博士論文（要約）

# Effects of Neuromuscular Electrical Stimulation on Voluntary Motor Control in the Lower-limb Muscles

（神経筋電気刺激が下肢筋の随意制御に与える影響）

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## Abstract

Neuromuscular electrical stimulation (NMES) has been effectively used as a technique to generate muscle contractions of paralyzed muscles in neurorehabilitation. In particular, NMES for activating ankle dorsiflexors is widely used in people with neurological disorders to improve their walking ability. However, underlying mechanisms of NMES still remain unclear. The aim of this dissertation was to investigate the effects of NMES on voluntary motor control in the lower limbs. In order to achieve this aim, the objectives of this research project were to investigate: (1) voluntary motor control of ankle dorsiflexors (Chapter 2); (2) corticospinal excitability during force control of ankle dorsiflexors (Chapter 3); and (3) the effects of NMES combined with voluntary contractions of ankle dorsiflexors on the time course of corticospinal excitability changes and the force control ability (Chapter 3). First, in Chapter 2, behavioral aspects of ankle dorsiflexion force control were investigated, specifically the effects of bilateral motor control and leg dominance. The results showed that bilateral force control resulted in larger performance error and more force fluctuations compared to unilateral condition only during tonic (feedback controlled) contractions. No significant effects of the leg dominance were found. Second, in Chapter 3, neurophysiological aspects of force control were investigated, specifically corticospinal excitability during force control using transcranial magnetic stimulation (TMS). This study has shown that unilateral control significantly facilitated corticospinal excitability to a larger extent compared to bilateral contractions, especially during the preparation phase. Third, in

Chapter 4, effects of NMES on corticospinal excitability and the motor performance were investigated in the lower limbs. This study revealed that voluntary contractions combined with NMES facilitated corticospinal excitability during the intervention, while NMES alone condition did not show significant effects. The findings in this project advanced the fundamental understanding of the lower-limb neuromuscular control and the effects of NMES, which can contribute to development of novel interventions in rehabilitation using for individuals with neurological impairments.

## Table of Contents

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## Abbreviations

| | |
|---|---|
| ANOVA | analysis of variance |
| BD | bilateral dominant |
| BN | bilateral non-dominant |
| BUC | bilateral vs. unilateral control |
| CNS | central nervous system |
| CV | coefficient of variation |
| DOM | dominant leg vs. non-dominant leg |
| EEG | electroencephalography |
| EMD | electromechanical delay |
| EMG | electromyography |
| FES | functional electrical stimulation |
| LTP | long-term potentiation |
| M-wave | motor wave |
| MEP | motor evoked potential |
| MVC | maximum voluntary contraction |
| $M_{max}$ | maximum motor response |
| NIRS | near-infrared spectroscopy |

| | |
|---|---|
| NMES | neuromuscular electrical stimulation |
| PMT | pre-motor time |
| RM | repeated measures |
| RMS | root mean square |
| RT | reaction time |
| SCI | spinal cord injury |
| SD | standard deviation |
| Sol | soleus |
| TA | tibialis anterior |
| TMS | transcranial magnetic stimulation |
| UD | unilateral dominant |
| UN | unilateral non-dominant |
| VOL | voluntary contraction |
| fMRI | functional magnetic resonance imaging |
| rMT | resting motor threshold |

# Chapter 1.

# Introduction

## 1.1. Introduction

Neuromuscular electrical stimulation (NMES) has been effectively used as a technique to generate muscle contractions in rehabilitation of people with neurological impairments (Popovic, Curt, Keller, & Dietz, 2001; Street & Singleton, 2018). By stimulating paralyzed muscles, NMES can be used to produce functional movements such as grasping, reaching, walking and cycling, which is referred to as functional electrical stimulation (FES) (Collins 2007). FES for ankle dorsiflexion can prevent foot drop (i.e., limited active ankle dorsiflexion), which is widely used in people with neurological disorders to improve their walking ability (Dunning, O'Dell, Kluding, & McBride, 2015; Kluding et al., 2013). Recent rehabilitation guidelines have therefore proposed that FES is a useful device for assisting clinical interventions. For instance, the American Heart Association Guidelines for Stroke Adults Rehabilitation recommend that FES is a reasonable intervention for clinical treatment of stroke patients (Winstein et al., 2016). In addition, Evidence-Based Review of Stroke Rehabilitation in Canada has ranked FES for gait rehabilitation with the highest evaluation (Teasell et al., 2016). Furthermore, NMES has a potential to improve muscle strength (Yan, Hui-Chan, & Li, 2005) and cardiovascular fitness (Davis, Hamzaid, & Fornusek, 2008; Hettinga & Andrews, 2008), and reduce spasticity (Solomonow et al., 1997; Yan et al., 2005) and pain (Babault, Cometti, Maffiuletti, & Deley, 2011). Because of such ability to restore function and to reduce secondary complications related to motor impairments, it is generally accepted that NMES can improve the quality of life for people with neurological disorders (Sheffler et al., 2013).

In the last few decades, neurorehabilitation interventions combining NMES with voluntary engagement have played an important role in restoring functional movements (Hara, Obayashi, Tsujiuchi, & Muraoka, 2013; Popovic, Curt, Keller, & Dietz, 2001; Stein et al., 2010). A large number of studies have been conducted to solve the neurophysiological underlying mechanisms of NMES (Collins, Burke & Gandevia, 2002; Collins 2007; Gandolla et al., 2016; Mang, Clair, & Collins, 2011; Thompson & Stein, 2004). Specifically, transcranial magnetic stimulation (TMS), which is a noninvasive technique to assess the excitability of the corticospinal pathway (Rossini et al., 2015), has been used to provide evidence that NMES for ankle dorsiflexors increases the corticospinal excitability (Everaert, Thompson, Chong, & Stein, 2009; Mrachacz-Kersting et al., 2017) with long-lasting aftereffects (Khaslavskaia & Sinkjaer, 2005; Thompson, Duffield, Abel, & Pomerantz, 2011; Thompson & Stein, 2004). However, neural effects, specifically corticospinal changes during the interventions using NMES, remain unclear. Therefore, it is important to provide an in depth understanding of how and to what extent NMES can induce acute changes in corticospinal excitability during the interventions.

In our daily living, accurate force control in the lower limb is an essential skill during activities such as going up or down the stairs, stepping over obstacles or driving a vehicle. However, the effects of NMES on force control ability are not well understood. In rehabilitation, NMES is applied unilaterally rather than bilaterally. To our knowledge; however, only one study investigated whether bilateral lower-limb movements influence accuracy of force control (Noble, Eng, & Boyd, 2014). It is therefore significant to investigate whether there are differences between unilateral and bilateral ankle dorsiflexion force control and to what extent the corticospinal pathway is involved in the force control. Since it is well known that NMES for ankle dorsiflexors can induce neural plasticity (Khaslavskaia & Sinkjaer, 2005; Thompson, Lapallo, Duffield, Abel, & Pomerantz, 2011; Knash, Kido, Gorassini, Chan, & Stein, 2003; Mang et al., 2011), an in-depth understanding of the ankle dorsiflexion force control will contribute to expanding knowledge to use NMES efficiently for enhancing motor cortical and corticospinal excitability. Therefore, this work will first investigate motor control during ankle dorsiflexion in Chapter 2 (Study 1) as well as corticospinal excitability in Chapter 3 (Study 2). Following the investigation of mechanisms of voluntary motor control, this dissertation will explore the effects of NMES from neurophysiological aspects and behavioral aspects specifically focusing on corticospinal excitability and force control of ankle dorsiflexors during short-term intervention in Chapter 4 (Study 3). These results will provide insight into how to further develop NMES interventions for neurorehabilitation of the lower limbs.

## 1.2. Background (Literature review)

### 1.2.1. Force control of ankle dorsiflexors

In daily life, the ankle joint plays an important role to stabilize posture during sitting, standing and walking (Brockett & Chapman, 2016; Linens, Ross, Arnold, Gayle, & Pidcoe, 2014).

In addition, the ankle movement requires sufficient range of motion and accurate force control to perform activities such as walking up or down the stairs, stepping over obstacles and driving a vehicle, so on. The ability to produce accurate and steadily force output is generally referred to as force control (Chow & Stokic, 2011). Force control has been studied in a variety of paradigms and it has been reported that ankle force control can be affected by muscle fatigue (Gueugnon, Torre, Mottet, & Bonnetblan, 2014), age (Tracy, Maluf, Stephenson, Hunter, & Enoka, 2005), and neurological disorders such as stroke (Chow & Stokic, 2011; Yen & Li, 2015) and Parkinson's disease (Neely et al., 2013). However, little is still known about neurophysiological aspects of force control during ankle dorsiflexors. Noble et al., (2014) investigated motor cortical areas associated with coordination of bilateral ankle plantarflexion using functional magnetic resonance imaging (fMRI). They found that bilateral ankle dorsiflexion required more cortical activation than unilateral condition, but no meaningful differences were shown in force control performance (i.e., error) during force matching tasks.

Furthermore, the brain imaging studies have provided the evidence that the motor cortex has greater activity during ankle dorsiflexion compared to plantarflexion (Trinastic et al., 2010) and stronger connectivity with dorsiflexors compared to plantarflexors (Petersen, Willerslev-Olsen, Conway, & Nielsen, 2012). Ankle dorsiflexion and the heel strike during the gait cycle are unique characteristic to human walking (Capaday, 2002). It is known that many patients with strokes have problems with the ability to produce ankle dorsiflexion, which can result in foot drop (Dunning et al., 2015; Knutson, Fu, Sheffler, & Chae, 2016). Therefore, cortical activity seems to play an important role for precise force control of ankle dorsiflexors after stroke. To improve this clinical issue it is significant to investigate not only performance accuracy but also involvement of the motor cortex and corticospinal pathways during force control.

### 1.2.2. Bilateral and unilateral movement

NMES for lower-limb rehabilitation is generally applied unilaterally to improve the impaired limb function. However, it is not fully clear whether there is a difference between unilateral and bilateral voluntary ankle dorsiflexion force control. It has been shown that bilateral maximal contraction of both limbs produces less force and motor unit activations, compared to the sum of that produced under unilateral maximal contractions of right and left limbs (Howard & Enoka, 1991; Kawakami, Sale, MacDougall, & Moroz, 1998; Oda & Moritani, 1994; Škarabot, Cronin, Strojnik, & Avela, 2016). Reaction time (RT) studies have shown longer RT during bilateral hand movements compared to unilateral movements (Taniguchi, Burle, Vidal, & Bonnet, 2001; Vieluf, Aschersleben, & Panzer, 2016). Regarding force control, a force-matching elbow flexion task demonstrated that bilateral control produced larger errors compared to unilateral control (Gueugnon et al., 2014). However, these previous studies have mainly investigated upper-limbs tasks, while studies investigating the lower limbs have focused on maximal contractions or dynamic movement performance (Škarabot, Cronin, et al., 2016). Hence, it is necessary to investigate whether bilateral performance affects precise force control during low-level muscle contractions in the lower limbs (Chapter 2).

Furthermore, previous works have shown increased corticospinal excitability prior to movement onset during unilateral (Geertsen, Zuur, & Nielsen, 2010) and bilateral (Schneider, Lavoie, Barbeau, & Capaday, 2004) ankle dorsiflexion, suggesting that there is cortical involvement during movement preparation. However, these studies have not directly compared differences in the time course of neural activations between unilateral and bilateral lower-limb movements. Understanding the underlying neural mechanism between these movements with regards to contraction phases can provide further insight into movement coordination of the lower limb.

### 1.2.3. Neuromuscular electrical stimulation (NMES)

#### 1.2.3.1. Principles of NMES

NMES artificially induces muscle contraction to produce functional movements. When the electrical pulses are applied to motor nerves, action potentials are elicited which cause the discharge of motoneurons. If the action potentials reach the target muscle, they induce muscle contraction (Popovic, Curt, Keller, & Dietz, 2001). Furthermore, Collins et al. (2002) introduced stimulation of the nerves via the ‘reflex pathway’ to evoke the sensory volley during electrical stimulation which recruits motor units and activates motoneurons in the spinal cord to generate muscle contractions. NMES / FES stimulations can be delivered through surface electrodes positioned on the skin (percutaneous stimulation) or implanted electrodes (Knutson et al., 2016). Although implanted electrodes can stimulate the nerves selectively, they require surgical interventions. Hence, the percutaneous stimulation is typically used because of easy and convenient use in clinical setting. Surface electrodes are placed on the nerve trunk or muscle belly of the target muscle. Strength of the muscle contraction is determined by adjusting stimulating pulse parameters: pulse frequency, width, and amplitude. Varying these parameters has different effects on recruitment of motor unit and activation of sensory axons (Milosevic, Masani, Popovic, & Nakazawa, 2017). One of the significant differences between electrically induced contraction and voluntary contraction is the recruitment order of motor units. During voluntary contraction, motor units are recruited from slow to fast orderly which is fatigue-resistant, while the recruitment order of NMES is nonselective or random (Gregory & Bickel, 2005; Maffiuletti, 2010). Although NMES has benefits, there are also negative effects such as rapid muscle fatigue and discomfort associated with stimulation (Barss et al. 2018).

#### 1.2.3.2. Effects on functional improvements

Walking ability is one of the most important goals for recovery in people who suffer neurological disorders (Kapadia et al., 2014; Tan et al., 2014). However, the limited active ankle dorsiflexion (i.e., foot drop) due to central nervous system (CNS) injury results in decreased foot clearance during the swing phase of the gait cycle and often prevents patients from improving walking ability. Since the first foot drop stimulator was applied by Liberson et al. (1961) to compensate for the limited ankle function, electrical stimulation has been widely used in rehabilitation. In this case, the electrical stimulation is applied to the common peroneal nerve or the tibialis anterior (TA) muscle belly to activate the ankle dorsiflexors during the swing phase. Moreover, FES is applied to other leg muscles, such as the hamstrings and gluteus muscles (Cho, Kim, Chung, & Hwang, 2015; Chung, Kim, Cha, & Hwang, 2014; Street & Singleton, 2018). Effects of the FES on walking ability have been reported in patients with CNS disorders such as stroke (Cho et al., 2015; Chung et al., 2014; Everaert et al., 2013; Kluding et al., 2013; Tan et al., 2014), multiple sclerosis (Stein, Everaert, Roy, Chong, & Soleimani, 2013; Stein et al., 2010), and spinal cord injury (SCI) (Kim, Eng, & Whittaker, 2004; Stein et al., 2013; Street & Singleton, 2018). A systematic review which included six randomized controlled trials identified the superior effects of FES on decreasing Physiologic Cost Index, which is an assessments of exertion based on heart rate (Farris et al., 2014) in stroke patients

(Dunning et al., 2015). Another review in people with SCI reported that locomotor training with FES has greater effects on walking ability compared to training without FES (Morawietz & Moffat,, 2013). It has been noted that FES has a potential to induce not only immediate effects of walking function but also carry-over effects after interventions (Stein et al. 2010). Stein et al. (2010) investigated the aftereffects of foot-drop stimulator in people with CNS disorders. They showed that three months of daily use of FES resulted in the improvement of walking speed and decrease of walking effort without the stimulation after the intervention. In order to investigate the neurophysiological underlying mechanism of the functional improvements after FES, numerous studies have been conducted and they showed that electrical stimulation can induce neural plasticity.

#### 1.2.3.3. Effects on neural modulation

Evidence shows that NMES can be used as a neurorehabilitation tool which can enhance not only functional improvement but also neuromodulation after CNS injury (Knutson et al., 2016). In order to investigate the neurological effects of NMES, imaging studies using fMRI (Gandolla et al., 2014, 2016), functional near-infrared spectroscopy (NIRS) (Hara, Obayashi, Tsujiuchi, & Muraoka, 2013; Muthalib, Ferrari, Quaresima, Kerr, & Perrey, 2018), and electroencephalographic (EEG) (Qiu et al., 2016) have been conducted. Qiu et al.(2016) showed that the EEG oscillatory pattern in the sensorimotor area during NMES-induced movements are more correlated with active movements rather than passive movements. This result suggests that NMES can alter voluntary movements in the sensorimotor cortical area. Muthalib et al.(2018) reported that when NMES was combined with voluntary movements, cortical activation were increased (i.e., increased oxyhemoglobin and decreased deoxyhemoglobin) in the sensorimotor areas to a similar extent as during voluntary movements. Taken together, it seems that NMES has possibility to induce somewhat voluntary movement-like cortical activations.

Furthermore, another set of investigations also used transcranial magnetic stimulation (TMS) to study the effects of NMES. TMS elicits motor evoked potential (MEP) in the target muscle of which amplitude represents corticospinal excitability (Rossini et al., 2015; Terao & Ugawa, 2002). It has been suggested that afferent inputs from peripheral nerve stimulation can induce cortical reorganization (Ridding & Rothwell, 1999), which can be quantified through changes in the MEP size. A number of studies have shown increased MEP after repetitive peripheral nerve stimulation in both upper-limb muscles (Mang, Clair, & Collins, 2011; Ridding, Brouwer, Miles, Pitcher, & Thompson, 2000; Ridding & Rothwell, 1999) and lower-limb muscles (Khaslavskaia, Ladouceur, & Sinkjaer, 2002; Knash, Kido, Gorassini, Chan, & Stein, 2003; Mang et al., 2011; Mang, Lagerquist, & Collins, 2010; Thompson et al., 2011). In clinical applications of NMES, Everaert et al. (2009) reported that people with non-progressive disorders (i.e., stroke, SCI, surgical complication, head injury and cerebral palsy) in a chronic stage improved their walking speed along with increase of MEP amplitudes after three months NMES use. Thompson et al. (2011) showed that increased corticospinal excitability after 30 min of NMES while the aftereffects also lasted for 30 min in in people with incomplete SCI. This suggests that underlying mechanism of the aftereffects of NMES may be an accumulation of the short-term corticospinal excitability.

To date, necessity of voluntary involvement (actual movement or motor imagery) during NMES is well established, which contributes to neural modulation in supraspinal and spinal levels (Everaert et al., 2009; Gandolla et al., 2016; Jochumsen et al., 2016; Kaneko, Hayami, Aoyama, & Kizuka, 2014; Kato et al., 2019; Khaslavskaia & Sinkjaer, 2005; Mang, Bergquist, Roshko, & Collins, 2012; Mrachacz-Kersting et al., 2017). The possible mechanism has been commonly explained by long-term potentiation (LTP) following Hebbian learning principles (Everaert et al., 2009; Gandolla et al., 2016; Knutson, Fu, Sheffler, & Chae, 2016; Milosevic, Masugi, Sasaki, Sayenko, & Nakazawa, 2019; Rushton, 2005). If presynaptic firing and postsynaptic discharge synchronized, the synapse is strengthened (Hebb, 1949). It has been suggested that NMES can trigger the LTP at synapses between antidromic input from NMES and descending drive due to voluntary engagement (Rushton, 2005) (Figure 1). The LTP seems to contribute to improvement of motor function and induce therapeutic effects of NMES. Therefore, it is believed that combination with voluntary involvement plays a key role during NMES interventions. Previous studies have investigated the effects of the combined intervention on corticospinal excitability compared to

NMES alone and/or voluntary contraction alone during wrist extension (Taylor, Lewis, & Taylor, 2012) and ankle dorsiflexion (Jochumsen et al., 2016; Khaslavskaia & Sinkjaer, 2005). Jochumsen et al. (2016) demonstrated that short period NMES (both of muscle- and nerve-located stimulation) combined with voluntary movement induced larger corticospinal excitability changes, compared to NMES alone and voluntary movements. Specifically, when electrical stimulation was applied on the muscles, the results showed increase in MEPs for 30 min after the intervention. However, these results need to be interpreted with caution. This is because they added electrical stimulation to voluntary contractions which led to larger total amount of force, compared to when NMES was applied alone and/or voluntary contractions alone. Consequently, the largest force was produced using a combination of NMES and voluntary contractions, which seems to affect the results because of higher motor unit recruitments and larger sensory feedback. Therefore, there still remains a need for an efficient method to compare changes in the corticospinal excitability under the same amount of force generation during different conditions. Understanding these changes in the corticospinal excitability during the course of the interventions will undoubtedly provide important implications for optimizing rehabilitation interventions.

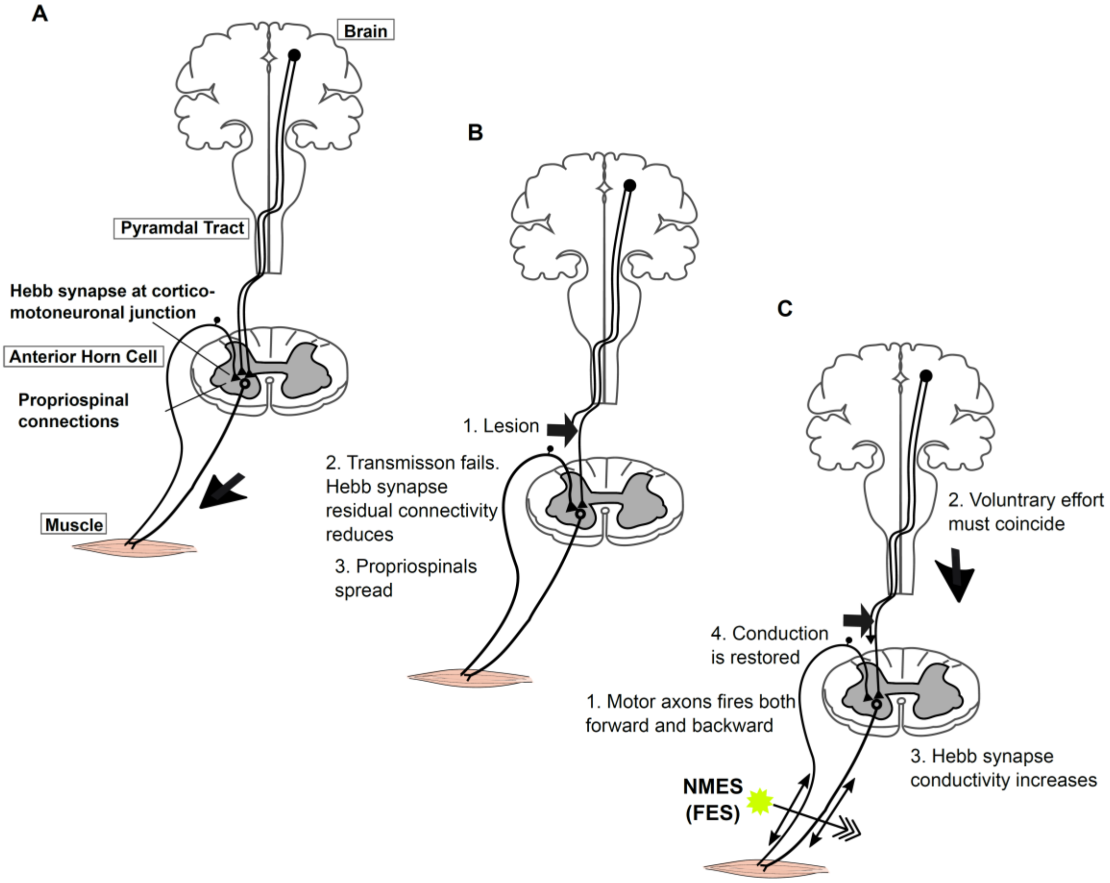

**Figure 1. Hypothesis of NMES inducing Hebbian synapse conductivity. (A)** Normally, the conductivity of Hebb-type pyramidal tract and anterior horn cell would be sustained. **(B)** However, stroke or spinal cord lesion leads to weak synaptic conduction due to reduce of the pyramidal tract population. Furthermore, instead of the reduced Hebb-type connection, propriospinal control will increase resulting in development of spasticity. **(C)** NMES could increase strength of the Hebb synapse conductivity, only if antidromic activity from the electrical stimulation is synchronized with voluntary effort. (Cited and modified from Rushton 2005)

### 1.2.3.4. Effects on force control

Although NMES has many benefits, as described above, the effects on force control are still not well understood. It has been suggested that neuromodulation has influences on force generation (Taylor & Martin, 2009). Taylor & Martin (2009) showed that synaptic transfer between corticospinal and motoneurons can be enhanced by facilitation of neural plasticity, which led to increase of voluntary output (i.e., increased error). On the other hand, a review by Ljubisavljevic (2006) has reported that motor learning and skill acquisition are associated with the increase of corticospinal excitability; that is, cortical plasticity could lead to behavioral improvement (i.e., reduced error). Recently, Saumur and Mochizuki (2018) demonstrated that reaction time was not correlated with MEP amplitudes, but significant correlations between the magnitude of muscle responses and MEP amplitudes existed. These previous studies have raised questions about whether NMES has effects on force control and induces behvioral changes as a consequence of neural plasticity.

## 1.3. Dissertation Objectives

The main aim of this dissertation was to investigate the effects of NMES on voluntary motor control in the lower-limb muscles. To achieve the aim, the objectives of this dissertation were to investigate: (i) the lower-limb motor control from behavioral aspects and neurological aspects (Study 1 and Study 2), and (ii) the effects of NMES on the motor control and the corticospinal excitability (Study 3). Specifically, the objectives and specific research questions were to:

1) **Study 1 -** Investigate accuracy of force control during unilateral and bilateral voluntary ankle dorsiflexion.

   **Objective:** The first objective of my research was to compare force-control performance between unilateral and bilateral control.

**Research question:** How is ankle dorsiflexion force control affected by bilateral movement? Are there any differences between dominant and non-dominant leg during ankle dorsiflexion force control?

2) **Study 2 -** Investigate corticospinal excitability during ankle dorsiflexor force control.

   **Objective:** The second objective of my research was to compare corticospinal excitability between unilateral and bilateral force-control tasks.

   **Research question:** To what extent is corticospinal excitability facilitated during unilateral and bilateral ankle dorsiflexion force control? Are there any differences of that between ballistic and tonic tasks?

3) **Study 3 -** Investigate the effects of NMES combined with voluntary ankle dorsiflexion contractions on the real-time changes in the corticospinal excitability and force control.

   **Objective:** The final objective of my research dissertation was to identify the time course of changes in the corticospinal excitability during NMES alone, NMES combined with voluntary contraction, and voluntary contractions alone.

   **Research question:** To what extent would the corticospinal excitability increase during different NMES and voluntary interventions? To what extent would accuracy and response time be affected as a result of the interventions?

First, this dissertation sought relevant literatures in the area, including the lower-limb force control and principles of NMES (Chapter 1). Secondly, it will provide evidence from current research which answers research questions above (Chapter 2, 3, and 4). Finally, it will refer to clinical contribution and future direction (Chapter 5).

# Chapter 2.

## Force control of ankle dorsiflexors in young adults:

## effects of bilateral control and leg dominance

The material presented in this chapter has been published in a peer-reviewed journal article:

Yamaguchi, A., Milosevic, M., Sasaki, A., & Nakazawa, K. (2020). Force Control of Ankle Dorsiflexors in Young Adults: Effects of Bilateral Control and Leg Dominance. *Journal of Motor Behavior*, 52(2), 226-235. https://doi.org/10.1080/00222895.2019.1609408

## 2.1. Abstract

We investigated whether bilateral lower-limb control and leg dominance affect force control ability in 15 healthy young adults (9 males and 6 females, age 26.8±4.1 years). Participants performed isometric ankle dorsiflexion force control tasks, matching a visual target (10% of maximal effort) as quickly and precisely as possible in ballistic and tonic tasks. Performance was evaluated using force error, force steadiness, amount of muscle activity of the tibialis anterior, and response time characteristics. Results showed no significant effects of leg dominance during both ballistic and tonic tasks, while bilateral condition resulted in significantly larger error, less force steadiness, compared to unilateral condition, and only during the tonic task. Consequently, bilateral control, specifically in tasks utilizing feedback control (i.e., tonic task) might affect force control ability, possibly because of the interhemispheric inhibition to meet bilateral task complexity and integrate afferent bilateral sensory information from both right and left legs.

**Keywords:** Force control; ankle dorsiflexion; bilateral control; leg dominance

## 2.2. Introduction

The ability to accurately and steadily produce force output is generally referred to as force control (Chow & Stokic, 2011). Accurate force control is important for performing activities of daily living such as standing, walking, control of the feet during driving, or other object manipulation. Force control has been studied in a variety of paradigms to investigate effects of sensory feedback on desired force outputs (Simon & Ferris, 2008; Yen & Li, 2015). It has been reported that force control can be affected by muscle fatigue (Gueugnon, Torre, Mottet, & Bonnetblan, 2014), age (Tracy, Maluf, Stephenson, Hunter, & Enoka, 2005), and stroke (Chow & Stokic, 2011; Yen & Li, 2015). Bilateral movements with homologous limbs lead to affected performance compared to unilateral performance both of upper limbs and lower limbs (Skarabot, Cronin, Strojnik, & Avela, 2016; Vieluf, Aschersleben, & Panzer, 2017). Bilateral maximal contraction of both limbs produces less force and motor unit activation compared to the sum of values produced under unilateral maximal contraction of right and left limbs (Skarabot et al., 2016; Vandervoort, Sale, & Moroz, 1984). In addition, reaction time (RT) studies showed longer RT in bilateral hand movements compared to unilateral condition (Taniguchi, Burle, Vidal, & Bonnet, 2001; Vieluf et al., 2017). Moreover, a force matching task of elbow flexion demonstrated that bilateral control produced larger error compared to unilateral control (Gueugnon et al., 2014). It has been suggested that bilateral movements are a specific case of dual-motor tasking and more complex nature than unilateral movements (Serrien, Cassidy, & Brown, 2003; Swinnen & Wenderoth, 2004), which require considerable interhemispheric communication (Carson, 2005; Serrien, 2009). However, previous studies which investigated the lower limbs mainly focused on the maximal contractions or dynamic movement performance (Skarabot et al., 2016). To our knowledge, only one study investigated whether bilateral lower-limb movements influence the accuracy of force control (Noble, Eng, & Boyd, 2014). Noble et al. (2014) compared brain activation and the magnitude of produced force during bilateral with those of unilateral plantarflexion force control. In their study, participants were provided visual feedback of the force produced under both feet and they were instructed to match the forces to the target which appeared on the screen. The findings showed bilateral condition required more cortical activation than unilateral condition, but no meaningful difference (i.e., the small difference with statistical significance) in behavioral results. This study tended to focus on neuroimaging analysis and it allowed limited analysis of the magnitude of produced force as performance comparison. Therefore, in order to provide better understanding of the bilateral force control in the lower limbs, this study evaluated the performance with not only the magnitude of the forces but also force steadiness, the amount of muscle activity, and timing of the force production. In addition, previous studies showed that motor pathways have different activation patterns in ballistic and tonic contraction of ankle plantarflexors (Keller, Taube, & Lauber, 2018; Taube, Lundbye-jensen, Schubert, Gollhofer, & Leukel, 2011). Therefore, in order to test the task-specific effects, both the ballistic and tonic tasks were evaluated in this study.

Furthermore, it is known that limb dominance also affects motor control. The dominant leg is defined as the leg which controls objects during the performance of motor tasks (e.g., kicking a ball), while the non-dominant leg is defined as the leg which provides postural support and stabilization during movements (Sadeghi, Allard, Prince, & Labelle, 2000). A previous study showed better ball-juggling performance by the dominant leg than non-dominant leg (Grouios, Hatzitaki, Kollias, & Koidou, 2009). Ludwig, Simon, Piret, Becker, and Marschall (2017) demonstrated that the dominant leg exhibits less stability than the non-dominant leg during single leg landing in soccer players. However, with regards to the force control in the lower limbs, there are inconsistencies across studies. A plantarflexor force-matching task demonstrated the asymmetry in the lower limbs (Savage, Allen, & Proske, 2015). On the other hand, no effects of leg dominance were revealed on ankle isometric force control in a combined ankle movement with dorsiflexion, plantarflexion, inversion, and eversion (Yen et al., 2018). Therefore, it is still unclear if there is a dominance effect on the force control in the lower limbs. The objective of this study was to investigate the effect of bilateral control and leg dominance during ankle dorsiflexor force control in healthy participants. We hypothesized that bilateral performance would be less accurate and require longer response with less muscle activation compared to unilateral performance. In addition, we hypothesized that the dominant leg would produce force more accurately and faster compared to the non-dominant leg in the ankle dorsiflexor force-matching task.

## 2.3. Methods

### 2.3.1. Participants

Fifteen healthy participants were recruited in this study (9 males and 6 females, age = 26.8±4.1 years, weight = 61.6±12.8kg, and height = 167.8±9.7cm (mean±SD)). Exclusion criteria were history of musculoskeletal, visual, and mental disorders. To determine the dominant leg, participants were asked which leg they would use to: (i) kick a ball, (ii) stamp out a simulated fire, (iii) pick up a marble, and (iv) trace shapes using their foot (Schneiders et al., 2010). Answering affirmatively on 3 or more as right or left determined the dominant leg, while answering 2 as right and 2 as left required the participants to be excluded. Overall, all participants in this study were right leg dominant and nobody was excluded. Prior to the experiment, all participants gave written informed consent. The study protocol was approved by the Committee of the Graduate School of Arts and Sciences at The University of Tokyo.

### 2.3.2. Force match task

Ankle force was measured using two strain gauge load cells (LCB03K060L; A&D Inc., Tokyo, Japan), which were calibrated prior to the experiments. During the experiment, participants remained sitting on a height adjustable chair with hips flexed at 90°, knee flexed at 90°, and ankle dorsiflexion of 90° angle. Using a strap band, each foot was fixed to a metal footplate which was attached to a load cell (Figure 1). A screen was placed in front of the participants at a distance of 70cm at the eyes′ height. The target and the visual feedback of the produced force were provided on the monitor. The visual feedback was created using LabVIEW software (National Instruments Corporation, Austin, TX) and data were sampled at 2000Hz (DAQ; National Instruments Corporation, Austin, TX).

**Figure 1.** Experimental setup of the force match test. Participants were seated with hip and knee flexion and ankle dorsiflexion at 90°. Each foot was strapped on to a separate metal foot plate, each constraining a load cell.

First, participants performed isometric maximum voluntary contraction (MVC) of ankle dorsiflexion unilaterally. They were instructed to maximally flex the ankle for 5s. Two trials were repeated for each foot, with at least 1min rest between trials. Participants were verbally encouraged to produce maximum force of ankle dorsiflexion. The average force of the middle 2s window during the 5s contraction was obtained as the maximum force for each trial and the higher force value of two trials was used as the MVC force. The raw force signals of ankle dorsiflexion were converted to the %MVC force and visualized on the monitor using LabVIEW software (National Instruments Corporation, Austin, TX). The target level during the force-matching tasks was set at 10% of the MVC force for both legs, such that only one target line appeared, although the absolute force value may have been different between the right and left leg.

The task-specific activation of motor pathways was demonstrated in the ballistic and tonic contraction (Taube et al., 2011). Therefore, to investigate the force control ability, we examined two tasks: 1) Ballistic – square wave with 1s width moved from right to left on the monitor randomly every 3–5s; and 2) Tonic – square wave with 5s width moved from right to left on the monitor randomly every 5–8s. During both the Ballistic and Tonic tasks, participants were asked to generate the force as quickly and precisely as possible when the rising edge of the target appeared. During the Ballistic task, participants were required to relax immediately after reaching the target, while during the Tonic task, they were required to maintain the target level in the plateau phase and relax when the falling edge of the square wave appeared.

Each task (i.e., Ballistic and Tonic) was completed under three different conditions: (a) unilateral contraction by dominant leg; (b) unilateral contraction by non-dominant leg; (c) bilateral contraction by dominant and nondominant leg simultaneously, resulting in six trials (two tasks three conditions) for each participant. Visual feedback of two lines, representing the right force in red and left force in white, were shown during the bilateral condition, while one line for right or left force only was shown during the unilateral condition. For each trial, a total of 10 targets were presented (the Ballistic task required about 60s, while the Tonic task required about 120s in total). Before the start of the experiment, participants practiced the trials to become familiarized with each task and the visual feedback information, with specific explanations about how right and left force feedback was displayed. The order of the task and the condition was randomized separately for each participant. First, the order of the task (i.e., the Ballistic and Tonic) was randomized. Secondly, the order of the condition (i.e., unilateral dominant, unilateral non-dominant, and bilateral) was randomized within each task.

### 2.3.3. Electromyography (EMG)

Electromyography (EMG) signals were recorded on the tibialis anterior (TA) muscles bilaterally using bipolar Ag–AgCl surface electrodes (Vitrode F-150S; Nihon Koden, Tokyo, Japan) that were placed on the center of the muscle belly with 2cm separation. The EMG signals were amplified (1000) and filtered (band-pass: 15–1000Hz) using a multichannel EMG amplifier (MEG-6108;

Nihon Koden, Tokyo, Japan). All EMG and force data were digitized using an analog-to-digital (A/D) converter system at a sampling frequency of 2000Hz (PowerLab 16/s; AD Instruments, Bella Vista, Australia) and saved on the computer.

### 2.3.4. Data analysis

**Force data**

For the Ballistic task analysis, the peak force was normalized to its respective MVC. For the Tonic task analysis, the force data were separated into the initial phase (the first 1.5s window from the target onset) and plateau phase (3s window after the initial phase) of each contraction (Figure 2(B)). To quantify accuracy, the Ballistic and Tonic tasks were evaluated using: i) error ($\text{Error}_{\text{ballistic}}$ and $\text{Error}_{\text{tonic}}$) – difference between the percentage of the peak force and the target in the Ballistic task (Figure 2(A)) and difference between the mean value during the plateau phase and the target in the Tonic task (Figure 2(B)). In addition, the Tonic task was evaluated using: ii) steadiness (i.e., force fluctuation) by coefficient of variation ($\text{CV}_{\text{tonic}}$) – the ratio between standard deviation (SD) and mean force ($\text{CV}_{\text{tonic}} = \text{SD}/\ \text{mean} \times 100\%$)(Tracy et al., 2005) during the plateau phase (Figure 2(B)).

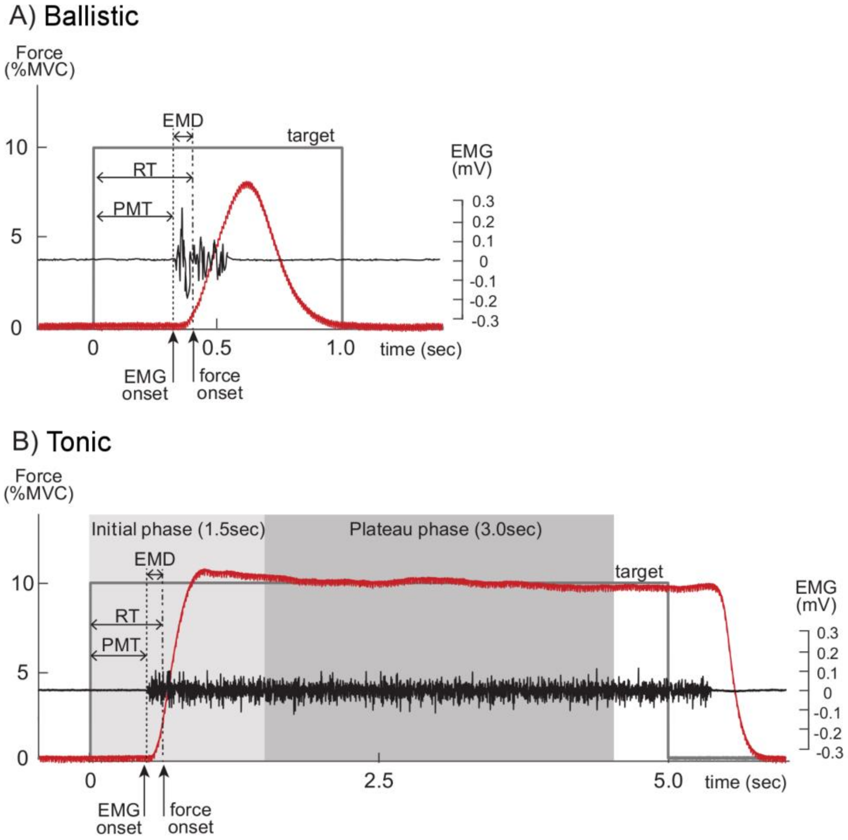

**Figure 2.** Representative trials of: A) Ballistic task; B) Tonic task for the force matching test. Shown are the Reaction time (RT) - the interval from the target appearance to the force onset; Pre-motor time (PMT) - the interval from the target appearance to the EMG onset; Electromechanical delay (EMD) - the time lag between the onset of muscle activation and the onset of force generation.

**EMG data**

EMG signals were first rectified and low-pass filtered at 2.5Hz using a 4th-order Butterworth filter.

To quantify the amount of muscle activity, the Ballistic and Tonic tasks were evaluated using root mean square ($RMS_{ballistic}$ and $RMS_{tonic}$) – RMS after the onset of muscle activity in the 500ms for the Ballistic task and 3s window in the plateau phase for the Tonic task. Baseline was defined as the 500ms period prior to the target onset. The EMG onset and force onset were detected at the points where it exceeded the mean plus three standard deviation of the baseline (Hodges & Bui, 1996) using a custom software MATLAB (The MathWorks, Natick, MA) and confirmed visually for each contraction. $RMS_{ballistic}$ and $RMS_{tonic}$ were normalized to RMS of MVC trial and normalized RMS data were used for analysis.

**Timing characteristics**

To quantify response time characteristics, the Ballistic and Tonic tasks were evaluated using: i) reaction time ($RT_{ballistic}$ and $RT_{tonic}$) – defined as the interval from the target appearance to the force onset (Le Mansec, Nordez, Dorel, & Jubeau, 2018); ii) pre-motor time ($PMT_{ballistic}$ and $PMT_{tonic}$) – defined as the interval from the target appearance to the EMG onset (Le Mansec et al., 2018); iii) electromechanical delay ($EMD_{ballistic}$ and $EMD_{tonic}$) – defined as the time lag between the onset of muscle activation and the onset of force generation (Yavuz, Sendemir-Urkmez, & Turker, 2010). All data processing was performed using custom software in MATLAB (The MathWorks, Natick, MA).

### 2.3.5. Statistics

Statistical analyses were performed using the two-way repeated measures analysis of variance (ANOVA) to evaluate the effects of bilateral control (BUC: bilateral vs. unilateral control) and leg dominance (DOM: dominant leg vs. non-dominant leg) on the Ballistic and Tonic tasks separately.

Since the Shapiro–Wilk test showed that all measures were not normally distributed, a logarithmic transformation was performed to normalize the data prior to doing the ANOVA analysis (Tabachnick & Fidell, 2007). To correct for multiple tests, the p values were adjusted based on the Holm correction method (McLaughlin & Sainani, 2014). Specifically, during the Tonic task, six variables (Error, CV, RMS, PMT, EMD, and RT) were analyzed, while during the Ballistic task, five variables (Error, RMS, PMT, EMD, and RT) were analyzed. Therefore, for the Tonic task and the Ballistic task, the raw p values were multiplied by from six (for the lowest p value) to one (for the largest p value) and from five to one, respectively. Statistical significance at $p<.05$ was accepted. When significant interaction effect was found, paired samples t-test was used to confirm the effect for each factor separately. All tests were performed using SPSS version 23 (IBM SPSS Inc., Armonk, New York).

## 2.4. Results

### 2.4.1. MVC Force

The mean MVC force of the dominant side was 263.8±73.4 N (mean±SD) and the non-dominant side was 264.1±73.0 N (mean±SD). No significant difference was found between the dominant and non-dominant foot force ($p>.05$).

### 2.4.2. Force error and CV

Results of force error and CV are summarized in Figure 3. For the Ballistic task, $\text{Error}_{\text{ballistic}}$ showed no main effects (BUC: $p>.05$; DOM: $p>.05$) and no interaction ($p>.05$) (Figure 3(A)). For the Tonic task, $\text{Error}_{\text{tonic}}$ also showed no main effect of DOM ($p>.05$) and no interaction ($p>.05$), but a significant BUC effect ($p<.01$) (Figure 3(B)). Moreover, for the Tonic task, $\text{CV}_{\text{tonic}}$ showed no main effect of DOM ($p>.05$) and no interaction ($p>.05$), but a significant BUC effect ($p<.01$) (Figure 3(C)).

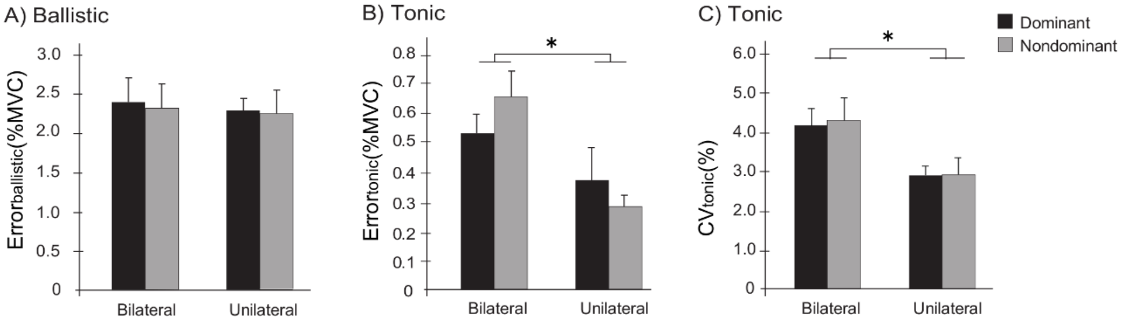

**Figure 3.** Error for the: A) Ballistic task ($\text{Error}_{\text{ballistic}}$); B) Tonic task ($\text{Error}_{\text{tonic}}$); and C) coefficient of variation ($\text{CV}_{\text{tonic}}$) for the Tonic task. Shown are results for bilateral and unilateral conditions and for dominant (black bar) and non-dominant (gray bar) conditions (mean±SE). Note: The significance levels were corrected based on Holm method (McLaughlin & Sainani, 2014).

### 2.4.3. Muscle activations

Results of muscle activations are summarized in Figure 4. For the Ballistic task, $\text{RMS}_{\text{ballistic}}$ showed no main effects (BUC: $p>.05$; DOM: $p>.05$) and no interaction ($p>.05$) (Figure 4(A)). For the Tonic task, $RMS_{tonic}$ showed no main effects (BUC: p>.05; DOM: p>.05) and no interaction (p>.05) (Figure 4(B)).

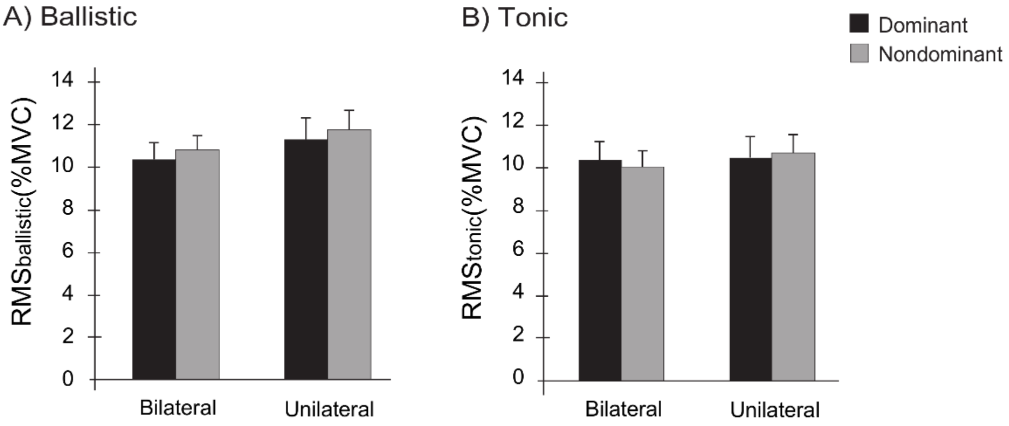

**Figure 4.** Root mean square (RMS) of the: A) Ballistic task ($RMS_{ballistic}$); and B) Tonic task ($RMS_{tonic}$) normalized to MVC value for bilateral and unilateral conditions and for dominant (black bar) and non-dominant (gray bar) conditions (mean±SE). Note: The significance levels were corrected based on Holm method (McLaughlin & Sainani, 2014).

### 2.4.4. Time parameters: PMT, EMD, and RT

Descriptive and statistical results for the time parameters are presented in Table 1. For both the Ballistic and Tonic tasks, there were no main effects of BUC and DOM, and no interaction for all parameters.

**Table 1.** Results of time characteristics comparisons for the Ballistic and Tonic tasks of pre-motor time (PMT), electromechanical delay (EMD), and reaction time (RT) showing the mean ± SE.

| Task | Measure (ms) | DOM | BUC | | Statistics: Two-way RM ANOVA | | |
|---|---|---|---|---|---|---|---|
| | | | Bilateral | Unilateral | BUC | DOM | Interaction |
| Ballistic | PMT | Dominant | 369±125 | 357±118 | $F_{(1,14)}$=.39 | $F_{(1,14)}$=.03 | $F_{(1,14)}$=.00 |
| | | Non-dominant | 366±122 | 360±137 | p=1.000 | p=.871 | p=.982 |
| | EMD | Dominant | 66±21 | 60±21 | $F_{(1,14)}$=2.22 | $F_{(1,14)}$=.18 | $F_{(1,12)}$=.12 |
| | | Non-dominant | 64±22 | 60±22 | p=.790 | p=1.000 | p=.739 |
| | RT | Dominant | 475±111 | 462±149 | $F_{(1,14)}$=1.75 | $F_{(1,14)}$=1.01 | $F_{(1,14)}$=1.12 |
| | | Non-dominant | 477±108 | 418±150 | p=.828 | p=1.000 | p=.309 |
| Tonic | PMT | Dominant | 413±166 | 375±137 | $F_{(1,14)}$=5.60 | $F_{(1,14)}$=.11 | $F_{(1,14)}$=.14 |
| | | Non-dominant | 413±168 | 382±142 | p=.099 | p=1.000 | p=.718 |
| | EMD | Dominant | 68±25 | 57±17 | $F_{(1,14)}$=4.06 | $F_{(1,14)}$=.00 | $F_{(1,14)}$=.44 |
| | | Non-dominant | 62±13 | 58±16 | p=.128 | p=1.000 | p=.516 |
| | RT | Dominant | 482±156 | 432±134 | $F_{(1,14)}$=7.10 | $F_{(1,14)}$=.00 | $F_{(1,14)}$=.499 |
| | | Non-dominant | 475±171 | 440±141 | p=.072 | p=.993 | p=.491 |

Comparisons were performed using the two-way repeated measures (RM) analysis of variance (ANOVA) to test for the effect of BUC: bilateral vs. unilateral and DOM: dominant vs. non-dominant leg. BD: bilateral dominant; UD: unilateral dominant; BN: bilateral non-dominant; and UN: unilateral non-dominant. Note: The p-values were adjusted based on Holm method (McLaughlin & Sainani, 2014). A significance level of 0.05 was applied. Statistically significant differences were not observed.

## 2.5. Discussion

The purpose of our study was to investigate whether simultaneous bilateral control and leg dominance have effects on force control of ankle dorsiflexors. To our knowledge, this study is the first to investigate the effect of bilateral motor performance on force control in terms of not only magnitude of error but also force steadiness and time characteristics in the lower limbs. Overall, our results suggest that leg dominance has no effects, while bilateral control affects the force-matching performance of ankle dorsiflexion.

### 2.5.1. Lower-limb bilateral force control

Our results showed that the bilateral condition resulted in larger error ($\text{Error}_{\text{tonic}}$) with more fluctuations ($\text{CV}_{\text{tonic}}$) (Figure 3) compared to the unilateral condition, and this was observed only in the Tonic task but not in the Ballistic task. These findings are in line with those of a previous study of the upper limbs which revealed that the bilateral condition resulted in larger error during elbow flexion (Gueugnon et al., 2014) compared to the unilateral condition. In addition, a previous study also showed a small but significant difference in force control error between the bilateral and unilateral condition in plantarflexion (Noble et al., 2014). Our findings support the notion that bilateral control could have an influence on force control compared to unilateral performance not only in the upper limbs but also in the lower limbs. However, contrary to this hypothesis, no significant difference in response times was found. The results showed slightly longer response times (PMT, EMD, and RT) in both the Ballistic and Tonic tasks (Table 1) compared to the results of previous studies that investigated other lower-limb joint movements/muscles (Le Mansec et al., 2018; Yavuz et al., 2010). These differences are most likely due to the different target muscles, contraction level, and methodologies used in these studies (Yavuz et al., 2010). Furthermore, not only quick responses, but also accuracy (i.e., to match the target) were required in our study, which entails a more complex cognitive processing leading to increased RT (Yarkoni, Barch, Gray, Conturo, & Braver, 2009). Therefore, the task complexity of this study might have contributed to similar response times in the unilateral and bilateral conditions.

This study showed no significant difference in the amount of muscle activity (RMS) between unilateral and bilateral force control, while a larger error and fluctuation were observed during bilateral performance. The underlying mechanisms could be related to the modulation of the peripheral and central motor excitability during bilateral force control.

With regard to peripheral motoneuron excitability, Yao et al. (2000) indicated that increased force fluctuation is caused by motor unit synchronization especially during low force contraction. Given the evidence, increased force fluctuation during bilateral condition in this study might be caused by motor unit synchronization. However, the previous study also showed increased EMG amplitudes along with increased motor unit synchronization. On the other hand, no significant differences of RMS between conditions were observed in the current study. Therefore, the synchronization is less likely to induce the force fluctuation.

Furthermore, in terms of the central commands, neural interaction between hemispheres seems to play an important role here. It has been widely accepted that during unilateral motor task performance, one hemisphere inhibits the activation of the opposite side in order to facilitate neural lateralization for certain unilateral movements (Bloom & Hynd, 2005; Ferbert et al., 1992). On the other hand, the overlapping of the interhemispheric inhibition has been suggested to negatively affect bilateral performance (Ferbert et al., 1992; Otsuki, 1983; Taniguchi et al., 2001; Vieluf et al., 2017). Therefore, our results could also have been caused by interhemispheric inhibitory interaction, which induced the attenuated performance. In addition, it has been reported that during asymmetrical movement of the upper limbs, excitatory cross-talk between the hemispheres is effectively inhibited in order to suppress mirror movement (Daffertshofer, Peper, & Beek, 2005). In our study, the targets randomly appeared and participants were shown two lines indicating left and right foot force, which required the distinct control of each limb. Therefore, excitatory cross-talk between hemispheres also might have been inhibited to prevent mirror movement in our study, which would suggest that inhibitory interaction between hemispheres could have affected the bilateral motor performance. To fully confirm these neural mechanisms, further study is needed. It is also to be noted that following two lines during the bilateral condition might have affected the performance due to visuomotor processing load (Tracy, 2007). However, a previous study suggested that increasing visual information during bilateral motor tasks does not necessarily impair the performance (Hu & Newell, 2011). Our results showed no significant difference of the $\text{Error}_{\text{ballistic}}$ between unilateral and bilateral conditions, suggesting limited influence of the excessive visual information on the performance. Nonetheless, the effects of visual feedback during unilateral and bilateral force control on the performance should also be further investigated.

Importantly, our results showed significant differences only in the Tonic task ($\text{Error}_{\text{tonic}}$ and $\text{CV}_{\text{tonic}}$) which required more feedback control compared to the Ballistic task, utilizing sensory information processing during task performance (Bastian, 2006; Shumway-Cook & Woollacott, 2017). In this study, the Tonic task required feedback control especially in the plateau phase to maintain the force output. During feedback control, force is adjusted to the desired level based on sensory feedback to modify the motor command (Desmurget & Grafton, 2000; Kawato, 1999). In addition, it has been suggested that fast movements do not solely depend on feedback control since significant time delays are required to process the sensory information (Bastian, 2006; Kawato, 1999). The involvement of sensory feedback from both the right and left limbs requires high attention. In addition, as mentioned before, bilateral force matching in this study would demand more complex visuomotor information processing compared to unilateral task because of the simultaneous bilateral control following the visual feedback of two produced force lines. Such dual-tasking effects, especially during the tasks utilizing feedback control, probably causes bilateral interference for precise force control. On the other hand, the Ballistic task possibly utilized feedforward control, which refers to control that occurs based on prediction using the efference copy of the motor command (Bastian, 2006; Shumway-Cook & Woollacott, 2017). In feedforward control, once participants learn the task, internal models are made to anticipate the appropriate force (Desmurget & Grafton, 2000; Grafton, Schmitt, Van Horn, & Diedrichsen, 2008). Thereafter, they can produce proper force based on the internal models, which allows precise responses. Consequently, due to the different control strategy between the Ballistic and Tonic tasks in our study, the bilateral condition seemed to induce attenuated performance during the Tonic task only. Moreover, previous studies demonstrated that there were different modulations of motor pathways between tonic and ballistic contraction (Keller et al., 2018; Taube et al., 2011). Therefore, it may be assumed that the task specific modulation of motor pathways could also affect performance.

For neurological and musculoskeletal rehabilitation, these findings suggest that bilateral force control tasks in the lower limbs, especially during tasks utilizing feedback control, are more challenging and require voluntary involvement compared to unilateral control, which is essential in rehabilitation (Carson, 2005). A recent review suggested that unilateral and bilateral training has different target goals (Lee, Kim, Park, & Park, 2017). Our findings seem to support the point. However, future studies to explore the different training effects between unilateral and bilateral force control in the lower limbs are required.

### 2.5.2. Leg dominance

Our results showed no significant effects of leg dominance on the force-matching tasks. We hypothesized that the dominant leg would have more accurate control and quicker responses compared to the non-dominant leg. However, this was not confirmed in this study. It has been suggested that the effect of limb dominance is task-specific (Yen et al., 2018). Skilled movements utilizing corticospinal connections showed more lateralization in foot performance than unskilled movements (Kalaycıoglu, Kara, Atbasoglu, & Nalcacı, 2008). Functional laterality between the dominant and non-dominant leg has been reported in tasks which demand dynamic motion such as kicking a ball (King & Wang, 2017), getting up from a chair (Bond, Cook, Swartz, & Laroche, 2017), and tracing a circle with one foot while standing (Wang & Newell, 2013). In contrast, a study showed that there are no significant differences between the legs in tasks such as isometric ankle force control (Yen et al., 2018), quiet bilateral standing (Wang & Newell, 2013), and single-leg standing (King & Wang, 2017). Therefore, our findings also suggest that limb dominance might not have influenced the static tasks.

Our results are contrary to those of studies that demonstrated clear handedness in the upper limbs (Goble & Brown, 2008; Li et al., 2015). This may be because functional differences clearly exist between the upper limbs and lower limbs. The underlying mechanism which controls the upper limbs may not be directly transferable to the lower limbs. In daily life, unilateral skill and the dexterous function of the hands are more prevalent during activities such as during reaching, grasping, and manipulating objects (Winstein, Wing, & Whitall, 2003). In contrast, the function of ankle dorsiflexors requires cyclic patterns, such as during gait, stepping, or swimming (Swinnen, 2002). A neuroimaging study showed that the degree of brain laterality was less in the lower limbs than in the upper limbs (Volz, Eickhoff, Pool, Fink, & Grefkes, 2015). Volz et al. (2015) showed using fMRI that hand movements increased brain laterality, while unilateral foot movements activated bilateral brain facilitation with less lateralization of brain activity. These results are likely to be associated with hand functions, which allow fine motor control in daily life (Volz et al., 2015). Overall, our study suggests that there is no difference between the dominant and non-dominant leg in the ability to control the static force of ankle dorsiflexion.

## 2.6. Conclusions

This study extends the understanding of the effects of simultaneous bilateral control with homologous lower limbs and leg dominance on static force control. While no influence of leg dominance was shown, bilateral force control affected performance, specifically in tasks requiring feedback control. Consequently, our results suggest that bilateral motor-tasking might influence force control performance, possibly because of the interhemispheric inhibitory interaction.

## 2.7. Acknowledgements

We would like to thank Kohtaroh Hagio for his technical support.

# Chapter 3.

## Changes in corticospinal excitability during bilateral and unilateral lower-limb force control tasks

The material presented in this chapter is currently under review in a peer-reviewed journal (first round of revisions):

Yamaguchi, A., Sasaki, A., Masugi Y., Milosevic, M.,& Nakazawa, K. (2019 submitted). Changes in corticospinal excitability during bilateral and unilateral lower-limb force control tasks. *Experimental Brain Research*, (EXBR-D-19-00612)

## 3.1. Abstract

Understanding of the modulation in the corticospinal circuits with regards to muscle contraction phases can provide important insight into motor control of the lower limbs. The objective of this study was to compare corticospinal excitability during: (1) unilateral and bilateral; and (2) ballistic and tonic ankle dorsiflexion force control. Fifteen healthy young adults (age: 25.2±2.8 years) participated in this study. Participants performed unilateral and bilateral isometric ankle dorsiflexion force control tasks, which required matching a visual target (10% of maximal effort) as quickly and precisely as possible during ballistic and tonic contractions. Transcranial magnetic stimulation (TMS) was applied over the primary motor cortex to elicit motor evoked potentials (MEPs) from the right tibialis anterior during: (i) pre-contraction phase; (ii) ascending contraction phase; (iii) plateau phase (tonic tasks only); and (iv) at rest (control). Peak-to-peak MEP amplitude was computed to compare corticospinal excitability during each experimental condition. MEP amplitudes significantly increased during unilateral contraction compared to bilateral contraction in the pre-contraction phase. There were no significant differences in the MEP amplitudes between the ballistic tasks and tonic tasks in any parts of the contraction phase. Although different strategies are required during ballistic and tonic contractions, the extent of corticospinal involvement appears to be similar. Furthermore, our results suggest that unilateral muscle contraction increases corticospinal excitability compared to bilateral contraction during movement preparation. It is assumed that intrainter hemispheric interaction seems to involve the motor control. However, this study investigated only corticospinal excitability that could not fully explain the underlying mechanisms. Further studies assessing the neurological involvement of the cortical interaction are required.

**Keywords**

Ankle dorsiflexion; corticospinal excitability; transcranial magnetic stimulation (TMS); force control; unilateral; bilateral.

# Chapter 4.

## Effects of neuromuscular electrical stimulation and voluntary ankle dorsiflexion on corticospinal excitability and motor performance

The material presented in this chapter is in preparation for publication:

Yamaguchi, A., Sasaki, A., Milosevic, M.,& Nakazawa, K. Effects of neuromuscular electrical stimulation on the time course of changes in corticospinal excitability and motor performance of ankle dorsiflexion.

## 4.1. Abstract

The aims of this study were to investigate: (1) time course of changes in corticospinal excitability during neuromuscular electrical stimulation (NMES) and voluntary contraction of the tibialis anterior (TA) muscle; and (2) their effects on motor performance. Ten healthy young adults performed three interventions on separate days: (i) NMES – the TA muscle was stimulated unilaterally with an intensity that produced 20% of isometric maximal voluntary contraction (MVC) force; (ii) NMES+VOL - participants maintained voluntary ankle dorsiflexor contraction at 10% of MVC force, while NMES aided in increasing the total force output to 20% of MVC force; and (iii) VOL - participants maintained voluntary ankle dorsiflexor contraction at 20% of MVC force. All interventions were applied intermittently: 5 sec ON / 20 sec OFF for a total of 16 min. The target force and cue for contraction were provided on a monitor. Corticospinal excitability was evaluated using motor evoked potentials (MEP) in the right TA and soleus muscles, which was elicited using transcranial magnetic stimulation (TMS) applied over the left (contralateral) primary motor cortex. Maximum motor response ($M_{max}$) was also evaluated by stimulating the common peroneal nerve. To evaluate motor performance, ankle dorsiflexion isometric force-matching task (a visual target set at 10% of MVC level which appeared for 1 sec) was used to evaluate error and reaction time before and for 30 min after each intervention. MEPs and $M_{max}$ were evaluated before, during (in NMES OFF periods), and for 30 min after each intervention. During NMES+VOL and VOL conditions, the

TA corticospinal excitability (MEP/$M_{max}$) was significantly facilitated immediately after starting the intervention (within 4 min) and maintained for the duration of the intervention, but the responses returned to baseline immediately after the intervention. However, no statistically significant effects were observed during NMES condition. In addition, there were no significant differences between interventions through the time course. NMES and NMES+VOL conditions did not affect the motor performance. Our findings suggest that afferent inputs from NMES combined with voluntary contraction rapidly facilitate neural modulation of activity-dependent synaptic plasticity, but the effects of short-term intervention may not have any aftereffects in the corticospinal excitability. Voluntary engagement during NMES could be an important element for inducing rapid corticospinal modulation.

**Keywords:** Corticospinal excitability; transcranial magnetic stimulation (TMS); neuromuscular electrical stimulation (NMES); ankle dorsiflexion.

# Chapter 5.

# General Discussion

## 5.1. Summary of Dissertation

The objectives of this dissertation were to investigate: (1) voluntary motor control of ankle dorsiflexors (Study 1; Chapter 2); (2) corticospinal excitability during force control of ankle dorsiflexors (Study 2; Chapter 3); and (3) the effects of NMES on voluntary motor control of the lower limb and the time course of corticospinal excitability changes (Study 3; Chapter 4).

The findings presented in this dissertation advance the fundamental understanding of the lower-limb neuromuscular system and the effects of NMES, which can contribute to development of NMES intervention in rehabilitation. The presented findings have expanded knowledge in particular : (1) the difference between unilateral and bilateral force control in the lower limb (Study 1; Chapter 2); (2) the corticospinal excitability during the lower-limb force control in the different contraction phases（Study 2; Chapter 3); and (3) neural modulation during NMES and motor control after NMES (Study 3; Chapter 4). The specific contributions of each study are discussed next.

## 5.2. Contributions to Knowledge

### 5.2.1. Effects of bilateral control and leg dominance – Study 1 (Chapter 2)

First, I have conducted a study that explored ankle dorsiflexion force control. This study investigated two different motor tasks: ballistic and tonic contractions, with bilateral, unilateral dominant leg and unilateral non-dominant leg. The results showed that bilateral condition resulted in larger error and more force fluctuations compared to unilateral condition only during tonic contraction. Furthermore, contrary to the upper limb, no significant differences between dominant and non-dominant leg were found.

Although a large number of studies have investigated the upper-limb force control, little has been reported about the lower-limb force control. Therefore, this study contributed to providing a better understanding of motor control in the lower limbs. Importantly, the interhemispheric inhibition was mainly discussed as underlying mechanism of the different performance between unilateral and bilateral motor control, suggesting that mutual interhemispheric inhibition might affect bilateral performance. However, because of the methodological limitation, this study could not reach the conclusion of the neural effect. Nevertheless, Study 1 provided the insight into the motor control in the lower limb. The work in Study 1 (Chapter 2) was published in the Journal of Motor Behavior (Yamaguchi et al., 2019).

### 5.2.2. Corticospinal excitability during lower-limb force control - Study 2 (Chapter 3)

In the second study, the underlying neurophysiological mechanisms of the force-control performance were investigated. Using TMS, corticospinal excitability was assessed and the findings presented clear evidence that unilateral control significantly facilitated corticospinal excitability to a larger extent compared to bilateral contraction, especially during the preparation phase. Although no significant differences of motor performance between dominant and mon-dominant leg were observed in the Study 1, it is not clear whether the results can be observed in the non-dominant leg because we investigated only dominant leg.

Previous studies have shown that performing motor tasks bilaterally leads to lower voluntary force output, larger error, or longer reaction times, compared to unilateral performance (i.e., bilateral deficit) (Ferbert et al., 1992; Otsuki, 1983; Vieluf, Godde, Reuter, & Voelcker-Rehage, 2013). Therefore, our findings can suggest that the neural modulation during movement preparation might have influence on the better performance during unilateral control. However, it is not clear whether the larger facilitation has relationship with better performance (i.e., less error and less fluctuation) during unilateral condition compared to bilateral condition observed in the Study 1. There were no significant differences of reaction time in both Ballistic and Tonic tasks between unilateral and bilateral condition. In addition, no significant differences of the error in the Ballistic task between the conditions. Therefore, it seems that corticospinal facilitation is higher during unilateral condition, but the early phase of contraction might be controlled similarly between two conditions. If there are significant differences of performance such as time-to-peak force and CV (during Ballistic task) between unilateral and bilateral condition in the Study 1, it can be suggested that corticospinal facilitation during movement preparation may affect the performance. In other words, mutual inhibition may have influence on the motor performance during bilateral task.

Consequently, further analysis is required to reach the conclusion.

Furthermore, during plateau phase in the Tonic task, no significant differences of MEP amplitudes were observed in the Study 2, while bilateral motor control more affected performance compared to unilateral control in the Study 1. Therefore, it seems that there is no correlation between MEP amplitudes and motor performance during plateau phase. Given the results, the possible mechanism under the affected control during bilateral condition seems to be dual-tasking effect. The Tonic task, especially during plateau phase requires sensory feedback from both the right and left limbs with high attention. In addition, bilateral force matching in this study would demand more complex visuomotor information processing compared to unilateral task because of the simultaneous bilateral control following the visual feedback of two produced force lines. Such information processing utilizing feedback control probably causes bilateral interference for precise force control If there was no visual feedback, participants would depend on proprioceptive information then there would be no significant differences of motor control between unilateral and bilateral conditions. In order to test hypothesis, further research is needed.

Another limitation is that the involvement of the cortical networks (inhibitory/ facilitatory interaction between hemispheres) was assumed, but this study only measured motor evoked potential (MEP) that could not fully explain the underlying neurophysiological mechanisms and reach the conclusion. Therefore, further study is required.

### 5.2.3. Effects of NMES – Study 3 (Chapter 4)

In the third study, I investigated effects of NMES on the time course of the corticospinal excitability and motor performance in the lower limb. Based on the former studies (Study 1 and 2 in Chapters 2 and 3), it can be understood that unilateral control would more facilitate corticospinal excitability during NMES interventions rather than bilateral control. Therefore, this study applied NMES only the dominant leg.

In addition, considering the use of NMES in clinical setting and to avoid muscle fatigue (See Chapter 1), the intervention was applied over a relatively short duration (16 min). The presented findings demonstrated that NMES combined with voluntary contraction caused acute increase of corticospinal excitability during the intervention, which was facilitated earlier compared to when the intervention involved only voluntary contractions. However, the effects were not shown when NMES was applied alone during the intervention. Significantly, the facilitation returned to baseline level immediately after the intervention. Furthermore, contrary to hypothesis, the force control was not significantly affected by short-term NMES interventions. These results suggest that voluntary engagement is an important factor to induce acute corticospinal excitability during NMES. Specifically, the state-dependent facilitation (i.e., interhemispheric facilitation changes depending on movement preparation (Reis et al., 2008) in the motor cortex seems to play an important role. The findings of Study 2 showed facilitation of the corticospinal excitability before the movement onset (movement preparation), which may have contributed to enhanced neural modulation during the combined intervention to induce LTP-like facilitation. However, contrary to previous studies, aftereffect neural modulation was not observed after any of the interventions in Study 3, which seems to be related to unaltered motor performance. This could be because homeostatic regulation might inhibit the long-lasting facilitation to avoid hyper activation in the neural circuits (Turrigiano & Nelson, 2004). On the other hand, studies using paired associative stimulation (PAS) technique have shown considerable effects on lasting facilitation of MEP without the homeostatic regulation (Mrachacz-Kersting & Stevenson, 2017; Roy, Norton, & Gorassini, 2007). It has been revealed that neural excitability changes (i.e., neural plasticity) induced by PAS follow spike-timing dependent rule that neural excitability in the cortical networks changes depending on the timing of the synchronous events between afferent inputs and inputs from cortical activation resulting in increased excitability (LTP-like facilitation) or depression of corticospinal circuits (Roy et al., 2007; Stefan, 2000). During combined voluntary and NMES intervention in our current study, LTP-like facilitation might be induced; however, there is a possibility that not only LTP- but also inhibitory-like mechanism might be induced during the intervention. This is because stimulation timing was not strictly managed in our protocol, resulting in little facilitation effects in MEP responses in some participants during the intervention. Therefore, correct and strict temporal synchronization with stimulation of the periphery (i.e., NMES followed by voluntary contraction) may be an important factor for inducing effects after the stimulation. However, further investigation will be required to fully confirm the speculation.

Since this study investigated only the dominant leg, it is unclear the effects of bilateral NMES interventions. In the Study 2, MEP amplitudes during pre-contraction phase in bilateral condition were significantly larger than control condition (rest). It is reported that the LTP-like facilitation depends on the activity of the brain state (Reis et al., 2008). There is therefore possibility that not only unilateral but also bilateral NMES intervention will facilitate corticospinal excitability during the short-term intervention. However, it has been suggested that one of the possible reasons of the bilateral deficit is muscle fatigue (Škarabot et al., 2016). As mentioned in the Chapter 1, fatigability is major issue of using NMES. Therefore, bilateral NMES intervention may induce muscle fatigue which would affect motor performance (Gueugnon, Torre, Mottet, & Bonnetblan, 2014).Furthermore, Ruddy et al. (2016) has suggested that sensory information from one limb arrives not only contralateral but also ipsilateral hemisphere which contributes to modulate the motor control. However, the authors demonstrated that this sensorimotor integration between hemisphere has been observed not in the lower limbs but in the upper limbs (Ruddy, Jaspers, Keller, & Wenderoth, 2016). Therefore, bilateral sensory input from NMES of the lower limbs might not induce the somatosensory integration between hemisphere, which would affect motor control. In order to test these hypotheses, investigation of the bilateral NMES effects on motor performance is required.

## 5.3. Clinical Contributions

Overall, this dissertation provided further insight into the lower-limb neuromuscular system and how combined use of NMES with voluntary contraction affects neural plasticity in the corticospinal tract. From clinical consideration, it is significant to take into account the effectiveness of training for restoration of function. The findings in the Study 2 and 3 suggest that unilateral training seems to enhance force control. On the other hand, bilateral training especially tonic tasks which require feedback strategy might induce more neural facilitation due to information processing. Therefore, it is important for therapists to consider the task-dependent effects of unilateral/bilateral training from neurological perspectives. Furthermore, the findings in the Study 3 suggest that the combined intervention of simple repeated stimulation and voluntary contraction during relatively short period can be applied patients in the early stage of rehabilitation when they cannot execute dynamic movements such as walking. Significantly, this dissertation strongly supports the importance of the active engagement during NMES. Enhancing neural plasticity is a key element in motor functional recovery. Therefore, appropriate setting of the parameters which more focuses on inducing aftereffects rather than immediate facilitation is required. This work provides additional support for

Hebbian synaptic strengthening, near-synchronization of afferent inputs from electrical stimulation and voluntary drive. Moreover, the findings underline the necessity of voluntary contraction with joint movements which increases proprioceptive information and active engagement of the users.

## 5.4. Limitation

It should be noted that this dissertation has some limitations. First, through this work, all results were from only healthy young adults. Hence, it is uncertain whether the findings can be found in the patient population such as stroke and spinal cord injury. Secondly, the investigation of the neural circuits (inhibition/excitation) in the cortex during unilateral and bilateral motor control (Chapter 2 and 3) were not addressed. To fully confirm the underlying mechanism of the motor control, further research is demanded (See Future Directions). In addition, since the third study evaluated force control ability after intervention, the association between motor performance and corticospinal excitability remains unclear. Therefore, it is required to assess the motor performance during the NMES intervention when corticospinal excitability is facilitated.

## 5.5. Future Directions

This dissertation provided neurophysiological and clinical contributions. However, it raises some questions. How will neural circuits be involved in the unilateral and bilateral performance? How can aftereffects be prolonged by NMES? To answer these questions, there are three directions in the future research. First, using paired-pulse protocols of TMS, the investigation of short latency intracortical inhibition and facilitation (Nakamura, Kitagawa, Kawaguchi, & Tsuji, 1997) and interhemispheric inhibition (Ferbert et al., 1992) would be useful to investigate the interaction within and between hemispheres. It would contribute to more deeply understanding of the neurophysiological mechanisms of the lower-limb motor control and the effects of NMES. Secondly, to identify the effective approach using electrical stimulation to promote neural plasticity would have a great impact on neurorehabilitation. Therefore, it is required to investigate the protocol optimizing effect of NMES, particularly the individual setting not only stimulation intensity but also timing, duration, and other parameters. Finally, inducing more active engagement and facilitating motivation to activate the brain state during NMES might be useful for neural plasticity. For example, playing game (Fu et al., 2019) or brain-machine-interface-controlled FES (McGie et al., 2015; Mrachacz-Kersting et al., 2017) is a possible approach. Moreover, multimodality intervention has been paid attention as advanced methods to enhance neural modulation (Stein et al., 2013). NMES combined with neuromodulation tool such as repetitive TMS (T. Yamaguchi et al., 2018) or transcranial direct current stimulation (Menezes et al., 2018) have shown the possibility to enhance noteworthy neural facilitation along with functional improvements. Since such multimodality has not been well established yet, it is highly recommended to provide evidence. Overall, neurorehabilitation has remarkably developed and new technology has been investigated broadly. Further research for evidence-based practice would have great benefits in people with neurological disorders.

## 5.6. Final Remarks

This work has explored the lower-limb neuromuscular control and the effects of NMES. Specifically, the findings in this project advanced the fundamental understanding of the lower-limb motor control and provided the significant considerations of using NMES. Consequently, the findings helped to expand knowledge of the neural modulation and deeply understand NMES. I hope the findings presented in this work will contribute to development of novel interventions using in rehabilitation for individuals with neurological impairments.

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