

A Lack of Modulation of Motor Evoked Potential in Sensory-impaired Individuals with Spinal Cord Injuries

Ya-Ju Chang^{1,†,*} Tsung-Hsun Hsieh^{1,2,†} Yi-Ming Huang³
Miao-Ju Hsu^{4,5} Alice May-Kuen Wong^{1,6}

¹Physical Therapy Department and Graduate Institute of Rehabilitation Science, Chang Gung University, Taoyuan 333, Taiwan, ROC

²Institute of Biomedical Engineering, National Cheng Kung University, Tainan 701, Taiwan, ROC

³General Education Center, Tzu Chi College of Technology, Hualien 880, Taiwan, ROC

⁴Physical Therapy, Kaohsiung Medical University, Kaohsiung 807, Taiwan, ROC

⁵Department of Rehabilitation, Kaohsiung Medical University Hospital, Kaohsiung 807, Taiwan, ROC

⁶Department of Physical Medicine and Rehabilitation, Chang Gung Memorial Hospital, Taoyuan 333, Taiwan, ROC

Received 27 Nov 2009; Accepted 20 Apr 2010; doi: 10.5405/jmbe.705

Abstract

Corticospinal excitability can be facilitated by peripheral electrical stimulation (ES) in healthy individuals. This facilitation could possibly be via the muscle afferent pathway, however, no direct evidence has been documented. This study was to examine the corticospinal excitability following ES in spinal cord-injured (SCI) individuals with sensory impairments to justify the mechanism. Eight individuals with sensory impairments following SCI and nine healthy subjects were recruited. Motor evoked potentials (MEPs), silent period (SP) elicited by transcranial magnetic stimulation (TMS), and H-reflex elicited by median nerve stimulation were recorded on flexor carpi radialis (FCR) muscle before, during, immediately and 30 minutes after low-intensity 20-Hz median nerve electrical stimulation (ES). The result showed that the MEP increased to $154 \pm 29\%$ ($p < 0.01$) of initial in healthy controls but not in SCI individuals following ES. The H-reflex did not change in both groups. The SP increased (from 41.8 ms to 53.8 ms, $p < 0.05$) in healthy controls following ES. The SP was not present in individuals with SCI. These data confirm that the lasting facilitation of corticospinal excitability elicited by peripheral nerve stimulation is due to supra-segmental modulation and the muscle afferent is an essential pathway which contributes to the facilitation.

Keywords: Transcranial magnetic stimulation, H-reflex, Peripheral electrical stimulation, Spinal cord injury

1. Introduction

Neural plasticity is an intrinsic property in the human sensorimotor cortex. Over the past years several studies have provided evidence that additional afferent input, motor learning and brain injury may lead to the long-term reorganization of motor cortex [1-5]. From the clinical aspect, the reorganization of motor cortex is considered as a possible factor correlated with recovery of motor function [6-8]. Clarifying the underlying mechanism leading to the reorganization of motor cortex is important in neurological rehabilitation.

Recent advanced tools in clinical neurophysiology have been used to non-invasively evaluate the plasticity of the human brain. Changes in the organization of the cortex have been investigated in imaging studies using positron emission

tomography (PET) [9] or functional magnetic resonance imaging (fMRI) [10] and in functional testings with transcranial magnetic stimulation (TMS) [2,6,11]. Some research even employed both PET and TMS, which provided more sufficient evidence showing possible areas and mechanisms in cortical reorganization [12-14]. Of these techniques, TMS has high temporal resolution to objectively assess brain plasticity to any experimental or clinical intervention (ie, sensory input).

The central nerve system (CNS) has been shown to be plastic depending on the sensory input [15,16]. Motor evoked potential (MEP) elicited by TMS on motor cortex was altered when afferent input was blocked by anesthetic technique [17]. It was concluded that somatosensory input and the sensorimotor interaction are assumed to be important for central plasticity. In human studies, it was also found that an increase in afferent input by electrical stimulation (ES) could facilitate the MEP in the muscles being stimulated, and the facilitation persisted up to 30 minutes post stimulation [18-20].

† These authors contributed equally to this work

* Corresponding author: Ya-Ju Chang

Tel: +886-3-2118800 ext. 5515; Fax: +886-3-2118700

E-mail: yjchang@mail.cgu.edu.tw

However, not all types of afferent stimulation facilitate motor cortex excitability. Ridding and colleagues stimulated digital nerve of fingers 4 and 5 and found no MEP facilitation, suggesting that cutaneous input alone is not sufficient to produce a change in the excitability of the corticospinal projection [21]. Part of the reasons might attribute to the stimulation intensity being below motor threshold, which is too low to induce some types of afferent conduction, such as Ia and Ib. Recent studies have shown only ES with an intensity above motor threshold was able to facilitate the MEP [19-21], denoting that muscle afferents might have a more important role in driving these excitability changes. There is still no direct evidence to indicate muscle afferent that converges at the cortex is the only pathway that can induce MEP facilitation.

To elucidate the mechanism by which muscle afferents serve as a critical contributor to the MEP facilitation following peripheral ES, we assumed that individuals with sensory nerve impaired, such as spinal cord injury (SCI) patients, might have no central and/or peripheral neurological changes following peripheral nerve stimulation. Since individuals with ASIA (American Spinal Injury Association) class C or D injury had impaired sensory but spared motor function, they were potential to serve as a good control of blocked sensation. This study was conducted to identify the possible sites and the mechanism of central reorganization after above-motor threshold ES.

2. Methods

2.1 Subjects

Nine individuals with no neurological and physical disabilities (five females, four males) aged 21–27 years (24.3 ± 2.3 years; mean \pm S.D.) and eight subjects with SCI (two females, six males) aged 25–55 years (42 ± 11.17 years; mean \pm S.D.) participated. Subjects with no physical disabilities had no previous history of neuromuscular disease. Subjects with SCI were in Class C or D according to the ASIA Impairment Scale [22]. The sensory levels were above C6, as confirmed by neurological examinations performed by a neurologist. The motor score of flexor carpi radialis (FCR) was equal to or greater than 3 in manual muscle testing (MMT), and the stretch reflex was present. All subjects participated with informed consent, and the testing protocols had been approved by our internal review board in accordance with the Helsinki Declaration.

2.2 Electromyography recording and H-reflex

The experimental setup is shown in Fig. 1. One hand of each subject was randomly selected for testing. The testing hand was strapped to a custom-designed hand plate which was used to measure the wrist isometric flexion/extension force. The wrist was kept at 0° flexion and 90° supination, and the elbow was kept in comfortable position. The surface electromyography (EMG) of the FCR was recorded by a bipolar surface electrode with a fixed interelectrode distance of 2 cm (B&L Engineering, Canada). The recording electrode was located on the muscle belly of FCR, with the direction parallel to the muscle fiber (Fig. 1(A)). A reference electrode was placed on the styloid process. The EMG activity was on-site

preamplified with a factor of 350 and was further amplified at the mainframe amplifier. The mainframe amplifier had a input impedance greater than 10 M Ω , a common mode rejection ratio of 100 dB at 60 Hz, and a gain range from 0.5 to 100,000 times (Gould, Inc., Valley View, OH, USA). The raw EMG data were fed through a 60-Hz notch filter and a band-pass (10–1000 Hz) filter to eliminate environmental interference and motion artifacts. EMG activity was monitored on an oscilloscope and digitized by a 12-bit resolution analog-to-digital converter (Metrabyte DAS 1600) at 4000 Hz.

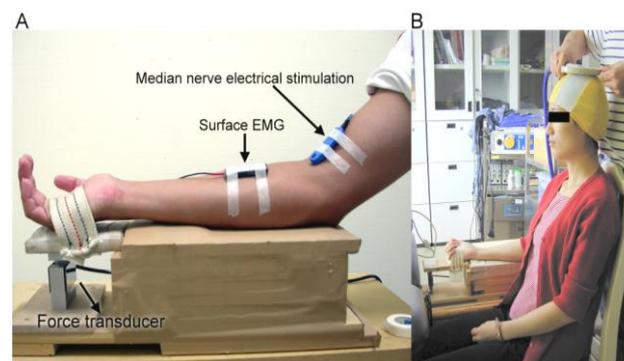


Figure 1. Experimental setup for measuring (A) H-reflex on medial nerve and (B) motor evoked potentials on FCR muscle in response to ES and TMS, respectively.

The H-reflex and maximum M-wave of the FCR muscle were evoked by the median nerve ES (Stimulator model DS7A, Digitimer Ltd., England) with the stimulating electrode placed on the cubital fossa. The pulse duration was from 0.5 to 1 ms, and the stimulation frequency was set at 0.1 Hz. The stimulation intensity for maximum M-waves was set at supramaximum. The stimulation intensity for H-reflexes was set to elicit about 80% of maximal H-reflex with a preceding M-wave clearly shown. This preceding M-wave was used to confirm that the stimulation electrode was not moved and the stimulation intensity was unvaried during the whole testing session.

2.3 Transcranial magnetic stimulation

The MEP of FCR was elicited by the TMS (Magstim 200, Magstim Co., Dyfed, UK) using a round coil with 9-cm outside diameter and anticlockwise-oriented current (side A facing up) over the contralateral scalp. The magnetic pulse was monophasic, with rise time at 0.1 ms, and the maximum duration less than 1 ms. The maximum output of the coil was 1.5 Tesla. The optimal scalp location for consistently producing largest MEPs in the target muscle (FCR) at the lower intensity was marked, and this location was used for the remainder of the experiment. The coil was manually maintained by one of the experimenters so that the position and orientation of the coil were kept constant throughout the experiment. The resting motor threshold (RMT) was defined as the minimum TMS intensity required to elicit at least five out of 10 MEPs greater or equal to 50 μ V in consecutive trials [23,24] in the relaxed FCR. The stimulation intensity for the experiment was set at 20% above the RMT. Silence period (SP) was measured with TMS during active contraction (10% of maximal voluntary contraction) for each subject.

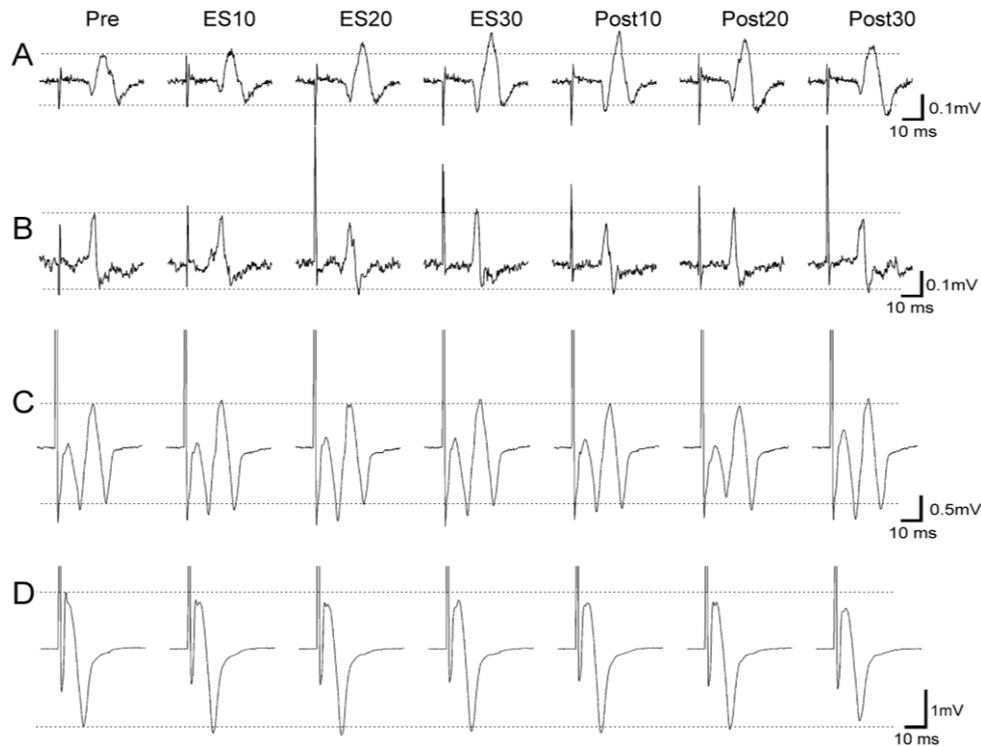


Figure 2. Raw data from representative subjects at before, during and after ES intervention. The MEPs of a healthy control (A) and an SCI subject (B). There is a clear facilitation of the MEP in the healthy control subject but no facilitation effect in the SCI subject after the period of ES. Examples of changes in H-reflex (C) and M-wave (D) in a healthy control subject. The amplitude of H-reflex and M-wave were not significantly increased during and post ES intervention.

2.4 Repetitive peripheral nerve electrical stimulation

In the healthy and SCI groups, subjects received 30 minutes of median nerve stimulation by the same stimulating electrode used for eliciting M-waves and H-reflexes of FCR. The stimulation intensity was set to elicit 10% of maximum M-wave, with obviously visible muscle contraction. The stimulation frequency was set at 25 Hz, and the on/off time was set at 800 ms/800 ms. The ES pattern continued in 10-min blocks for a total period of 30 min. Before, during, and immediately, 10 minutes, 20 minutes, and 30 minutes after median nerve stimulation, ten MEPs, H-reflexes, maximal M-waves and SPs were recorded.

2.5 Data analysis and statistics

The peak-to-peak amplitudes of the MEP, H-reflex and M-wave were measured. For each subject before and after peripheral stimulation, the excitability of the spinal motor neuron pool was assessed by the H_{max} expressed as a percentage of the M_{max} ($\%M_{max}$). Similarly, the excitability of the corticospinal tract was assessed by the MEP amplitude expressed as $\%M_{max}$.

The duration of the SP was detected by measuring the time from the end of the MEP to the earliest re-emergence of the background EMG [25]. The definition of onset time was the first relevant decrease in EMG activity (lower than three standard deviations of the resting baseline EMG). The offset time of the SP was determined in similar criteria using the first significant rise in EMG activity [26]. SP duration was determined from five averaged TMS responses.

For each subject, amplitudes of MEP, H-reflex, maximal M-wave and silent period durations were averaged separately for the time periods before and after intervention. All data were presented as mean \pm SEM.

Data were analyzed using SAS version 9.1. A two-way repeated-measures analysis of variance (ANOVA) with post-hoc Tukey test was used to determine and compare the effect of median nerve stimulation on the MEP, H-reflex, maximal M-wave and SP in different groups. The factors were stimulation conditions (seven levels: pre-stimulation, during stimulation \times 3, and post-stimulation \times 3) and groups (two levels: healthy and SCI group). The significance level was set at $p < 0.05$ and post-hoc tests were performed where appropriate.

3. Results

Figures 2(A) and 2(B) show examples of MEP during ES intervention in one subject of healthy controls and one subject in the SCI group. Changes in MEP amplitude during and after ES differed between groups (significant two-way interaction of group by time, $F = 4.7$, $p < 0.001$), indicating the subjects in the two groups responded differently to median nerve stimulation. According to post-hoc analysis, MEP amplitude of FCR increased significantly ($154 \pm 29\%$, $p = 0.01$) after 30 minutes of above-motor threshold median nerve ES only in healthy controls and the MEP amplitude remained increased up to 20 min post ES ($150 \pm 30\%$, $p = 0.02$; Fig. 3(A)). In SCI group, the MEP amplitude of FCR did not change with ES intervention ($F = 0.81$, $p = 0.5707$; Fig. 3(A)).

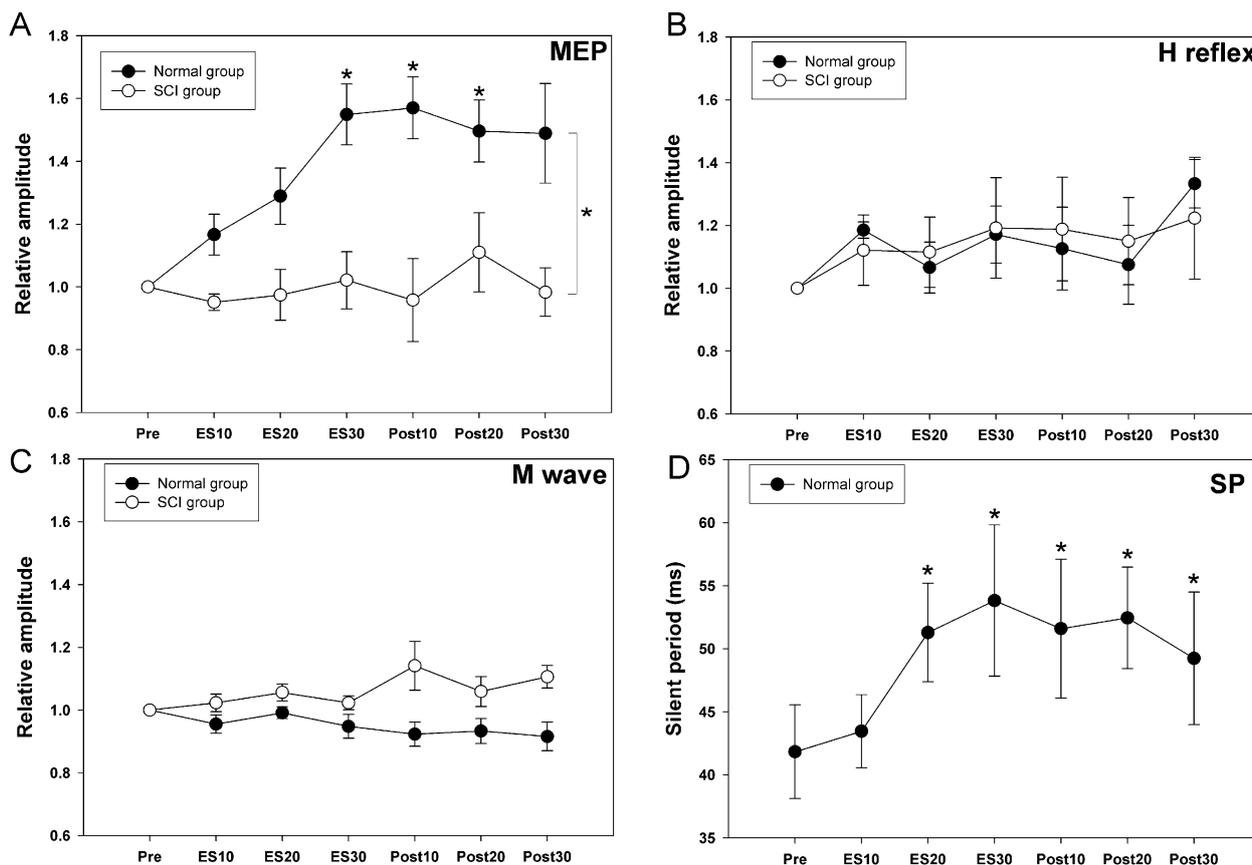


Figure 3. (A-D) Time-course changes of MEP, H-reflex, M-wave and SP responses after ES intervention. Data are shown for the baseline (Pre), during (first to third ES sessions) and post 10, 20 and 30 min following ES. (A) Note MEP increased in the healthy control group after ES and remained increased throughout the period of 20 min ($*p < 0.05$). In contrast to the healthy control group, the SCI group showed no significant MEP change after the application of ES. (B and C) The H-reflex and M-wave amplitude did not increase with stimulation time. (D) The SP increased with ES intervention and maintained for 30 min following ES in the healthy control group ($*p < 0.05$). Error bars show \pm SEM.

In terms of H-reflex amplitude, there was no significant interaction between stimulation condition and group (2-way ANOVA, $F = 0.39$, $p = 0.88$), indicating the subjects in two groups did not respond differently to median nerve stimulation. The main effect of ANOVA showed that the H-reflex amplitude did not change significantly during and after median nerve stimulation ($F = 1.79$, $p = 0.11$). For the time-course measurement of H-reflex, the example from an individual subject is displayed in Fig. 2(C), and group results are presented in Fig. 3(B). There was no significant difference in H-reflex during ES intervention in both groups ($p > 0.05$).

Figure 2(D) shows the example of maximum M-wave recorded from one healthy control subject before and after 30 min ES. After 30 minutes of median nerve stimulation, the amplitude of the maximum M-waves did not change significantly in two groups ($p > 0.05$ for all time points), indicating that the recording electrodes were stable during each test (Fig. 3(C)).

In terms of SP, all subjects in the SCI group did not show the SP, and the SP was not restored after 30-minute median nerve stimulation. The statistical analysis was performed only in the healthy group. In the healthy group, the SP of FCR increased slightly but significantly from 41.83 ± 11.14 ms to 53.82 ± 16.97 ms immediately after 30-minute median nerve

stimulation ($p < 0.05$), and the SP remained at longer durations (49.23 ± 15.76 ms) at 30 minutes post ES ($p < 0.05$; Fig. 3(D)). Figure 4 shows typical SP recordings of one healthy control subject at pre, during and post peripheral nerve ES. We can observe that there is a lengthening in SP after ES.

4. Discussion

The major finding of this study was that 30-minute median nerve ES was able to increase the MEP of FCR, and the increase persisted up to 20 minutes post stimulation in healthy subjects. The MEP failed to increase in subjects with sensory impairment following SCI. The H-reflex did not change either during or after 30 minutes of median nerve stimulation in both groups. This study provides direct evidence that sensory input is a critical factor to induce facilitated MEP.

The finding that the MEP after above-motor threshold ES increased and was maintained at least 20 minutes after ES ceased in healthy subjects (Fig. 3(A)) is consistent with the previous studies' findings on above-motor threshold repetitive ES of peripheral nerves for hand muscles [18,21,24], leg muscles [19,20] and pharynx muscles [27], although some of them utilized a longer stimulation duration (60~120 min) [18,20,21,27].

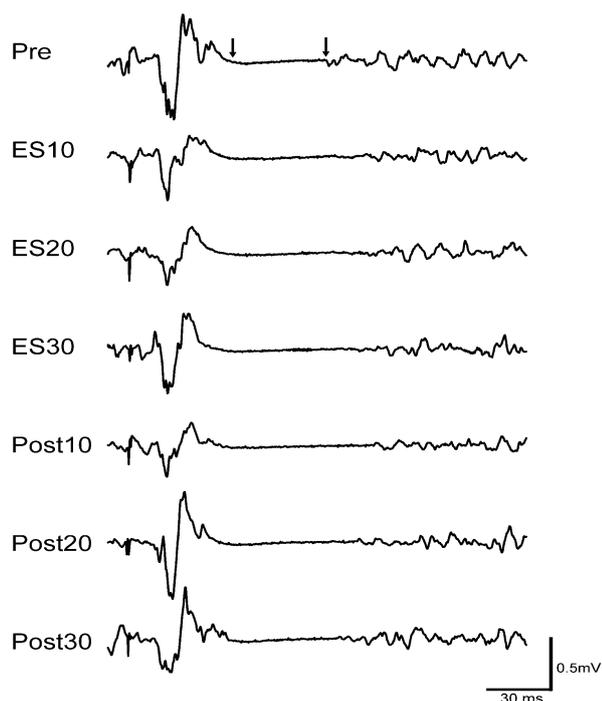


Figure 4. Example of SP evoked by single-pulse transcranial magnetic stimulation (TMS), with 10% of maximal voluntary contraction in FCR muscle. The arrows indicate the beginning and the end of the SP. SP is illustrated for a representative subject at Pre, during (10, 20, 30 min) and post (10, 20, 30 min) ES intervention. The SP duration showed significant increase after stimulation.

To answer what led to the increase of MEP after ES intervention, as described in our result of H-reflex, the H-reflexes in healthy and SCI subjects were not changed during ES and 30-min follow-up, suggesting that MEP facilitation induced by ES was not due to excitability changes at the level of spinal motor neurones. This is also suggested by other researchers [19,20]. Repetitive electrical nerve stimulation reported no changes in the H-reflex [19], F-wave [21] and brainstem ES [24], indicating the facilitation of MEP is most likely under the motor cortex.

The MEP was significantly increased in healthy control subjects after 30-min peripheral nerve ES. The MEP was not changed in individuals with sensory impairment following SCI. Since the SCI subjects in our study had no brain injury, the unchanged MEP should be attributed to a direct pathway deprivation or disturbance. In our study, the three subjects with less sensory impairment demonstrated only slight increase in MEP, ranging from 109% to 126% of rest MEP amplitude. Therefore, the MEP can be facilitated to some extent by peripheral nerve stimulation in subjects with partial afferent preservation.

Enhancement of corticospinal excitability (MEP facilitation) was observed after not only peripheral electrical stimulation but also voluntary contractions [28] or combined use of both of the above methods by functional electrical stimulation (FES) [29], denoting the firing of afferent pathway induced by muscle contraction should be a key factor. The above-motor threshold ES, similar to voluntary contractions, was able to induce muscle contraction, which also activated

muscle afferent, including Ia and Ib fiber. The intensity of peripheral nerve stimulation in our study was above motor threshold. Therefore, repetitive stimulation of the median nerve at the elbow simultaneously activated the FCR muscle, its afferent, and cutaneous fibers. Since pure sensory level stimulation failed to facilitate the MEP [21,24], the facilitated MEP in our study should come from muscle afferent. Our study found that the MEP was not facilitated in the SCI group, further indicating that activation of motor neuron without accompanied afferent conduction could not facilitate the MEP. Although the specific afferent to mediate the facilitation of MEP could not be identified in the present study, it is speculated that the effect is mediated through the proprioceptive sensors of the muscle.

An animal study has discovered the existence of the projection of Ia afferent input to primary motor cortex (M1) [30]. In human study, Steyvers and colleagues activated Ia afferent of FCR with tendon vibration at 75 and 120 Hz and found increased MEP amplitude [31]. They concluded that the excitatory effect of muscle tendon vibration on the M1 was mediated by Ia afferent input. However the Ia afferent we activated was on median nerve, rather than muscle spindle directly. To verify if the excitatory effect of supraspinal level after nerve ES comes from Ia pathway, further investigations are needed. The Ib afferent might also be activated since muscle contraction was induced during repetitive stimulation protocol. It has been suggested that the afferent from Golgi tendon organs may contribute to the direct projections to the cerebral cortex in cat [32], but the evidence has not been established in humans yet.

Theoretically the pulse induced by ES should activate Ia fiber and therefore might have effect on the excitability of alpha motor neuron pool or monosynaptic pathway, which was represented as the amplitude of H-reflex on the EMG. Similar to our study, previous studies [19] that measured H-reflex following a short-term ES showed no alternation. However, using vibration as a stimulating source to excite Ia afferent showed opposite results. Following vibration, there was a long-lasting depression of the H-reflexes of the tibia anterior and abductor pollicis brevis muscles [33]. The depression could be due to the result of presynaptic inhibition [34]. The different responses could be due to different types of Ia input stimulation. ES directly excites Ia afferent fiber, while vibrations firstly activate muscle spindle and convey excitation along Ia fiber. Apparently, the pathways that the vibration-induced pulses involved are more complicated, although one of their common pathways is Ia fiber.

The present study found that 30 minutes of ES prolonged the SP slightly in healthy control subjects (Fig. 3(D)). This trend is consistent with a previous report which showed a 28% increase in SP increase after 60-minute stimulation [18]. The total stimulation time and the stimulation intensity in Knash et al.'s study were different from ours, and their effect on SP could not be excluded [19]. The underlying mechanisms of the SP prolongation after ES are not well known. Several studies suggested that the early phase of the SP is due to spinal mechanisms and the late phase of the SP is cortical in origin

[35,36]. Since neither the H-reflex amplitude nor the latency changed after ES in our study, the spinal mechanisms were least likely to be changed after ES. Knash et al. suggested that the prolongation of SP after ES was likely to be the supraspinal effect, as the same effect occurred on the MEP facilitation [19]. One might speculate that the prolongation of SP and facilitation of MEP after ES were originated from the same cortical mechanisms. However, from our observation in disproportional change of MEPs and SP, it is suggested that not all of the increased SP can be accounted for MEP facilitation. The prolongation of SP and the facilitation of MEP probably originated from different cortical neurons, which was also suggested by other researchers [37].

The silence period was not seen in sensory-impaired individuals with SCI. The 30 minutes of ES prolonged the SP in healthy control subjects but did not restore the SP in individuals with SCI. Loss of the silence period would be the representation of weak or absent cortical inhibition and may contribute to restoration of useful motor function in individuals with incomplete SCI [38]. Shimizu and colleagues reported the loss of the cortical silent period in three patients with cervical spinal cord lesions [12]. They suggested sensory afferent impairment in SCI individuals is likely to be the key to cause motor cortical reorganization and thus, lead to loss of the silence period.

5. Conclusion

The absence of an increase in MEP following peripheral nerve ES in sensory-impaired SCI individuals provided direct evidence indicating that muscle afferents are an essential pathway for facilitating corticospinal excitability. Further study with long-term ES is suggested to determine the efficiency of plasticity in the CNS.

Acknowledgement

This work was supported by research grants from the National Science Council, Taiwan (NSC-94-2314-B-182-003).

References

- [1] M. Tinazzi, G. Zanette, D. Volpato, R. Testoni, C. Bonato, P. Manganotti, C. Miniussi and A. Fiaschi, "Neurophysiological evidence of neuroplasticity at multiple levels of the somatosensory system in patients with carpal tunnel syndrome," *Brain*, 121(Pt. 9): 1785-1794, 1998.
- [2] J. Classen, J. Liepert, S. P. Wise, M. Hallett and L. G. Cohen, "Rapid plasticity of human cortical movement representation induced by practice," *J. Neurophysiol.*, 79: 1117-1123, 1998.
- [3] C. M. Stinear, P. A. Barber, J. P. Coxon, M. K. Fleming and W. D. Byblow, "Priming the motor system enhances the effects of upper limb therapy in chronic stroke," *Brain*, 131: 1381-1390, 2008.
- [4] R. Chen, L. G. Cohen and M. Hallett, "Nervous system reorganization following injury," *Neuroscience*, 111: 761-773, 2002.
- [5] J. H. Fang, J. J. J. Chen, I. S. Hwang and Y. Z. Huang, "Review: repetitive transcranial magnetic stimulation over the human primary motor cortex for modulating motor control and motor learning," *J. Med. Biol. Eng.*, 30: 193-201, 2010.
- [6] J. Liepert, H. Bauder, H. R. Wolfgang, W. H. Milner, E. Taub and C. Weiller, "Treatment-induced cortical reorganization after stroke in humans," *Stroke*, 31: 1210-1216, 2000.
- [7] A. Cruz Martinez, J. Munoz and F. Palacios, "The muscle inhibitory period by transcranial magnetic stimulation: study in stroke patients," *Electromyogr. Clin. Neurophysiol.*, 38: 189-192, 1998.
- [8] L. R. Hoffman and E. C. Field-Fote, "Cortical reorganization following bimanual training and somatosensory stimulation in cervical spinal cord injury: a case report," *Phys. Ther.*, 87: 208-223, 2007.
- [9] S. T. Grafton, J. C. Mazziotta, S. Presty, K. J. Friston, R. S. Frackowiak and M. E. Phelps, "Functional anatomy of human procedural learning determined with regional cerebral blood flow and PET," *J. Neurosci.*, 12: 2542-2548, 1992.
- [10] A. Karni, G. Meyer, P. Jezard, M. M. Adams, R. Turner and L. G. Ungerleider, "Functional MRI evidence for adult motor cortex plasticity during motor skill learning," *Nature*, 377: 155-158, 1995.
- [11] A. T. Barker, R. Jalinous and I. L. Freeston, "Non-invasive magnetic stimulation of human motor cortex," *Lancet*, 1: 1106-1107, 1985.
- [12] T. Shimizu, T. Nariyai, T. Maehara, T. Hino, T. Komori, H. Shimizu, S. Hirai and M. Senda, "Enhanced motor cortical excitability in the unaffected hemisphere after hemispherectomy," *Neuroreport*, 11: 3077-3084, 2000.
- [13] M. Rijntjes and C. Weiller, "Recovery of motor and language abilities after stroke: the contribution of functional imaging," *Prog. Neurobiol.*, 66: 109-122, 2002.
- [14] J. J. Kew, M. C. Ridding, J. C. Rothwell, R. E. Passingham, P. N. Leigh, S. Sooriakumaran, R. S. Frackowiak and D. J. Brooks, "Reorganization of cortical blood flow and transcranial magnetic stimulation maps in human subjects after upper limb amputation," *J. Neurophysiol.*, 72: 2517-2524, 1994.
- [15] M. C. Ridding and J. C. Rothwell, "Afferent input and cortical organisation: a study with magnetic stimulation," *Exp. Brain Res.*, 126: 536-544, 1999.
- [16] D. V. Buonomano and M. M. Merzenich, "Cortical plasticity: from synapses to maps," *Annu. Rev. Neurosci.*, 21: 149-186, 1998.
- [17] J. P. Brasil-Neto, L. G. Cohen, A. Pascual-Leone, F. K. Jabir, R. T. Wall and M. Hallett, "Rapid reversible modulation of human motor outputs after transient deafferentation of the forearm: a study with transcranial magnetic stimulation," *Neurology*, 42: 1302-1306, 1992.
- [18] M. C. Ridding, D. R. McKay, P. D. Thompson and T. S. Miles, "Changes in corticomotor representations induced by prolonged peripheral nerve stimulation in humans," *Clin. Neurophysiol.*, 112: 1461-1469, 2001.
- [19] M. E. Knash, A. Kido, M. Gorassini, K. M. Chan and R. B. Stein, "Electrical stimulation of the human common peroneal nerve elicits lasting facilitation of cortical motor-evoked potentials," *Exp. Brain Res.*, 153: 366-377, 2003.
- [20] S. Khaslavskaja, M. Ladouceur and T. Sinkjaer, "Increase in tibialis anterior motor cortex excitability following repetitive electrical stimulation of the common peroneal nerve," *Exp. Brain Res.*, 145: 309-315, 2002.
- [21] M. C. Ridding, B. Brouwer, T. S. Miles, J. B. Pitcher and P. D. Thompson, "Changes in muscle responses to stimulation of the motor cortex induced by peripheral nerve stimulation in human subjects," *Exp. Brain Res.*, 131: 135-143, 2000.
- [22] F. M. Maynard, Jr., M. B. Bracken, G. Creasey, J. F. Ditunno, Jr., W. H. Donovan, T. B. Ducker, S. L. Garber, R. J. Marino, S. L. Stover, C. H. Tator, R. L. Waters, J. E. Wilberger and W. Young, "International Standards for Neurological and Functional Classification of Spinal Cord Injury. American Spinal Injury Association," *Spinal Cord*, 35: 266-274, 1997.
- [23] P. M. Rossini, A. T. Barker, A. Berardelli, M. D. Caramia, G. Caruso, R. Q. Cracco, M. R. Dimitrijevic, M. Hallett, Y. Katayama, C. H. Lucking and et al., "Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee," *Electroencephalogr. Clin. Neurophysiol.*, 91: 79-92, 1994.
- [24] A. Kaelin-Lang, A. R. Luft, L. Sawaki, A. H. Burstein, Y. H. Sohn and L. G. Cohen, "Modulation of human corticomotor

- excitability by somatosensory input," *J. Physiol.*, 540: 623-633, 2002.
- [25] M. A. Garvey, U. Ziemann, D. A. Becker, C. A. Barker and J. J. Bartko, "New graphical method to measure silent periods evoked by transcranial magnetic stimulation," *Clin. Neurophysiol.*, 112: 1451-1460, 2001.
- [26] J. Vry, M. Linder-Lucht, S. Berweck, U. Bonati, M. Hodapp, M. Uhl, M. Faist and V. Mall, "Altered cortical inhibitory function in children with spastic diplegia: a TMS study," *Exp. Brain Res.*, 186: 611-618, 2008.
- [27] S. Hamdy, J. C. Rothwell, Q. Aziz, K. D. Singh and D. G. Thompson, "Long-term reorganization of human motor cortex driven by short-term sensory stimulation," *Nat. Neurosci.*, 1: 64-68, 1998.
- [28] P. Balbi, A. Perretti, M. Sannino, L. Marcantonio and L. Santoro, "Postexercise facilitation of motor evoked potentials following transcranial magnetic stimulation: a study in normal subjects," *Muscle Nerve*, 25: 448-452, 2002.
- [29] A. Kido Thompson and R. B. Stein, "Short-term effects of functional electrical stimulation on motor-evoked potentials in ankle flexor and extensor muscles," *Exp. Brain Res.*, 159: 491-500, 2004.
- [30] P. Zarzecki, Y. Shinoda and H. Asanuma, "Projection from area 3a to the motor cortex by neurons activated from group I muscle afferents," *Exp. Brain Res.*, 33: 269-282, 1978.
- [31] M. Steyvers, O. Levin, S. M. Verschueren and S. P. Swinnen, "Frequency-dependent effects of muscle tendon vibration on corticospinal excitability: a TMS study," *Exp. Brain Res.*, 151: 9-14, 2003.
- [32] A. K. McIntyre, U. Proske and J. A. Rawson, "Cortical projection of afferent information from tendon organs in the cat," *J. Physiol.*, 354: 395-406, 1984.
- [33] M. G. Espiritu, C. S. Lin and D. Burke, "Motoneuron excitability and the F wave," *Muscle Nerve*, 27: 720-727, 2003.
- [34] H. Hultborn, S. Meunier, E. Pierrot-Deseilligny and M. Shindo, "Changes in presynaptic inhibition of Ia fibres at the onset of voluntary contraction in man," *J. Physiol.*, 389: 757-772, 1987.
- [35] U. Ziemann, J. Netz, A. Szelenyi and V. Homberg, "Spinal and supraspinal mechanisms contribute to the silent period in the contracting soleus muscle after transcranial magnetic stimulation of human motor cortex," *Neurosci. Lett.*, 156: 167-171, 1993.
- [36] P. Fuhr, R. Agostino and M. Hallett, "Spinal motor neuron excitability during the silent period after cortical stimulation," *Electroencephalogr. Clin. Neurophysiol.*, 81: 257-262, 1991.
- [37] U. Ziemann, J. C. Rothwell and M. C. Ridding, "Interaction between intracortical inhibition and facilitation in human motor cortex," *J. Physiol.*, 496(Pt. 3): 873-881, 1996.
- [38] N. J. Davey, H. C. Smith, E. Wells, D. W. Maskill, G. Savic, P. H. Ellaway and H. L. Frankel, "Responses of thenar muscles to transcranial magnetic stimulation of the motor cortex in patients with incomplete spinal cord injury," *J. Neurol. Neurosurg. Psychiatr.*, 65: 80-87, 1998.
-

