Modulation of motor cortical excitability after peripheral magnetic versus electrical stimulation in the forearm

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Abstract

This study found that inhibition of motor cortical excitability was induced by peripheral magnetic and electrical stimulation, and investigated the possibility that peripheral stimulation has similar effects to transcranial magnetic stimulation (TMS) on motor cortical excitability. In recent years, techniques combining movement and TMS have been used to aid the recovery of motor function after stroke. The presence of abnormal transcallosal inhibition of intact motor cortex following stroke may inhibit the activity of lesioned motor cortex in the contralateral hemisphere, which has been suggested to disrupt the recovery of motor function. In addition, several studies have suggested that the inhibition of intact motor cortex might be effective for the recovery of motor function. However, TMS is not an appropriate treatment for all patients, because of potential adverse events caused by the strong magnetic fields involved. Therefore, the current study focused on the effects of peripheral stimulation on cortical excitability in motor cortex.

Previous studies have reported that the peripheral afferents resulting from voluntary movement, passive movement, electrical stimulation, and magnetic stimulation affect cortical excitability in the primary motor cortex. Ridding et al. reported that facilitation of cortical excitability was induced by 10 Hz electrical mixed nerve stimulation for 2 h. Moreover, in another study, 20 Hz peripheral magnetic stimulation was applied transcutaneously to the area of muscle supplying the terminal nerve branches of the finger and hand extensor muscles using a circular coil. Similarly, previous studies have examined the use of peripheral electrical and magnetic stimulation to aid the recovery of motor function by facilitating cortical excitability of the motor cortex. Other reports have confirmed the facilitation of cortical excitability of the primary motor cortex via high-frequency and long-duration stimulation. However, few studies have examined whether magnetic and electrical stimulation can induce inhibition of motor cortical excitability under certain conditions.

TMS induces different effects on cortical excitability with different magnetic stimulation parameters, such as stimulation frequency and intensity. For example, low-frequency repetitive TMS (rTMS) of 1 Hz has been reported to decrease motor cortical excitability, and many previous studies have used TMS of supra-threshold intensity. In addition, muscle twitch caused by TMS is thought to be involved in the inhibition of motor cortical excitability. In the current study, peripheral magnetic and electrical stimulation were administered over the forearm to induce muscle twitch similar to that induced by TMS, to investigate the inhibition of motor cortical excitability caused by peripheral stimulation. The effect of peripheral stimulation was evaluated by comparing the motor evoked potential (MEP) amplitude evoked by TMS applied to the primary motor cortex before and after peripheral stimulation. Next, the stimulation frequency (above 1 Hz) and stimulation site (the contralateral or ipsilateral forearm for the target motor cortex) were altered to investigate the effects (facilitation or inhibition) of motor cortical excitability induced by peripheral stimulation. In addition, the MEP amplitude evoked by magnetic and electrical stimulation was compared to investigate the differences in motor cortical excitability induced by each stimulation type.

The results revealed that 1 Hz magnetic and electrical stimulation of the contralateral forearm caused a decrease in MEP amplitude in response to TMS applied to the left motor cortex after stimulation, compared with before stimulation. These results were similar to the effects of 1 Hz supra-threshold rTMS, suggesting that inhibition of motor cortical excitability may have been induced by 1 Hz magnetic and electrical stimulation. Moreover, changing the stimulation frequency and stimulation site of magnetic and electrical stimulation over the forearm increased MEP amplitude after stimulation under some conditions. Taken together, these findings confirmed that both magnetic and electrical stimulation induced similar modulation of MEP amplitude, suggesting that magnetic and electrical stimulation exert similar effects on motor cortical excitability.

The current findings suggest that 1 Hz magnetic and electrical stimulation over the contralateral forearm evoked inhibition of motor cortical excitability that was similar to

that induced by supra-threshold TMS of 1 Hz. In addition, modulation of motor cortical excitability was evoked by changing the stimulation frequency and stimulation site of magnetic and electrical stimulation. Importantly, these effects occurred both for magnetic stimulation and electrical stimulation.

Contents

Chapter 1

General introduction

1-1 Transcranial magnetic stimulation (TMS)

1-1-1 History and characteristics of TMS

Investigation of brain function has traditionally required invasive surgery to open the skull, limiting the scope of feasible research, particularly in healthy subjects. In 1980, Merton et al. reported a noninvasive method for stimulating the brain directly using high-voltage electrical stimulation applied through electrodes on the scalp (Merton et al., 1980). This was called transcranial electrical stimulation (TES). In the TES paradigm, the delivery of high-voltage electric shocks to the primary motor area was reported to induce muscle responses. Electric stimulation was applied not only to the brain, but also to the spinal cord (Merton et al. 1982). TES operates via stimulation of the cortex by an electric current flowing between two electrodes positioned on the scalp. The electric current flows radially from an anode to a cathode, and the partial current penetrates the scalp and activates neurons. However, because the brain is electrically protected by the high impedance of the skull, scalp and hair, electrical stimulation can cause pain and discomfort to participants. In addition, localization of electrical stimulation to a target area of the cortex is difficult. Transcranial magnetic stimulation (TMS) was developed as a method for direct brain stimulation in 1985 by Barker and colleagues, to resolve several of the limitations associated with TES (Barker et al., 1985a). TMS has been applied in various fields, and has a range of benefits: 1) magnetic stimulation is a noninvasive and relatively painless method, 2) because stimulation is not attenuated by the high impedance of the skull and scalp, the brain can be stimulated directly by a magnetic stimulation coil positioned on the scalp, 3) the magnetic stimulation coil can be positioned on the skull to alter cortical excitability in a specific brain region (Barker et al., 1985b, Hallett, 2000).

1-1-2 Principle and structure of TMS

In magnetic stimulation, a high-current pulse is produced by a magnetic wire coil. Magnetic fields are produced with lines of flux passing perpendicularly to the plane of the coil when placed on the scalp in a tangential position. In TMS, magnetic fields can reach up to approximately 2 T, and typically last for around 100 μs. Moreover, these magnetic fields generate an electric current that flows in the opposite direction to the electric current in the magnetic coil, called the eddy current (Figure 1-1). The eddy current flows in loops that are parallel to the plane of the magnetic coil. The generation of the eddy current is explained by Faraday's law of electromagnetic induction, as well as Lenz's law. The strongest eddy current occurs close to the circumference of the magnetic coil itself. The eddy current becomes weaker near the center of the magnetic coil, and there is no current at the center. Although it has been established that neuronal networks are activated by induced eddy currents, the precise extent of neuronal activation is currently unclear. However, it has been found that neuronal activation varies with the intensity of magnetic stimulation, and that cortical excitability can be modulated by eddy currents (Maeda et al., 2000, Touge et al., 2001, Ridding and Rothwell 2007, Hallett, 2007).

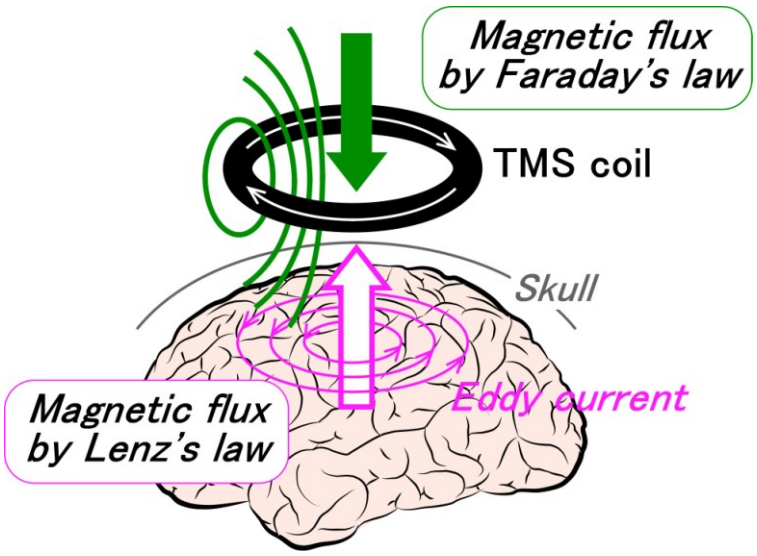


Figure 1-1 Direction of current flow in a magnetic coil and the induced current in the brain

TMS involves several functional limitations. Because the magnetic field falls off rapidly with distance from the magnetic coil surface, direct stimulation is limited to the outer parts of the cerebral cortex located near the skull (Hallett, 2000, Hallett, 2007, Ridding et al., 2007). As magnetic stimulation techniques have developed, magnetic coils of various shapes have been introduced. A round coil has been used since the development of TMS, inducing a powerful magnetic field that enables extensive stimulation. However, round coils do not produce a focal site of stimulation. In contrast, figure-eight-shaped coils enable focal stimulation with a focal resolution of 5 mm, enabling stimulation of a much smaller cortical area of 1–2 cm^2. Figure-eight-shaped coils are constructed so that two round coils are attached at an angle (under 180 degrees), with an area of overlap. The overlapping part of the coil increases the magnetic field intensity, enabling figure-eight-shaped coils to produce more effective and focal magnetic stimulation (Figure 1-2) (Ueno et al., 1988, Ueno et al., 1990, Thielscher et al. 2004, Ravazzani et al., 1996). Moreover, figure-eight-shaped coils with an angle of approximately 90–100 degrees exhibit increased power at the intersection, and can stimulate deeper regions of cortex.

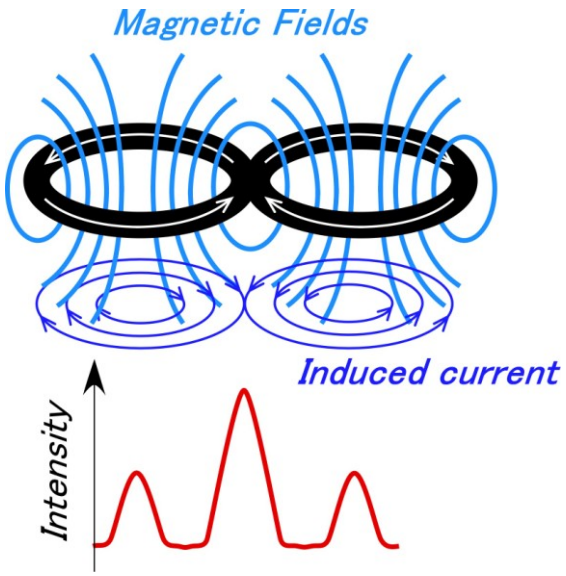


Figure 1-2 Magnetic coil shape and resultant stimulus intensity in the brain

The development of figure-eight-shaped flat coils has enabled TMS stimulation with directionality. The descending volley elicited by TMS with a figure-eight-shaped flat coil depends on the direction of the induced current. For example, when the coil is placed on a hand-related region of the motor area, the thresholds for a monophasic stimulator are lowest when the eddy current of a magnetic coil flows in the posterior-anterior (PA) direction, perpendicular to the central sulcus (Sakai et al., 1997, Mills et al., 1992). In addition, responses with the shortest latency occur when the eddy current flows in a latero-medial direction (Werhahn et al., 1994, Di lazzaro, 2003). Thus, the effect of TMS varies with the direction of the induced current, and depends on the pulse waveform output by the stimulator (Brasil et al., 1992), which can be biphasic or monophasic. For a monophasic pulse, the direction of induced current is always in the postero-anterior or antero-posterior direction. This method has been used in a number of previous studies examining the motor threshold (Mills et al., 1997, Rossini et al., 1992, Triggs et al., 1994). In addition, monophasic pulses in the induced current passing through the motor cortex in the postero-anterior direction are more effective than those traveling in the antero-posterior direction (Kammer et al., 2001). Alternatively, biphasic pulses can be applied with repetitive transcranial magnetic stimulation (rTMS). rTMS was introduced by Pascual-Leone et al. in 1987, and has been suggested to have value as a treatment for the pathological physiology of depression (Pascual-Leone et al., 1996). High-frequency rTMS has since been used for treatment of a range of psychiatric conditions, in addition to depression. (Pascual-Leone et al., 1996a, George et al., 1997).

1-1-3 Nerve conduction in TMS

Many of the basic principles of TES also apply to TMS (Di Lazzaro et al., 2004). The effects of TMS applied over the primary motor area appear to be similar to those of TES. Both TMS and TES have been shown to excite corticospinal neurons at short latencies, consistent with direct activation of neurons in the cortex, and at longer latencies, as measured by direct recording from the surface of the spinal cord (Boyd et al., 1986, Burke et al., 1993). However, the two methods vary in terms of the latency of responses to stimulation.

In the motor cortex, it has been reported that TMS tends to recruit I-waves at threshold, whereas TES tends to recruit D-waves (Thompson et al., 1991, Burke et al., 1993). In electrical stimulation of the brain, the vertical component of current flow has been found to favor direct excitation of pyramidal tract neurons (Day et al. 1989). Thus, the production of early D-wave activity by TES appears to reflect direct activation of descending axons in the corticospinal tract (Patton et al. 1954). With higher intensities of stimulation, D-wave activity is followed by I-wave activity, with a periodicity of approximately 1.5 ms (Patton et al. 1954, Day et al. 1989). In contrast, magnetic stimulation appears to induce eddy currents under the magnetic coil, predominantly in the horizontal plane, stimulating horizontally-oriented neurons within the cortex, including interneurons, pyramidal tract axon collaterals and afferent axons from cortical and subcortical sites.

TMS over the motor cortex tends to activate I-waves at lower intensities than D-wave activity (Thompson et al., 1991, Berardelli et al., 1990). In addition, the latency of I-wave activity is delayed compared with D-wave activity. I-wave latencies are commonly categorized by numbers corresponding to the duration of the latency, in order: I1, I2, and I3 (Kernell and Chien-Ping, 1967). The interval of each descending volley is 1.5 ms, corresponding to the latency of an individual synapse (Kernell and Chien-Ping, 1967). The D-wave produced by a TMS pulse is recruited at intensities much greater than threshold. TMS over the motor cortex typically evokes I-wave activity, and the resulting effect of descending volley stimulation can be observed in

motor-evoked potential (MEP) recordings. The MEP latency induced by TMS is typically around 1.5 ms longer than that evoked by TES (Berardelli et al., 1990, Edgley et al., 1990). The MEP latency of TMS shortens and becomes equal to that induced by TES, because stronger TMS evokes D-waves (Kaneko et al., 1996, Di lazzaro, 2003). Recruitment of various components of the corticofugal discharge by TMS depends on the intensity of stimulation, the shape of the coil, the pulse configuration, and the relative threshold of each volley to the direction of the induced current flow in the cortex (Hallett, 2007, Rossini et al. 2015, Groppa et al., 2012).

1-1-4 The alteration of cortical excitability with TMS

Several studies have reported that low-frequency magnetic stimulation of 1 Hz decreases motor cortex excitability, whereas high-frequency magnetic stimulation of above 5 Hz increases motor cortex excitability (Wassermann et al., 1998, Pascual-Leone A et al. 1994, Chen et al., 1997). Pascual-Leone et al. reported that the characteristics of MEPs depend on the intensity and frequency of repetitive stimulation (Pascual-Leone et al., 1994). In one study, stimulus frequencies of 1, 3, 5, 10, 20 Hz were tested, and rTMS began at the threshold intensity (100% threshold) and progressively increased in steps of 10% of threshold up to the maximal intensity of the stimulator's output (Pascual-Leone et al., 1994). The results showed that rTMS of 20 pulses at 5 Hz at 150% threshold evoked larger MEPs in subjects at rest, and the MEP amplitude induced by rTMS of 20 pulses at 10 Hz gradually increased for all participants at an intensity of 110%–130% of motor threshold. With rTMS trains of 1 Hz stimulation, no consistent alteration of MEP amplitude was observed. Adjustment of the amplitude of MEPs produced in the target muscle by magnetic stimulation showed effects that depended on rTMS frequency and intensity, including inhibition and facilitation of cortical excitability (Pascual-Leone et al. 1994).

Berardelli et al. examined the neurophysiological mechanisms underlying the facilitation of MEPs after serial magnetic stimulation. They applied a single TMS pulse

to the motor cortex at 200–900 ms after a train of 20 pulses of 5 Hz rTMS with a 1-min interval between trains. The results revealed that applying 5 Hz rTMS to the motor cortex at an intensity of 120% of motor threshold produced a transient increase in cortical excitability. Moreover, their findings suggested that the after-train facilitation of MEPs was cortical in origin, showing that MEPs induced by rTMS (which tends to activate the same neurons via corticocortical synapses) were facilitated, whereas MEPs induced by transcranial electrical stimulation (TES) (which tends to activate corticospinal neurons directly) were not. In addition, although the afferent input from the twitches evoked by each type of TMS might have been expected to increase spinal cord excitability, H-reflexes after the train were suppressed rather than enhanced. Therefore, the results suggested that facilitation of cortical excitability may occur in the cortex, but not in the spinal cord. The facilitation of cortical excitability may induce activity in the stimulated cortical region by increasing the excitability of pyramidal cells and their excitatory inputs. Thus, the excitatory reduction of cortical inhibition mechanisms may play a role in the facilitatory effects of magnetic stimulation (Berardelli et al., 1998).

In contrast, low-frequency TMS has been found to cause inhibition of cortical excitability. Chan et al. applied 0.1 Hz rTMS at an intensity of 105% of the motor threshold to the left motor cortex for 1 h (a total of 360 pulses). The average MEP amplitude induced by each group of 30 pulse stimuli (5 min) was normalized using the average MEP amplitude of the first 60 pulse stimuli (10 min), which was defined as the baseline. The results demonstrated that the MEP amplitude of the right abductor pollicis brevis (APB) muscle was not significantly reduced or increased by 1 h of rTMS. Moreover, 90 pulses of 0.1 Hz rTMS (15 min) were applied before and after an intervention stimulus of 0.9 Hz rTMS at an intensity of 115% of the motor threshold for 810 magnetic stimulation pulses (15 min). The results indicated that MEP amplitude in the APB was reduced following rTMS compared with before rTMS, and this effect continued for 15 min. These findings suggest that low-frequency rTMS may decrease the efficacy of cortico-cortical synapses or the excitability of postsynaptic corticospinal

neurons, possibly reflecting changes in extrinsic input to the motor cortex. In addition, the results suggested that the observed decrease in motor cortical excitability may be mediated by long-term depression (LTD), because the stimulus parameters used in the study (1 Hz, 900 pulses) resembled the stimulation conditions used for inducing LTD in CA1 cells of hippocampal slices (Chen et al., 1997, Dudek et al., 1992, Mulkey et al., 1992). In another study, Maeda et al. applied 240 pulses of 1, 10 and 20 Hz rTMS at an intensity of 105%, on two different days. The results indicated a significant decrease in MEP amplitude following 1 Hz rTMS, and a significant increase of MEP amplitude following 20 Hz rTMS, on both day 1 and day 2. This effect was greater on day 2. The researchers suggested that this effect may have been related to LTD- and long-term potentiation (LTP)-like effects (Maeda et al., 2000).

Moreover, decreased cortical excitability is associated not only with stimulation frequency but also stimulation intensity (sub- or supra-motor threshold). Romero et al. studied the effects of sub-threshold 1 Hz rTMS on cortical excitability. They applied 1 Hz rTMS at sub-threshold intensity (90% at the resting motor threshold, RMT) for 10 min, and the position of TMS was determined as the scalp position from which TMS evoked MEPs of greatest amplitude in the first dorsal interosseous (FDI) muscle. The effect was evaluated by measuring MEP amplitude induced by intracortical facilitation and inhibition. The results revealed that a significant decrease of mean MEP amplitude was induced by intracortical facilitation, while intracortical inhibition was not affected. In addition, this report suggested that the effect of sub-threshold stimulation with 1 Hz rTMS was intracortical, and that the effect of an rTMS train may preferentially result in decreased intracortical facilitation via an inhibitory mechanism (Romero et al., 2002).

Several possible mechanisms underlying the decrease of cortical excitability with supra-threshold 1 Hz rTMS have been proposed. Fitzgerald et al. applied 1 Hz rTMS at an intensity of 85% (sub-threshold) or 115% (supra-threshold) at the RMT or the active motor threshold (AMT) for 15 min. The results showed a significant decrease in MEP amplitude following 1 Hz rTMS only with stimulation of 115% of the AMT. However, no changes were observed in cortical inhibition, cortical facilitation or the cortical silent

period (CSP). In terms of decreased cortical excitability with supra-threshold 1 Hz rTMS, this report suggested that supra-threshold rTMS may change the magnitude of MEPs via a spread of stimulation to adjacent premotor areas rather than the primary motor cortex itself. This suggestion is supported by a previous study demonstrating that stimulation of the dorsal pre-motor cortex at an intensity of 90% of the AMT decreased MEP amplitude, while stimulation of the same intensity was insufficient to produce changes when applied directly to the motor cortex (Gerschlager et al. 2001).

In one study, Lang et al. applied 1 Hz rTMS at the sub-threshold (90% of RMT) and supra-threshold level (115% of RMT) to the left motor cortex for 15 min. To assess changes of corticospinal and intracortical excitability in response to rTMS, MEPs induced by TMS were recorded from the contralateral FDI muscle, before and after rTMS. Inter-stimulus intervals of 2 ms and 12 ms were used to investigate short-latency intracortical inhibition (SICI) and intracortical facilitation (ICF), and the CSP was measured to assess the duration. A 1 Hz repetitive electrical nerve stimulation (rENS) was applied to the right ulnar nerve at the wrist as a control experiment to test corticospinal excitability by supra-threshold 1 Hz rTMS for 15 min. The results revealed that a decrease in MEP amplitude was induced by 1 Hz rTMS supra-threshold stimulation and 1 Hz rENS, but was not observed with 1 Hz rTMS sub-threshold stimulation. Regarding the effects on intracortical excitability, prolongation of the CSP and decreased ICF were confirmed, but no alteration of SICI was observed. Importantly, the results confirmed that corticospinal excitability and intracortical inhibition were induced by 1 Hz supra-threshold rTMS. Moreover, this report indicated that supra-threshold low-frequency rTMS was superior to sub-threshold low-frequency rTMS for facilitating inhibitory circuits in the stimulated primary motor cortex. As a potential mechanism of the increased efficacy of supra-threshold 1 Hz rTMS, these findings suggest that the stronger after-effect may be due to reafferent feedback activation of primary motor cortex caused by rTMS-evoked muscle twitches. Moreover, this hypothesis is also in accord with evidence from functional neuroimaging studies. Bestmann et al. applied rTMS at supra-threshold (110% of RMT) or sub-threshold

intensity (90% of AMT) to primary motor cortex, functional magnetic resonance imaging (fMRI) results confirmed that supra-threshold rTMS caused a consistent increase in regional synaptic activity, while sub-threshold rTMS elicited no fMRI-detectable activity in the stimulated region. Moreover, it was suggested that reafferent feedback from evoked muscle twitches may represent the dominant input to the motor system via motor cortex during supra-threshold rTMS (Baudewig et al., 2001, Bestmann et al., 2004).

These findings suggest that the modulation of cortical excitability may depend on stimulation parameters, such as frequency, intensity, duration and inter-train interval of magnetic stimulation. Based on these characteristics of TMS, the modulation of cortical excitability by high- and low-frequency rTMS has enabled detailed investigation of motor and cognitive function (Torii et al., 2012, Maeda et al., 2000, Touge et al., 2001, Hallett, 2007, Birgit et al., 2010, Hartwig et al., 2000). Moreover, TMS has been utilized as a valuable tool when combined with various diagnostic instruments, including electroencephalography (EEG), single-photon emission computed tomography (SPECT), fMRI, and positron emission tomography (PET) (Kähkönen et al., 2005, George et al., 1999, Nahas et al., 2001, Paus et al., 1997). However, for therapeutic applications, TMS is not appropriate for all patients, exclusion criteria include the presence of metallic hardware, implanted brain electrodes, pregnancy, and heart disease (Rossi et al. 2009).

1-2 Motor evoked potentials (MEPs)

Methods using MEPs involve stimulating motor cortex while recording the surface electromyogram from a target muscle. When TMS or TES is applied to the motor cortex at appropriate stimulation intensity, MEPs can be recorded in the contralateral extremity muscles (Ridding et al., 2007, Hasey, 2001, Mano et al., 2003, Mano et al., 1993a, Pascual-Leone et al., 1998). Barker et al. reported that TMS can be used to activate the corticospinal tract (Barker et al., 1985a). Activation by TMS was found to cause contraction of the contralateral muscle of the stimulation point on the cortex, examined by measuring the latency and amplitude of evoked potentials in electromyography (EMG) recordings from the muscles. MEPs were constructed from the EMG record, providing valuable information about the physiology of the corticospinal tract (Petersen et al., 2003). The mechanism underlying the production of MEPs can be described as follows. Excitatory postsynaptic potentials (EPSPs) are produced when stimulation reaches the anterior horn of spinal cord motor neurons. In the case of weak stimulation, EPSPs do not fire in response to the arrival of a single spinal cord volley. By increasing stimulation intensity, several subsequent I-waves (I2 or I3) produce temporal summation in EPSPs. EPSP firing then occurs when spinal cord volleys arrive at the membrane potential, which is necessary for depolarization. Therefore, the timing of firing is delayed compared with the arrival of the first spinal cord volley (Edgley et al., 1997, Kernell et al., 1967). Because EPSPs induced by TMS are initially small, they do not arrive at the same time as motoneuronal firing. In contrast, in D-wave activity induced by TES, EPSPs exhibit greater magnitude than those induced by TMS, because the conduction velocity is faster. Therefore, D-wave activity fires easily at the time of arrival (Edgley et al., 1997). EPSPs produce depolarization, and excitation occurs when the membrane potential reaches a threshold. The excitation transmits along a peripheral axon as a nerve impulse, causing muscle fibers to contract via the myoneural junction. As a result, an EMG response is produced in the contralateral muscle to the cortex

receiving magnetic stimulation.

MEPs provide information about transmission in the corticospinal pathways and spinal motoneurons. The sum of these synaptic events and postsynaptic excitability determines the activation of corticospinal cells. In addition, indirect pathways through spinal interneurons may also contribute to the activation of spinal motoneurons. MEP amplitude is determined by the excitability of spinal motoneurons, their intrinsic membrane properties and the distribution of the synaptic activation that crosses the motoneuronal pool (Petersen et al., 2003). MEP amplitude is also affected by synapses of corticospinal cells onto spinal motoneurons because of changes in transmitter release (Gandevia et al., 1999). Therefore, MEP amplitude can be used to evaluate the excitability of the corticospinal tract, which is a cerebrocortical output pathway (Petersen et al., 2003). MEP amplitude is also related to EEG changes, and is affected by factors that affect corticospinal excitability (Rossini et al., 1991, Pascual-Leone et al., 1998). For example, MEPs depend on the intensity and frequency of repetitive magnetic stimulation (Pascual-Leone et al., 1994). MEPs recorded during volitional contraction of the target muscle are reported to be increased compared with a resting period, and this effect was found to depend on muscle contraction (Hess et al., 1986, Rothwell et al. 1991, Taylor et al. 1997, Di Lazzaro et al. 1999a, Martin et al. 2006). Another study found that mental imagery of contraction of the target muscle produced facilitation of MEPs similar to that produced by volitional contraction (Rossini et al., 1991). This facilitation was not found to occur in MEPs evoked by TES (Pascual-Leone et al., 1998). Because the response evoked by TES is not typically affected by the excitability of corticospinal cells, the difference in this effect provides insight into the intracortical mechanisms of TMS (Pascual-Leone et al., 1998, Petersen et al., 2003). Moreover, the modulation of MEP amplitude evoked by rTMS may be associated with the cortex (Berardelli et al., 1998). Taken together, these findings suggest that MEPs evoked by TMS can provide an appropriate index of excitatory cerebral changes. In terms of the motor threshold, MEP amplitude can be used as a valuable measure for determining the appropriate stimulation intensity of TMS and TES. The motor threshold is defined as

the lowest stimulation intensity at which particular MEP amplitude can be induced. This measure can be divided into the AMT and the RMT. Many studies have used MEP amplitude to evaluate the cortical effects of stimulation over peripheral nerves or muscles, while MEP latency provides information about the conduction time from the site of stimulation in the cortex (Petersen et al., 2003).

1-3 Influence of peripheral stimulation on cerebral cortex

Peripheral stimulation is commonly used for the recovery of motor function in the human brain and typically consists of motor tasks, electrical stimulation, and magnetic stimulation. A number of studies have used MEP amplitude to evaluate the cortical effects of stimulation over peripheral nerves or muscles (Cramer et al., 1999, Reid et al., 2014, Kaelin-Lang et al., 2002, Chen et al., 1999, Struppler et al., 2007). As described in the previous section, MEP amplitude can be used to evaluate the excitability of the corticospinal tract. Thus, it is possible that peripheral stimulation-related changes in MEP amplitude reflect modulation at the level of the motor cortex. Alternatively, the effect may be related to spinal motoneuronal changes. The F-wave, M-wave and H-reflex have been used to investigate the effects of peripheral stimulation on spinal motoneurons. F-waves reflect the excitability of only a sub-portion of the spinal motoneuron pool, providing an indicator of excitability changes in spinal motoneurons (Mercuri et al., 1996). In contrast, M-waves reflect excitability changes occurring at the neuromuscular junction and muscle, and the H-reflex is considered an index of spinal motoneuron excitability (Mercuri et al., 1996).

In a previous study of peripheral electrical stimulation, Ridding et al. investigated whether prolonged, repetitive mixed nerve stimulation of the ulnar nerve leads to a change in cortical excitability in primary motor cortex. They delivered electrical stimulation to the ulnar nerve on the wrist via surface electrodes in trains of 1 ms duration square-wave pulses with a frequency of 10 Hz, for 2 h. MEPs generated in the hand muscles induced by focal TMS were recorded before and after a period of prolonged repetitive electrical nerve stimulation of the ulnar nerve at the wrist. TMS was applied at 120% of RMT at the optimal scalp site for evoking responses in the right FDI. To confirm the excitability of spinal motoneurons after 2 h of ulnar nerve stimulation, F-waves were recorded from the left FDI muscle, evoked by supra-threshold electrical stimulation of the ulnar nerve at the wrist. The result indicated that MEPs evoked in the FDI were increased after prolonged repetitive electrical nerve

stimulation to the ulnar nerve. In addition, this report found that F-wave activity in the hand muscles of the FDI were not altered after prolonged repetitive electrical nerve stimulation. Thus, this report suggested that MEP changes were not caused by stimulus-induced increases in the excitability of spinal motoneurons (Ridding et al., 2000).

Kaelin-Lang et al. investigated the mechanisms underlying the increase in cortico-motoneuronal excitability to stimulated body parts following somatosensory stimulation. Using similar protocols to those described in a previous study by Ridding et al., they applied electrical stimulation to the ulnar nerve at the wrist with a stimulation frequency of 10 Hz, duration of 1 ms, and stimulation time of 2 h. The stimulation intensity was 50–100 V. MEP amplitude and M-responses from FDI, the APB and abductor digiti minimi (ADM) were recorded before and after a 2-h period of ulnar nerve electrical stimulation at the wrist. Moreover, to differentiate excitability changes at cortical and subcortical sites, they recorded supramaximal peripheral M-responses and MEPs to brainstem electrical stimulation (BES). The results revealed an increase of MEP amplitude induced by TMS at an intensity of 140% of RMT in the ADM. Moreover, a 2-h period of ulnar nerve electrical stimulation that caused increases of TMS-evoked MEP amplitudes did not affect amplitudes or areas of the MEPs following BES, or maximal peripheral M responses. These results suggested the lack of significant excitability changes in the muscle, neuromuscular junction and spinal cord. Thus, this report suggested that the site of the interaction of somatosensory stimulation is the motor cortex itself, which receives somatotopically organized projections from the primary somatosensory cortex. It is also possible that other structures of the motor system that receive somatotopically organized somatosensory inputs are involved in this sensorimotor interaction (Kaelin-Lang et al., 2002).

Tinazzi et al. investigated alteration of cortical excitability using a higher stimulation frequency than that used in Kaelin-Lang et al.'s study described above. An electrical stimulation frequency of 150 Hz was applied to the flexor carpi radialis (FCR) muscle via a pair of self-adhesive electrodes in trains of 100 μs duration with an asymmetrical

rectangular biphasic waveform for 30 min. Stimulation intensity was approximately 1.5 mA below the motor threshold, and did not induce muscle twitch or pain. MEPs were recorded simultaneously from the FCR and extensor carpi radialis (ECR) muscle belly induced by TMS at 130% of RMT, before and after electrical stimulation. To investigate whether the observed excitability was caused in cortical or spinal sites, they recorded MEPs to TMS and H-waves, as well as maximal peripheral M responses, from forearm flexor muscles before and after 30 min of electrical stimulation. Moreover, they investigated the effects of cutaneous input on cortical excitability of forearm flexor muscles by stimulating the lateral forearm cutaneous nerve. The results indicated that the MEP evoked by TMS was decreased after electrical stimulation over the FCR. In contrast, it was increased after electrical stimulation over the ECR. Electrical stimulation at a stimulation frequency of 150 Hz did not modify the amplitude of maximal peripheral M responses or of H-waves, suggesting the lack of significant changes at the muscle, neuromuscular junction or spinal cord. Based on these results, the authors suggested that the observed inhibition and facilitation of MEPs occurred within the motor cortex. Moreover, stimulation of the cutaneous afferents of the forearm cutaneous nerve that innervates the skin close to the FCR muscle did not significantly inhibit MEPs measured from the forearm flexor muscles. In addition, the results suggested that cutaneous input did not significantly contribute to motor cortical inhibition, and muscle afferents were likely to be mainly responsible for the observed modulation of motor cortical excitability (Tinazzi et al. 2005).

Because magnetic stimulation can be used non-invasively in humans, it is appropriate not only for brain stimulation, but also afferent stimulation. Magnetic stimulation applied to the area of muscle that supplies terminal branches has been proposed as an alternative method of transcutaneous electrical stimulation, known as peripheral magnetic stimulation. Muscle contractions caused by peripheral magnetic stimulation are elicited by depolarization of the terminal motor branches, which mostly activates proprioceptive afferents. The primary effects of peripheral magnetic stimulation at the central level are caused by this proprioceptive inflow to the central nervous system. In

addition, peripheral magnetic stimulation avoids activation of cutaneous receptors as well as the activation of mechanoreceptor afferents from the skin and fiber groups III and IV, because the biologically effective electrical field of peripheral magnetic stimulation is considerably smaller than that of transcutaneous electrical stimulation. In addition, because the magnetic field depends upon the ion environment, it can penetrate deeper areas of muscle, whereas the current caused by an electrical field will take the path of lowest resistance, thus being relatively spatially limited to areas near the surface (Struppler et al., 2004, Struppler et al., 2007).

Moreover, Stefan et al. demonstrated the importance of the conjoint activity of somatosensory afferents and intrinsic cortical motor circuits using paired stimulation that synchronized peripheral nerve electrical stimulation and TMS. Using this method, MEPs were increased when the somatosensory input of electrical stimulations was synchronous at the level of the motor cortex (Stefan et al., 2000).

Struppler et al. used PET to investigate the central reorganization mechanisms involved in the improvement of repetitive finger movements in patients under treatment with repetitive peripheral magnetic stimulation. Between PET scanning sessions, repetitive peripheral magnetic stimulation was transcutaneously applied to the area of muscle supplying the terminal nerve branches of the finger and hand extensor muscles, using a circular TMS coil. Repetitive peripheral magnetic stimulation was applied at a stimulation frequency of 20 Hz, with a total of 5000 stimuli and average amplitude of 1.2 T. After every 30 impulses, a break of 4 s was provided, to induce repetitive contractions and relaxations simultaneously with the sensation of movement and vibration. To investigate the conditioning effect of the repetitive peripheral magnetic stimulation, a simple motor task (index finger extension) was used. A simple motor task was executed before and 45 min after the repetitive peripheral magnetic stimulation. Improvement of repetitive finger movements was evaluated using the displacement amplitude and displacement velocity of finger extension, and the motor activity due to convulsions was recorded using EMG of the index finger flexors and extensors. The results revealed an improvement of displacement amplitude and displacement velocity

in the flexors and extensors after repetitive peripheral magnetic stimulation. In addition, motor activity due to convulsions was significantly decreased. PET results after repetitive peripheral magnetic stimulation indicated significant increases of regional cerebral blood flow (rCBF) in the contralateral premotor cortex and posterior parietal cortex, compared with before repetitive peripheral magnetic stimulation. In addition, the results suggested that patients' improvement in the motor task was related to an increase of neural activation. Based on these results, the authors proposed a possible mechanism to explain the effects of repetitive peripheral magnetic stimulation, as follows. First, repetitive peripheral magnetic stimulation causes controlled muscle contractions, generating proprioceptive inflow to the central nervous system. Two pathways may be involved, activation of mechanoreceptors of the stimulated muscles during the induced contraction (indirect), and via the direct activation of the underlying sensorimotor afferents. The afferent inflow to the central nervous system projects via the fast conducting myelinated nerve fibers primarily to the systems related to the movement of the finger and hand. In addition, the impulses reach the primary and secondary somatosensory cortex via the thalamus, and are processed further in the premotor and parietal areas. Thus, simultaneously to the induced movement, the proprioceptive inflow leads to concomitant perception of movement and vibration. These findings suggest that increased activation of the parieto-premotor network following repetitive peripheral magnetic stimulation reflects a significant conditioning effect of peripheral magnetic stimulation at the cortical level (Struppler et al., 2007).

Behrens et al. applied repetitive peripheral magnetic stimulation over the soleus muscle belly in a healthy subject, and compared spinal excitability with a sham stimulation condition. Repetitive peripheral magnetic stimulation was applied at a frequency of 15 Hz, with 20 trains of 100 stimuli (a total of 2000 stimuli) and 40% of stimulator output. The maximal H-reflex and maximal M response evoked by electrical stimulation of the posterior tibial nerve were used for evaluating spinal excitability of repetitive peripheral magnetic stimulation. Spinal excitability was measured before and 2 min after repetitive peripheral magnetic stimulation or sham stimulation. While the

results revealed no effect on H-reflex amplitudes, a significant decrease of maximal M-responses was found following repetitive peripheral magnetic stimulation. Thus, the authors concluded that repetitive peripheral magnetic stimulation did not influence spinal excitability (Behrenset al., 2011). In addition, peripheral magnetic stimulation has been used in a range of clinical research, including the palliation of pain (Pujol et al., 1998, Lo et al., 2011, Leung et al., 2014), improvement of spasticity (Flamand et al., 2012, Krewer et al., 2014, Nielsen et al., 1996, Krause et al., 2005), and treatment after stroke (Struppler et al., 2003, Struppler et al., 2007). In addition, peripheral magnetic stimulation has been used for measuring muscle function (respiratory and skeletal) (Man et al., 2004). Taken together, the findings of previous studies suggest that changes induced by electrical stimulation and peripheral magnetic stimulation affect cortical activity.

Moreover, changes of MEP amplitude related to motor tasks at the cortical level have been found in peripheral muscular movement, including the finger, hand and arm. Tinazz et al. reported that although an increase in MEP amplitude was demonstrated during voluntary movement of the finger, the H-reflex remained unchanged (Tinazzi et al., 1998). Thus, the authors suggested that the change of bilateral MEP amplitude occurs at the cortical level. In addition, comparison of the effects of TMS and TES suggests the cortical neuronal networks targeting pyramidal neurons may be the sites at which most of the facilitation of motor cortical excitability induced by TMS take place. Stedman et al. applied transcutaneous electrical stimulation to the spinal cord to investigate spinal cord excitability (Stedman et al., 1998). During the volitional contraction of the dominant FDI, MEP amplitude induced by TMS indicated a significant increase, while no significant difference was found with transdermal electrical stimulation of the spinal cord. Hence, the authors concluded that the facilitation of cortical excitability occurred at the cortical level. Several brain imaging studies have used fMRI (Cramer et al., 1999, Kim et al., 1993, Rao et al., 1993) and PET (Shibasaki et al., 1993) to examine the activation of the motor cortex in contralateral and ipsilateral finger movements. Similar results have been reported in the

voluntary movement of the hand or arm (Reid and Serrien, 2014, Ziemann et al., 2001, Mazzocchio et al. 1994, Kawashima et al., 1998). Taken together with the findings described above (Ridding et al., 2000, Kaelin-Lang et al., 2002, Stedman et al., 1998, Behrens et al., 2011, Struppler et al., 2007), the current findings suggest that changes induced by peripheral magnetic and electrical stimulation may influence cortical activity.

1-4 The purpose of this study

The cortical excitability of the motor cortex can be altered by TMS, and by peripheral stimulation. TMS has been found to affect the excitability of the cerebral cortex via facilitation and inhibition, depending on the stimulation parameters used, including the frequency, intensity, duration and inter-train interval of magnetic stimulation. Previous studies have indicated the possibility that high-frequency TMS of greater than 5 Hz increases motor cortex excitability, whereas low-frequency TMS of 1 Hz decreases motor cortex excitability (Chen et al., 1997, Romero et al., 2002, Maeda et al. 2000, Pascual-Leone et al. 1994, Berardelli et al., 1998, Wassermann et al., 1998). MEP amplitude reflects corticospinal excitability, and has been found to be affected by a number of the same factors that affect corticospinal excitability (Pascual-Leone et al. 1998). Many previous studies have used MEPs to evaluate cortical excitability induced by TMS in the primary motor cortex (Chen et al., 1997, Romero et al., 2002, Maeda et al. 2000, Pascual-Leone et al. 1994, Berardelli et al., 1998, Wassermann et al., 1998). Berardelli et al. suggested that the facilitation of cortical excitability induced by 5 Hz rTMS applied to the primary motor cortex occurs in the cortex, but not in the spinal cord. In addition, they reported that the facilitation of cortical excitability may induce activity in the stimulated cortical region by increasing the excitability of pyramidal cells and their excitatory inputs (Berardelli et al., 1998). In contrast, Chen et al. found that MEP amplitude decreased following 0.9 Hz rTMS to the primary motor cortex, showing an inhibitory effect on cortical excitability. Based on these findings, the authors suggested that low-frequency rTMS may decrease the efficacy of corticocortical synapses or the excitability of postsynaptic corticospinal neurons (Chen et al., 1997).

Moreover, the cortical excitability induced by rTMS in the primary motor cortex may depend on the stimulation intensity as well as the stimulation frequency (sub- or supra-motor threshold) (Romero et al., 2002, Lang et al. 2006). Low-frequency repetitive TMS (rTMS) at a frequency of 1 Hz has been reported to decrease motor cortical

excitability, and many studies have used supra-threshold stimulation intensity (Chen et al., 1997, Maeda et al. 2000). The inhibition of motor cortical excitability is thought to play a role in muscle twitch induced by TMS. However, not all types of TMS alter cortical excitability. Chen et al. confirmed that 0.1 Hz rTMS at an intensity of 105% of the motor threshold for the primary motor cortex for 1 h did not affect cortical excitability (Chen et al., 1997).

Previous studies have suggested that the alteration of cortical excitability induced by peripheral stimulation (electrical or magnetic) occur at the cortical level rather than in the spinal cord. These findings suggest that the electrical or magnetic stimulation with a high frequency or long duration (several minutes or hours) applied over the periphery can cause facilitation of motor cortical excitability (Ridding et al., 2000, Kaelin-Lang et al., 2002, Struppler et al., 2007, Behrens et al., 2011).

As discussed above, it has been well established that electrical or magnetic stimulation with a high frequency or long duration over the periphery can facilitate cortical excitability in the primary motor cortex (Ridding et al., 2000, Kaelin-Lang et al., 2002, Stedman et al., 1998, Behrens et al., 2011, Struppler et al., 2007). However, few other studies have reported that magnetic and electrical stimulation can induce inhibition of motor cortical excitability under certain conditions. Thus, the current study focused on the inhibitory effects of induced cortical excitability in the motor cortex using supra-threshold rTMS. The current study hypothesized that if inhibition of cortical excitability is induced by muscle twitch caused by supra-threshold rTMS, inhibition of cortical excitability would be elicited by direct stimulation for the forearm. Thus, the current study investigated the possibility that peripheral stimulation has similar effects to TMS on motor cortical excitability, by examining the inhibition of motor cortical excitability induced by peripheral stimulation. To induce inhibition of motor cortical excitability, a stimulation frequency of 1 Hz was used, similar to the frequency used in previous studies of supra-threshold TMS over the forearm. Moreover, the stimulation frequency and stimulation site of peripheral stimulation were varied to investigate the underlying changes in cortical excitability in the primary motor cortex induced by

peripheral stimulation. In this study, magnetic stimulation and electrical stimulation were used as methods of peripheral stimulation. Both magnetic stimulation and electrical stimulation cause muscle twitches by stimulating muscle fibers. This study compared the effects of magnetic and electrical stimulation on motor cortical excitability to investigate differences in the alteration of motor cortical excitability caused by each stimulation method. The effects of peripheral stimulation were evaluated by comparing the MEP amplitude induced by TMS applied to the primary motor cortex before and after peripheral stimulation. For the measurement of MEPs, we used TMS parameters that do not affect cortical excitability, with a stimulation frequency 0.1 Hz and stimulation intensity of 105% of RMT (Chen et al., 1997).

Chapter 2

The modulation of motor cortical excitability by supra-threshold rTMS

Reference paper

Modulation of amplitude and latency of motor evoked potential by direction of transcranial magnetic stimulation, Aya Sato, Tetsuya Torii, Masakuni Iwahashi, Yuji Itoh, and Keiji Iramina, Journal of Applied Physics 115, 17B304, 2014

2-1 Introduction

Transcranial electrical stimulation (TES) is a noninvasive technique for stimulating the human brain, first reported by Merton et al. about 35 years ago (Merton et al., 1980). This technique involves direct stimulation of the brain using high-voltage electrical stimuli delivered through electrodes on the scalp. TES attracted early attention as a breakthrough technique for noninvasive stimulation of the brain and spinal cord, and was applied to the investigation of movement and brain function, as well as being used as a diagnostic tool. However, the electrical stimulation involved in TES is painful, limiting its usefulness with patients and healthy participants. Five years after the development of TES, transcranial magnetic stimulation (TMS) was introduced by Barker et al. (Barker et al., 1985a). Repetitive TMS (rTMS) in which trains of TMS stimuli are delivered, has been used by Pascual-Leone et al. for the treatment and investigation of neurological diseases of the central nervous system (Pascual-Leone et al., 1996). Because TMS stimulates the brain using eddy currents produced by a magnetic coil, it is not affected by the high impedance of the skull and scalp. Therefore, in contrast with TES, participants do not experience discomfort during stimulation. The effects of TMS are similar to TES, and both are thought to affect cortical excitability (Merton et al., 1980, Nitsche et al., 2001, Barker et al., 1985b, Hallett, 2000, Ridding et al., 2007). However, the latency of motor evoked potentials (MEPs) induced by rTMS are slightly longer compared with the latency of MEPs induced by TES. In addition, stimulating the cortex through the intact scalp by rTMS using a figure-eight-shaped coil enables more focal stimulation in comparison with TES, in which localization is relatively imprecise (Merton et al., 1980, Ueno et al., 1990). The effects of magnetic stimulation are thought to depend on a range of stimulus parameters, including frequency, intensity, and duration (Pascual-Leone et al., 1994, Touge et al., 2001, Fitzgerald et al., 2002, Torii et al., 2012). For example, high-frequency (5–25 Hz) rTMS has been found to induce an increase in motor cortical excitability during or following trains of stimulation (Pascual-Leone et al., 1994, Maeda et al., 2000, Peinemann et al.,

2000, Romeo et al., 2000). In contrast, decreased motor cortical excitability has been reported to be induced by low-frequency (e.g., 1 Hz) rTMS (Chen et al., 1997, Siebner et al., 1999, Maeda et al., 2000, Muellbacher et al., 2000, Touge et al., 2001). Chen et al. reported that rTMS delivered to the primary motor cortex with an intensity of 115% of the resting motor threshold (RMT) and a frequency of 0.9 Hz decreased MEP amplitude for 15 min after the end of the train, while MEP amplitude was unaffected by rTMS of an intensity of 105% of the RMT and a frequency of 0.1 Hz for 1 h (Chen et al., 1997). Moreover, with the same stimulus frequency (1 Hz), it was reported that the effect of magnetic stimulation depended on whether the stimulus intensity was supra-threshold or sub-threshold (Fitzgerald et al., 2002). Hence, the effect of magnetic stimulation does not change cortical excitability under all conditions, and appears to depend on stimulation parameters. In addition, the effects of magnetic stimulation on cortical excitability may vary in a complex way depending on the particular combination of stimulation parameters.

Various combinations of stimulation parameters have been utilized in previous studies and treatment methods. However, some reports have investigated the effects of changing both the stimulus intensity and the direction of the eddy current. The current study focused on inhibition of motor cortical excitability, and investigated changes in cortical excitability in the motor cortex induced by alteration of the magnetic coil direction and rTMS with higher stimulation intensity than that used in previous studies. MEPs during rTMS were measured, and confirmed temporal changes of MEP amplitude. Moreover, changes in MEP latency induced by the direction of the stimulation coil were investigated. Thus, the current study investigated alterations of motor cortical excitability induced by magnetic stimulation of low frequency and supra-threshold intensity.

2-2 Experimental methods

Six healthy participants (four male and two female, mean age 30.7 ± 6.9 years) were enrolled in this study. None of the participants had a history of psychiatric illness, neurological disorders, or disturbance of motility, and all participants provided informed consent. The protocol was approved by the Kyushu University institutional review board. The participants were instructed to maintain a fixed head position, keep their eyes open, and refrain from moving the limbs and fingers throughout the experiment

2-2-1 MEP measurement conditions and stimulus characteristics for repetitive transcranial magnetic stimulation

Figure 2-1 illustrates the MEP measurement conditions and the stimulus characteristics for rTMS. TMS delivered to the primary motor cortex was used for evoking MEPs. For each participant, the optimal scalp position over the left primary motor cortex was determined for recording electromyograms from the right abductor pollicis brevis (APB) muscle. A Magnetic Stimulator AAA-15887 (Nihonkohden, Tokyo, Japan) device with a figure eight-shaped flat coil (65 mm double coil) was used as the magnetic stimulator to deliver TMS. To measure the RMT for each participant, the magnetic stimulation coil was placed tangentially to the scalp, and was positioned laterally at a 45 degrees angle to induce current in a posterior-to-anterior (PA) direction. The stimulation coil was secured with a coil holder and the coil position was continuously monitored throughout the experiment. Each participant's individual RMT was defined as the minimal stimulator output that elicited MEP responses with a peak-to-peak amplitude greater than 50 μV, produced in response to at least five of 10 successive pulses (Rossini et al., 1994), with a magnetic pulse width of 200 μs.

rTMS was delivered via the same magnetic stimulator device and stimulation coil used for the measurement of MEPs. Because this magnetic stimulator produces a monophasic pulse waveform, the direction of induced current could be confirmed (Mills

et al., 1997, Rossini et al., 1992, Triggs et al., 1994). rTMS was delivered with a stimulation frequency of 0.1 Hz and a total of 60 magnetic pulses. The position of the stimulation coil generated an induced current in the PA or anterior-posterior (AP) direction in the brain. The stimulation coil was secured by a coil holder after the optimal stimulation was identified, and the coil position was continuously monitored throughout the experiment. The magnetic stimulation intensity was set at 120% of RMT for each participant.

Electromyography

Neuropack X1 (Nihon Kohden, Tokyo, Japan) was used to record MEPs from the right APB muscle induced by TMS through surface silver/silver-chloride (Ag-AgCl) electrodes. A ground electrode was placed over the right metacarpophalangeal joint of the thumb. The electromyogram signals were amplified with a 5 Hz to 3 kHz band-pass filter and digitized with a sampling rate of 10 kHz.

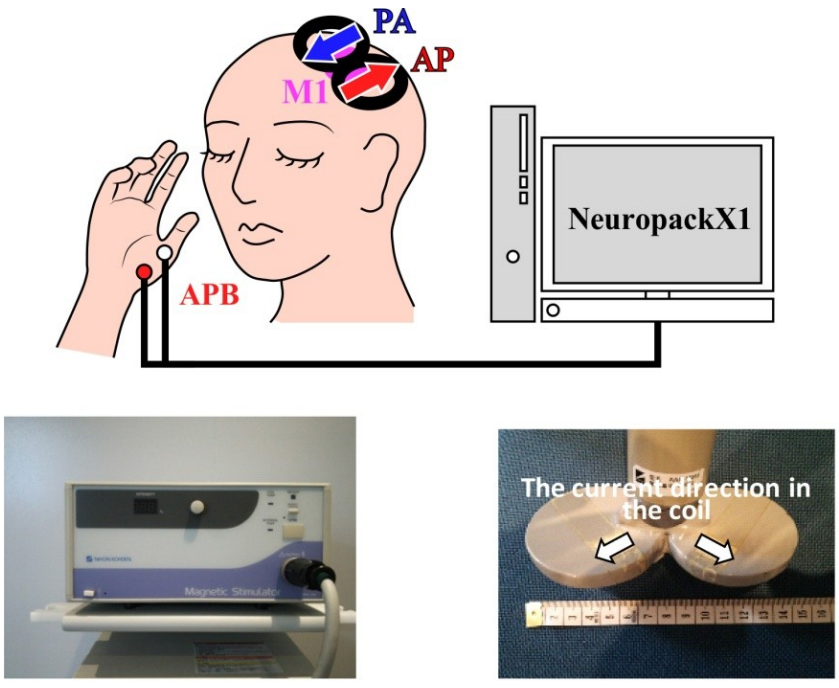


Figure 2-1 the Experimental environment

Data analysis

The peak-to-peak amplitudes and latency of MEPs were used to evaluate responses to magnetic stimulation. MEPs induced by TMS with peak-to-peak amplitude greater than 50 μV were used for analysis. The effects of current direction (PA or AP) were evaluated by comparing the average MEP amplitude of the first 10 magnetic pulses (as a baseline) and subsequent sets of 10 magnetic pulses in each direction condition.

Paired t-tests were used to compare the average MEP amplitude between the baseline and the subsequent 10 magnetic pulses. To evaluate MEP latencies, the initial magnetic stimulation was used for comparisons, regardless of the direction of induced current. In addition, the effects of PA and AP direction on MEP latency were compared across 60 magnetic pulses.

2-3 Results

Figure 2-2 shows MEPs induced by the PA and AP directions of the intracerebral induced current. These MEPs are an example from two participants who exhibited a characteristic pattern, and similar tendencies were observed in all other participants. The MEP latency evoked by induced current in the AP direction was delayed compared with that in the PA direction. This delay was observed in both the rising edge and peak of MEPs.

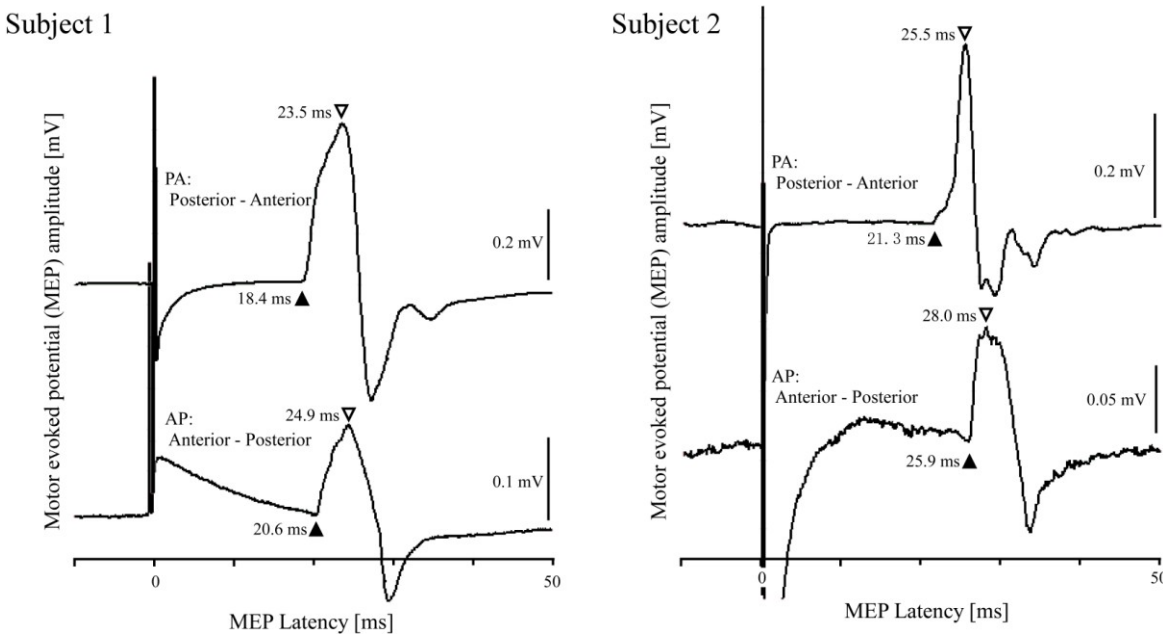


Figure 2-2 Comparison of MEP latencies on the APB to direction of the induced current at PA and AP

This figure shows the MEP responses from two subjects after first magnetic stimulation (the average of first-10th magnetic pulses) in each induced current direction (PA and AP). The MEP latency was measured at two points, the rising edge: upward-pointing triangles, the peak: downward-pointing triangles

Figure 2-3 shows the modulation of MEP latency compared between different induced current directions, for all participants. Comparison of MEP latencies in the PA and AP directions confirmed that the delay shown in Figure 2-2 was exhibited by all participants. The average delay time was 2.31 ms ($p < 0.01$) for the rising edge, and 2.45 ms ($p < 0.01$) for the peak.

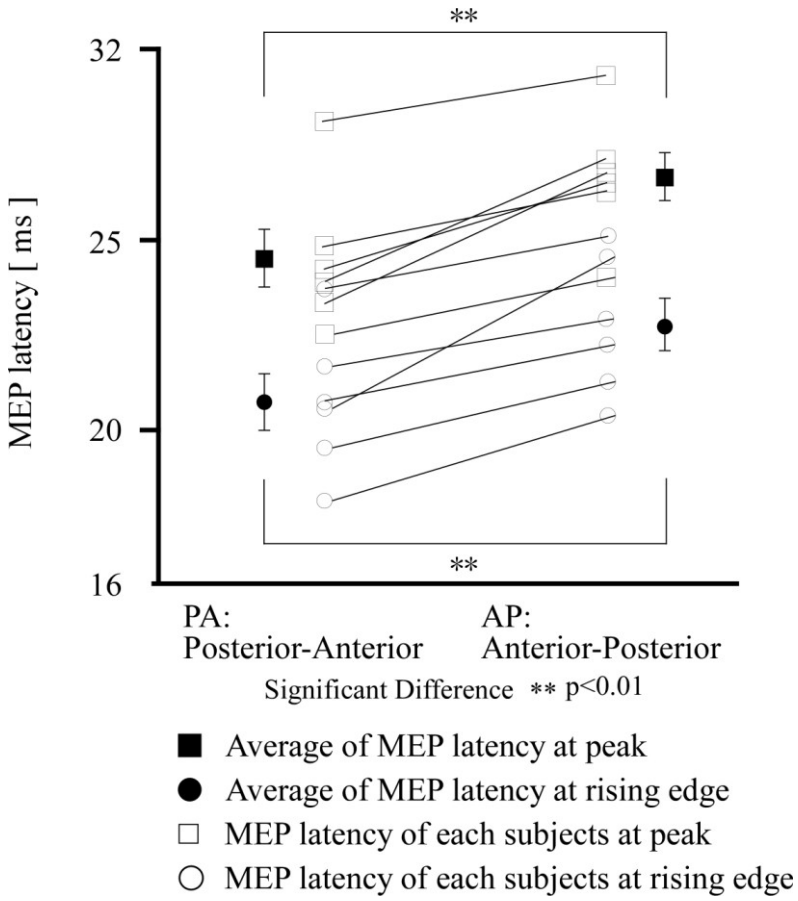


Figure 2-3 The MEP latencies elicited by intracerebral induced current in the PA and AP directions

The black symbol shows the latency mean and standard error at the rising edge and peak. The white symbol shows the MEP latency for each subject. The square symbol is the latency of the MEP peak, and the circle symbol is the latency of the MEP rising edge.

Figure 2-4 shows the modulation of MEP amplitude in the PA and AP directions. Compared with the baseline, the average MEP amplitude for the 31st-40th magnetic pulses increased by up to 150% ($p < 0.01$), and the average MEP amplitude of the 41st-50th magnetic pulses was increased by up to 153% ($p < 0.05$). However, for the average MEP amplitude for the 11th-20th, 21st-30th and 51st-60th magnetic pulses, there was no significant difference ($p > 0.05$) in amplitude compared with the baseline. In contrast, for induced current in the AP direction, MEP amplitude was unaltered across the 60 magnetic pulses.

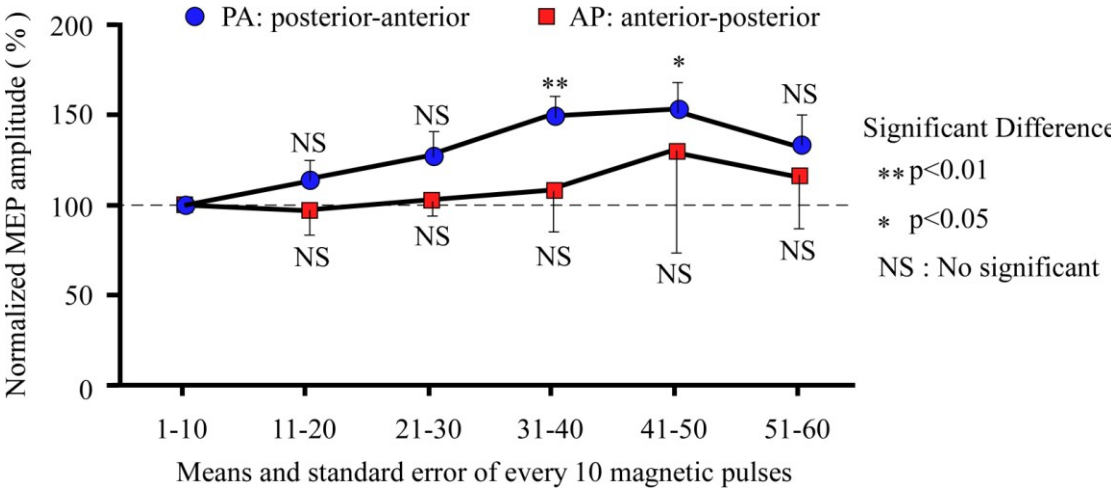


Figure. 2-4 Modulation of MEP amplitude during magnetic stimulation

Plots in the figure show the average and standard errors of induced MEP amplitude every 10 magnetic pulses. The average MEP amplitude induced by every 10 magnetic pulses was normalized by the average MEP amplitude of the first 10 magnetic pulses.

2-4 Discussion

The current study examined the effects of supra-threshold rTMS on cortical excitability in the primary motor cortex. The possibility that motor cortical excitability could be altered with rTMS was examined by varying the stimulus intensity and direction of the magnetic stimulation coil. First, the results confirmed that suprathreshold rTMS (120% of RMT) induced a tendency for MEP amplitude to be decreased by continuation of the magnetic pulse after a gradual increase of MEP amplitude. Next, it was confirmed that altering the direction of the magnetic coil delivering suprathreshold rTMS caused differences in MEP amplitude. These two findings suggest that changes of motor cortical excitability were dependent on the combination of stimulus intensity and the direction of the eddy current.

Since TMS was developed in 1985, it has been was well established that magnetic stimulation to motor cortex can be used to alter cortical excitability (Barker et al., 1985ab, Hallett, 2000, Maeda et al., 2000, Boylan et al., 2001, Ridding et al., 2007, Hamada et al., 2007). However, in one previous study, Chen et al. reported that motor cortical excitability was unaffected by 1 hour of TMS with a stimulus frequency of 0.1 Hz and stimulus intensity of 105% of RMT (Chen et al., 1997). In the same study, it was reported that a decrease of MEP amplitude was induced by TMS with a stimulus frequency of 0.9 Hz and stimulus intensity of 115% of RMT. Moreover, another study reported that the effects of TMS with a stimulus frequency of 1 Hz were dependent on stimulus intensity (Fitzgerald et al., 2002). Based on the previous findings that a stimulus frequency of 0.1 Hz does not influence motor cortical excitability under some conditions, and that supra-threshold stimulus intensity can decrease motor cortical excitability, this study investigated the effects of TMS on motor cortical excitability. The results of the current study confirmed that TMS with a stimulus frequency of 0.1 Hz affected the motor cortical excitability. For example, the current results revealed that 0.1 Hz rTMS at a stimulation intensity of 120% of RMT induced a tendency to gradually facilitate motor cortical excitability when the induced current was in the PA

direction. In contrast, for the induced current in the AP direction, t-tests revealed no significant differences in MEP amplitude. This effect on motor cortical excitability may be related to the higher stimulation intensity used in the current study compared with previous studies. Thus, these results suggest that an increase in magnetic stimulation intensity strongly affects cortical excitability. This possibility is in accord with several previous reports suggesting that cerebrocortical excitability depends on stimulation parameters such as stimulation intensity (Fitzgerald et al., 2002, Berger et al., 2011). This possibility is in accord with several previous reports suggesting that cerebrocortical excitability depends on stimulation parameters such as stimulation intensity (Fitzgerald et al., 2002, Berger et al., 2011). As noted above, TMS with supra-threshold stimulus intensity, can cause a decrease in MEP amplitude. Lang et al. suggested that the decrease of cortical excitability induced by TMS of supra-threshold intensity may be caused by afferent feedback activation (Lang et al., 2006). They applied 1 Hz rTMS at sub-threshold (90% of RMT) and supra-threshold (115% of RMT) intensity to the left motor cortex for 15 minutes. To assess changes in corticospinal and intracortical excitability induced by rTMS in the current study, we measured MEPs, short-latency intracortical inhibition (SICI) and intracortical facilitation (ICF) before and after rTMS. The results revealed a decrease in MEP amplitude and ICF with 1 Hz rTMS at supra-threshold intensity, whereas no changes in SICI were observed. These findings suggest that 1 Hz rTMS of supra-threshold intensity induced inhibition of corticospinal excitability and a decrease in intracortical facilitation.

This study confirmed alteration of the motor cortical excitability in every 10 magnetic pulses between the 1st and 60th pulses. The results revealed that the MEP amplitude of the 51st–60th magnetic pulses did not exhibit the gradual facilitatory tendency shown by the earlier stimuli. Several previous studies suggested that the absence of facilitation of motor cortical excitability was associated with inhibition of motor cortical excitability caused by afferent feedback activation following facilitation of motor cortical excitability (Lang et al., 2006, Bestmann et al, 2004). This notion is supported by the decrease in MEP amplitude observed in previous studies (Lang et al.,

2006). Thus, the decrease in MEP amplitude observed in the current study may reflect inhibition of motor cortical excitability caused by the continuous delivery of 60 magnetic pulses. Taken together, these previous findings and the current results suggest that an inhibitory effect occurs after gradual facilitation of motor cortical excitability.

In the current study, not only stimulus intensity but also the direction of the stimulation coil were modified, and when the induced current was in the AP direction, no significant modulation of motor cortex excitability was observed. The direction of the stimulation coil is considered to be an important parameter in magnetic stimulation. Changing the position and angle of the magnetic coil has been used in many studies as a sham stimulation condition to evaluate the effects of magnetic stimulation (Siebner et al., 2000, Boylan et al., 2001). The current results support the notion that realistic sham stimulation can be produced by altering the stimulation coil direction. A previous study reported that a difference in the latency of corticospinal volleys was elicited by induced current in the latero-medial (LM) and PA directions, with anodal stimulation (Nakamura et al., 1996). In addition, magnetic stimulation in the PA direction preferentially generated indirect waves (I-waves), and that in the LM direction preferentially generated direct waves (D-waves). Moreover, previous reports have suggested that magnetic stimulation induced the current to flow forward in a posterior preferentially elicited I1-wave, then flow backward in an anterior elicited I3-wave induced approximately 2.5 ms after the onset of the I1 wave (Sakai et al., 1997, Kernell et al., 1967). The current results confirmed that the difference in MEP latency between PA and AP direction was approximately 2.5 ms. This difference in MEP latency induced by magnetic stimulation suggests that the elicitation of I1 and I3 waves are deeply related. Therefore, the current findings support Day et al.'s hypothesis that induced current in the forward direction evokes an I1 wave volley, while induced current in the opposite direction elicits an I3 wave volley (Day et al., 1989).

2-5 Conclusion

The purpose of the current study was to clarify the modulation of motor cortical excitability induced by magnetic stimulation with a supra-threshold stimulus frequency and different directions of induced intracerebral current. MEP latency and amplitude was used to evaluate the effects of magnetic stimulation. MEPs induced by TMS were measured from the right APB, at the optimal scalp position over the left primary motor cortex. A figure eight-shaped flat coil was used to stimulate the left primary motor cortex with repetitive transcranial magnetic stimulation (rTMS) delivered at a stimulus intensity of 120% of the participant's RMT, with a stimulus frequency of 0.1 Hz and a total 60 magnetic pulses. The peak-to-peak amplitudes and latency of MEPs were used to evaluate responses to magnetic stimulation. MEPs were derived from right APB and recorded continuously during rTMS. Changes in MEP amplitude were analyzed for every group of 10 pulses, and the first 10 of the 60 stimulation pulses were used as a baseline. Thus, the effects of the conditional magnetic stimulation in this study were evaluated by comparing the average MEP amplitude of the first 10 magnetic pulses and each subsequent set of 10 magnetic pulses.

The effects of PA and AP direction on MEP latency were compared across 60 magnetic pulses. For induced current in the PA direction, MEP amplitude significantly increased at the 31st–40th and 41st–50th magnetic pulses, indicating increased cortical excitability. In the 1st–50th magnetic pulses, no significant alterations of cortical excitability were observed, but a non-significant tendency toward a gradual facilitatory effect was apparent. The 51st–60th magnetic pulses did not show this facilitatory tendency, and appeared to exhibit inhibition of cortical excitability. In contrast, no alteration of cortical excitability was observed with current in the AP direction. The latency of the rising edge and peak of MEPs revealed that the MEP latency evoked by induced current in the AP direction was delayed in comparison with the PA direction.

The current results revealed that even a magnetic stimulation frequency of 0.1 Hz induced changes in cortical excitability that depended on both the stimulus intensity of

TMS and the direction of the induced current. In addition, these findings suggest that an inhibitory effect on cortical excitability occurs after temporary facilitation of cortical excitability.

Chapter 3

Alteration of motor cortical excitability by peripheral magnetic stimulation

Reference paper

Basic study on the influence of inhibition induced by the magnetic stimulation on the peripheral nerve, Aya Sato, Tetsuya Torii, Masakuni Iwahashi, and Keiji Iramina, Journal of Applied Physics 117, 17B303, 2015

3-1 Introduction

Magnetic stimulation utilizes magnetic fields produced by short high-current pulses flowing through a wire coil, generating an eddy current directly below the device. The direction of the induced eddy current is opposite to the flow of the electric current in the magnetic coil (Hallett, 2000, Hallett, 2007, Ridding et al., 2007). Transcranial magnetic stimulation (TMS) can deliver stimulation to a target site through the skin or skull via this eddy current, and is a relatively painless and noninvasive procedure for participants (Barker et al., 1985a). Since TMS was developed by Barker et al. in 1985, it has been widely used as a safe tool for the investigation of physiological function. It has been established that low-frequency magnetic stimulation of 1 Hz decreases motor cortex excitability, whereas high-frequency magnetic stimulation of above 5 Hz increases motor cortex excitability (Chen et al., 1997, Romero et al., 2002, Maeda et al. 2000, Pascual-Leone et al. 1994, Berardelli et al., 1998, Wassermann et al., 1998). The effect of TMS on cortical excitability has been applied to the diagnosis and treatment of various diseases, including depression, stroke, relief of neural pain, and Parkinson's disease (Pascual-Leone et al., 1996, George et al., 1997, Murase et al., 2004, Takeuchi et al., 2005, Kim et al., 2006, Khedr et al., 2005, Lefaucheur et al., 2001, Yip et al., 2013, Shimamoto et al., 2001, Kleinjung et al., 2005). However, TMS is not an appropriate treatment for all patients, and exclusion criteria include the presence of metallic hardware, implanted brain electrodes, pregnancy, and heart disease (Rossi et al. 2009).

Because magnetic stimulation is a noninvasive technique, it can be used for afferent stimulation in addition to brain stimulation. Magnetic stimulation in areas of muscle that supply terminal branches has been proposed as an alternative method of transcutaneous electrical stimulation, called peripheral magnetic stimulation. Like functional neuromuscular stimulation, peripheral magnetic stimulation stimulates action potentials in motor axons that evoke muscle contraction. However, the eddy currents induced by peripheral magnetic stimulation penetrate tissue and stimulate deeper tissue regions than

neuromuscular stimulation (Machetanz et al., 1994, Krewer et al., 2014).

A previous study used positron emission tomography (PET) to investigate the central reorganization mechanisms involved in the improvement of simple movement by peripheral magnetic stimulation (Struppler et al., 2007). Peripheral magnetic stimulation was applied with a stimulation frequency of 20 Hz for a total of 5000 stimuli with an average amplitude of 1.2 T, delivered to the area of muscle supplying terminal nerve branches of the finger and hand extensor muscles. PET scanning after peripheral magnetic stimulation revealed significant increases of regional cerebral blood flow (rCBF) in the contralateral premotor cortex and the posterior parietal cortex, suggesting that improvement in motor task performance was related to increased neural activation. This finding indicates that increased activation of the parieto-premotor network following repetitive peripheral magnetic stimulation reflects a significant conditioning effect at the cortical level (Struppler et al., 2003, Struppler et al., 2007). Moreover, another previous study suggested that peripheral magnetic stimulation with 2000 stimuli at a stimulation frequency of 15 Hz over the soleus muscle belly did not influence spinal excitability (Behrens et al., 2011). Thus, these previous studies suggest that alterations of cortical excitability induced by peripheral magnetic stimulation may occur at the cortical level rather than the spinal cord.

Muscle contraction induced by peripheral magnetic stimulation has the advantage of causing substantially less discomfort than peripheral electrical stimulation (Bischoff et al., 1994). As such, peripheral magnetic stimulation has been used for a range of clinical applications, including the palliation of pain (Pujol et al., 1998, Lo et al., 2011, Leung et al., 2014), promotion of sensorimotor recovery, improvement of spasticity (Flamand et al., 2012, Krewer et al., 2014, Nielsen et al., 1996, Krause et al., 2005), and stroke (Struppler et al., 2003, Struppler et al., 2007). In addition, peripheral magnetic stimulation has been used for measuring muscle function (respiratory and skeletal) (Man et al., 2004). In addition, peripheral magnetic stimulation has been used for measuring muscle function (respiratory and skeletal) (Man et al., 2004).

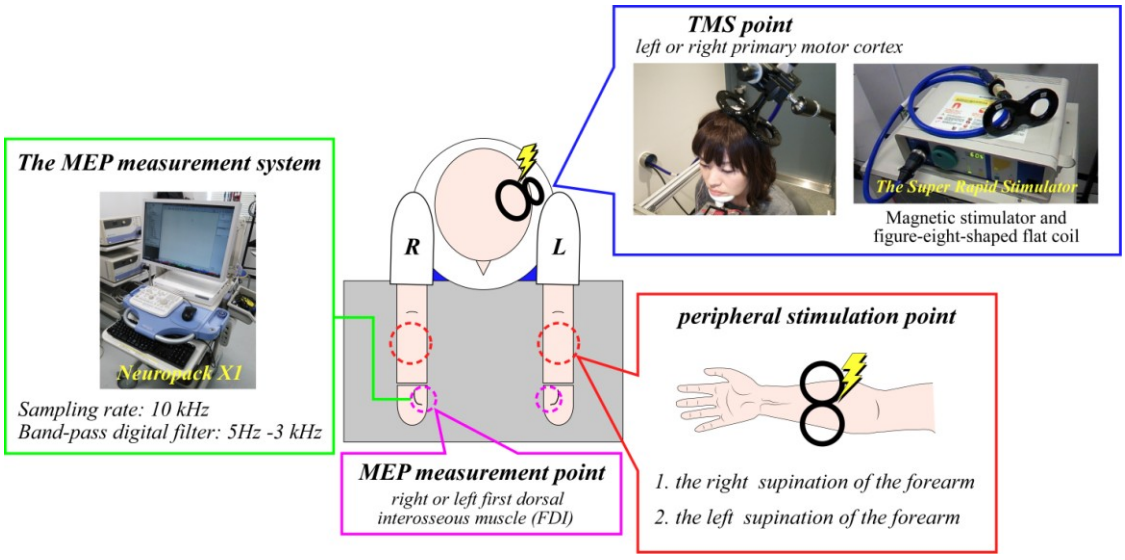
The effects of peripheral magnetic stimulation vary according to the stimulation parameters, which are determined by a combination of coil design, location, duration, frequency and intensity. Peripheral magnetic stimulation methods commonly utilize stimulation sites positioned over the spinal roots or muscle, and a stimulus frequency of around 20 Hz. However, stimulation parameters have not been standardized. Moreover, few previous studies have focused on the inhibition of cortical excitability by peripheral magnetic stimulation. One previous TMS study suggested that supra-threshold TMS of a low frequency inhibited motor cortical excitability (Chen et al., 1997, Maeda et al. 2000). These effects have been proposed to be caused by muscle-twitch evoked by TMS, and it has been found to play a role in inducing the inhibition of motor cortical excitability (Lang et al., 2006). Thus, the current study focused on the ability of peripheral magnetic stimulation to penetrate deeper regions of muscle. Accordingly, we investigated whether peripheral magnetic stimulation over the forearm has an influence on the inhibition of motor cortical excitability. Moreover, the stimulation frequency and site of peripheral magnetic stimulation were changed to investigate the influence on motor cortical excitability.

3-2 Experimental methods

A total of 29 healthy participants (17 male and 12 female, mean age 26.04 ± 8.31 years) were enrolled in this study. None of the participants had a history of psychiatric illness or neurological disorders or disturbance of motility, and all participants provided informed consent. The protocol was approved by the institutional review boards of Kyushu University and Tokai University.

Experimental environment

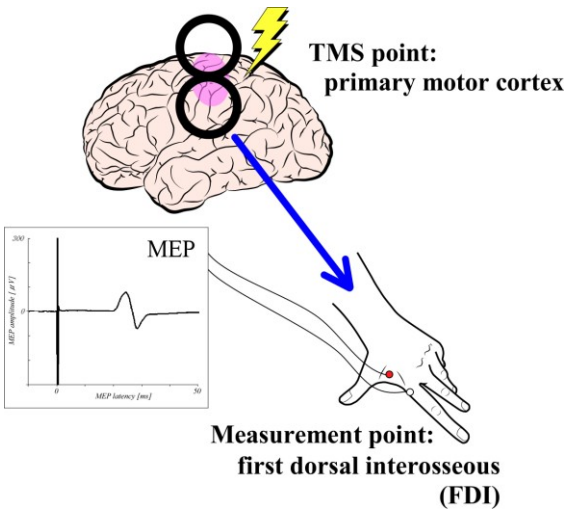
Figure 3-1 illustrates the experiment environment used in this study. Participants were seated in a comfortable chair and instructed to maintain relaxed muscles throughout the experiment. Moreover, participants were instructed to maintain a fixed head position, to hold the forearm in a supine position while peripheral magnetic stimulation was performed using a stand, to keep their eyes open, and to refrain from moving their limbs and fingers.



Figre 3-1 Experimetal environment

Measurement condition of motor evoked potentials (MEPs)

TMS was delivered to the primary motor cortex for evoking MEPs. Applying TMS to the motor cortex with an appropriate stimulation intensity and position enables MEPs to be recorded with electromyography in the contralateral extremities (Ridding et al., 2007, Hasey, 2001, Mano et al., 2003, Mano et al., 1993a) (Figure 3-2). A Super Rapid Stimulator (Magstim Co. Ltd, Whitland, Carmarthenshire, UK) device with a figure eight-shaped flat coil (70 mm double coil) was used as the magnetic-stimulating device for delivering TMS. The electromyograms induced by TMS were measured at the first dorsal interosseous (FDI) muscle using Neuropack X1 (Nihon Kohden, Tokyo, Japan), with surface electrodes (Ag-AgCl). For each subject, the magnetic stimulation coil was placed tangentially to the scalp over the primary motor cortex at the optimal position for evoking MEPs from the contralateral FDI muscle, and was positioned laterally at a 45 degrees angle to induce current in the posterior-to-anterior direction. The stimulation coil was secured with a coil holder after determining the optimal stimulation area, and the coil position was continuously monitored throughout the experiment. The individual resting motor threshold (RMT) for each participant was defined as the minimal stimulator output eliciting MEP responses with peak-to-peak amplitude greater than 50 μV produced in at least five of 10 successive pulses (Rossini et al., 1994). The magnetic pulse width was 200 μs.



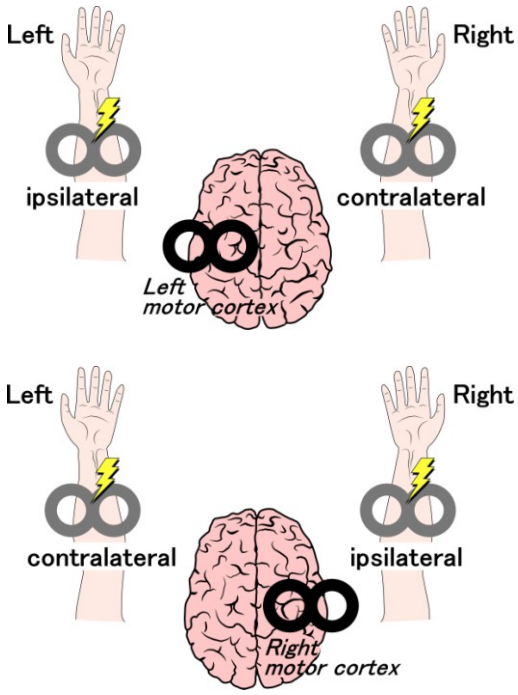
Figre 3-2 Measurement of MEP

Electromyography

Electromyograms induced by TMS were recorded with silver/silver-chloride (Ag-AgCl) surface electrodes at the right or left first FDI muscles. The ground electrode was placed over the measurement side metacarpophalangeal joint of the index finger. Neuropack X1 (Nihon Kohden, Tokyo, Japan) was used as an electromyogram recording device. The electromyogram signals were amplified with a band-pass filter between 5 Hz and 3 kHz, digitized with a sampling rate of 10 kHz.

Peripheral magnetic stimulation

The stimulus site of peripheral magnetic stimulation was the contralateral or ipsilateral forearm in relation to the primary motor cortex of the target area (Figure 3-3). Participants held the forearm of the stimulated side in an extended supine position on the table. A Super Rapid Stimulator (Magstim Co. Ltd, Whitland, Carmarthenshire, UK) was used as a magnetic stimulator to deliver peripheral magnetic stimulation.



Figre 3-3 The stimulus site of peripheral magnetic stimulation

The magnetic stimulation coil was an air-cooled figure-eight-shaped flat coil (70-mm diameter). The figure-eight-shaped flat coil was placed over the muscle belly of the supine forearm between the wrist and elbow on the stimulated side, such that the current induced by the coil would flow along the nerves. The stimulation coil was placed tangentially to the forearm, and was fixed with a coil holder. The magnetic pulse width was 200 μs. The stimulation frequency was altered in each experimental condition. The stimulation intensity was adjusted by the minimal stimulator output to produce a slight wag of the finger for each participant (the average stimulation intensity was 40.58% for the contralateral forearm, and 40% for the ipsilateral forearm).

Experimental procedure

The experimental paradigm was divided into three phases, as shown in Figure 3-4. In the first phase, TMS was performed to evoke MEPs from the contralateral FDI muscle. The stimulation frequency and intensity of TMS were respectively set at 0.1 Hz, and 105% of each participant's RMT. It has been previously reported that this stimulation frequency and intensity did not affect motor cortex excitability (Chen et al., 1997). MEPs induced by TMS were measured from the contralateral FDI muscle over the primary motor cortex. MEPs with peak-to-peak amplitude of greater than 50 μV induced by TMS were analyzed in sets of 10 recorded MEPs. These MEPs were used to evaluate the effect of the peripheral stimulation as a baseline. In the second phase, peripheral magnetic stimulation was applied over the forearm of the stimulated side immediately after the first phase. In this phase, peripheral magnetic stimulation was applied with a combination of different stimulation sites and stimulation frequencies.

The experimental conditions were as follows:

I. Peripheral magnetic stimulation of the contralateral forearm (right forearm) for left primary motor cortex ($M1_{left}$)

I-1. $M1_{left}$ -1 Hz-right (50): frequency 1 Hz, 50 pulses

I-2. $M1_{left}$ -1 Hz-right (100): frequency 1 Hz, 100 pulses

I-3. $M1_{left}$ -5 Hz-right: frequency 5 Hz, 500 pulses

I-4. $M1_{left}$ -10 Hz-right: frequency 10 Hz, 500 pulses

II. Peripheral magnetic stimulation of ipsilateral forearm (left forearm) to left primary motor cortex ($M1_{left}$)

II-1. $M1_{left}$ -1 Hz-left: frequency 1 Hz, 100 pulses

II-2. $M1_{left}$ -10 Hz-left: frequency 10 Hz, 500 pulses

III. Peripheral magnetic stimulation of contralateral forearm (left forearm) to right primary motor cortex ($M1_{right}$)

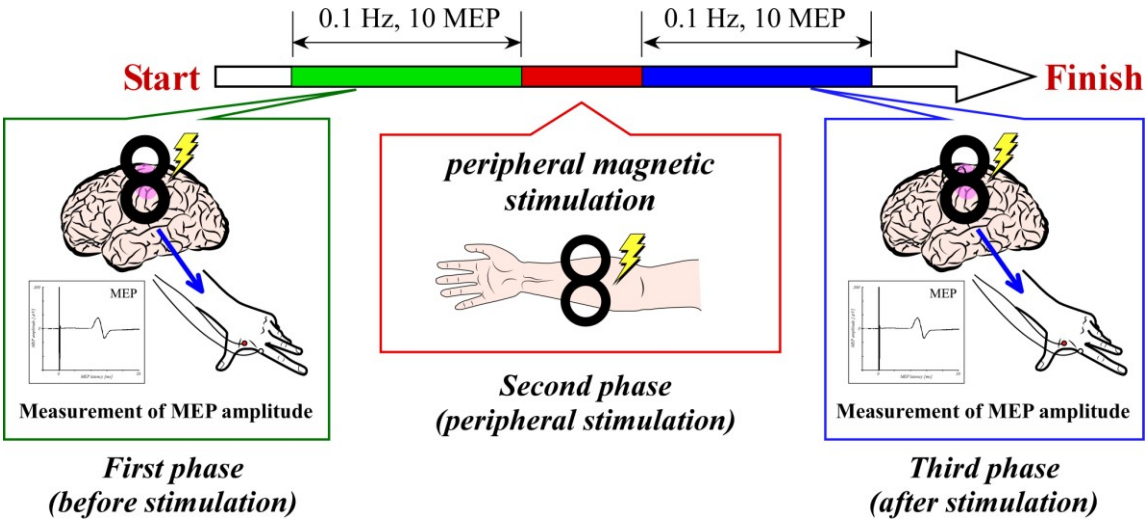
III-1. $M1_{right}$ -1 Hz-left: frequency 1 Hz, 100 pulses

IV. Peripheral magnetic stimulation of ipsilateral forearm (right forearm) to right primary motor cortex ($M1_{right}$)

IV-1. $M1_{right}$ -1 Hz-right: frequency 1 Hz, 100 pulses

To confirm the effects of peripheral magnetic stimulation, sham stimulation was also performed in this phase. For sham stimulation, the coil was positioned so that the device did not touch the forearm. No magnetic stimulation was delivered during sham stimulation, and the device issued only a sound.

Finally, in the third phase, TMS was performed with the same set up as in the first phase, immediately after the second phase. Similarly to the first phase, MEPs induced by TMS was also recorded. The effects of peripheral magnetic stimulation on cortical excitability were evaluated by comparing the mean MEP amplitudes recorded in the first phase (before peripheral magnetic stimulation) and the third phase (after peripheral stimulation). For statistical analysis, paired t-tests were employed to compare the average MEP amplitude before and after peripheral magnetic stimulation.



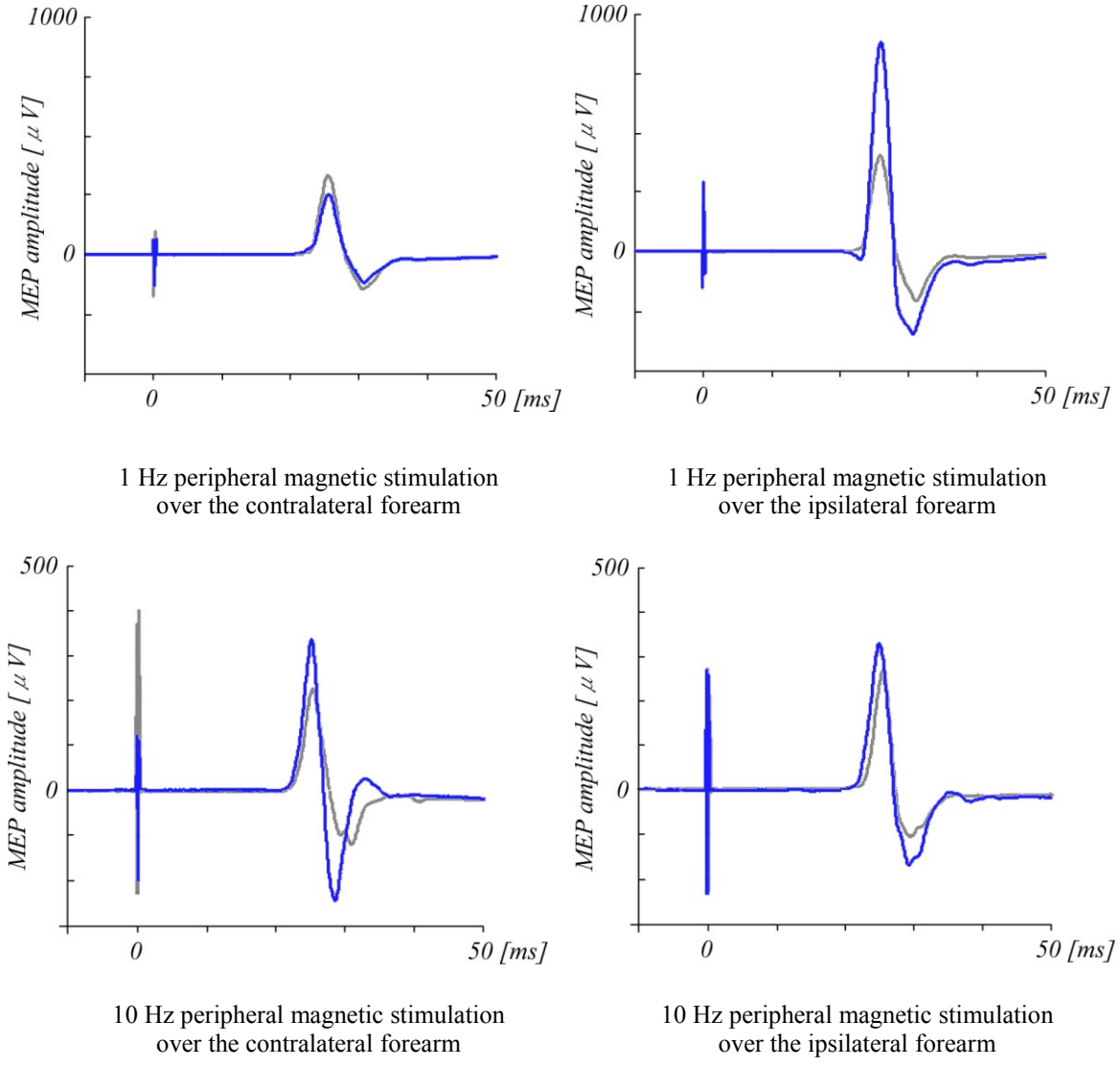
Figre 3-4 Experiment pocedure

3-3 Results

3-3-1 Change of stimulation site of peripheral magnetic stimulation

Figure 3-5 shows the MEPs induced by peripheral magnetic stimulation over the contralateral and ipsilateral forearm for the left motor cortex. Figure 3-5 (A) shows the MEP amplitudes from one participant who showed characteristic responses to 1 Hz and 10 Hz stimulation. Each graph shows MEPs with peak-to-peak amplitude of greater than 50 μV averaged over 10 trials, induced by TMS. A similar pattern was observed in almost participants. When we used the same TMS setup for the first and third phase, the MEP amplitudes recorded before and after peripheral magnetic stimulation (i.e., the first and third phase) were used to evaluate the effect of peripheral magnetic stimulation on cortical excitability.

With 1 Hz peripheral magnetic stimulation over the contralateral forearm ($M1_{left}$ -1 Hz-right (100)), the MEP amplitude following peripheral magnetic stimulation was decreased compared with before peripheral magnetic stimulation. In contrast, the MEP amplitude after 1 Hz peripheral magnetic stimulation over the ipsilateral forearm ($M1_{left}$ -1 Hz-left) was increased compared with before peripheral magnetic stimulation. The MEP amplitude following 10 Hz peripheral magnetic stimulation was increased in both the contralateral and ipsilateral forearms ($M1_{left}$ -10 Hz-right and $M1_{left}$ -10 Hz-left) compared with before peripheral magnetic stimulation.



1 Hz peripheral magnetic stimulation over the contralateral forearm

1 Hz peripheral magnetic stimulation over the ipsilateral forearm

10 Hz peripheral magnetic stimulation over the contralateral forearm

10 Hz peripheral magnetic stimulation over the ipsilateral forearm

Figure 3-5 (A) The alteration of MEPs induced by peripheral magnetic stimulation over the contralateral and ipsilateral forearm for left motor cortex in one subject.

The gray line represents an MEP before peripheral magnetic stimulation, and the blue line represents an MEP after the peripheral magnetic stimulation.

Figure 3-5 (B) and (C) show the normalized average MEP amplitudes with different stimulation sites. Because there were individual differences in the MEP amplitudes induced by TMS, normalization using each MEP amplitude recorded before peripheral magnetic stimulation was performed. The average MEP amplitude after peripheral magnetic stimulation was normalized using the average MEP amplitude before peripheral magnetic stimulation in each participant. A paired t-test was used to examine whether there were significant differences in average MEP amplitude between each experimental condition and the peripheral magnetic stimulation. The data are presented as mean and standard error, and a 5% level of significance was used for all experiments.

Figure 3-5 (B) shows the normalized average MEP amplitude in the sham and $M1_{left}$-1 Hz-right (50). The average MEP amplitude after sham stimulation did not exhibit a significant difference compared with before sham stimulation (n = 7). The average MEP amplitude after $M1_{left}$ -1 Hz-right (50) was decreased significantly

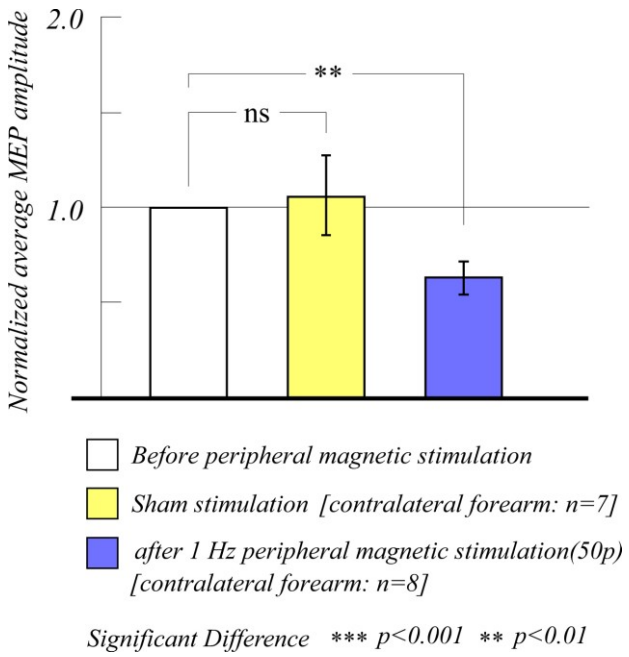


Figure 3-5 (B) Comparison of normalized average MEP amplitude evoked by sham stimulation and $M1_{left}$ -1 Hz-right (50)

The white bar shows the normalized average MEP amplitude before peripheral magnetic stimulation. This bar is always 1.0. The colored bars show the normalized average MEP amplitude after peripheral magnetic stimulation at each stimulus site.

compared with the average MEP amplitude before peripheral magnetic stimulation ($M1_{left}$ -1 Hz-right (50): n = 8, p < 0.01). The mean decrease in the average MEP amplitude was approximately 64%.

Figure 3-5 (C) shows the normalized average MEP amplitude for each different site or frequency condition. The average MEP amplitude after $M1_{left}$ -1 Hz-right (100) was decreased significantly compared with the average MEP amplitude before peripheral magnetic stimulation (n = 13, p < 0.001). The mean decrease in average MEP amplitude was approximately 65%. In contrast, the average MEP amplitude after $M1_{left}$ -10 Hz-right increased significantly compared with the average MEP amplitude before peripheral magnetic stimulation (n = 14, p < 0.01). The mean increase in average MEP amplitude was approximately 132%.

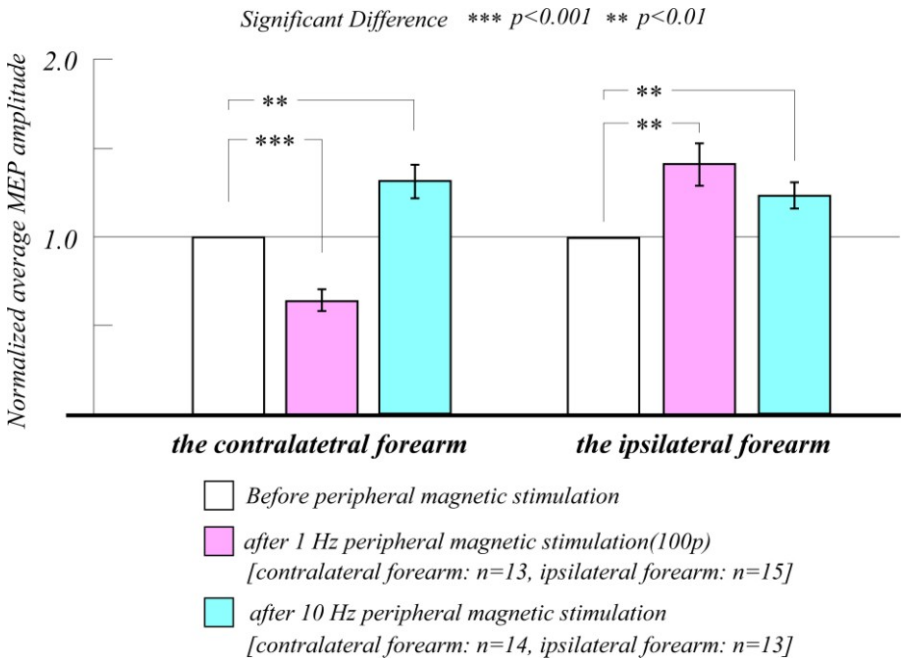


Figure 3-5 (C) Comparison of normalized average MEP amplitude evoked by peripheral magnetic stimulation at different stimulation sites

The white bar shows the normalized average MEP amplitude before peripheral magnetic stimulation. This bar is always 1.0. The colored bars show the normalized average MEP amplitude after peripheral magnetic stimulation at each stimulus site.

The average MEP amplitude after $M1_{left}$ -1 Hz-left and $M1_{left}$ -10 Hz-left was significantly increased compared with the average MEP amplitude before peripheral magnetic stimulation ($M1_{left}$ -1 H-left: n = 15, p < 0.01, $M1_{left}$ -10 Hz-left: n = 13, p < 0.01). The mean increases in average MEP amplitude were approximately 142% for $M1_{left}$ -1 Hz-left, and approximately 123% for the $M1_{left}$ -10 Hz-left.

Figure 3-6 shows the normalized average MEP amplitude with 1 Hz peripheral magnetic stimulation over the contralateral or ipsilateral forearm in relation to the target motor cortex (for left motor cortex: $M1_{left}$ -1 Hz-right (100), $M1_{right}$ -1 Hz-left, for right motor cortex: $M1_{left}$ -1 Hz-left, $M1_{right}$ -1 Hz-right). For the contralateral forearm, the average MEP amplitude after $M1_{left}$ -1 Hz-right (100) was significantly decreased compared with the average MEP amplitude before peripheral magnetic stimulation (n =

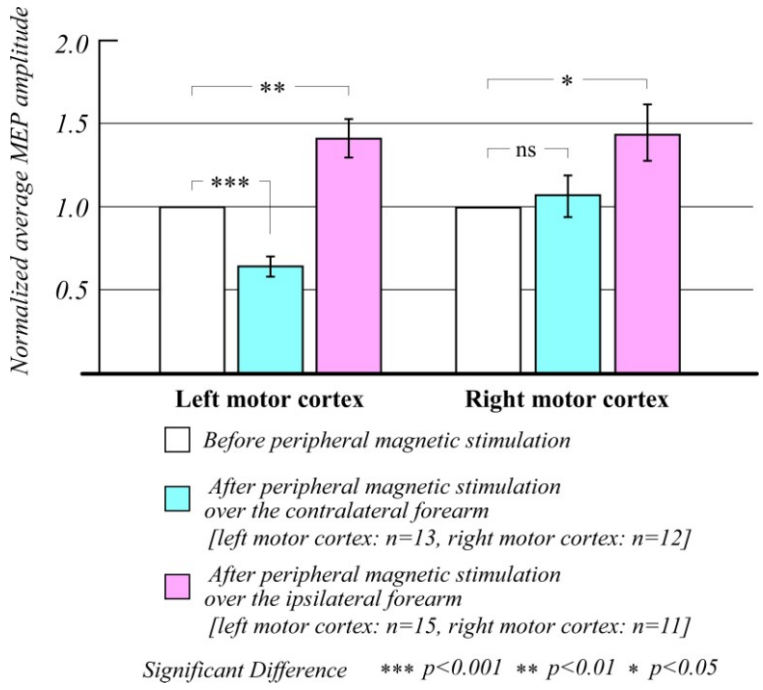


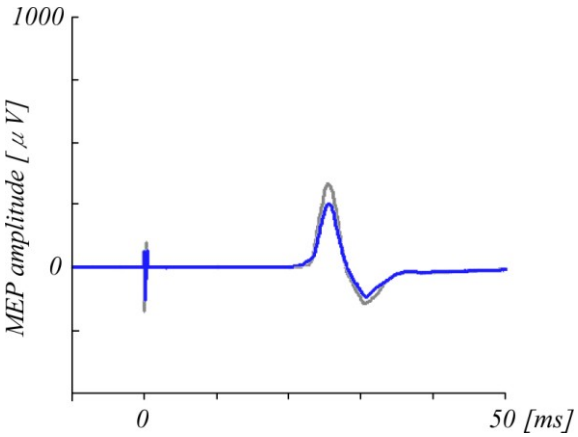
Figure 3-6 Comparison of MEP amplitude evoked by peripheral magnetic stimulation in the left and right motor cortex

The white bar shows the normalized average MEP amplitude before peripheral magnetic stimulation. This bar is always 1.0. The colored bars show the normalized average MEP amplitude after peripheral magnetic stimulation at each stimulus site.

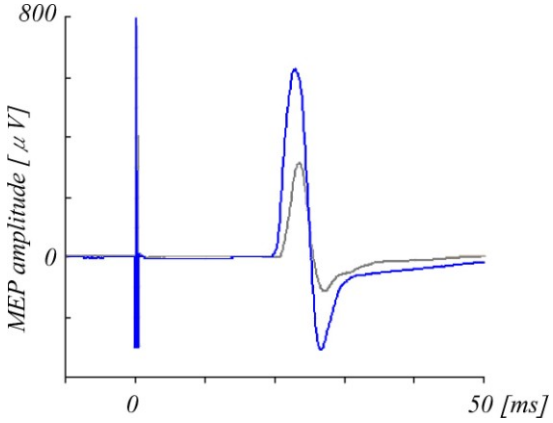
13, $p < 0.001$). In contrast, no significant difference was observed in the average MEP amplitude after $M1_{right}$ -1 Hz-left ($n = 12$, $p = 0.3$). For the ipsilateral forearm, the average MEP amplitude after $M1_{left}$ -1 Hz-left and $M1_{right}$ -1 Hz-right was significantly increased compared with the average MEP amplitude before peripheral magnetic stimulation ($M1_{left}$ -1 Hz-left: $n = 15$, $p < 0.01$, $M1_{right}$ -1 Hz-right: $n = 11$, $p < 0.05$). The mean increases in average MEP amplitude were approximately 142% for $M1_{left}$ -1 Hz-left, and 154% for $M1_{right}$ -1 Hz-right.

3-3-2 Effect of different stimulation frequencies of peripheral magnetic stimulation

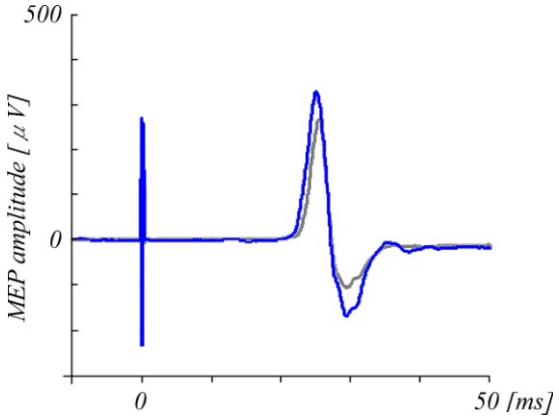
Figure 3-7 shows MEPs in response to different stimulation frequencies of peripheral magnetic stimulation over the contralateral forearm in relation to the left motor cortex. These MEPs were observed using a similar method to that described in 3-3-1 (Figure 3-5). These MEP data are an example from one participant who showed a characteristic tendency in response to peripheral magnetic stimulation at each



1 Hz peripheral magnetic stimulation
over the contralateral forearm



5 Hz peripheral magnetic stimulation
over the contralateral forearm



10 Hz peripheral magnetic stimulation
over the contralateral forearm

Figure 3-7 The alteration of MEPs induced by the difference of stimulation frequency of peripheral magnetic stimulation in one subject

The gray line represents an MEP before peripheral magnetic stimulation, and the blue line represents an MEP after the peripheral magnetic stimulation.

stimulation frequency. The results showed that MEP amplitudes following 5 Hz and 10 Hz peripheral magnetic stimulation ($M1_{left}$ -5 Hz-right and $M1_{left}$ -10 Hz-right) were increased compared with before peripheral magnetic stimulation.

Figure 3-8 shows the normalized average MEP amplitude with different stimulation frequencies. The normalization was performed using a similar method to that described in section 3-3-1 above.

The average MEP amplitude after $M1_{left}$ -1 Hz-right (100) was significantly decreased compared with the average MEP amplitude before peripheral magnetic stimulation ($n = 13$, $p < 0.001$). In contrast, the average MEP amplitude after $M1_{left}$ -5 Hz-right was significantly increased compared with the average MEP amplitude before peripheral magnetic stimulation ($M1_{left}$ -5 Hz-right: $n = 11$, $p < 0.05$). The mean increase in average MEP amplitude was approximately 137%. The average MEP amplitude after M1left -10 Hz-right significantly increased compared with the average MEP amplitude before peripheral magnetic stimulation ($n = 14$, $p < 0.01$). The mean increase in average MEP amplitude was approximately 132%.

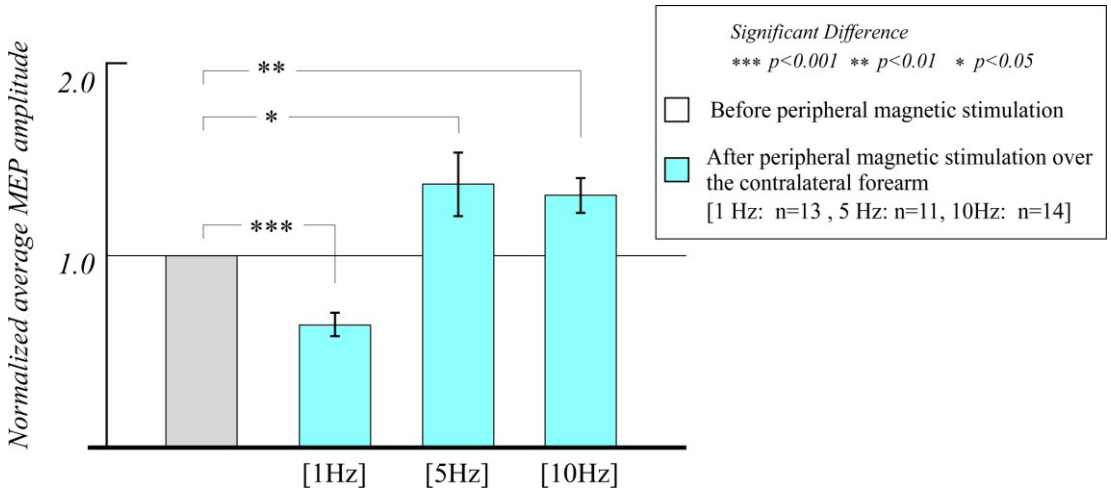


Figure 3-8 The normalized average MEP amplitude with different stimulation frequencies.

The white bar shows the normalized average MEP amplitude before peripheral magnetic stimulation. The bar is always 1.0. The colored bars show the normalized average MEP amplitude after peripheral magnetic stimulation at each stimulus frequency.

3-3-3 Changes in MEP amplitude decrease after peripheral magnetic stimulation

Figure 3-9 shows the variation in the decrease of the average MEP amplitude after $M1_{left}$ -1 Hz-right (50) (n=8), $M1_{left}$ -1 Hz-right (100) (n=13) peripheral magnetic stimulation over the contralateral forearm to the left motor cortex. Each MEP amplitude after peripheral magnetic stimulation was normalized using the MEP amplitude before peripheral magnetic stimulation, for each subject. The MEP amplitude exhibited a 1–10 times decrease for almost all MEPs, compared with before peripheral magnetic stimulation.

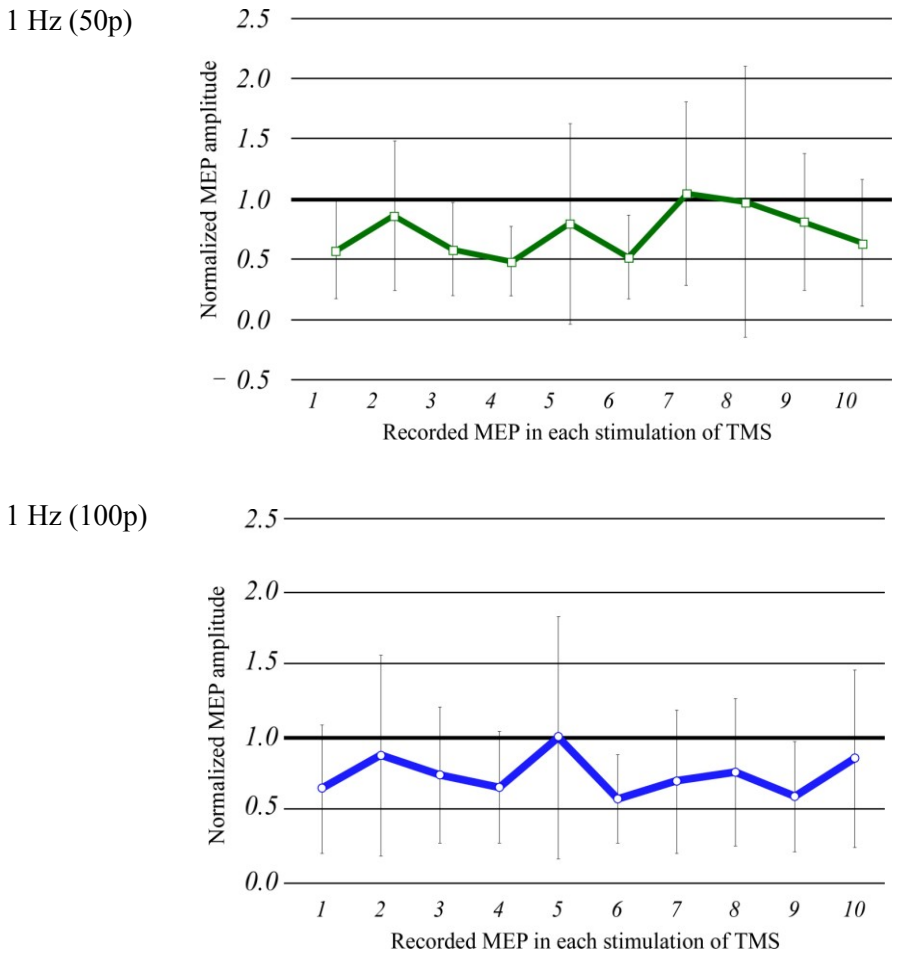


Figure 3-9 Variation in the average MEP amplitude decrease

The solid line shows the variation of the normalized average MEP amplitude before peripheral magnetic stimulation. The average MEP amplitude before peripheral magnetic stimulation is always shown as 1.0. Bars show standard deviations.

3-4 Discussion

Previous studies of peripheral stimulation reported that peripheral magnetic stimulation affects the excitability of the motor cortex. In addition, in PET study, it was reported that peripheral magnetic stimulation over the area of muscle supplying terminal nerve branches of the finger and hand extensor muscles had a conditioning effect on the cortical activity level (Struppler et al., 2003, Struppler et al., 2007). Moreover, another study reported that 15 Hz repetitive peripheral magnetic stimulation over the soleus muscle in healthy subjects did not affect spinal cord excitability (Behrens et al., 2011). Thus, taken together with these findings, the current results suggest that the alteration of motor cortical excitability induced by peripheral magnetic stimulation occurs at the cortical rather than in the spinal cord.

Many previous studies of peripheral magnetic stimulation have investigated the recovery of motor function via the facilitation of cortical excitability in the motor cortex (Struppler et al., 2003, Struppler et al., 2007). However, few studies have examined whether peripheral magnetic stimulation can induce inhibition of motor cortical excitability under certain conditions. Thus, the current study focused on previous TMS findings of inhibition of motor cortical excitability. The facilitation or inhibition of motor cortical excitability induced by TMS may be affected by the stimulation frequency and intensity of magnetic stimulation. It has been well established that inhibition of motor cortical excitability is induced by low-frequency rTMS (1 Hz), whereas facilitation of motor cortical excitability is induced by high-frequency rTMS (Chen et al., 1997, Romero et al., 2002, Maeda et al. 2000, Pascual-Leone et al. 1994, Berardelli et al., 1998, Wassermann et al., 1998). Moreover, in many studies, supra-threshold intensity has been used to induce inhibition of motor cortical excitability with low-frequency TMS. Muscle twitch caused by TMS is thought to play a role in the inhibition of the motor cortical excitability. Thus, in the current study, the current study applied the same stimulation frequency used in previous TMS studies to induce inhibition of motor cortical excitability over the forearm (Chen et al., 1997, Lang

et al., 2006). Moreover, the current study used other stimulation frequencies and sites to investigate the possibility that peripheral magnetic stimulation parameters influence motor cortical excitability.

MEP amplitude is a well established measure for evaluating the excitability of the corticospinal tract, which is a cerebrocortical output pathway (Petersen et al., 2003). In addition, MEP amplitude has been used to evaluate the cortical effects of stimulation over peripheral nerves or muscles, because it is affected by several factors that also influence corticospinal excitability (Pascual-Leone et al., 1998). Therefore, in the current study, the current study used MEP amplitude to evaluate the influence of peripheral magnetic stimulation on motor cortical excitability using a TMS stimulation frequency (0.1 Hz) and intensity (resting motor threshold 105%) that would not be expected to affect motor cortical excitability to elicit MEPs in primary motor cortex, before and after peripheral magnetic stimulation (Chen et al., 1997).

Figure 3-10 shows the peripheral magnetic stimulation frequency and the corresponding effect at each stimulation site in the current study. “Increase” and “Decrease” in the figure show the changes of MEP amplitude after peripheral magnetic stimulation over the contralateral and ipsilateral forearm.

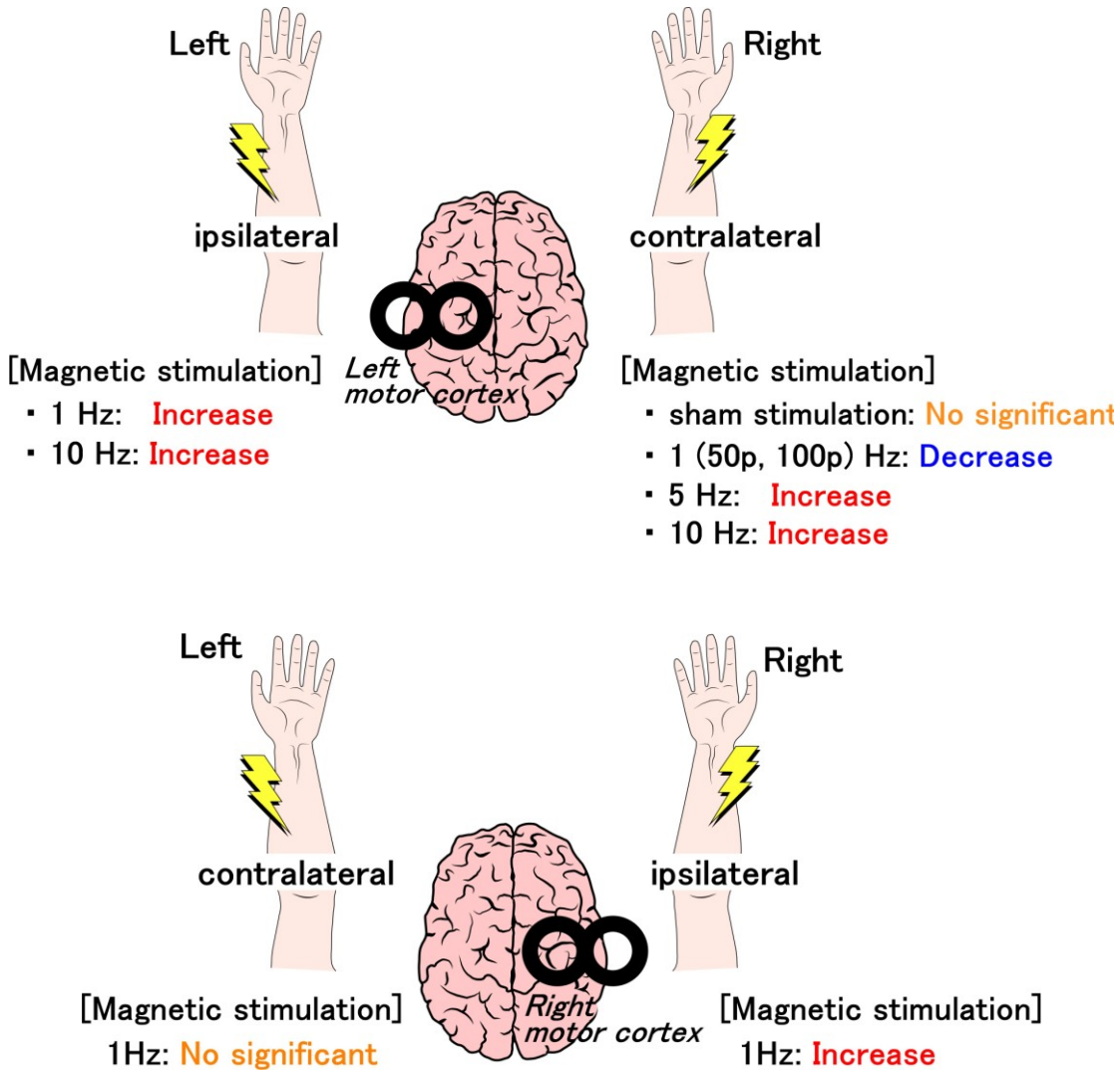


Figure 3-10 Summary of results

Figure shows the change of MEP amplitude over the contralateral or ipsilateral forearm:
the upper figure/ for left primary motor cortex, the lower figure/ for right primary motor cortex

The contralateral forearm to left primary motor cortex

In the current study, in the contralateral forearm in relation to the left primary motor cortex, a decrease in MEP amplitude after 1 Hz peripheral magnetic stimulation (M1left -1 Hz-right (100)) and 1 Hz (M1left -1 Hz-right (50)) were observed. In contrast, MEP amplitudes after 5 Hz and 10 Hz stimulation were increased compared with before peripheral magnetic stimulation. MEP amplitude can be used to evaluate the excitability of the corticospinal tract (Petersen et al., 2003). Therefore, the alteration of MEP amplitude observed in the current study suggests that peripheral magnetic stimulation may have an influence on motor cortical excitability. In the peripheral magnetic stimulation over the contralateral forearm for the left motor cortex, this study found the possibility to affect the facilitation (increase of MEP amplitude) and the inhibition (decrease of MEP amplitude) of the motor cortical excitability. In addition, sham stimulation over the contralateral forearm was performed. The results revealed that MEP amplitude before and after sham stimulation exhibited no significant differences. This result suggests that peripheral magnetic stimulation affects MEP amplitude.

Peripheral magnetic stimulation causes muscle twitches by affecting muscle fibers, and activates the proprioceptive afferent nerve, which has been hypothesized to induce proprioceptive inflow to the central nervous system (Behrens et al., 2011, Struppler et al., 2007). Activation of the primary somatosensory cortex can be caused by proprioceptive afferents, and muscle twitch induces changes in the proprioceptive input (Mima et al., 1999). The current findings suggest that peripheral magnetic stimulation may have activated the afferent nerve of the proprioceptors, causing proprioceptive signals induced by peripheral magnetic stimulation over the forearm to flow into the primary somatosensory cortex. Functional and anatomical interactions exist between the primary somatosensory and primary motor cortical areas (Catsman-Berrevoets et al., 1980, Jenny, 1979, Jones et al., 1979). Moreover, a previous study reported the importance of conjoint activity of somatosensory afferents and intrinsic cortical motor circuits (Stefan et al., 2000). Thus, the alteration of motor cortical excitability observed in the current study suggests that peripheral magnetic stimulation over the forearm

flows into the contralateral primary somatic sensory cortex, and that motor cortical excitability is adjusted jointly by both the primary sensory and primary motor cortex.

A previous study of repetitive TMS (rTMS) reported that supra-threshold rTMS (stimulation frequency: 1 Hz, stimulation intensity: 115% of RMT) over the primary motor cortex decreased MEP amplitude in the contralateral FDI muscle, indicating inhibition of motor cortical excitability (Lang et al., 2006). In addition, the results confirmed the inhibition of motor cortical excitability using a control experiment with 1 Hz electrical stimulation delivered over the wrist. The authors suggested that the findings may have been caused by the activation of afferent feedback evoked by muscle twitches induced by supra-threshold rTMS (Lang et al., 2006). Additionally, a previous rTMS study incorporating functional magnetic resonance imaging (fMRI) reported that the primary sensory and primary motor cortical areas were both activated by supra-threshold rTMS (Bestmann et al., 2004). In addition, it was suggested that the afferent feedback from muscle movements induced by supra-threshold rTMS may represent the dominant input to the motor system via the primary motor cortex.

In the current study, peripheral magnetic stimulation over the contralateral forearm to the left or right primary motor cortex at the same stimulation frequency (1 Hz) used in previous studies were applied, with supra-threshold rTMS (Maeda et al. 2000, Bestmann et al., 2004, Lang et al., 2006). Moreover, the current study applied a stimulation frequency and intensity of TMS to elicit MEPs that would not be expected to affect motor cortical excitability because it would not be affected by TMS-induced muscle twitch. The results indicated that MEP amplitude was decreased by 1 Hz peripheral magnetic stimulation over the contralateral forearm to the left motor cortex. The results of a previous study suggest that the current findings may have been related to afferent feedback caused by muscle twitch (Lang et al., 2006). Therefore, the current study results suggest that afferent feedback related to muscle twitch induced by 1 Hz peripheral magnetic stimulation over the contralateral forearm to the left motor cortex may have affected the inhibition of motor cortical excitability.

In addition, a decrease in average MEP amplitude after 1 Hz peripheral magnetic stimulation was observed (Figure 3-9). This finding suggests that the effect of peripheral magnetic stimulation on the inhibition of motor cortical excitability was not transient, but continued to affect MEPs after stimulation. Moreover, the study described in Chapter 2 revealed alteration of MEP amplitude from the right FDI when supra-threshold rTMS was delivered to the left primary motor cortex. The results showed that MEP amplitude showed a tendency to decrease, following a gradual increase. Based on this finding, the current study speculates that the influence on the inhibition of motor cortical excitability occurred after gradual facilitation. If afferent feedback is associated with the inhibition of motor cortical excitability, the effect of peripheral magnetic stimulation on the inhibition of motor cortical excitability may also occur after gradual facilitation.

The current study has suggested that 5 Hz and 10 Hz peripheral magnetic stimulation affect the facilitation of motor cortical excitability of the left motor cortex. Previous studies have reported that MEPs recorded during the volitional contraction of a target muscle were increased compared with a resting period, and depended on the intensity of muscle contraction (Taylor et al., 1997, Di Lazzaro et al., 1999a, Martin et al., 2006). In addition, another previous study reported that peripheral magnetic stimulation of 20 Hz increased the activation of the contralateral sensorimotor cortex (Struppler et al., 2007). Based on these findings, the current study speculate that the different changes of MEP amplitude induced by different stimulation frequencies the current study observed may have been associated with the contractive force of the muscle following peripheral magnetic stimulation.

The ipsilateral forearm to left primary motor cortex

In the ipsilateral forearm to left primary motor cortex, the current study found increased MEP amplitude after 1 Hz ($M1_{left}$ -1 Hz-left) and 10 Hz ($M1_{left}$ -10 Hz-left) peripheral magnetic stimulation. This finding of increased MEP amplitude suggests that peripheral magnetic stimulation may have affected the facilitation of motor cortical excitability. In addition, peripheral magnetic stimulation of the ipsilateral forearm to left primary motor cortex may have affected the right cerebral cortex via a mechanism similar to that of peripheral magnetic stimulation to the contralateral forearm. Excitatory information is caused by stimulation, and then transmitted to the cerebral cortex on the opposite side through the corpus callosum. A previous study confirmed that excitatory information is transmitted to the right somatic sensory area through the corpus callosum when the left somatic sensory area was electrically stimulated with an electrode (Palmer et al., 2012). Moreover, another previous study suggested that information from peripheral magnetic stimulation first transmits to somatosensory cortex (Mima et al., 1999, Behrens et al., 2011, Struppler et al., 2007). In terms of the current findings, this suggests that stimulation due to peripheral magnetic stimulation over the left forearm was transmitted from the right somatic sensory cortex to the left somatosensory cortex. Thus, the influence of peripheral magnetic stimulation over the ipsilateral forearm on facilitation of motor cortical excitability may be related to the transmission of excitatory information. A previous TMS study reported increased MEP amplitude of the ipsilateral FDI in response to supra-threshold rTMS (110–150% of R < T) (Schambra et al., 2003). In addition, an fMRI study reported activation of ipsilateral motor cortex during unilateral motor tasks (Kim et al., 1993, Rao et al., 1993). Thus, these previous findings are in accord with the current results.

The contralateral and ipsilateral forearm to right primary motor cortex

In this study, 1 Hz peripheral magnetic stimulation to the contralateral or ipsilateral forearm to the right motor cortex (M1right -1 Hz-left and M1right -1 Hz-right) were delivered. No significant changes in mean MEP amplitude were observed after peripheral magnetic stimulation over the contralateral forearm. This result differed from the effects of 1 Hz peripheral magnetic stimulation of the contralateral forearm in relation to the left motor cortex. It should be noted that all participants in the current experiment delivering 1 Hz peripheral magnetic stimulation were right-handed. It is known that the cerebrum has bilateral asymmetry. Right-handedness has been associated with distinct anatomical asymmetry of the left hemisphere (Corballis, 1998, Amunts et al., 1996). In addition, previous studies revealed that the intrasulcular length of the precentral gyrus in normal right-handed subjects showed conspicuous asymmetry (greater on the left than the right) (Amunts et al, 1997). Moreover, an fMRI study reported that ipsilateral activation was greater when performing motor tasks with the non-dominant (left) than dominant (right) hand in right-handed people (Dassonville et al., 1997). On this basis of these findings, the current study speculates that handedness-related cerebral asymmetry may be associated with the differences in cortical excitability observed in the current study. Therefore, the influence on the inhibition of motor cortical excitability using 1 Hz peripheral magnetic stimulation in the current study may have been related to differences in the handedness of participants. However, future experiments with left-handed participants will be necessary to clarify the effects of handedness on cortical excitability.

In contrast, an increase in mean MEP amplitude was observed after peripheral magnetic stimulation over the ipsilateral forearm. This result was similar to the effects of peripheral magnetic stimulation over the ipsilateral forearm in relation to the left motor cortex. Thus, the current findings suggest that peripheral magnetic stimulation over the ipsilateral forearm affected the facilitation of motor cortical excitability regardless of cerebral asymmetry. In addition, these results indicate that while inhibition of motor cortical excitability was induced by peripheral stimulation over the

contralateral forearm in relation to the left motor cortex, motor cortical excitability in the right motor cortex may have been facilitated.

3-5 Conclusion

The purpose of the current study was to investigate whether peripheral magnetic stimulation affects motor cortical excitability. To this end, MEPs before and after peripheral magnetic stimulation were measured. In addition, TMS over the primary motor cortex was used to induce MEPs using stimulation frequencies and intensities of levels that would not be expected to affect motor cortical excitability. Peripheral magnetic stimulation was applied with a range of frequencies (1, 5, 10 Hz) over the contralateral or ipsilateral forearm in relation to the target motor cortex. The results revealed a decrease of MEP amplitude with 1 Hz peripheral magnetic stimulation over the contralateral forearm for the left motor cortex. In contrast, increased MEP amplitude was observed with 1 Hz peripheral magnetic stimulation over the ipsilateral forearm. Peripheral magnetic stimulation over the ipsilateral forearm for the right motor cortex increased MEP amplitude. MEP amplitude can be used to evaluate the excitability of the corticospinal tract. Therefore, the current findings indicate that 1 Hz peripheral magnetic stimulation over the contralateral forearm for the left motor cortex may have affected the inhibition of cortical excitability in the left motor cortex. Moreover, this type of stimulation appears to affect facilitation of cortical excitability in the right motor cortex, while inhibiting cortical excitability in the left motor cortex. These findings suggest that inhibition of motor cortical excitability induced by peripheral magnetic stimulation is associated with afferent feedback caused by muscle twitch. Moreover, facilitation of motor cortical excitability by peripheral magnetic stimulation over the ipsilateral forearm may occur via the transmission of excitatory information through the corpus callosum. he current findings suggest that 5 Hz peripheral magnetic stimulation over the contralateral forearm and 10 Hz peripheral magnetic stimulation over the contralateral and ipsilateral forearms may affect the facilitation of motor cortical excitability. In addition, these findings suggest that different stimulation frequencies and sites of peripheral magnetic stimulation exert different influences on motor cortical excitability.

Chapter 4

Alteration of motor cortical excitability with peripheral electrical stimulation

4-1 Introduction

Electrical stimulation has been used extensively in human studies involving stimulation over the skull and peripheral structures. Stimulation over the skull is commonly referred to as transcranial electrical stimulation (TES). TES is a useful diagnostic tool, enabling percutaneous stimulation of the human brain (Merton et al., 1980). However, TES involves substantial pain and discomfort for participants, because its electrical properties are affected by the high impedance of the skull, scalp and hair. To overcome these limitations, transcranial magnetic stimulation (TMS) was developed in 1985 (Barker et al., 1985a) as an alternative brain stimulation method that does not involve pain or discomfort. However, devices for delivering TES stimulation are substantially simpler than TMS devices. In addition, because TES induces direct excitation of pyramidal tract neurons, the latency of motor evoked potentials (MEPs) induced by TES is slightly shorter compared with the latency of MEPs induced by TMS (Di Lazzaro et al., 2004, Day et al., 1989).

Electrical stimulation of peripheral structures, known as peripheral electrical stimulation, has attracted attention in the rehabilitation of neurological and musculoskeletal disorders. Functional electrical stimulation has been widely used as a treatment for recovering lost movement, including the facilitation of voluntary contraction in neurological conditions following stroke and spinal cord injury (Ragnarsson, 2008, Powell et al., 1999, Embrey et al., 2010). Percutaneous implanted electrodes and surface electrodes can be used for functional electrical stimulation, and a method called transcutaneous electrical nerve stimulation (TENS) has been widely used in pain treatment. Administering TENS for pain control typically involves high-frequency stimulation of peripheral nerves, and a number of pain relief studies have used frequencies of 100 Hz or more (Moran et al., 2011, Sluka et al., 2005). TENS is primarily used for acute and chronic pain, articular rheumatism, and during labor (Brosseau et al., 2003, Johnson et al., 2011, Dowswell et al., 2009).

Previous studies have reported that peripheral electrical stimulation affects the excitability of the motor cortex, suggesting that the method may be useful for functional improvement of swallowing in dysphagia, as well as improvement of hand or foot movement (Kaelin-Lang et al., 2002, Ridding et al., 2000, Khaslavskaia et al., 2005, Fraser et al., 2002, Hamdy et al., 1998). Previous studies of the excitatory effects of sensory input on the motor system have typically used a stimulation frequency of 10 Hz. It has been found that the effects of peripheral electrical stimulation vary with different electrical stimulation frequencies (Chipchase et al., 2011). One previous study reported that the extent and direction of the change in motor cortex excitability induced by peripheral electric stimulation were associated with changes in somatosensory cortical excitability (Schabrun et al., 2012). Another previous study suggested that the combination of motor cortex activation and stimulation of the somatosensory cortex may be useful for improving motor function (Kimberley et al., 2004). Many previous studies of peripheral electrical stimulation have focused on the recovery of motor function by the facilitation of cortical excitability of the motor cortex. Overall, these studies have confirmed the facilitation of cortical excitability of primary motor cortex by stimulation with a high frequency and long duration (Maeda et al. 2000, Pascual-Leone et al. 1994, Berardelli et al., 1998, Wassermann et al., 1998). Moreover, previous studies have suggested that the cortical excitability induced by electrical stimulation of the periphery occurs at a cortical level (Ridding et al., 2000).

It has been well established that high-frequency magnetic stimulation of more than 5 Hz increases motor cortex excitability, whereas low-frequency magnetic stimulation of less than 1 Hz decreases motor cortex excitability (Wassermann et al., 1998, Pascual-Leone et al., 1994). Thus, the current study sought to investigate whether peripheral electrical stimulation has the same effects on motor cortical excitability such as TMS. Few studies have examined whether peripheral electrical stimulation can induce inhibition of motor cortical excitability under certain conditions. Therefore, the current study focused on the inhibitory effects of peripheral stimulation on motor cortical excitability. Moreover, peripheral electrical stimulation over the forearm with a

lower stimulation frequency (1 Hz) was applied and shorter duration was compared with previous studies, to induce inhibition of motor cortical excitability.

4-2 Experimental methods

A total of 22 healthy participants (15 male and seven female, mean age 27.91 ± 8.88 years) were enrolled in this study. None of the participants had a history of psychiatric illness or neurological disorders or disturbance of motility, and all participants provided informed consent. The protocol was approved by the institutional review boards of Kyushu University and Tokai University.

Experimental environment

Figure 4-1 illustrates the experimental environment used in this study. Participants sat on a chair in a resting condition, and were instructed to maintain muscle relaxation through the experiment. In addition, participants were instructed to maintain a fixed head position, to place the forearm in a supine position while peripheral electrical stimulation was applied, to keep their eyes open, and to refrain from moving the limbs and fingers.

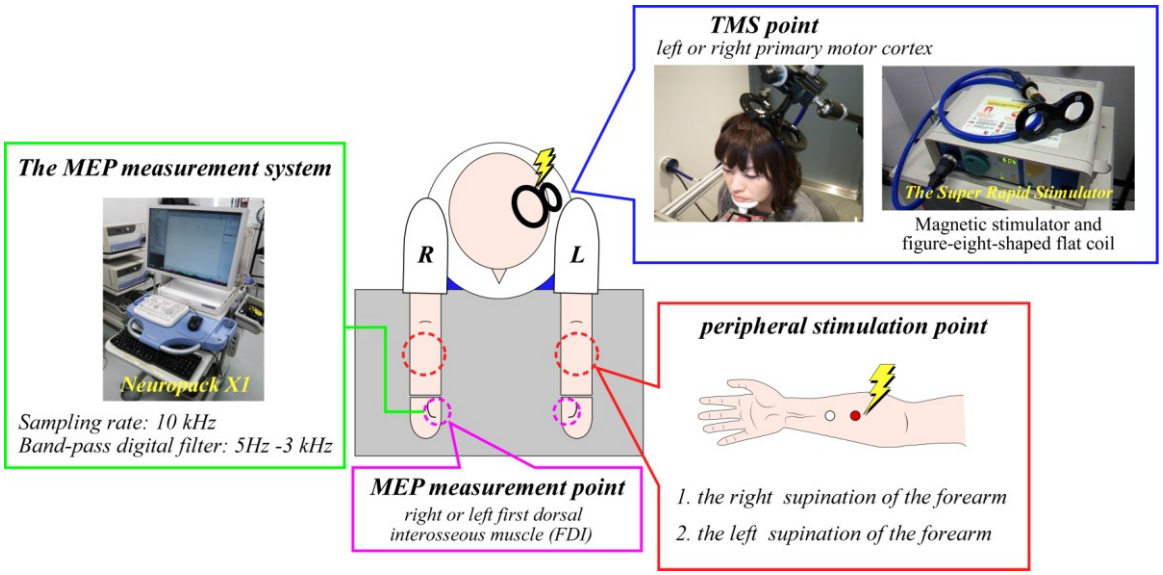


Figure 4-1 Experimental environment

MEPs were induced by applying TMS to the primary motor cortex. For each participant, the optimal scalp position over the left primary motor cortex was determined to record electromyograms from the right first dorsal interosseous (FDI) muscle. A Super Rapid Stimulator (Magstim Co. Ltd, Whitland, Carmarthenshire, UK) with a figure eight-shaped flat coil (70 mm double coil) was used as the magnetic stimulator to deliver TMS. The magnetic stimulation coil was placed tangentially to the scalp, and was positioned laterally at 45 degree angle to induce current in a posterior-to-anterior direction. The stimulation coil was secured with a coil holder after determining the optimal stimulation area, and the coil position was continuously monitored throughout the experiment. A Neuropack X1 (Nihon Kohden, Tokyo, Japan) device was used to record the electromyogram from the FDI muscle induced by TMS using silver/silver-chloride (Ag-AgCl) surface electrodes. Each participant's resting motor threshold (RMT) was defined as the minimal stimulator output eliciting MEP responses with a peak-to-peak amplitude greater than 50 μV produced in at least five of 10 successive pulses (Rossini et al., 1994). The magnetic pulse width was 200 μs. The stimulation frequency and intensity of TMS were respectively set at 0.1 Hz and 105% of each participant's RMT, with a magnetic pulse width of 200 μs.

Electromyography

The electromyograms induced by TMS were recorded using Ag-AgCl surface electrodes over the right FDI muscles. The ground electrode was placed over the right metacarpophalangeal joint of the index finger. Neuropack X1 (Nihon Kohden, Tokyo, Japan) was used as a recording device for the electromyogram. The electromyogram signals were amplified with a band-pass filter between 5 Hz and 3 kHz, digitized with a sampling rate of 10 kHz.

Peripheral electrical stimulation

Two levels of peripheral electrical stimulation frequency were tested: 1 Hz and 10 Hz. Participants placed their forearm on the stimulated side on the table, in an extended supine position. Peripheral electrical stimulation was applied over the muscle belly of the right or left forearm through surface electrodes. The peripheral electrical stimulation was delivered with a stimulus frequency of 1 Hz (100 pulses) or 10 Hz (500 pulses) with a pulse duration of 0.2 ms. Stimulation was applied over the muscle belly of the right or left flexor forearm through Ag-AgCl surface electrodes. Neuropack Four mini MEB-5304 (Nihon Kohden, Tokyo, Japan) was used as an electrical stimulation device. Electrical stimulation was delivered using a square wave with pulse duration of 0.2 milliseconds. The stimulation intensity was adjusted to produce a slight wag of the finger for each participant. The average stimulation intensity was 7.86 mA (± 2.48) for the contralateral forearm, and 7.76 mA (± 2.17) for the ipsilateral forearm.

Experimental procedure

The experimental paradigm design was divided into three phases, as shown in Figure 4-2. In the first phase, TMS was applied to the left primary motor cortex to evoke MEPs from the right FDI muscle. The stimulation frequency and intensity of TMS were respectively set at 0.1 Hz and 105% of the RMT of each participant. It has been previously reported that this stimulation frequency and intensity did not affect motor cortical excitability (Chen et al., 1997). MEPs with peak-to-peak amplitude of greater than 50 μV induced by TMS were included in the analysis of each group of 10 MEPs. In the second phase, peripheral electrical stimulation was delivered to the forearm immediately after the first phase. In this phase, peripheral electrical stimulation was applied with various combinations of stimulation position and frequency.

The experimental conditions were as follows:

I. Peripheral electrical stimulation of contralateral forearm (right forearm) to left primary motor cortex ($M1_{left}$)

I-1. $M1_{left}$ -1 Hz-right

I-2. $M1_{left}$ -10 Hz-right

II. Peripheral electrical stimulation of ipsilateral forearm (left forearm) to left primary motor cortex ($M1_{left}$)

II-1. $M1_{left}$ -1 Hz-left

II-2. $M1_{left}$ -10 Hz-left

Finally, in the third phase, TMS was performed with the same setup as in the first phase, immediately after the second phase. Similarly to the first phase, MEPs induced by TMS was recorded. The effect of peripheral electrical stimulation on motor cortical excitability was evaluated by comparing the mean MEP amplitudes recorded in the first phase (before peripheral electrical stimulation) and the third phase (after peripheral electrical stimulation). For statistical analysis, paired t-tests were employed to compare the average MEP amplitude before and after peripheral electrical stimulation.

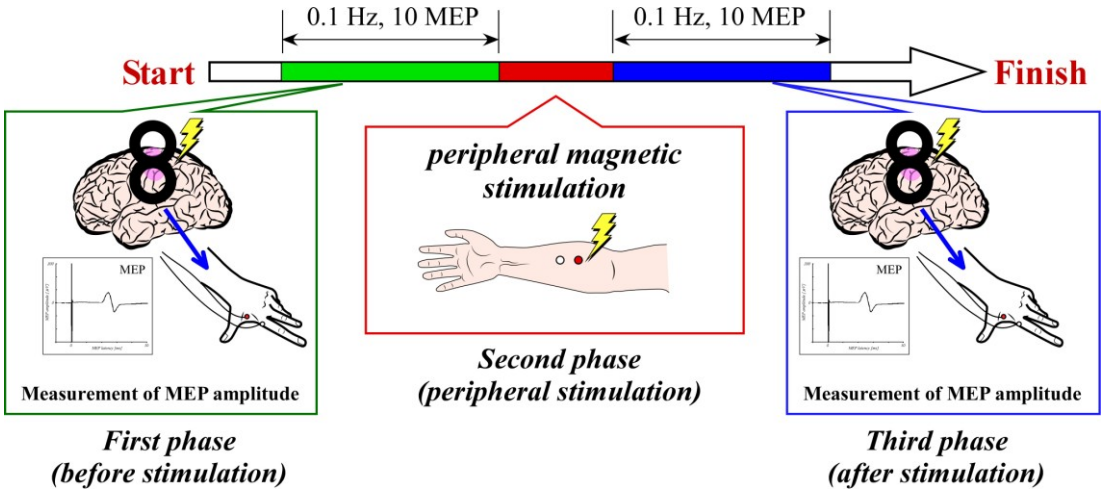
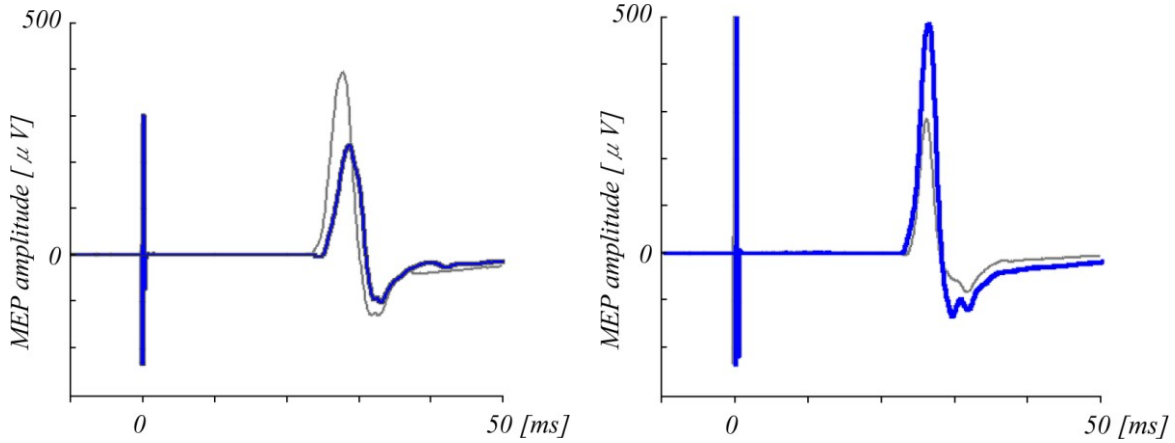


Figure 4-2 Experimental pocedure

4-3 Results

Figure 4-3 shows the MEPs induced by peripheral electrical stimulation over the contralateral and ipsilateral forearm to the left motor cortex. The figure shows MEPs averaged over 10 trials from one participant who exhibited a representative pattern of responses to each stimulus frequency. A similar pattern was observed in almost participants. TMS was performed with the same setup in the first and third phases, and the MEP amplitude recorded before and after peripheral electrical stimulation (i.e., in the first and third phases) was used to evaluate the effect of peripheral electrical stimulation on motor cortical excitability.

Figure 4-3 (A) shows the MEPs induced by 1 and 10 Hz peripheral electrical stimulation over the contralateral forearm. With 1 Hz peripheral electrical stimulation ($M1_{left}$ -1 Hz-right), the MEP amplitude following peripheral electrical stimulation was decreased compared with before peripheral electrical stimulation. In contrast, the MEP amplitude after 10 Hz peripheral electrical stimulation ($M1_{left}$ -10 Hz-right) was increased compared with before peripheral electrical stimulation.



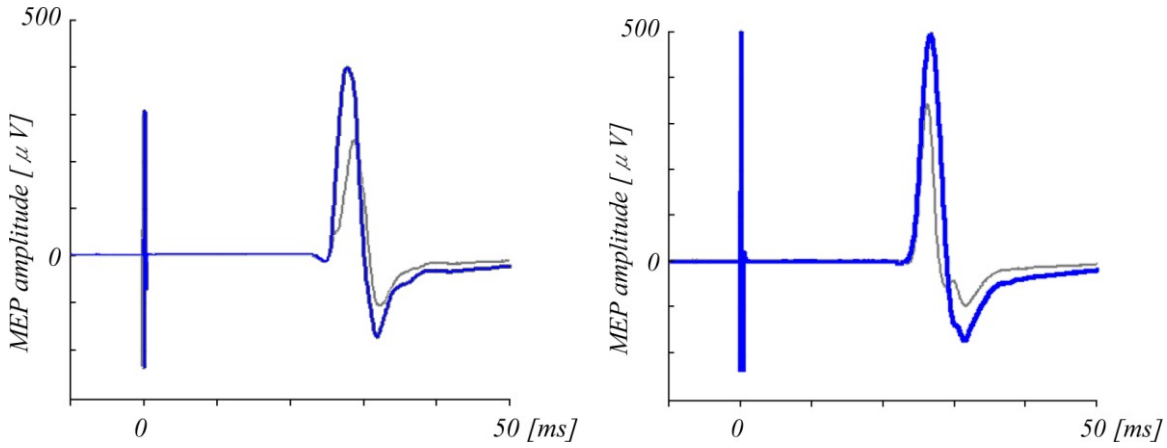
1 Hz peripheral electrical stimulation　　10 Hz peripheral electrical stimulation

Figure 4-3 (A) Alteration of MEPs induced by peripheral electrical stimulation over the contralateral forearm to the left motor cortex in one subject

The gray line represents an MEP before peripheral magnetic stimulation, and the blue line represents an MEP after peripheral magnetic stimulation.

Figure 4-3 (B) shows MEPs induced by 1 and 10 Hz peripheral electrical stimulation over the ipsilateral forearm. The MEP amplitude following 1 and 10 Hz peripheral electrical stimulation was increased compared with before peripheral electrical stimulation.

Figure 4-4 shows the normalized average MEP amplitude in each experimental condition of peripheral electrical stimulation. Because there were individual differences between the MEP amplitudes induced by TMS, the average MEP amplitude after peripheral electrical stimulation was normalized using the average MEP amplitude before peripheral electrical stimulation for each participant. Paired t-tests were employed to compare the average MEP amplitude before and after the peripheral electrical stimulation. The data are presented as mean and standard error, and a level of significance of 5% was used for all experiments.



1 Hz peripheral electrical stimulation　　10 Hz peripheral electrical stimulation

Figure 4-3 (B) Alteration of MEPs induced by peripheral electrical stimulation over the ipsilateral forearm to the left motor cortex in one subject

The gray line represents an MEP before peripheral magnetic stimulation, and the blue line represents an MEP after peripheral magnetic stimulation.

With peripheral electrical stimulation of the contralateral forearm to the left motor cortex, the average MEP amplitude of $M1_{left}$ -1 Hz-right was decreased significantly compared with the average MEP amplitude before peripheral electrical stimulation ($n = 15$, $p < 0.001$). The mean decrease in the average MEP amplitude was approximately 77%. In contrast, the average MEP amplitude after $M1_{left}$ -10 Hz-right significantly increased compared with the average MEP amplitude before peripheral electrical stimulation ($n = 17$, $p < 0.05$). The mean increase in average MEP amplitude was approximately 128%. With peripheral electrical stimulation of the ipsilateral forearm to the left motor cortex, the average MEP amplitude of $M1_{left}$ -1 Hz-left and $M1_{left}$ -10 Hz-left was increased significantly compared with the average MEP amplitude before peripheral electrical stimulation ($M1_{left}$ -1 Hz-left: $n = 14$, $p < 0.05$, $M1_{left}$ -10 Hz-left: $n = 13$, $p < 0.05$). The mean increase in average MEP amplitude was approximately 128% for $M1_{left}$ -1 Hz-left and approximately 145% for $M1_{left}$ -1 Hz-left.

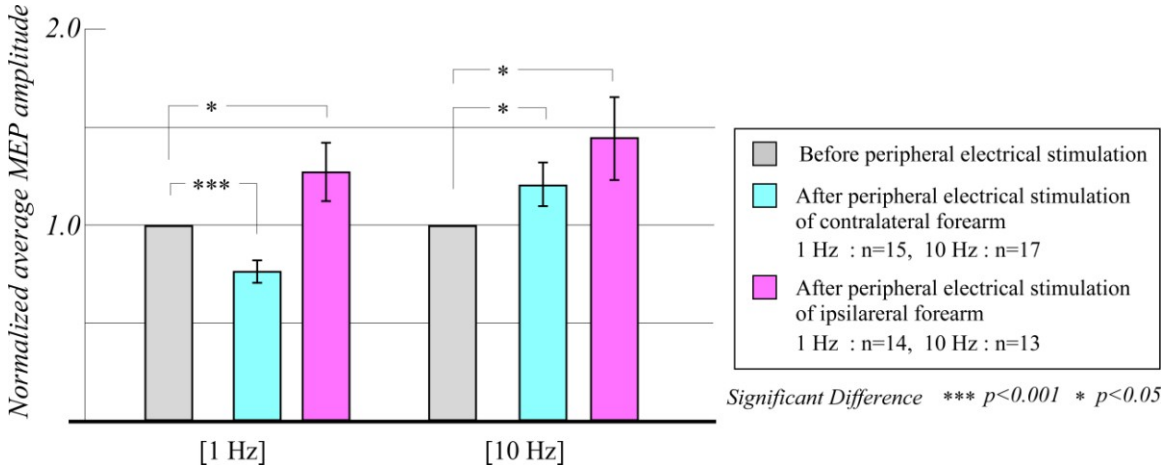


Figure 4-4 Comparison of normalized average MEP amplitudes evoked by different stimulation sites of peripheral electrical stimulation

The white bar shows the normalized average MEP amplitude before peripheral electrical stimulation. This bar is always 1.0. The colored bars show normalized average MEP amplitudes after peripheral electrical stimulation at each stimulus site.

4-4 Discussion

Influence of peripheral electrical stimulation on left motor cortical excitability

Motor cortical excitability is known to be affected by TMS and peripheral stimulation (Wassermann et al., 1998, Maeda et al. 2000, Pascual-Leone A et al. 1994, Ridding et al., 2000, Struppler et al., 2007), and peripheral electrical stimulation has been widely used for the recovery of motor function and neuropathic rehabilitation (Ragnarsson, 2008, Powell et al., 1999, Embrey et al., 2010). Many previous studies have reported that peripheral electrical stimulation has a direct influence on motor cortical excitability in the motor cortex (Kaelin-Lang et al., 2002, Ridding et al., 2000, Khaslavskaia et al., 2005, Fraser et al., 2002, Hamdy et al., 1998). A number of studies have reported that motor cortical excitability can be modulated by TMS. While low-frequency TMS induces inhibition of motor cortical excitability, TMS of 5 Hz or greater has been found to have facilitatory effects (Chen et al., 1997, Romero et al., 2002, Maeda et al. 2000, Pascual-Leone et al. 1994, Berardelli et al., 1998, Wassermann et al., 1998). However, TMS is not appropriate for all patients (Rossi et al. 2009). Thus, in the current study, whether peripheral electrical stimulation has a similar effect to TMS on motor cortical excitability was examined. To test the modulation of motor cortical excitability by peripheral electrical stimulation, several stimulation parameters were changed, including stimulation frequency and site. The results revealed different effects on MEP amplitude with different stimulation frequencies of peripheral electrical stimulation.

Ridding et al. measured MEPs and F-wave activity after 10 Hz mixed nerve electrical stimulation for 2 hours (Ridding et al., 2000). The results revealed an increase in MEP amplitude after prolonged repetitive electrical nerve stimulation. However, F-wave activity, which reflects excitability changes in spinal motoneurons, exhibited no change (Ridding et al., 2000). Moreover, another report recorded supramaximal peripheral M-responses and MEPs in response to brainstem electrical stimulation (BES) after peripheral electrical stimulation (Kaelin-Lang et al., 2002). The findings suggest that

alterations of motor cortical excitability induced by peripheral electrical stimulation may occur at the cortical level. Therefore, changes in MEP amplitude induced by peripheral electrical stimulation were used to evaluate the influence on motor cortical excitability, measuring MEP amplitudes before and after peripheral electrical stimulation. To elicit MEPs, a stimulation frequency and intensity of TMS (0.1 Hz, 105% of RMT) that would not be expected to affect motor cortical excitability were applied.

Peripheral electrical stimulation has been found to activate afferent nerves by affecting the stimulated muscle, causing stimulation to flow into the somatosensory cortex (Schabrun et al., 2001, Ridding et al., 2000). The activation of the primary somatosensory cortex can be substantially activated by proprioceptive afferents, and muscle twitch has been found to induce changes in proprioceptive input (Mima et al., 1999). In addition, functional and anatomical interactions exist between primary somatosensory and primary motor cortical areas (Catsman-Berrevoets et al., 1980, Jenny, 1979, Jones et al., 1979). Animal models of motor cortical plasticity have confirmed the importance of conjoint activity of somatosensory afferents and intrinsic motor cortical circuits (Stefan et al., 2000). These findings suggest that peripheral electrical stimulation over the forearm may flow into the primary somatosensory cortex, causing motor cortical excitability to be adjusted jointly by the somatosensory and motor cortices.

The contralateral forearm to the left primary motor cortex

In this study, we applied 1 Hz and 10 Hz peripheral electrical stimulation over the contralateral forearm to the left motor cortex. Lang et al. reported that supra-threshold repetitive TMS (rTMS, 1 Hz, 115% of RMT) over the primary motor cortex induced inhibition of motor cortical excitability (Lang et al., 2006). Their results suggested that the inhibition of motor cortical excitability may have been associated with the activation of afferent feedback evoked by muscle twitch induced with supra-threshold rTMS (Lang et al., 2006). In addition, a previous study using functional magnetic resonance imaging (fMRI) suggested that afferent feedback from muscle movements induced by supra-threshold rTMS may represent the dominant input to the motor system via the primary motor cortex (Bestmann et al., 2004). These findings suggest that muscle twitch due to peripheral electrical stimulation over the contralateral forearm may affect the inhibition of motor cortical excitability. Thus, in the current study, peripheral electrical stimulation via an electrode over the contralateral forearm at the same stimulation frequency (1 Hz) as in the previous study by Lang and colleagues were applied. (Lang et al., 2006). Results of the current study revealed a decrease in MEP amplitude after 1 Hz peripheral electrical stimulation, demonstrating an inhibitory effect on motor cortical excitability. Moreover, the current findings suggest that afferent feedback caused by muscle twitch following peripheral electrical stimulation was associated with the inhibition of motor cortical excitability.

In contrast with 1 Hz peripheral electrical stimulation, the current study found that 10 Hz peripheral electrical stimulation caused an increase in MEP amplitude. Previous studies reporting excitatory effects of sensory input on the motor system have typically used stimulation below 10 Hz (Mima et al., 2004, Ridding et al., 2000). One previous study reported increased MEP amplitude following 10 Hz peripheral electrical stimulation for 2 hours, and repetitive stimulation of the nerve at the wrist simultaneously activated muscles and afferents (Ridding et al., 2001). It is likely that this stimulation produced convergent input from these stimulated muscles to the sensorimotor cortex (Ridding et al., 2000, Ridding et al., 2001). Other reports have

suggested that motor effects are likely to depend on the frequency of somatosensory stimulation and stimulation of muscle afferents (Kaelin-Lang et al., 2002, Fraser et al., 2002, Tinazzi et al., 2005). Other reports have suggested that motor effects are likely to depend on the frequency of somatosensory stimulation and stimulation of muscle afferents (Kaelin-Lang et al., 2002, Fraser et al., 2002, Tinazzi et al., 2005). Moreover, a previous study of voluntary contraction suggested that the magnitude of MEPs depended on the intensity of volitional contraction of the target muscle (Taylor et al., 1997, Di Lazzaro et al., 1998, Martin et al., 2006).

These findings suggest that differences in muscle twitch responses caused by different stimulation frequencies may influence motor cortex excitability. In the current study, muscle twitch was induced using an electrode over the forearm. Therefore, the current study expected that the stimulation input to the somatosensory cortex would be reinforced by the summation of muscle twitch induced with 10 Hz peripheral electrical stimulation, compared with 1 Hz stimulation. This notion is supported by a previous fMRI study reporting that the activation of the contralateral somatosensory cortex was induced by 5–15 Hz electrical stimulation of the median nerve (Kampe et al., 2000). Motor cortical excitability is likely to be modulated jointly by the somatosensory and motor cortices (Catsman-Berrevoets et al., 1980, Jenny, 1979, Jones et al., 1979, Stefan et al., 2000). Thus, the current study expected a facilitatory effect on motor cortical excitability to be elicited by 10 Hz peripheral electrical stimulation. The current findings demonstrated facilitation of motor cortical excitability despite the use of a relatively short duration of peripheral electrical stimulation compared with previous studies. Although previous studies have used supra-threshold TMS (115–120% of RMT) to measure MEPs, in the current study we used an intensity and frequency of TMS that was not expected to influence motor cortical excitability (Chen et al., 1997, Maeda et al. 2000, Pascual-Leone et al. 1994, Berardelli et al., 1998, Wassermann et al., 1998, Lang et al., 2006). A previous study reported that the use of high-intensity TMS to measure MEPs caused the duration of inhibition of motor cortical excitability induced by high-frequency electrical stimulation to become stable and long (Tinazzi et al., 2005).

Therefore, supra-threshold TMS may affect the increase in MEP amplitude caused by a long duration of peripheral electrical stimulation. To measure MEPs in the current study, the current study applied a TMS protocol that was not expected to affect motor cortical excitability. Thus, the current findings demonstrated that the facilitatory effects on motor cortical excitability were caused by short-duration peripheral electrical stimulation.

The ipsilateral forearm to left primary motor cortex

The current results revealed that MEP amplitude induced by 1 Hz and 10 Hz peripheral electrical stimulation over the ipsilateral forearm to the left motor cortex was increased compared with before stimulation. In addition, the right somatosensory cortex is thought to be affected by peripheral electrical stimulation in the contralateral forearm, resulting in the transmission of excitatory information to the left somatic sensory cortex through the corpus callosum (Palmer et al., 2012). Previous TMS studies have provided further evidence for the presence of interhemispheric inhibition and facilitation, and some of these effects are mediated via the corpus callosum (Ugawa et al., 1993, Ferbert et al., 1992, Di Lazzaro et al., 1999). Moreover, a previous study using peripheral stimulation suggested that electrical stimulation of the median nerve was associated with an increase in motor cortical excitability (Kimberley et al., 2004). In addition, other studies have reported activation of the ipsilateral motor cortex during a unilateral movement task (Kim et al., 1993, Rao et al., 1993). Taken together, these findings suggest that 1 and 10 Hz peripheral electrical stimulation applied over the ipsilateral forearm in the current study may have induced a facilitatory effect on motor cortical excitability. Moreover, 10 Hz peripheral electrical stimulation would be expected to cause facilitation of cortical excitability in the left motor cortex regardless of the stimulation site (contralateral or ipsilateral forearm), in accord with the current findings.

Comparison of peripheral magnetic and electrical stimulation

This study delivered peripheral stimulation over the forearm to induce muscle twitch similar to TMS, to investigate changes in motor cortical excitability caused by peripheral stimulation. Thus, both magnetic and electrical peripheral stimulation were tested to induce muscle twitch, with stimulation frequencies of 1 Hz and 10 Hz. The stimulation intensity was standardized at the minimal level producing a slight wag of the finger for each participant. Magnetic or electrical stimulation to the contralateral and ipsilateral forearm to the left motor cortex were applied. The stimulation coil (magnetic stimulation) or surface-electrode (electrical stimulation) was placed over the muscle belly of the supine forearm between the wrist and elbow on the stimulated side.

Figure 4-5 shows the normalized average MEP amplitude for both magnetic and electrical stimulation in this experiment. Because there were individual differences in MEP amplitudes induced by TMS, the average MEP amplitude after magnetic or electrical stimulation was normalized using the average MEP amplitude before magnetic or electrical stimulation for each participant. Paired t-tests were used to examine significant differences in average MEP amplitude between each experimental condition. The data are presented as mean and standard error, and a level of significance of 5% was used for all experiments.

For the contralateral forearm, the average MEP amplitudes after 1 Hz magnetic and electrical stimulation were significantly decreased compared with the average MEP amplitude before stimulation. In contrast, for the ipsilateral forearm, the average MEP amplitude after 1 Hz magnetic and electrical stimulation was significantly increased compared with the average MEP amplitude before stimulation. In addition, the current study found that 10 Hz magnetic and electrical stimulation significantly increased the average MEP amplitude after stimulation compared with before stimulation. These effects were confirmed with both forearms.

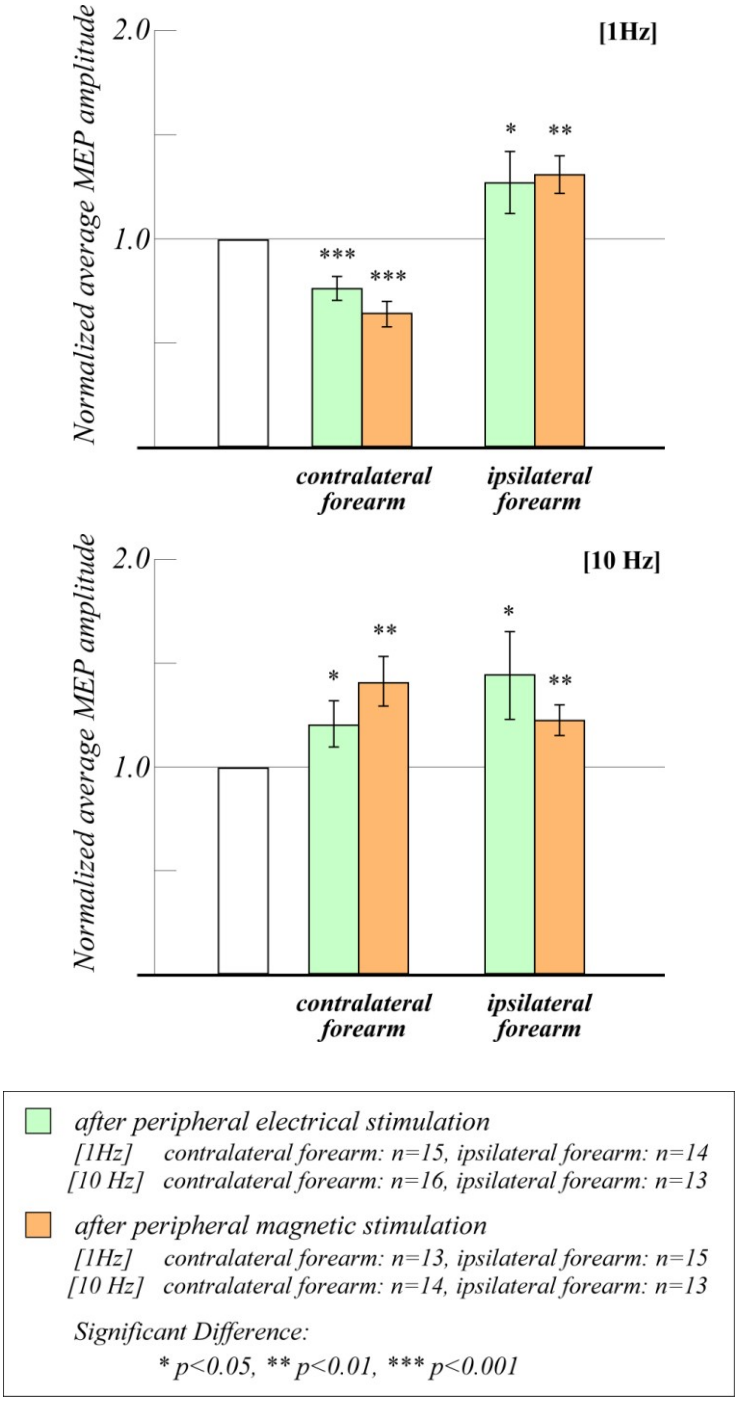


Figure 4-5 Comparison of normalized average MEP amplitude evoked by magnetic and electrical stimulation over the forearm

The white bar shows the normalized average MEP amplitude before magnetic and electrical stimulation. This bar is always 1.0. The colored bars show the normalized average MEP amplitude after magnetic and electrical stimulation.

The summary of results in Table 4-1 shows the mean decrease or increase in average MEP amplitude. The percentages show the mean decrease or increase of the average MEP amplitude for each experimental condition. The value before magnetic and electrical stimulation was set at 100%.

The current study compared the MEP amplitude evoked by the same stimulation frequency to investigate whether the occurrence of muscle twitch induced by magnetic and electrical stimulation influenced motor cortical excitability. A previous study measured somatosensory evoked potentials induced by magnetic and electrical stimulation (Zhu et al., 1991). The results indicated that electrical stimulation failed to elicit any cerebral potential after anesthetic blockade of the cutaneous nerves, whereas

Table 4-1 the mean decrease or increase of the average MEP amplitude

	The contralateral forearm	
	1 Hz	10 Hz
Magnetic stimulation	**Decrease** The mean decrease of the average MEP amplitude: 64.4 %	**Increase** The mean increase of the average MEP amplitude: 131.6 %
Electrical stimulation	**Decrease** The mean decrease of the average MEP amplitude: 76.8 %	**Increase** The mean increase of the average MEP amplitude: 127.8 %

	The ipsilateral forearm	
	1 Hz	10 Hz
Magnetic stimulation	**Increase** The mean decrease of the average MEP amplitude: 141.6 %	**Increase** The mean increase of the average MEP amplitude: 123.3 %
Electrical stimulation	**Increase** The mean decrease of the average MEP amplitude: 121.4 %	**Increase** The mean increase of the average MEP amplitude: 144.8 %

cerebral potentials evoked by magnetic stimulation applied to the muscle belly did not rely on the activation of cutaneous receptors.

Zhu et al. suggested that magnetic stimulation operates via the activation of muscle afferents secondary to the induced transient contraction of the stimulated skeletal muscle (Zhu et al., 1991). Thus, magnetic stimulation is thought to penetrate cutaneous receptors and activate afferent nerves indirectly via muscle twitch, whereas electrical stimulation activates cutaneous receptors directly, as well as causing muscle twitch.

In the current study, similar results in all experimental conditions were observed regarding the modulation of MEP amplitude with magnetic and electrical stimulation. Although magnetic and electrical stimulation have different influences on cutaneous receptors, both are thought to activate proprioceptive afferent nerves (Schabrun et al., 2012, Behrens et al., 2011, Struppler et al., 2007). Moreover, it has been reported that the pain involved in peripheral electrical stimulation may affect motor cortical excitability because of the resulting muscle response (sensory effects or muscle contraction) (Chipchase et al., 2011). In the current study, peripheral magnetic and electrical stimulation with similar stimulation conditions were applied (i.e., with a stimulation intensity that was not painful). Therefore, the peripheral magnetic and electrical stimulation used in this study were expected to have a similar influence on motor cortical excitability induced by stimulation frequency. This prediction is in accord with observation of the current study of similar effects on motor cortical excitability of magnetic stimulation and electrical stimulation. In addition, it is possible that the effects of peripheral magnetic and electrical stimulation on motor cortical excitability observed in of the current study were elicited by direct muscle twitch.

Because electrical stimulation activates not only the somatosensory system but also the cutaneous receptors, such as nociceptors, it causes pain and discomfort for participants (particularly in peripheral nerve neurostimulation). In contrast, magnetic stimulation avoids activation of cutaneous receptors, including nociceptors, and the activation of mechanoreceptor afferents from the skin. Thus, magnetic stimulation is less painful than electrical stimulation (Struppler et al., 2004), and is considered more

useful than electrical stimulation in many situations. However, magnetic stimulation has an upper limit in terms of stimulation frequency because of the structure of the stimulation device and its safety precautions (Rossi et al., 2009).

4-5 Conclusion

The purpose of this study was to investigate whether peripheral electrical stimulation had a modulatory effect on motor cortical excitability similar to the effects of TMS. To examine this question, we delivered 1 and 10 Hz peripheral electrical stimulation over the contralateral or ipsilateral forearm to the left motor cortex. To evaluate the effects on motor cortical excitability, MEPs were measured over the right or left FDI muscle before and after peripheral electrical stimulation. To induce MEPs, TMS to the left motor cortex with an intensity and frequency that was not expected to influence cortical excitability was applied. The results revealed that 1 Hz peripheral electrical stimulation over the contralateral forearm induced a significant decrease of MEP amplitude compared with before peripheral electrical stimulation. In contrast, peripheral electrical stimulation over the ipsilateral forearm induced a significant increase in MEP amplitude. These results suggest that 1 Hz peripheral electrical stimulation can have inhibitory or facilitatory effects on motor cortical excitability depending on the stimulation site. In addition, the current study found that 10 Hz peripheral electrical stimulation over the contralateral and ipsilateral forearms also had facilitatory effects on motor cortical excitability. These results suggest that peripheral electrical stimulation may have different effects on motor cortical excitability with different stimulation sites and frequencies. Thus, findings of the current study suggested that the observed inhibitory effect on motor cortical excitability was associated with muscle twitch-related afferent feedback caused by peripheral electrical stimulation over the contralateral forearm. Moreover, the facilitatory effects of peripheral electrical stimulation over the ipsilateral forearm on motor cortical excitability may have been related to the transmission of excitatory information through the corpus callosum. The current study induced a facilitatory effect on motor cortical excitability using a shorter duration of peripheral electrical stimulation than that used in previous studies (Ridding et al., 2000, Ridding et al., 2001). This effect on motor cortical excitability may be related to the intensity of TMS used in the measurement of MEPs. The current results suggest that peripheral

electrical stimulation may have similar effects on motor cortical excitability to TMS, revealing a similar impact of varying stimulation parameters.

Moreover, this study investigated the influence of muscle twitch caused by magnetic and electrical stimulation on motor cortical excitability. Thus, the current study applied magnetic stimulation and electrical stimulation to induce muscle twitch in the forearm. The results revealed magnetic and electrical stimulation had similar effects, suggesting that both stimulation types may activate proprioceptive afferent nerves, despite exerting different effects on cutaneous receptors. These findings suggest that the influence of peripheral magnetic and electrical stimulation on motor cortical excitability may be caused by direct muscle twitch rather than cutaneous receptors. Overall, magnetic and electrical stimulation appear to have a similar influence on motor cortical excitability. Thus, magnetic stimulation may be more useful than electrical stimulation, involving substantially less discomfort for participants.

Conclusion

The present study investigated the modulation of motor cortical excitability by peripheral magnetic stimulation and peripheral electrical stimulation

The current study measured MEPs over the FDI muscle before and after peripheral stimulation to evaluate the influence of peripheral stimulation on motor cortical excitability. The effect of peripheral stimulation on motor cortical excitability in the primary motor cortex was evaluated by comparing the MEP amplitude before and after peripheral stimulation. The TMS protocol for inducing MEPs over the primary motor cortex used a stimulation intensity and frequency that was not expected to affect cortical excitability. For peripheral stimulation, the current study delivered magnetic stimulation and electrical stimulation over the contralateral or ipsilateral forearm to the target motor cortex. A stimulation coil (magnetic stimulation) or surface-electrode (electrical stimulation) was placed over the muscle belly of the supine forearm between the wrist and elbow on the stimulated side. Magnetic stimulation of 1, 5 and 10 Hz was delivered to the contralateral forearm to the left motor cortex. The frequency of electrical stimulation was 1 or 10 Hz. In addition, magnetic stimulation was also delivered over the contralateral forearm to the right motor cortex. Peripheral magnetic and electrical stimulation of 1 and 10 Hz were applied over the ipsilateral forearm to the left motor cortex. The results revealed that MEP amplitude induced by 1 Hz peripheral magnetic and electrical stimulation over the contralateral forearm to the left motor cortex decreased compared with before stimulation.

Previous studies reported that MEP amplitude was decreased by 1 Hz supra-threshold rTMS, suggesting an inhibitory effect on motor cortical excitability (Chen et al., 1997; Maeda et al. 2000). In the current study, muscle twitch over the forearm was evoked using magnetic stimulation and electrical stimulation using similar a stimulation frequency (1 Hz) to previous studies. The results revealed similar findings to those of studies using 1 Hz supra-threshold rTMS, suggesting that 1 Hz peripheral magnetic and

electrical stimulation had an inhibitory effect on motor cortical excitability. These findings indicate that inhibition of motor cortical excitability induced by peripheral magnetic and electrical stimulation was associated with afferent feedback caused by muscle twitch. Moreover, the results suggested that peripheral magnetic stimulation may affect the facilitation of cortical excitability in right motor cortex, while inhibiting cortical excitability of the left motor cortex.

In the current study, magnetic and electrical stimulation over the contralateral forearm induced an increase in MEP amplitude with higher stimulation frequencies. These results suggest that the alteration of motor cortical excitability evoked by peripheral magnetic and electrical stimulation may be modulated by stimulation frequency. When magnetic and electrical stimulation was applied over the ipsilateral forearm, the increase of MEP amplitude was observed over the ipsilateral forearm to the left and right motor cortex, and occurred regardless of stimulation frequency. These results suggest that magnetic and electrical stimulation over the ipsilateral forearm affected facilitation of motor cortical excitability. The influence of peripheral stimulation over the ipsilateral forearm on motor cortical excitability may be related to the transmission of excitatory information through the corpus callosum.

In this study, similar results were confirmed with all experimental conditions testing the modulation of MEP amplitude by magnetic and electrical stimulation. Magnetic and electrical stimulation may involve different effects on cutaneous receptors, but both activate proprioceptive afferent nerves (Schabrun et al., 2012; Struppler et al., 2007). Therefore, the current results suggest that magnetic and electrical stimulation may have similar modulatory effects on motor cortical excitability. The current study found that 1 Hz peripheral stimulation over the contralateral forearm had a similar effect to supra-threshold rTMS regarding the inhibition of motor cortical excitability. The results of this study may be useful for informing the development of treatments to improve bilateral balance in the brain by adjusting motor cortical excitability with peripheral stimulation. The current study proposes that magnetic stimulation is more useful than electrical stimulation in most situations, involving less discomfort for participants.

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