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Modulation of excitability of human motor cortex (M1) by 1 Hz transcranial magnetic stimulation of the contralateral M1

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Abstract

Objective: Previous studies demonstrated that single-pulse transcranial magnetic stimulation (TMS) of one motor cortex (M1) exerts a brief inhibitory effect on the contralateral M1. The purpose of this study was to test the hypothesis that 30 min of 1 Hz TMS of M1 will result in a lasting increase in excitability in the contralateral M1.

Methods: Healthy volunteers were tested on 2 separate days, before (baseline) and after one of two interventions: (a) stimulation of M1 with 1 Hz TMS for 30 min at 115% of resting motor threshold, and (b) sham stimulation. Recruitment curves to TMS, pinch force, and simple reaction time were assessed in the hand contralateral to the unstimulated motor cortex.

Results: The main finding of this study was that 30 min of 1 Hz significantly increased recruitment curves in the contralateral motor cortex in the real stimulation condition relative to sham ($P < 0.005$, factorial analysis of variance (ANOVA)). This change outlasted the stimulation period for at least 15 min and occurred in the absence of changes in pinch force or reaction time.

Conclusions: These results raise the potential for inducing lasting modulation of excitability in M1 by 1 Hz TMS of the other M1, a phenomenon possibly reflecting modulation of interhemispheric interactions.

Significance: It is conceivable that 1 Hz TMS applied to M1 may be used to modulate excitability in the opposite motor cortex for therapeutic purposes. Published by Elsevier Science Ireland Ltd.

Keywords: Transcranial magnetic stimulation; Physiology; Motor system; Excitability

1. Introduction

Single-pulse transcranial magnetic stimulation (TMS) applied to the primary motor cortex (M1) modulates the amplitude of motor evoked potentials (MEPs) elicited by timed stimulation of the other M1 (Ferbert et al., 1992; Boroojerdi et al., 1996; Gerloff et al., 1998). This phenomenon reflects the predominantly inhibitory interaction between homonymous body part representations in M1 in humans (Ferbert et al., 1992) and may play a role in motor control (Meyer et al., 1998) and motor learning (Andres et al., 1999). Interestingly, TMS of one M1 appears to elicit blood flow changes in the opposite M1 (Fox et al., 1997; Paus et al., 1998; Siebner et al., 2000).

Behavioral and functional studies lend credence to the idea that the corpus callosum plays a major role in interhemispheric inhibition (Ferbert et al., 1992; Gerloff et al., 1998). In children, immature callosal connections correlate with the absence of interhemispheric inhibition and the presence of mirror movements (Heinen et al., 1998). In patients with dysfunction of the corpus callosum due to multiple sclerosis (Boorojerdi et al., 1998), cerebrovascular insult (Boroojerdi et al., 1996), or corpus callosum atrophy (Meyer et al., 1995), interhemispheric inhibition is delayed or absent. Lesions affecting the anterior portions of the corpus callosum preclude interhemispheric inhibition while lesions located elsewhere along the corpus callosum or subcortically leave inhibition intact (Meyer et al., 1995; Boroojerdi et al., 1996). In monkeys, this anterior portion of the corpus callosum interconnects the motor cortices (Pandya and Seltzer, 1986).

Previous studies demonstrated that low frequency TMS for 15–30 min over M1 decreases the excitability of the stimulated motor cortex (Chen et al., 1997; Muellbacher et al., 2000). In this study, we sought to determine whether downregulation of excitability in one M1 by low frequency TMS could elicit an increased excitability in the contralateral, unstimulated M1. A previous study demonstrated that a relatively short period of TMS at an intensity of approxi-

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mately 105% resting motor threshold (rMT) failed to elicit this effect (Wassermann et al., 1998). Based on this experience, we modified stimulation parameters, prolonging the duration of stimulation and increasing the stimulus intensity. We found that 1 Hz stimulation of M1 led to a lasting enhancement in excitability in the contralateral unstimulated M1.

2. Methods

Ten healthy volunteers (7 men, 3 women), all right-handed and with a mean age of 68 years (range, 55–81 years), gave their written informed consent to participate in the study, approved by the NINDS Institutional Review Board.

2.1. Experimental procedure

Subjects sat in an upright chair and had both hands resting on a pillow. Measures of corticomotor excitability (recruitment curves), simple reaction time, and pinch force were obtained from the hand ipsilateral to the stimulated M1 before and after low frequency TMS or sham stimulation. The two different stimulation modalities were applied randomly at the same time of the day on 2 different days. The order (sham/real TMS) and the stimulated hemispheres (right or left) were counterbalanced. TMS stimulation was delivered using a water-cooled figure-of-8 TMS coil (70 mm diameter per wing) connected to a Cadwell rapid-rate magnetic stimulator (Cadwell Laboratories Inc., Kennewick, WA) with maximal output of 2.0 T. The magnetic coil was immobilized by a coil holder at the optimal position for stimulation of first dorsal interosseus (FDI). In the real stimulation condition, real TMS at 115% rMT intensity for FDI was delivered at 1 Hz for 30 min. In the sham stimulation condition, the coil was tilted 45° off the surface of the head with the edge of the plastic block encasement touching the scalp. The sound of stimulation and the weight of the coil were comparable in both conditions.

Silver–silver chloride surface EMG electrodes were taped in a tendon-belly arrangement overlying the FDI muscles of both hands. Electromyographic (EMG) activity was amplified using an EMG device (Counterpoint Electromyograph, Dantec Electronics, Skovlunde, Denmark) with bandpass filtering between 10 and 3000 Hz. The signal was digitized at a frequency of 4 kHz and fed off-line to a data acquisition system built with the Labview graphical programming language (Kaelin-Lang and Cohen, 2000). Using its 'conditional trigger' feature, TMS stimuli were delivered only when the FDI was relaxed (EMG activity < 50 μV peak-to-peak amplitude for at least 1 s preceding the TMS stimulus). EMG activity from FDI was monitored on a separate oscilloscope set at high gain (100 μV per division) to ensure EMG silence during the experiment.

For the ascertainment of recruitment curves and motor thresholds, the magnetic coil was placed tangentially to the scalp with the intersection of the two coils pointing backward and laterally 45° from the midline. Stimuli were delivered at 0.1 Hz, a rate that per se does not affect cortical excitability (Chen et al., 1997), to the unstimulated M1 position optimal for activation of FDI, and the position was marked. rMT was defined as the minimal stimulation intensity producing at least 5 MEPs >50 μV from 10 consecutive TMS stimuli (Rossini et al., 1994). Mean MEP amplitudes obtained in response to 10 TMS stimuli were obtained at 4 TMS stimulus intensities: 90, 110, 130, and 150% of rMT. Two subjects could not be stimulated at 150% due to high initial motor thresholds. Pinch force was measured according to a previously described protocol that exhibits good validity and test–retest reliability (Mathiowetz et al., 1984). Subjects performed 6 pinch trials lasting 3 s with 15 s of rest between. The pinch waveforms were fed off-line for storage and analysis. Simple reaction time was determined according to a previously described protocol (Pascual-Leone et al., 1992). The ipsilateral arm was positioned, on either the armrest or the pillow, based on the subject's comfort preference. Subjects were instructed to respond to an auditory tone by moving the index finger in a brief downwards tap. Tones were delivered by an auditory stimulator (Grass stimulator S10CTCMA, Grass Instrument Division, Astro-Med Inc., West Warwick, RI), which was activated by a program written on SuperLab software. 'Go' tones and EMG responses from the counterpoint were fed off-line for storage and analysis. Behavioral and electrophysiological measurements were obtained in that order within a 15 min time window following stimulation.

2.2. Statistical Analysis

All post-stimulation measurements were normalized to pre-stimulation values for each individual. Recruitment curves were analyzed using factorial ANOVA with factors stimulation (real TMS and sham) and intensity (90, 110, 130 and 150% rMT). Pinch strength and reaction times were analyzed using paired t tests. Significance was established at $P < 0.05$. All results are given as mean ± standard error of the mean.

3. Results

Baseline rMT were comparable in the two sessions for the stimulated (52.8 ± 1.9%) and unstimulated M1 (55.7 ± 2.3%). Recruitment curves after TMS of the contralateral M1 were larger than after sham stimulation (ANOVA, factor stimulation, $F = 8.24$, $P < 0.005$; Fig. 1) in the absence of significant differences for the factor intensity. After TMS of the contralateral M1, mean MEP amplitudes increased to 112.9 ± 15.5% (90%MT, $n = 10$), 178.7 ± 58.5% (110%MT, $n = 10$), 175.8 ± 40.1% (130%MT, $n = 10$), and 167.6 ± 30.7% (150%MT, $n = 9$) relative to baseline. After sham stimulation, mean MEP amplitudes were 89.8 ± 13.3% (90% rMT, $n = 10$),

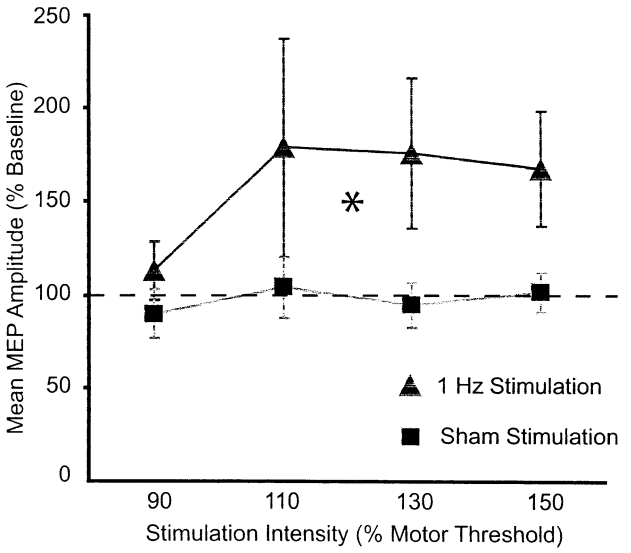

Fig. 1. Changes in recruitment curves elicited by stimulation (90, 110, 130, and 150% of rMT) of M1 after 30 min of 1 Hz or sham stimulation of the contralateral M1. MEP amplitude changes are expressed relative to baseline (pre-stimulation and pre-sham) values. Note that 1 Hz TMS stimulation led to a larger increase in recruitment curves than sham ($*P < 0.005$).

103.9 ± 16.1% (110% rMT, $n = 10$), 94.7 ± 12.1% (130% rMT, $n = 10$), and 101.4 ± 10.7 (150% rMT, $n = 8$) relative to baseline. Neither pinch force nor simple reaction times changed in either of the two conditions (see Table 1).

4. Discussion

Interhemispheric interactions may contribute to motor learning (Andres et al., 1999) and to defining the temporal and spatial features of voluntary movements (Meyer et al., 1998). Lesions of the corpus callosum, a structure that links homonymous areas of both cerebral hemispheres, result in impaired coordination and learning (Meyer et al., 1998) and deficits in interhemispheric inhibition (Meyer et al., 1998; Boroojerdi et al., 1996; Boroojerdi et al., 1998). Interhemispheric inhibition is also affected after unilateral hemispheric lesions. Each human motor cortex exerts inhibitory influences on the opposite motor cortex (Ferbert et al., 1992; Gerloff et al., 1998) that under normal conditions are held in balance. Disruption of this balance by occlusion of the middle cerebral artery, for example, leads to increased excitability of the opposite motor cortex in rats (Reinecke et al., 1999). In humans, ischemic stroke is associated with increased excitability of the opposite, intact motor cortex (Liepert et al., 2000). These findings are consistent with the concept that the lesioned hemisphere exerts a diminished inhibitory influence over the intact one (Boroojerdi et al., 1996), leading to a relative release of excitability in the intact hemisphere. It would be of interest to develop non-invasive strategies to modulate this balance. A previous failed attempt used TMS at an intensity of approximately 105% rMT for 15 min (Wassermann et al., 1998). Taking this experience into account, we prolonged the stimulation duration to 30 min and increased the stimulus intensity to 115% rMT. Under these experimental conditions, we found that 30 min of 1 Hz TMS, but not sham stimulation, of the motor cortex led to enlarged recruitment curves obtained from the opposite motor cortex. Recruitment curves represent a reliable and sensitive measure of corticomotor excitability influenced by changes in the γ-aminobutyric acid (GABA)ergic system and by sodium and calcium channel properties (Boroojerdi et al., 2001). Changes in recruitment curves outlasted the stimulation period for at least 15 min. While the precise mechanisms underlying these changes are unknown, including influences on spinal cord function, the duration is most consistent with the temporal characteristics of post-tetanic potentiation (PTP), a brief synaptic enhancement mechanism that persists for seconds to minutes (Zucker and Regehr, 2002). PTP occurs secondary to increases in pre-synaptic intracellular calcium and sodium resulting from prolonged stimulation, and from delays in the reuptake and extrusion of intracellular calcium following stimulation (Zucker and Regehr, 2002).

Table 1
Pinch force and simple reaction times normalized to pre-intervention values

	Pinch force		Reaction time	
Subject	After real	After sham	After real	After sham
1	96.35	92.68	112.15	84.85
2	97.45	106.27	111.86	119.77
3	103.42	108.05	134.58	92.62
4	112.75	120.43	96.93	86.71
5	93.61	105.02	86.99	127.07
6	101.84	98.96	99.94	98.58
7	80.70	86.73	98.66	77.42
8	89.41	97.57	95.74	105.06
9	104.99	113.81	74.30	107.65
10	94.42	108.33	98.74	91.90
Average	97.49	103.79	100.99	99.16
SEM	2.82	3.16	5.09	4.99

Finally, the excitability changes elicited by 1 Hz TMS were not accompanied by behavioral modifications as measured by pinch force or simple reaction time. It remains to be determined if there are no behavioral gains after this intervention or if our measures were not sensitive enough to detect them. Overall, our findings indicate that 1 Hz TMS of the motor cortex can elicit a lasting increase in excitability in the contralateral M1. It is conceivable that TMS stimulation, using a protocol previously reported to downregulate excitability in one M1, may be used to restore excitability in the opposite M1 in settings where cortical excitability is diminished.

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