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Effect of sensory inputs on the motor evoked potentials in the wrist flexor muscle during the robotic passive stepping in humans*

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Abstract— **The purpose of this study was to reveal whether the stepping-related afferent feedback modulates the motor evoked potentials (MEPs) in the wrist flexor muscle in humans. MEPs generated in flexor carpi radialis muscle (FCR) by transcranial magnetic stimulation (TMS) were recorded during robotic-assisted passive stepping and standing conditions. TMS were applied at fifteen scalp sites (3 ×5 cm grid in anterior-posterior direction and medial-lateral direction, respectively) centered on the "hot spot" which was defined as an optimal site for eliciting the MEP in FCR during passive standing task, The MEP amplitudes were measured for each stimulus sites, and then compared between different conditions.**

During passive stepping, the MEP amplitudes in FCR muscle were significantly increased in six adjacent stimulus sites of the hot spot, This result suggests that stepping-related afferent feedback induces expansion of excitatory area in motor cortex for FCR muscle.

I. Introduction

In recent neurorehabilitation, the treadmill training with partial body weight support is one of the training for patient with walking function disabilities such as spinal cord injury or stroke patient [1][2]. In this training patient's leg stepping movement is supported by physiotherapist or robotic device. In generally, it is considered that repetitive stepping-related afferent feedback to central nervous system changes the neural circuit generating rhythmic limb movement [3]. This idea is confirmed by findings from animal experiment [4], however in human study, it is still unclear how the stepping-related afferent affect the central nervous system, especially innervating arm movement.

During human bipedal walking, it is considered that there is significant interaction between arm movement center and leg stepping center [5]. In recently, our group revealed that stepping-related afferent feedback suppressed the excitability of H-reflex pathway for forearm muscle [6]. This study implicates that stepping-related afferent feedback has important role for neural mechanism in cervical spinal cord during walking.

However, it is still unknown how the ascending input from legs affects the motor cortex innervating arm muscle. Therefore in this study, using transcranial magnetic stimulation (TMS) mapping in which motor evoked potentials (MEPs) is recorded by stimulating at multiple scarp sites, we investigate the effect stepping-related afferent on excitability of forearm motor cortex.

II. Methods

A. Subjects

Eight male volunteers (Age: 22-34 years old) who have never had neurological disorders in previously were participant in this study. Prior to experiments, all subjects gave informed written consent to experimental procedure which was approved by local ethical committee, according to the Declaration of Helsinki (1964).

B. General procedure

A driven gate orthosis system Lokomat® (Hocoma AG, Vokeltswil, Switzerland) was used to produce passive leg stepping in this study. A detail of Lokomat® was described in the article of Colombo et al. [7]. Briefly, this system consists of a robotic orthosis, a body weight support mechanism and a treadmill. The Lokomat system assists the hip and knee joint movement of bilateral legs. The control parameters including the range of angle and guidance force for each joint are adjustable through the controller. To prevent foot drop at the initial swing phase of passive stepping, subjects' toes were suspended by foot lifter which consists of elastic band and springs.

Through the experiment, the right wrist and forearm of subject was put on a fixed-base with a wrist at 0° and an elbow at 90°, and then firmly fixed at wrist and elbow by elastic bands, in order to minimize the unfavorable arm movement. In addition, to prevent the unfavorable neck motion, head and trunk was firmly fixed with a immobilizing brace.

C. Passive experimental task

In order to generate the stepping-related afferent feedback and to minimize the voluntary command for treadmill stepping, subject performed passive stepping task. Passive stepping is defined as stepping movement driven by Lokomat system. During passive stepping task, subject wore a Lokomat

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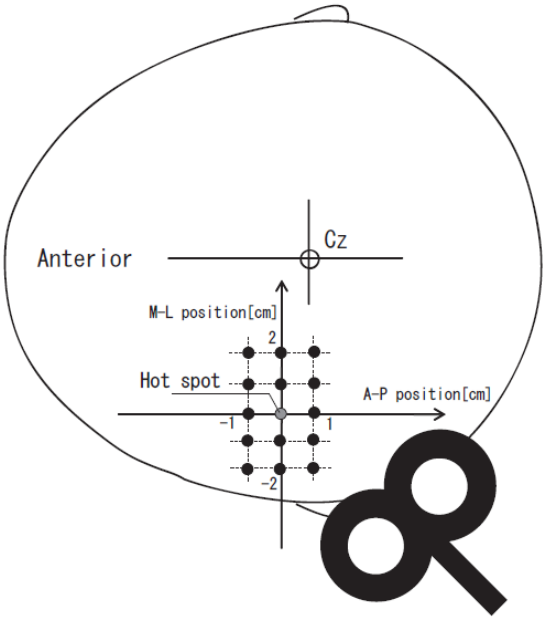

Figure 1. Brief sketch of stimulus sites for TMS mapping. Each filled circle means stimulus site. Gray filled circle is the optimal scarp site for eliciting MEPls in FCR muscle during passive standing task.

orthosis and asked to keep whole body relaxation. The treadmill speed was kept constant at 2.0km/h (0.56 m/s), and the range of hip and knee joint angles were set to 45° and 60°, respectively. Moreover, as the control task, subjects performed passive standing task what is defined as standing made by body weight support mechanism of Lokomat. During passive standing, subjects were asked to be made to stand on the treadmill with whole body relaxation.

D. Recordings

Electromyographies (EMGs) for right *flexor carpi radialis* (FCR), *extensor carpi radialis* (ECR), *tibial anterior* (TA), *soleus* (SOL), *rectus femurs* (RF) and *biceps femurs* (BF) muscles were recorded by Ag/AgCl surface electrodes. Before putting the electrodes on skins above each muscle, to reduce the impedance, the skins were cleaned by alcohol and scratched by sand paper. All EMG data were amplified 1000 times and band-pass filtered between 15Hz to 3000Hz.

Hip and knee joint angles were recorded by the potentiometers which are embedded into the Lokomat's hip and knee joints, respectively.

All signals were converted into digital data by 5000Hz using Micro1401 A/D convertor (CED Ltd, Cambridge England) and stored into the hard disk

E. TMS mapping

In order to elicit the MEPs in right FCR muscle, Magstim200 (Mgstim, UK) electromagnetic stimulator was used. An eight-shaped stimulus coil for TMS was placed on the left temporal region to induce electric current flowing in the motor cortex with posterior to anterior direction.

At the start of experiment, as a landmark of stimulus coil location, we made rectangle grid which line interval was 1cm on the swimming cap which subject had worn. Then, "hot spot", which was defined as an optimal site for eliciting the MEP in FCR during passive standing task, and resting motor threshold (rMT) during passive standing were detected. Resting motor threshold was defined as the lowest intensity which can elicit a MEPs of at least 50 μV in 5 out of 10 consecutive trials at rest.

Stimuli were delivered at fifteen scalp sites (3 ×5 cm grid in anterior-posterior direction and medial-lateral direction, respectively) centered on the "hot spot" (Figure 1).

The stimulus intensity was adjusted to 1.2 times of resting motor threshold (1.2×rMT) for FCR during passive standing. For each stimulus site, MEPs were evoked seven times.

During passive stepping task, the magnetic stimulations were applied at mid stance phase of stepping. Stimulations were applied every three step cycle (interstimulus interval was around six seconds.) during passive stepping and were delivered at every six seconds during passive standing.

E. Data analysis

The peak-to-peak amplitude of obtained MEPs were measured and normalized by the maximal motor response (Mmax) for FCR muscle. Mmax was evoked by the electrical stimulation at median nerve with 1ms rectangular pulse using bipolar electrode that placed above the medial condyle of humerus. Normalized MEPs were averaged with respect to each stimulus site.

Root-mean-squared EMGs for FCR, ECR and the other leg muscle during 50 ms prior to magnetic stimulation was measured as the background EMG (BG EMG) and normalized by maximum voluntary contraction (MVC) for each muscle measured at the end of experiment.

III. Results

During passive stepping, background FCR and ECR activities were silent (bellow 1% of MVC). Moreover, BG EMG for leg muscles were small (bellow 12% of MVC). According to one-way repeated measured analysis of valance (ANOVA) for FCR and ECR BG EMG, there were no significant differences between each session (FCR; $F(1.119, 7.831) = 4.403$, $p = 0.067$, ECR; $F(1.020, 3.060) = 0.981$, $p = 0.396$). For leg muscles BG EMG, there were also no significant differences ($p > 0.05$).

MEPs for FCR muscle were evoked 15–20 ms after magnetic stimulation to primary motor cortex. Figure 2 shows superimposed MEP waveform obtained from single subject. Location of waveform indicates the position of stimulation. For all subjects, during passive stepping, MEP amplitudes evoked by stimulation at surrounding hot spot tended to be increase compared with corresponding MEPs during passive standing task. On the other hands, when stimulating at hot spot, for three of eight subjects, MEP amplitude were increased during passive stepping, however for the others, FCR MEP amplitude were slightly increased or decreased.

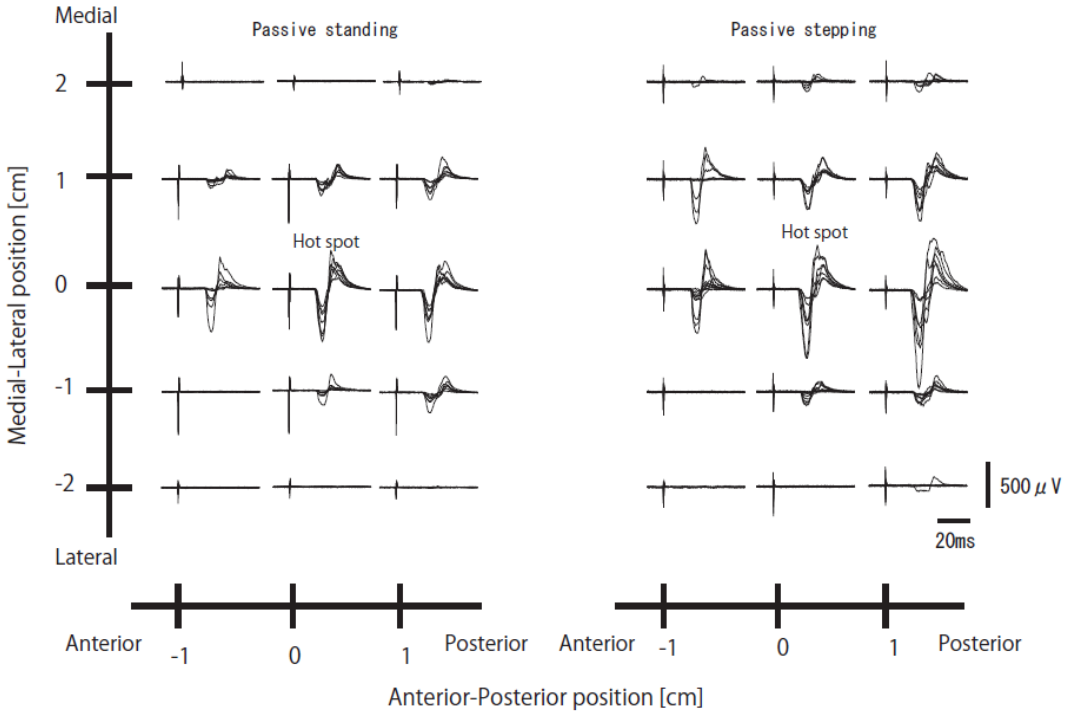

Figure 2. Superimposed MEP waveforms produced by TMS in FCR muscles at each scalp position in single subject during passive standing (left) and stepping (right) task. The location of the MEP waveforms corresponds to the scalp sites from where they were evoked.

Figure 3 illustrates the grant mean of MEP amplitude for all subjects. As the results in two-way ANOVA (the factors were two level of tasks, fifteen level of stimulus site, and their interaction.), there were main effect of passive experimental task ($F(1,7) = 23.973$, $p = 0.002$) and main effect of stimulus site ($F(2.957, 20.70) = 7.457$, $p=0.001$). In addition, there was also significant interaction on FCR MEP amplitude between tasks and stimulus site ($F(3.160,22.12) = 4.349$, $p = 0.014$). For each stimulus site, the Student's t-test were applied to detect the differences of MEPs between during passive standing and passive stepping. As a result, significant differences were noted when stimulating at six stimulus sites, where were neighbor to hot spot, traveling to respectively 1 cm for anterior and medial direction from hot spot, and traveling to 1 cm for posterior and lateral direction (Figure 3). When stimulating at the hot spot, the MEP amplitude during passive stepping was slightly larger than during passive standing, but there was no significance ($t(7) = -0.980$, $p = 0.360$).

IV. Discussion

The main findings of this study were that there was no significant difference of MEP response in FCR muscle between during passive standing and passive stepping when stimulating at the hot spot, and that the MEPs evoked by stimulation at scalp sites neighbor to hot spot during passive stepping were significantly larger than that of passive standing task. These findings suggest that stepping-related afferent feedback induces expansion of excitatory area in motor cortex for FCR muscle.

A. Methodological

MEPs induced by TMS, in generally, reflect the excitabilities of corticospinal tract including spinal motoneuron. Therefore, it is well known that MEP amplitude depends on the background excitability of target muscle [8]. In this study, BG EMG for FCR muscle was kept bellow 1% of MVC through the experiment. Moreover, there were no significant differences between each sessions. Therefore, it can be considered that modulations of MEP amplitudes were not due to difference of the background excitability of FCR.

In addition, it is well known that spinal motoneuron is sensitive to the other muscle activities, such as reciprocal Ia inhibition [9]. Baldissera et al. shown that the volley of group Ia afferent from ECR could elicit the reciprocal Ia inhibition to FCR motoneurons [10]. In this study, all subjects were asked to keep whole body rest during evoking MEPs. Therefore, any BG EMG of ECR were not seen for all subject (bellow 1% of MVC), and there were no significant differences of ECR activity. This suggests that the difference of MEP amplitude between different tasks and different stimulus sites were not caused by the changes of reciprocal Ia inhibition form ECR to FCR motoneuron. In addition, it seems that modulation of MEP amplitudes are not due to differences of leg muscle excitabilities, because BG EMGs for leg muscles were same between different sessions.

In addition, MEP amplitude depend on the stimulus intensity. Through the experiment, we used same magnetic stimulus intensity (~1.2×rMT). Thus facilitation of the MEP amplitude during passive stepping was not due to changes stimulus intensity.

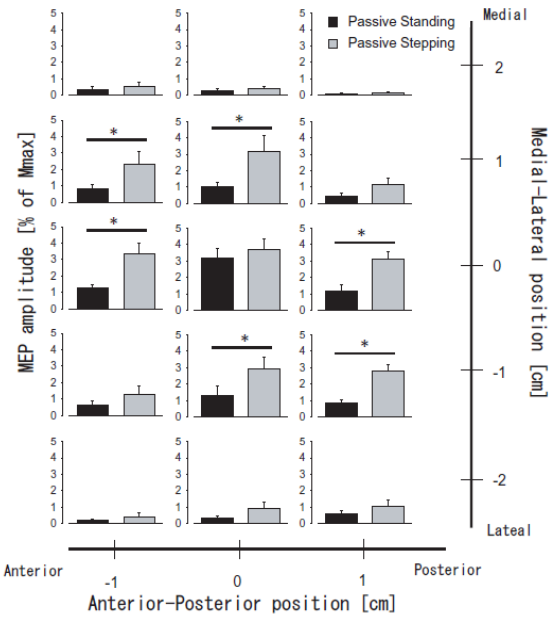

Figure 3.Mean of MEP amplitude in FCR muscles at each stimulus site during passive standing and stepping. The location of the graphs corresponds to the scalp sites from where they were evoked. * indicates significant difference of MEP amplitude between during passive stepping and during passive standing task for each stimulus site.($p<0.05$)

B. Facilitation of MEPs in FCR muscle during passive leg stepping

The result of our study that MEP amplitudes for FCR muscle evoked by stimulating at surrounding hot spot tend to facilitate during passive stepping is similar to previous report of conditioning by remote rhythmic movement [11]. Decisive difference between our study and previous one is degree of voluntary drive contribution to maintain rhythmic leg movement. In our study, we asked subjects to keep relax their whole body during passive stepping task. Indeed, the peak EMG of SOL muscle during passive stepping was below 18% of MVC although that of during voluntary walking is normally around 80% of MVC [12]. Therefore, it seems that the effect of voluntary walking command to facilitate the MEP amplitude was exceedingly small during passive walking task.

In our study, facilitatory effect of passive stepping on corticospinal excitability was significant at neighborhood of hot spot and not significant at hot spot. On the other hand, Zehr et al. (2007) revealed that rhythmic voluntary leg movement significantly facilitated the corticospinal excitability for FCR hot spot [11]. This discrepancy was probably due to deference of the degree of voluntary command. Moreover, for difference of passive stepping effect between on hot spot and that's surround site, although we have to investigate more detail, at least it seems that stepping-related afferent feedback induces expansion of excitatory area in motor cortex for FCR muscle.

C. Functional implication

In this study, it was revealed stepping-related afferent feedback tend to facilitate the corticospinal pathway from cortical area for FCR muscle. Expansion of cortical excitatory area and change of representation was often reported after motor skill learning with improving motor performance [13]. Moreover in previous report which investigate leg or arm H-reflex during remote extremity movement [6][11][14], it was revealed that excitability of H-reflex pathway is suppressed. This inhibition is thought to be due to presynaptic inhibition facilitated by lower limb movement [11][14]. In our laboratory, it was revealed in recently that FCR H-reflex pathway is suppressed by stepping-related afferent, probably with presynaptic inhibition [6]. Therefore from these H-reflex study and our present results, stepping-related afferent feedback may help the voluntary control of arm movement.

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