Somatosensory Inputs Induced by Passive Movement Facilitate Primary Motor Cortex Excitability Depending on the Interstimulus Interval, Movement Velocity, and Joint Angle

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Abstract—Somatosensory inputs affect primary motor cortex (M1) excitability; however, the effect of movement-induced somatosensory inputs on M1 excitability is unknown. This study examined whether M1 excitability is modulated by somatosensory inputs with passive movement in 29 healthy subjects. Motor-evoked potentials (MEPs), elicited by transcranial magnetic stimulation (TMS) were recorded from the first dorsal interosseous (FDI) muscle (Experiment 1). M- and F-waves were measured from the FDI muscle (Experiment 2). Passive movements of the index finger were performed in the adduction direction. TMS pulses were preceded by starting passive movements with interstimulus intervals (ISIs) of 30, 60, 90, 120, 150, 180, and 210 ms. TMS or electrical stimulation was performed in the midrange of the metacarpophalangeal joint during passive movements. MEPs were significantly facilitated at 90, 120, and 150 ms (p < 0.05). No M- or F-wave changes were observed for any ISI. In addition, we investigated whether MEP changes were dependent on passive movement velocity and joint angle. Passive movement was performed at two movement velocities (Experiment 3) or joint angles (Experiment 4). MEP facilitation was observed depending on the movement velocities or joint angles. These experiments demonstrated that somatosensory inputs induced by passive movements facilitated M1 excitability depending on the ISIs, passive movement velocity, and joint angle. © 2018 The Authors. Published by Elsevier Ltd on behalf of IBRO. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Key words: passive movement, motor-evoked potential, afferent facilitation, somatosensory input, movement velocity, joint angle.

INTRODUCTION

Motor control is coordinated by somatosensory information from the limbs (Rothwell et al., 1982; Sanes et al., 1984), and primary motor cortex (M1) excitability is modulated by somatosensory input (Chen et al., 1999; Tokimura et al., 2000; Turco et al., 2017). Indeed, this M1 modulation can be observed by neurophysiological methods using transcranial magnetic stimulation (TMS), which can non-invasively evaluate corticospinal excitability in humans. Previous studies have shown that motor-evoked potentials (MEPs) induced by TMS are reduced at approximately 20 ms when they are preceded by sensory nerve stimulation for the fingers or mixed nerve stimulation for the median nerve (Tokimura et al., 2000; Di Lazzaro et al., 2005; Tamburin et al., 2005) and are facilitated at intervals of approximately 40–80 ms (Komori et al., 1992; Devanne et al., 2005; Degardin et al., 2011; Kojima et al., 2014). These two time-dependent phases are known as short-latency afferent inhibition (SAI) and afferent facilitation (AF), respectively, and have been used to explore sensorimotor integration in humans (Sailer et al., 2003; Kessler et al., 2005; Degardin et al., 2011; Cash et al., 2015; Bocquillon et al., 2017; Dubbioso et al., 2017; Lei and Perez, 2017).

In previous studies, peripheral nerve electrical stimulation has been used to induce SAI (Bailey et al., 2016; Ruddy et al., 2016) and AF (Komori et al., 1992; Bocquillon et al., 2017). This means that somatosensory input evoked by electrical stimulation reaches to the M1 through sensory nerves, which contribute to M1 excitability changes. However, it is unclear whether somatosensory input induced by movement affects M1 excitability as well as peripheral nerve electrical stimulation. In this study, we investigated the effect of somatosensory input induced by movement on M1 excitability. We used TMS to assess M1 excitability, and passive movement was used to elicit somatosensory input with movement. Our previous study showed that M1 excitability increases 125 ms after starting passive movements of the index
finger, suggesting that somatosensory input with passive movements evoke AF (Nakagawa et al., 2017). However, it remains unclear whether passive movements evoke SAI and AF depending on the time between the start of passive movements and TMS. We believed that the time between the start of passive movements and TMS as well as peripheral nerve electrical stimulation affect M1 excitability changes.

Somatosensory inputs with passive movement include various sensory stimuli, including those involving cutaneous, muscle spindle, and joint receptors (Xiang et al., 1997; Mima et al., 1999); these somatosensory inputs are processed by the primary somatosensory cortex (Kaas, 2004). However, somatosensory inputs from muscle spindles reach not only primary somatosensory cortex but also M1 (Lucier et al., 1975; Zarzecki et al., 1978). In addition, previous studies have reported that cutaneous, muscle spindle, and joint receptors (Xiang et al., 1997; Mima et al., 1999); these somatosensory inputs are processed by the primary somatosensory cortex (Kaas, 2004). However, somatosensory inputs from muscle spindles reach not only primary somatosensory cortex but also M1 (Lucier et al., 1975; Zarzecki et al., 1978). In addition, previous studies have reported that somatosensory inputs from muscle spindles reach not only primary somatosensory cortex but also M1 (Lucier et al., 1975; Zarzecki et al., 1978). In addition, previous studies have reported that somatosensory inputs from muscle spindles reach not only primary somatosensory cortex but also M1 (Lucier et al., 1975; Zarzecki et al., 1978). In addition, previous studies have reported that somatosensory inputs from muscle spindles reach not only primary somatosensory cortex but also M1 (Lucier et al., 1975; Zarzecki et al., 1978).

The aims of this study were to (1) reveal whether M1 excitability depends on the time between the start of passive movement and TMS (Experiments 1 and 2) and (2) reveal whether M1 excitability modulation depends on movement velocity (Experiment 3) and the joint angle of passive movement (Experiment 4).

EXPERIMENTAL PROCEDURES

Subjects
We recruited a total of 29 right-handed healthy subjects (24 men and 5 women; mean ± standard deviation, 23.1 ± 4.2 years; age range, 20–43 years) in this study. Handedness was confirmed using the Edinburgh handedness inventory (Oldfield, 1971). The results showed that all subjects were right-handed (score mean ± standard deviation, 91.1 ± 15.4), with no history of neurological or psychiatric disorders. TMS was performed in accordance with current TMS safety guidelines (Rossi et al., 2009). This study conformed to the Declaration of Helsinki and was approved by the ethics committee of Niigata University of Health and Welfare.

Surface electromyography
Subjects sat in a comfortable reclining chair with a mounted headrest during all experiments. Surface electromyography (EMG) was recorded from the right first dorsal interosseous (FDI) muscle via disposable Ag/AgCl electrodes 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. EMG recording always was conducted in online mode during passive movement to confirm background EMG activity.

M- and F-wave recordings evoked by TMS
TMS 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. This position served to activate the corticospinal system trans-synaptically via horizontal cortico-cortical connections (Di Lazzaro et al., 2008). The individual position and orientation of the coil were registered according to magnetic resonance imaging using a Visor2 TMS Neuronavigation system (Emerge Medical Imaging Solutions GmbH, Berlin, Germany) to ensure the same stimulation location and orientation. T1-weighted MR images were obtained using a 1.5-T system before the experiments (Signa HD, GE Healthcare, Milwaukee, WI, USA). The TMS intensity was set to evoke a baseline MEP with a peak-to-peak amplitude of approximately 1 mV in the FDI muscle, at an intertrial interval of 5.0 s. Subjects kept their eyes open with their attention directed to a fixed point on a black monitor in front of them and were instructed to relax.

Passive movement task
The passive movement task was performed using a custom-made device consisting of a controller for setting the movement velocity and range and a motor device to deliver the set passive movement sequence. The movement device was composed 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 rotary shaft of the motor. The zero position was defined as the intermediate position of the metacarpophalangeal joint. The right index finger was fixed by a belt attached to the rotating plate and moved passively in the adduction direction from Y° to 10° adductions based on the anatomical limb position (the explanation of Y° is given below).
**Experiment 1: The effect of interstimulus interval between the start of the passive movement and TMS on MEPs**

Twenty healthy subjects (17 men and 3 women; mean ± standard deviation, 23.0 ± 1.8 years; age range, 21–25 years) participated in Experiment 1. The purpose of Experiment 1 was to investigate whether somatosensory input induced by passive movement affected corticospinal excitability depending on the time between the start of the passive movement and TMS. The schema of Experiment 1 is shown in Fig. 1. Passive movements of the index finger in the adduction direction were performed at a velocity of 80°C/s based on our previous study (Nakagawa et al., 2017). The interstimulus interval between the start of the passive movement and TMS (ISI_mep) was set at 30, 60, 90, 120, 150, 180, and 210 ms. We selected these ISIs, from 30 to 210 ms, because they were predicted to elicit SAI and AF by peripheral nerve electrical stimulation. In this study, the abduction angle (−) of the index finger for the starting position was regulated in each ISI to give a TMS in the intermediate position of the index finger \(Y = -2.4^\circ (30\text{ ms}); -4.8^\circ (60\text{ ms}); -7.2^\circ (90\text{ ms}); -9.6^\circ (120\text{ ms}); -12.0^\circ (150\text{ ms}); -14.4^\circ (180\text{ ms});\) and \(-16.8^\circ (210\text{ ms})\) because MEPs may change depending on joint angle position of the index finger. The MEPs at rest were recorded 20 times before the passive movement task. In the passive movement task, MEPs were recorded 20 times for each ISI in randomized order per ISI.

The modulation of corticospinal excitability was induced by repeat pairs of electrical stimulation to the peripheral nerve and TMS in a specific fixed ISI (approximately 21–25 ms) that was known from the paired associative stimulation protocol (Stefan et al., 2004). MEPs may be modulated by both passive movement and TMS. Therefore, we measured resting MEPs after the passive movement task.

**Experiment 2: The effect of interstimulus interval between the start of the passive movement and peripheral nerve electrical stimulation on M- and F-waves**

Eighteen healthy subjects (14 men and 4 women; mean ± standard deviation, 23.4 ± 5.1 years; age range, 21–43 years) participated in Experiment 2. The purpose of Experiment 2 was to investigate whether somatosensory input induced by passive movement affected peripheral and spinal motoneuron responses depending on the time between the start of passive movement and electrical stimulation to the ulnar nerve. The passive movement task was used in the same manner as Experiment 1. The abduction angle of the index finger for the starting position was regulated for each ISI to give electrical stimulation in the intermediate position of the index finger. However, the ISI (ISI_el) was not the same for Experiment 1 because the parts of stimulation differed between the experiments (M1 vs. ulnar nerve), e.g., the timing of the activated spinal motoneurons was different between the experiments. Therefore, we calculated MEP and M- and F-wave latencies for individual subjects and regulated ISI_el to activate the spinal motoneurons with similar timing as...
that in Experiment 1 (Fig. 2). We used the following formulas according to a previous study (Shulga et al., 2015):

\[
A = \text{MEP latency (conduction time from M1 to recording electrode)}
\]

\[
B = \frac{\text{F-wave latency} - \text{M-wave latency}}{2} \quad \text{(conduction time from electrical stimulation for the ulnar nerve to the spinal motoneurons)}
\]

\[
C = \frac{\text{F-wave latency} + \text{M-wave latency}}{2} \quad \text{(conduction time from spinal motoneurons to the recording electrode)}
\]

\[
\text{ISI}_{el} = \text{ISI}_{mep} + (A - C) - B
\]

Electrical stimulation at rest was performed 50 times before the passive movement task. In the passive movement task, electrical stimulation was recorded 50 times for each ISI in a randomized order per ISI. Moreover, electrical stimulation at rest was also performed 50 times after the passive movement task. The ISI_el used in Experiment 2 was adjusted for individual subjects in the range of 21–25, 51–55, 81–85, 111–115, 141–145, 171–175, and 201–205 ms.

**Experiment 3: The effect of passive movement velocity on MEPs**

Fifteen healthy subjects (12 men and 3 women; mean ± standard deviation, 24.1 ± 5.5 years; age range, 20–43 years) participated in Experiment 3. The purpose of Experiment 3 was to investigate whether passive movement affected corticospinal excitability depending on movement velocity. The schema of Experiment 3 is shown in Fig. 3. Passive movements of the index finger in the adduction direction were performed at velocities of 40°/s and 160°/s (slow velocity vs. fast velocity). The ISI_mep was set at 30, 90, and 150 ms. In this study, the abduction angle (−) of the index finger for the starting position was regulated for each ISI and movement velocity to give TMS of the intermediate position of the index finger \([Y_1 (40°/s) = -1.2° (30 ms); -3.6° (90 ms); -6.0° (150 ms); Y_2 (160°/s) = -4.8° (30 ms); -14.4° (90 ms); and -24.0° (150 ms)]\). The MEPs at rest were recorded 20 times in two sets before the passive movement task. In the passive movement task, MEPs were recorded 20 times for each ISI and movement velocity in randomized order per ISI × movement velocity.

**Experiment 4: The effect of passive movement angle on MEPs**

Fifteen healthy subjects (12 men and 3 women; mean ± standard deviation, 22.5 ± 1.6 years; age range, 21–25 years) participated in Experiment 4. The purpose of Experiment 4 was to investigate whether passive movement affected corticospinal excitability depending on joint angle. The schema of Experiment 4 is shown in Fig. 4. Passive movements of the index finger in the adduction direction were performed at a velocity of 80°/s. The ISI_mep was set to 30, 90, and 150 ms. In this study, the abduction (−) or adduction angle (+) of the index finger for the starting position was regulated for each ISI and joint angle to give TMS in the 10° abduction or 10° adduction position of the index finger \([Y_1 (10° \text{ abduction}) = -12.4° (30 ms); -17.2° (90 ms); -22.0° (150 ms); Y_2 (10° \text{ adduction}) = 7.6° (30 ms); 2.8° (90 ms); and -2.0° (150 ms)]\) (shortening position vs. extension position for the FDI muscle). The MEPs at rest were recorded 20 times for each position (intermediated position, 10° abduction position, and 10° adduction position) before the passive movement task to confirm potential changes by the effect of joint angle in the rest. In the passive movement task, MEPs were recorded 20 times for each ISI and joint angle in randomized order per ISI × joint angle.

**Data analysis and statistics**

We used LabChart 7 software (AD Instruments) for the analysis of MEPs and M- and F-waves. The peak-to-peak amplitudes of 20 MEPs and 50 M-waves were averaged for
the resting conditions and for each ISI within the subjects. The peak-to-peak amplitudes of the F-waves were also averaged for the resting conditions and each ISI. F-wave persistence (%) was calculated based on the F-wave amplitude that elicited an EMG response of more than 50 μV. A single sweep was inspected visually, and trials with artifacts were rejected if the root mean square background EMG activity exceeded 30 μV.

In Experiment 2, the latencies of MEP and M- and F-waves was defined as the onset of the response where the signal deviated from the baseline (Shulga et al., 2015).

Statistical analysis was performed using PASW statistics software version 21 (SPSS; IBM, Armonk, NY, USA). A one-way repeated-measures ANOVA was performed to determine the effect of ISI (eight ISIs) on the MEP amplitude, M-wave amplitude, F-wave amplitude, and F-wave persistence in Experiments 1 and 2. Paired t-test was used to compare the MEP amplitude, M-wave amplitude, F-wave amplitude, and F-wave persistence before and after the passive movement task. In Experiment 3, the resting MEPs were recorded 20 times in two sets and randomly allocated for each baseline. A two-way repeated-measures ANOVA was performed to determine the effect of movement velocity (40°/s or 160°/s) and ISI (baseline, ISI_30, 90, and 150 ms) on the MEP amplitude. The resting MEPs recorded at the abduction and adduction positions were allocated for each baseline. A two-way repeated-measures ANOVA was performed to determine the effect of joint angle (10° abduction position and 10° adduction position) and ISI (baseline, ISI_30, 90, and 150 ms) on the MEP amplitude in Experiment 4. We calculated an effect size (η^2) for all results of the ANOVA. When the Mauchly test of sphericity could not be assumed, the Greenhouse–Geisser correction statistic was used. When a significant main effect or interaction was found, Bonferroni’s post hoc analysis for ISI was used to test for significant comparison. Post-hoc paired t-tests were also performed to compare the movement velocity or joint angle for each ISI in Experiments 3 and 4. Significance was set at p < 0.05.

RESULTS

Experiment 1: The effect of interstimulus interval between the start of the passive movement and TMS on MEPs

Fig. 5 shows the MEP amplitude and trigger setting of TMS and passive movement measured for each ISI (baseline, ISI_30, 60, 90, 120, 150, 180, and 210 ms) in a representative subject. Fig. 6 plots the average (±SE) of MEP amplitude for all subjects (n = 20). The TMS intensity (mean ± SD) of all subjects was 55.9 ± 7.0%. A one-way repeated-measures ANOVA showed a significant effect of ISI (F_{3,632} = 8.744, p < 0.001, η^2 = 0.315) on MEP amplitude. Post-hoc analysis showed the MEP amplitude increased at ISI_90, 120, and 150 ms compared with baseline (p < 0.05). Paired t-tests showed no significance between baseline and post (baseline, 1.00 ± 0.01 mV; post, 1.00 ± 0.03 mV).

Experiment 2: The effect of interstimulus interval between the start of the passive movement and peripheral nerve electrical stimulation on M- and F-waves

We calculated MEP and M- and F-wave latencies for individual subjects to activate the spinal motoneurons with similar timing as that in Experiment 1. The mean...
Experiment 3: The effect of passive movement velocity on MEPS

Fig. 8 shows the average (±SE) of MEP amplitude for all subjects measured at each movement velocity (40°/s and 160°/s) and ISI (baseline, ISI_30, 90, and 150 ms; n = 15). The TMS intensity (mean ± SD) of all subjects was 55.5 ± 7.0%. A two-way repeated-measures ANOVA showed a significant effect of movement velocity (F_7, 14 = 42.714, p < 0.001, η^2_p = 0.753), ISI (F_3, 42 = 42.538, p < 0.001, η^2_p = 0.752) and in their interaction (F_21, 84 = 44.731, p < 0.001, η^2_p = 0.762) on MEP amplitude. For movement velocity, post hoc analysis showed that no MEP changes were observed between the 40°/s and 160°/s velocities in baseline, but MEP changes were observed between the 40°/s and 160°/s velocities each ISI (p < 0.05). In the ISI for 40°/s, post hoc analysis showed that the MEP increased at ISI_90 ms compared with baseline (p < 0.05), but no MEP changes were observed at either ISI_30 and 150 ms compared with baseline. In the ISI for 160°/s, post hoc analysis showed that the MEP decreased at ISI_30 ms compared with baseline (p < 0.05), and the MEP increased at ISI_90 and 150 ms compared with baseline (p < 0.05).

Experiment 4: The effect of passive movement angle on MEPS

Fig. 9 shows the average (±SE) of MEP amplitude for all subjects measured for each movement position (intermediated position, 10° abduction position, 10° adduction position) and ISI (baseline, ISI_30, 90, and 150 ms; n = 15). The TMS intensity (mean ± SD) for all subjects was 53.2 ± 7.2%. A one-way repeated-measures ANOVA showed no significant effect of joint angle (F_2, 28 = 0.950, p = 0.399, η^2_p = 0.064) on the MEP amplitude at rest (intermediated position, 1.01 ± 0.01 mV; 10° abduction position, 1.02 ± 0.02 mV; 10° adduction position, 0.99 ± 0.02 mV). A two-way repeated-measures ANOVA showed a significant effect of joint angle (F_2, 28 = 7.054, p = 0.019, η^2_p = 0.335), ISI (F_3, 42 = 11.938, p < 0.001, η^2_p = 0.460) and in their interaction (F_6, 84 = 3.114, p = 0.036, η^2_p = 0.182) on MEP amplitude. For joint angle, post hoc analysis indicated no MEP changes between the 10° abduction and 10° adduction positions at each of baseline and ISI_30 ms, but MEP changes were observed between the 10° abduction and 10° adduction positions in each ISI_90 and 150 ms (p < 0.05). In the ISI for the 10° abduction position, post hoc analysis showed that the MEP

latencies (±SE) of the MEP and M- and F-waves were 20.8 ± 0.3, 4.8 ± 0.1, and 27.8 ± 0.4 ms, respectively. The mean ISI_el (±SE) for all subjects were 23.1 ± 0.24, 53.1 ± 0.24, 83.1 ± 0.24, 113.1 ± 0.24, 143.1 ± 0.24, 173.1 ± 0.24, and 203.1 ± 0.24 ms, respectively. Moreover, the mean electrical stimulation intensity (mean ± SD) was 15.1 ± 3.7 mA; no subjects reported feeling pain.

Fig. 7 plots the average (±SE) of M- and F-wave amplitude and F-wave persistence for all subjects (n = 18). A one-way repeated-measures ANOVA showed no significant effect of ISI (F_{7, 119} = 0.742, p = 0.636, η^2_p = 0.042) on the M-wave amplitude. Similarly, a one-way repeated-measures ANOVA showed no significant effect of ISI (F_{7, 119} = 1.210, p = 0.302, η^2_p = 0.066) on the F-wave amplitude. Moreover, a one-way repeated-measures ANOVA showed no significant effect of ISI (F_{7, 119} = 1.137, p = 0.345, η^2_p = 0.063) on F-wave persistence. Paired t-tests for M- and F-wave amplitudes and the F-wave persistence showed no significance between baseline and post (M-wave amplitude: baseline, 13.84 ± 0.86 mV; post, 14.09 ± 0.71 mV; F-wave amplitudes: baseline, 0.15 ± 0.01 mV, post, 0.14 ± 0.02 mV; F-wave persistence: baseline, 51.2 ± 7.2%, post, 45.8 ± 7.4%).
increased at ISI_90 ms compared with baseline (p < 0.05), but no MEP changes were observed at ISI_30 and 150 ms compared with baseline. In the ISI for the 10° adduction position, post hoc analysis showed that the MEP increased at ISI_90 and 150 ms compared with baseline (p < 0.05), but no MEP changes were observed at ISI_30 ms compared with baseline.

**DISCUSSION**

Our study investigated the influence of somatosensory inputs induced by passive movement on M1 excitability by applying TMS to the M1. We provide novel evidence for the effects of ISI, passive movement velocity, and joint angle on M1 excitability.

In this study, MEPs induced by TMS were increased 90, 120, and 150 ms after passive movement, and thus ISI-dependent MEP changes were observed between the start of passive movement and TMS. Our previous study reported that the MEP increased after 125 ms from the start of passive movement of the index finger (Nakagawa et al., 2017); however, it remained unclear whether MEP modulation depends on ISI. Several previous studies have reported about the effects of somatosensory input induced by electrical stimulation on M1 excitability. For example, MEP depression occurs at approximately 20–30 ms after peripheral nerve electrical stimulation (Tokimura et al., 2000; Di Lazzaro et al., 2005; Tamburin et al., 2005), and MEP facilitation occurs at approximately 40–80 ms after peripheral nerve electrical stimulation (Komori et al., 1992; Devanne et al., 2009; Degardin et al., 2011; Kojima et al., 2014), which is known as SAI and AF. These studies revealed a time-dependent change of MEP between electrical stimulation and TMS. The present study also revealed a time-dependent change of MEP between passive movement and TMS.
and TMS. In the present study, MEP facilitation was observed 90, 120, and 150 ms after starting passive movement, suggesting that somatosensory input with passive movement elicits AF. However, AF induced by electrical stimulation occurs at approximately 40–80 ms after electrical stimulation (Komori et al., 1992; Devanne et al., 2009; Degardin et al., 2011; Kojima et al., 2014); thus, the AF latencies are different between our study, which used passive movement, and previous studies, which used electrical stimulation. We considered that the difference in induction methods of somatosensory input for passive movement and electrical stimulation may affect AF latency. Electrical stimulation stimulates sensory or mixed nerves directly, but passive movement stimulates these nerves indirectly. Neuroimaging studies used magnetoencephalography have shown that the first peak of the somatosensory evoked magnetic field appears at approximately 21–22 ms after median nerve stimulation for the wrist (Onishi et al., 2016), but the first peak appeared at approximately 35–40 ms after extension passive movement of the index finger (Onishi et al., 2013; Sugawara et al., 2016). Therefore, somatosensory input induced by passive movement takes approximately twice the time to arrive at the cerebral cortex compared with electrical stimulation, and thus, AF latency of passive movement would be late compared with the AF latency of electrical stimulation. Due to the above reasons, we believe that MEP facilitation elicited by passive movement also reflects AF, and our results showed that MEP changes are dependent on ISI.

The MEP increased 90, 120, and 150 ms after starting the passive movement, but M- and F-waves remained unchanged. The MEP reflects corticospinal excitability, while M- and F-waves reflect muscle, neuromuscular junction, or spinal motoneuron response. This study confirmed only MEP modulation; therefore, we conclude that M1 excitability appears to change. In fact, AF and SAI induced by electrical stimulation originate at the cortical level (Tokimura et al., 2000; Devanne et al., 2009). Moreover, neuroimaging studies have reported that M1 is activated by passive movement in healthy subjects (Weiller et al., 1996; Xiang et al., 1997; Onishi et al., 2013; Piitulainen et al., 2015; Sugawara et al., 2016). In Experiment 2, we calculated MEP and M- and F-wave latencies because the timing of the activation of spinal motoneurons differed between TMS to the M1 and electrical stimulation to the ulnar nerve. We used the formula in Fig. 2 in order to activate the spinal motoneurons at the same time from the initiation of passive movement between TMS and electrical stimulation. Therefore, we could examine, in real time, the effect of passive movement on the activation of the spinal motoneuron between TMS and electrical stimulation.
No MEP or M- and F-wave changes were observed before and after the passive movement task. Previous studies have shown that the modulation of corticospinal excitability is induced by repeat pairs of electrical stimulation to peripheral nerves and TMS in specific fixed ISI (approximately 21–25 ms) that were known as the paired associative stimulation protocol (Stefan et al., 2002, 2004). We needed to evaluate the effect before and after the passive movement task because MEP or M- and F-wave change may occur during repeat pair stimulations of passive movement and TMS. We believed that if these repeat pairs stimulation affect MEP or M- and F-wave, this study cannot accurately examine the effect of passive movement task on M1. However, the effect was not confirmed before and after the passive movement task by a combination with passive movement and TMS; therefore, we think that these measurements were able to be performed in a felicitous manner.

Our study revealed that AF induced by passive movement depends on movement velocity and the joint angle of passive movement. We hypothesized that AF depends on the movement velocity and the joint angle of passive movement if somatosensory input from the muscle spindle involved in AF is induced by passive movement. Muscle spindle activity has been shown to increase with faster movement (Burke et al., 1978; Edin and Abbs, 1991) or longer muscle extension (Cordo et al., 2002). AF increased at a 160°/s velocity compared with a 40°/s velocity and increased at the 10° adduction compared with the 10° abduction (e.g., 10° abduction was extended longer for the FDI muscle compared with 10° abduction). However, no MEP changes were confirmed in the midrange, 10° adduction, or 10° abduction of the index finger at rest conditions, suggesting that MEP changes induced by passive movement can exclude the effect of the index finger position in Experiment 4. From these results, it appears that AF involves in somatosensory input from the muscle spindle because the muscle spindle activity depends on movement velocity and muscle extension. Passive movement of 160°/s velocity elicited SAI, but the 40°/s velocity did not. We speculate that muscle spindle activity also participates in SAI because SAI depends on movement velocity, similar to AF. This study predicted high muscle spindle activity at 160°/s velocity compared with 40°/s velocity. Therefore, the amount of somatosensory input is large passive movement of 160°/s velocity compared with 40°/s velocity. We believe this factor affects the emergence of SAI.

Cutaneous nerve stimulation not including muscle spindle activity can also elicit AF and SAI (Classen et al., 2000; Tamburin et al., 2005; Kojima et al., 2014; Ruddy et al., 2016). These reports indicate that somatosensory inputs from each muscle spindle and cutaneous participate in the generation of AF and SAI. However, our study showed that AF was modulated depending on movement velocity and the joint angle of passive movement and that SAI depends on movement velocity. These findings suggest that the AF and SAI observed in our study were strongly influenced by the somatosensory input from the muscle spindle. However, we did not examine movement velocity and joint angle effects on long latency ISIs, such as ISI_180 ms and 210 ms; these effects should be investigated in future studies to elucidate the detailed effect of passive movement on M1 excitability.
CONCLUSION

In summary, the present data provide that somatosensory input induced by passive movement affected MEPs depending on the ISI between the start of passive movement and TMS (Experiment 1). However, no M- and F-wave changes were observed, indicating that the muscle, neuromuscular junctions, and motoneuron responses were not affected during passive movement (Experiment 2). The MEP changes also were induced depending on movement velocity and the joint angle of passive movement (Experiments 3 and 4). We believe that the MEP facilitation with passive movement was due to the enhancement of M1 excitability, suggesting that this phenomenon includes AF as well as AF elicited by peripheral nerve electrical stimulation. The AF changes were observed depending on movement velocity and the joint angle of passive movement, indicating that somatosensory input from the muscle spindle affects the M1 facilitation. The novel findings of this study should provide new insight into the neurophysiological mechanisms underlying sensorimotor integration, such as reaching behavior (Georgopoulos et al., 2007; Merchant et al., 2008) or motor learning (Pavilides et al., 1993) in humans.

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CONFLICTS OF INTEREST

The author declares no conflicts of interest.

CONTRIBUTIONS OF AUTHORS

HO and RS conceived the study and designed the experiments. RS and ST performed the experiments. SM and SK performed data interpretation. RS and ST performed the experiments. HO and RS wrote the final manuscript. HO and RS conceived the study and designed the writing the manuscript. HO and RS wrote the SM and SK performed data interpretation. RS and ST

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