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REGULATION OF PRIMARY MOTOR CORTEX EXCITABILITY BY REPETITIVE PASSIVE FINGER MOVEMENT FREQUENCY

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Abstract—Somatosensory input induced by passive movement activates primary motor cortex (M1). We applied repetitive passive movement (RPM) of different frequencies to test if modulation of M1 excitability depends on RPM frequency. Twenty-seven healthy subjects participated in this study. Motor-evoked potentials (MEPs) elicited by transcranial magnetic stimulation (TMS) to left M1 were recorded from the right first dorsal interosseous muscle (FDI) to assess corticospinal excitability (experiment 1: $n = 15$), and F-waves were measured from the right FDI as an index of spinal motoneuron excitability (experiment 2: $n = 15$). Passive abduction/adduction of the right index finger was applied for 10 min at 0.5, 1.0, 3.0, and 5.0 Hz. Both 0.5 Hz-RPM and 1.0 Hz-RPM decreased MEPs for 2 min ($p < 0.05$), and 5.0 Hz-RPM decreased MEPs for 15 min compared with baseline ($p < 0.05$); however, there was no difference in MEPs after 3.0 Hz-RPM. No F-wave changes were observed following any RPM intervention. Based on the results of experiments 1 and 2, we investigated whether RPM modulates cortical inhibitory circuit using the paired-pulse TMS technique (experiment 3: $n = 12$). Short-interval intracortical inhibition (SICI) was measured using paired-pulse TMS (inter-stimulus interval of 3 ms) before and after 1.0, 3.0, and 5.0 Hz-RPM. Both 1.0 and 5.0 Hz-RPM increased SICI compared with baseline ($p < 0.05$). These experiments suggest that M1 excitability decreases after RPM depending on movement frequency, possibly through frequency-dependent enhancement of cortical inhibitory circuit in M1.

Key words: repetitive passive movement, motor-evoked potential, transcranial magnetic stimulation, short-interval intracortical inhibition.

INTRODUCTION

Passive movement exercises are frequently used for brain injury rehabilitation to maintain or improve mobility and range of motion; they may also induce beneficial and sustained neuroplastic changes. Neuroimaging studies have revealed that passive movements without motor commands activate not only primary somatosensory cortex (S1) but also primary motor cortex (M1) in healthy subjects (Weiller et al., 1996; Xiang et al., 1997; Druschky et al., 2003; Terumitsu et al., 2009; Onishi et al., 2013; Piitulainen et al., 2015). This sensorimotor cortex (SM1) activation in response to passive movement was not observed in patients with severe distal sensory neuropathy, suggesting that peripheral somatosensory afferent activation contributes to SM1 activation (Reddy et al., 2001). Passive movement training with repeated proprioceptive stimulation for several weeks can induce neuroplastic changes of SM1 in both hemiplegic stroke patients (Nelles et al., 2001) and healthy subjects (Carel et al., 2000), although the SM1 activation patterns differ between patients and healthy subjects (Nelles et al., 1999, 2001). Additionally, transcranial magnetic stimulation (TMS) studies have shown modulation of motor-evoked potentials (MEPs) recorded from target muscle, a measure of cortical excitability, after repetitive passive movement (RPM) for several tens of minutes (Mace et al., 2008; Miyaguchi et al., 2013). However, the precise relation between specific RPM parameters and M1 responses is still debatable. For instance, Miyaguchi et al. (2013) reported that RPM to the index finger for 10 min at 0.5 Hz decreased MEP amplitude (indicative of reduced M1 excitability). They concluded that the depression of MEP (Target muscle, first dorsal interosseous muscle) was induced by somatosensory inputs with passive finger movements. In contrast, Mace et al. (2008) reported that RPM to the wrist for 60 min at a mean frequency of 1.0 Hz increases MEP amplitude in forearm muscles. However, no changes were observed in cortical inhibition and facilitation circuits. In another study, McDonnell et al. (2015) performed RPM on 3 consecutive days, and MEPs were measured 5 days after cessation of the RPM. In the results, no changes were observed in MEP amplitudes and Map area and volume (Target muscle, abductor pollicis brevis) after RPM to

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Abbreviations: AMT, active motor threshold; EMG, electromyographic; FDI, first dorsal interosseous; ISI, inter-stimulus interval; MEP, motor-evoked potential; MRI, magnetic resonance imaging; M1, primary motor cortex; PED, post-exercise depression; RM-ANOVA, repeated-measures analysis of variance; RMT, resting motor threshold; RPM, repetitive passive movement; SICI, short-interval intracortical inhibition; SM1, sensorimotor cortex; S1, primary somatosensory cortex; TMS, transcranial magnetic stimulation.

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the thumb for 30 min at 0–240° s^{-1} (McDonnell et al., 2015). Therefore, MEP changes after RPM varied between three previous studies. These previous studies used different movement frequencies, ranges, and durations as well as target muscles, suggesting that RPM parameters differentially modulate M1 excitability.

In the present study, we focused on one RPM parameter, movement frequency, because previous TMS studies using peripheral nerve electrical stimulation and vibratory stimulation demonstrated MEP modulation dependent on stimulation frequency (Naito et al., 2002; Mang et al., 2010; Golaszewski et al., 2012). Thus, movement frequency may be one of the important parameters governing the effects of RPM on M1 excitability. We conducted multiple experiments to investigate the RPM frequency dependence of M1 excitability. The RPM protocol, such as movement frequency, time, and range, were decided on the basis of a previous study (Miyaguchi et al., 2013). We first examined the effects of different RPM frequencies on corticospinal excitability by observing changes in TMS-evoked MEPs (experiment 1). However, these MEP changes reflect alterations in both spinal and cortical neuron, so we also assessed F-waves, which selectively reflect spinal motoneuron excitability (Guiloff and Modarres-Sadeghi, 1991; Fisher, 1996) in experiment 2. Finally, we measured short-interval intracortical inhibition (SICI) in response to paired-pulse TMS (Kujirai et al., 1993) to assess the effect of RPM on cortical inhibitory circuits (experiment 3). This study would provide new knowledge regarding the influences of RPM on M1 excitability by clarifying the effects on MEPs, F-waves, and SICI.

EXPERIMENTAL PROCEDURES

Subjects

Twenty-seven healthy subjects (17 males and 10 females; mean ± standard deviation, 21.0 ± 2.0 years; age range, 20–30 years) participated in this study. Twenty-five subjects were right handed, and two were left handed. All subjects met the safety criteria of the TMS adult safety screen (Keel et al., 2001). All subjects provided written informed consent before participation. This study conformed to the guidelines stated in the Declaration of Helsinki and was approved by the ethics committee of Niigata University of Health and Welfare.

Surface electromyographic recordings

Subjects sat in a comfortable reclining chair with a mounted headrest during all experiments. Surface electromyographic (EMG) activity was recorded from the right first dorsal interosseous (FDI) muscle via disposable Ag/AgCl electrodes (shape, oval; size, 44.3 mm × 22 mm; inter electrode distance, 10 mm) in a belly-tendon montage. EMG data were sampled at 4000 Hz using an A/D converter (Power Lab 8/30, AD Instruments, Colorado Springs, CO, USA), amplified (100×) (A-DL-720-140, 4 Assist, Tokyo, Japan), band-pass filtered (20–1000 Hz), and stored on a personal computer for later off-line analysis.

Motor-evoked potential recordings evoked by transcranial magnetic stimulation

Transcranial magnetic stimulation was performed through a figure-of-eight coil (diameter, 9.5 cm) connected to a Magstim 200 stimulator (Magstim, Dyfed, UK). The coil was held tangentially to the skull over the left M1 area at the location producing the largest and most consistent MEP in the FDI muscle (hotspot) with the handle pointing posterolaterally at 45° to the sagittal plane. The individual position and orientation of the coil were registered according to magnetic resonance imaging (MRI) using the Visor2 TMS Neuronavigation system (eemagine Medical Imaging Solutions GmbH, Berlin, Germany) to ensure the same stimulation location and orientation before and after RPM intervention and across sessions. T1-weighted MR images were obtained using a 1.5-T system before the experiment (Signa HD, GE Healthcare, Milwaukee, WI, USA). The TMS intensity was set to evoke a baseline MEP with peak-to-peak amplitude of approximately 1 mV in the FDI muscle at an inter-stimulus interval (ISI) of 5.0 s (0.2 Hz).

Paired-pulse stimulation

Short-interval intracortical inhibition was measured using a TMS double-stimulation protocol including 3 ms ISI revealing inhibitory effects (Kujirai et al., 1993). For induction of SICI, a first subthreshold conditioning stimulation is followed almost immediately (ISI = 3 ms) by a second suprathreshold test stimulation. Paired-pulse stimuli were delivered through a figure-of-eight coil (diameter, 9.5 cm) connected to two Magstim 200 stimulators via a Bistimu module (Magstim, Dyfed, UK). Prior to experiments, we determined the resting motor threshold (RMT), defined as the minimum stimulation intensity that elicited a MEP of no less than 50 μV in 5 of 10 trials in the relaxed FDI muscle, and the active motor threshold (AMT), defined as the minimum stimulation intensity that elicited a MEP of no less than 200 μV in 5 of 10 trials while subjects maintained approximately 5% maximum voluntary contraction of the FDI muscle (Ridding et al., 1995). The first conditioning stimulation for SICI was delivered at 70% of AMT (Nitsche et al., 2005; Kidgell et al., 2013). Kujirai et al. (1993) first used RMT for conditioning stimulation intensity. However, 70% of the AMT was selected in this study because the inhibitory effect of the RMT was very strong. The second suprathreshold test stimulation 3 ms after the first was delivered at 115%, 120%, 125%, and 130% of RMT (for reasons specified below).

Passive movement task

The passive movement task was applied using a custom-made device consisting of a controller (Fig. 1A) for setting the movement velocity and range, and a motor device to deliver the set passive movement sequence (Fig. 1B). The movement device was comprised of a plastic plate, rotating plate, and stepper motor. Subjects placed their right palm on the plastic plate, aligning the center of the metacarpophalangeal joint of the right index finger to the