Hz. They showed that paired-pulse MEP amplitude increases steadily during iTMS and that single-pulse MEP amplitude is increased for several minutes after the end of stimulation. Thickbroom and coworkers (2006) suggested that these changes were due to an increase in synaptic efficacy at cortical level.

In the present study we present recordings of corticospinal activity evoked by paired cortical stimulation during iTMS and by single pulse TMS before and after iTMS over motor cortex in one conscious subject who had a cervical spinal electrode implanted chronically for control of pain. To further investigate the level at which iTMS acts, we compared MEPs to TMS and cervico-medullary junction stimulation in a separate group of healthy subjects.

2. Subject and methods

As described in previous publications (Di Lazzaro et al., 1998), we recorded descending corticospinal activity evoked by transcranial magnetic stimulation of the motor cortex directly from the high cervical epidural space of a conscious patient (aged 48 years) with no abnormality of central nervous system who had an electrode inserted for control of intractable dorso-lumbar pain.

The patient gave his written informed consent. The study was performed according to the Declaration of Helsinki and approved by the Ethics Committee of the Medical Faculty of the Catholic University of Rome.

The patient was not taking centrally acting medication at the time of the experiments. Recordings were made simultaneously from the epidural electrode and from the relaxed first dorsal interosseous muscle (FDI) of the left hand. MEPs and the corticospinal volleys were amplified and filtered (bandwidth 3 Hz–3 kHz) by D360 amplifiers (Digitimer, Welwyn Garden City, Herts). Epidural recordings were made between the most proximal and distal of the 4 electrode contacts on the epidural electrode. These had a surface area of 2.54 mm^2 and were 30 mm apart. The distal contact was connected to the reference input of the amplifier. Amplitude of the volleys was measured from onset to peak, where onset was defined either as the immediately preceding trough, or as the initial deflection from baseline. Data were collected on a computer and stored for later analysis using a CED 1401 A-D converter (Cambridge Electronic Design, Cambridge, UK).

Magnetic stimulation was performed with a high power Magstim 200 (Magstim Co., Whitland, Dyfed) connected to a Bistim module. A figure-of-eight coil with external loop diameters of 9 cm was held over the right motor cortex at the optimum scalp position to elicit motor responses in the contralateral FDI. Intensities were expressed as a percentage of the maximum output of the stimulator. Resting motor threshold (RMT) was defined according to the recommendations of the IFCN Committee (Rossini et al., 1994) as the minimum stimulus intensity that produced a liminal MEP (>50 μV in 50% of 10 trials) with the tested muscle at rest.

Two different orientations of the stimulating coil over the motor strip were used, with the induced current flowing either in a latero-medial (LM) or in a posterior–anterior (PA) direction. RMT was determined separately for LM and PA stimulation. LM magnetic stimulation at 110% RMT was used to identify the latency of the earliest (D-wave) descending volley (Di Lazzaro et al., 2004). PA magnetic stimulation was performed at rest at increasing stimulus intensities, starting from a value equal to RMT to a value corresponding to RMT plus 20% of the maximum stimulator output (MSO) in steps of 5% of MSO. Five sweeps were averaged at each intensity of stimulation. The recordings were performed before iTMS and 3 min after the end of iTMS.

For iTMS, stimuli of equal strength were delivered at an ISI of 1.5 ms. Stimulus intensity was set to an intensity that, when delivered as a pair, generated a MEP of an amplitude of approximately 0.5 mV. A period of 13 min of iTMS was performed, during which stimuli were delivered at 0.2 Hz.

Epidural volleys and MEPs evoked by paired-pulse stimulation during iTMS were averaged in blocks of 12 trials.

2.1. Cervico-medullary junction stimulation

In five different subjects [mean age 32.6 ± 9.1 (SD) years], the effects produced by iTMS on MEPs evoked by transcranial magnetic stimulation were compared with those produced by iTMS on MEPs evoked by cervico-medullary junction stimulation (CMEPs). iTMS was applied at 0.2 Hz for 13 min, while MEPs and CMEPs were recorded in the baseline state and 3 min after the end of iTMS.

Stimulus intensity was set to an intensity that generated a MEP of an amplitude of approximately 0.2 mV in relaxed FDI both for cortical and cervico-medullary junction stimulation, the same stimulus intensity was used in baseline conditions and after iTMS. This rather small baseline was chosen since most subjects were uncomfortable if we used cervicomedullary stimulation at higher intensities. The responses to 5 stimuli were averaged at rest after cortical and cervico-medullary junction stimulation in all subjects. Cervicomedullary junction stimulation was performed by passing an electrical pulse (100 μs. D180A stimulator, Digitimer, Welwyn Garden City, UK) between Ag and AgCl surface electrodes fixed over the mastoids (Ugawa et al., 1991). Stimulus intensity varied from 32% to 50% of maximum stimulator output in different subjects. Transcranial magnetic stimulation and cervico-medullary junction stimulation were randomly intermixed both before and after iTMS.

2.2. Statistics

The amplitude of the baseline corticospinal volleys (the sum of individual I-wave amplitude) and that of the baseline MEPs evoked by single pulse magnetic stimulation at increasing stimulus intensities were compared independently with the corresponding responses after iTMS using a two-way ANOVA with INTENSITY (five steps) and TIME (pre and post iTMS) as main factors. Because only one subject was studied, we compared the individual trials before and after iTMS.

In control subjects, the responses evoked by cortical and cervico-medullary junction stimulation in baseline conditions were compared with the corresponding responses evoked after iTMS using Student's paired t tests.

3. Results

3.1. Epidural recordings

LM magnetic stimulation evoked the earliest descending wave, with a latency of 2.1 ms. The short latency of this wave is consistent with direct activation of corticospinal axons. We have therefore termed this volley D wave (Di Lazzaro et al., 2004).

Single pulse PA magnetic stimulation evoked a series of descending waves (Fig. 1), the earliest volley recruited at RMT intensity had a latency which was 1.5 ms longer than the earlier volley recruited by LM magnetic stimulation. Since the earliest volley elicited by LM magnetic stimulation is probably a D-wave, we have termed the later volleys recruited by PA magnetic stimulation as I-waves, numbered in order of their appearance. At the higher stimulation intensity used, a D wave was also recorded after PA magnetic stimulation (Fig. 1).

Fig. 1 shows epidural volleys and MEPs recorded at increasing stimulus intensities before and after iTMS. The two-way ANOVA for MEPs with INTENSITY and TIME

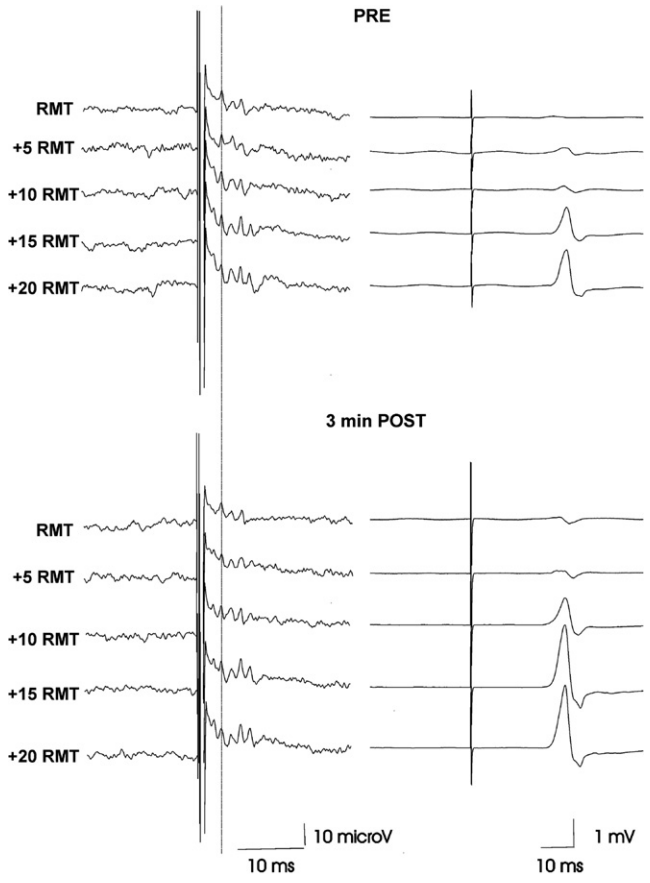

Fig. 1. Epidural volleys (left) and motor evoked potentials (right) evoked by single pulse magnetic stimulation at increasing stimulus intensities in baseline conditions (upper traces) and 3 min after the end of repetitive paired pulse transcranial magnetic stimulation performed for 13 min. Each trace is the average of five trials. The vertical line is aligned to the peak latency of the I1 wave. There is a pronounced increase of the amplitude of MEPs after iTMS that is particularly evident at higher stimulus intensities. There is only a slight increase of epidural volley amplitude after iTMS.

as main factors revealed a significant effect both for INTENSITY ($F_{4,40} = 39.4$, $p < 0.001$) and TIME ($F_{1,40} = 35.4$, $p < 0.001$). There was a pronounced and significant increase of MEP amplitude after iTMS; 3 min after iTMS the amplitude of MEP evoked at RMT plus 20% of MSO was 3.8 mV, a more than 200% increase when compared with the MEP evoked by a stimulus of the same intensity before iTMS. A pronounced increase was also evident with a stimulus intensity of 10% and 15% of MSO above RMT. This marked increase in MEP after iTMS was paralleled by a slight but non-significant change in epidural volley amplitude (Fig. 1). The two-way ANOVA for epidural volleys with INTENSITY and TIME as main factors revealed a significant effect for INTENSITY ($F_{4,40} = 22.9$, $p < 0.001$) but no significant effect for TIME ($F_{1,40} = 2.94$, $p > 0.05$) (Fig. 2).

Fig. 3 shows epidural volleys and MEPs recorded during iTMS. Throughout the period of iTMS, MEP amplitude increased steadily. Seven minutes after the beginning of iTMS the amplitude of MEP was 0.6 mV with a 170%

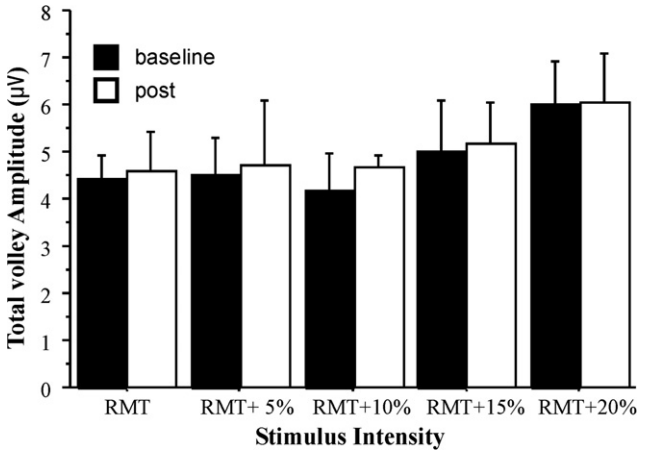

Fig. 2. Mean amplitude of the total volley (the sum of the amplitudes of individual I waves) in baseline conditions and after iTMS evoked at increasing stimulus intensities. Error bars indicate standard deviations. A two-way ANOVA with INTENSITY and TIME as main factors reveals a significant effect for INTENSITY ($F_{4,40} = 22.9$, $p < 0.001$) but no significant effect for time ($F_{1,40} = 2.94$, $p > 0.05$).

increase when compared with the MEP recorded during the first minute of iTMS, and by the end of the intervention period had increased by 360%. The pronounced increase in amplitude of MEPs was paralleled only by a slight increase in the amplitude of epidural volleys (Fig. 3). By the end of the intervention the amplitude of the total volley (the sum of the amplitude of individual I waves) was 14.7 μV with an 8% increase when compared with the amplitude of the total volley recorded during the first minute of iTMS.

3.2. Cervico-medullary junction stimulation

In the five studied subjects, iTMS produced a pronounced facilitation of MEPs evoked by transcranial magnetic stimulation [mean amplitude of the MEPs evoked after iTMS 256 ± 103% (mean ± SD) of the amplitude of the MEPs recorded before iTMS ; $p < 0.05$] but had no effect on CMEPs evoked by cervico-medullary junction stimulation [mean amplitude of the CMEPs evoked after iTMS 82 ± 26.2% (mean ± SD) of the amplitude of the CMEPs recorded before iTMS; $p > 0.05$].

4. Discussion

The present results demonstrate that the pronounced increase of the MEP amplitude induced by repetitive paired TMS at I-wave periodicity is associated with only a slight increase in the excitability of cortical circuits generating the I waves. Thus, there is a discrepancy between change in amplitude of MEPs and the increase in corticospinal activity as evaluated with I wave recordings.

The lack of strict correspondence between the change in MEP size and descending volleys is puzzling. Previous rTMS studies showed that rTMS protocols that led to an

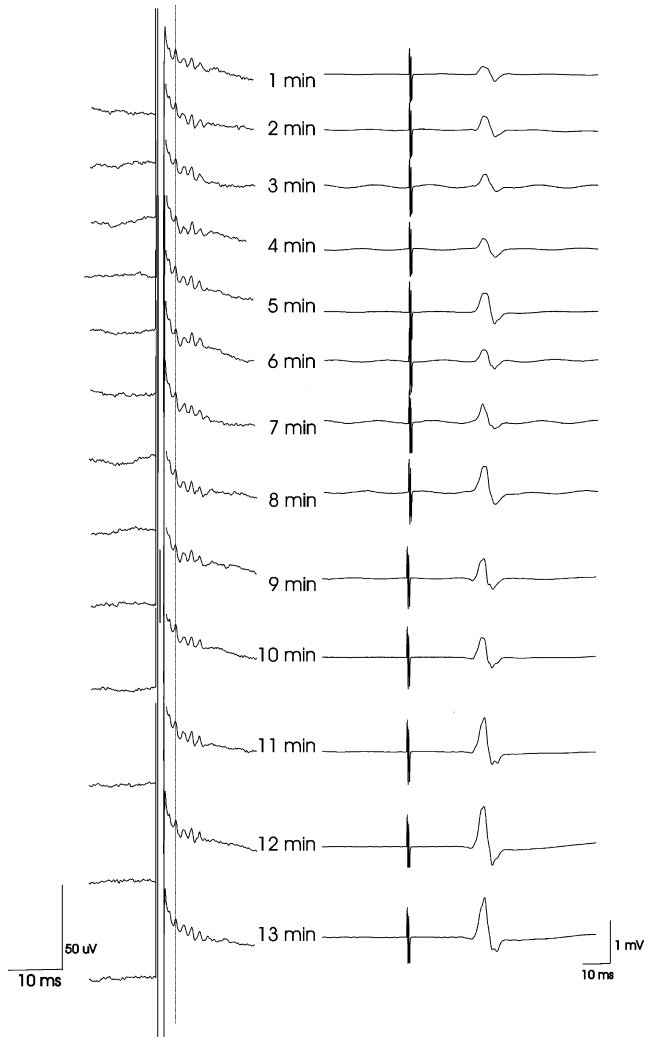

Fig. 3. Epidural volleys (left) and motor evoked potentials (right) evoked by repetitive paired pulse transcranial magnetic stimulation. Each trace is the average of twelve trials. The vertical line is aligned to the peak latency of the earliest of the I1 wave. There is a pronounced increase of the amplitude of MEPs during iTMS that is paralleled only by a slight increase of the amplitude of corticospinal volleys.

increase (Di Lazzaro et al., 2002a) or a suppression of MEPs (Di Lazzaro et al., 2005) also resulted in a comparable change of the descending volleys. Why then are the increased MEPs during iTMS not accompanied by a comparable increase of the descending volleys? There are two possible explanations for this. (1) The iTMS protocol together with producing an increase in cortical excitability could raise the excitability of spinal mechanisms so that motoneurones are more readily discharged by a given descending volley. Thus the increase of MEP would be larger than the increase of the volley. (2) The second possibility is that the descending volleys are not a good reflection of the total corticospinal output produced by TMS. Effectively iTMS could activate excitatory output to FDI over and above that which can be observed in the epidural volleys: the MEP could be larger even though the measurable volley showed only a minor increase.

With regard to the first possibility, the lack of any effect of iTMS on CMEPs evoked by cervicomedullary junction stimulation, recently demonstrated by Hamada et al. (2006) and confirmed by the present study, strongly suggests that there is no change in the excitability of spinal motor neurons and confirms that the change in excitability takes place at supraspinal level. With regard to the second possibility, it is possible that the epidural volleys do not represent all the activity destined for the FDI muscle evoked by TMS. There may be additional activity that is more dispersed that is not evident in the records. If this is increased by iTMS, then the MEP would be larger even though the increase in the I-wave activity is rather limited. There is some evidence to support the idea that dispersed descending activity could contribute to the facilitation of MEPs. We have recently demonstrated that the facilitation of MEPs produced by paired magnetic stimulation at interstimulus intervals of 10–25 ms (intracortical facilitation, ICF) is not associated with an increase in corticospinal output as evaluated through epidural activity recording though it is cortical in origin (Di Lazzaro et al., 2006). Thus, the same phenomenon could be produced by iTMS.

It should be considered that the epidural recording was performed in a patient with chronic pain. Because noxious stimuli affect motor cortex excitability (Valeriani et al., 1999), we cannot exclude the possibility that the presence of pain influenced the response of the motor cortex to iTMS in our patient. However, the patient showed facilitation of the MEPs similar to that described in normal subjects by Thickbroom et al. (2006). Moreover, the aim of this recording was to compare the changes observed in MEP amplitude with those observed in corticospinal activity. Thus, in the presence of a pronounced MEP facilitation the epidural recordings obtained in our patient provided valuable information about the origin of the facilitation independently from any possible pain-related change in cortical excitability.

In conclusion, we found that iTMS leads to an increase in corticomotor excitability at a supraspinal level, and that this may include circuits in addition to those involved in I-wave generation.

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