Time-course changes in corticospinal excitability for reciprocal muscles during repetitive slow passive movements

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Objective: To examine the time course of changes in corticospinal excitability for reciprocal muscles associated with repetitive slow passive movements.

Methods: Eight neurologically healthy subjects participated in this study. Motor evoked potentials were recorded from the right flexor carpi radialis and extensor carpi radialis muscles with transcranial magnetic stimulation (TMS). Passive movement of the wrist was in a cyclic pattern of extension and flexion through a range of 90° (flexion 45° to extension 45°) at a rate of 0.15 Hz for 50 cycles. TMS was triggered to coincide with the wrist passing at the midrange. We constructed a state-changing model which includes the trend process, autoregressive process, and random variation and assessed the model using the Ljung-box test.

Results: The models were significantly approximated with both muscles, and the trends of the model were negative in both muscles.

Conclusion: Corticospinal excitabilities for reciprocal muscles decrease during repetitive slow passive movements. These effects were related to postexercise cortical depression, which could cause plastic changes in the brain during the motor process.

Key words: repetitive passive movement, corticospinal excitability, time-course change, cortical depression

Introduction

Passive movement exercises are often used in rehabilitation to maintain and improve the range of motion. Furthermore, it is also suggested that these exercises improve motor function for patients who have suffered a stroke[1-3] and improve their proprioceptive function as well.[4,5] Therefore, passive movement is suggested that not only improve range of motion but also affect the improvement of various functions. This phenomenon afforded by passive movements results in the input of afferent activity by the activity of skin receptors, muscle spindles, and joint receptors. These affected the primary sensory areas, primary motor areas, and supplementary movements. For the above, passive movement changes activity of cortical excitability[6-9] and possible modulate excitability of the corticospinal pathway, as well.

Mace et al.[10] reported that the corticospinal excitability increases by 1 Hz in repetitive passive movements over a period of 60 minutes. This is caused by long-term potentiation (LTP) in which repetitive sensory signals of receptors reach the primary motor cortex.[11] On the other hand, Edwards et al.[12] reported that corticospinal excitability decreases during repetitive passive movements from lengthening muscles. They suggested that the exercise cycle and the exercise time were both affected. Miyaguchi et al.[13] reported that corticospinal excitability decreases after 0.5 Hz repetitive passive movement for 10 minutes, and postexercise depression (PED) is caused. PED reduces corticospinal excitability by multiple mechanisms, including long-term depression,

decreased neurotransmitter levels, decreased excitability of intracortical glutamatergic networks, and increased excitability of inhibitory GABAergic networks.[14] This phenomenon is reported as originating in the cortex, because H and F waves which are spinal reflex components are not changed.[15] Furthermore, Sasaki et al.[16] reported that cortical spinal excitability was reduced by the repetitive passive movements of 0.5 Hz, 1.0 Hz, 3.0 Hz, and 5.0 Hz for 10 minutes. They suggested that the rate of decrease depends on the speed and cycle of movement. Furthermore, it has been reported that corticospinal excitability of lengthening muscles is decreased, and that of shortening muscles is increased. This phenomenon suggested that that was caused by reciprocal inhibition.[17-20]

Thus, corticospinal excitability changes caused by passive movements are not constant. There are increases[10] and decreases,[13,16] furthermore, when the joint movement is repeated, the shortening and lengthening muscles alternate with each other as the direction of movement changes. The time-course changes of the shortened muscles relative to the muscles have not been clarified. In daily activities such as brushing teeth, styling hair, washing, and wiping, for a person to perform smooth joint movements, it is necessary to activate reciprocal muscles in a coordinated manner under a slow movement speed. If PED occurs in the corticospinal excitability projecting to the reciprocal muscles by repetitive dynamic joint movements in a slow cycle, it is speculated that the corticospinal excitability decreases in the time course.

Elucidating these provides not only changes in the corticospinal excitability of the main muscles, as in previous reports, but also changes in the corticospinal excitability of the reciprocal muscles involved in repetitive passive movements. Usually, passive movements are used as the purpose to evaluate flexibility based on range of joint motion in rehabilitation therapy. If this study reveals that the changes in corticospinal excitability are associated with joint movements, clues can be obtained associated with the neural control by the cortical spinal cord. Therefore, the purpose of this study was to examine the time-course changes of corticospinal excitability of the reciprocal muscles with repetitive slow passive movements.

Materials and Methods

Subjects
Eight neurologically healthy subjects participated in this study (6 men/2 women, average age 25.4 ± 5.8 years, $21-37$ years). All the subjects met the safety criteria for transcranial magnetic stimulation (TMS)[21] and gave written informed consent to participate. This study was conducted in accordance with the Declaration of Helsinki and was approved by the research ethics committee of Kitasato University School of Health Sciences (2015-024).

Passive movement
Passive movements were controlled by Cybex 770-NORM (Computer Sports Medicine (CSMi), Stoughton, MA, USA). The subjects sat on the experiment chair with the forearm fixed on the support with a band. The joint movement was flexion and extension of the right wrist joint in the pronation position. The zero position was defined as the neutral position of the flexion and extension. During joint movement, repeated 50 times in the $90°$ range from $45°$ to $45°$ and the velocity of motion was controlled at $15°$/sec (0.17 Hz).

Electromyography (EMG)
EMG was recorded from two muscles of each subject: the flexor carpi radialis muscle (FCR) and the extensor carpi radialis muscle (ECR). Surface electrodes were attached to the muscle belly of both muscles, and a ground electrode was attached around the elbow joint. Prior to attaching the electrodes, degreasing with ethanol was performed to reduce skin resistance. EMG signals were digitized by an amplifier (A-DL-720/140, 4ASSIST, Tokyo) and then uploaded into a personal computer via an A/D converter (PowerLab 8/30; AD Instruments, Nagoya, Izumi). The sampling frequency was 1 kHz, and the bandpass filter was $5-1,000$ Hz. Waveforms were analysis using LabChart7 (AD Instruments).

TMS
Motor evoked potentials (MEPs) were recorded from the right FCR and ECR muscles with TMS. TMS is a method for percutaneously stimulating neurons in the brain and is used to evaluate corticospinal excitability and induce excitability changes.[22] The optimal coil position over the left M1 region was defined so that maximum and similar MEPs could be derived from the FCR and ECR muscles. The resting motor threshold (RMT) used was the lowest stimulus intensity that was induced to MEPs with a peak-to-peak amplitude exceeding 50μV in at least 5 of 10 consecutive trials from the FCR. The stimulus intensity during the experiment was 1.2 times of the RMT. The TMS timing during passive movements was the forearm joint $0°$ and controlled by an electronic goniometer (twin axis electrogoniometer; Biometrics, Gwent, UK).

Procedure

The subjects were instructed to relax in the chair, in the sitting position, for all the experimental measurements (Figure 1). Before the MEP measurements, the subjects practiced not to make background effects on the EMG monitor during passive movements. The monitor was removed during MEP measurements.

The MEPs at rest were measured 10 times with the forearm fixed at $0°$ before performing the passive movements (Pre). Subsequently, the MEPs during the passive movements were measured 100 times (Passive). TMS timing was when the forearm passes through $0°$ moved from dorsiflexion to palmarflexion (FCR: shortening; ECR: lengthening) and from palmarflexion to dorsiflexion (FCR: lengthening; ECR: shortening) (Figure 2). After the passive movement, the MEPs at rest were measured 10 additional times with the forearm

fixed at $0°$ (Post).

Statistical analyses

The MEPs were excluded when background effects on the EMG of $20\,\mu$V or more occurred in the 50 msec period before TMS. The MEP data were normalized by linear transformation and expressed as Z scores.

$$Z\ score = \frac{x_i\text{-}M}{s} \qquad \text{(Eq. 1)}$$

where x_i is the MEP amplitude, M is average of MEP amplitude, s is the standard error of the MEP amplitude. Paired-t tests were used to compare the MEP amplitude, before and after the passive movements, and again to compare lengthening and shortening during passive movements.

Furthermore, we constructed a state-changing model, which includes a trend process, autoregressive process, and random variation to fit the temporal dependence structure of a time series as follows:

$$f(t) = \alpha_t + \sum_{i=1}^{p} \phi_i \chi_{t\text{-}i} + \varepsilon_t \qquad \text{(Eq. 2)}$$

where α is the slope of corticospinal excitability, p is the order of the model, ε is the residual of a white noise process, and t is the number of TMSs during repetitive passive movements. If a state-changing model is applicable, the ε value in Equation (2) should be
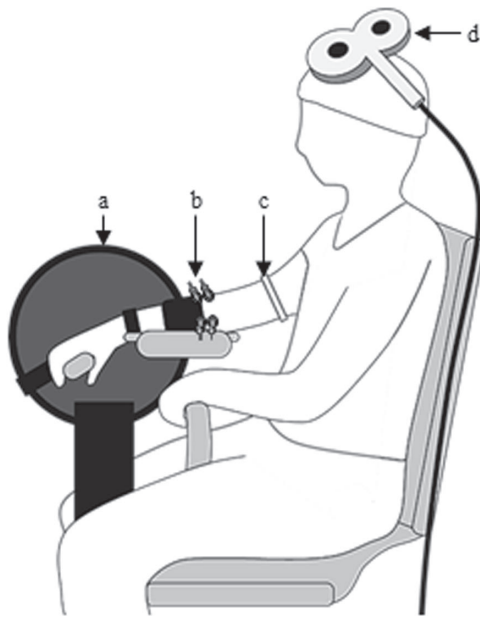

Figure 1. Overall view of the equipment and subject's posture for the measurement of motor evoked potentials (MEPs)

The subjects were instructed to relax in the chair in a sitting position during all the measurements. (a) Cybex 770-NORM; Computer Sports Medicine (CSMi); the joint movement was flexion and extension of the subject's right wrist joint, and the subject's forearm was pronated. (b) Surface electrode, (c) ground electrode; (b) and (c) were attached for the measurement of surface electromyography in the flexor carpi radialis (FCR) and extensor carpi radialis (ECR) muscles. (d) Coil for transcranial magnetic stimulation (TMS); the position of (d) over the left M1 region was defined such that maximum and similar MEPs could be derived from the FCR and ECR muscles.
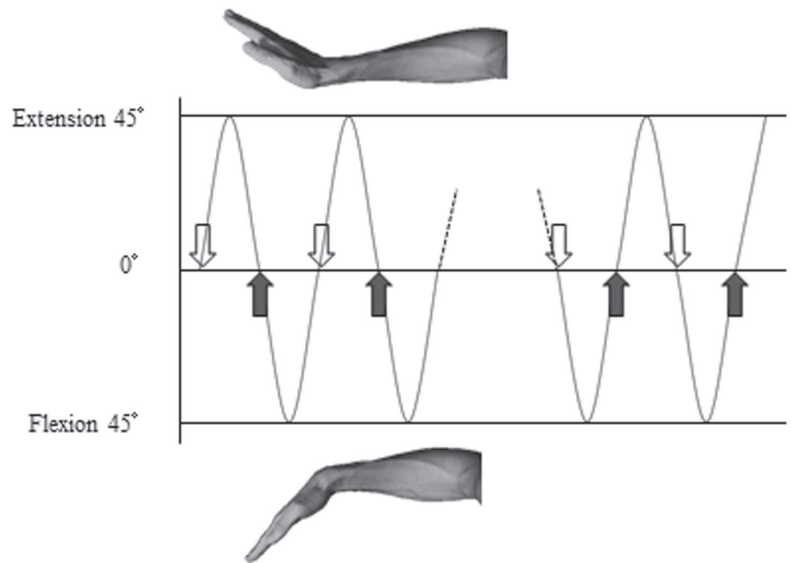

Figure 2. Measurement of corticospinal excitability during passive movements

The timing of TMS during passive movements is when the position of the wrist passed $0°$. MEPs were induced 100 times from flexion to extension (FCR: shortened; ECR: lengthening) and from extension to flexion (FCR: lengthening; ECR: shortening), 50 times each.

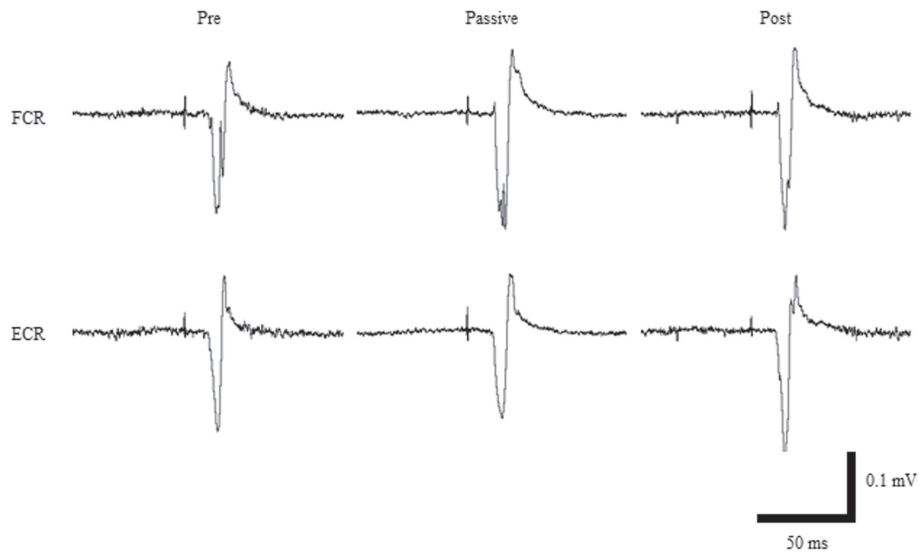Time-course changes in corticospinal excitability for reciprocal muscles

Figure 3. MEP waveforms of one representative subject

Pre, before passive movement; Passive, during passive movement; Post, after passive movement

Table 1. MEP amplitude of all subjects

Subject	FCR			ECR		
	Pre	Passive	Post	Pre	Passive	Post
1	0.12 ± 0.10	0.24 ± 0.32	0.08 ± 0.08	0.18 ± 0.19	0.15 ± 0.14	0.08 ± 0.07
2	0.08 ± 0.05	0.14 ± 0.16	0.11 ± 0.07	0.87 ± 0.42	0.70 ± 0.57	0.84 ± 0.25
3	0.15 ± 0.06	0.15 ± 0.11	0.18 ± 0.09	0.50 ± 0.20	0.66 ± 0.57	0.64 ± 0.23
4	0.44 ± 0.17	0.41 ± 0.30	0.44 ± 0.16	0.44 ± 0.09	0.64 ± 0.24	0.53 ± 0.18
5	0.26 ± 0.15	0.33 ± 0.19	0.41 ± 0.14	0.36 ± 0.19	0.64 ± 0.28	0.44 ± 0.16
6	0.25 ± 0.30	0.41 ± 0.55	0.70 ± 0.49	0.23 ± 0.26	0.52 ± 0.59	0.75 ± 0.22
7	0.13 ± 0.04	0.25 ± 0.21	0.15 ± 0.05	0.20 ± 0.09	0.29 ± 0.21	0.31 ± 0.16
8	0.18 ± 0.09	0.18 ± 0.17	0.12 ± 0.09	0.17 ± 0.08	0.17 ± 0.12	0.12 ± 0.07

Mean ± standard deviation (mV); MEP, Motor evoked potential; FCR, flexor carpi radialis; ECR, extensor carpi radialis; Pre, before passive movement; Passive, during passive movement; Post, after passive movement
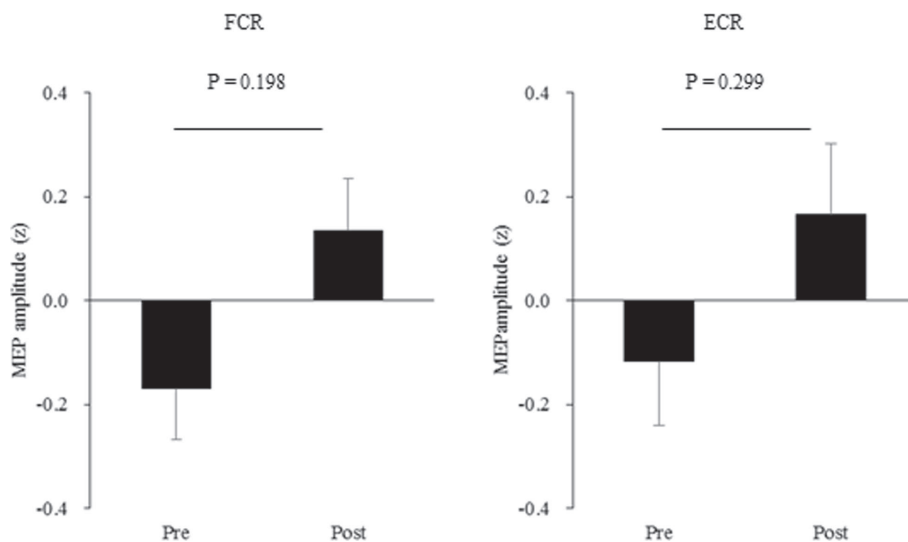

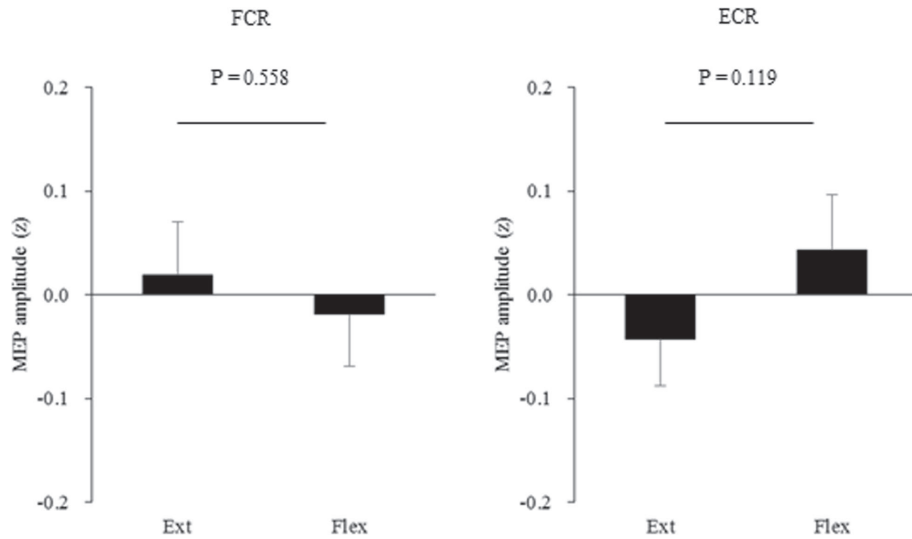**Figure 4.** Pre- and post-MEP amplitude values in FCR and ECR muscles

FCR

ECR

P = 0.558

P = 0.119

Figure 5. MEPs (z value) of shortening and lengthening during passive movements
Ext, extension; Flex, flexion
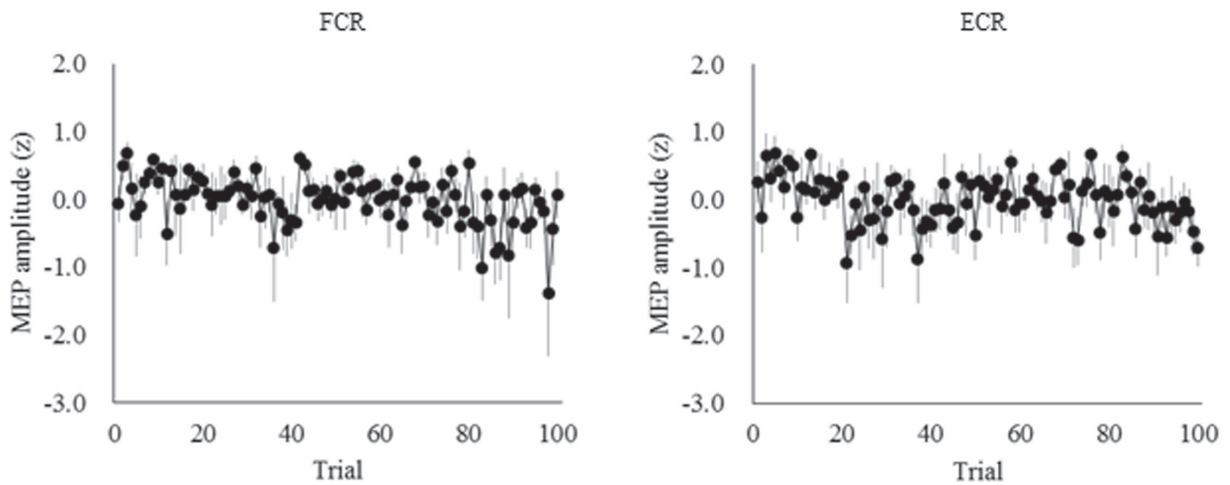
FCR

ECR

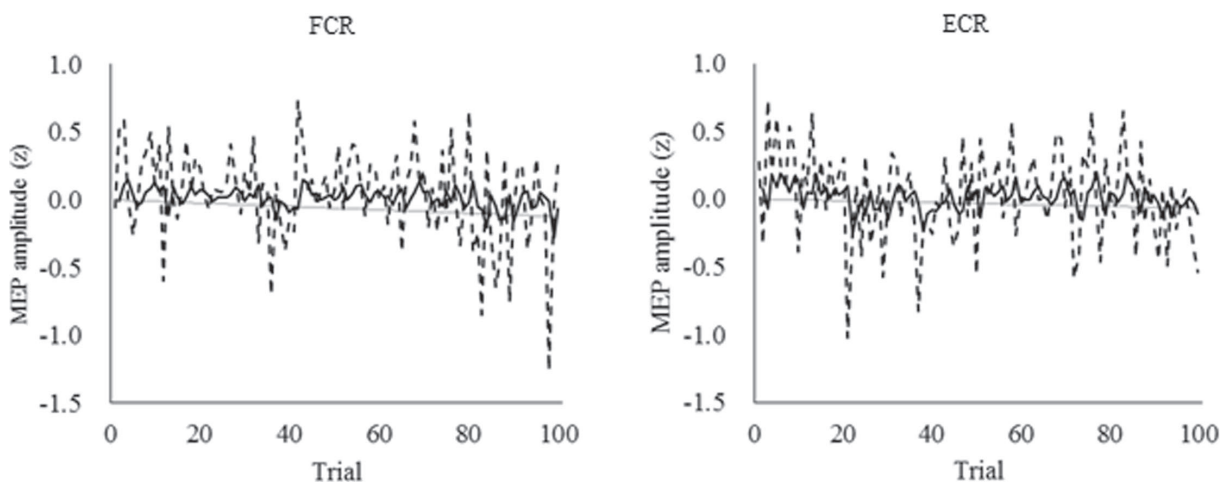**Figure 6.** Time-course changes of MEPs (z value) in FCR and ECR muscles

FCR

ECR

Figure 7. MEPs (z value) by an excitability model. State-changing model, $f(t) = \alpha t + \sum_{i=1}^{p} \phi_i \chi_{t-i} + \varepsilon_t$; gray line, αt; solid line, $\sum_{i=1}^{p} \phi_i \chi_{t-i}$; dashed line, ε_t; α value, (FCR, -0.001; ECR, -0.001); order of time series model (p), (FCR, 1; ECR, 1)

uncorrelated with any other. Therefore, to assess the applicability of the model, the Ljung-Box test was performed to measure the independence of ε as the residual of the white noise process.

Results

MEP waveforms of one representative subject recorded Pre, Post, and during Passive movement are shown in Figure 3. There was no characteristic difference in the peak-to-peak amplitude of MEPs for Pre, Passive, or Post. A total of 78 data (4.9%) were excluded due to background effects on the electromyograms above $20\,\mu$V out of the 1,600 data on MEPs.

Changes in corticospinal excitability before and after passive movement
The average $\pm$ standard deviation of MEP amplitude is shown in Table 1. MEP amplitude between the Pre and Post passive movements were not significant (*t*-test: FCR, P = 0.198, ECR, P = 0.299) (Figure 4).

Differences in corticospinal excitability lengthening and shortening during passive movements
MEP amplitude (z value) between the lengthening and shortening muscles during passive movements were not significant (*t*-test: FCR, P = 0.558, ECR, P = 0.119) (Figure 5).

Time-course changes of corticospinal excitability associated with the excitability-change model
Figure 6 shows the time-course changes of the MEP amplitude (z value) of FCR and ECR. Figure 7 shows the results of splitting components of the MEP amplitude (z value) which was composed of trend (αt), autoregression ($\sum_{i=1}^{p}\phi_i\chi_{t-i}$), and random variable ($\varepsilon_t$). Time-course changes of corticospinal excitability associated with the excitability-change model were significantly approximated with both muscles (Box-Ljung test: FCR, P = 0.966, ECR, P = 0.932). The α values of the trend of the state-change model were negative in both muscles (FCR, -0.001; ECR, -0.001). Furthermore, the order (p) of the time-course change model in autoregression were both 1, indicating that the corticospinal excitability is affected with 1-bin time lag.

Discussion
Changes in corticospinal excitability before and after passive movements
There was no difference in the corticospinal excitability

at rest obtained from FCR and ECR before or after passive movements. Previous studies reported that the corticospinal excitability is reduced by PED.[13,16,23] Sasaki et al.[16] reported that the corticospinal excitability was affected by the speed and cycle of joint movements, and Otsuka et al.[23] reported that the corticospinal excitability affected rest time and attention. Tuiki et al.[24] reported that to cause PED, more than 600 passive movements are necessary. In the present study, the movement speed was slower than that in the previous study and did not produce significant PED during passive movement. PED was originated intracortical phenomenon, and the mechanisms of this reported that long-term depression, decreased neurotransmitter levels, decreased excitability of the glutamatergic network in the cortex, and suppression increased excitability of GABAergic networks has been shown.[14] Teo et al.[15] reported that PED occurs in passive exercises without fatigue, but occurs more strongly in voluntary and heavy exercise. It is presumed that the continuous stimulus in the passive movement on slow movement speed, input to the proprioceptive changes the neural activity in the cortex and causes PED. But, to generate more changes, stronger stimulations (faster speed and larger range of motion) were necessary.

Differences in corticospinal excitability between shortening and lengthening muscles
Corticospinal excitability during passive movements showed no significant differences in MEP amplitude in either the FCR or ECR muscles during lengthening and shortening. It was suggested that that was not affected by muscle lengthening and shortening. Chye et al.[17] reported that MEPs derived from shortening muscles during passive movements increased and derived from lengthening muscles decreased due to the effect of reciprocal inhibition. Reciprocal inhibition changes the excitability of the muscle spindle at the spinal level and causes inhibition of antagonistic muscles. The previous study[17] reported that passive movement speed was 1.0 Hz. However, in the present study, the speed was as low as 0.17 Hz. The slow speed of passive movement did not produce significant activity at the primary nerve ending, and did not show a significant difference between the lengthening and shortening of muscles.

Time-course changes of corticospinal excitability during passive movements
Edwards et al.[16] reported that the MEP amplitude of lengthening muscle during passive movements decreased in time courses. This was the same in the present study.

It was also clarified that the same tendency was observed for MEPs of the shortening muscle. Previous reports suggest that corticospinal excitability is reduced by 10 to 15 minutes of passive repetitive movements at 0.5 Hz and 1.0 Hz, and that involved PED.[13,16] Tuiki et al.[24] reported that to generate PED required more than 600 times of passive movements. These results suggest that when passive movements are performed, PED occurs and corticospinal excitability gradually decreases. In the present study, passive movements were at a slow speed and repeated 100 times (50 repetitive). Although there was no change in corticospinal excitability before or after passive movements, PED occurred even with 100 repetitive passive movements using a slow speed; and it was thought that corticospinal excitability decreased in time courses.

On the other hand, Mace et al.[10] reported that corticospinal excitability increased after 60 minutes of passive movements at 1.0 Hz. This suggested that LTP is involved. They are generated by repetitive afferent input from proprioceptive receptors to the primary motor cortex. However, in the present study, there was no increase in corticospinal excitability during passive movements. This was thought due to the fact that LTP was not generated because of the slow speed 0.17 Hz.

The use of repetitive passive movements for rehabilitation
Passive movements are widely used for neurorehabilitation of stroke, traumatic brain injury, and neurological disorders because the skin receptors, muscle spindles, and joint receptors associated with passive movements cause plastic changes in the brain in the primary sensory area, primary motor area, supplementary motor area, and the occipital lobe.[6-9] Passive movements are expected to have therapeutic effects on the nerve system in addition to improved physical flexibility.[1-3] In the present study, it was considered that corticospinal excitability during passive movement decreased in the time course and PED occurred. In daily activities such as brushing teeth, styling hair, and washing the body, in order to perform smooth movements, it is necessary to activate reciprocal muscles in a coordinated manner at a slow speed.

In the present study, PED occurred in the corticospinal excitability in the reciprocal muscles by repeating slow passive movements. It has been reported that the brain activity changes in the process of learning by repeating exercises, the active site also changes, and the brain activity intensity changes as well.[25] In the present study, it is not clear about the effect of PED associated with repetitive passive movements to motor learning; therefore, this warrants further examination.

In conclusion, we examined the time-course changes of corticospinal excitability of reciprocal muscles with repetitive slow passive movements. As a result, the MEP amplitude of reciprocal muscles with repetitive passive movements approximated the excitability change model, and the corticospinal excitability of reciprocal muscles decreased in a time-course fashion. This is thought to be due to PED, which may cause plastic changes to occur in the brain during the motor process. This study suggests that the effects of repetitive slow passive movements affect not only joint flexibility but also corticospinal neural control.

Conflicts of Interest: None

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