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ORIGINAL ARTICLE

Boosting and consolidating the proprioceptive cortical aftereffect by combining tendon vibration and repetitive TMS over primary motor cortex

Luisa Perasso[1] · Laura Avanzino[1] · Giovanna Lagravinese[1] · Alessandro Giannini[1] · Emanuela Luisa Faelli[1] · Ambra Bisio[1] · Angelo Quartarone[2,3] · Vincenzo Rizzo[4] · Piero Ruggeri[1] · Marco Bove[1]

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Abstract

Tendon vibration of a limb elicits illusory movements in the direction that the vibrated muscle would be stretched, followed by a transient perception of movement in the opposite direction, that was demonstrated to correspond to a "cortical" aftereffect (Goodwin et al. Science 175:1382–1384, 1972). Primary motor cortex (M1) excitability of the non-vibrated antagonist muscle of the vibrated muscle increased during vibration and decreased thereafter. The cortical aftereffect is of interest when considering the possibility to use tendon vibration in rehabilitation for restoring unbalance activity between antagonistic muscles but, due to its short-lasting duration, has not been explored so far. We investigated the possibility to consolidate the cortical aftereffect by combining tendon vibration with a concomitant high-frequency 5-Hz repetitive transcranial magnetic stimulation (rTMS) protocol. The distal tendon of the flexor carpi radialis muscle (FCR) was vibrated and concomitantly a 2-min 5-Hz rTMS protocol was administered on the left hemi-scalp hot spot of the vibrated FCR or its antagonist muscle (extensor carpi radialis (ECR)). We found that this protocol induced a pattern of unbalanced M1 excitability between vibrated muscle and its antagonist with increased excitability of the FCR and decreased excitability of ECR cortical areas, which persisted up to 30 min.

Keywords Vibration · Repetitive transcranial magnetic stimulation · Cortical excitability · Aftereffect

Introduction

Tendon vibration can elicit illusory movements of the limb in the direction that the vibrated muscle would be stretched, followed by a transient perception of movement in the opposite direction after vibration (aftereffect) [1–5]. Kito and colleagues [6] conducted a psychophysical and a transcranial magnetic stimulation (TMS) study of this aftereffect. They confirmed the existence of the proprioceptive movement aftereffect, depending on the duration of the preceding vibration. Further, they showed that this proprioceptive movement aftereffect was accompanied by a proprioceptive cortical aftereffect. Indeed, stimulation of the motor cortex (M1) showed that responses in the antagonist muscle to the vibrated muscle increased during vibration and decreased thereafter. This change in M1 excitability, recorded after the removal of vibration, and referred here as proprioceptive cortical aftereffect, correlated with the illusory proprioceptive movement aftereffect.

The authors proposed that proprioceptive aftereffect was probably elicited by the cortical processing of the peripheral change of unbalanced proprioceptive information from the two antagonistic muscles caused by the reduction of spindle discharge in the vibrated muscle after the vibration. Indeed, evidence of short-lasting reduction of spontaneous spindle activity after the vibration has been shown [7, 8]. The proprioceptive cortical aftereffect is an interesting phenomenon when considering the possibility to use tendon vibration in a

✉ Luisa Perasso
luisa.perasso@unige.it

[1] Department of Experimental Medicine, Section of Human Physiology and Centro Polifunzionale di Scienze Motorie, University of Genoa, Viale Benedetto XV 3, 16132 Genoa, Italy

[2] Department of Biomedical, Dental Sciences and Morphological and Functional Images, University of Messina, Messina, Italy

[3] IRCCS Centro Neurolesi "Bonino Pulejo", S.S. 113, Via Palermo, C.da Casazza, 98124 Messina, Italy

[4] Department of Clinical and Experimental Medicine, University of Messina Messina, Messina, Italy

rehabilitative setting with the aim of restoring unbalance activity between antagonistic muscles as it happens for spasticity. However, all these recent observations showed that this aftereffect is short-lasting, and thus, it is difficult to translate this phenomenon in a clinical setting.

In humans, it is possible to induce long-lasting changes in cortical excitability taking advantage of neuroplasticity mechanisms induced by non-invasive brain stimulation (NIBS) techniques such as trancranial magnetic stimulation (TMS) per se or combined to a variety of peripheral stimuli ranging from electrical stimuli delivered on a peripheral nerve to laser stimulation of the hand or auditory stimuli [9, 10].

Concurrent application of TMS stimuli with peripheral stimulations could induce Hebbian plasticity at the cortex when there is a close temporal connection between the two stimuli, following the principles of associative plasticity [9, 10]. In this case, long-term potentiation or depression phenomena could occur depending on timing features [9, 10]. Alternatively, if timing between synaptic input and postsynaptic activity cannot be precisely defined, as it could occur during the administration of peripheral continuous vibration, concurrent application of NIBS protocols could theoretically induce homeostatic or non-homeostatic plasticity mechanisms [11].

To test for this, we designed a stimulation protocol in which the distal tendon of the right flexor carpi radialis muscle (FCR) was vibrated, and concomitantly, a 2-min 5-Hz repetitive transcranial magnetic stimulation (rTMS) protocol was administered on the left hemi-scalp hot spot of the vibrated muscle (FCR) or its antagonist (i.e., extensor carpi radialis (ECR) muscle). As control conditions, we also evaluated the effect of vibration of the distal tendon of the FCR and 2-min 5-Hz rTMS protocol per se.

Material and methods

The study was composed of three different experiments: preliminary experiment, main experiment, and control experiment (Fig. 1).

Subjects

Ten healthy participants (6 males, 4 females; mean age ± SD = 29.8 ± 3.7 years) were enrolled in the preliminary experiment, 18 subjects (10 males, 8 females; mean age ± SD = 26.6 ± 2.9 years) took part in the main experiment, and 7 subjects (4 males and 3 females; mean age ± SD = 29.7 ± 4.2 years) in the control experiment. All subjects were right handed, in good health, and without any nervous, orthopedic, muscular, or cognitive disorders. The experiments conformed to the standards set by the Declaration of Helsinki.

Study design

In all the experiments, subjects were seated comfortably on a chair, blindfolded, and with the right arm semi-pronated and placed on a support that allowed them to keep the limb in a relaxed position and to maintain the wrist angle at 0°.

Preliminary experiment

The preliminary experiment aimed at evaluating changes in motor cortex excitability of the vibrated (FCR) and its antagonist (ECR) muscles *during* a stimulation protocol that consisted in 2-min FCR muscle tendon vibration. FCR and ECR motor cortex excitability were measured before (PRE) and during the FCR vibration (Fig. 1; preliminary experiment).

Main experiment

The main experiment aimed to evaluate changes in motor cortex excitability of the vibrated (FCR) and its antagonist (ECR) muscles *after* a stimulation protocol that consisted in (i) FCR muscle tendon vibration only or (ii) the combination of FCR muscle tendon vibration with a train of 5-Hz rTMS stimuli administered in separate days either on ECR or FCR hot spots.

Participants were divided into two groups. In the first group ($N = 10$; 5 males and 5 females; mean age ± SD = 28.4 ± 5.5 years), we measured corticospinal excitability of the ECR muscle (ECR group), while in the second group ($N = 8$; 5 males and 3 females; mean age ± SD = 24.2 ± 2.5 years), the corticospinal excitability of the FCR muscle was assessed (FCR group). Each group participated to three different experimental sessions. The first session corresponded to the tendon vibration on the FCR muscle (V FCR). In the second session, we applied a train of 5-Hz rTMS stimuli on the hot spot of the ECR muscle simultaneously with the tendon vibration protocol (V FCR and rTMS ECR). In the third session, we applied a train of 5-Hz rTMS stimuli on the hot spot of the FCR muscle simultaneously with the tendon vibration protocol (V FCR and rTMS FCR). The order was counterbalanced among the participants. Measurements of corticospinal excitability were performed before (PRE) the conditioning protocols, immediately after (POST), and 30 min (POST 30) after (Fig. 1; main experiment).

Control experiment

The aim of the control experiment was to verify that the 2-min 5-Hz rTMS protocol applied on ECR hot spot per se was not

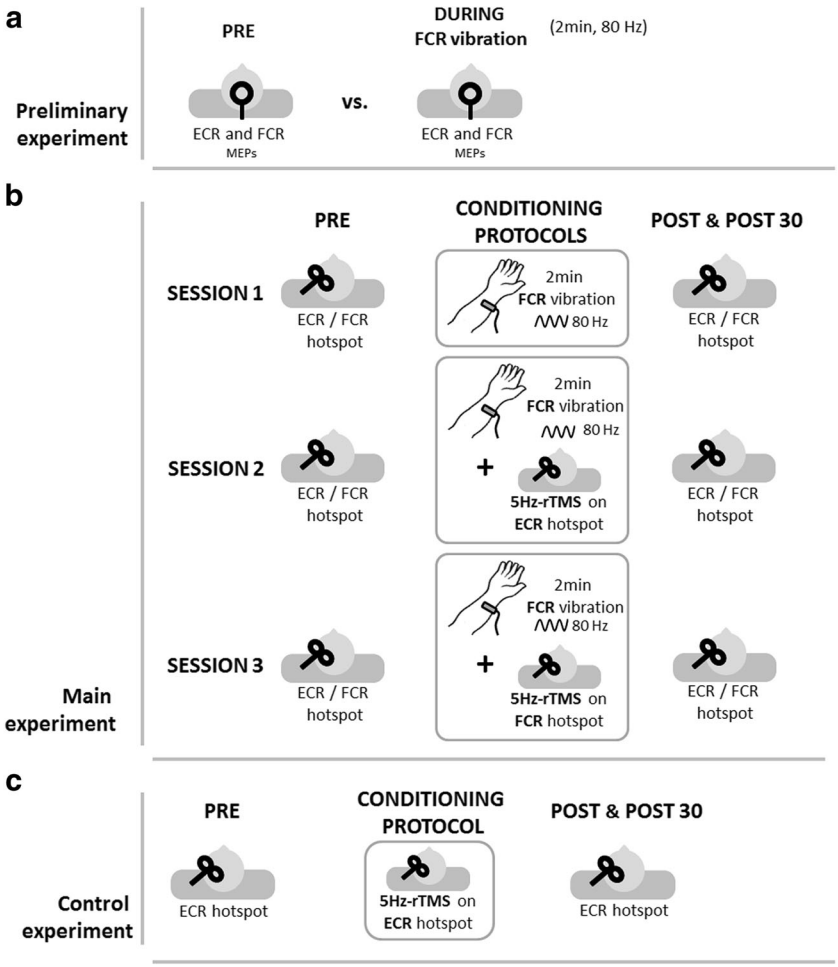

Fig. 1 Experimental paradigm. Preliminary experiment. Motor evoked potentials (MEPs) of the flexor carpi radialis (FCR) and extensor carpi radialis (ECR) of the right arm recorded before (PRE) and during a 2 min FCR vibration protocol (80 Hz). Main experiment. The main experiment was divided in three different sessions. SESSION 1: participants received a tendon vibration on the FCR muscle. SESSION 2: a train of 5 Hz repetitive transcranial magnetic stimulation (5 Hz-rTMS) stimuli on the hot spot of the ECR muscle was administered to the participants simultaneously with the tendon vibration on the FCR muscle (2 min in duration, 80 Hz). SESSION 3: the procedure applied in SESSION 2 was replicated expect for the hot spot of the 5 Hz-rTMS protocol that was set to the hot spot of the FCR muscle. MEPs values were acquired before (PRE) the conditioning protocols, immediately and 30 min after (POST and POST 30, respectively), by mean of a figure-of-eight coil, positioned over the ECR hot spot, in one group of subject, and FCR hot spot, in the other group. Control experiment. 5 Hz-rTMS protocol (2 min in duration) was applied over the hot spot of the ECR muscle and MEPs values were acquired before (PRE), immediately and 30 min after the stimulation (POST and POST 30, respectively)

able to induce changes in the corticospinal excitability of the conditioned muscle. The corticospinal excitability of ECR muscle was assessed before (PRE), immediately after (POST), and 30 min after (POST 30) the rTMS protocol (Fig. 1; control experiment).

Stimulation protocols

Vibration procedure

In all subjects, the distal tendon of the flexor carpi radialis muscle (FCR) at the radio-carpal joint of the right wrist was vibrated for 2 min at a frequency of 80 Hz and an amplitude of 0.5 mm. This vibration amplitude was chosen to be subthreshold for the tonic vibration reflex [2, 12] and in order to activate the Ia afferents as selectively as possible [13]. The vibrator (Vibralgic model, Electronic Conseil, France) was fixed horizontally by means of an elastic strap that passed around the right arm. In pilot trials before the experiment, we confirmed that the participants could completely relax their vibrated limb with no reflex movement, and they experienced illusory hand movements (wrist extension) during tendon vibration.

rTMS procedure

Focal rTMS was applied over the left M1 with a Magstim Rapid stimulator (Magstim Co., Whitland, Wales, UK) and a

flat figure-of-eight coil with mean loop diameter of 9 cm. The handle of the coil pointed backwards and laterally at an ~45° angle from the midline. The coil was placed tangentially to the scalp. The protocol consisted of a train of 600 stimuli, at a frequency of 5 Hz, which were continuously delivered at 90% of active motor threshold (AMT) of the right ECR muscle on the hot spot of the right ECR and at 90% of AMT of the right FCR muscle on the hot spot of the right FCR. AMT was determined at 10% of the maximum voluntary contraction and was defined as the minimum intensity eliciting a clear-cut contralateral MEP in 5 out of 10 consecutive trials. We chose this protocol since Quartarone et al. demonstrated that it could selectively shape the excitability of the intracortical circuits without significantly affecting corticospinal excitability [14].

Single-pulse TMS

During preliminary experiment, single-pulse TMS was applied over the primary motor cortex using a Magstim 200 stimulator (Magstim Co., Whitland, Wales, UK) with a monophasic current waveform connected to a round coil (130-mm diameter) placed over the vertex with the handle (held by the experimenter) oriented posteriorly in the sagittal direction. An anticlockwise coil-current was used to stimulate the left hemisphere. The vertex was measured using standard clinical procedures and was marked with a color wax pen. At the beginning of each experiment, the stimulus intensity needed to evoke MEPs of approximately 0.5–0.8-mV peak-to-peak amplitude in the target muscle was defined. Fifteen MEPs were recorded before FCR vibration and during FCR vibration.

During the main experiment and the control experiment, single-pulses were delivered using the same Magstim 200 stimulator connected to a figure-of-eight-shaped coil held tangentially to the scalp. The center of the junction of the coil was placed over the area of the left primary motor cortex (M1) at the optimal position (hot spot) to elicit motor-evoked potentials (MEPs) in the contralateral ECR or FCR, with the handle pointing backwards and ~45° away from the midline. Thanks to the use of a figure-of-eight-shaped coil, the optimal site of stimulation (hot spot), defined as the lowest threshold site giving a response specifically in the ECR and FCR muscles at rest, was found by moving the coil around the M1 of the target muscles. This procedure allowed also testing corticospinal excitability from the same site that underwent rTMS conditioning during main experiment. At the beginning of each experiment, the stimulus intensity needed to evoke MEPs of approximately 0.5–0.8-mV peak-to-peak amplitude in the target muscle was defined. This intensity was used to evaluate MEPs changes before (PRE), immediately after (POST), and 30 min after (POST 30) the conditioning protocols. Fifteen MEPs were recorded at each testing time.

Electromyographic recording

Electromyographic (EMG) activity was recorded from Ag/AgCl surface electrodes placed over the ECR muscle or FCR in a belly-tendon montage. The ground electrode was placed at the elbow. The signal was amplified, filtered (20 Hz to 1 kHz) and sampled at 5 kHz. Each recording epoch lasted 400 ms, of which 100 ms preceded the TMS. We controlled the EMG activity in real-time during vibration to ensure that vibration trials were not contaminated by muscle activity. Muscle activity during the conditioning protocols was lower than 10 μV and not different from muscle activity at rest ($p > 0.1$).

Data and statistical analysis

Measurements of MEPs were made on single trials. The amplitude of contralateral MEPs was evaluated by taking the peak-to-peak difference in the raw EMG signals. Mean values of MEP amplitude were calculated for each subject in each experimental condition.

Preliminary experiment: a RM-ANOVA with muscle (two levels: ECR and FCR) and time (two levels: PRE and during) was applied on MEP amplitude in order to compare the cortical activity related to the vibrated (FCR) and its antagonist (ECR) muscles before and during muscle vibration.

In the main experiment, MEP data were entered in a RM-ANOVA with session (V FCR, V FCR and rTMS ECR, and V FCR and rTMS FCR) and time (PRE, POST, POST 30) as the within-subject factors and muscle (ECR and FCR) as the between-subject factor. MEP data from the control experiment were subjected to the RM-ANOVA with time (PRE, POST, POST 30) as the within-subject factor. Significant interactions were interpreted with Newmann-Keuls post hoc analysis. Significance for all procedures was set at a level of 0.05. Statistical analysis was performed with SPSS 22.0.

Results

Preliminary experiment

The results of the RM-ANOVA on MEP amplitudes acquired in the preliminary experiment showed a significant muscle × time interaction ($F(1,5) = 10.19$, $p = 0.040$). Post hoc comparisons revealed a significant increase of ECR MEP values during FCR muscle vibration with respect to the baseline condition (pre 0.56 ± 0.04 mV, during 0.79 ± 0.06 mV; $p = 0.001$), while no differences appeared between the MEP values of the FCR muscle (pre 0.45 ±

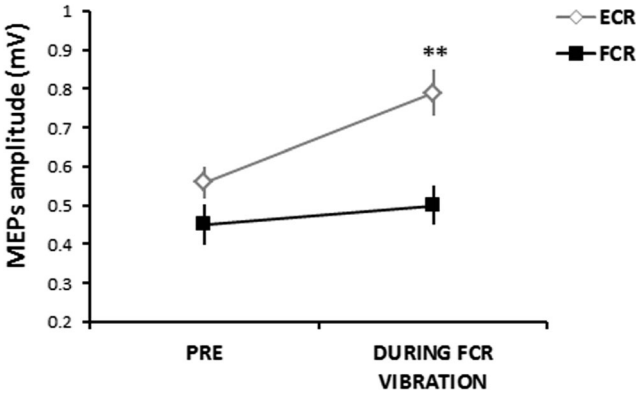

Fig. 2 Preliminary experiment. Mean amplitude of the motor evoked potentials (MEPs) acquired from extensor carpi radialis (ECR, white diamonds) and flexor carpi radialis (FCR, black diamonds) muscles before (PRE) and during a 2-min vibration of FCR tendon. Error bars represent standard error. A significant increase was observed during FCR muscle vibration in ECR muscle (**, $p < 0.01$)

0.05 mV, during 0.5 ± 0.05 mV; $p = 0.16$) (see also Fig. 2). Other statistical results are reported in Table 1.

Main experiment

RM-ANOVA showed a significant interaction session × time × muscle ($F(4,64) = 3.61$, $p = 0.010$). Post hoc analysis showed that MEP amplitudes before the application of the conditioning protocols (PRE) were similar across the different experimental sessions in each muscle (always $p > 0.05$) and that the different conditioning protocols exerted different effects on corticospinal excitability of the ECR and FCR muscles (Fig. 3).

The mere tendon vibration on the FCR muscle (V FCR; Fig. 3a) did not induce any change in cortical excitability of the FCR muscle after the conditioning protocol (PRE vs. POST vs. POST30, p always > 0.05), whereas immediately after the conditioning protocol, there was a trend for a decrease in ECR MEP amplitude (PRE vs. POST, $p = 0.08$).

When the protocol V FCR and 5-Hz rTMS ECR was applied, corticospinal excitability of right ECR significantly

Table 1 Summary of results: statistical results of preliminary and main experiments

Factor	*F* ratio	*p* value
Preliminary experiment		
Muscle	6.72	0.048
Time	30.82	0.003
Main experiment		
Session	1.97	0.15
Time	0.44	0.65
Muscle	1.41	0.25
Session × time	0.95	0.44
Session × muscle	2.64	0.09
Time × muscle	3.49	0.04

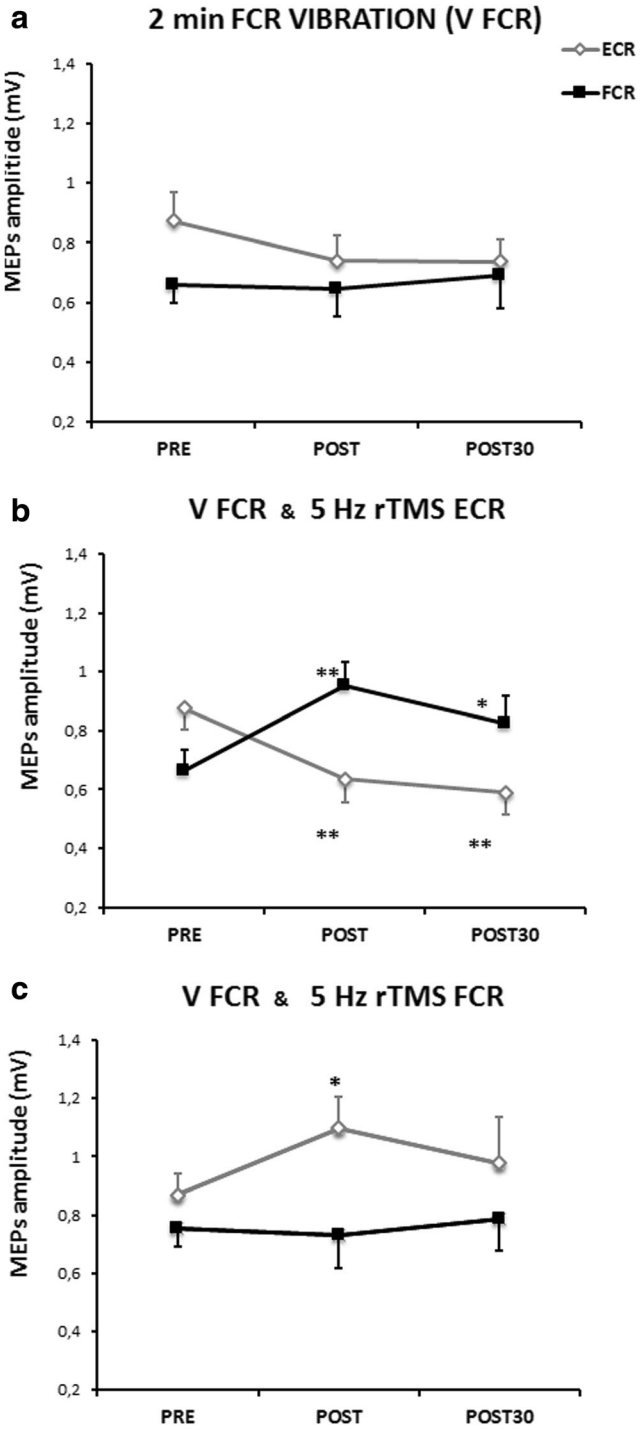

Fig. 3 Main experiment. Cortical excitability changes after the administration of the three conditioning protocols: flexor carpi radialis (FCR) tendon vibration (A), FCR tendon vibration simultaneously with 5 Hz-rTMS on right extensor carpi radialis (ECR) hot spot (B) and FCR tendon vibration with 5 Hz rTMS-on right FCR hot spot (C). Abscissa indicates the time at which motor evoked potentials (MEPs) were recorded (PRE, before the conditioning protocol; POST, after the end of the conditioning protocol; POST 30, 30 min after the end of the conditioning protocol). Ordinate indicates the amplitude MEPs values expressed in mV acquired in ECR (white diamonds) and FCR (black squares) muscles. Mean data ± standard errors are shown. Asterisks indicate significant differences between POST and POST30 with PRE, *$p < 0.05$, **$p < 0.01$

decreased after the conditioning protocol (POST vs. PRE, $p = 0.001$) and still remained depressed 30 min after it (POST 30 vs. PRE, $p = 0.001$, POST 30 vs. POST, $p = 0.47$) (Fig. 3b). Differently, corticospinal excitability of right FCR significantly increased after the V FCR and 5-Hz rTMS ECR conditioning protocol (POST vs. PRE, $p < 0.001$) and still remained augmented 30 min after it (POST 30 vs. PRE, $p = 0.045$; POST 30 vs. POST, $p = 0.09$).

The application of the protocol V FCR and 5-Hz rTMS FCR (Fig. 3c) induced a decrease incorticospinal excitability of right ECR only immediately after the conditioning protocol (POST vs. PRE, $p = 0.045$; POST30 vs. POST, $p = 0.33$) and no change incorticospinal excitability of right FCR. Other statistical results are reported in Table 1.

Control experiment

When applied alone, 2-min 5-Hz rTMS on the ECR hot spot did not induce any change in the contralateral ECR muscle corticospinal excitability (mean MEP ± SE; PRE 0.56 ± 0.02 mV; POST 0.54 ± 0.05 mV; POST 30 0.55 ± 0.03 mV; $F(2,12) = 0.42$, $p = 0.66$).

Discussion

The results of the present study provide evidence that combining a vibratory stimulus over FCR tendon with 5-Hz rTMS over the ECR motor cortical representation resulted in an increase of the proprioceptive cortical aftereffect respect to what observed with the only vibratory stimulus. Indeed, we observed that the combination of FCR tendon vibration and 5-Hz rTMS over the ECR cortical area was able to induce a pattern of unbalanced M1 excitability between the vibrated muscle and its antagonist with an increased excitability of the FCR cortical area and decreased excitability of ECR cortical area that persisted up to 30 min and was greater than that observed when vibration was administered alone.

Illusory perception of movement can be induced using muscle vibration [1]. Vibration of joint extensors of any body part triggers the illusion of flexion, and vibration of joint flexors, and the illusion of extension. Vibration is thought to cause movement illusions by activating muscle spindles [15], i.e., the stretch receptors that are normally active during stretching of a muscle. At a cortical level, this illusory movement is accompanied by an unbalanced excitability of the vibrated muscle and its antagonist with an increased excitability of the antagonist muscle and decreased excitability of vibrated muscle [6, 16, 17].

Our findings of the preliminary experiment confirmed that, during the vibration, cortical excitability of the antagonist to the vibrated muscle (here, ECR) is increased, giving rise to an illusion of wrist extension. Cortical excitability of the vibrated FCR muscle did not change, differently from the results by Kito and colleagues [6], showing a slight increase in the cortical excitability of the vibrated muscle. However, different studies reported that the effect of vibration on M1 excitability strongly depends on the duration and the pattern (continuous or intermittent) of application of vibratory stimuli [18, 19].

When vibration stops, an illusion of return movement in the opposite direction respect to the illusory movement during vibration has been extensively reported [1, 5, 6, 20]. Apart peripheral mechanisms of muscle spindles adaptation [7, 8], central processes have been called into question to explain this phenomenon. Indeed, stimulation of the M1 showed that responses in the antagonist to the vibrated muscle increased during vibration and decreased thereafter [6]. Our findings in the first session of the *main experiment* showed a trend of decreased, while not significant, cortical excitability of the antagonist (ECR) muscle. A reduction of excitability in those corticospinal cells that were preferentially activated by the spindle inputs during the vibration period (here those controlling ECR) has been hypothesized [6].

Here, we found that 5-Hz rTMS when delivered over the ECR muscle cortical area together with vibration of FCR tendon increased this proprioceptive cortical aftereffect. We could hypothesize that a metaplasticity mechanism occurred: the likely larger increase of excitability of ECR corticospinal neurons due to the combination of spindle inputs and 5-Hz rTMS stimulation might have been followed by a long-lasting decrease of excitability of these M1 neurons [21].

Further, we cannot exclude that the long-lasting decrease in ECR MEP amplitude and increase in FCR MEP amplitude observed when vibration was removed might have been sustained by the control of descending pathway on Ia interneurons at the spinal level.

Regarding the cortical aftereffect after the application of the other conditioning protocol (V FCR and 5-Hz rTMS FCR), we observed only an increased excitability of ECR corticospinal pathway immediately after the end of stimulation and no change in FCR corticospinal neuron excitability. First, we do not think that this result reflects a change in synaptic plasticity at a cortical level as described before. Indeed, vibration of the FCR tendon targeted the ECR cortical representation, as shown by previous findings [6] and by our preliminary experiment. The 5-Hz rTMS over the FCR area targeted instead the FCR cortical representation, but 2 min of 5-Hz rTMS was unable to induce per se any change in cortical excitability, as demonstrated in our control experiment. However, it has already been shown that neuromodulation at a cortical level can induce, during the stimulation period, a change in the excitability of Ia interneurons at the spinal level and consequently a change in reciprocal inhibition [22] over FCR and ECR α motor neurons. Thus, a spinal mechanism can be hypothesized to explain the transient increase in ECR MEP amplitude. It is tempting to speculate that when tendon

FCR vibration and 5-Hz rTMS FCR were removed, the FCR Ia interneurons at the spinal level that were activated by both these inputs reduced their activity, thus releasing the ECR α motor neurons and inducing a transient increase in ECR MEP amplitude.

A limitation of the study is that we did not specifically record any psychophysical measure related to the proprioceptive movement aftereffect. It would be interesting to assess in future study whether the prolonged cortical aftereffect observed after FCR vibration and 5-Hz rTMS ECR is accompanied also by a prolonged proprioceptive movement aftereffect.

Conclusions

We showed for the first time that combining 5-Hz rTMS targeting the cortical representation of the muscle antagonist to the vibrated one, together with a peripheral vibration, might induce at a cortical level a strong and long-lasting imbalance of the excitability of the two antagonistic muscles.

Our finding can result in a take-home message when focal vibration is used in rehabilitative treatments, when re-establishing a pattern of unbalanced activity between agonist and antagonist muscles is needed such as to reduce spasticity, to facilitate muscle contraction for functional activity, to stimulate the proprioceptive system to obtain an efficient motor control, or to use as a proprioceptive training to restore sensorimotor organization in the movement disorders [23–25].

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

Human and animal rights and informed consent The authors declare that all participants gave written informed consent to the study.

Ethical approval All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and of the national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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