Behavioral correlates of corticomuscular coherence and its underlying neural circuitry

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Chapter 1

General Introduction

1.1 The Brain's Corticospinal System and its Oscillatory Activities

The generation of voluntary movement is associated with neural activity in several brain areas, including the primary motor cortex (M1), somatosensory cortex, basal ganglia, thalamus, and cerebellum (Fig. 1-1). In particular, the M1 plays a role in outputting motor commands to the periphery. M1 neurons, called pyramidal cells, have axons that project directly via the corticospinal tract to alpha motoneurons and interneurons in the spinal cord (Fig. 1-2). Subsequently, motor commands are transmitted to the skeletal muscles via alpha motoneurons. The muscle contractions are consequently detected by proprioceptors, and these proprioception signals are conveyed back to the spinal cord via afferent sensory fibers, such as type Ia, Ib, and II sensory fibers, and then to the thalamus. Finally, the thalamus conveys proprioceptive information to the primary somatosensory cortex (S1). In addition, since S1 has direct connections to M1, a feedback loop that includes descending and ascending pathways is formed between the cortex and the muscle.

The oscillatory neuronal activity has long been considered a feature that might encode some aspects of movement in monkeys and humans. Indeed, it has been

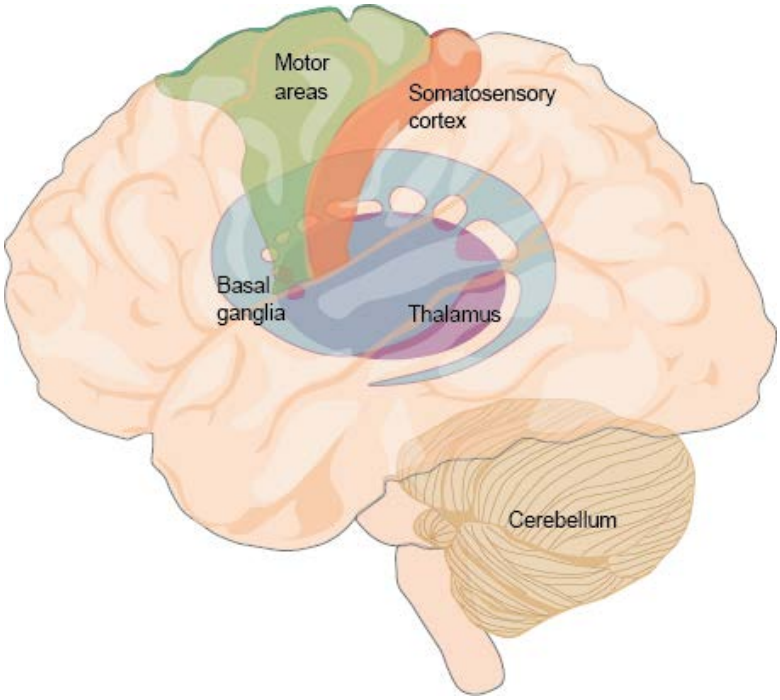

Figure 1-1. Cerebral areas that coordinate voluntary movement. Both the basal ganglia and cerebellum affect cortical motor areas via thalamic connections. These interactions contribute to the smooth execution of skilled movement and are important for motor learning.

demonstrated that movements elicit specific changes in the oscillatory frequency (Jasper and Penfield, 1949; Gastaut, 1952). For example, beta-band (15–30 Hz) oscillations in the sensorimotor cortex have been reported to reflect the neural activity related to voluntary movement (Halliday et al., 1995; Mima et al., 2000). Using simultaneous measurement of single unit spike trains and local field potentials in the M1 of monkeys, Murthy and Fetz (1996) demonstrated that beta-oscillations are generated by the synchronized firing of cortical neurons during reaching movements. In humans, Halliday et al. (1995) were the first to report significant beta-frequency

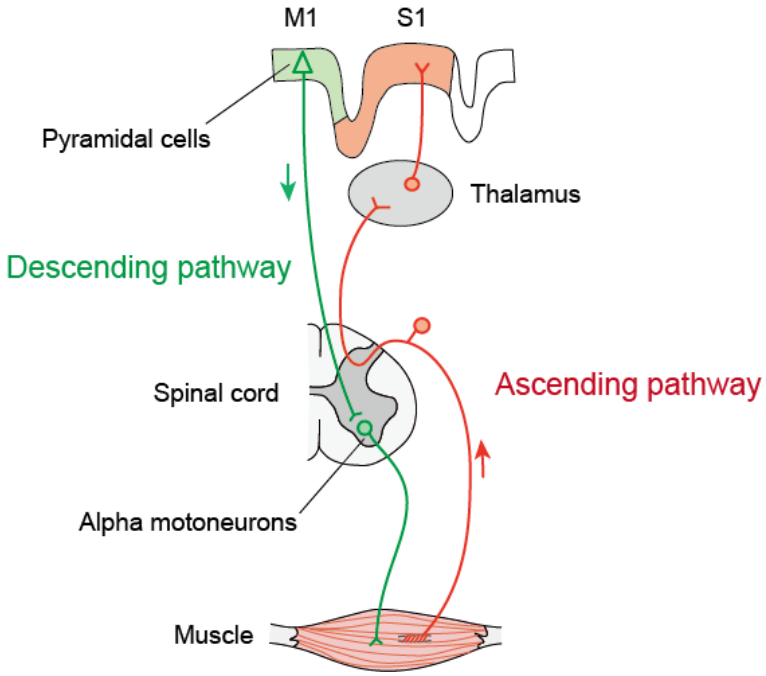

Figure 1-2. Descending and ascending pathways. Pyramidal cells in the primary motor cortex (M1) project alpha motoneurons to the spinal cord via the pyramidal tract. Somatosensory feedback from the muscle is transmitted to the primary somatosensory cortex (S1) via the thalamus.

coherence between the sensorimotor cortex activity (measured using electroencephalography [EEG]) recorded from the sensorimotor cortex and the muscle activity (measured using electromyography [EMG]) during voluntary muscle contractions. Significant coherence between EEG and EMG has also been found to be localized in M1 (Mima et al., 2000, Fig. 1-3).

Such an oscillatory neural activity is often synchronized with those recorded in distinct neural sites, suggesting that the oscillatory synchronization plays a functional

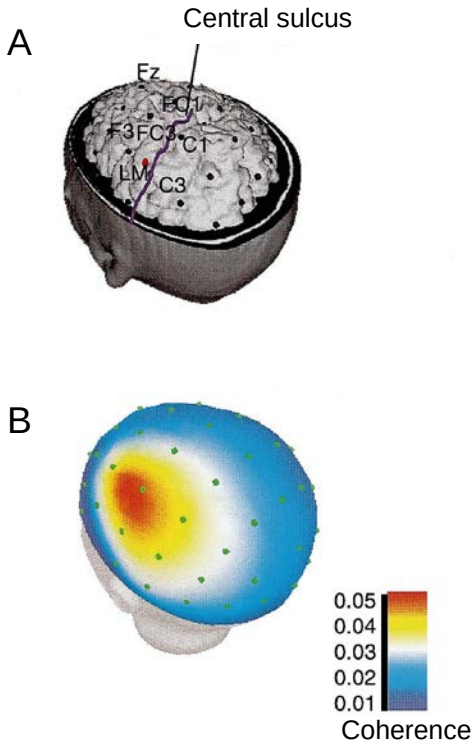

Figure 1-3. Localization of coherence between electroencephalogram (EEG) and electromyogram (EMG). A) Positions of electrodes vertically projected onto the cortical surface. B) Topographic distribution of the coherence between EEG and EMG within the beta-frequency band, calculated during contractions of the abductor pollicis brevis (modified from Mima et al., 2000).

role in effective communication between distant neuron groups, such as those between different cortical areas, and those between the cortex and the muscle (von Stein et al., 2000; Gross et al., 2004; Hummel and Gerloff, 2005; Rose and Buchel, 2005).

It is now well established that the activity in the sensorimotor cortex, measured via EEG or magnetoencephalography (MEG), is coherent with the EMG activity in

contralateral limb muscles in the beta band during weak-to-moderate tonic isometric voluntary contractions (Farmer et al., 1993; Conway et al., 1995; Salenius et al., 1997; Halliday et al., 1998; Gross et al., 2000; Kilner et al., 2000; Mima et al., 2000; Kristeva et al., 2002). Initially, this corticomuscular coherence (CMC) was considered to reflect the descending information flow from the cortex to the muscle because the phase shift between EEG and EMG was correlated with the estimated conduction delay (Gross et al., 2000; Mima et al., 2000). Indeed, activities of the corticospinal output neuron directly influence the generation of beta-frequency rhythm and contribute to CMC (Jackson et al., 2002). However, several previous studies have suggested that the situation is not quite that straightforward.

For the calculation of the coherence between cortical and muscle activities, the coherence phase should be correlated with the conduction delay, including the central and peripheral axonal conduction times and the synaptic delay at the motoneuron (Fig. 1-4). Riddle and Baker (2005) examined the conduction delay estimated from the phase-frequency regression after arm cooling, which slows the peripheral nervous conduction velocities in both afferent and efferent nerves. Based on their results, the delay was increased to approximately twice the delay observed in efferent axons. In deafferentations in neurological disorders, the oscillatory coupling is significantly

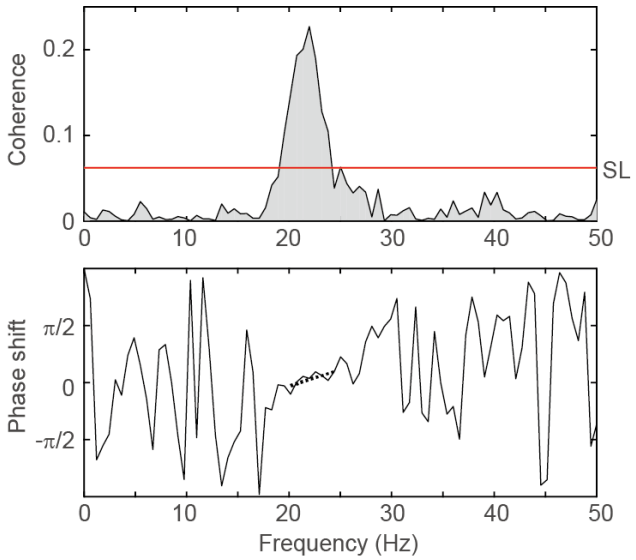

Figure 1-4. Coherence and phase shift spectrum calculated between EEG and EMG during contraction of the tibial anterior muscle. Group delay was observed in a frequency band in which coherence is significant. Cortical-muscular time lag can be estimated from a regression line (dashed line). SL: Significant level coherence.

reduced between muscles (Kilner et al., 2004) and between the cortex and muscle (Pohja and Salenius, 2003), though the cortical oscillatory power in the beta-frequency band is not different from that of healthy participants (Patino et al., 2006). This evidence indicates that CMC is derived not only from descending motor commands but also from ascending sensory feedback from the contracting muscle. Therefore, CMC is currently considered to be a mutual interaction between central activities associated with the motor output and sensory input from the periphery.

1.2 Corticomuscular Coherence

CMC is not necessarily observed consistently during voluntary movement. Firstly, several studies have reported that CMC can be altered by various factors. For instance, the magnitude of CMC increases after the visuo-motor training task, which requires precise motor control using somatosensory information (Perez et al., 2006). Perez et al. (2004) had reported that the excitability of the corticospinal cells increases after the same motor training task. Thus, these findings suggested that CMC enhanced by the increase of the cortical excitability contributes to motor learning by promoting effective communication between the sensorimotor cortex and the contracting muscle. In addition, previous studies have reported that CMC decreases under conditions of divided attention (Kristeva et al., 2002; 2007), and increases during cognitive effort (Safri et al., 2006; 2007). These findings indicated that the cortical excitability increased by cognitive demands can change the CMC magnitude. Moreover, Ushiyama et al. (2011a) demonstrated that the CMC magnitude was enhanced by muscle fatigue. This finding suggested that, in order to maintain the muscle contraction level during fatigue, many more motor units are recruited by the increase of motor commands from the M1, or that the corticospinal beta-oscillation encourages the synchronization of motor units firing. Thus, several points at cortical and spinal levels must be associated with the change in

the CMC magnitude. Therefore, the mechanism underlying CMC should be elucidated from the interaction between multiple neural circuits at the cortical and spinal levels.

Secondly, numerous cross-sectional studies have reported individual differences in CMC according to the participants' characteristics, including the presence of neurological disorders (Salenius et al., 2002; Fang et al., 2009), sports experience and habitude (Vecchio et al., 2008; Ushiyama et al., 2010), and age (Farmer et al., 2007; Graziadio et al., 2010). From these findings, it has been considered that the connection between the cortex and the contracting muscle, indicated by CMC, can be modified by neurological disorders, sports training, and development. Furthermore, a recent study demonstrated that the magnitude of CMC varies among healthy young individuals, and that the stronger the CMC, the greater is the beta-frequency band oscillation in EEG and EMG (Ushiyama et al., 2011b). These findings implied that the CMC magnitude has the potential to determine individual motor function. However, the behavioral correlates of CMC and the neural circuitry underlying the individual differences are not yet clear.

1.3 Influence of Corticomuscular Coherence on Motor Function

What kind of motor performance can be affected by neural oscillation in the corticospinal system? First, the stability of the muscle force may be considered. In

patients with Parkinson's disease, CMC is observed at a lower frequency (5–12 Hz) than in healthy adults (Volkmann et al., 1996; Hellwig et al., 2000). This neural oscillation is exposed as a tremor and inhibits the smooth physical movement of the limbs. In the case of healthy adults, fluctuation in the beta-frequency band is observed in the muscle force as microtremor (Gilbertson et al., 2005). Although beta-oscillations associated with microtremor should impair the force stability, several studies have suggested that beta-oscillations represent the cortical state that maintains the steady motor output (Gilbertson et al., 2005; Androulidakis et al., 2006, 2007; Kristeva et al., 2007). In one such study, the beta-band CMC magnitude was reported to increase in participants who resisted a stretch perturbation to the finger when a warning cue indicated that the stretch would occur (Androulidakis et al., 2007). In contrast, a cue indicating that the participants must make a voluntary reaction to a subsequent stimulus produced a drop in CMC. These previous findings suggested that the neural oscillations in the sensorimotor cortex and the contracting muscle might underpin a corticospinal state in which pre-recruiting cortical and spinal neurons exerting motor outputs is favored.

Furthermore, neural oscillations might affect the reaction time (RT) at the initiation of new movements. For example, tremor at rest in Parkinson's disease prolongs the RTs

(Staude et al., 1995). In the case of healthy participants, transcranial alternating-current stimulation at 20 Hz enhances the beta-band CMC and slows the velocity of a joystick held by the hand when initiating voluntary movements (Pogosyan et al., 2009). Furthermore, it has been suggested that the beta-band oscillation in the periphery is not constant throughout a motor task, even during steady contractions (Gilbertson et al., 2005). Therefore, it is highly possible that ballistic reaction performance is interrupted by the increase of beta-band CMC.

1.4 Mechanisms underlying Corticomuscular Coherence

CMC has been suggested to reflect the descending/ascending transmission of beta-oscillation between the sensorimotor cortex and muscles (Kilner et al., 2004; Riddle and Baker, 2005). Generally, the thalamocortical loop, including the motor cortex, basal ganglia, and thalamus, is well-known as a neural oscillator originating cortical rhythms (Lopes da Silva, 1991). In addition, a previous study reported that the subthalamic nucleus relaying the thalamocortical loop is associated with the generation of cortical beta-oscillations from the measurement in patients with Parkinsonism (Marsden et al., 2001). Therefore, it is widely accepted that the beta-oscillation generated by the activities in the thalamocortical loop is transmitted from M1 to the

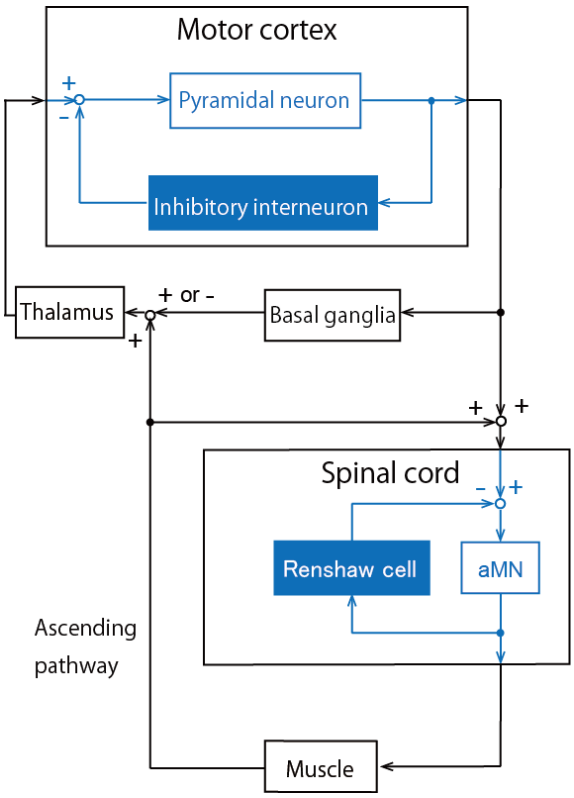

Figure 1-5. A corticospinal circuit associated with corticomuscular coherence (CMC). The author described this model from evident neural circuits reported to be associated with CMC or beta-oscillation in the corticospinal system in humans (Marsden et al., 2001; Baker and Baker, 2003; Williams and Baker, 2009). The nuclei and pathways between them are shown in black, and those on the cellular level are shown in blue. This model does not represent a common corticospinal system including all skeletal muscles, but it merely summarizes the present hypothesis visually. As neural circuits modulating CMC, two interneurons were the focus of this dissertation. It was hypothesized that intracortical inhibition (ICI) in the motor cortex is related to generation of beta-frequency oscillations in the motor cortex, and that recurrent inhibition (RI) produced by Renshaw cells reduces oscillations in the spinal cord. PN: pyramidal neurons; aMN: alpha motoneurons.

muscle through the descending pathway. Furthermore, this oscillation is fed back from the muscle to S1 through the ascending pathway during human voluntary movements. However, the question remains as to why there are individual differences in CMC that reflect the bidirectional transmission of beta-oscillation? In this dissertation, the author focused on two inhibitory neural circuits (i.e., intracortical inhibition and recurrent inhibition), which can be associated with the generation or modulation of CMC in addition to the above-mentioned neural system including the descending/ascending pathway and thalamocortical loop (Fig. 1-5). Intracortical inhibition (ICI) has been previously reported to generate the cortical beta-oscillation (Baker and Baker, 2003), and recurrent inhibition (RI) in the spinal cord is known to prevent the synchronization of spinal motoneurons (Matthews, 1997). In the next section, the author will outline the physiological characteristics of these inhibitory neurons and the quantitative methods used to measure them.

1.4.1 Intracortical Inhibition and its Assessment

Negative-feedback systems are well known to generate oscillatory output (Ernst, 1995; Destexhe et al., 1998; Pauluis et al., 1999; Bressloff and Coombes, 2002); this implies that inhibitory neural circuits are associated with CMC. A pharmacological study

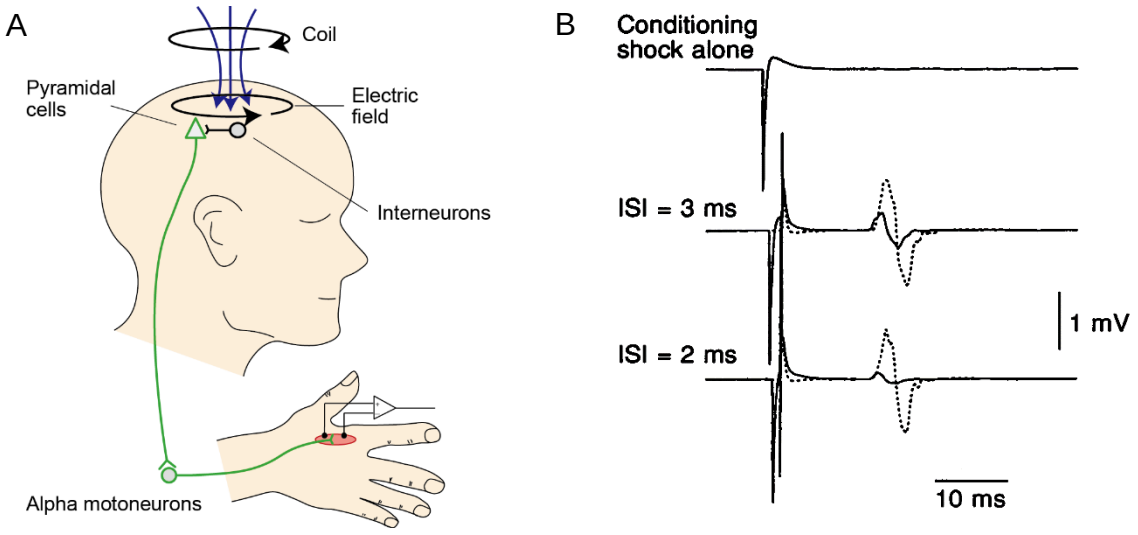

Figure 1-6. A) Principle of transcranial magnetic stimulation (TMS). A rapidly changing magnetic field generated by the TMS coil induces an electric current in cerebral tissue. A motor response is recorded from muscles (modified from Kobayashi and Pascaual-Leone, 2003). **B) Motor responses elicited by paired-pulse TMS.** EMG responses in the first dorsal interosseous (FDI). The first trace shows the absence of any responses to the conditioning stimulus when it is delivered alone. The lower two records have two superimposed traces, which include the response to the test stimulus given alone (dashed lines), and the response to the test stimulus delivered 3 ms and 2 ms after a conditioning stimulus (solid lines) (modified from Kujirai et al., 1993).

reported that 20 Hz oscillations in the sensorimotor cortex are partially produced by local cortical circuits relying on the gamma-aminobutyric acid A receptor ($GABA_A$)-mediated inhibition (Baker and Baker, 2003). Thus, the author hypothesized that ICI is a factor that causes the individual differences in CMC.

ICI can be noninvasively quantitated by transcranial magnetic stimulation (TMS) in humans. The TMS coil generates a rapidly changing magnetic field, and electric currents running parallel to the skin surface are elicited by electromagnetic induction (Fig. 1-6A). TMS indirectly stimulates layer-V pyramidal neurons via interneurons (I-waves) that originate in cortical layers II and III (Di Lazzaro et al., 2012). The resulting motor-evoked potential (MEP) is recorded using EMG. Single-pulse TMS is clinically used to examine the functional connections between the cortex and muscles. Kujirai et al. (1993) first described the assessment of ICI by using paired-pulse TMS applied to the motor cortex through the same coil. They further demonstrated that the ICI can be elicited by a subthreshold conditioning stimulus (CS) followed by a suprathreshold test stimulus (TS). At an inter-stimulus interval (ISI) of 1–6 ms, the test motor response was inhibited by the CS (Fig. 1-6B).

Evidence from pharmacological studies has proposed that the depressed MEP is presumably derived from $GABA_A$-mediated inhibition. Ziemann et al. (1996; 2003) showed that $GABA_A$ agonists enhance ICI. In M1, the cortical layer II has the highest concentration of GABAergic neurons (Jones, 1993), and includes prominent vertical inhibitory projections (Keller, 1993). Therefore, it is probable that the ICI-induced paired-pulse TMS reflects activities of inhibitory interneurons existing in layer II of the

cortex. In the present dissertation, the author supposed that the influence of ICI on CMC is assayed by paired-pulse TMS during voluntary muscle contraction.

1.4.2 Recurrent Inhibition in the Spinal Cord and its Assessment

If the oscillatory descending drive was directly transmitted to the periphery, the CMC magnitude would be sufficiently determined by measuring the cortical neural activity. However, the oscillations can be modulated at the spinal level. Renshaw cells, which are found in the gray matter of the spinal cord, cause RI of motoneurons. Namely, these spinal interneurons are excited by collaterals from motoneurons (Renshaw, 1941) (Fig. 1-7). This negative-feedback system regulates the motoneuron excitability and stabilizes their firing rates. Thus, RI is known to regulate the oscillations in the muscle activity by preventing the synchronization of the spinal motoneuron activity (Stein and Oguztoreli, 1984; Windhorst, 1996; Matthews, 1997). The Hoffmann reflex (H-reflex) elicited by electrical nerve stimulation will be described before the assessment of RI by using paired-pulse stimulations. When the peripheral nerve is electrically stimulated, a response called the H-reflex can be observed in the EMG readings of the homonymous muscle (Fig. 1-8A); this response differs depending on the stimulus intensity. Thus, a stimulus with a higher intensity evokes action potentials in small-diameter fibers, and

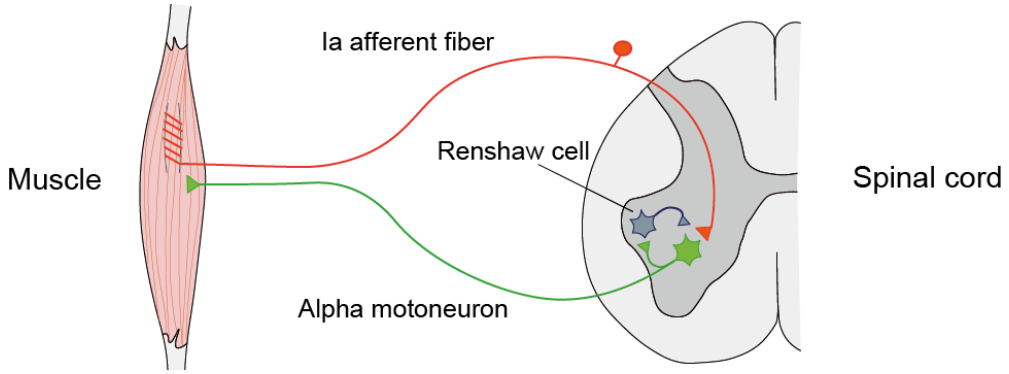

Figure 1-7. Renshaw cells produce RI. Renshaw cells are excited by collaterals from motoneurons and inhibit those same motoneurons. This negative feedback system regulates motoneuron excitability and stabilizes firing rate.

elicits large responses by recruiting more motor units. At low stimulus intensity, a pure H-reflex is elicited, because the activation threshold of Ia afferent fibers is lower than that of motor axons, which have a smaller diameter. As the stimulus intensity increases, the motor axons become also activated and two distinct responses can be observed, namely the M-wave and H-reflex (Fig. 1-8B). When the stimulus intensity is increased even further, the M-wave becomes larger and the H-reflex disappears; finally, only a pure M-wave of maximal peak-to-peak amplitude can be seen (Fig. 1-8C). The M-wave is the response elicited when the motor axons are stimulated, and the evoked volley is propagated orthodromically to the muscle. However, the H-reflex is the response elicited when the Ia afferent fibers are stimulated. Furthermore, the evoked volley is propagated to the spinal cord where the Ia afferent fibers project monosynaptically to

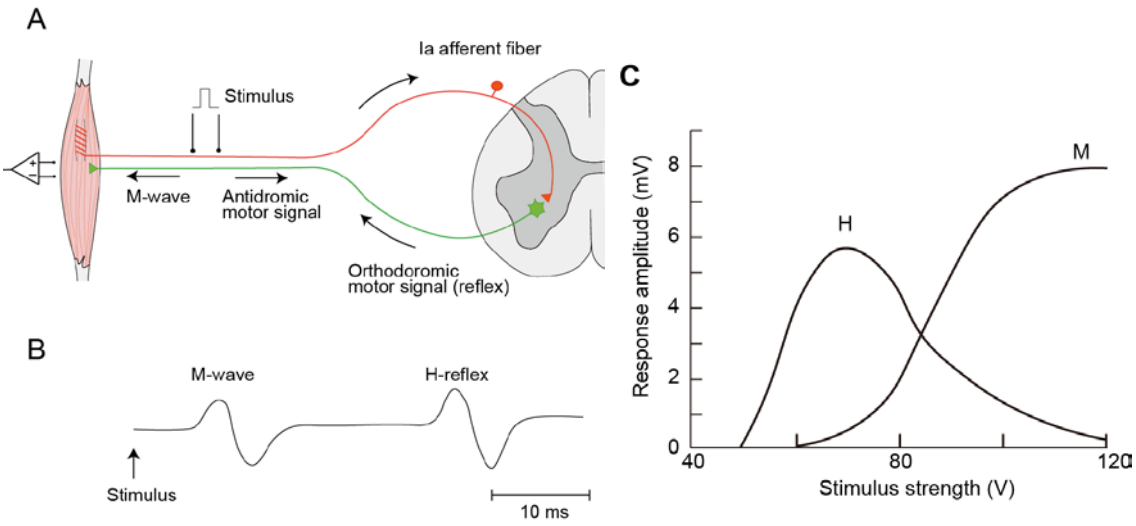

Figure 1-8. Mechanism of the H-reflex. A) The H-reflex is evoked by electrically stimulating Ia afferent fibers from muscle spindles in mixed nerves. The sensory fibers excite alpha motoneurons, which in turn activate the muscle. Muscle activation is detected using EMG. B) At intermediate stimulus strengths motor axons in the mixed nerve are excited, as are the spindle afferents. Excitation of motoneurons produces an M-wave that precedes the H-reflex, as seen in EMG traces. C) At low stimulus strengths only an H-reflex is produced because only the spindle afferents are excited. As the stimulus strength increases, the magnitude of the H-reflex also increases, then declines, because the orthodromic motor signals generated reflexively by the spindle afferents are cancelled by antidromic signals initiated by the electrical stimulus in the same motor axons. At very high stimulus strengths, only an M-wave is evoked (modified from Sheippati et al., 1987).

alpha motoneurons. The absence of the H-reflex at high stimulus intensities is due to the collision of action potentials in the fibers of motoneurons that antidromically propagate to the cell body with those that orthodromically propagate from the cell body via the

projection from Ia afferent fibers.

Moreover, a mechanism to evaluate RI using the paired H-reflex method is described here. Paired-pulse electrical stimulation is composed of two types of stimuli (Stim1 and Stim2) with an interval of 10–20 ms. The intensity of Stim1 is adjusted so that no direct motor responses (M-wave) are evoked (Fig. 1-9A), and the intensity of Stim2 is greater than that of Stim1. The effects of RI are assessed by a second H-reflex (H'), which is generated by a supramaximal stimulation (Stim2) to alpha motor fibers (Fig. 1-9C). The preceding Stim1 not only elicits an H-reflex but also activates the Renshaw cells, thus providing an inhibitory feedback to the same alpha motoneuron pool. When Stim2 is applied 10 ms after Stim1, the H-reflex discharge evoked by Stim1 collides with an antidromic motor volley caused by Stim2. However, the Ia inputs induced by Stim2 can activate the alpha motoneurons, which subsequently evoke the H' reflex. Given that this H' reflex is affected by an inhibitory input from RI, which is activated by Stim1, its amplitude is smaller than the H-reflex evoked by the single pulse of Stim1. This mechanism indicates that the H-reflex inhibited by RI can be detected by the paired-pulse H-reflex method.

Evidence from a previous pharmacological study has proposed that the depressed H-reflex is presumably derived from RI exerted by Renshaw cells. Mazzocchio and

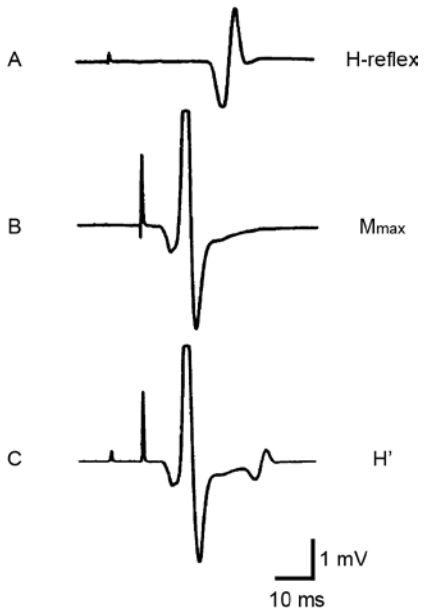

Figure 1-9. Recurrent inhibition is assessed from motor responses elicited by different stimulation conditions. A) Only an H-reflex is observed when Stim1 is given alone. B) Stim2 elicits a pure M-wave without a subsequent H-reflex. C) Combined Stim1 and Stim2 with an interval of 10 ms produces an H-reflex inhibited by RI (H') (modified from Mazzocchio et al., 1994).

Rossi (1989) demonstrated that the acute administration of L-acetylcarnitine, a central cholinergic substance, decreased the amplitude of an H' reflex elicited by the paired-pulse electrical stimulation. The drug can enhance the recurrent inhibition, since Renshaw cells are mainly excited by motor axon collaterals, which are mediated by the action of acetylcholine (Curtis and Ryall, 1966). Therefore, it is considered that the RI-induced paired-pulse electrical stimulation reflects activities of the Renshaw cells. In the present dissertation, the author hypothesized that the influence of RI on CMC can be

assayed by the paired-pulse H-reflex method during voluntary muscle contraction.

1.5 Purpose of the Dissertation

As described in Chapter 1.2, CMC has been reported to be related to motor skill training (Perez et al., 2006) and sports experience (Vecchio et al., 2008; Ushiyama et al., 2010), and reflects different neural activity patterns among healthy individuals (Ushiyama et al., 2011b). These findings suggested that CMC may be useful for examining the individual differences in motor skills and/or motor learning at the neurophysiological level. However, the influence of CMC on motor performance has not been investigated by kinesiological methods. In addition, the neural mechanisms that are associated with the individual differences in CMC are not yet clear. Therefore, the purpose of this dissertation was to investigate the influence of CMC differences among healthy individuals on motor function and its underlying mechanisms. To investigate the kinesiological characteristics of CMC, it is important to indicate the direction of applied researches. Clarifying the neural circuitry underlying the individual differences in CMC will enable the next step of developing a method to manipulate CMC. Therefore, the author used two methodological approaches in this dissertation, namely kinesiological and electrophysiological evaluations.

In the first study (presented in Chapter 2), the author investigated the way CMC affects the human body movements. For this, the author used an RT task, whereby RTs were taken as an index of motor function, and further evaluated the relationship between RTs and CMC. Previous studies have reported that beta-oscillations in the periphery impair the initiation of new movements (Gilbertson et al., 2005). Therefore, the RT was expected to be prolonged by beta-band corticomuscular coupling.

In the second study (presented in Chapter 3), the author investigated the neural mechanisms that determine the individual differences in CMC. Thus, the author focused on two inhibitory interneuron circuits at the cortical and spinal levels, which can be noninvasively assessed using electrophysiological methods. Firstly, the author examined the ICI using the paired-pulse TMS method. The author expected to observe a positive correlation between ICI and the CMC magnitude or the associated beta-band oscillations, because the ICI is known to contribute to the generation of beta-oscillations in the sensorimotor cortex (Baker and Baker, 2003). Secondly, the author examined the RI using the paired H-reflex method. A previous stimulation study reported that RI plays a ‘neural filter’ role and reduces the magnitude of CMC at 10 and 20 Hz (Williams and Baker, 2009). Based on these previous findings, the author hypothesized that ICI and RI are likely to underlie individual differences in CMC.

The human neural system controls the voluntary movements through the interaction of motor outputs and sensory inputs between the sensorimotor cortex and the muscle; CMC is an index that can inclusively evaluate this interaction. This study revealed the neural mechanisms underlying CMC and its potential effect on movement. This study also discussed the individual differences in motor skills and whether or not this could be used to improve the human motor performance.

Chapter 2

Prolonged Reaction Time during Episodes of Elevated Beta-band Corticomuscular Coherence and Associated Oscillatory Muscle Activity

2.1 Introduction

Beta-band coherence between the sensorimotor cortex and the muscle has been well studied since it was first reported in both, monkeys (Baker et al., 1997) and humans (Conway et al., 1995) around 20 years ago. Numerous cross-sectional studies have reported that the magnitude of CMC is affected by various factors including neurological disorders (Salenius et al., 2002; Grosse et al., 2003; Fang et al., 2009), sports experience and habitude (Vecchio et al., 2008; Ushiyama et al., 2010), and age (Farmer et al., 2007; Graziadio et al., 2010). Based on electrophysiological data, these studies have speculated about the effects of changes in corticomuscular coupling on the motor function.

Several recent studies reported that the CMC magnitude varies among individuals, even within the same population, i.e., healthy young adults (Hashimoto et al., 2010; Ushiyama et al., 2010; 2011b). Furthermore, it has been quantitatively demonstrated that the stronger the magnitude of EEG-EMG coherence, the more prominent is the

beta-band grouped discharge in EMG signals (Ushiyama et al., 2011b). These findings indicated that the differences in motor performance among individuals are the result of variations in EMG activation patterns depending on the strength of CMC. However, further electrophysiological and kinematic analyses are needed to clarify the functional role of CMC in motor function.

It has recently been estimated that beta-oscillations in the corticospinal system affect new ballistic movements. Indeed, Pogosyan et al. (2009) demonstrated that transcranial alternating-current stimulation at 20 Hz enhances beta-band CMC, and slows the velocity when initiating voluntary movements. Considering this phenomenon along with previous finding indicating a relationship between the magnitude of CMC and EMG beta-oscillation (Ushiyama et al., 2011b), it may be possible that the magnitude of CMC is a determinant of the variation in the kinesiological index related to the initiation of movement among individuals. Thus, the author hypothesized that the individual differences in CMC produce variations in the generation of new ballistic movements from the steady contraction state. Furthermore, it seems likely that the beta-oscillation in the periphery is not constant throughout the task, even during steady contractions (Gilbertson et al., 2005). Given that moment-to-moment changes in the magnitude of CMC may vary the strength of oscillations in the periphery, the author

hypothesized that ballistic reaction performance may be interrupted when the magnitude of beta-band CMC is naturally elevated.

This study aimed to test the two hypotheses mentioned above. First, the author examined the inter-participant differences in RT depending on the magnitudes of CMC. Second, in the participants who showed significant CMC, the author examined the intra-participant differences in RT depending on the magnitude of beta-band oscillation during preliminary contraction. The author used the tibialis anterior (TA) muscle as the recorded muscle because it has been reported that distally located lower limb muscles show the greatest CMC among various upper and lower limb muscles (Ushiyama et al., 2010). Furthermore, the TA is widely used to determine neuromuscular activation characteristics (Thomas et al., 1989; Bongiovanni et al., 1990; Bongiovanni and Hagbarth, 1990; Knaflitz et al., 1990; Halliday et al., 2003; Lévénez et al., 2005; Perez et al., 2006), because it is the primary muscle involved in ankle dorsiflexion, accounting for approximately 60% of the physiological cross-sectional area of all ankle dorsiflexors (Friederich and Brand, 1990). Furthermore, the TA muscle is flat, straight, and superficial, making it amenable to surface EMG recording.

2.2 Materials and Methods

2.2.1 Participants

Fifteen healthy young adults (aged 21–33 years; 11 males and four females) with no history of neurological disorders voluntarily participated in this study. Only healthy young adults without remarkable sports experience were recruited, because CMC and RT may be influenced by factors such as age and sports experience. All participants provided informed consent for the study after receiving a detailed explanation of the purpose, potential benefits, and risks involved. The experimental procedures were approved by the local ethics committee of the Faculty of Science and Technology, Keio University.

2.2.2 Recordings

EEG was recorded from the region of the scalp overlying the sensorimotor cortex using five Ag/AgCl electrodes that were 10 mm in diameter, placed at Cz (defined by the international 10–20 system) and 20 mm at frontal, back, left lateral, and right lateral positions. The reference electrode was placed at A2 (right earlobe), while the ground electrode for both EEG and EMG was placed on the right patella. The EEG signals were derived using the Hjorth transformation (Hjorth, 1975), a popular method for deriving

local electric fields, which consists of subtracting the averaged signals of the four surrounding electrodes from the monopolar-derived signals recorded from a center electrode. Surface EMG was recorded from the TA, over the muscle belly, using bipolar Ag/AgCl electrodes that were 10 mm in diameter with an inter-electrode distance of 20 mm. During the recording, the impedance of the EEG and EMG electrodes was kept below 5 kΩ and 20 kΩ, respectively.

All analog EEG and EMG signals were amplified and band-pass filtered (EEG 0.5–100 Hz; EMG 5–500 Hz) using a standard EEG/EMG recording system (Neuropack MEB-4308; Nihon Kohden Corporation, Tokyo, Japan). Force signal was recorded with a custom-ordered ankle-dynamometer (MK-808052; ME incorporated, Nagano, Japan) and low-pass filtered at 50 Hz. All signals were converted to digital signals at a sample frequency of 1 kHz by an analog-to-digital converter, with 12-bit resolution (DAQCard-6062E; National Instruments Inc., Austin, TX, USA), controlled by the data logger software originally designed using MATLAB (The MathWorks Inc., Natick, MA, USA).

2.2.3 Experimental Protocol

Each participant was comfortably seated on a chair connected to the dynamometer.

Before experimentation, participants were instructed to practice maximal voluntary contractions (MVC). Each MVC lasted approximately 3 s and participants completed three to five practice trials. The present aim was to confirm that the differences in peak force values over periods of stable force output were smaller than 5% in the last three trials. After this was confirmed, participants performed the MVC task once, and the peak force from this trial was used as a measure for the MVC force. Furthermore, the obtained MVC force value was confirmed to be within the range of the practice trials. After a rest period of 90–120 s, the participants performed a steady contraction task requiring sustained isometric voluntary contraction of the TA at 30% of MVC for 60 s to evaluate whether they had significant EEG-EMG coherence. Consistently with recent studies (Hashimoto et al., 2010; Ushiyama et al., 2010; Ushiyama et al., 2011b), the author used 30% of MVC as the contraction level for measuring coherence between EEG and EMG for the following reasons: (1) the magnitude of beta-band CMC is not affected by the contraction levels of weak to moderate isometric contraction of the TA (Brown et al., 1998; Ushiyama et al, 2012); (2) compared with lower contraction levels, the beta-band oscillations in the EMG signals could be observed more clearly; and (3) the effects of muscle fatigue on CMC could be avoided because it takes much longer than 60 s to induce muscle fatigue in the TA by sustained isometric dorsiflexion at 30%

of MVC (Beck et al., 2005; Griffith et al., 2010). During the task, visual feedback about the level of the dorsiflexion force was provided via a level meter on a computer screen positioned at 1.2 m in front of the participants. The participants were instructed to maintain their exerted force as close as possible to a line corresponding to 30% of their MVC force.

Following a rest period that took place after the steady contraction task, participants performed a ballistic contraction task. The RT paradigm was constructed based on a previously described method (Duclos et al., 2008). It is common for a ballistic movement from a tonic contraction to be preceded by 40–50 ms of EMG silence, accompanying a clear drop in force (Moritani and Shibata, 1994). To eliminate the potential effects of this period of EMG silence on the present data, the participants were given a sufficient practice period (i.e., producing ballistic contractions from a tonic contraction state for 10–20 repetitions). This was done to ensure that they would be able to achieve ballistic dorsiflexion without the preceding EMG silence and associated force drop. After sufficient practice, the participants performed isometric dorsiflexion at 30% of MVC for 4–6 s. During this preliminary contraction trial, the participants were given two computer-generated auditory signals indicating “ready” and “go” (frequency, 250 Hz; duration, 400 ms). The “go” signal followed the “ready” signal after a randomized

period between 1.0 and 2.0 s. The participants were required to perform ballistic dorsiflexion as quickly as possible in response to the “go” signal. After one ballistic contraction, they were asked to rest for approximately 4–5 s while relaxing the TA, and subsequently restarted the next preliminary contraction. This task was repeated 100 times with a 2–3 minute rest period once every 10 trials.

2.2.4 Data Analyses

(I) Steady contraction task: To assess the data for the steady contraction task, the magnitude of CMC was evaluated for each participant. Although the necessity of full wave rectification for EMG has been discussed (Halliday and Farmer, 2010; McClelland et al., 2014), the author used the rectification to detect the motor unit synchronized activities. Raw EEG and rectified EMG signals were segmented into artifact-free epochs 1024 ms in duration, with no overlap (58 epochs). Each 1024 ms data epoch was Hanning-windowed to reduce spectral leakage (Farmer et al., 1993; Baker et al., 1997; Gross et al., 2000). Correlations between the EEG and rectified EMG ($C_{xy}(f)$) were calculated by coherence using the following equation (Halliday et al., 1995):

$$\left|\boldsymbol{C_{xy}(f)}\right| = \frac{\left|\overline{\boldsymbol{P_{xy}(f)}}\right|^{\mathbf{2}}}{\overline{\boldsymbol{P_{xx}(f)}} \cdot \overline{\boldsymbol{P_{yy}(f)}}} \qquad (\mathbf{2}-1)$$

where $\overline{P_{xx}(f)}$ and $\overline{P_{yy}(f)}$ are the averaged power-spectral density functions (PSD) of the EEG and the rectified EMG signals throughout the epochs for a given frequency *f*, respectively, and $\overline{P_{xy}(f)}$ is the averaged cross-spectral density function between the EEG and rectified EMG signals throughout the epochs. The coherence function provides a normative measure of linear correlation on a scale from 0 to 1, where 1 indicates a perfect linear correlation.

To confirm whether or not the maximal peaks of the coherence spectrum actually exist within the beta-band (15–30 Hz), the frequency range for the latter quantitative analyses was set at 3–50 Hz (including alpha-, beta-, and gamma-bands), and the 95% confidence limit of the EEG-EMG coherence was defined according to the equation reported in previous studies (Rosenberg et al., 1989; Halliday et al., 1995). To eliminate the possibility that the resulting coherence value was judged to be significant due to a statistical error, a Bonferroni correction for multiple comparisons across the 48 frequency bins (i.e., between 3 and 50 Hz) was applied to the equation defining the significant level coherence (SL) (Kilner et al., 2000; Ushiyama et al., 2011b). Thus, when the confidence limit is α, the SL is estimated as follows:

$$\boldsymbol{SL(\alpha) = 1 - \left[\frac{1}{N} \cdot (1 - \alpha)\right]^{1/(L-1)}} \qquad (\mathbf{2} - 2)$$

where *N* is the number of frequency bins and *L* is the number of epochs. Since an *N* of 48, *L* of 58, and α of 0.95 were chosen, the SL was determined to be 0.114.

(II) Ballistic contraction task: As mentioned above, the participants practiced ballistic contractions before the measurements were acquired. This was done to reduce the chance of obtaining ballistic contractions that had brief periods of EMG silence and associated drops in force before the reaction. Despite this, a drop in force has been observed in a few trials from several participants. To address this, the author conducted an off-line analysis wherein the author carefully checked the EMG and force signals before the reaction in every trial, and omitted the trials with apparent periods of EMG silence (approximately 40–50 ms) (Moritani and Shibata, 1994) and associated drops in force. Similarly, the author also omitted the trials in which the acceleration of ballistic contraction was clearly slower than in the other trials. RT was defined by reference to Duclos et al. (2008), as follows: The time when the force level exceeded mean + 3 standard deviations (SD) of the force data for the 3 s period prior to the go signal was determined as the reaction onset. Therefore, the author measured the interval between

the “go” signal and the reaction onset, and defined this interval as RT.

First, the author divided the participants into two groups based on the data from the steady contraction task; i.e., those participants showing significant EEG-EMG coherence in the beta-band (CMC+, n = 8) and those participants showing no significant coherence within any frequency range for the present analyses (CMC-, n = 7). As previously reported (Ushiyama et al., 2011b), a rhythmic grouped discharge in EMG within the beta-band was observed in all CMC+ participants, but not in all CMC- participants (Fig. 2-1). The author determined the mean value of RT for each participant, and examined the group differences in RT between CMC+ and CMC- participants by conducting a two-sample t-test.

Upon a detailed visual observation of the data from the steady contraction task, the author found that the extent of the grouped discharge changed from moment to moment in the CMC+ participants, i.e., the grouped discharge in EMG did not always occur, but it occurred at random on the order of a few hundred milliseconds (Fig. 2-2). Similarly, in the ballistic contraction tasks performed by CMC+ participants, the author found that the extent of the grouped discharge during preliminary contractions differed on a trial-by-trial basis. To examine the hypothesis that RT is influenced by the presence or absence of grouped discharge in EMG just before the reaction, which may be associated

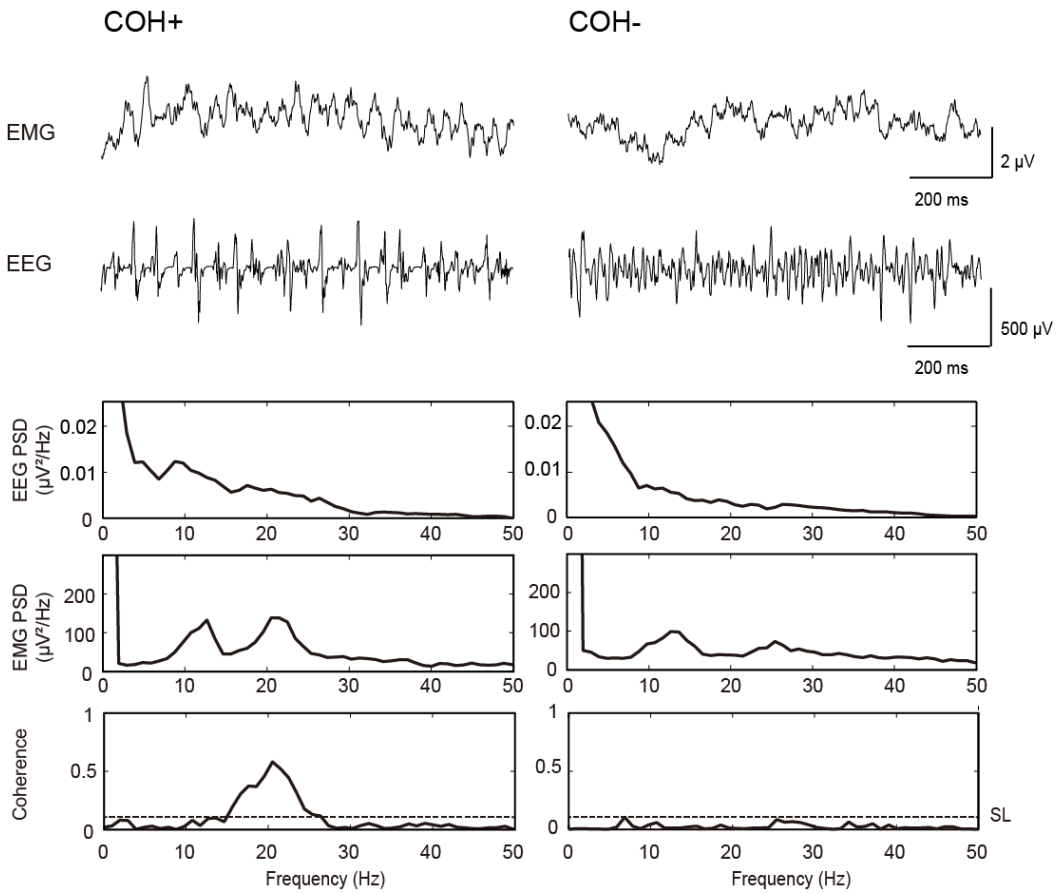

Figure 2-1. Representative samples of raw EEG signals, raw EMG signals, power spectral density functions (PSDs) for EEG and rectified EMG signals, and coherence spectra between EEG and rectified EMG signals during tonic isometric voluntary contraction of the tibialis anterior muscle (TA). Data for a participant who showed significant EEG-EMG coherence (CMC+), and data for a participant who did not show significant EEG-EMG coherence (CMC-) are shown, respectively. In the coherence spectra, the estimated significance levels of coherence (SLs, 0.114) are shown as horizontal dashed lines.

with corticomuscular coupling, the author selected trials with rhythmic beta-band grouped discharge associated with a significant short silent period (10–20 ms) (GD+)

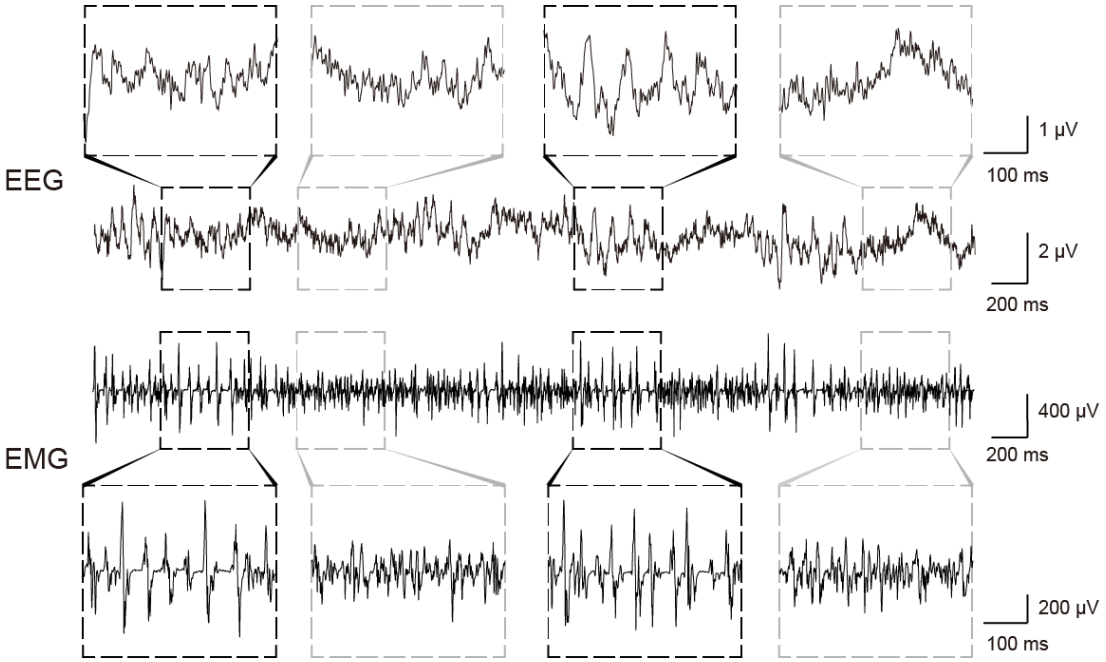

Figure 2-2. An example of moment-to-moment changes in the extent of beta-oscillations observed in raw EEG signals and raw EMG signals during a tonic isometric voluntary contraction performed by a CMC+ participant. Top: wide-scale EEG signals; bottom: wide-scale EMG signals. Oscillatory activity is clearly observed in the raw EEG and EMG signals during the time intervals framed by black squares, but not during the time intervals framed by gray squares.

and those with no grouped discharge (GD-) from all the trials for each participant, as follows: First, from the data for the steady contraction task, the author determined the characteristic frequency band (CFB) of PSD for the rectified EMG for each CMC+ participant by defining the frequency band where the EMG-PSD exceeded its mean value within 3–50 Hz (Fig. 2-3). The CFB was determined from a broad range of frequencies (3–50 Hz) to avoid arbitrary assessments of the CFB of grouped discharges

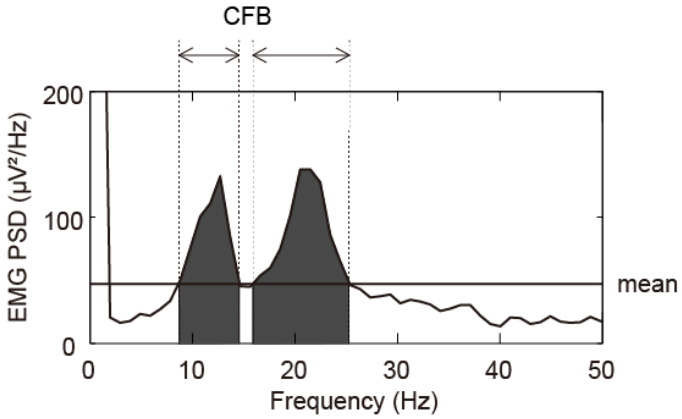

Figure 2-3. The PSD of rectified EMG signals during a steady contraction task performed by a CMC+ participant. The author estimated the mean of the PSD to be within 3-50 Hz, and defined the frequency band at which the PSD exceeded the estimated mean value as the characteristic frequency band (CFB). The horizontal solid line indicates the mean value of PSD within 3-50 Hz. See 2.2.4 Data Analysis (p. 33) for more details.

on individual EMG traces. The result confirmed that the CFB included the beta-band (and not any higher components [35–50 Hz]) in all the CMC+ participants. Subsequently, using the data for the ballistic contraction task, the author calculated the EMG-PSD for the period 512 ms before the onset of ballistic activities in the EMG for each trial, and determined the ratio of the sum of PSD within CFB to that of the entire frequency range (3–256 Hz). The onset of the ballistic EMG activities was defined as the point 31 ms before the reaction was detected in the force signals, according to the duration of the electromechanical delay reported by Corcos et al. (1992). The author

sorted the data for all the analyzed trials in ascending order based on the above-mentioned ratios, and defined the top 25 trials as GD+ and the bottom 25 trials as GD- trials. For all of the CMC+ participants, based on a careful visual inspection, the top 25 trials clearly showed the grouped discharge, while the bottom 25 trials did not. A t-test confirmed a significant difference in the mean value of the ratio of PSD within CFB between GD+ and GD- for all CMC+ participants (GD+, 0.161 ± 0.041; GD-, 0.105 ± 0.035; $p = 0.011$). The author determined the mean RT values for both the GD+ and GD- trials for each participant, and examined the group differences in RT between the GD+ and GD- trials by conducting a paired t-test. For each participant, differences in the mean RT values between the GD+ and GD- trials were tested using a two-sample t-test. The author specifically focused on the differences in RT between the GD+ and GD- trials in the CMC+ participants only. This was due to the fact that the number of trials showing a clear grouped discharge in the CMC- participants was insufficient for a statistical comparison in RT between the GD+ and GD- trials.

To confirm whether or not the magnitude of corticomuscular coupling differed statistically between the GD+ and GD- trials, the author also calculated the EEG-EMG coherence by gathering data from the time-point 512 ms before the reaction. Subsequently, the author compared the magnitude of EEG-EMG coherence between the

GD+ and GD- trials for each CMC+ participant. The author tested for differences in the peak values of EEG-EMG coherence between the GD+ and GD- trials using a paired t-test. In addition, the pooled coherence was calculated for all CMC+ participants. Coherence was normalized using the arc hyperbolic tangent transformation for statistical analyses (Halliday et al, 1995). This enabled the comparison of the averaged tendency of the EEG-EMG coherence between the GD+ and GD- trials.

Additionally, to make sure that there were no temporal changes in the RT and in the magnitude of EEG-EMG coherence based on time-dependent changes in several factors such as attention and muscle fatigue, the author compared the RT and the peak magnitude of the EEG-EMG coherence between the first and last 25 trials. The EEG-EMG coherence calculation included data from 512 ms before each reaction. All statistical analyses were performed using PASW statistics software (SPSS Japan Inc., Tokyo, Japan).

2.3 Results

The group RT data (means ± SDs) of the CMC+ and CMC- participants were compared. A two-sample t-test detected no significant inter-participant differences in RT between the CMC+ and CMC- groups (CMC+, 730 ± 29 ms; CMC-, 744 ± 42 ms; $p = 0.646$).

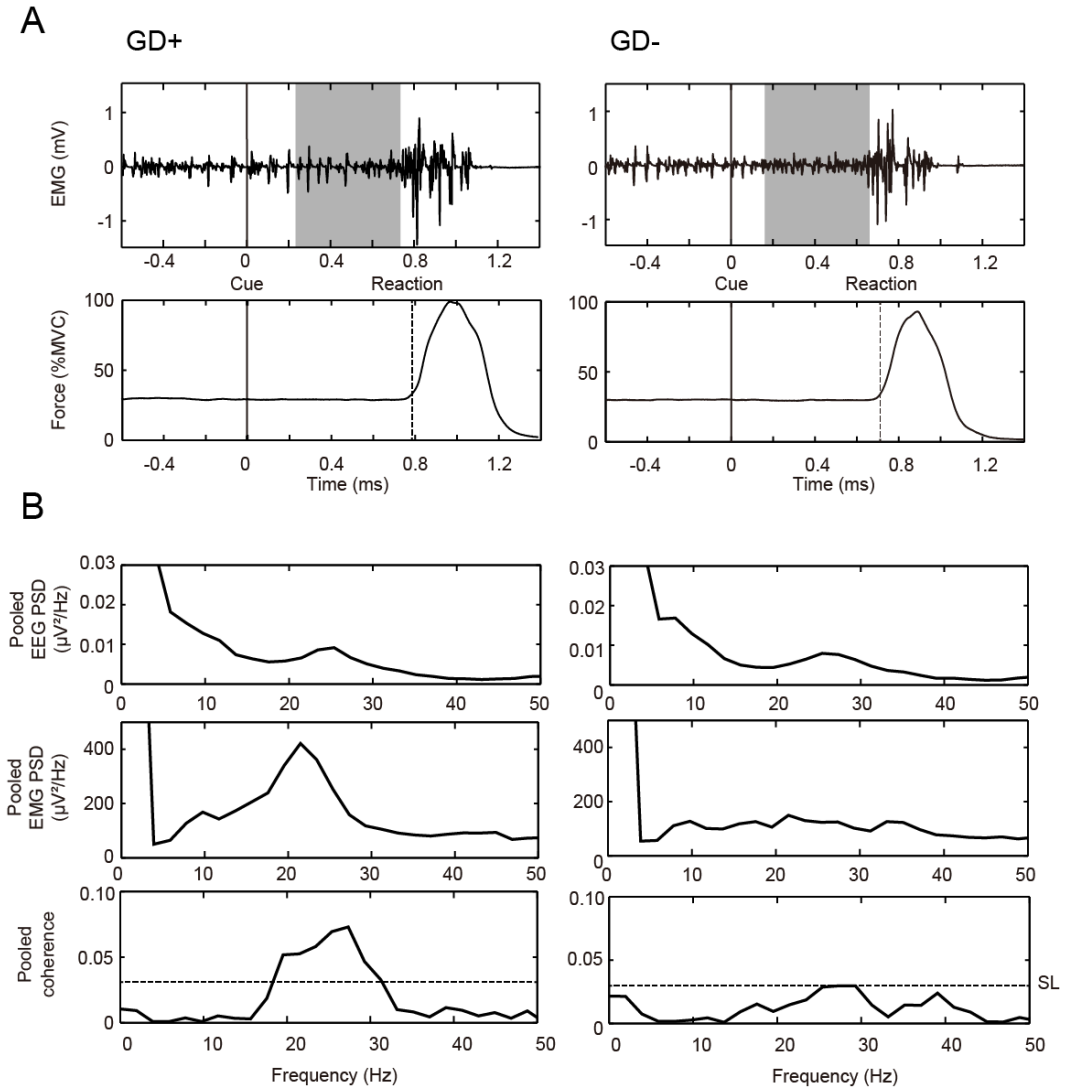

Figure 2-4. A) Representative examples of raw EMG and force signals during the ballistic contraction task for the GD+ and GD- trials. The time point at which the go signal was given is indicated by a vertical solid line. Reaction onset (vertical dashed line) was set as the time point when the force level became greater than mean + 3 standard deviations (SD) of the force level 3 s prior to the go signal. EMG signals for the 512 ms shagged with gray were used to analyze whether grouped discharge was present or not. **B) Pooled PSDs for the EEG and rectified EMG signals, and pooled CMC before reaction onset.** In the pooled coherence spectra, the estimated SL (= 0.031) is shown as a horizontal dashed line.

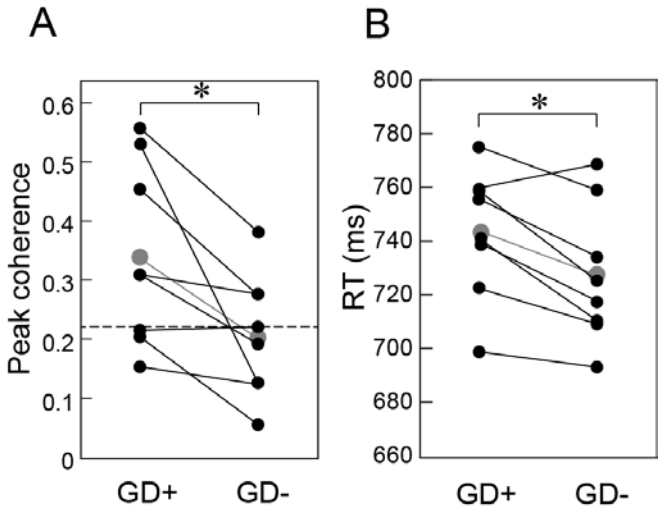

Figure 2-5. A) Comparison of the magnitude of CMC between the GD+ and GD- trials. The author calculated the coherence between the raw EEG and rectified EMG signals for the 512 ms prior to the reaction onset in the GD+ and GD- trials for each COH+ participant. Plots show the peak coherence values within the beta-band for the GD+ and GD- trials for each subject. Gray circles indicate group means. The estimated SL (= 0.227) is shown as a horizontal dashed line (*$p < 0.05$). **B) Comparison of RT between the GD+ and GD- trials.** Each plot shows the mean RT values for the GD+ and GD- trials for each subject. Gray circles indicate group means (*$p < 0.05$).

To illustrate the effect of the trial-by-trial changes in beta-band oscillatory EMG activity on RT, representative examples of raw EMG and force signals from GD+ and GD- trials, respectively, are shown in Fig. 2-4A. Not surprisingly, GD+ trials produced more prominent grouped discharge in EMG. RT seemed to be prolonged on the order of a few dozen milliseconds in GD+ trials compared with GD- trials (the dashed line

compares the onset of the reaction in the GD+ trials with that of GD- trials, shown in Fig. 2-4A). The author further plotted the pooled PSDs for the raw EEG signals and the rectified EMG signals and the pooled coherence spectra between the raw EEG and rectified EMG signals in the shaded time range shown in Fig. 2-4B. The magnitude of the pooled coherence was clearly larger in the GD+ trials than in GD- trials. The peak value of the pooled coherence spectrum in GD+ was greater than SL, but not in GD- trials. The author further included data obtained 512 ms before the reaction onset when calculating the EEG-EMG coherence for each CMC+ participant, and compared the peak values of the coherence spectrum between the GD+ and GD- trials. Figure 2-5A illustrates the group EEG-EMG coherence data from the GD+ and GD- trials. According to an earlier mathematical study, if coherence is determined from a small number of data epochs (for example $\leq$ 30 epochs), then the estimated magnitude of coherence is potentially biased from the true value (Carter et al, 1973). Despite this, a statistical t-test detected a significant group difference in the transformed peak value of coherence between the GD+ and GD- trials (GD+, 0.34 ± 0.15; GD-, 0.21 ± 0.10; p = 0.011, Fig. 2-5A). In addition, the peak values of the coherence spectrum were observed within the beta-band in all CMC+ participants.

Figure 2-5B illustrates the group data for the RT values from the GD+ and GD-

Table 2-1. Reaction time of GD+ and GD- for each CMC+ participant

	RT (ms)		
Participant	GD+	GD-	*p*
1	741 ± 51	711 ± 54	0.048*
2	739 ± 36	718 ± 27	0.019*
3	756 ± 52	735 ± 57	0.172
4	723 ± 40	710 ± 36	0.222
5	776 ± 58	760 ± 63	0.353
6	759 ± 48	726 ± 40	0.011*
7	699 ± 19	694 ± 31	0.508
8	760 ± 41	769 ± 52	0.512

Values are mean ± standard deviation of reaction time (RT) of GD+ and GD- trials for each CMC+ participant. *Differences between GD+ and GD- trials are statistically significant ($p < 0.05$).

trials. Note that each plot indicates the mean RT value in GD+ or GD- trials for each CMC+ participant. A statistical t-test detected a significant group difference in RT between the GD+ and GD- trials (GD+, 744 ± 24 ms; GD-, 728 ± 26 ms; $p = 0.012$, Fig. 2-5B). Table 2-1 shows the mean ± SD of the RT values from the GD+ and GD- trials for each CMC+ participant. The RT was longer in the GD+ than in GD- trials for seven of eight participants, and this difference was statistically significant in three of eight participants.

The statistical comparisons of RT and peak EEG-EMG coherence between the first and last 25 ballistic contraction trials revealed no significant temporal differences were

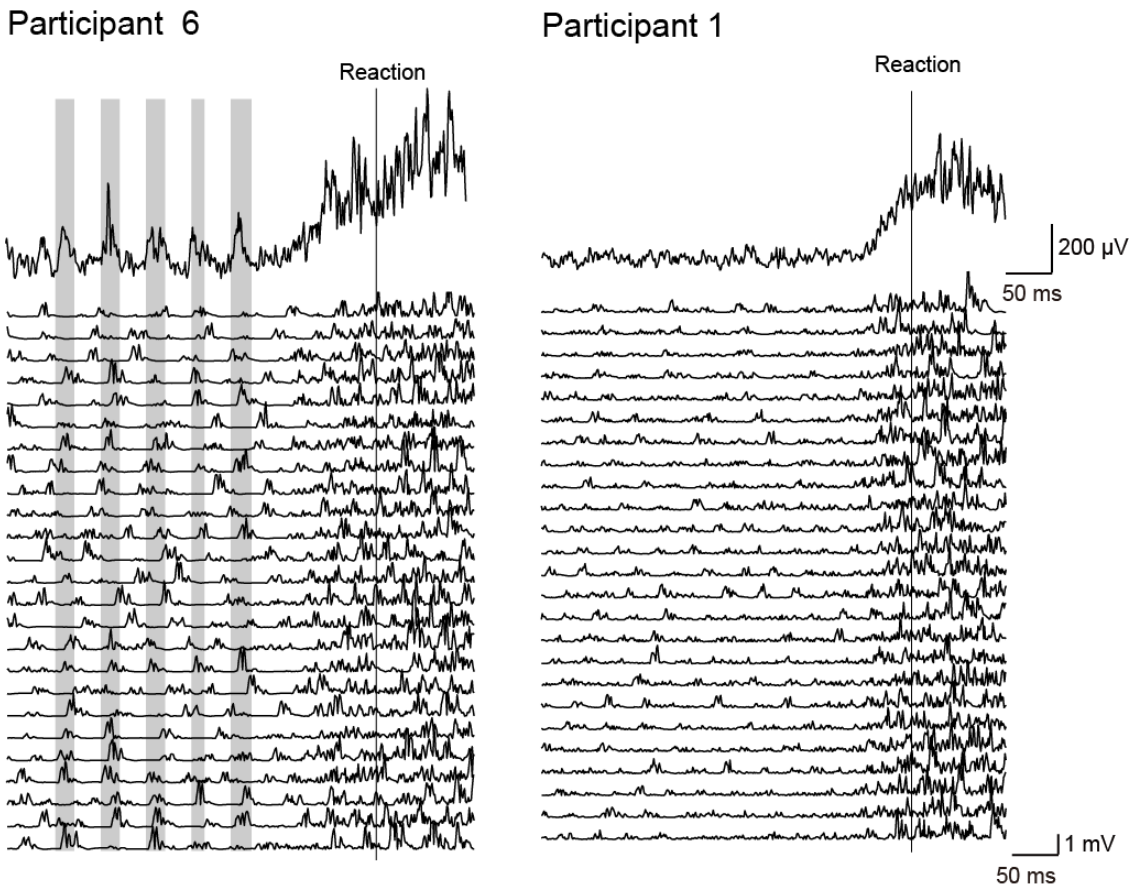

Figure 2-6. Back-averaged rectified EMG from the GD+ trials for 2 CMC+ participants. The author averaged the rectified EMG signals from all the GD+ trials for each CMC+ participant with reference to the timing of reaction (n = 25). The top graph shows back-averaged rectified EMG signals. The bottom 25 plots contain the rectified EMG signals from each GD+ trial. For participant 6 (left), synchronized grouped discharge seemed to occur in some trials (shaded sections), and therefore oscillatory activity was observed in the back-averaged rectified EMG. On the other hand, in participant 1 (right), although grouped discharge was observed in each trial, the timing of the grouped discharge was not synchronized. Thus, oscillatory activity was not observed in the back-averaged rectified EMG.

detected in terms of RT (first 25 trials, 738 ± 33 ms; last 25 trials, 737 ± 29 ms; p = 0.45) and peak EEG-EMG coherence (first 25 trials, 0.251 ± 0.088; last 25 trials, 0.276 ± 0.076; p = 0.32).

Figure 2-6 illustrates representative data from two participants, with back-averaged rectified EMG triggered by the reaction onset in the GD+ trials at the top of the figure, and rectified EMG from each trial in the other 25 plots. In Participant 6, the reaction onset seemed to be time-locked to the phase of grouped discharge in some trials (see shaded areas in Fig. 2-6), resulting in an evident beta-oscillation in the back-averaged rectified EMG. In two out of eight CMC+ participants, the beta-oscillation was seen in the back-averaged rectified EMG, as described for Participant 6. However, in the other six participants, no oscillatory activity was observed in the back-averaged rectified EMG (as for Participant 1, shown in the right panels of Fig. 2-6), although grouped discharge was observed in each trial. This finding indicated that, for most participants, the reaction was not time-locked to the timing of grouped discharge.

2.4 Discussion

The present study was designed to examine the influence of beta-synchrony in the corticospinal system during a preliminary isometric contraction on motor function

relevant to new ballistic movements. The main findings are as follows: (1) there were no inter-participant differences in RT that were dependent on the CMC magnitude during an isometric contraction; and (2) there were significant intra-participant differences in RT that were dependent on the extent of the beta-band oscillatory activity in EMG during a preliminary contraction.

2.4.1 Potential Mechanisms underlying Intra-participant Differences in Reaction Time

Several recent studies have attempted to examine the influence of the beta-oscillation on reaction movements. For example, it was reported that new movements are decelerated when beta-band microtremor (as recorded by an accelerometer) is elevated during tonic extension of the index finger (Gilbertson et al., 2005). On the basis of this finding, the author divided the trials performed by the CMC+ participants into either GD+ or GD- trials, by quantifying the extent of grouped discharge in EMG. This enabled the estimation of the effects of beta-band oscillatory EMG activity on motor performance as measured by RT. The author found that RT was significantly prolonged in the GD+ compared with the GD- trials, although the observed difference was very small (approximately 10–30 ms). Furthermore, using coherence analyses, the author found that the magnitude of the EEG-EMG coherence immediately before the reaction was

significantly stronger in the GD+ than the GD- trials. Thus, it is reasonable to assume that the beta-oscillation observed in the raw EMG in the GD+ trials was generated during periods of elevated CMC. These data would provide supportive evidence that the occasional occurrences of beta-band microtremor reported by Gilbertson et al. (2005), which decelerated new ballistic movements, were likely due to these moment-by-moment changes in the CMC strength.

One might expect the magnitude of the EEG-EMG coherence and RT to vary in the later trials because of the potential effects of attention/stress, practice, and/or fatigue resulting from the large number of ballistic contraction trials performed by the participants. Indeed, previous studies have reported that the beta-band CMC is influenced by several factors, such as attention (Kristeva et al., 2002; Johnson et al., 2012) and muscle fatigue (Yang et al., 2010; Ushiyama et al., 2011a). To address this, the author statistically compared the RT and the magnitude of EEG-EMG coherence (i.e., peak coherence) between the first and last 25 trials. However, the results indicated no significant differences between the first and last 25 trials, suggesting that factors such as attention/stress, practice, and/or fatigue had a limited impact on the present findings.

In two CMC+ participants, beta-oscillations before the reaction movement were

observed in the back-averaged rectified EMG triggered by the reaction onset. In these participants, the reaction onset might have been time-locked to the phase of the beta-oscillation, which could explain the significant prolongation of RT in the GD+ trials. This association between the phase of oscillatory activity and reaction onset is similar to that of resting tremor in patients with Parkinsonism (Wierzbicka et al., 1993; Staude et al., 1995), essential tremor (Elble et al., 1994), and action tremor in patients with multiple sclerosis (Wong et al., 2008). However, a phase-dependent onset of reaction was observed in only two of the eight participants. Thus, this explanation may only apply to some participants. Another potential mechanism regarding the cause of the beta-oscillation-related prolongation of the reaction component of new ballistic movements is discussed below.

It is possible that the prolonged RT in the GD+ trials was a result of de-synchronization in the firing rate of cortical neurons due to beta-synchrony in the corticospinal system. Indeed, 20–40 Hz oscillatory synchrony in local field potentials (LFP) in the motor cortex has been associated with clamping of motor cortical single unit firing rates in monkeys (Murthy and Fetz, 1996). Additionally, it has been well documented that elevation in beta-synchrony at the level of the motor cortex contributes to the maintenance of a steady-state force output in healthy participants (Conway et al.,

1995; Brown, 2000; Kilner et al., 2000). Thus, the author suggest that, while beta-band CMC appears to play a role in clamping a rhythm of synchrony in motoneurons to maintain efficiently a steady force output, it might take more time to de-synchronize the coupled oscillatory neural activity in the corticospinal system that is needed to elevate the force level rapidly.

Using a brain-computer-interface technique, Boulay et al. (2011) demonstrated that voluntary increases in the beta-rhythm of the sensorimotor area with motor imagery are associated with longer reaction times than when the sensorimotor beta-rhythm is decreased. In contrast, the trial–by-trial changes in beta-synchrony in the corticospinal system observed in the present study were involuntary. However, taken together, it can be suggested that the extent of beta-synchrony in cortical cell populations within the sensorimotor cortex affects the motor behavior as measured by RT. The nonprimary motor cortex and/or basal ganglia would be one of the candidates for a modulator of neural activity in the corticospinal tract. Indeed, Marsden et al. (2001) reported significant coherence between the LFP of the subthalamic nucleus and EEG recorded over the supplementary motor cortex or the sensorimotor cortex in term of both the beta- and gamma-bands during isometric wrist contractions. Moreover, in patients with Parkinsonism, a beta-band activity in LFP recorded from the subthalamic nucleus has

been reported to decrease prior to movement, and there is a positive correlation between the latency of onset of the beta-power reduction in LFP and RT both among (Kühn et al., 2001) and within participants (Williams et al., 2005). In light of these findings, the author suggests that neural loops between cortical and subcortical areas modulate beta-synchrony in the corticospinal system, and that the elevated synchrony may antagonize the processing necessary for the reaction movement. Thus, it is possible that some central mechanisms, such as the basal ganglia-cortex loop, play a key role in generating/modulating beta-synchrony in the sensorimotor cortex from moment to moment. These could be responsible for the intra-participant variance in RT between the GD+ and GD- trials.

It has recently been suggested that not only central oscillations cause CMC. Baker and Baker (2003) reported that the administration of benzodiazepines, which enhance the size of $GABA_A$ inhibitory postsynaptic potentials (IPSPs), increased the beta-power of EEG over the sensorimotor cortex, but did not change the magnitude of EEG-EMG coherence. Thus, the authors also suggested that CMC is not just a phenomenon that simply reflects the propagation of central oscillations to the periphery through the corticospinal tract. Additionally, it was demonstrated that the peripheral sensory input from the muscles affects CMC by evaluating the modulation of MEG-EMG coherence

after induction of ischemic sensory deafferentation (Pohja et al., 2003), and the phase of coherence between EEG and EMG following arm cooling (Riddle and Baker, 2005). Moreover, Witham et al. (2011) demonstrated that directed coherence between the EEG and EMG during a precision grip task was significant in both descending (EEG→EMG) and ascending (EMG→EEG) directions within the beta-band. Thus, in addition to the descending central drive, the ascending sensory inputs may also contribute to the generation/modulation of CMC. It is possible that the gain of afferent information such as visual and/or proprioceptive feedback momentarily varies in response to force fluctuation, and is subsequently integrated into a motor command. Thus, the author suggest that the extent of beta-synchrony in the corticospinal system changes in the process of sensorimotor binding, and therefore affects the performance of new movements.

2.4.2 Potential Mechanisms behind the Lack of Inter-participant Difference in Reaction Time

Contrary to the hypothesis, there was no significant difference in RT between CMC+ and CMC-. One might expect that the inter-participant differences in RT were caused by physical factors, such as the distance from the cortex to the muscle due to height, rather

than by the magnitude of the CMC. However, the variance in the latency of MEP induced by TMS is known to be in the range of several milliseconds for the TA of healthy participants (approximately, 32 ± 3 ms) (Cacchio et al., 2009). In contrast, the RT in the present study varied on a time scale of several tens of milliseconds among participants. Thus, it seems that the variance in time required for a neural transmission to travel from M1 to a muscle is too small to be a main contributor to the variance in RT. Thus, it is unlikely that the length of the corticospinal tract caused the inter-participant variance in RT.

Furthermore, one might question whether or not the differences in electromechanical delay (EMD), such as the duration between the onset of EMG activity and the reaction onset detected via force signals, are a contributing factor to the inter-participant variance of RT. Certainly, differences in EMD among participants were observed. However, similarly to a previous report (Corcos et al., 1992), the observed EMD in the present study was approximately 30 ms, thus short compared to the RT in the present study, as is expected considering that it represents the amount of time required for a neural transmission to travel from the cortex to muscle. Thus, although the potential influence of EMD to the observed variance cannot be completely excluded, the findings indicated that EMD was not a major contributing factor in the

inter-participant variance in RT.

On the other hand, the variance in the central processing time required for ballistic reactions could be a factor in the observed inter-participant differences in RT, rather than the extent of beta-synchrony in the corticospinal system. The neural signal processing related to the ballistic reaction performed in this study can be divided into the following steps: (1) cognition of auditory input; (2) central processing such as planning of movement; (3) motor command in M1; and (4) firing of spinal motoneuron populations. Considering the latency of MEP induced by TMS, it is reasonable to assume that the processing time required prior to the involvement of M1 is greater than the time for the transmission of the motor command from M1 to the muscle, and therefore differs greatly among individuals. Thus, the variance in the time required for central processing, such as planning of a movement, is likely to be the main cause of inter-participant variance in RT, masking the beta-synchrony-dependent factor of delayed RT. Therefore, the author suggest that enhanced CMC does slow the reaction of new movements, while no significant differences between CMC+ and CMC- trials were detected because the RT was more affected by inter-participant differences in central processing. The author speculates that the time required for the central processing was not particularly variable among trials within each participant, and it followed the present

detection of the intra-participant differences in RT based on the magnitude of the beta-band corticomuscular coupling.

One might claim that the participants were not divided into two groups depending on the “real” magnitude of CMC (this might be due to technical limitations of EEG recording), and that this prevented the detection of significant inter-participant differences in RT between the CMC+ and CMC- trials. Indeed, the electrical field measured by EEG depends on several factors, including the direction of the electrical current flow, which is affected by the orientation of the corticospinal neurons relative to the electrodes, the depth of the corticospinal neurons relative to the scalp, and the thicknesses of the scalp and skull (Nunez, 1989; Yan et al., 1991; Malmivuo et al., 1997; Olejniczak, 2006). Thus, there were potentially some cases in which the cortical activity actually did oscillate within the beta-band, but was not recorded correctly from the EEG electrodes. In a previous study with 100 healthy individuals (Ushiyama et al., 2011b), some participants had clear beta-band oscillations in EMG, but not in EEG, resulting in a lack of CMC. In the present study, however, no CMC- participants had clearly observable beta-oscillations in EMG, while the beta-oscillations were visible in all CMC+ participants (although it changed moment-to-moment). Thus, while the author cannot entirely refute the possibility that the above-mentioned technical limitations

regarding the EEG recordings may have affected the measurement of EEG-EMG coherence, this would not have a considerable impact on the interpretation of the present data.

In this experiment, the author demonstrated that, although there was no significant difference in RT among individuals, RT was significantly longer in the GD+ compared with the GD- trials in CMC+ participants. This finding suggested that CMC prolongs the initiation of new movements, thus reinforcing the need to examine the detailed physiological mechanisms underlying CMC.

Chapter 3

Inhibitory Interneuron Circuits at Cortical and Spinal Levels are Associated with Individual Differences in Corticomuscular Coherence

3.1 Introduction

CMC has been considered to reflect the mutual interaction between the sensorimotor cortex and contracting muscles via descending motor pathways and ascending somatosensory pathways (Mima et al., 2000; Ohara et al., 2000; Pohja and Salenius, 2003; Kilner et al., 2004; Riddle and Baker, 2005). The magnitude of CMC varies among individuals even in healthy young adults (Hashimoto et al., 2010; Ushiyama et al., 2010; 2011b). However, the physiological mechanisms underlying the inter-individual differences in CMC are still unclear. The first study (Chapter 2) demonstrated the influence of CMC on RT. A recent study also reported the significant correlation between the force fluctuation and CMC among healthy individuals (Ushiyama et al., 2017). Thus, the difference in CMC is not dependent on technical limitations of EEG/EMG, but should be caused by physiological mechanisms.

Negative-feedback systems are known to generate oscillatory output (Ernst et al., 1995; Destexhe et al., 1998; Pauluis et al., 1999; Bressloff and Coombes, 2000); this

implies that inhibitory neural circuits are associated with CMC. A pharmacological study reported that 20 Hz oscillations in the sensorimotor cortex are partially produced by local cortical circuits relying on $GABA_A$-mediated ICI (Baker and Baker, 2003). Thus, the author hypothesized that ICI is a factor of individual differences in cortical beta-oscillations, and also in CMC if oscillatory descending drives are directly transmitted to the periphery. However, the oscillations can be modulated at the spinal level. Renshaw cells are known to regulate the oscillations in muscle activity by preventing the synchronization of the spinal motoneuron activity (Stein and Oguztoreli, 1984; Matthews, 1996; Windhorst, 1996). Therefore, the author formulated the second hypothesis that the RI of Renshaw cells is a second factor of the individual differences in CMC.

In this chapter, the author aimed to test the two aforementioned hypotheses. First, the author examined the relationship between CMC and ICI using the paired-pulse TMS method among healthy participants. The surface EMGs from the first dorsal interosseous (FDI) muscle were measured in the ICI experiments because MEPs are detected from the finger muscles in TMS. Second, the author examined the relationship between CMC and RI using the paired-pulse H-reflex method among healthy participants. The author measured the surface EMGs from the soleus (SOL) in the RI

experiments, because RI, which can be quantitated by the H-reflex method (Bussel and Pierrot-Deseilligny, 1997), has been mostly evaluated from the SOL (Capaday and Stein, 1987; Crone and Nielsen, 1989). Finally, the author integrated the results from the two experiments and evaluated the cortical and spinal factors related to the inter-individual differences in CMC.

3.2 Materials and Methods

The experiments were approved by the local ethics committee of the Faculty of Science and Technology, Keio University, Yokohama, Japan, and were conducted in accordance with the Declaration of Helsinki. All participants provided their informed consent for the study after receiving a detailed explanation of the purpose, potential benefits, and risks involved.

3.2.1 Participants

In total, 16 healthy young adults (11 male and 5 female participants; aged 21–35 years) with no history of neurological disorders voluntarily participated in this study. Eleven participants (6 male and 5 female participants; aged 21–24 years) attended the ICI experiment (EXP_{ICI}), and 12 participants (8 male and 4 female participants; aged 22–35 years) attended the RI experiment (EXP_{RI}). Seven individuals (3 male and 4 female

participants) participated in both experiments. Only healthy young adults without remarkable sports experience were recruited, because factors such as age and sports experience can influence the CMC, ICI, and RI.

3.2.2 Recordings

EEG was recorded from the scalp region overlying the sensorimotor cortex using five Ag/AgCl electrodes (diameter, 10 mm) placed at areas representative of the muscles to be investigated in each experiment (i.e., C3 and 20 mm frontal, back, left, and right positions in EXP_{ICI}; Cz and four surrounding positions in EXP_{RI}, defined by the International 10–20 system). The reference electrode for EEG was placed at A1 (left earlobe) and the ground electrode on the forehead. EEG signals were derived using the spatial Laplacian filter (Hjorth, 1975). Surface EMG was recorded from the right FDI in EXP_{ICI} or from the right SOL and TA muscles in EXP_{RI}. The bipolar Ag/AgCl electrodes were attached to the belly of each muscle with an inter-electrode distance of 20 mm.

In EXP_{ICI}, the EEG/EMG signals were amplified, band-pass filtered (EEG, 1–200 Hz; EMG, 10–500 Hz), and digitized at 1200 Hz using the EEG/EMG recording system (gUSB amp; Gugaer Technologies, Graz, Austria). The force signal was

recorded with a strain gauge (DPM711B; Kyowa Electronic Instruments, Japan), and digitized at 1200 Hz by an analogue-to-digital converter (DAQCard-6062E; National Instruments Inc., Austin, TX, USA). In EXP_{RI}, the EEG signals were amplified, band-pass filtered (2–500 Hz), and digitized at 2400 Hz using the same recording system. The EMG signals were amplified and band-pass filtered (20–1000 Hz) using the bio-signal recording system (Neuropack X1 MEB-2306; Nihon Kohden Corporation, Tokyo, Japan). The plantar flexion force was recorded with the ankle-dynamometer (MK-808052; ME incorporated, Nagano, Japan) and low-pass filtered at 50 Hz. The EMG and force signals were digitized at 2400 Hz by an analogue-to-digital converter (NIUSB-6259 BNC; National Instruments Inc.). The measurement programs were originally designed using MATLAB (The MathWorks Inc., Natick, MA, USA).

3.2.3 Stimulation

TMS: The TMS was applied using a figure-eight shaped coil connected to two Magstim 200 magnetic stimulators (Magstim, Whitland, UK). The optimal coil position where MEPs in the FDI could be evoked with the lowest stimulus was marked with ink to ensure an exact repositioning of the coil throughout the experiment. The handle of the coil oriented backward so that the induced current was directed from posterior to

anterior. At this position, the motor threshold (MT) intensity was defined as the lowest stimulator output intensity, capable of inducing an MEP of at least 50 μV peak-to-peak amplitude in relaxed muscles in at least half of the 10 trials. A sub-threshold CS was set at 80% of the MT, and a supra-threshold TS was set at 120% of the MT (Christova et al., 2006). Only the TS was delivered for the single-pulse, while the CS was applied through the same coil at 3 ms prior to the TS for the paired-pulse (Kujirai et al., 1993). Prior to the experiment, the author confirmed that the MEPs were not evoked by only the CS during weak contractions. This stimulus condition has been previous used in numerous studies as a *de facto* standard for the assessment of ICI, and thus a control condition for this stimulation was not conducted (Ziemann et al., 1996; Ferreri et al., 2011; Guerra et al., 2016). Therefore, the paired-pulse TMS was used in this dissertation without any negative-control condition.

H-reflex: The H-reflex of the SOL was evoked by electrically stimulating the posterior tibial nerve. The cathode shaped as a half-ball (2 cm diameter; TF-98003, Unique Medical, Tokyo, Japan) was placed over the popliteal fossa. The anode Ag/AgCl electrode (2000 mm^2; 019-768500, VIASYS Healthcare, Woking, UK) was placed immediately proximal to the patella. Two stimuli with different intensities (Stim1 and Stim2) as a 1 ms rectangular pulse were delivered by an electronic stimulation system

(SEN-3301/SS-104J; Nihon Kohden, Tokyo, Japan). Stim1 was adjusted so that the maximal amplitude of the H-reflex was observed, and Stim2 was defined to elicit a maximal M-wave (Mmax) followed by no H-reflex during the contraction (about 110% of the stimulus intensity at which an Mmax was first elicited). Only Stim1 was provided for the single-pulse, while both Stim1 and Stim2 were given together with an interval of 10 ms for the paired-pulse (Bussel and Pierrot-Deseilligny, 1977). The preceding Stim1 not only elicits an H-reflex but also activates the Renshaw cells, which in turn feedback inhibition to the same α-motoneuron pool. When Stim2 is applied just 10 ms after Stim1, the H-reflex discharge evoked by Stim1 collides an antidromic motor volley caused by the following Stim2. However, the Ia inputs caused by Stim2 can activate the alpha motoneurons, evoking thus the second H-reflex (H'). As this H' reflex is affected by an inhibitory input from RI, which is activated by Stim1, its amplitude is smaller than that of the H-reflex evoked by the single-pulse method. Because of this mechanism, the H-reflex inhibited by RI can be detected by the paired-pulse H-reflex method.

3.2.4 Experimental Protocol

EXP_{ICI}: Each participant was comfortably seated in a chair, and the right hand was supported by the splint with the strain gauge. Before the experiment, the author

measured force levels of the FDI during MVC. Firstly, the participants performed isometric voluntary contraction tasks of the FDI at 5% of MVC without stimulation. The participants repeated the FDI contraction for 15 s with a rest interval of 5 s for 35 times in total (Kristeva et al., 2007). During this task, participants were given a visual feedback about the level of the abduction force provided via a level meter on a computer screen positioned 0.5 m in front of them, and were instructed to maintain their exerted force with accuracy.

Subsequently, TMS was applied over the hand area of the left M1 60 times (single-pulse, 30 times; paired-pulse, 30 times) in a random order during the isometric contraction. The participants were instructed to perform 5% MVC abduction for 15 s and were provided the stimuli twice in a trial at unpredictable times within 5 s ± 500 ms and 13 s ± 500 ms after the onset of a contraction. The task included a series of 30 trials of 15 s each with a rest interval of 5 s.

EXP_{RI}: Each participant was comfortably seated in a chair with an ankle dynamometer. Before the experiment, the MVC of the SOL was measured. Firstly, the participants performed an isometric voluntary contraction task of the SOL at 15% MVC for 60 s without stimulation. The participants were given the feedback of plantar flexion force level provided on the screen positioned 1.2 m in front of them, and were instructed to

keep their force levels.

Subsequently, the stimulus was provided to the participants during the contraction. Before the measurement, the intensities of Stim1 and Stim2 were determined during the isometric contraction at 15% MVC. The participants repeated the contraction for 7 s with a rest interval of 15 s for 40 times in total, and were provided the stimulus (single-pulse or paired-pulse) at unpredictable times within 6 s ± 500 ms after an onset of the contraction (i.e., single-pulse, 20 times; paired-pulse, 20 times in total). After the experiment, the participants were instructed to perform additional contractions and were provided only Stim2, to obtain Mmax responses.

3.2.5 Data Analyses

Coherence analysis: For the data of the no-stimulation tasks, the power spectral density was evaluated using Welch's method for EEG and the EMG signals and CMC were rectified. Before the following analyses, EEG signals were band-pass filtered (2–100 Hz), and Laplacian-filtered signals at C3 were calculated for EXP_{ICI} or at Cz for EXP_{RI}. To detect the motor unit grouped discharge, the rectification was used for EMG. This pre-processing was necessary to extract the envelope of the modulation wave (Halliday and Farmer, 2010; Boonstra and Breakspear, 2012; Ward et al., 2013; Dakin et

al., 2014). Raw EEG and rectified EMG signals were segmented into artefact-free epochs including 2048 data points. Non-overlapped 245 epochs were obtained in total (7 epochs per contraction for 15 s) in EXP_{ICI} and 70 epochs from contraction for 60 s in EXP_{RI}. Each epoch was convoluted with Hanning-window to reduce the spectral leakage (Farmer et al., 1993; Baker et al., 1997; Gross et al., 2000). The correlations between the EEG and rectified EMG were determined using the coherence function (Halliday et al., 1995) (see 2-1, p. 31), and the SL was estimated (Rosenberg et al., 1989; Halliday et al., 1995; Kilner et al., 2000) (see 2-2, p. 32). Furthermore, the ratio of the sum of the PSD within the beta-band (15–30 Hz) to that of 3–50 Hz frequency range for EEG-PSD was determined, and these values were defined as the EEG beta-PSD.

ICI estimation: Firstly, signal averaging for 30 EMG responses obtained from each of single-pulse and paired-pulse TMS methods was performed, and peak-to-peak amplitudes of the averaged waves were defined as MEPs. Subsequently, to confirm that ICI was elicited by the present paired-pulse TMS method, the differences in MEP between single-pulse and paired-pulse methods were examined using Wilcoxon signed-rank test (single = 3.05 ± 1.98 mV; paired = 1.85 ± 1.40 mV, $p = 0.008$). The ratio of the conditioned MEP to the unconditioned MEP was determined as a measure of

ICI. Accordingly, a smaller value indicated a greater inhibition.

RI estimation: Firstly, as in the ICI estimation, signal averaging for 20 EMG responses obtained from each stimulation was provided, and peak-to-peak amplitudes of the averaged waves were defined as H or H'. Subsequently, to confirm that RI was elicited by the present paired-pulse H-reflex method, the differences between H and H' were examined using Wilcoxon signed-rank test (single = 6.75 ± 2.99 mV; paired = 0.88 ± 0.72 mV, p = 0.002). The ratio of H' to H was determined as a measure of RI, and smaller RI meant greater inhibition.

Statistical analyses: Coherence was normalized using the arc hyperbolic tangent transformation for statistical analyses (Halliday et al, 1995). To confirm whether there were significant correlations between ICI and the peak magnitude of CMC between ICI and EEG, beta-PSD between RI and the peak value of CMC and between RI and EEG beta-PSD, Pearson correlation coefficients between these values were determined. All statistical analyses were performed using the SPSS software (IBM SPSS Inc., Armonk, New York, USA).

3.3 Results

3.3.1 Intracortical Inhibition and Corticomuscular Coherence

The CMC was calculated from the EEG/EMG data during the isometric contraction of the FDI without TMS. The results indicated that the magnitude of CMC differed among the present participants. The values of the ICI were also calculated from the MEPs during the contractions with TMS. Figure 3-1 shows raw EEG and EMG signals, EEG and rectified EMG-PSDs, CMC, and MEPs recorded from two representative participants showing significant CMC (CMC+) and nonsignificant CMC (CMC−). Grouped discharges were observed in raw EMG waves of the CMC+ participant, and the beta peak was remarkable in the rectified EMG-PSD of the CMC+ participant than in that of the CMC− participant. However, the MEP reduction because of the paired-pulse method was observed more clearly in the CMC− participant than in the CMC+ participant. These comparisons between the CMC+ and CMC− participants were in contrast with the first hypothesis that the stronger the ICI, the greater the CMC. No significant correlation was detected between the peak values of ICI and CMC across all participants (p = 0.197) (Fig. 3-2A). However, EEG beta-PSD correlated significantly and negatively with ICI (Fig. 3-2B) (r = −0.559, p = 0.037); thus, the stronger the ICI, the more prominent were the EEG beta-oscillations. As shown in Fig. 3-1, the CMC+

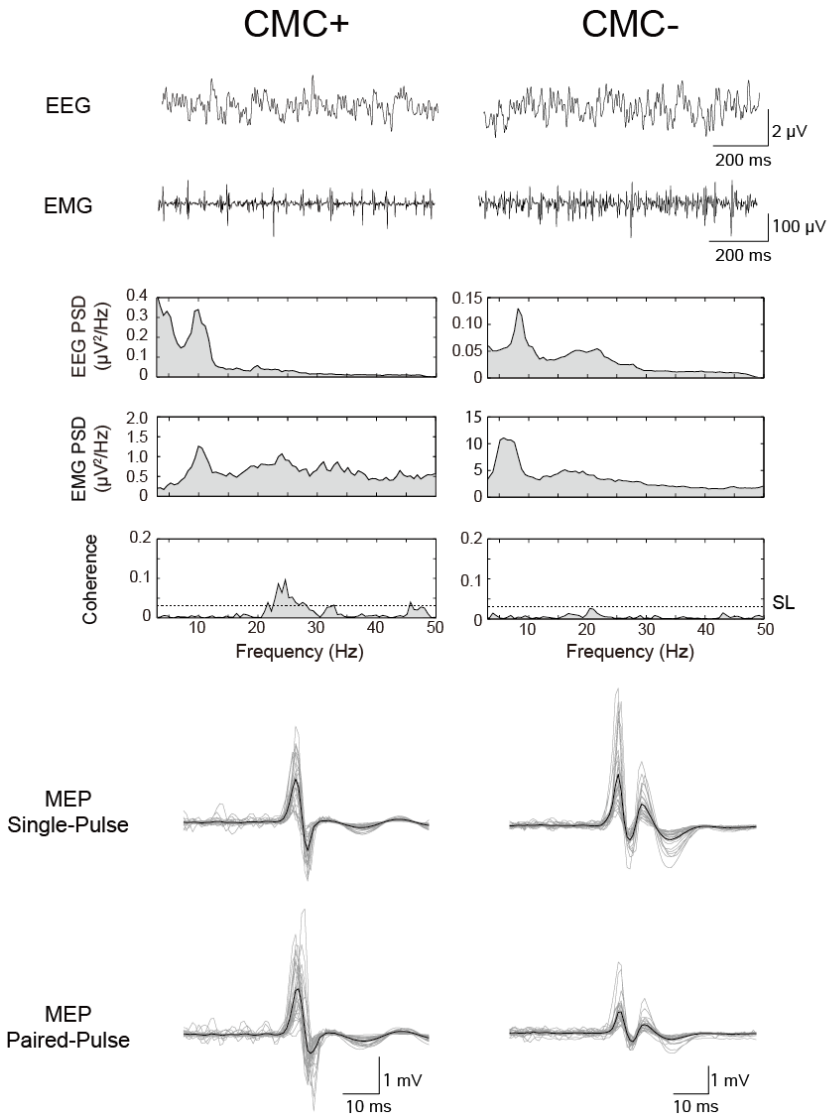

Figure 3-1. Representative examples of EEG/EMG data and motor-evoked potentials (MEPs) for a participant who showed significant CMC (CMC+) and a participant who did not (CMC−). Raw EEG signals, raw EMG signals, PSDs for EEG and rectified EMG signals, CMC spectra during isometric contraction of the FDI, and MEPs elicited by single-pulse and paired-pulse TMS are shown. In the CMC spectra, the estimated SLs (= 0.030) are shown as horizontal dotted lines. In MEPs, gray lines show the individual EMG responses of 30 trials, and black lines show averaged waves.

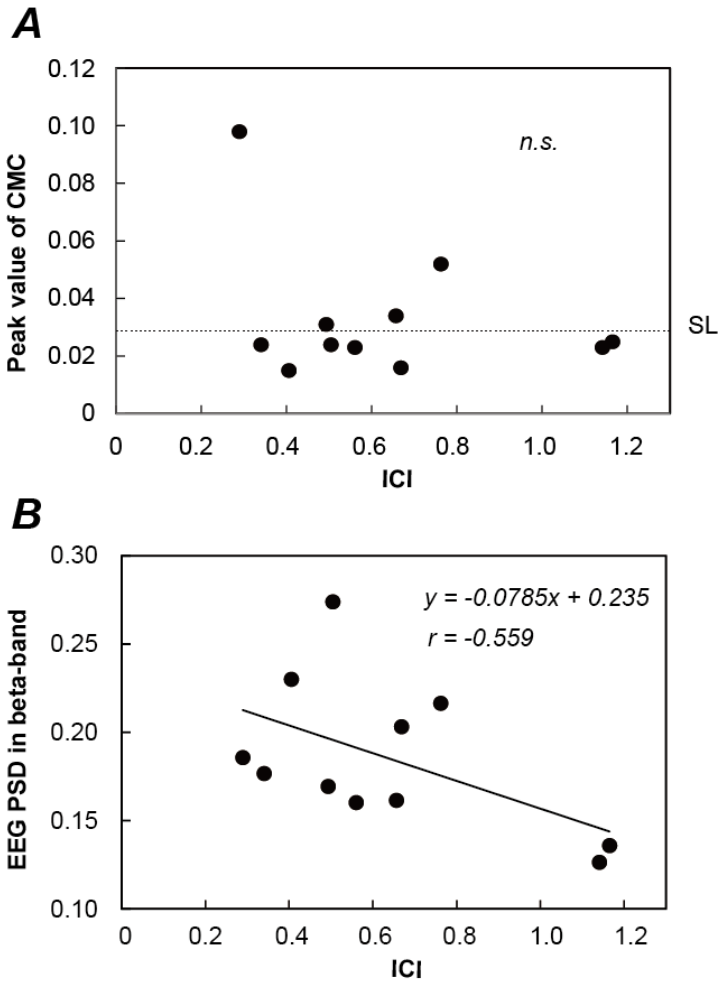

Figure 3-2. A) The relationship between ICI and the peak value of CMC during isometric contraction of the FDI across all participants. A horizontal dashed line shows the estimated SL (= 0.030). There was no significant correlation between CMC and ICI (p = 0.197). **B) The relationship between ICI and EEG PSD in beta-band across all participants.** EEG PSD in beta-band indicates the ratio of the sum of EEG-PSD within the beta-band (15–30 Hz) to that of 3–50 Hz frequency range. There was a significant correlation between them (r = − 0.559, p = 0.037). The solid line shows the estimated regression line.

participants had a more distinct beta-band power in EEG PSD than the CMC− participant, although the beta-oscillations were observed in the raw EEG waves of both participants.

3.3.2 Recurrent Inhibition and Corticomuscular Coherence

The CMC was calculated from the EEG/EMG data during isometric contraction of the SOL without electrical nerve stimulation and the results indicated that the magnitude of CMC in the SOL differed among the present participants. The values of RI from the H-reflex amplitudes measured in the RI experiment (EXP_{RI}) were also calculated. Figure 3-3 shows the raw EEG and EMG signals, EEG and rectified EMG-PSDs, CMC, and H-reflexes recorded from two representative participants (i.e., different individuals from the representative participants shown in Fig. 3-1). As shown in Fig. 3-3, the CMC+ participant showed remarkable peaks at 22 Hz in EEG, rectified EMG, and CMC, and oscillatory activities were observed in the raw EEG/EMG in contrast with the CMC− participant. An amplitude reduction from H to H’ was more prominent in the CMC− participant than in the CMC+ participant; a certain level of reduction was observed between both participants. This difference between the participants implies that RI is stronger in CMC− participants than in CMC+ participants. To confirm

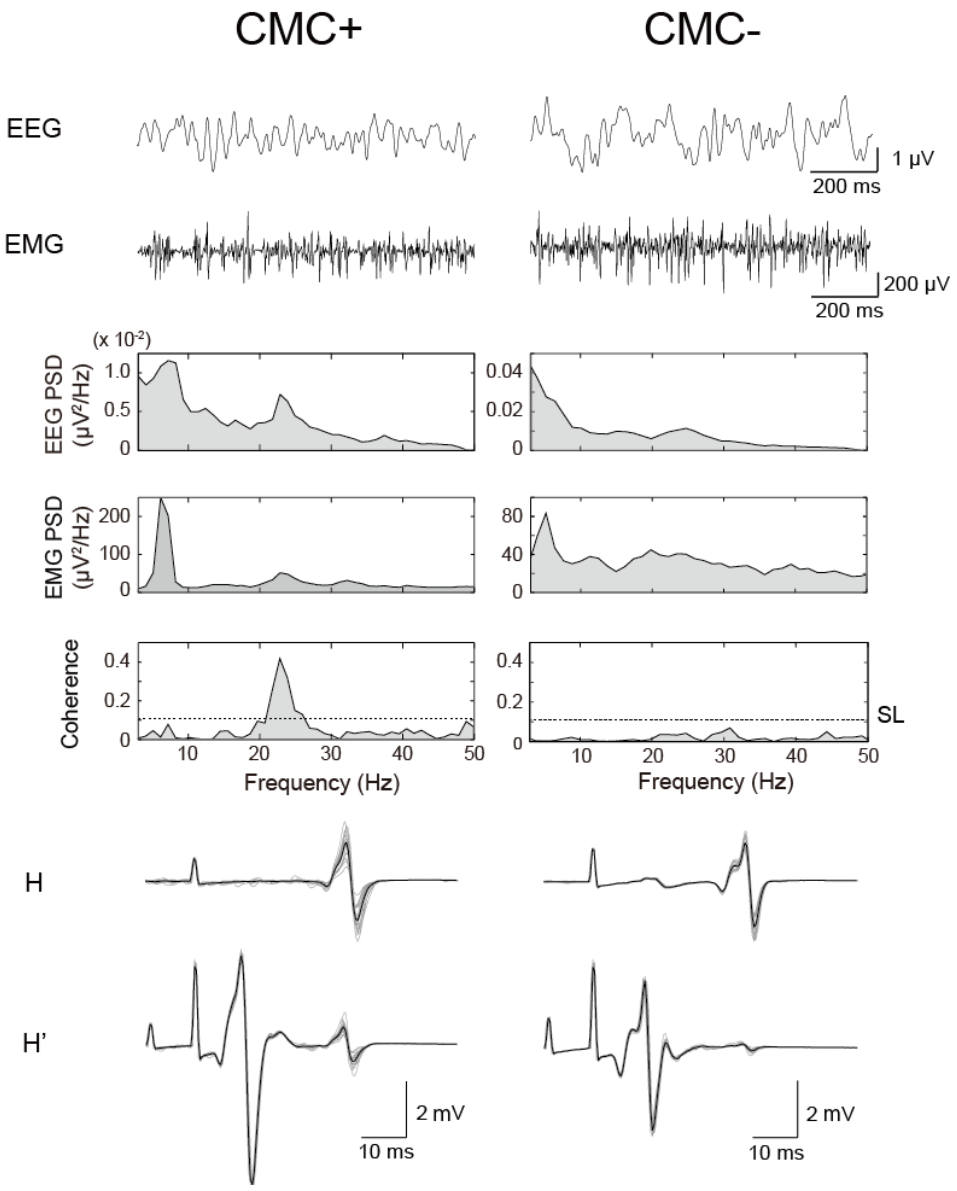

Figure 3-3. Representative examples of EEG/EMG data and H-reflexes for CMC+ and CMC−. Raw EEG signals, raw EMG signals, PSDs for EEG and rectified EMG signals, CMC spectra during isometric contraction of the soleus (SOL), and H-reflexes elicited by single (H) and paired-pulse (H') electrical nerve stimulation are shown. Data for CMC+ and CMC− are shown, respectively. In the CMC spectra, horizontal dashed lines show the estimated SL (= 0.091). In H-reflexes, grey lines show individual EMG responses of 20 trials, and black lines show averaged waves.

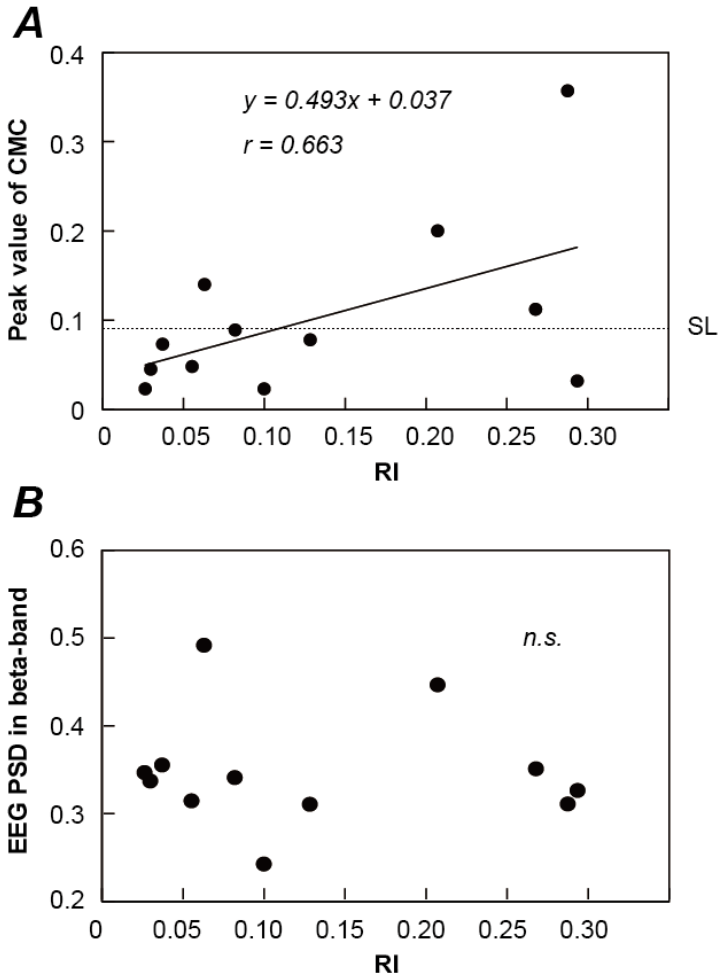

Figure 3-4. A) The relationship between RI and the peak value of CMC during the isometric contraction of the SOL across all participants. A horizontal dashed line shows the estimated SL (= 0.091). A significant correlation was observed between RI and CMC (r = 0.663, p = 0.009). The solid line shows the estimated regression line. **B) The relationship between RI and EEG PSD in beta-band across all participants.** EEG PSD in beta-band indicates the ratio of the sum of EEG-PSD within the beta-band (15–30 Hz) to that of 3–50 Hz frequency range. There was no significant correlation between them (p = 0.270).

whether the correlation between CMC and RI was significant, the peak values of CMC and RI during contraction task were plotted for all participants (Fig. 3-4A). According to the difference between representative participants, there was a significant positive correlation between them (r = 0.663, p = 0.009); thus, the stronger the RI, the weaker was the CMC. On the other hand, there was no significant correlation between RI and EEG beta-PSD (p = 0.26; Fig. 3-4B).

3.3.3 Inter-individual Correlation between Corticomuscular Coherence Recorded from First Dorsal Interosseus and Soleus

The association between the peak values of CMC recorded from the FDI and the SOL were plotted for seven individuals who participated in both EXP_{ICI} and EXP_{RI}. A significant positive correlation was observed between them (r = 0.882, p = 0.004; Fig. 3-5).

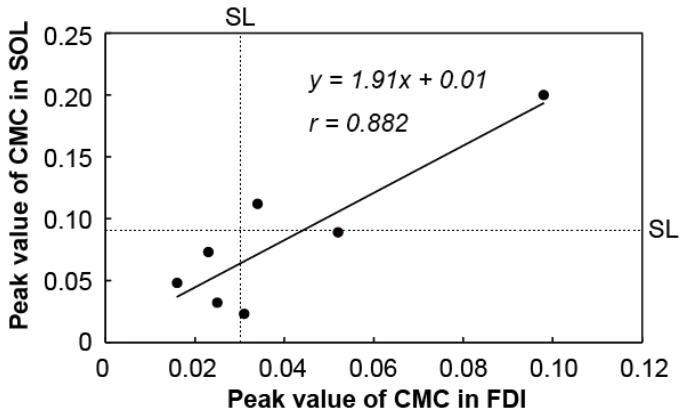

Figure 3-5. The relationship between peak values of CMC recorded from the FDI and the SOL. The horizontal and vertical dashed lines show the estimated SL for the FDI (= 0.030) and for the SOL (= 0.091), respectively. There was a significant positive correlation between them (r = 0.882, p = 0.004). The solid line shows the estimated regression line.

3.4 Discussion

3.4.1 Intracortical Inhibition and Corticomuscular Coherence

Firstly, the author demonstrated that there is a distinct variation in EEG beta-PSD across the participants, similarly to the previous study including 100 participants (Ushiyama et al., 2011b), and a significant negative correlation between the strength of ICI and EEG beta-PSD. Note that the stronger the ICI, the larger was the EEG beta-PSD (Fig. 3-2B). The ICI value measured by a paired-pulse TMS method represents the strength of inhibition of $GABA_A$-mediated interneurons (Ziemann et al., 1996). Thus, the present results suggested that the greater the inhibition of $GABA_A$-mediated interneurons, the

more prominent the beta-band-synchronized activities of neurons within the sensorimotor cortex. Oscillations occur by the reverberation around feedback loop with a conduction delay. An intracortical circuit was shown that generated oscillations as an emergent network property arising from their local circuit connectivity (Traub et al., 1996; Bush and Sejnowski, 1996: Wang and Buzsáki, 1996; Pauluis et al., 1999). A modeling study showed that the inhibitory interneurons played a key role in determining the oscillation frequency and amplitude, such that an increase in the inhibitory connections leads to an increase in the strength of oscillations (Pauluis et al., 1999). Concurrently, a pharmacological study reported that 20 Hz oscillations in the sensorimotor cortex were strengthened by the administration of a drug enhancing $GABA_A$-mediated inhibition (Baker and Baker, 2003). In addition, a genetic study identified a significant linkage between beta-oscillation in EEG and a set of $GABA_A$ receptor genes (Porjesz et al., 2002). Taken together, these findings indicate that the strength of intracortical inhibitory interneuron activities might be determined by the genetic variation of GABA receptor, and this might be a factor determining the inter-individual differences in the magnitude of EEG beta-oscillation.

However, as shown in Fig. 3-2B, the correlation observed between the ICI and EEG beta-oscillation was not strong, but only moderate ($r = -0.559$; $p = 0.037$). Not only ICI,

but also other neural activities, might be associated with producing oscillatory neural activities in the sensorimotor cortex. Neurons in M1 are known to exhibit an intrinsic tendency to fire rhythmically (Wetmore and Baker, 2004; Chen and Fetz, 2005). It has been suggested that cell populations tend to synchronize repetitive firing at rates close to beta-band because the probability of firing increases at approximately 30 ms after the previous action potential. Furthermore, Roopun et al. (2006) reported that layer V pyramidal neurons have gap-junctional connections between their axons, which lead to strong electrical coupling in the absence of a synaptic activity. Therefore, although ICI should be a determinant of individual strength of the beta-oscillation in the sensorimotor cortex during isometric contraction, there might be other neural factors associated with cortical oscillations.

A significant correlation was observed only between the value of ICI and EEG beta-oscillation, but not between the ICI and the magnitude of CMC among participants (Fig. 3-2A). Beta-band CMC is considered to be a bidirectional phenomenon including descending and ascending neural signal flow (Pohja and Salenius, 2003; Kilner et al., 2004; Riddle and Baker, 2005). Thus, oscillations descending from the sensorimotor cortex to the muscles are not the sole determinant of the magnitude of CMC. Comparing the power spectra of representative individuals (Fig. 3-1), the CMC+ participant showed

a more prominent EMG PSD in beta-band than the CMC− participant, which is in agreement with the positive correlation between CMC and EMG beta-PSD reported previously among individuals (Ushiyama et al., 2011b); thus, the CMC− participant had more distinct beta-PSD in EEG rather than the CMC + participant. It is difficult to consider that the cortical oscillation is simply transmitted to the muscle.

3.4.2 Recurrent Inhibition and Corticomuscular Coherence

Subsequently, the author focused on the spinal modulation of oscillatory corticospinal loop activity. The spinal cord is not only a relay point between the motor cortex and muscles but also a regulator of the activation of spinal motoneurons by its neural circuits. It is known that RI produced by Renshaw cells regulates motoneuron excitability and stabilizes the firing rate. Moreover, this negative feedback system has been reported as a mechanism for the reduction of oscillatory muscle activation by preventing motoneuron synchronization (Stein and Oguztoreli, 1984; Windhorst, 1996; Matthews, 1997). Therefore, to determine whether the RI is associated with the individual magnitude of CMC, the author performed EXP_{RI} using H-reflex method (Bussel and Pierrot-Deseilligny, 1977).

The results from the RI experiment demonstrated a significant positive correlation

between the strength of RI and the magnitude of CMC (Fig. 3-4A). This indicates that the greater the RI generated by spinal Renshaw cells, the weaker is the magnitude of CMC. Recently, Williams and Baker (2009) reported that this inhibitory feedback plays a role as ‘neural filter’ and improves the physiological tremor by reducing the magnitude of CMC at 10 and 20 Hz.

In addition, the author considered the possibility that the spinal oscillation modulated by RI may influence cortical beta-oscillation via ascending feedback. However, no significant correlation was detected between the RI and EEG beta-oscillation across the individuals (Fig. 3-4B). This implies that some cortical-specific modifications have greater influences on the cortical oscillation than the effect of modulation by RI via ascending feedback. Thus, the author suggest that the modulation by Renshaw cell activity works to weaken the oscillation derived from the cortex as ‘neural filter,’ although the effect of modulation by RI may not be transmitted to a great extent; therefore, the strength of the RI was positively correlated with the magnitude of CMC.

3.4.3 Methodological limitations

In the ICI experiment, the author recorded the EMG from the FDI; however, in the RI

experiment, the EMG was recorded from the SOL. As reported previously (Ushiyama et al., 2010), a remarkable inter-participant difference in CMC was observed from distal lower limb muscles than from those of upper limb. Therefore, the author used mainly the TA or SOL for the EEG-EMG assessments (Ushiyama et al., 2010; Ushiyama et al., 2012). Moreover, the H-reflex is usually recorded from the SOL (Capaday and Stein, 1987, Crone and Nielsen, 1989), and in the present experience, it was very difficult to record the H-reflex from upper limb muscles in East Asian population. Therefore, the author decided to record the EMG from the SOL in EXP_{RI}. However, it is not easy to detect MEPs from lower limb muscles because the representative area of the lower limb in the motor cortex is located deep in the longitudinal fissure. Thus, most of the ICI studies using TMS method would have used the upper limb muscles to record MEPs (Kujirai et al., 1993; Münchau et al., 2002). Hence, the author selected the FDI that has been widely used to detect MEPs as a target muscle in EXP_{ICI}.

While this difference in the recorded muscles between the two experiments was unavoidable because of the aforementioned technical limitations, one might claim that the background neural networks vary between motor areas of different muscles. As shown in Fig. 3-5, the author observed a strong significant correlation between the peak values of CMC for these muscles, although the strength of CMC for the FDI was much

weaker than that for the SOL. Thus, the inter-individual variations in CMC seem to be retained across muscles. This strong correlation led us to speculate that the tendency of the cortical and/or spinal motoneurons to fire synchronously is partially common among skeletal muscles.

However, the author should not discuss the physiological mechanisms underlying “CMC variation among muscles” and “CMC variation among individuals” in a similar manner. For example, the significant positive correlation between CMC and RI in the SOL suggests that the strength of RI is a factor of individual difference in the CMC recorded from the SOL. However, the CMC in the FDI is weaker than that in the SOL, although it is generally assumed that the RI is absent in intrinsic hand muscles (Katz et al., 1993; Illert and Kümmel, 1999). Thus, the author cannot explain the difference in the magnitude of CMC between the FDI and the SOL from the view point of RI at the spinal level. Differences in the CMC across individuals and/or muscles would be enmeshed with physiological factors such as the density of cortical projection (Jankowska et al., 1975; Asanuma et al., 1978), or the strength of local inhibitory circuits such as ICI and RI, and other historical factors such as development, age, and frequency of muscle use.

The EEG and EMG assessments also included technical limitations derived from

nonphysiological factors. For example, the electrical field depends on the thickness of the scalp and skull in the case of EEG recordings (Nunez, 1989; Yan et al., 1991; Malmivuo et al., 1997; Olejniczak, 2006) and the spatial filter design of EMG is influenced by fat/skin tissues (Farina et al., 2002) and electrode locations (Roy et al, 1986; Jensen et al., 1993). These factors influence the EEG/EMG amplitudes. However, the magnitude of coherence is known to reflect the constancy of the amplitude ratio and/or the phase difference between two signals throughout the data. Thus, the influence of the aforementioned factors is considered limited. Moreover, the present study succeeded in detecting significant correlations between the neural inhibitions and beta-band oscillatory activities in the corticospinal pathway using electrophysiological methods, and indicated that the inter-individual differences in CMC presumably derive from physiological factors. Therefore, the finding that neural factors associated with beta-band CMC were found physiologically is even more significant. These data demonstrated that the individual magnitude of CMC is associated with inner physiological factors both at the cortical and spinal levels. Taking the present two main findings on ICI and RI together, the author suggest that the magnitude of CMC includes the effects of cortical and spinal inhibitory circuits, such as ICI and RI, on synchronous neural activities. The cortical inhibitory circuits should have a role in the generation of

cortical beta-oscillations. On the other hand, the spinal inhibitory circuits presumably modulate the synchronizations of the spinal alpha motoneurons (Fig. 3-6). Previous studies have regarded CMC not only as the phenomenon reflecting the descending information flow but also as the bidirectional interaction between sensorimotor cortex and contralateral muscles. The present study would provide additional speculations that the CMC is associated not only with the neural loop including efferent and afferent pathways but also with the local loops at the cortical and spinal levels.

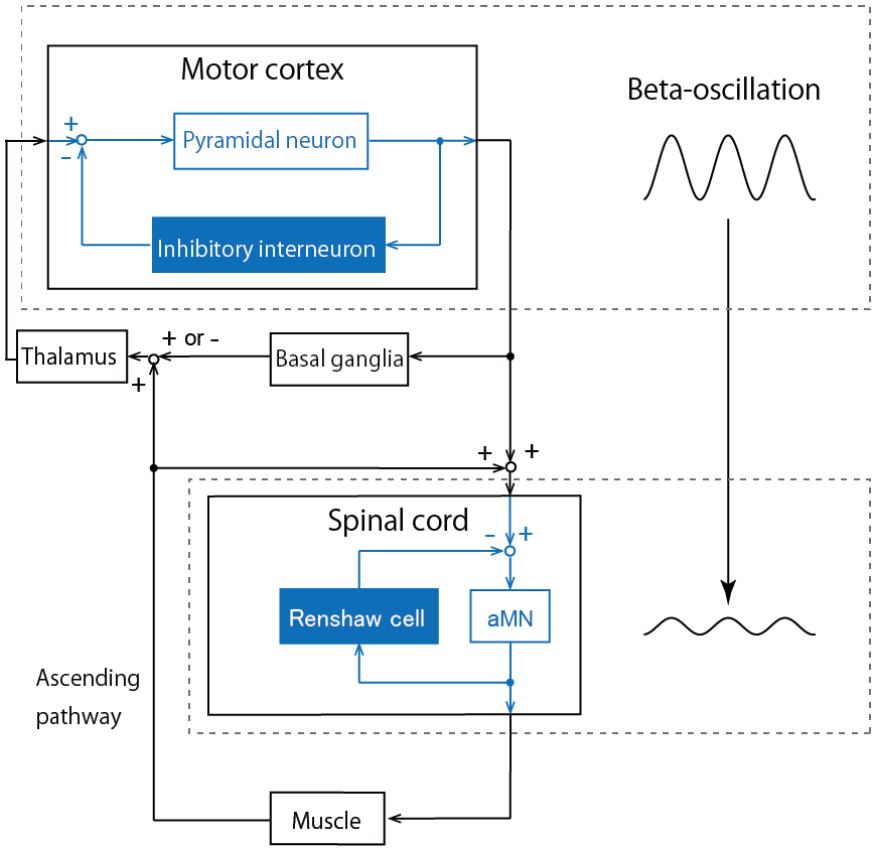

Figure 3-6. Model for the neural system associated with the development of CMC during voluntary isometric contraction. The present two main findings suggest the roles of ICI and RI for beta-oscillation in the corticospinal pathway. At first, the negative correlation between ICI and cortical beta-oscillation suggested that the negative feedback loop between pyramidal neurons and ICI generates beta-oscillation. Next, the positive correlation between RI and CMC suggested that RI of Renshaw cell desynchronizes alpha-motoneurons (aMNs) firing and attenuates the amplitude of beta-oscillation derived from the motor cortex.

Chapter 4

Conclusions

The purpose of the research completed during this dissertation was to elucidate the function and mechanism of CMC differences among healthy individuals. To this aim, the author investigated the influence of CMC differences on behavior, and the underlying neural activities that determine these individual differences. The author approached these questions using kinesiological and electrophysiological methods.

In Chapter 2, the author demonstrated that there were no inter-participant differences in RT depending on the magnitude of CMC. Within participants, however, RT was significantly delayed relative to the beta-band oscillatory muscle activity during the preliminary contraction. In addition, the magnitude of CMC was significantly elevated when grouped discharge was present. These results suggested that the generation of a new movement is delayed when CMC is elevated. Because the delay of movement initiation is as small as several tens of milliseconds, it was difficult to detect a significant difference in RT between individuals. The present finding that moment-to-moment changes of CMC in individuals characterize the RT delay suggested possible improvement of movement initiation by neural manipulations of CMC in the order of several tens of milliseconds.

In Chapter 3, to reveal neural circuitry underlying inter-individual differences in CMC, the author evaluated the relationship between ICI and RI, and CMC. As a result, the author demonstrated two main findings: (1) there was significant correlation between ICI and beta-oscillation in EEG, and (2) there was significant correlation between RI and CMC magnitude. These two findings suggested that the individual magnitude of CMC is determined by inner physiological factors at both the cortical and spinal levels, such as ICI and RI. Although the findings from the two experiments should not be directly integrated without any careful consideration on the difference in neuromuscular characteristics of the examined muscles, it is probable that ICI is associated with generation of the beta-oscillations in the motor cortex, and RI presumably modulates beta-frequency synchrony of spinal motoneurons. Therefore, the present study provided additional speculations that CMC is associated not only with the neural loop, including efferent and afferent pathways, but also local loops at the cortical and spinal levels.

The kinesiological approach in Chapter 2 revealed that generation of new movement is prolonged during elevated beta-band CMC and associated oscillation in muscle. Although this functional influence derived from CMC is not large enough to interfere with daily life, it is large enough to determine the presence of medals in 100

meters of Olympic games competing with a difference of one hundredth of a second, and may also delay the driver's responses and thus increase the likelihood of traffic accidents, for example. The author should also mention the limited population in this study. The present study treated only untrained healthy young adults, and excluded any neurological patients or well-trained participants. Moreover, the prolonged reaction time was observed under the specific experimental environment. Although further investigation is needed to assess the actual interferences from these various factors, the present finding indicated a remarkable possibility that the CMC prolongs the initiation of new movement on a time scale of milliseconds. Applying the same examination to different participants will reveal the association with age and sports experience, and will also lead to the general comprehension of the mechanism of the neural system that characterizes the human motor performance.

The electrophysiological approach in Chapter 3 revealed that ICI and RI are related to individual differences in corticospinal oscillation in the beta-band. The findings helped understanding the possible neural targets for the behavioral improvement by functional manipulation of neurons in the future. In this chapter, the author showed only the correlations evaluated from different muscles among individuals; thus, future studies are needed to confirm the causalities between the neural circuitry proposed in the

present dissertation. These studies may validate the CMC by the neural manipulation using reinforcement learning, as should the possibility to induce motor performance changes.

In healthy young adults, although various factors such as motor learning (Perez et al., 2006), attention (Kristeva et al., 2002; 2007), and fatigue (Yang et al., 2010; Ushiyama et al., 2011) have been reported to alter the CMC magnitude, it is difficult to suggest that the same mechanisms underlie the CMC changes caused by these factors. Therefore, the present dissertation considered that the CMC magnitudes change via at least two different mechanisms; from central origins such as motor learning and attention, and from peripheral origins including muscle fatigue. This dissertation partially but distinctively demonstrated the potential neural mechanisms by examining the correlations between neural activities and CMC at both the cortical (i.e., ICI) and spinal levels (i.e., RI). Based on the present results, and because it became possible to decide parametrically an experimental design that can investigate the causality based on the present results, future researches are warranted to determine the influences of these neural circuits on CMC generation and motor function with high evidence.

While this dissertation examined the kinesiological characteristics and the neural mechanisms of CMC in healthy young adults, it cannot explain the CMC changes due to

development, disease, or recovery. Previous studies have reported that CMC intensity and frequency band differ according to age (Farmer et al., 2007; Graziadio et al., 2010) and the presence of neurological disorders (Marsden et al., 2001; Salenius et al., 2002). Indeed, Graziadio et al. (2010) reported a negative correlation between the CMC magnitude and the stability of the muscle activity in young adults, but not in children and elderly adults. Thus, the kinesiological influences of CMC might differ according to developmental stage. In addition, the oscillation accompanying CMC in Parkinson's disease is reportedly derived from the subthalamic nucleus (Marsden et al., 2001). Therefore, the corticospinal model proposed in this dissertation cannot be directly applied to the context of disease. The interactions of multiple neural circuits including ICI and thalamocotical loops should be investigated by simultaneous measurement of ICI and LFP recorded from subthalamic nucleus in Parkinson's patients. However, the model proposed by the present study in healthy participants will help to efficiently determine a target neural circuit in clinical research constrained experimental methods and recruitment of participants. Therefore, it is important that the present study identified the influence of ICI and RI on the corticospinal oscillation.

Overall, the present findings suggested the behavioral correlates and underlying neural circuitry of CMC. Based on the findings of this dissertation, we will be able to

reach the next steps, such as investigation of RT in the different population, or confirmation of the causalities between the inhibitions and the beta-oscillation. In the future, these forthcoming studies will support our understanding of the functional significance and neural mechanisms of corticospinal oscillation during human voluntary movements, improvement of motor performance by the neural manipulation, and pathological clarification of neurological disorders.

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References

Androulidakis AG, Doyle LMF, Gilbertson TP, Brown P (2006) Corrective movements in response to displacements in visual feedback are more effective during periods of 13-35 Hz oscillatory synchrony in the human corticospinal system. Eur J Neurosci 24:3299–3304.

Androulidakis AG, Doyle LMF, Yarrow K, Litvak V, Gilbertson TP, Brown P (2007) Anticipatory changes in beta synchrony in the human corticospinal system and associated improvements in task performance. Eur J Neurosci 25:3758–3765.

Asanuma H, Hongo T, Jankowska E, Marcus S, Shinoda Y, Zarzecki P (1978) Pattern of projections of individual pyramidal tract neurons to the spinal cord of the monkey. J Physiol (Paris) 74:235–236.

Baker MR, Baker SN (2003) The effect of diazepam on motor cortical oscillations and corticomuscular coherence studied in man. J Physiol 546:931–942.

Baker SN, Olivier E, Lemon RN (1997) Coherent oscillations in monkey motor cortex and hand muscle EMG show task-dependent modulation. J Physiol 501.1:225–241.

Beck RB, O'Malley MJ, Stegeman DF, Houtman CJ, Connolly S, Zwarts MJ (2005) Tracking motor unit action potentials in the tibialis anterior during fatigue. Muscle and Nerve 32:506–514.

Bongiovanni LG, Hagbarth KE (1990) Tonic vibration reflexes elicited during fatigue from maximal voluntary contractions in man. J Physiol 423:1–14.

Bongiovanni LG, Hagbarth KE, Stjernberg L (1990) Prolonged muscle vibration reducing motor output in maximal voluntary contractions in man. J Physiol 423:15–26.

Boonstra TW, Breakspear M (2012) Neural mechanisms of intermuscular coherence: implications for the rectification of surface electromyography. J Neurophysiol 107:796–807.

Bressloff PC, Coombes S (2000) Dynamics of Strongly Coupled Spiking Neurons. Neural Comput 12:91–129.

Brown P (2000) Cortical drives to human muscle: The Piper and related rhythms. Prog Neurobiol 60:97–108.

Brown P, Salenius S, Rothwell JC, Hari R (1998) Cortical correlate of the Piper rhythm in humans. J Neurophysiol 80:2911–2917.

Bush P, Sejnowski T (1996) Inhibition synchronizes sparsely connected cortical neurons within and between columns in realistic network models. J Comput Neurosci 3:91–110.

Bussel B, Pierrot-Deseilligny E (1977) Inhibition of human motoneurons, probably of

Renshaw origin, elicited by an orthodromic motor discharge. J Physiol 269:319–339.

Cacchio A, Cimini N, Alosi P, Santilli V, Marrelli A (2009) Reliability of transcranial magnetic stimulation-related measurements of tibialis anterior muscle in healthy subjects. Clin Neurophysiol 120:414–419.

Capaday C, Stein RB (1987) Difference in the amplitude of the human soleus H reflex during walking and running. J Physiol 392:513–522.

Carter GC, Knapp C, Nuttall AH (1973) Statistics of the estimate of the magnitute-coherence function. IEEE Trans Audio Electroacoust 21:388–389.

Chen D, Fetz EE (2005) Characteristic membrane potential trajectories in primate sensorimotor cortex neurons recorded in vivo. J Neurophysiol 94:2713–2725.

Christova MI, Pondev NG, Christova LG, Wolf W, Dengler R, Kossev AR (2006) Motor cortex excitability during unilateral muscle activity. J Electromyogr Kinesiol 16:477–484.

Conway BA, Halliday DM, Farmer SF, Shahani U, Maas P, Weir AI, Rosenberg JR (1995) Synchronization between motor cortex and spinal motoneuronal pool during the performance of a maintained motor task in man. J Physiol 489:917–924.

Corcos DM, Gottlieb GL, Latash ML, Almeida GL, Agarwal GC (1992) Electromechanical delay: An experimental artifact. J Electromyogr Kinesiol 2:59–68.

Crone C, Nielsen J (1989) Methodological implications of the post activation depression of the soleus H-reflex in man. Exp Brain Res 78:28–32.

Curtis DR, Ryall RW (1966) The acetylcholine receptors of Renshaw cells. Exp Brain Res 2(1):66–80.

Dakin CJ, Dalton BH, Luu BL, Blouin JS (2014) Rectification is required to extract oscillatory envelope modulation from surface electromyographic signals. J Neurophysiol 112:1685–1691.

Destexhe A, Contreras D, Steriade M (1998) Mechanisms underlying the synchronizing action of corticothalamic feedback through inhibition of thalamic relay cells. J Neurophysiol 79:999–1016.

Di Lazzaro V, Profice P, Ranieri F, Capone F, Dileone M, Oliviero A, Pilato F (2012) I-wave origin and modulation. Brain Stimul 5:512–525.

Duclos Y, Schmied A, Burle B, Burnet H, Rossi-Durand C (2008) Anticipatory changes in human motoneuron discharge patterns during motor preparation. J Physiol 586:1017–1028.

Elble R, Higgins C, Hughes L (1994) Essential tremor entrains rapid voluntary

movements. Exp Neurol 126:138–143.

Ernst U, Pawelzik K, Geisel T (1995) Sychronization Induced by Temporal Delays in Pulse-Coupled Oscillators. Phsical Rev Lett 74:1570–1573.

Fang Y, Daly JJ, Sun J, Hvorat K, Fredrickson E, Pundik S, Sahgal V, Yue GH (2009) Functional corticomuscular connection during reaching is weakened following stroke. Clin Neurophysiol 120:994–1002.

Farina D, Cescon C, Merletti R (2002) Influence of anatomical, physical, and detection-system parameters on surface EMG. Biol Cybern 86:445–456.

Farmer SF, Bremner FD, Halliday DM, Rosenberg JR, Stephens JA (1993) The frequency content of common synaptic inputs to motoneurones studied during voluntary isometric contraction in man. J Physiol 470:127–155.

Farmer SF, Gibbs J, Halliday DM, Harrison LM, James LM, Mayston MJ, Stephens JA (2007) Changes in EMG coherence between long and short thumb abductor muscles during human development. J Physiol 579:389–402.

Ferreri F, Pasqualetti P, Määttä S, Ponzo D, Ferrarelli F, Tononi G, Mervaala E, Miniussi C, Rossini PM (2011) Human brain connectivity during single and paired pulse transcranial magnetic stimulation. Neuroimage 54:90–102.

Friederich JA, Brand R (1990) Muscle fiber architecture in the human lower limb. J Biomech 23:91–95.

Gastaut H (1952) Electrocorticographic study of the reactivity of rolandic rhythm. Rev Neurol 87:176–182.

Gilbertson T, Lalo E, Doyle L, Di Lazzaro V, Cioni B, Brown P (2005) Existing Motor State Is Favored at the Expense of New Movement during 13-35 Hz Oscillatory Synchrony in the Human Corticospinal System. J Neurosci 25:7771–7779.

Graziadio S, Basu A, Tomasevic L, Zappasodi F, Tecchio F, Eyre JA (2010) Developmental tuning and decay in senescence of oscillations linking the corticospinal system. J Neurosci 30:3663–3674.

Griffith EE, Yoon T, Hunter SK (2010) Age and load compliance alter time to task failure for a submaximal fatiguing contraction with the lower leg. J Appl Physiol 108:1510–1519.

Gross J, Tass PA, Salenius S, Hari R, Freund HJ, Schnitzler A (2000) Cortico-muscular synchronization during isometric muscle contraction in humans as revealed by magnetoencephalography. J Physiol 527.3:623–631.

Gross J, Schmitz F, Schnitzler I, Kessler K, Shapiro K, Hommel B, Schnitzler A (2004) Modulation of long-range neural synchrony reflects temporal limitations of visual attention in humans. Proc Natl Acad Sci U S A 101:13050–13055.

Grosse P, Guerrini R, Parmeggiani L, Bonanni P, Pogosyan A, Brown P (2003) Abnormal corticomuscular and intermuscular coupling in high-frequency rhythmic myoclonus. Brain 126:326–342.

Guerra A, Pogosyan A, Nowak M, Tan H, Ferreri F, Di Lazzaro V, Brown P (2016) Phase Dependency of the Human Primary Motor Cortex and Cholinergic Inhibition Cancelation during Beta tACS. Cereb Cortex 26:3977–3990.

Halliday DM, Rosenberg JR, Amjad AM, Breeze P, Conway BA, Farmer SF (1995) A framework for the analysis of mixed time series/point process data-theory and application to the study of physiological tremor, single motor unit discharges and electromyograms. Prog Biophys Mol Biol 64:237–278.

Halliday DM, Conway BA, Farmer SF, Rosenberg JR (1998) Using electroencephalography to study functional coupling between cortical activity and electromyograms during voluntary contractions in humans. Neurosci Lett 241:5–8.

Halliday DM, Farmer SF (2010) On the need for rectification of surface EMG. J Neurophysiol 103:3547; author reply 3548-3549.

Halliday D, Conway B, Christensen L, Hansen N, Petersen N, Nielsen JB (2003) Functional Coupling of Motor Units Is Modulated During Walking in Human Subjects. J Neurophysiol 89:960–968.

Hashimoto Y, Ushiba J, Kimura A, Liu M, Tomita Y (2010) Correlation between EEG-EMG coherence during isometric contraction and its imaginary execution. Acta Neurobiol Exp (Wars) 70:76–85.

Hellwig B, Häußler S, Lauk M, Guschlbauer B, Köster B, Kristeva-Feige R, Timmer J, Lücking CH (2000) Tremor-correlated cortical activity detected by electroencephalography. Clin Neurophysiol 111:806–809.

Hjorth B (1975) An on-line transformation of EEG scalp potentials into orthogonal source derivations. Electroencephalogr Clin Neurophysiol 39:526–530.

Hultborn H, Jankowska E, Lindstrom S (1971) Relative contribution from different nerves to recurrent depression of Ia IPSPs in motoneurones. J Physiol 215:637–664.

Hummel F, Gerloff C (2005) Larger interregional synchrony is associated with greater behavioral success in a complex sensory integration task in humans. Cereb Cortex 15:670–678.

Illert M, Kümmel H (1999) Reflex pathways from large muscle spindle afferents and recurrent axon collaterals to motoneurones of wrist and digit muscles: A comparison in cats, monkeys and humans. Exp Brain Res 128:13–19.

Jackson A, Spinks RL, Freeman TCB, Wolpert DM, Lemon RN (2002) Rhythm generation in monkey motor cortex explored using pyramidal tract stimulation. J

Physiol 541:685–699.

Jankowska E, Padel Y, Tanaka R (1975) Projections of pyramidal tract cells to α-motoneurones innervating hind-limb muscles in the monkey. J Physiol 249:637–667.

Jasper H, Penfield W (1949) Electrocorticograms in man: Effect of the voluntary movement upon the electrical activity of the precentral gyrus. Arch Psychiat Z Neurol 183:163–174.

Jensen C, Vasseljen O, Westgaard RH (1993) The influence of electrode position on bipolar surface electromyogram recordings of the upper trapezius muscle. Eur J Appl Physiol Occup Physiol 67:266–273.

Johnson AN, Shinohara M (2012) Corticomuscular coherence with and without additional task in the elderly. J Appl Physiol 112:970–981.

Jones E (1993) GABAergic neurons and their role in cortical plasticity in primates. Cereb Cortex 3:361–372.

Katz R, Mazzocchio R, Penicaud A, Rossi A (1993) Distribution of recurrent inhibition in the human upper limb. Acta Physiol Scand 149:183–198.

Keller A (1993) Intrinsic synaptic organization of the motor cortex. Cereb Cortex 3:430–441.

Kilner JM, Baker SN, Salenius S, Hari R, Lemon RN (2000) Human cortical muscle coherence is directly related to specific motor parameters. J Neurosci 20:8838–8845.

Kilner JM, Fisher RJ, Lemon RN (2004) Coupling of oscillatory activity between muscles is strikingly reduced in a deafferented subject compared with normal controls. J Neurophysiol 92:790–796.

Knaflitz M, Merletti R, De Luca CJ (1990) Inference of motor unit recruitment order in voluntary and electrically elicited contractions. J Appl Physiol 68:1657–1667.

Kobayashi M, Pascual-Leone A (2003) Basic principles of magnetic stimulation. Lancet 2:145–156.

Kristeva R, Patino L, Omlor W (2007) Beta-range cortical motor spectral power and corticomuscular coherence as a mechanism for effective corticospinal interaction during steady-state motor output. Neuroimage 36:785–792.

Kristeva-Feige R, Fritsch C, Timmer J, Lücking CH (2002) Effects of attention and precision of exerted force on beta range EEG-EMG synchronization during a maintained motor contraction task. Clin Neurophysiol 113:124–131.

Kühn AA, Williams D, Kupsch A, Limousin P, Hariz M, Schneider GH, Yarrow K, Brown P (2004) Event-related beta desynchronization in human subthalamic

nucleus correlates with motor performance. Brain 127:735–746.

Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, Wroe S, Asselman P, Marsden CD (1993) Corticocortical inhibition in human motor cortex. J Physiol 471:501–519.

Lévénez M, Kotzamanidis C, Carpentier A, Duchateau J (2005) Spinal reflexes and coactivation of ankle muscles during a submaximal fatiguing contraction. J Appl Physiol 99:1182–1188.

Lopes da Silva F (1991) Neural mechanisms underlying brain waves: from neural membranes to networks. Electroencephalogr Clin Neurophysiol 79:81–93.

Malmivuo J, Suihko V, Eskola H (1997) Sensitivity distributions of EEG and MEG measurements. IEEE Trans Biomed Eng 44:196–208.

Marsden JF, Limousin-Dowsey P, Ashby P, Pollak P, Brown P (2001) Subthalamic nucleus, sensorimotor cortex and muscle interrelationships in Parkinson's disease. Brain 124:378–388.

Matthews PB (1997) Spindle and motoneuronal contributions to the phase advance of the human stretch reflex and the reduction of tremor. J Physiol 498.1:249–275.

Mazzocchio R, Rossi A (1989) Further evidence for Renshaw inhibition in man. A combined electrophysiological and pharmacological approach. Neurosci Lett 106:131–136.

Mazzocchio R, Rossi A, Rothwell J (1994) Depression of Renshaw recurrent Inhibition by activation of corticospinal fibers in human Upper and Lower-Limb. J Physiol 481.2:487–498.

McClelland VM, Cvetkovic Z, Mills KR (2012) Rectification of the EMG is an unnecessary and inappropriate step in the calculation of Corticomuscular coherence. J Neurosci Methods 205:190–201.

McClelland VM, Cvetkovic Z, Mills KR (2014) Inconsistent effects of EMG rectification on coherence analysis. J Physiol 592:249–250.

Mima T, Simpkins N, Oluwatimilehin T, Hallett M (1999) Force level modulates human cortical oscillatory activities. Neurosci Lett 275:77–80.

Mima T, Steger J, Schulman AE, Gerloff C, Hallett M (2000) Electroencephalographic measurement of motor cortex control of muscle activity in humans. Clin Neurophysiol 111:326–337.

Moritani T, Shibata M (1994) Premovement electromyographic silent period and α-motoneuron excitability. J Electromyogr Kinesiol 4:27–36.

Münchau A, Bloem BR, Irlbacher K, Trimble MR, Rothwell JC (2002) Functional connectivity of human premotor and motor cortex explored with repetitive

transcranial magnetic stimulation. J Neurosci 22:554–561.

Murthy VN, Fetz EE (1996) Synchronization of neurons during local field potential oscillations in sensorimotor cortex of awake monkeys. J Neurophysiol 76:3968–3982.

Nunez PL (1989) Generation of human EEG by a combination of long and short range neocortical interactions. Brain Topogr 1:199–215.

Ohara S, Nagamine T, Ikeda A, Kunieda T, Matsumoto R, Taki W, Hashimoto N, Baba K, Mihara T, Salenius S, Shibasaki H (2000) Electrocorticogram-electromyogram coherence during isometric contraction of hand muscle in human. Clin Neurophysiol 111:2014–2024.

Olejniczak P (2006) Neurophysiologic basis of the EEG. J Clin Neurophysiol 23:186–189.

Patino L, Chakarov V, Schulte-Mönting J, Hepp-Reymond MC, Kristeva R (2006) Oscillatory cortical activity during a motor task in a deafferented patient. Neurosci Lett 401:214–218.

Pauluis Q, Baker SN, Olivier E (1999) Emergent oscillations in a realistic network: The role of inhibition and the effect of the spatiotemporal distribution of the input. J Comput Neurosci 6:27–48.

Perez MA, Lundbye-Jensen J, Nielsen JB (2006) Changes in corticospinal drive to spinal motoneurones following visuo-motor skill learning in humans. J Physiol 573:843–855.

Perez MA, Lungholt BKS, Nyborg K, Nielsen JB (2004) Motor skill training induces changes in the excitability of the leg cortical area in healthy humans. Exp Brain Res 159:197–205.

Pfurtscheller G, Lopes FH (1999) Event-related EEG / MEG synchronization and desynchronization : basic principles. Clin Neurophysiol 110:1842–1857.

Pogosyan A, Gaynor LD, Eusebio A, Brown P (2009) Boosting Cortical Activity at Beta-Band Frequencies Slows Movement in Humans. Curr Biol 19:1637–1641.

Pohja M, Salenius S (2003) Modulation of cortex-muscle oscillatory interaction by ischaemia-induced deafferentation. Neuroreport 14:321–324.

Porjesz B et al. (2002) Linkage disequilibrium between the beta frequency of the human EEG and a $GABA_A$ receptor gene locus. Proc Natl Acad Sci U S A 99:3729–3733.

Renshaw B (1941) Influence of discharge of motoneurons upon excitation of neighbouring motoneurons. J Neurophysiol 4:167–183.

Riddle CN, Baker SN (2005) Manipulation of peripheral neural feedback loops alters human corticomuscular coherence. J Physiol 566:625–639.

Roopun AK, Middleton SJ, Cunningham MO, LeBeau FEN, Bibbig A, Whittington MA, Traub RD (2006) A beta2-frequency (20-30 Hz) oscillation in nonsynaptic networks of somatosensory cortex. Proc Natl Acad Sci U S A 103:15646–15650.

Rose M, Buchel C (2005) Neural Coupling Binds Visual Tokens to Moving Stimuli. J Neurosci 25:10101–10104.

Rosenberg JR, Amjad AM, Breeze P, Brillinger DR, Halliday DM (1989) The Fourier approach to the identification of functional coupling between neuronal spike trains. Prog Biophys Mol Biol 53:1–31.

Roy SH, De Luca CJ, Schneider J (1986) Effects of electrode location on myoelectric conduction velocity and median frequency estimates. J Appl Physiol 61:1510–1517.

Safri NM, Murayama N, Igasaki T, Hayashida Y (2006) Effects of visual stimulation on cortico-spinal coherence during isometric hand contraction in humans. Int J Psychophysiol 61:288–293.

Safri, NM, Murayama N, Hayashida Y, Igasaki T (2007) Effects of concurrent visual tasks on cortico-muscular synchronization in humans. Brain Res 1155:81–92.

Salenius S, Portin K, Kajola M, Salmelin R, Hari R (1997) Cortical control of human motoneuron firing during isometric contraction. J Neurophysiol 77:3401–3405.

Salenius S, Avikainen S, Kaakkola S, Hari R, Brown P (2002) Defective cortical drive to muscle in Parkinson's disease and its improvement with levodopa. Brain 125:491–500.

Schieppati M (1987) The Hoffmann reflex: A means of assessing spinal reflex excitability and its descending control in man. Prog Neurobiol 28:345–376.

Schoffelen JM, Oostenveld R, Fries P (2005) Neuronal coherence as a mechanism of effective corticospinal interaction. Science 308:111–113.

Staude G, Wolf W, Ott M, Oertel WH, Dengler R (1995) Tremor as a factor in prolonged reaction times of Parkinsonian patients. Mov Disord 10:153–162.

Stein RB, Oguztoreli MN (1984) Modification of muscle responses by spinal circuitry. Neuroscience 11:231–240.

Thomas CK, Woods JJ, Bigland-Ritchie B (1989) Impulse propagation and muscle activation in long maximal voluntary contractions. J Appl Physiol 67:1835–1842.

Traub RD, Whittington MA, Colling SB, Buzsáki G, Jefferys JG (1996) Analysis of gamma rhythms in the rat hippocampus in vitro and in vivo. J Physiol 493.2:471–484.

Ushiyama J, Masakado Y, Fujiwara T, Tsuji T, Hase K, Kimura A, Liu M, Ushiba J (2012) Contraction level-related modulation of corticomuscular coherence differs between the tibialis anterior and soleus muscles in humans. J Appl Physiol

112:1258–1267.

Ushiyama J, Katsu M, Masakado Y, Kimura A, Liu M, Ushiba J (2011a) Muscle fatigue-induced enhancement of corticomuscular coherence following sustained submaximal isometric contraction of the tibialis anterior muscle. J Appl Physiol 110:1233–1240.

Ushiyama J, Suzuki T, Masakado Y, Hase K, Kimura A, Liu M, Ushiba J (2011b) Between-subject variance in the magnitude of corticomuscular coherence during tonic isometric contraction of the tibialis anterior muscle in healthy young adults. J Neurophysiol 106:1379–1388.

Ushiyama J, Takahashi Y, Ushiba J (2010) Muscle dependency of corticomuscular coherence in upper and lower limb muscles and training-related alterations in ballet dancers and weightlifters. J Appl Physiol 109:1086–1095.

Ushiyama J, Yamada J, Liu M, Ushiba J (2017) Clinical Neurophysiology Individual difference in β-band corticomuscular coherence and its relation to force steadiness during isometric voluntary ankle dorsiflexion in healthy humans. Clin Neurophysiol 128:303–311.

Vecchio F, Del Percio C, Marzano N, Fiore A, Toran G, Aschieri P, Gallamini M, Cabras J, Rossini PM, Babiloni C, Eusebi F (2008) Functional cortico-muscular coupling during upright standing in athletes and nonathletes: a coherence electroencephalographic-electromyographic study. Behav Neurosci 122:917–927.

Volkmann J, Joliot M, Mogilner A, Ioannides A, Lado F, Fazzini F, Ribary U, Llinas R (1996) Central motor loop oscillations in Parkinsonian resting tremor revealed by magnetoencepahlography. Neurology 46:1359–1370.

von Stein A, Chiang C, König P (2000) Top-down processing mediated by interareal synchronization. Proc Natl Acad Sci U S A 97:14748–14753.

Wang XJ, Buzsáki G (1996) Gamma oscillation by synaptic inhibition in a hippocampal interneuronal network model. J Neurosci 16:6402–6413.

Ward NJ, Farmer SF, Berthouze L, Halliday DM (2013) Rectification of EMG in low force contractions improves detection of motor unit coherence in the beta-frequency band. J Neurophysiol 110:1744–1750.

Wetmore DZ, Baker SN (2004) Post-spike distance-to-threshold trajectories of neurones in monkey motor cortex. J Physiol 555:831–850.

Wierzbicka MM, Staude G, Wolf W, Dengler R (1993) Relationship between tremor and the onset of rapid voluntary contraction in Parkinson’s disease. J Neurol Neurosurg Psychiatry 56:782–787.

Williams D, Kuhn A, Kupsch A, Tijssen M, Van Bruggen G, Speelman H, Hotton G,

Loukas C, Brown P (2005) The relationship between oscillatory activity and motor reaction time in the parkinsonian subthalamic nucleus. Eur J Neurosci 21:249–258.

Williams ER, Baker SN (2009) Renshaw cell recurrent inhibition improves physiological tremor by reducing corticomuscular coupling at 10 Hz. J Neurosci 29:6616–6624.

Windhorst U (1996) On the role of recurrent inhibitory feedback in motor control. Prog Neurobiol 49:517–587.

Witham CL, Riddle CN, Baker MR, Baker SN (2011) Contributions of descending and ascending pathways to corticomuscular coherence in humans. J Physiol 589:3789–3800.

Wong MFK, Miall RC, Bain PG, Liu X (2008) The onset of voluntary reactive movement is temporally influenced by the central oscillation in action tremor caused by multiple sclerosis. Neurosci Lett 445:122–125.

Yan Y, Nunez PL, Hart RT (1991) Finite-element model of the human head: scalp potentials due to dipole sources. Med Biol Eng Comput 29:475–481.

Yang Q, Siemionow V, Sahgal V, Yue GH (2010) Single-Trial EEG-EMG coherence analysis reveals muscle fatigue-related progressive alterations in corticomuscular coupling. IEEE Trans Neural Syst Rehabil Eng 18:97–106.

Ziemann U (2003) Pharmacology of TMS. Suppl Clin Neurophysiol 56:226–231.

Ziemann U, Lönnecker S, Steinhoff BJ, Paulus W (1996) Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. Ann Neurol 40:367–378.