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Delayed facilitation of motor cortical excitability following repetitive finger movements

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Abstract

Objectives: To define motor cortical excitability changes occurring at various times after non-fatiguing bimanual exercise of the index fingers.

Methods: Twenty healthy right-handed subjects were studied with transcranial magnetic stimulation (TMS) of the right non-dominant hemisphere. They performed regular (3–4/s) repetitive opening–closing bilateral movements of the index finger onto the thumb. Motor evoked potentials (MEPs) of the left first dorsal interosseus (FDI) and rate of the repetitive finger movements were determined (1) before exercise, (2) immediately following 3 exercise periods of 30, 60 and 90 s, and (3) over a subsequent 30 min rest period.

Results: Rate of movement did not show significant change during any of the exercise periods but did increase significantly when tested after 15 min of rest. MEPs immediately after 30 and 60 s of exercise were facilitated whereas MEPs after 90 s of exercise did not differ from baseline measures. MEP amplitudes were significantly increased after rest of approximately 15 min compared to the baseline MEPs. In contrast, motor potentials evoked by peripheral nerve stimulation were unchanged throughout the experimental test periods.

Conclusions: Motor cortical excitability relating to an intrinsic finger muscle (FDI) was facilitated beginning 15 min after a brief period of non-forceful, repetitive activity of that muscle. This delayed facilitation of motor cortex after exercise may represent a form of short-term potentiation of motor cortical excitability.

Keywords: Transcranial magnetic stimulation; Bimanual motor task; Short-term potentiation; Cortical excitability; Central fatigue

1. Introduction

Transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (TES) of the motor cortex that elicit motor evoked potentials (MEPs) in somatic muscles have been used to explore the dynamics of central motor involvement before, during, and following motor activity. Motor cortex excitability is affected immediately before movement onset (Starr et al., 1988; Reynolds and Ashby, 1999), continues during the course of movement (Ljubisavljevic et al., 1996; Sacco et al., 1997; Aranyi et al., 1998; Tinazzi and Zanette, 1998), and may even persist following movement (Brasil-Neto et al., 1993, 1994; McKay et al., 1995; Zanette et al., 1995; Bonato et al., 1996; Liepert et al., 1996; Samii et al., 1996, 1997). If movements are continued until 'exhaustion' (defined by an inability to maintain at least 50% of maximal force), MEPs are reduced for up to 15 min, a phenomenon termed post-exercise depression (Brasil-Neto et al., 1993, 1994; McKay et al., 1995; Liepert et al., 1996; Samii et al., 1996, 1997). The duration of post-exercise depression is extended in patients with central nervous system lesions (Liepert et al., 1996). If the exercise is non-exhausting, an early transient facilitation of MEPs can occur for up to 4 min after completing the exercise (Brasil-Neto et al., 1993, 1994; Samii et al., 1996, 1997). The neural mechanisms underlying both facilitation and depression of MEPs following exercise are believed to reside within the motor cortex. These changes of motor cortical excitability have been considered relevant for the experience of 'fatigue' or well-being accompanying motor activity (Brasil-Neto et al., 1993, 1994; McKay et al., 1995; Liepert et al., 1996; Samii et al., 1996).

In the present study, we examined central motor processes accompanying bimanual repetitive finger exercise in a virtually forceless motor task that was maintained well before performance was affected. We were interested in the dynamics of motor cortical excitability after completing the

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exercise. Subjects made regular bilateral movements of the index fingers at about 3–4 Hz, a rate that could be sustained without decrement for many minutes. We showed (1) a transient facilitation of excitability immediately following some of the exercises, (2) an absence of post-exercise depression following all of the exercises, and (3) an unexpected delayed enhancement of MEPs beginning between 15 and 30 min after ending the exercises.

2. Subjects and methods

Twenty right-handed healthy subjects (11 women and 9 men, ranging in age between 18 and 62 years, mean 32 years) were studied. The experimental procedures and stimulation methods were explained to each subject. All subjects signed informed consent forms following university guidelines for approved projects involving human subjects.

Subjects were tested in a supine position on a padded examination table. The subject's head rested on a contouring pillow with eyes open. We tested the excitability of the non-dominant right motor cortex while recording from the first dorsal interosseus (FDI) of the left hand. Surface electrodes were placed over the belly of the left FDI muscles referenced to another electrode on the metacarpo-phalangeal joint of the index finger. Acoustic feedback of the muscle potentials was provided to the subject from a loudspeaker to encourage relaxation of the muscles when not exercising and to provide a monitor of FDI muscle contractions during exercise.

2.1. Transcranial magnetic stimulation

TMS was performed using a round (90 mm) coil placed over the hand motor area of the right hemisphere overlying the central sulcus until the optimal stimulation site (hot spot) was localized for eliciting threshold motor responses in the contralateral hand muscle during relaxation (Caramia et al., 1998). The cortical motor threshold of the FDI muscle was defined using a display gain of 100 μV/division and delivering stimuli in steps progressively increasing by 5% of stimulator output until MEPs of about 100 μV were evoked in 100% of trials. Stimulator output was then decreased in steps of 2% until MEPs of about 100 μV were evoked in 50% of the trials (Rossini et al., 1994). Once the optimal coil location was determined, the position of the external perimeter of the coil on the scalp was marked to allow for repositioning. TMS testing of the effects of motor tasks was performed during a brief tonic contraction of the FDI muscle contralateral to stimulated hemisphere. This evaluation was performed with cortical stimuli delivered at 105% of motor threshold for each individual subject. Motor evoked potentials (MEPs) from left FDI were amplified and stored for subsequent measurement.

2.2. Motor task

The subjects performed bimanual repetitive opening–closing movements of the index finger towards the thumb with both digits extended at a regular rate of about 3–4 Hz. Positron emission tomography (PET) studies indicate that significant changes in brain metabolism are already achieved by performing finger tapping at 1.5 Hz (Chollet et al., 1991); therefore, we assumed that 3–4 Hz would represent a good compromise between the elicitation of significant cortical excitability changes and the possibility of sustaining consistency in the motor performance. The movement primarily engages the first dorsal interossei (FDI) muscles (Tomberg and Caramia, 1991). The subjects were trained to make the movements so that the distal portion of the palmar surface of the thumb made contact with the palmar side of the middle interphalangeal joint of the index finger. Subjects were able to master the movements within a few repetitions. The spread of movement to other fingers was minimized by taping the middle, ring, and little fingers of the left hand together.

2.3. Experimental procedure

TMS was delivered while the subject performed a brief sustained voluntary opposition of the left index finger onto the thumb to activate the FDI. The subjects were instructed to make this contraction with 20% of maximal force (since it has been demonstrated that from 10 to 50% of maximal contraction post-exercise facilitation does not change, Samii et al., 1996) and to imagine the flexion of the index finger before initiating the movement. The level of the ongoing EMG activity during contraction was then monitored both by acoustic feedback and by asking the subjects to try and keep within a band displayed visually on a video screen. Subjects were warned before making the contraction by the phrase 'ready, steady, go' and then maintained the contraction for a few seconds while a TMS pulse was delivered.

The protocol consisted of a baseline period, followed by 3 consecutive exercise periods of 30, 60 and then 90 s followed by a rest period of 30 min (Fig. 1). TMS was tested every 3 s for a total of 4 trials during the baseline period, immediately after each of the exercise periods, and again during the rest period. In the rest period, TMS was tested after 15 min in all 20 subjects (at 15, 20 and 30 min in 12 of the 20 subjects, and at 7.5, 12, 15, 20 and 30 min in 3 subjects).

After the 90 s exercise period, subjects were instructed to listen to the acoustic EMG, monitored with a 100 μV/division gain, and keep their hands completely relaxed. Coil position was held in a fixed position to this point. After rest, the coil was repositioned according to the scalp markings and TMS was applied at the threshold level determined in the baseline period to insure correct placement of the coil.

At the end of the final 90 s exercise period, subjects were

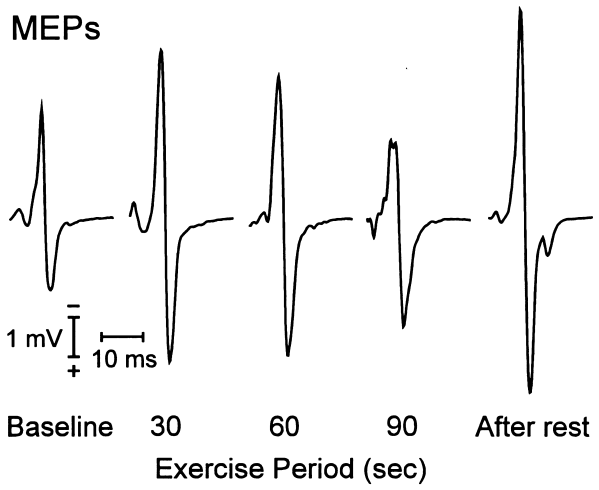

Fig. 1. Motor evoked potentials (MEPs) to transcranial magnetic stimulation (TMS) collected at each of the intervals from a single subject during the experimental protocol. Segments (32 ms) from the total sweep containing the MEP complex are shown.

asked if they were 'fatigued' and if so to describe the experience of fatigue. Subjects who described 'fatigue' used expressions such as 'burning', 'aching', and 'tiredness'.

2.4. Finger movement

Finger movement was measured using 3 separate methods. (1) The rate of contraction during each of the exercise periods (30, 60 and 90 s) was defined in 10 of the subjects during the TMS experiments by monitoring the acoustic output of the EMG during exercise and tallying the total number of contractions. (2) A separate study was performed to quantify the rate of contraction without TMS starting with a baseline exercise period (10 s), followed by exercise periods of 30, 60 and 90 s, and a final exercise period (10 s) after 15 min of rest. Seven subjects were tested on separate occasions. (3) Finger movements were recorded during 10 min of continuous exercise in 3 subjects. The rate of movement was computed from the total number of contractions (EMG) over 10 s epochs.

2.5. Peripheral nerve stimulation

Muscle potentials were elicited by electrical supramaximal stimulation (square pulses, 100 μs duration) of the ulnar nerve at the wrist in 5 subjects. Muscle recordings were obtained using surface electrodes placed over the belly of the left FDI muscles and referenced to an electrode on the metacarpo-phalangeal joint of the index finger. The signal was amplified (bandpass 20 Hz–5 kHz) and stored for subsequent analysis. The subjects performed the same motor task as in the TMS experiment. Stimuli were applied when the subject was relaxed during the baseline period, after each exercise period (30, 60 and 90 s) and after a 15 min rest period using the same intensity and stimulus position.

2.6. Data measurement

MEP amplitude was defined as the peak-to-peak excursion of the largest negative and positive deflection occurring after the stimulus onset (Rossini et al., 1994). We defined the amplitude of the MEP as the average of the two largest MEPs in each sequence of 4 stimuli. We found that the average of the largest two was statistically equivalent to the average of all 4. MEP amplitudes were expressed as a percentage of the baseline MEP amplitude set as 100%.

In the peripheral nerve stimulation studies, the peak-to-peak amplitudes of the compound motor potential were measured.

2.7. Statistical methods

MEP amplitudes were evaluated as a function of time (baseline, immediately after exercise periods of 30, 60 and 90 s, and following rest) for all subjects, and separately as a function of gender, and subject age ($<$30, 31–39 and $>$40 years). An analysis of the subjective description of experiencing or not experiencing fatigue following the exercise was also performed. The Wilcoxon signed-rank test was used for comparison of paired data; significance was reported for $P < 0.01$ to hold experiment wise error at $P < 0.05$.

Measures of rate (finger movement) and amplitude (motor potentials) across exercise periods were separately tested for significance using analysis of variance procedures (ANOVA) for repeated measures. Post-hoc tests among the means were conducted using Fisher's test and paired t tests. Regression procedures were used to evaluate the relationship between the rate of FDI contraction and exercise time.

3. Results

3.1. Rate of movement

3.1.1. With TMS

Movement rates determined from the total counts (monitored by acoustic output) in each exercise period (30, 60 and 90 s) were not significantly different (4.0/s, 3.9/s and 3.8/s, respectively).

3.1.2. Without TMS

The rate of movement was measured (Fig. 2) without TMS for (1) a baseline exercise period (10 s), (2) for 3 exercise periods (30, 60 and 90 s), and (3) for a post-rest (15 min) exercise period (10 s). Rate of contraction showed a significant increase after 15 min of rest (4.5/s) (t test, $P < 0.05$) compared to both baseline (3.8/s) and at the end of the 60 (3.8/s) and 90 s (3.7/s) periods of exercise.

3.1.3. 10 min repetitive exercise

The mean movement rate of the index finger decreased as a function of time over a 10 min period of repetitive exercise

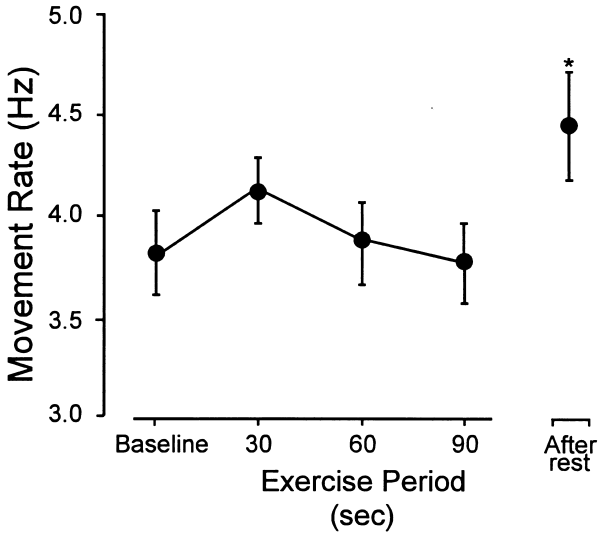

Fig. 2. Movement rate at baseline, during the 3 exercise periods, and after 15 min of rest for 7 subjects. There was a significant increase in movement rate ($P < 0.05$) after rest (4.5/s, indicated by *) compared to baseline (3.8/s) and at 60 (3.8/s) and 90 s (3.7/s) periods of exercise. Standard errors (± 1) are indicated.

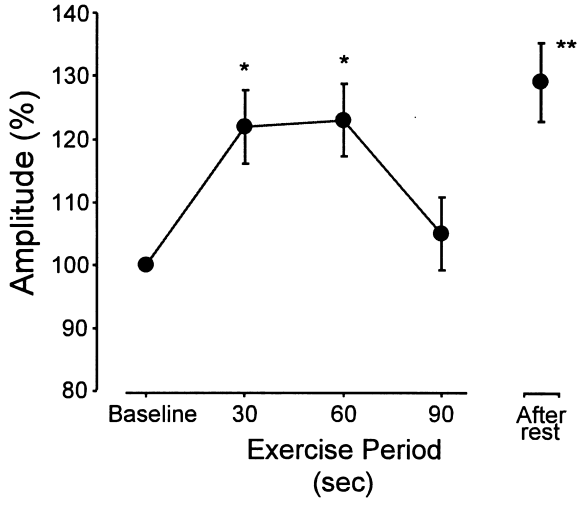

Fig. 4. MEP amplitudes (expressed as a % of baseline MEP) are shown for all subjects at baseline, immediately after each of the 3 exercise periods, and after 15 min of rest. There was a significant ($P < 0.01$) post-exercise facilitation (compared to baseline, indicated by *) immediately after the 30 and 60 s exercise periods but no significant change after 90 s of exercise. There was a significant ($P < 0.01$) delayed facilitation after rest (indicated by **) compared to baseline and immediately after the 90 s exercise period. Standard errors (± 1) are indicated.

(Fig. 3). The slope of the function was negative and significant ($P < 0.001$, $r = -0.95$). The change of rate during the first 90 s of exercise was not significant (3.97/s at 30 s versus 3.77/s at 90 s), but by 240 s the rate was slowed from the rate at 30 s (3.60/s; t test, $P < 0.01$).

We conclude that the exercise period of 90 s used in this study was not accompanied by a significant slowing of the rate of movement. We found there was a speeding of rate of movement after 15 min of rest compared to baseline and exercise periods.

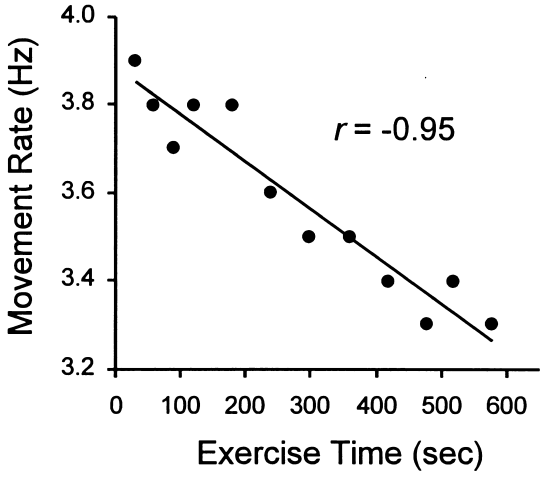

Fig. 3. Relationship between movement rate of the index finger onto the thumb during 10 min of repetitive exercise. The results are based on the means from 3 subjects. The correlation between movement rate and duration of exercise was significant for a negative trend ($P < 0.001$, $r = -0.95$).

3.2. Transcranial magnetic stimulation

MEP amplitudes were modified both during and after the exercise periods (Figs. 1 and 4, Table 1). MEPs were significantly increased (a post-exercise facilitation) immediately following the 30 and 60 s of exercise ($P < 0.01$) but not after 90 s of exercise. Following a rest of 15 min, MEP amplitudes increased significantly (averaging 129% of baseline) when compared to MEPs evoked both at baseline and immediately following the 90 s exercise ($P < 0.01$).

When we recognized after testing several subjects that MEPs had a delayed facilitation after 15 min of rest, we modified the protocol in subsequent subjects to test MEPs at other times during the rest period. In 12 subjects, we tested MEPs after 15, 20 and 30 min of rest. On average, the facilitation of MEP defined at 15 min (120%) was reduced at both 20 (110%) and 30 min (108%). However, there were individual differences as to the time of maximal MEP facilitation: 5 subjects had maximal MEPs at 15 min; 4 subjects were maximal at 20 min; and 3 subjects were maximal at 30 min. We also tested 3 individuals at regular intervals throughout the rest period. The delayed facilitation (120%) of MEPs present at 15 min was not present at either the 12 (95%) or 7.5 min (94%) test times.

There were no significant differences in the time-course of MEP amplitude changes as a function of gender or subject age (<30, 31–39 and >40 years). However, significant differences in MEP amplitudes immediately after exercise were found as a function of the subjective experience of 'fatigue' following the exercise. There were 10 subjects who reported in the affirmative when asked if they felt 'fati-

Table 1
Time-course of MEP amplitude (% of baseline)

Time-course	All subjects ($n = 20$)	'Fatigue group' ($n = 10$)	'Non-fatigue group' ($n = 10$)
Baseline	100.0	100.0	100.0
After exercise (30 s)	122.3*[a]	110.1	134.5**
After exercise (60 s)	123.8**	116.8**	130.7*
After exercise (90 s)	105.2	88.9***	121.3*,***
After rest	128.9**	125.0*	132.8*

[a] $*P < 0.05$, compared to baseline; $**P < 0.01$, compared to baseline; $***P < 0.01$, fatigue versus non-fatigue group.

gue' (6 females and 4 males) and 10 subjects who answered in the negative (3 females and 7 males). The experience of fatigue was reported with equal probability in either hand. MEP amplitudes immediately after the 90 s of exercise were significantly reduced ($P < 0.01$) in the 'fatigued' group compared to the 'non-fatigued' group (89% versus 121%; Fig. 5, Table 1). However, both of these MEP values were not different from MEP baseline amplitudes. The measure of movement rate was available for 4 fatigued and 5 non-fatigued subjects; no significant differences in movement rate were found between the fatigued and non-fatigued groups.

3.3. Peripheral nerve stimulation

Differences in motor potential amplitudes were not significant over the different exercise periods and the rest period indicating that peripheral nerve conduction and neuromuscular conduction were not affected (baseline, 25.1 mV; 30 s, 26.1 mV; 60 s, 25.9 mV; 90 s, 26.0 mV; and after rest, 25.6 mV).

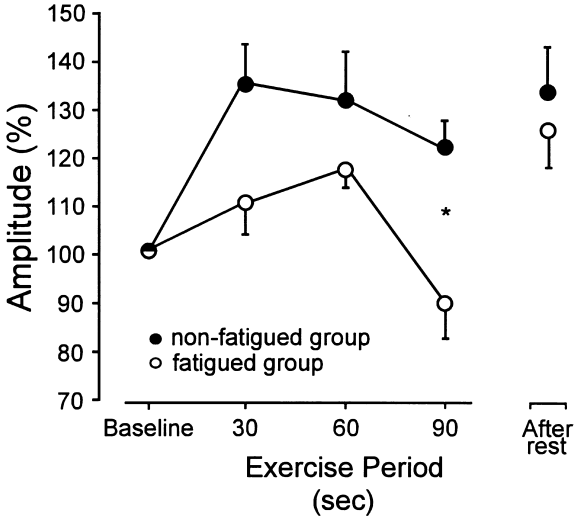

Fig. 5. MEP amplitudes divided between subjects who experienced a sense of 'fatigue' or 'no fatigue' following the 90 s exercise period. MEPs were smaller for the fatigued group than the non-fatigued group but only the differences (indicated by *) after the 90 s exercise period reached a significant level ($P < 0.01$). Standard errors (± 1) are indicated.

4. Discussion

The results of this study show that motor cortical excitability was facilitated between 15 and 30 min after completion of a 90 s period of non-exhausting repetitive finger movements. We also identified that the rate of finger movement becomes speeded after 15 min of rest. These results are distinguished from previous studies of recovery of motor cortical excitability following exhausting repetitive movements involving fingers (Liepert et al., 1996), sustained contraction of wrist (Samii et al., 1997), or sustained contractions of proximal upper limb muscles (Sacco et al., 1997). These latter studies showed a post-exercise depression of motor cortical excitability that persisted for as long as 15 min without identification of a subsequent facilitation of motor cortex. Motor performance was likewise depressed during this recovery period. The exercises in all of these studies induced muscular fatigue and exhaustion. In contrast, the exercises used in the present study were virtually forceless and relatively brief in duration, and did not adversely affect performance. Such differences may explain the absence of post-exercise depression of MEPs in our present study. However, other investigators who have examined motor cortical excitability following 'non-fatiguing' exercise (Brasil-Neto et al., 1993, 1994; Samii et al., 1996, 1997) have identified a transient period of facilitation immediately after completing the exercise. This facilitation ended after 4 min of rest, well short of the 15 min defined in the present study for the appearance of delayed facilitation of MEPs.

The exercise we studied in the present paper involved precise and repetitive movement of the index finger without a need to exert force. The index finger was extended and repetitively tapped the same area of the thumb without a significant decline of rate for the 90 s of exercise. Moreover, the movements involved distal hand muscles which are used for precise activities whereas proximal muscles, studied in many of the former studies, are used for large movements such as maintaining posture (Rossi et al., 1999). Yahagi and Kasai (1998) have shown that MEP amplitudes of distal muscles can show significant increases even during imagination without actually making any movements.

Our results defined a post-exercise facilitation immediately after the 30 and 60 s of repetitive movements but no

post-exercise facilitation or depression after the 90 s of exercise. When we divided the subjects by their report of 'fatigued' or 'not fatigued' following the 90 s period of exercise, the fatigued group showed smaller MEP amplitudes than the non-fatigued group (89 versus 121%, $P < 0.01$). We suspect that exercise periods longer than 90 s might be accompanied by a significant post-exercise depression. The 90 s period of exercise we used either did not produce facilitation or depression of motor cortical excitability, or produced a balance of both types of excitability change.

The changes in motor cortical excitability described in this study are central in origin as FDI potentials evoked by electrical stimulation of the ulnar nerve were not modified during the exercise and rest periods. In other experiments on the effects of exercise on motor cortical excitability, the role of spinal or peripheral nerve changes have been excluded (Brasil-Neto et al., 1993; McKay et al., 1995; Zanette et al., 1995).

The increased MEP amplitude at 15 min might be interpreted as an effect of the wearing-off of fatigue, however, previous studies already defined that MEP recovery time is 8.5 ± 2.22 min after the last exercise set (Samii et al., 1996). We measured MEPs at 12 min after rest and did not find significant differences in amplitude with respect to the baseline values. The delayed facilitation of FDI motor cortex defined in the present study appears only after a 15 min period of rest, therefore making it unlikely to be related to the post-exercise facilitation occurring immediately after exercise. The delayed facilitation we observed may be functional evidence of intracortical synaptic reorganization consequent on the performance of repetitive motor tasks (Buonomano and Merzenich, 1998). Repeated activation of excitatory synapses in the central nervous system induces both short-term (STP) and long-term potentiation (LTP) (Keller et al., 1990; Asanuma and Pavlides, 1997; Benke et al., 1998) and both of these processes have been suggested as participating in motor learning. Both types of synaptic potentiation affect NMDA (*N*-methyl-D-aspartate) glutamate receptors leading to the formation of new synapses or the unmasking of other excitatory aminoacid receptors on motor neurons (Ghirardi et al., 1995).

We are intrigued by the similarities between the appearance of delayed facilitation of motor cortex excitability following brief and non-fatiguing exercise demonstrated in the present study and the timing of warm-up exercises used by musical performers and athletes to enhance subsequent performance. Warm-up exercises are typically not strenuous and are separated from the performance by several minutes, factors that may prepare the motor cortex for subsequent optimal excitability.

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