Using Cutaneous Receptor Vibration to Uncover the Effect of Transcranial Magnetic Stimulation (TMS) on Motor Cortical Excitability

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Background: Little is known about how vibrational stimuli applied to hand digits affect motor cortical excitability. The present transcranial magnetic stimulation (TMS) study investigated motor evoked potentials (MEPs) in the upper extremity muscle following high-frequency vibratory digit stimulation.

Material/Methods: High-frequency vibration was applied to the upper extremity digit II utilizing a miniature electromagnetic solenoid-type stimulator-tactor in 11 healthy study participants. The conditioning stimulation (C) preceded the test magnetic stimulation (T) by inter-stimulus intervals (ISIs) of 5–500 ms in 2 experimental sessions. The TMS was applied over the primary motor cortex for the hand abductor pollicis-brevis (APB) muscle.

Results: Dunnett's multiple comparisons test indicated significant suppression of MEP amplitudes at ISIs of 200 ms (P=0.001), 300 ms (P=0.023), and 400 ms (P=0.029) compared to control.

Conclusions: MEP amplitude suppression was observed in the APB muscle at ISIs of 200–400 ms, applying afferent signaling that originates in skin receptors following the vibratory stimuli. The study provides novel insight on the time course and MEP modulation following cutaneous receptor vibration of the hand digit. The results of the study may have implications in neurology in the neurorehabilitation of patients with increased amplitude of MEPs.

MeSH Keywords: Evoked Potentials, Motor • Pacinian Corpuscles • Transcranial Magnetic Stimulation • Vibration

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Background

The somato-motor cortices can be modulated by different afferent stimuli [1–3]. The application of a vibratory stimulus to the human body is followed by the activation of specific cutaneous and muscular receptors. Cutaneous receptors consist of low-threshold mechanoreceptors innervated by large myelinated fibers transmitting touch and vibration sensation. Low and high-frequency vibrations mostly activate the Meissner (20–50 Hz) and Pacinian (60–400 Hz) corpuscles [4], respectively. Muscle spindles are activated by mechanical vibrations and can evoke the tonic vibration reflex [5,6]. Muscle and cutaneous vibration receptors provide strong proprioceptive stimuli to the primary somatosensory (S1) and primary motor (M1) cortices via Ia afferent nerves [7–9]. Sensorimotor integration has been documented in animal models and healthy human study participants using transcranial magnetic stimulation (TMS) [10–13].

By measuring motor-evoked potentials (MEPs), the TMS studies performed in healthy study participants have shown that low-amplitude muscle vibration induces various changes in corticospinal excitability [14–21]. In post-stroke patients, muscle vibration reduces muscle tonus, resting motor threshold (RMT), and increases amplitudes of MEPs and motor map size [22–28]. Due to these muscle vibration effects of reducing corticospinal excitability abnormalities in post-stroke patients, muscle vibration may be used as a complementary therapy alongside conventional physiotherapy to promote neural plasticity and motor recovery [24,29]. Compared to muscle receptor vibration, very little is known about the effect of digit vibration on motor cortical excitability. There are only studies employing cutaneous electrical stimulation delivered to the hand digits showing that subsequent hand muscle MEPs were either inhibited [1,30,31] or had no effect [32,33]; the inhibitory effect has been demonstrated at magnetic stimuli intensities of 5–20% above the RMT [31,34].

The present TMS study investigated the conditioning effects of high-frequency vibratory stimuli delivered percutaneously to the tip of the upper extremity digit II. The conditioning vibration preceded the TMS over the M1 by inter-stimulus intervals (ISIs) of 5–14 ms and 18–500 ms in 2 experimental sessions. It was therefore of interest to investigate the time course of MEP modulation in the hand muscle following cutaneous high-frequency vibration of the hand digit. A slight supra-threshold vibration intensity was used for each study participant, perceived as comfortable [35]. Vibration at a frequency of 120 Hz was used as an optimal frequency for activating Pacinian corpuscles [8,36], and the intensity of magnetic test stimulation was 120% above the RMT.

Testing the hypothesis of effects of cutaneous receptors vibration on corticospinal excitability might lead to a better understanding of the physiology of cutaneous receptors in neurorehabilitation.

Material and Methods

Participants

A total of 11 right-handed volunteer study participants (5 females and 6 males; age: 40.18±11.92 years; height: 178±7.1 cm; body mass: 71.9±12.6 kg, body mass index: 22.7±3.2 kg/m^2) participated in the study. Informed consent was obtained from all individual participants. Hand dominance was determined by the Edinburgh handedness inventory [37]. All participants were free of contraindications to TMS [38] and instructed to abstain from ingesting nicotine, alcohol, caffeine, and black tea (if consuming), and avoid strenuous physical activities for a minimum of 12 hours prior to each session to ensure a stable level of motor-cortical excitability. All study participants participated in a conditioning-test paradigm (C-T) where the test stimulus (magnetic) was applied at random ISIs, from 5–500 ms after the conditioning stimulus (stimulus to the upper extremity digit II) in 2 experimental sessions separated 2–7 days apart. Study participants were reclining comfortably in an electronically controlled chair with their forearm in a semi-pronated, resting position. The head support was adjusted for providing a comfortable head position during the session. All procedures performed in studies involving human participants were under the ethical standards of the institutional and national research committee (University of Split School of Medicine, Ref. number 2181-198-03-04-L7-4027) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Electromyographic activity

Study participants were first prepared by gently abrading the skin and then cleaning it with a solution of acetone, alcohol, isopropyl palmitate, and water. Electromyography (EMG) of the right abductor pollicis brevis (APB) was recorded with a pair of self-adhesive surface electrodes (Ambu® Blue Sensor BR, BR-50-K/12, Ballerup) in a belly-tendon montage. The reference electrode for the APB was placed on the metacarpophalangeal joint of the thumb, and the ground electrode was attached to the hand dorsum. Electrodes were attached to the Nexstim EMG electrode cable with a 1.5 mm touch-proof female safety connector (DIN 42-802) and connected to a 6-channel EMG. The characteristics of the EMG used in testing as a component of the TMS system are sampling rate equal to 3 kHz (per channel), resolution of 0.3 µV, the scale between −7.5 mV and 7.5 mV, common-mode rejection ratio >90 dB, peak-to-peak noise <5 µV and frequency band in the range of 10–500 Hz.

Digit vibration

Vibration at a frequency of 120 Hz (duration of 500 ms), and intensity slightly above the individual perceiving threshold, was applied to the tip of the right upper extremity digit II using a tactor,

Figure 1. Vibration stimulator with tactor on the upper extremity digit II, and surface electrodes over the abductor pollicis-brevis (APB) muscle. **Top:** Custom made vibration stimulator (upper). **Bottom:** The position of the tactor, a miniature electromagnetic solenoid-type stimulator (Dancer Design, St. Helens WA10 1 LX, UK), on digit II with surface electrodes (encircled in red) attached over the APB muscle.

a miniature electromagnetic solenoid-type stimulator (Dancer Design, St. Helens WA10 1 LX, UK). High-frequency vibration was used to excite Pacinian receptors, which are responsive to frequencies in the range of 100–400 Hz [39]. The tactor diameter is 18 mm, 12 mm in height, 5.4 grams weight, and with the drive voltage of the sine wave, 6 V peak. The amplitude of vibration varied with drive voltage to a good approximation. The tactor stimulator was attached to the skin with hypoallergenic adhesive tape (Transpore™, 3 M Health Care) (Figure 1) and was stable over the high frequency applied to digit II. For the study, our group developed a custom-made vibration stimulator prototype (Figure 1) with 3 channels delivering up to 300 Hz of vibration frequency with up to 5 seconds duration of vibration. In this study, one channel was used, and the vibration stimulator was triggered by a script written in Presentation software (Neurobehavioural Systems, Inc., Version 20.2) installed on a PC. A standard BNC cable was modified into a BNC-to-USB cable allowing connection between the PC and the Trig in of the vibration stimulator.

MRI acquisition

Magnetic resonance imaging (MRI) of the head for each study participant was performed with Siemens Magnetom Avanto,

Tim (76×18) strength 1.5 T. MRI images were obtained to suit the TMS requirements and were integrated with the TMS system and used for the 3-dimensional (3D) reconstruction of individual brain anatomy [40].

Navigated TMS (nTMS)

Navigated TMS (nTMS) was delivered using a figure-of-eight coil with a winding diameter of ca 50 mm, and an outer winding diameter of ca 70 mm connected to a Nexstim TMS II stimulator (integrated into mobile NBS chart) (Nexstim Oy, Helsinki, Finland). Computer-aided landmark identification ensured accurate alignment to the individual MRI data. The nTMS system uses a stereotactic navigation camera (3D optical tracking unit; Polaris® Vicra) to track the coil position for the study participant's head. The NBS system recorded the coil's orientation, location, and induced electric field for each stimulus pulse. The magnetic stimulation was triggered by the same script that triggered vibratory stimulation.

Experimental protocol

Figure 2 presents the experimental protocol. At the beginning of each session, baseline cortical excitability was measured by inducing MEPs over the M1 to determine RMT. The coil was positioned over the primary motor hand area of the left M1, and the standard reference method was used to determine RMT [41,42]. The RMT was defined as the lowest possible stimulus intensity that allowed the recording of five MEPs in the APB muscle with an amplitude of at least 50 µV in a series of 10 consecutive trials. After determining RMT, an intensity of 120% of maximum stimulator output was used to map the M1 hotspot for the APB muscle following peripheral vibration stimulation to the upper extremity digit II. The conditioning stimulus (vibration) preceded the test stimulus (single-pulse TMS over M1) by inter-stimulus intervals (ISIs) of 5, 6, 7, 8, 9, 10, 11, 12, and 14 ms (Experimental session 1); and of 18, 20, 25, 30, 40, 50, 100, 200, 300, 400, and 500 ms (Experimental session 2). In both sessions, magnetic pulses were given in random order at ISIs (session blocks) after the onset of vibration in all study participants. Each session block consisted of 10 trials with an inter-trial interval of 5.5 seconds. The control condition (control session block), i.e., TMS over M1 without peripheral stimulation, was included at the beginning of the experimental session. Study participants were instructed to remain completely relaxed, with eyes closed during mappings.

Data analysis and statistics

The latencies and amplitudes of MEP responses were analyzed by using a custom-made algorithm programmed in Matlab (MATLAB 2018b), allowing for automatic estimation of peak-to-peak amplitude and latency of MEPs. The statistical data
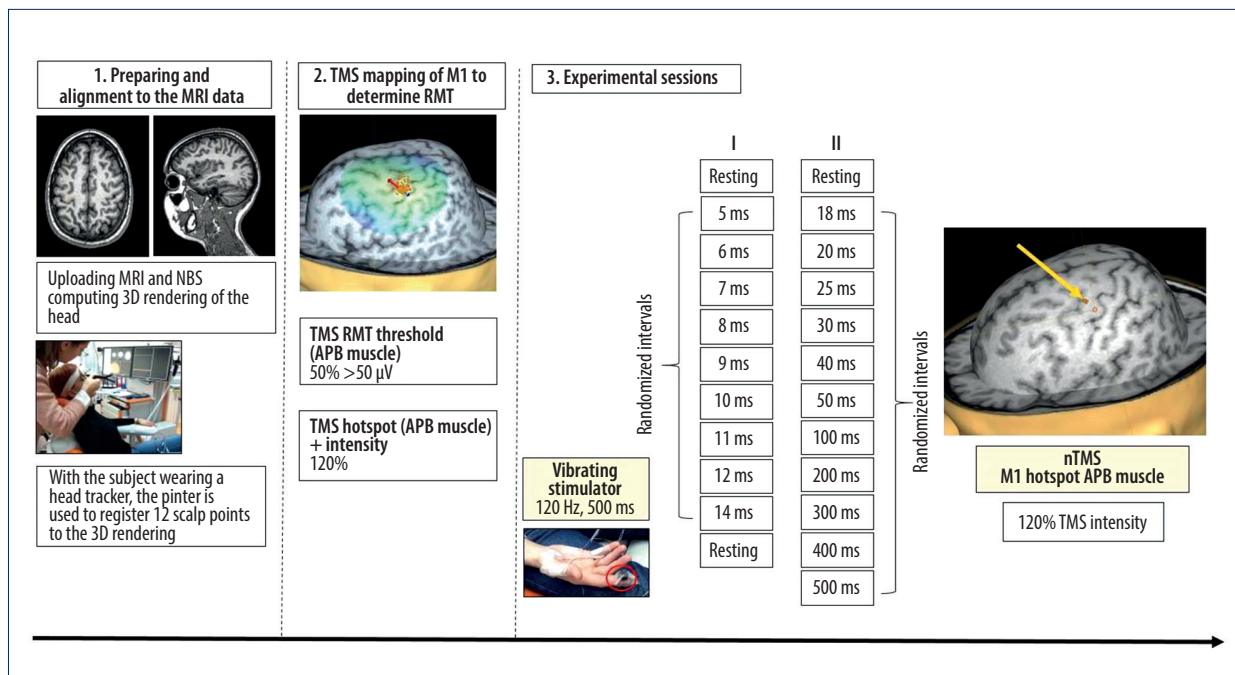
Figure 2. A course of study. After performing the head MRI for each study participant, MRI images were uploaded and 3D-rendered, and a co-registration process was performed. TMS mapping of M1 for APB was performed to determine RMT (RMT 100%) intensity. The cortical M1 hotspot for the APB muscle is showed in 3D, and RMT 120% intensity was used for magnetic brain stimulation of the M1 hotspot for the APB muscle following vibrating stimulation at time intervals of 5–14 ms (experimental session I), and 18–500 ms (experimental session II), including resting condition. APB – abductor pollicis brevis muscle; MRI – magnetic resonance imaging; MI – primary motor cortex; RMT – resting motor threshold.

analysis was conducted using STATISTICA 12 (StatSoft, Inc., Tulsa, OK, USA). A z-sample test was performed on MEP responses (amplitude and latency) to exclude possible inter-individual differences (±1.96 standard deviation). For each participant in every trial, the MEP response was transformed into z-scores. MEP responses that were more than ±2 standard deviation (95% confidence interval) from the mean were defined as outliers and excluded from further analysis. Kolmogorov-Smirnov and Shapiro Wilk's tests showed no departs from the normal distribution. Mauchly's Test of Sphericity indicated that the assumption of sphericity was not violated, therefore repeated measures ANOVA (*P*-value of 0.05) was conducted for time intervals (including control condition) in both experimental sessions to test whether vibrating stimulation which precedes magnetic stimulation at specific time intervals influenced MEP responses. In the case of significant effects, Dunnett's test of multiple comparisons to the control condition was calculated (*P*-value of 0.05).

Results

The MEP responses (latency and amplitude) did not differ significantly between study participants in either of the experimental sessions while using RMT 100% intensity (results did not deviate from±1.96 standard deviation). The RMT 100% and RMT 120% intensities of maximal stimulator output used in the mapping of the M1 for the APB muscle did not differ significantly between study participants in either of the experimental sessions (95% confidence interval). The descriptive statistics (mean±standard deviation) of RMT 100% and RMT 120% intensities, MEP responses (amplitude and latency values) at RMT 100%, and MEP responses (amplitudes and latency) for session blocks in both experimental sessions are presented in Tables 1 and 2. Relevant analyses of variance for both experimental sessions are shown in Table 3.

In the first experimental session, no significant differences were found for MEP latency ($F_{9,90}$=1.039, *P*=0.415*)* at different ISIs, while in the second experimental session, there was a significant difference of MEP latency ($F_{11,110}$=3.375, *P*<0.001). However, Dunnett's post hoc test indicated no main effects of MEP latency compared to control in the second experimental session. Furthermore, significant effects were found for MEP amplitudes due to changes in ISIs in the first ($F_{9,63}$=2.145, *P*<0.038) and second ($F_{11,110}$=4.678, *P*<0.001) experimental sessions (Figure 3). However, Dunnett's multiple comparisons test indicated a significant decrease of MEP amplitudes only in the second experimental session at ISIs of 200 ms (*P*=0.001), 300 ms (*P*=0.023) and 400 ms (*P*=0.029) compared

Table 1. RMT 100% and RMT 120% intensities for the experimental sessions I and II, including MEP latency and amplitude values acquired at RMT 100%.

Experimental session I (N=11)	Mean	SD
RMT 100% intensity	34.82	5.02
RMT 120% intensity	41.45	6.02
RMT 100% MEP amplitude (µV)	114.94	28.03
RMT 100% MEP latency (ms)	23.28	2.53

Experimental session II (N=11)	Mean	SD
RMT 100%	35.18	4.92
RMT 120%	41.82	5.91
RMT 100% MEP amplitude (µV)	167.15	65.44
RMT 100% MEP latency (ms)	23.83	1.95

RMT – resting motor threshold; MEP – motor evoked potential; SD – standard deviation.

Table 2. MEP responses (latency and amplitude).

Experimental session I (N=11)				
	MEP latency (ms)		MEP amplitude (µV)	
	Mean	SD	Mean	SD
Control	24.41	1.40	470.31	152.48
5 ms	24.65	1.37	337.04	186.54
6 ms	24.68	1.39	376.38	200.91
7 ms	24.65	1.56	430.01	285.41
8 ms	24.82	1.57	412.03	221.58
9 ms	24.89	1.65	418.71	218.42
10 ms	24.56	1.29	483.96	221.50
11 ms	24.67	1.68	508.61	283.48
12 ms	24.59	1.48	535.76	230.48
14 ms	24.72	1.62	434.16	250.38
Experimental session II (N=11)				
	MEP latency (ms)		MEP amplitude (µV)	
	Mean	SD	Mean	SD
Control	24.76	2.01	429.84	131.69
18 ms	24.47	1.80	422.45	154.57
20 ms	24.74	1.88	483.70	281.59
25 ms	24.63	1.93	409.13	100.09
30 ms	24.78	1.87	392.04	115.35
40 ms	24.98	1.87	315.32	156.86
50 ms	24.87	1.66	398.26	227.56
100 ms	25.02	1.79	279.23	178.19
200 ms	25.26	1.95	211.45	130.29
300 ms	25.23	1.86	256.91	121.72
400 ms	25.04	1.86	261.51	84.02
500 ms	25.04	1.84	293.36	149.40

MEP responses (latency and amplitude) for RMT 120% intensity used for magnetic brain stimulation of the M1 hotspot for the APB muscle following vibratory stimulation at the time intervals of 5–14 ms (experimental session I), and 18–500 ms (experimental session II). The control condition represents the situation when TMS was applied to the M1 hotspot for APB without vibration applied to the hand digit. MEP – motor evoked potential; RMT – resting motor threshold; SD – standard deviation; APB – abductor pollicis brevis muscle; M1 – primary motor; TMS – transcranial magnetic stimulation.

Table 3. Main effects of ANOVAs for both experimental sessions.

	Factor	Measurement	d.f.	F value	P value	Dunnett's post hoc test
Experimental session I	Session block Control – 5 – 6 – 7 – 8 – 9 – 10 – 11 – 12 – 14 (ms)	MEP latency (ms)	9	1.039	0.415	P>0.05
		MEP Amplitude (µV)	9	2.145	<0.038*	P>0.05
Experimental session II	Session block Control – 18 – 20 – 25 – 30 – 40 – 50 – 100 – 200 – 300 – 400 – 500 (ms)	MEP Latency (ms)	11	3.375	<0.001*	P>0.05
		MEP Amplitude (µV)	11	4.678	<0.001*	Control – 200 ms P=0.001* Control – 300 ms P=0.023* Control – 400 ms P=0.029*

* Significant results were expressed as $P<0.05$. Motor evoked potential (MEP) latency (ms) in the first experimental session did not differ significantly with changes in time session blocks. ANOVA indicated that MEP amplitude (µV) in the first experimental session, as well as latency (ms) and amplitude (µV) in the second experimental varied significantly. Dunnett's post hoc test indicated a significant decrease of amplitude only in the second experimental session for time session blocks of 200 ms, 300 ms, and 400 ms.
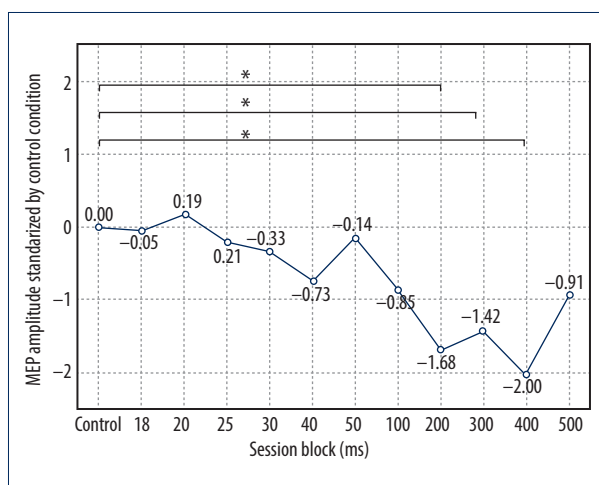

Figure 3. MEP amplitudes at ISIs in the second experimental session. The effect of ISIs (18-500 ms) on MEP amplitude (µV) is expressed as standardized results (z-value, 95% CI). Error bars represent standard deviation. A significant decrease of MEP amplitudes was found at ISIs of 200 ms, 300 ms, 400 ms compared to control. * Refers to $P<0.05$. MEP – motor evoked potential; ISIs – inter-stimulus intervals; CI – confidence interval.

to control (Figure 3, Table 3). Figure 4 shows mean MEPs from the APB muscle in 1 study participant for the control condition, and ISIs of 200 ms, 300 ms, and 400 ms.

Discussion

The functioning of the spinal cord circuitry is governed by multimodal afferent signaling and on supra-spinal influences from the motor cortex [43,44]. Previous TMS studies have shown that an external afferent input can alter the state of the spinal cord circuitries as well as cortical motor neurons [45]. The present study provides new findings on the time-course of MEP

amplitude modulation following cutaneous vibration of the digit. We have observed a decrement in MEP amplitude compared to the control condition at ISIs of 200, 300, and 400 ms.

We compared the results of our study with TMS studies that used vibrational stimuli over the muscles and electrical stimuli on digits and nerves and provided conclusions related to possible directions for future research and clinical value.

Muscle vibration and motor cortical excitability

Compared to the limited number of studies related to vibration of digits [46], more effort has gone into investigating modulations of MEPs by muscle vibration [12,13,47], which can enhance MEPs at specific ISIs [12,13]. Overall, those studies have found similar results, namely that muscle vibration resulted in MEP facilitation mediated by Ia afferent input [17,48]. The results of the neurophysiological effects of muscle vibration on corticospinal excitability have found their relevance in studies investigating the effect of muscle vibration in neurology patients. The TMS has been used to map the motor cortex before and after the muscle vibration, with testing of muscle tonus and motor function. Anti-spastic effects of vibratory stimuli to the spastic muscles of hemiparetic limbs have been found in post-stroke patients, as well changes in cortical excitability measures (i.e., RMT) and intracortical inhibitory circuits (i.e., short-interval intracortical inhibition and intracortical facilitation) [24].

Percutaneous electrical stimulation of the hand digits and nerves

Most TMS studies to date have shown that electrical stimulation of hand digits produces a decrease in MEP amplitude [1,30,31,34] at ISIs <30–40 ms. This inhibitory effect has been demonstrated to be dependent on the intensity of the TMS pulse [30,31,34], as well as the intensity of digit
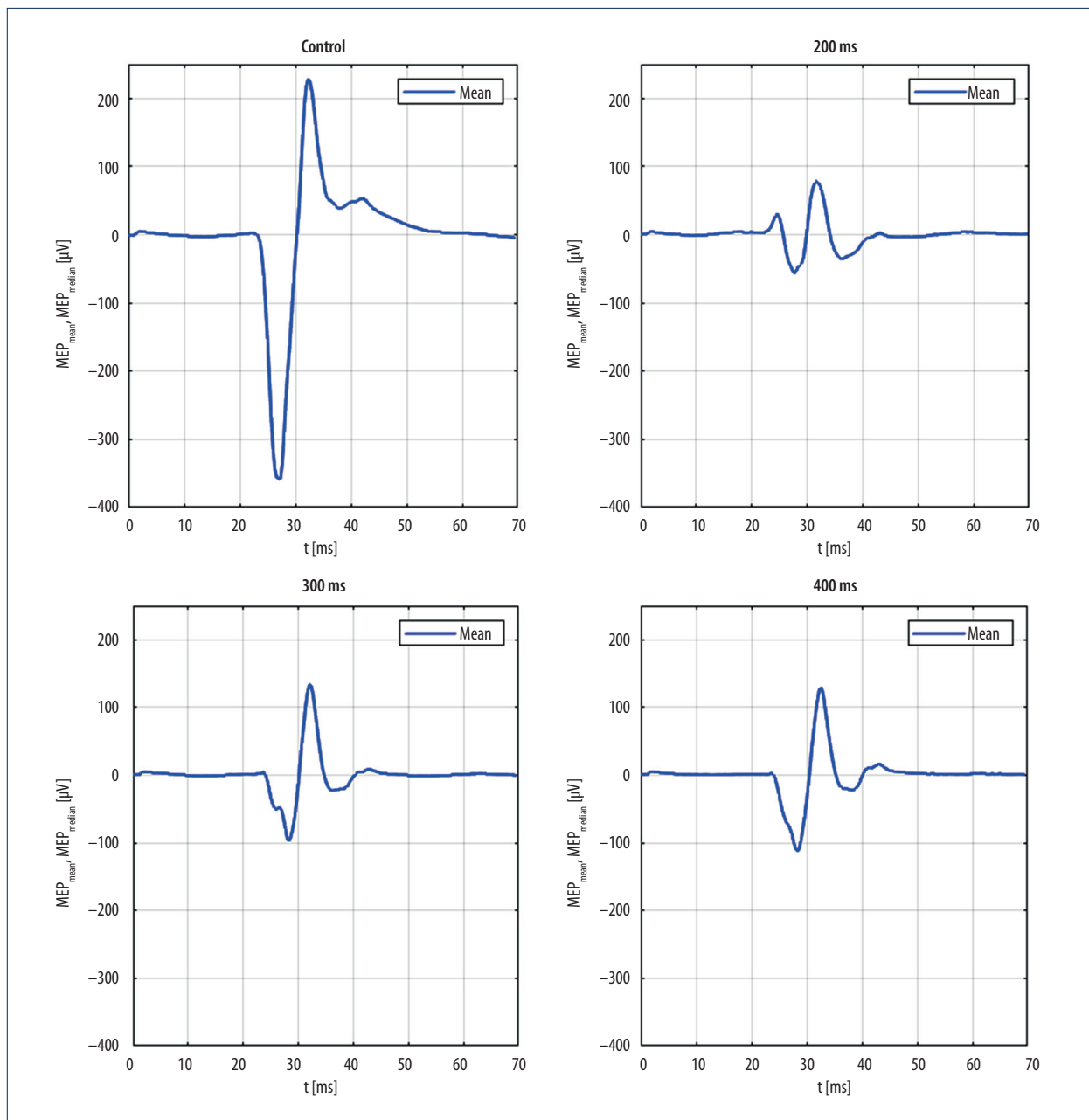
Figure 4. Mean MEPs for the control condition, and ISIs of 200 ms, 300 ms, and 400 ms recorded from the APB muscle in one study participant. Note: milliseconds, ms (on x-axis); microvolts, μV (on y-axis). MEP – motor evoked potential; ISIs – inter-stimulus intervals; APB – abductor pollicis-brevis.

stimulation [1,49], suggesting the involvement of different fiber types.

Further, many studies using TMS reported that prolonged low-frequency peripheral electrical stimulation over the nerves induces an increase in corticospinal excitability [50–56]. Electrical stimulation over peripheral nerves can also reduce short-latency afferent inhibition (SAI) reported having an important role in facilitating motor recovery in stroke patients [56–59].

Location of excitability changes

The present study showed a significant decrease in MEP amplitude at long ISIs (200–400 ms). Still, we cannot determine at which neural level these excitability changes occur, either at the cortical level [12,13,50,60,61] or at the spinal level [12,13,30,31,41,47,62]. The results of studies applying electrical stimulation over digits [30,31] suggest that MEP inhibition could be situated at the spinal level at ISIs ranging from

15–30 ms and at the cortical level at ISIs >30 ms. Saito et al. [56] have shown that electrical stimulation over the median nerve elicited at ISIs of 5 and 20 ms significantly increased the amplitude of MEP in the APB muscle and that these alterations are due to both the spinal interneuron and cortical motor changes in corticospinal excitability pathways. In studies modulating MEPs using muscle vibration, an increase in MEP amplitude was demonstrated at ISIs between 9 and 14 ms after the onset of muscle vibration and at ISIs of about 120 ms [12,13], which also points to changes in excitability at the spinal level and/or motor cortical level. Further, vibratory afferent inputs in the periphery can generate evoked potentials in somatomotor cortical areas (occurring around 200–400 ms), supporting the hypothesis that vibratory stimuli may affect the cortical level [8,63].

Study limitations

The present study has some limitations. First, we used the same stimulation parameters for the frequency of the vibrating stimulus and magnetic stimulation pulse with a single site of peripheral stimulation (upper extremity digit II). Future studies might take into account these limitations and investigate MEP modulation with recordings from different agonist and antagonistic hand muscles.

Conclusions

MEP amplitude suppression was detected at ISIs of 200, 300, and 400 ms while applying afferent vibratory stimuli to hand digit preceding the magnetic stimuli to the M1 for the hand muscle representation. The results may find potential neurorehabilitation benefit in neurological patients with increased peak-to-peak amplitude MEPs. Our findings underline the importance of further investigating the activation of somatosensory afferents with the vibration of hand digits for motor cortical plasticity in neurological patients [24,49,64,65]. Recent TMS studies demonstrated increased motor cortex excitability in amyotrophic lateral sclerosis (ALS) and other neurodegenerative diseases [66,67]. Further neurophysiological TMS studies are needed to investigate the neurophysiological background of hand digit vibration and other peripheral inputs (muscle vibration, percutaneous electrical stimulation of nerves and fingers) to reinforce possible implications of our findings in neurorehabilitation of neurological patients.

Conflict of interests

None.

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