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Suppression of Corticospinal Excitability During Negative Motor Imagery

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Sohn, Young H., Nguyet Dang, and Mark Hallett. Suppression of corticospinal excitability during negative motor imagery. *J Neurophysiol* 90: 2303–2309, 2003; 10.1152/jn.00206.2003. To investigate the effect of negative motor imagery on corticospinal excitability, we performed transcranial magnetic stimulation (TMS) studies in seven healthy subjects during imagination of suppressing movements. Subjects were asked to imagine suppression of TMS-induced twitching movement of their nondominant left hands by attempting to increase the amount of relaxation after receiving an auditory NoGo cue (negative motor imagery), but to imagine squeezing hands after a Go cue (positive motor imagery). Single- and paired-pulse TMS were triggered at 2 s after Go or NoGo cues. Motor-evoked potentials (MEPs) were recorded in the first dorsal interosseus (FDI), abductor pollicis brevis (APB), and abductor digiti minimi (ADM) muscles of the left hand. Paired-pulse TMS with subthreshold conditioning stimuli at interstimulus intervals of 2 (short intracortical inhibition) and 15 ms (intracortical facilitation) and that with suprathreshold conditioning stimuli at interstimulus interval of 80 ms (long intracortical inhibition) were performed in both negative motor imagery and control conditions. Compared with the control state (no imagination), MEP amplitudes of FDI (but not APB and ADM) were significantly suppressed in negative motor imagery, but those from all three muscles were unchanged during positive motor imagery. F-wave responses (amplitudes and persistence) were unchanged during both negative and positive motor imagery. During negative motor imagery, resting motor threshold was significantly increased, but short and long intracortical inhibition and intracortical facilitation were unchanged. The present results demonstrate that excitatory corticospinal drive is suppressed during imagination of suppressing movements.

INTRODUCTION

Motor imagery corresponds to a subliminal activation of the motor system, with a similar mechanism underlying movement preparation and execution (Decety 1996; Jeannerod and Frak 1999). Imagination of movement activates descending motor pathways (Gandevia and Rothwell 1987), modulates downstream autonomic (Decety et al. 1993) and spinal-reflex pathways (Oishi et al. 1994), and alters the transmission signals in cortical afferent pathways (Cheron and Borenstein 1992). Mental training with movement imagination enhances motor performance similar to actual physical training (Yue and Cole 1992), suggesting a possible role in rehabilitative strategies.

Transcranial magnetic stimulation (TMS) is a noninvasive test to assess human corticospinal excitability. Motor-evoked potentials (MEPs) following TMS were enhanced in the mus-

cles during imagination of their movements (Fadiga et al. 1999; Hashimoto and Rothwell 1999; Kasai et al. 1997; Rossini et al. 1999; Schnitzler et al. 1997; Yahagi et al. 1996). In contrast to imagination of movement (positive motor imagery), whether imagination of suppressing movement (negative motor imagery) alters corticospinal excitability has yet to be investigated. MEPs were suppressed and cortical inhibitory mechanisms were altered during volitional inhibition with NoGo tasks (Hoshiyama et al. 1996, 1997; Leocani et al. 2000; Sohn et al. 2003). However, the mechanism underlying negative motor imagery must be different from that of externally triggered volitional inhibition with a NoGo task. The latter is likely an active inhibitory process that suppresses a ready-to-go condition, while the former may represent substantial reduction in corticospinal excitatory drive, i.e., subliminal suppression or deactivation of motor system. Suprathreshold stimulation usually elicits muscle twitching of the contralateral hand. In this study, we evaluated the influence of imagination of suppressing this TMS-induced hand twitching (presumed to be negative motor imagery) on corticospinal excitability as well as various cortical inhibitory and facilitatory mechanisms.

METHODS

Subjects

We studied seven healthy, right-handed volunteers (6 men and 1 woman; mean age, 40 yr; range, 27–49 yr). All subjects gave their written informed consent. The experiment was approved by the institutional review board of the National Institute of Neurological Disorders and Stroke.

EMG recordings

MEPs of the first dorsal interosseus (FDI), abductor pollicis brevis (APB), and abductor digiti minimi (ADM) muscles of the nondominant left hand were recorded using silver-silver chloride surface EMG electrodes placed over these muscles in a belly-tendon montage. The EMG was amplified using a conventional EMG machine (Counterpoint, Dantec Electronics, Skovlunde, Denmark) with band-pass between 10 and 2,000 Hz. The signal was digitized at a frequency of 5 kHz and fed into a laboratory computer for further off-line analysis.

Magnetic stimulation

TMS was delivered through a 7-cm figure-of-eight coil connected to two Magstim 200 magnetic stimulators via a BiStim module

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(Magstim, Whitland, Dyfed, UK) and placed flat on the scalp over the right motor cortex. The intersection of the coil was placed tangentially to the scalp with the handle pointing backward and laterally at a 45° angle away from the midline. In this way, the current induced in the neural tissue was directed approximately perpendicular to the line of the central sulcus and therefore optimal for activating the corticospinal pathways transsynaptically (Brasil-Neto et al. 1992; Kaneko et al. 1996). With a slightly suprathreshold stimulus intensity, the stimulating coil was moved over the right hemisphere to determine the optimal position for eliciting MEPs of maximal amplitudes in FDI. The optimal position of the coil was then marked on the scalp with a pen to ensure coil placement throughout the experiment. TMS triggering and data acquisition were controlled using a LabVIEW program (National Instrument, Austin, TX) (Kaelin-Lang and Cohen 2000).

Single-pulse TMS

Resting motor threshold was determined to the nearest 1% of the maximum stimulator output, and it was defined as the minimal stimulus intensity required to produce MEPs of $>50 \mu\text{V}$ in ≥ 5 of 10 consecutive trials. Similarly, we defined motor threshold of 1 mV ($MT_{1\text{mV}}$) to the nearest 1% of the maximum stimulator output, and this was defined as the minimal stimulation intensity required to produce MEPs of $>1 \text{ mV}$ in ≥ 5 of 10 consecutive trials. Resting motor threshold and $MT_{1\text{mV}}$ were measured during rest. Peak-to-peak MEP amplitudes were measured in FDI, APB, and ADM at stimulation intensities of 140% resting motor threshold. TMS stimuli were delivered randomly between 5 and 7 s apart; 20 stimulations were given in each session (2 negative motor imagery, 1 positive motor imagery, and 2 control sessions). MEPs obtained during negative or positive motor imagery were compared with the average MEPs of control TMS and expressed as the percent change.

The silent period was measured in 12 trials at a stimulation intensity of $MT_{1\text{mV}}$ in moderately active FDIs. TMS was set to elicit stimuli only when the EMG activity of FDI was maintained within 10–20% of maximal voluntary contraction at least for 1 s (Kaelin-Lang and Cohen 2000). Silent period duration was defined as the interval between the magnetic stimulus and the first reoccurrence of rectified voluntary EMG activity, which was automatically calculated by a computerized program as previously described (Sohn et al. 2001).

Paired-pulse TMS

Using paired-pulse techniques, intracortical influences initiated by the conditioning stimulus modulate the responses produced by the test stimulus. With a subthreshold conditioning stimulus applied at very short interstimulus intervals of 1–5 ms, there is inhibition (short intracortical inhibition), while there is facilitation at intervals between 8 and 30 ms (intracortical facilitation) (Kujirai et al. 1993). Another form of inhibition is observed when a suprathreshold conditioning stimulus is applied 50–200 ms prior to test stimulus (long intracortical inhibition) (Valls-Sole et al. 1992). Absence of inhibition with direct activation of the corticospinal axons with transcranial electrical stimulation and reduced corticospinal waves suggest that both long and short intracortical inhibition occur in the cortex (Kujirai et al. 1993; Nakamura et al. 1997). Long and short intracortical inhibition seems to have different mechanisms, mediated by different types of neurons. Pharmacologically, short intracortical inhibition is primarily mediated by GABA_A receptors (Ziemann et al. 1996a), while long intracortical inhibition is subserved by GABA_B receptors (Werhahn et al. 1999), and intracortical facilitation is glutamatergic (Liepert et al. 1997). In addition, stronger test pulses reveal more short intracortical inhibition but less long intracortical inhibition (Sanger et al. 2001). Therefore separate populations of neuronal circuits appear to mediate these inhibitory phenomena (Sanger et al. 2001; Ziemann et al. 1996c).

Short intracortical inhibition and intracortical facilitation were ob-

tained in the resting FDI, using a subthreshold conditioning stimulus (70% resting motor threshold) followed by a suprathreshold test stimulus ($MT_{1\text{mV}}$). Single test pulses and paired stimuli with interstimulus intervals of 2 and 15 ms were randomly delivered 5 s apart. Twenty trials were recorded for single test and paired pulses at each interstimulus interval. For each interstimulus interval, the amplitude ratio of mean conditioned MEP to mean control MEP was calculated. Short intracortical inhibition and intracortical facilitation were defined as the MEP ratios obtained at interstimulus intervals of 2 and 15 ms. To adjust conditioning and test stimuli to achieve similar MEP amplitudes in both control and negative motor imagery conditions, we labeled the strength of TMS pulses as previously described (Sanger et al. 2001), so that resting motor threshold and $MT_{1\text{mV}}$ were also determined separately with the subjects during negative motor imagery.

Long intracortical inhibition was obtained in the resting FDI using a suprathreshold conditioning stimulus ($MT_{1\text{mV}}$) followed by a suprathreshold test stimulus ($MT_{1\text{mV}}$) at an interstimulus interval of 80 ms. $MT_{1\text{mV}}$ measured during negative motor imagery was used as conditioning and test stimuli during negative motor imagery. Long intracortical inhibition was defined as the average amplitude ratio of conditioned MEP following test stimulation to MEP following conditioning stimulation. Eighteen trials were recorded in the negative motor imagery and control conditions.

Spinal and peripheral excitability

Supramaximal electrical stimulation (0.2 ms square-wave constant current pulses) of the ulnar nerve at the wrist was used to assess spinal and peripheral motor excitability. While FDI was relaxed, the peak-to-peak amplitude and persistence of F-waves (average, 20 trials) and compound muscle action potential (maximum, 6 trials) were determined. Mean F-wave amplitude was expressed as the percent of maximum compound muscle action potential amplitude.

Experimental design

Volunteers sat comfortably with the left arm supported and were asked to remain relaxed throughout the experiment. Using a Click-Tone-Control module and Grass AM8 Audio Monitor (Grass Instrument, Quincy, MA), an auditory warning signal (1,000 Hz and 200 ms) was presented 1 s prior to the auditory Go (2,000 Hz and 200 ms) or NoGo signal (500 Hz and 200 ms). The loudness of these sounds was adjusted to be clearly differentiated but not produce any startle response. The Go and NoGo signals were presented in an equal proportion and randomly intermixed. TMS was applied 2 s after Go or NoGo signal. By LabVIEW, the timing and order of auditory signals and TMS were controlled, and the auditory signals and the following TMS were set to be elicited only when EMG activity of tested muscles was $<50 \mu\text{V}$ at least for 1 s.

For single-pulse TMS experiments, one control session (20 MEPs at 140% resting motor threshold) at rest without imagination was performed before motor imagery sessions. To become familiar with the experiment, volunteers practiced 20 trials of negative motor imagination without recording. Then, one block of 20 trials at 140% resting motor threshold was repeated with EMG recordings. In these trials, volunteers were asked to imagine only suppression of TMS-induced twitching of their left hand by trying to do more relaxation after both Go and NoGo signals. In the next block of 40 trials, volunteers were asked to imagine suppression of TMS-induced twitching only after NoGo signals and to imagine squeezing their left hands after a Go signal. One control session was repeated at the end of the experiments. For paired-pulse TMS experiments, conditioning stimulus was triggered 2 s after Go or NoGo signals. In this experiment, volunteers were asked only to imagine suppression after both Go and NoGo signals. Short and long intracortical inhibitions and intracortical facilitation were measured both at rest (control session) and during negative motor imagery. F-waves and compound muscle action po-

tentials were also measured both at rest (control session) and during negative motor imagery. EMGs from recording muscles were monitored throughout the experiment to ensure that there was no actual muscular contraction during the imagination.

After the experiment, volunteers estimated their performance of motor imagination by answering the following questions. 1) How easy was it to imagine suppression (and enhancing) of TMS-evoked movement (0 very easy, 10 very hard)? 2) What percent of trials do you think that you could imagine suppression of movement successfully (0–100%)?

Statistical analysis

Data are expressed as means \pm SE. MEP amplitudes and F-wave responses (amplitude and persistence) were compared among resting, negative, and positive motor imagery using an ANOVA test. An ANOVA with Bonferroni *t* procedure was employed to compare the two groups. Motor thresholds, conditioned MEPs, short and long intracortical inhibition, and intracortical facilitation were compared between negative motor imagery and resting conditions using the paired *t*-test. The correlation between MEP change and subjects' estimated performance of motor imagery was tested by nonparametric Spearman correlation analysis. $P < 0.05$ was considered significant.

RESULTS

The mean score rating the ease of imagination was 2.1, and the mean percent rating of successfulness of imagination was 85.7%. On-site monitoring and off-line analysis of EMG activity showed that all tested muscles were silent during motor imagery. These findings suggest that motor imagery was well performed without evoking muscle activation. None of the subjects expected that they could modulate MEPs by this type of imagination.

The TMS site was targeted to produce optimal MEPs for FDI. Accordingly, evoked resting MEP amplitudes were higher in FDI (4.97 ± 1.65 mV) than in ADM (3.18 ± 0.93 mV) and APB (2.65 ± 0.95 mV). There could be two strategies suppressing this TMS-evoked movement; stiffening of muscles to resist twitching and more relaxation to suppress activation. If they used the former strategy during their negative motor imagery task, it might have had a similar effect to positive motor imagery. We checked preliminarily the effect of imagination of stiffening in six subjects, which failed to show any

suppression in MEP amplitudes ($-2.2 \pm 9.9\%$ in FDI, $10.6 \pm 30.2\%$ in APB, and $5.8 \pm 10.3\%$ in ADM). Thus we asked them to use the latter strategy to suppress evoked movements.

Among the negative and positive motor imageries and the control condition, MEP amplitudes were significantly different in FDI ($F = 15.409$, $P = 0.0001$) and APB ($F = 4.799$, $P = 0.0214$), but not in ADM ($F = 2.774$, $P = 0.0891$). The Bonferroni *t* method revealed that, during negative motor imagery using the strategy of more relaxation, MEP amplitudes were significantly suppressed in FDI ($-26.7 \pm 5.9\%$, $P = 0.0014$) and tended to be suppressed in APB ($-20.7 \pm 8.7\%$, $P = 0.0578$), but not in ADM ($3.2 \pm 14.5\%$). In contrast, MEP amplitudes tended to increase in all tested muscles during positive motor imagery, but none attained statistical significance (Fig. 1). F-wave amplitudes and persistence and compound muscle action potential of both FDI and ADM were unchanged during both negative and positive motor imagery compared with the resting state (Fig. 2). F-wave amplitudes seemed to be different among resting, negative motor imagery, and positive imagery conditions, but the *P* values were far from the significance (>0.4). The subjects' estimated performance of motor imagination, both ease and success, was not correlated to the degree of MEP suppression.

Resting motor threshold was significantly increased during negative motor imagery (from $46.0 \pm 4.1\%$ to $48.7 \pm 4.8\%$, $P = 0.010$). Accordingly, MT_{1mV} was significantly higher in negative motor imagery ($57.0 \pm 5.2\%$) than that during the control session ($53.7 \pm 4.9\%$, $P = 0.022$). MEP amplitudes of FDI evoked by MT_{1mV} were comparable between the two conditions (1.23 ± 0.15 mV in control and 1.15 ± 0.15 mV in negative motor imagery; Fig. 3A), suggesting that test stimulation intensity was well adjusted between negative motor imagery and control conditions. The intensity of conditioning stimulation using 70% resting motor threshold was presumably well adjusted between the two conditions. Conditioned MEP amplitudes at interstimulus intervals of 2 and 15 ms were comparable between the negative motor imagery (0.57 ± 0.13 and 1.26 ± 0.24 mV, respectively) and control conditions (0.65 ± 0.10 and 1.41 ± 0.25 mV, respectively; Fig. 3A). Accordingly, short intracortical inhibition and intracortical facilitation were unchanged during negative motor imagery.

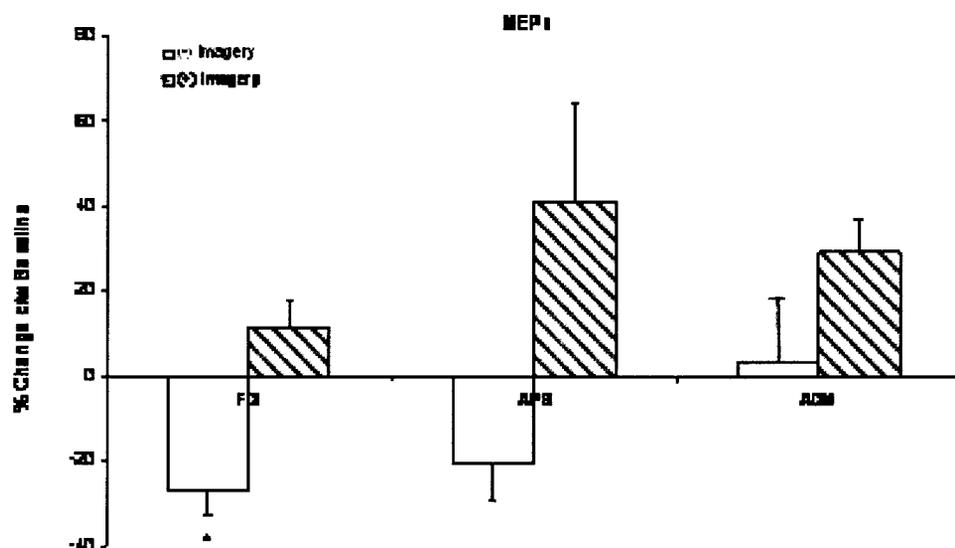


FIG. 1. Motor-evoked potential (MEP) amplitude change (%) in negative and positive motor imagery compared with control condition. Stimulation intensity was 140% resting motor threshold. Asterisks represent significant difference from control. During negative motor imagery, MEP amplitudes were significantly reduced in the 1st dorsal interosseus (FDI) and tended to be suppressed in abductor pollicis brevis (APB) muscles, while those were enhanced, although statistically insignificant, in all tested muscles during positive motor imagery.

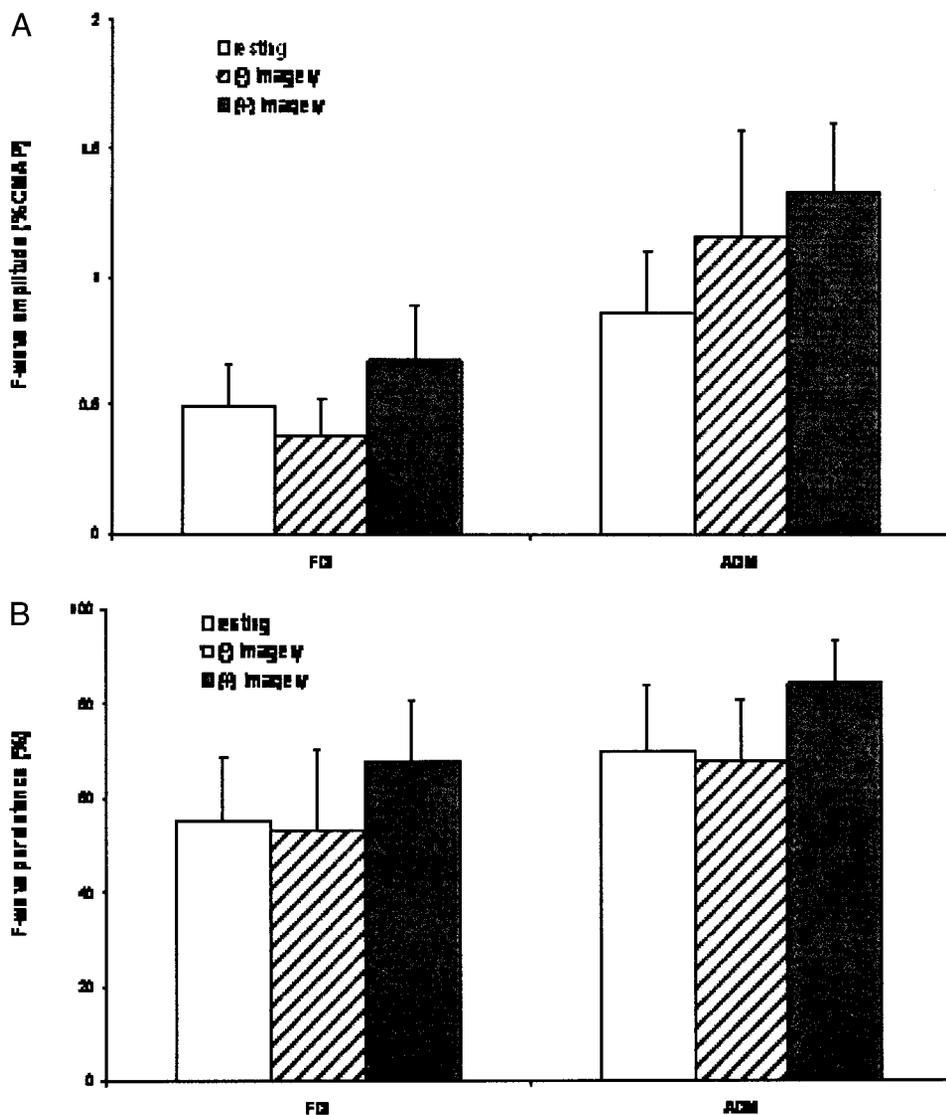


FIG. 2. F-wave amplitude (A) and persistence (B) during negative and positive motor imagery compared with resting state. Supramaximal electrical stimulation was applied to the ulnar nerve at the wrist ($n = 18$ in each subject). In both the FDI and abductor digiti minimi (ADM), there is no significant change in F-wave amplitude and persistence during negative and positive motor imagery compared with resting state.

The average duration of the silent period was 163 ± 14.3 ms (range, 112–234 ms). Thus the interstimulus interval of 80 ms was apparently within the range of the silent period in all subjects. Almost complete suppression of test MEPs (long intracortical inhibition $<10\%$) was observed in all but one subject when conditioning stimuli of MT_{1mV} were applied 80 ms earlier. During negative motor imagery, no significant change was observed in both test (control, 1.00 ± 0.16 mV; negative motor imagery, 1.12 ± 0.19 mV) and conditioned MEPs (control, 0.13 ± 0.09 mV; negative motor imagery, 0.16 ± 0.08 mV; Fig. 3B). Long intracortical inhibition was also comparable between the negative motor imagery ($17.8 \pm 9.8\%$) and control conditions ($14.4 \pm 7.6\%$).

DISCUSSION

Comments about the experiment paradigm are useful before discussing the results in detail. In this study, we attempted to test the influence of imagination of suppressing ongoing or forthcoming movement. However, in contrast to the imagination of movement, it is quite difficult to perform negative motor imagery without actual movement. Therefore instead of

voluntary movement, we asked volunteers to imagine suppression of hand twitching movements induced by TMS, although this situation may not fully mimic natural negative motor imagery. All subjects had previous experiences with TMS so they understood this. Subjects were instructed to relax, but we could not exclude the possibility of the involuntary stiffening of more proximal muscle; however, the chance of this possibility seems very low because it is apparently not easy to relax the distal part with concomitant stiffening of adjacent area. An inherent difficulty of such an imagery experiment is the lack of a behavioral index with which to assess imagination performance. We collected introspective information by inviting the subjects to answer specific questions after each experiment. Overall, the favorable responses to these questions suggest that subjects satisfactorily generated motor imagery of both movement and suppression. In addition, the opposite responses between negative and positive imagery also support the reliability of their imagination. We arbitrarily decided the interval between Go/NoGo cue and TMS as 2 s. It is possible that longer interval would produce more relaxation. However, since we tested both negative and positive motor imagery, a longer interval might cause loss of atten-

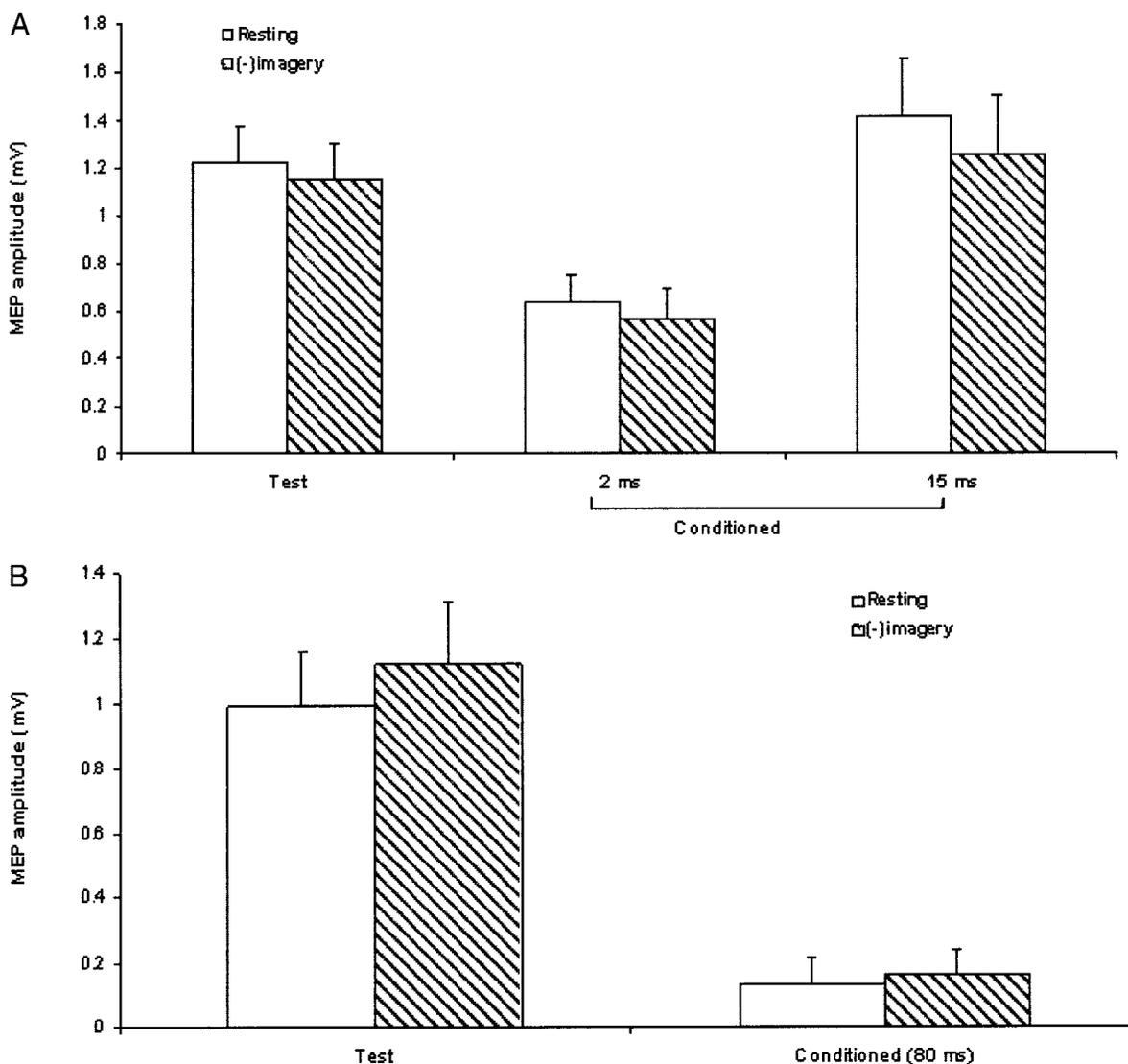


FIG. 3. Average MEP amplitudes (mV) of the FDI produced by conditioning and test stimuli in negative motor imagery and control conditions. *A*: short intracortical inhibition and intracortical facilitation used subthreshold conditioning stimulus (70% resting motor threshold) and suprathreshold test stimulation (MT_{1mV}) at 2- and 15-ms interstimulus intervals. Test and conditioned MEP amplitudes at both interstimulus intervals were comparable between the two conditions. *B*: long intracortical inhibition employed suprathreshold conditioning and test stimulation (MT_{1mV}) at interstimulus interval of 80 ms. Both test and conditioned MEP amplitudes were comparable for negative motor imagery and control conditions.

tion to the task performed, which is crucial for successful imagination.

The present results, MEP amplitude reduction in FDI, clearly demonstrate suppression of motor excitability during negative motor imagery. In addition, MEP amplitude tended to be suppressed in APB, although it did not attain statistical significance. No change in F-wave responses (amplitudes and persistence) suggests that this mental suppression affected mainly the supraspinal level. The reason why ADM was not suppressed during negative motor imagery was unclear. Possibilities included more attention (imagination) to the thumb and index finger than the little finger, nonoptimal site stimulation of ADM, or simply MEP variation in different muscles. During imagination of squeezing the hand, MEP amplitudes were enhanced in all tested muscles, but none attained statistical significance. In this study, since the right hemisphere has a dominant role in response inhibition (Garavan et al. 1999),

we tested the nondominant left hand that might result in less facilitation during positive motor imagery compared with the dominant hand (Yahagi and Kasai 1999). In addition, imagination of squeezing the hand, which we thought to be the opposite paradigm to the negative motor imagery used in this study, might be insufficient to detect MEP facilitation in each muscle because the facilitatory effect of positive motor imagery is specifically confined to the prime mover (Rossini et al. 1999).

We then evaluated various cortical inhibitory and facilitatory mechanisms in FDI to investigate possible mechanisms mediating negative motor imagery-related motor suppression using paired-pulse techniques. Before carrying out the paired-pulse experiments, we measured resting motor threshold and MT_{1mV} in both negative motor imagery and control conditions in FDI to adjust stimulation intensities of conditioning and test stimulation to produce MEPs of similar amplitudes between the

two conditions. Accordingly, both resting motor threshold and MT_{1mV} were significantly higher in negative motor imagery than in the control condition, which provides additional evidence for suppression of motor excitability during negative motor imagery. Comparable test MEP size between the two conditions confirmed that stimulation intensities were well adjusted. No significant difference was observed in conditioned MEP amplitude, short and long intracortical inhibition, and intracortical facilitation between the two conditions. This finding suggests that negative motor imagery does not influence either cortical inhibitory or facilitatory mechanisms and hence is less likely mediated by them. However, since we only used two interstimulus intervals in paired-pulse techniques, there could be changes in excitability at interstimulus intervals other than those we tested in this study. In the Go/NoGo reaction time task, increased inhibition in short intracortical inhibition and disinhibition of long intracortical inhibition with preserved resting motor threshold were observed during NoGo (Sohn et al. 2003). Thus the results of this study suggest that the mechanism underlying negative motor imagery differs from that of NoGo reaction task where more active motor inhibition occurs in response to external cues.

Resting motor threshold reflects the excitability of a central core of neurons, depending on the excitability of individual neurons and their local density. Since resting motor threshold can be influenced by drugs that affect voltage-gated sodium and calcium channels (Chen et al. 1997; Ziemann et al. 1996b), it presumably represents membrane excitability. The change in resting motor threshold with preserved intracortical inhibitory and facilitatory mechanisms suggests that negative motor imagery is more likely related to membrane excitability rather than GABAergic or glutamatergic intracortical interactions, although how to suppress membrane excitability is unknown. Positive motor imagery shares a similar mechanism underlying movement preparation and execution (Decety 1996), but it does not excite descending motor neurons. Thus in motor imagery, it is likely that the excitatory motor output generated for executing the action is counterbalanced by another inhibitory output that keeps the activation level of descending motor neuron below threshold but presumably higher than the resting state. Subthreshold electrical stimulation that predominantly stimulates pyramidal neurons directly often produces MEPs during positive motor imagery (Gandevia and Rothwell 1987), supporting subthreshold activation of motor neurons. In contrast, during negative motor imagery, either an increased inhibitory output or reduced motor neuronal activation level may result in suppression of corticospinal excitability. Like positive motor imagery that enhances motor performance as actual physical training (Yue and Cole 1992), the mental training of negative motor imagery might be useful to control pathologic conditions with enhanced motor excitability and concomitant involuntary movements.

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