Short-interval intracortical inhibition influences cortical excitability to the biceps brachii during arm cycling, but is not different from an intensity-matched tonic contraction

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ABSTRACT

Rhythmic and alternating movements, such as walking and cycling tasks, are studied to better understand the mechanisms of neural control involved in human voluntary motor output. Researchers can apply this understanding to current rehabilitative techniques commonly used among those suffering from disuse, disease, and disability. Studies have shown that although locomotor tasks are largely spinally-mediated, supraspinal centres (*above* the level of the spinal cord) are also involved in generating these movements. The motor cortex, for example, is comprised of both facilitative and inhibitory circuits which produce an overall effect on neurons projecting to muscles, resulting in either increased or decreased excitability. The mechanisms responsible for these effects are complex, variable depending on type of motor task, and are not well understood. Therefore, the purpose of this study was to examine a mechanism of cortical inhibition during arm cycling, which is a model of locomotor output.

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AMT	active motor threshold
bEMG	background electromyography
CMEP	cervicomedullary-evoked potential
CS	conditioning stimulus
EMG	electromyography
FDI	first dorsal interosseous
$GABA_A$	gamma-aminobutyric acid
H-reflex	Hoffmann's reflex
ICF	intracortical inhibition
IHI	interhemispheric inhibition
ISI	interstimulus interval
I-wave	indirect wave
LICI	long-interval intracortical inhibition
MEP	motor evoked potential
M_{max}	maximal muscle-wave
ms	milliseconds
mV	millivolts
MVC	maximal voluntary contraction
M-wave	muscle-wave
PAR-Q+	Physical Activity Readiness Questionnaire
ppTMS	paired-pulse transcranial magnetic stimulation
RPM	revolutions per minute
SICF	short-interval intracortical facilitation
SICI	short-interval intracortical inhibition
TES	transcranial electrical stimulation
TMES	transmastoid electrical stimulation
TMS	transcranial magnetic stimulation
TS	test stimulus

μs	microseconds
μV	microvolts

1.4 INTRODUCTION

1.4.0 Overview

Locomotor tasks, such as walking and cycling, are generated and controlled by the central nervous system. Neural pathways which originate at the level of the brain and brainstem along with integrative circuits in the spinal cord work together to produce motor output. The *excitability* (i.e. capability of being activated) of descending pathways from supraspinal (above the level of the spinal cord) and spinally-located structures to muscle is studied to determine the activity of these neural pathways under various conditions to give insight into their neural control.

Neural excitability during locomotor tasks is often directly compared to that of tonic contractions, to determine if changes in excitability during cycling are due to locomotor-specific mechanisms, or due to muscle activation in general. We have previously shown that supraspinal excitability was higher during arm cycling in comparison to an intensity- and position-matched tonic contraction (Forman et al., 2014). The supraspinal mechanism responsible for increased excitability during arm cycling was unknown. Therefore, the current study examines a possible supraspinal mechanism influencing excitability during arm cycling.

1.4.1 Purpose and Hypotheses

Specifically, the purpose of this study was to assess the activity of a cortical inhibitory circuit (short-interval intracortical inhibition; SICI) during arm cycling and tonic contraction to determine: (1) if SICI is present during the locomotor task of arm cycling and (2) if it is different between cycling and tonic tasks. SICI may influence supraspinal

excitability during arm cycling, and could possibly be a *contributing factor* for our previous finding of higher supraspinal excitability during arm cycling when compared to an intensity- and position-matched tonic contraction. Thus, we hypothesized that: (1) SICI would be present during arm cycling and that (2) the amount of SICI would be less during arm cycling compared to a tonic contraction.

CHAPTER 2 REVIEW OF LITERATURE

2.0 Introduction

The corticospinal tract, which originates in the motor cortex and descends through the spinal cord, is examined to better understand excitability changes throughout this descending pathway largely responsible for motor output. The excitability of this pathway is studied using various stimulation techniques, including transcranial magnetic stimulation (TMS), which is applied to the head over the motor cortex during rest, tonic contractions, or locomotor tasks such as walking or cycling. TMS elicits a response in the muscle of interest which is recorded using electromyography (EMG) surface recordings and is referred to as a motor-evoked potential (MEP). Changes in excitability, seen as a change in MEP size, indicate that somewhere along the corticospinal pathway there was a change in excitability. This change, however, could be due to changes at the supraspinal or spinal level (Burke et al., 1993; Nielsen et al., 1993; 1995) and TMS-evoked MEPs in isolation do not indicate the 'site' responsible for the change in excitability (i.e. supraspinal or spinal).

To determine if changes in excitability occur in the spinal cord, the spinal cord itself can be stimulated via transmastoid electrical stimulation (TMES), which involves placing stimulation electrodes on the neck. Stimulation of the spinal cord via TMES elicits a response in the muscle of interest which is recorded using EMG and is referred to as a cervicomedullary-evoked potential (CMEP). Therefore, MEPs indicate excitability of the descending pathway from motor cortex through the spinal cord and CMEPs indicate excitability of the spinal cord. Deductive reasoning then allows one to determine whether

changes in overall corticospinal excitability (MEP amplitudes) were due to changes in supraspinal or spinal excitability. For example, changes in MEP amplitude with no concurrent change in CMEP amplitude could suggest that changes in excitability occurred *above* the level of the spinal cord. In other words, indicating that changes in excitability were of supraspinal origin.

Supraspinal excitability refers to the excitability of neural centres above the level of the spinal cord, including inhibitory and facilitative interneurons within the motor cortex which summate to produce an overall output of either an inhibitory or facilitated response to pyramidal cells and descending motor pathways (i.e. the corticospinal tract) (Chen et al., 1998; Chen 2004; Di Lazzaro et al., 1998; Kujirai et al., 1993; Ziemann et al., 1996). To date, studies have shown that the motor cortex and supraspinal centres play an important, phase-dependent role in locomotor tasks when compared to tonic contractions or rest (Capaday et al., 1999; Christensen et al., 2001; Forman et al., 2014; 2015; Petersen et al., 1998; 2001; Sidhu et al., 2012a; 2012b).

The activity of cortical interneurons, particularly during locomotor tasks, has received little attention which signifies a need for further research to determine the influence of cortical circuits on the production of locomotor tasks. The following review of literature will explore evidence of the cortical contributions to locomotor tasks obtained from studies using various TMS techniques and will discuss the current state of knowledge surrounding modulation of descending drive to arm and leg muscles during human motor output, with a focus on locomotor tasks (i.e. locomotion and cycling).

2.1 Assessing Spinal and Cortical Excitability: Transcranial Magnetic Stimulation

2.1.0 Single-Pulse Stimulation

TMS is a non-invasive method of stimulating the motor cortex and results in a MEP which is recorded from the muscle of interest. Single-pulse TMS activates inhibitory and facilitative interneurons which summate together and result in either excitation or inhibition of the pyramidal tract. Net facilitation results in descending excitation of action potentials through the corticospinal tract which produces a MEP, whereas net inhibition of the pyramidal tract produces no action potentials and does not result in a MEP (Burke et al., 1993; Nielsen et al., 1993; 1995). As such, single-pulse TMS represents the excitability of the descending pathway from brain to muscle.

TMS can be conducted using a circular coil (Figure 2.1), figure-of-eight coil (Figure 2.2), or double-cone coil (Figure 2.3). Circular coils tend to have a diffuse effect; any nerve passing under the coil has an equal chance of being stimulated. These coils are relatively simple to use as placement does not have to be precise, and easily targets the upper limb area of the motor homunculus (Temesi 2013). Figure-of-eight coils are comprised of two circular coils with the electrical field greatest in the middle intersecting point of the two coil windings. This method is more precise and can be used to target somewhat more specific areas of the motor cortex (Temesi 2013). The double-cone coil conforms to the shape of the head and provides stimulation with the greatest amount of precision and depth. This is best used for stimulating the lower limbs, which are represented in the motor homunculus in a smaller, deeper portion of the motor cortex (Temesi 2013).

2.1.1 Paired-Pulse Stimulation

Though many studies use single-pulse TMS to assess corticospinal excitability, a growing number of studies also use paired-pulse TMS (ppTMS) as a reliable method of assessing cortical excitability (Chen et al., 1998; Chen 2004; Di Lazzaro et al., 1998; Kujirai et al., 1993; Ziemann et al., 1996). This stimulation technique pairs two stimulations at a predetermined interstimulus interval (ISI); a *subthreshold* conditioning stimulus (CS) is typically followed by a *suprathreshold* test stimulus (TS). Threshold refers to the intensity at which stimulation results in activation of cortical interneurons that project to the corticospinal tract, which then sends signals through the spinal cord to muscle and results in a recordable MEP (e.g. ≥ 50 μV at rest). The subthreshold CS activates cortical interneurons but is below the threshold required to activate the corticospinal tract and does not result in a MEP. A suprathreshold TS is above the threshold required to activate the corticospinal tract, and therefore will produce a MEP. When paired together, a CS will activate interneurons in the motor cortex and a TS will produce a MEP, which will be modulated by the activated interneurons activated via the CS. In this way, ppTMS shows the effect that activation of cortical interneurons, whether they be inhibitory or facilitative, has on MEPs.

Previous work has shown that paired-pulse TMS using a short ISI (~1 – 5 ms) activates *inhibitory* interneurons in the motor cortex which synapse onto the corticospinal tract and present as a decrease in conditioned MEP sizes in the muscle of interest (Kujirai et al., 1993; Ortu et al., 2008; Roshan et al., 2003; Sidhu et al., 2012c). This type of inhibition is referred to as SICI. Mechanistically, at this ISI, the subthreshold CS activates

the low threshold intracortical inhibitory interneurons without reaching the pyramidal tract axons, and the following suprathreshold TS reveals the effect of the inhibitory interneurons through a change in excitability of the motor cortex, when compared to an unconditioned TS. Thus, ppTMS at these ISIs result in MEPs that reflect the activity of SICI.

Single-pulse TMS activates a volley of excitation through the corticospinal tract resulting in several indirect waves (I-waves) that have been previously measured using spinal epidural recordings. Based on these recordings, SICI is known to reflect inhibition on late I-waves specifically, and appears to have two phases of inhibition, between 1 – 2 ms and 2 – 5 ms (Fisher et al., 2002). Inhibition resulting from an ISI of 1.1 – 1.5 ms is thought to be mediated by refractory periods of action potentials (Ortu et al., 2008) while SICI resulting from an ISI of 2 – 5 ms is suggested to reflect activation of $GABA_A$ receptors in the brain. The latter is based on the observation that pharmacological agents which enhance $GABA_A$ activity also increase SICI in both human and animal studies (Ziemann et al., 1996).

2.2 Cortical Involvement During Rhythmic and Alternating Motor Outputs

Locomotion is initiated via descending commands arising from supraspinal structures. Descending commands activate spinally located interneuronal circuits, referred to as central pattern generators (CPGs), capable of producing the characteristic rhythmic and alternating pattern of muscle activation of locomotion (Graham-Brown, 1911; 1912; Grillner & Wallén, 1985; Grillner & Zangger, 1975; Rossignol, 1996). Evidence for CPG-mediated motor outputs in animal models is quite extensive and direct, that is, decerebrate

animals are capable of locomotion in the absence of either or both of descending and sensory input. In humans, indirect evidence suggests that humans also have spinal CPGs for locomotor outputs such as arm and leg cycling and of course, locomotion itself (Capaday et al., 1999; Carroll et al., 2006; Pyndt & Nielsen, 2003; Zehr et al., 2004). As opposed to quadrupeds, humans require ongoing descending drive to engage in locomotor outputs. Cortical involvement in locomotor output has been previously investigated by using a subthreshold conditioning stimulus (i.e. via TMS) and studying its effect on either a secondary stimulation (i.e. H-reflex stimulation, ppTMS) or on the ongoing muscle activity (i.e. EMG). The following section discusses the respective findings of cortical involvement via these methodologies, and outlines the conclusions drawn by each.

Rhythmic and alternating motor outputs in the following section include walking, as well as leg and arm cycling, each of which has particular phases throughout their respective cycles. Corticospinal excitability is known to be phase-dependent (Capaday et al., Christensen et al., 2001; Forman et al., 2014; 2015; Petersen et al., 1998; 2001; Sidhu et al., 2012a; 2012b), so defining the phases of each rhythmic and alternating motor output is important for effective interpretation of results. The phases of walking are made relative to a dominant leg, and include both stance and swing phases. 'Swing' phases include early, late, and mid-swing when the limb is not in contact with the ground as opposed to the 'stance' phase, which includes early (heel strike), late (toe off), and mid-stance when the foot is flat on the ground (Figure 2.4).

Leg cycling is made relative to the dominant leg while the different phases, flexion and extension, typically refer to the knee joint. This can also be described as downstroke (from top dead centre of crank angle to bottom dead centre of crank angle) and upstroke

(from bottom dead centre of crank angle to top dead centre of crank angle); when the knee is extending out and down to create power and push the pedals, and when the knee is flexing and pulling up in a recovery motion, respectively (Figure 2.4). Similarly, arm cycling can be broken into distinct phases which can be described with respect to flexion and extension of the elbow joint, as is currently done in our lab. This motion can be described by making the crank angles during arm cycling relative to a clock face, with top dead centre represented as 12 o'clock and bottom dead centre as 6 o'clock (Figure 2.5). Thus, flexion about the elbow is the movement from 3 to 9 o'clock, and extension is the movement from 9 to 3 o'clock.

2.2.0 Evidence of Cortical Involvement: Corticospinal Excitability and H-reflex Studies

The use of TMS in conjunction with H-reflex can be used to measure corticospinal excitability and presynaptic inhibition within the spinal cord, respectively. When combined and used in a 'paired-pulse' paradigm, one can examine the contribution of the motor cortex to ongoing motor output by assessing the influence of subthreshold TMS on H-reflex amplitude (Burke et al., 1984; Cowan et al., 1986; Iles & Pisini, 1992; Nielsen et al., 1993). Additionally, transcranial electrical stimulation (TES) is believed to activate the corticospinal axon directly and therefore to be a measure of the corticospinal tract excitability which is not affected by cortical excitation or inhibition (Burke et al., 1990; 1994; Edgley et al., 1990; 1997; Nielsen et al., 1995; Petersen et al., 1998). The use of these stimulation techniques led to early evidence that the motor cortex was involved in rhythmic and alternating motor outputs, thought to be largely mediated via the spinal CPG.

Petersen et al. (1998) investigated the effect of subthreshold TMS on the soleus H-reflex during walking, quiet standing, an intensity-matched tonic plantar flexion task, and dynamic plantar flexion. Using a TMS intensity below the threshold of producing a discernable MEP (conditioning stimulus) and an H-reflex above the threshold to produce an M-wave (test stimulus) 1-5 ms later, the researchers were able to show significant TMS-evoked facilitation of the H-reflex during the stance phase of walking and dynamic plantar flexion and little to no facilitation during standing and tonic contractions (Figure 2.6). Additionally, the short-latency facilitation found during walking was produced at a lower TMS intensity than during quiet standing, indicating a lower threshold for excitation during walking. When TES was applied to the same conditions of walking and rest there was no difference in stimulation intensities or threshold, suggesting that the excitability of the subcortical portion of the corticospinal tract was not altered. Since TMS responses are influenced by excitability of cortical cells and TES responses are not, the authors postulate that the increase in excitability in TMS responses only shown through a decreased threshold during walking when compared to tonic contractions must be influenced by cortical interneuron excitability. Thus, the H-reflex facilitation shown during walking and dynamic motor outputs was likely indicative of increased excitability of the motor cortex.

Similarly, TMS has been used to assess MEPs from the soleus and tibialis anterior during walking as compared to tonic contractions. Specifically, Capaday et al. (1999) investigated the early swing and early stance phases of walking which were compared to intensity-matched tonic contractions, during which the subjects contracted isometrically to produce EMG activity comparable to the walking trials. The position of the leg during tonic contractions was representative of early swing phase with the participant seated. On

average, soleus MEPs were reduced by 26% during the stance phase of walking as compared with tonic contraction, while tibialis anterior MEPs were enhanced in comparison with tonic plantar flexion contractions. These results indicate the tibialis anterior muscle received more supraspinal input during walking, which shows modulation of excitability to be dependent on the muscle of interest and task. This may also represent differences in the neural connections from the motor cortex to various muscle group motor units during tasks, given that the tibialis anterior motoneurone pool has been suggested to have more direct monosynaptic connections from the motor cortex than the soleus (Brouwer & Ashby, 1990).

Following these studies, Christensen et al. (2001) used similar techniques to investigate the tibialis anterior muscle during walking. This group also found subthreshold TMS to facilitate the H-reflex during the stance phase of walking but no facilitation following TES. However, they showed that facilitation via TES *could* be elicited if stimulation intensity was increased substantially, showing TES thresholds for facilitation to be comparable to those seen previously by Petersen et al. (1998), furthering the evidence that TES activates the corticospinal axon directly. The facilitation of H-reflex following subthreshold TMS, with no effect following TES, suggests increased excitability of the motor cortex. Pyndt & Nielsen (2003) also investigated H-reflex conditioning of both the soleus and tibialis anterior muscles using TMS and expanded upon previous research to include eight different crank angles during *leg cycling*. H-reflex amplitude was facilitated with subthreshold TMS during cycling as compared to tonic contractions, suggesting an increase in cortical excitability during cycling. MEPs from the soleus muscle were found to be facilitated specifically during the early downstroke of leg movement and depressed

during upstroke. The results suggest that the corticospinal tract may have the most influence during early downstroke of the locomotor task. These findings further enhance the evidence of motor cortex contribution during walking as well as phase- and task-dependences.

Somewhat conflicting results using TMS and H-reflex conditioning have been shown in the upper limbs during *arm cycling* when compared with studies conducted on the lower limbs. Carroll et al. (2006) showed MEPs and conditioned H-reflex responses using subthreshold TMS to be depressed during the flexion phase of arm cycling in the flexor carpi radialis as compared to tonic contraction. Additionally, facilitation of the H-reflex using subthreshold TMS was found during tonic contractions and not during arm cycling, suggesting that input from the motor cortex was greater during the tonic contraction. These results are contradictory to what was shown to be previously found in the lower limbs (Capaday et al., 1999; Christensen et al., 2001; Petersen et al., 1998; Pyndt & Nielsen, 2003). The authors suggest subcortical systems must contribute to control of rhythmic arm movement. However, the flexor carpi radialis, though involved in the rhythmic and alternating motor output of arm cycling, does not demonstrate strong phase-dependent activation likely due to the fact that it is more of a wrist stabilizer in this particular movement. This may partially account of the differing results from those found previously, in which the muscles examined during locomotion and cycling demonstrated strong phase-dependent activation.

2.2.1 Evidence of Cortical Involvement: EMG Suppression

Stimulation of the motor cortex through subthreshold TMS is thought to activate excitatory and inhibitory interneurons, however, the stimulation intensity is too low to excite the corticospinal tract and cause a MEP response in muscle tissue (Davey et al., 1994; Petersen et al., 2001; Sidhu et al., 2012a). Therefore, a change in the EMG recordings seen as either an enhancement or depression of ongoing EMG trace following subthreshold TMS is a reflection of cortical excitation or inhibition, and not of the corticospinal tract (Di Lazzaro et al., 1998). The first evidence of cortical interneuron activity during both relaxed and active tasks showed EMG suppression following subthreshold TMS (Davey et al., 1994). The authors successfully revealed the motor cortex to have an indirect influence over voluntary muscle activity and suggested that TMS evokes excitation and inhibition via interneurons which ultimately affect the corticospinal output to the muscle (Davey et al., 1994).

Petersen et al. (2001) extended this area of research to study the activity of cortical interneurons during locomotion. Subthreshold TMS applied during walking resulted in suppression of ongoing EMG activity projecting to the tibialis anterior and soleus muscles. As TMS intensity reached threshold and above, a MEP was produced and EMG was facilitated. Alternatively, subthreshold TES resulted in facilitation of ongoing EMG activity (Petersen et al., 2001). This study confirms and expands on the findings from Davey et al. (1994) to show that the mechanism of EMG suppression is likely cortical in nature. The suppression observed was likely due to activation of low-threshold inhibitory

interneurons projecting to cortical motoneurones, thus reducing overall descending excitation of the motoneurone pools (Petersen et al., 2001).

This technique has been used more recently to investigate the cortical involvement in multiple leg muscles (i.e. rectus femoris, vastus lateralis, vastus medialis, biceps femoris, tibialis anterior, and soleus) during leg cycling when compared to a matched tonic contraction (Sidhu et al., 2012a). Sidhu and colleagues (2012a) reported that EMG suppression was elicited by subthreshold TMS in approximately half the subjects and muscles during the active phase (i.e. highest amount of average EMG activity recorded during cycling from the vastus lateralis muscle) of cycling. When present, EMG suppression occurred simultaneously in agonist-antagonist muscle pairs, which is a finding inconsistent with inhibition found from spinal reciprocal inhibitory centres (Table 2.1). This furthers the mounting evidence of cortical cells playing a direct role in rhythmic motor output. The authors argue that a lack of EMG suppression in some subjects might reflect a similar degree of cortical threshold for activation of inhibitory and excitatory intracortical interneurons, resulting in a 'cancelling out' effect of both suppression and facilitation. Additionally, EMG suppression was observed to be greater during tonic contractions than cycling. Therefore, subthreshold TMS activated a greater portion of inhibitory circuits at the cortical level which lead to greater suppression of EMG during the tonic contraction, in comparison to the leg cycling conditions. This finding is similar to previous studies (Capaday et al., 1999; Carroll et al., 2006), and suggests that the extent of cortical involvement may be more pronounced during tonic contractions, given the threshold differences for activation of these inhibitory circuits between tasks. This difference in cortical involvement may be a result of varying levels of voluntary activation, relative

intensity, afferent sensory feedback, or position differences between the two tasks, and is discussed further in the following sections of this review. It could also be a result of CPG activation during locomotor outputs which would require less cortical input than a tonic contraction to maintain the ongoing muscle activity.

2.2.2 Modulation of Corticospinal and Spinal Excitability During Cycling and Tonic Contractions

Pioneered by the Gandevia-led research group, *combining* TMS (measure of corticospinal excitability) and TMES (measure of spinal excitability) provides an indirect measure of supraspinal activity. By comparing CMEP amplitudes (via TMES) to MEP amplitudes (via TMS), one can deduce whether changes in excitability originate largely from either spinal or supraspinal centres, respectively. This technique is used to study supraspinal excitability during tonic contractions and locomotor tasks, and can reveal both task- and intensity-dependent differences.

During tonic contraction, research of this type has shown supraspinal excitability to be intensity-dependent (Martin et al., 2006; Oya et al., 2008; Pearcey et al., 2014; Philpott et al., 2014). Responses from muscles of both the upper and lower limbs have shown that MEPs and CMEPs are both modulated similarly and show increases in response until a plateau or decrease occurs between 50-75% MVC (Martin et al., 2006; Oya et al., 2008), indicating the increase in excitability to be spinally mediated. When factors such as resistance training and arm dominance are considered, MEPs tend to be lower in contractions below 50% MVC with no change in CMEP response, while in contractions

greater than 50% MVC, CMEPs tend to increase with no change in MEP response (Pearcey et al., 2014; Philpott et al., 2014). These studies suggest that the motor cortex may have more influence over motor unit output during submaximal contractions, while spinally-driven motor unit firing frequency and recruitment may dominate the motor output response during maximal contractions.

Comparison of MEPs and CMEPs have also been made during a locomotor task. Sidhu and colleagues (2012a) showed MEP and CMEP amplitudes to modulate similarly throughout leg cycling in the rectus femoris, vastus lateralis, and biceps femoris muscles, with larger amplitudes preceding the main EMG burst relative to the vastus lateralis. Additionally, there were possible differences in the degree to which normalized MEP and CMEP responses were facilitated prior to the EMG burst, which may reflect a small increase in cortical excitability prior to the maximal muscle activation. The authors state that phase-dependent changes appear to be driven mainly by changes at the spinal level, however cortical influences appear to be directly involved in the generation of cycling.

Following this study, Forman et al. (2014) used TMS and TMES to investigate supraspinal factors affecting the upper limbs during cycling and during intensity-matched tonic contractions at different positions of arm cycling. MEPs were found to be larger at the 3 and 6 o'clock positions (onset of flexion and mid-elbow flexion) as compared to tonic contractions, and CMEPs were found to be larger at the 3 o'clock position only. This study confirms an increase in supraspinal excitability during the active flexion phase of arm cycling, an increase in spinal motoneurone excitability at the onset of flexion, and supraspinal and spinal excitability to be phase- and task-dependent.

Similarly, this technique has been used to further our understanding of supraspinal activity throughout a locomotor task. Sidhu et al. (2012b) compared MEPs and CMEPs in the vastus lateralis muscle during a fatiguing cycling protocol to failure. Results showed no significant changes to MEPs or CMEPs throughout the exercise, however there was a possible tendency toward reduced cortical excitability during steady state cycling and task failure, based on normalized MEP and CMEP amplitudes which showed CMEPs remained unchanged while MEPs were significantly reduced. The authors suggest that the lack of increase in MEP amplitude showing cortical influence during this exercise may be due to increased intracortical inhibitory mechanisms.

To understand both cadence- and phase-dependent supraspinal changes in excitability, Forman et al. (2015) compared MEPs to CMEPs of the dominant biceps brachii muscle during various cadences of arm cycling during the flexion and extension phases. Results showed that during the flexion phase MEPs and CMEPs both increased with increased cadence. During the extension phase, the biceps brachii showed a similar increase in MEP amplitude but a *decrease* in CMEP amplitude with increased cadence (Figure 2.7). These results indicate that cadence- and phase-dependent changes are shown to occur during arm cycling. Within the flexion phase of arm cycling, changes in excitability with an increase in cadence (i.e. increase in muscle activity) are likely modulated via spinal centres. During the extension phase, however, changes in excitability appear to be mediated via supraspinal factors. Thus, although spinal excitability is largely responsible for phase-dependent changes during arm cycling, supraspinal excitability is also present, particularly during the extension phase of arm cycling (Forman et al., 2015).

These studies demonstrate that during a locomotor task, some phase-dependent changes in excitability are due to changes at the supraspinal level. These changes in supraspinal excitability can likely be explained by increases in cortical inhibitory interneuron activity, decreases in excitation, or both. To advance our knowledge of locomotor circuitry, cortical inhibition and facilitation can be studied to give insight into the mechanisms underlying the cortical influence on locomotor tasks.

2.3 Short-Interval Intracortical Inhibition During Motor Output

2.3.0 SICI During Rest and Tonic Contraction

SICI is recognized to be cortical in nature based on studies which compare trans-synaptic magnetic stimulation responses with direct electric stimulation of the corticospinal tract (Kujirai et al., 1993). For example, using ppTMS, conditioned MEPs measured from arm muscles have shown significant inhibition using an ISI of 1 – 5 ms and conditioning stimulation intensity of ~70 – 90% of active motor threshold (AMT), which is defined as seeing a discernable MEP in 50 – 60% of trials. Alternatively, electrical brain stimulation (such as through the TES technique) directly activates the corticospinal neurons and does not result in a decrease in MEP amplitude. Studies which examine SICI via ppTMS during rest and tonic contractions can provide insight into the intensity- and task-dependent characteristics of SICI.

Modulation of descending drive to arm muscles as a result of SICI has been investigated during both resting and active conditions. Inhibition has been found to be prominent in the first dorsal interosseous (FDI) muscle and biceps brachii while the muscles

are completely relaxed, however this inhibition is less pronounced during tonic contractions (Ortu et al., 2008; Hunter et al., 2016; Reynolds & Ashby, 1999; Ridding et al., 1995; Kujirai et al., 1993). For example, Ortu et al (2008) studied SICI and SICF (short-interval intracortical *facilitation*) in the resting and active (during tonic contraction) FDI muscle. SICF was only found during muscle activation and not during rest, whereas SICI was found in both conditions, and was highest during rest. Additionally, in cases which determine both resting and active thresholds separately, active conditions generally require a lower conditioning stimulus intensity (~70 – 80% of AMT) than the resting conditions (~80 – 95% of AMT). In each case, voluntary activation during a tonic contraction results in significantly less inhibition than during resting conditions. The decrease in observed inhibition during voluntary activation may therefore be due in part to the superimposition of excitatory circuits during muscle activation. Less inhibition during voluntary muscle activation may also be due to neural control 'fractionation', which reduces inhibition to the agonist muscles while maintaining inhibition in the non-contracting antagonist muscles (Ortu et al., 2008).

During tonic contraction, a conditioning stimulus reduces the conditioned MEP size maximally at a lower CS intensity, on average 70 – 80% of AMT, and less so at higher CS intensity of ~90% of AMT (Reynolds & Ashby, 1999; Ridding et al., 1995; Kujirai et al., 1993). Ortu et al (2008) investigated SICI using conditioning stimuli of 60 – 90% of AMT in the active FDI and found maximum inhibition at 70%. Additionally, they studied SICF and found facilitation of MEPs to only occur at a conditioning stimulus of 90% of AMT. This suggests that at higher conditioning stimulus levels (≥80% of AMT) in an active

muscle, facilitative interneuron mechanisms are recruited at the same time as SICI, thereby reduced the amount of observed inhibition.

Although modulation of SICI during locomotor and tonic tasks has not yet been directly compared, intracortical inhibitory neurons appear to be activated in a task-dependent manner within tonic tasks alone. Opie and colleagues (2014) found SICI modulation to be different between a finger abduction task and a finger-thumb grip task. Although both were tonic contractions, the grip task involving synergistic contractions resulted in decreased amounts of SICI relative to the abduction task. The idea that SICI is task-dependent based on coactivation and varied patterns of muscle activation creates expectation that there may be task-dependent differences seen between cycling and tonic contractions. This is particularly interesting because like the grip task, arm cycling involves many muscles working in a synergistic and co-ordinated manner to produce the motor output.

Intracortical inhibitory neurons appear to be activated in an intensity-dependent manner as demonstrated by previous studies which show SICI decreases during tonic contraction (Reynolds & Ashby, 1999; Ridding et al., 1995; Soto et al., 2006) and increases with relaxation (Buccolieri et al., 2004; Ortu et al., 2008). Additionally, an increase in intensity (i.e. voluntary activation), during tonic contractions has been shown to reduce the amount of SICI (Hess et al., 1999; Ortu et al., 2008).

2.3.1 SICI During Locomotor Tasks

The first study to investigate SICI during locomotion investigated responses from the posterior deltoid muscle which exhibit rhythmic and alternating swinging patterns during an ongoing walking task (Barthelemy & Nielsen, 2010). They showed SICI was the smallest during activation of the posterior deltoid muscle and was largest during the deactivation phase, further demonstrating SICI to characteristically increase during tasks with less muscle activity (i.e. intensity). A recent study examined changes in SICI in the extensor carpi radialis muscles of the right arm after lower limb aerobic exercise (i.e. leg cycling) and showed that SICI was significantly decreased following a session of moderate-intensity activity (Singh et al., 2014), which indicates that modulation of intracortical excitability is not limited to the exercised muscle. Both studies indicate that during locomotor tasks cortical inhibitory circuits are active and appear to have widespread influence on cortical excitability.

The only study that has investigated SICI from a prime muscle mover during a locomotor task explored the presence of SICI in the leg muscles during the activation and deactivation phases of cycling and also during a tonic contraction (Sidhu et al., 2012c). In all three conditions SICI was examined at the same intensity of motor output as determined via matched EMG levels. They showed that SICI was present in tonic contractions using a CS of 90% AMT and during the deactivation phase of cycling using a CS of 70% AMT (Figure 2.8). SICI was not present during the activation phase of cycling, suggesting that there was a phasic modulation of intracortical inhibitory pathways affecting corticospinal tract excitability. Importantly, though they also elicited SICI during tonic contraction of the

same musculature, the two motor outputs (i.e. cycling and tonic contraction) were not directly compared. Thus, it is unclear whether the degree of SICI was task-dependent.

These studies provide evidence of intracortical inhibitory interneurons as a significant mechanism contributing to phase- and task-dependent changes in supraspinal excitability during locomotor output. Also revealed is a gap in the literature, in which SICI has not been assessed during arm cycling, nor has SICI during rhythmic and alternating motor output been directly compared to intensity- and position-matched tonic contractions, all which are factors known to have different effects on corticospinal excitability.

2.4 Conclusion

Corticospinal excitability is phase- and task-dependent, as seen from studies investigating corticospinal activity during different stages of locomotion as well as those which compare a locomotion task to rest or a tonic contraction. Supraspinal excitability has been measured in studies using TMS and H-reflex (Capaday et al., 1999; Carroll et al., 2006; Christensen et al., 2001; Petersen et al., 1998; Pyndt & Nielsen, 2003), subthreshold TMS effects on EMG suppression (Davey et al 1994; Petersen et al., 2001; Sidhu et al., 2012a), and combinations of TMS and TMES (Forman et al., 2014; 2015; Sidhu et al., 2012a; 2012b). Supraspinal excitability may also be phase- and task-dependent, as suggested by differences found during different locomotor phases and between tasks (Forman et al., 2014; 2015; Sidhu et al., 2012a; 2012b, 2012c).

Cortical cells have been directly measured during an active locomotor task in few previous studies (Barthelemy & Nielsen, 2010; Sidhu et al., 2012c**,** Singh et al., 2014), none of which investigate the activity of the brain during arm cycling. Intracortical inhibition and facilitation circuits have been studied primarily during rest and tonic contractions, and results show that voluntary drive decreases inhibition (Ortu et al., 2008). This reveals an important gap in the literature surrounding the possible changes in cortical excitability during the spinally-mediated voluntary task of arm cycling. Further research could help to understand the mechanisms of cortical excitability during locomotor tasks be examining intracortical inhibitory networks.

2.5 Table & Figure Legend

Table 2.1: EMG suppression in lower leg muscles during leg cycling obtained with subthreshold TMS (Sidhu et al., 2012a).

Figure 2.1: Magnetic field produced by a circular coil. A) The lines of force produced as current flows through the windings of a circular coil. B) The magnetic field strength from a 90-mm circular coil. The magnetic field strength is greatest underneath the coil winding and decreases towards the centre or further away from the coil (Temesi 2013).

Figure 2.2: Magnetic field produced by a 70 mm figure-of-eight coil. The magnetic strength is greatest where the coil windings meet (Temesi 2013).

Figure 2.3: Magnetic field produced by a double-cone coil. The lines indicate the force of the magnetic field produced by the double-cone coil. The magnetic field strength is greatest on the underside where the coil windings meet (Temesi 2013).

Figure 2.4: Functional phases of walking gait and leg cycling with respect to the right limb. Movements are described by recovery-power for leg cycling and swing-stance for walking. Grey and the black blocks or arrows indicate the flexion and extension phases, respectively (Zehr et al., 2007).

Figure 2.5: Phases of arm cycling with respect to the elbow joint. The description of flexion and extension movements about the elbow are shown as positions relative to a clock face (Zehr et al., 2004).

Figure 2.6: Size of conditioned reflex during stance, tonic, dynamic, and walking tasks. Walk and dynamic conditions show significant large short-latency facilitation (2 – 4ms) as compared to rest (quiet standing). Standing and tonic conditions show large long-latency facilitation (Petersen et al., 1998).

Figure 2.7: Average MEP and CMEP amplitude at each phase and cadence. Average MEP (A and C) responses increase as cadence increases for both positions. Average CMEP (B and D) responses increase as cadence increases for the active 6 o'clock phase, and decreases for the inactive 12 o'clock phase (Forman et al., 2015).

Figure 2.8: SICI % across four CS intensities and muscle groups in static and cycling conditions. Inhibition occurred significantly during the deactivation phase using CS of 70% AMT, and during the static contractions using CS of 90% AMT (Sidhu et al., 2012c).

Table 2.1

Muscle and Percentage of Subjects in whom Suppression Was Seen	Latency of Facilitation, ms	Latency of Suppression, ms	Duration of Suppression, ms	Amount of Suppression (%)
VL (68)	21.4 ± 0.7	30.2 ± 1.3	6.0 ± 0.3	13.5 ± 1.4
RF (47)	20.0 ± 0.3	28.4 ± 0.9	6.4 ± 0.3	12.8 ± 1.1
VM (52)	21.8 ± 0.4	28.9 ± 0.8	8.0 ± 0.8	11.5 ± 1.5
BF (74)	21.3 ± 0.3	31.2 ± 1.4	7.4 ± 0.5	16.1 ± 2.0
TA (52)	27.0 ± 0.5	37.5 ± 0.8	7.1 ± 0.5	13.9 ± 1.5
SOL (42)	30.0 ± 0.5	43.7 ± 1.0	6.9 ± 0.8	16.9 ± 3.2

Values are means ± SE. Summary of latencies (facilitation and inhibition; ms), duration (ms), and amount of inhibition (percentage; %) in the muscle groups investigated (i.e., VL, RF, VM, BF, TA, SOL). n = number of subjects demonstrating inhibition out of total 19 subjects tested.

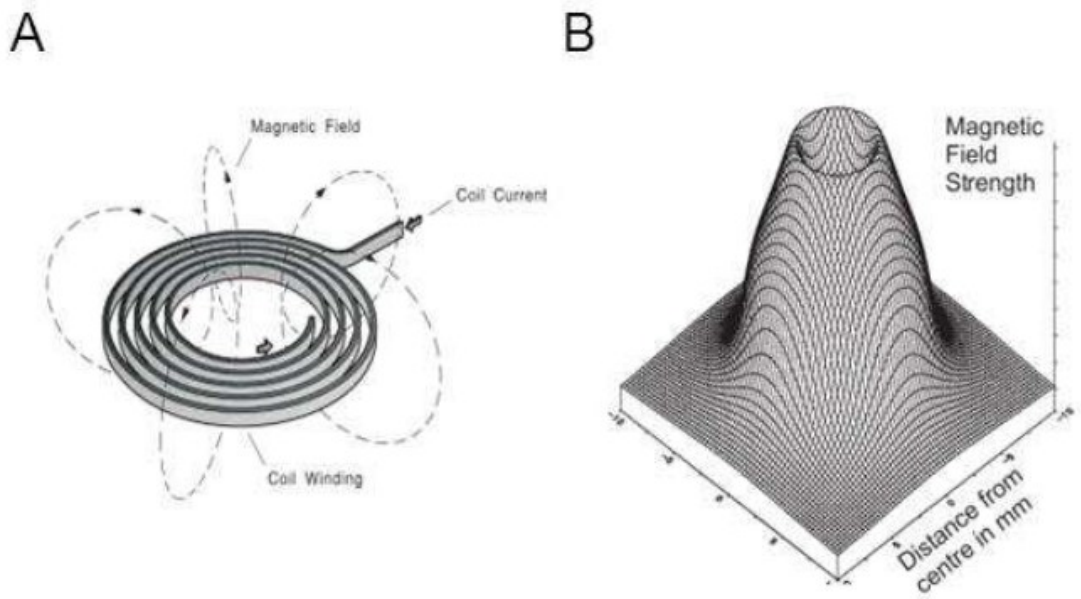
A
B
Magnetic Field
Coil Current
Coil Winding
Magnetic
Field
Strength
Distance from
centre in mm

Figure 2.1

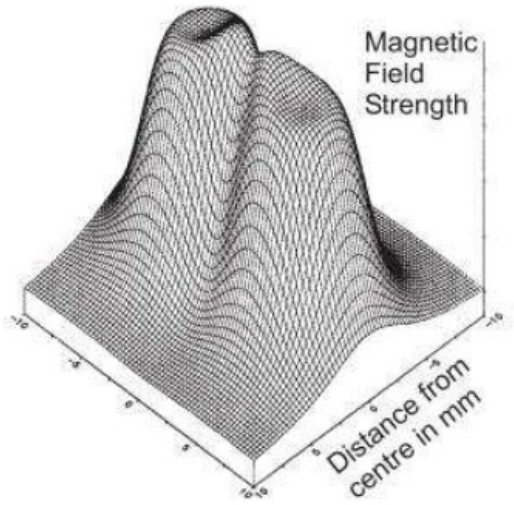

Figure 2.2

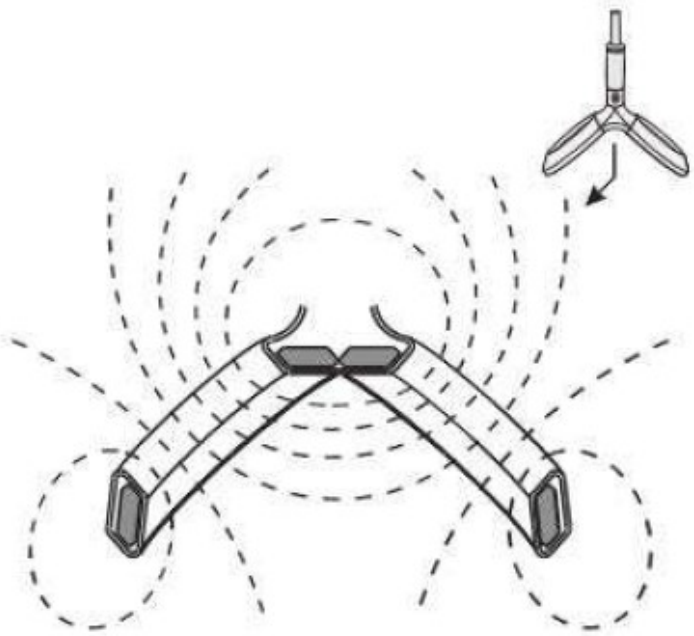

Figure 2.3

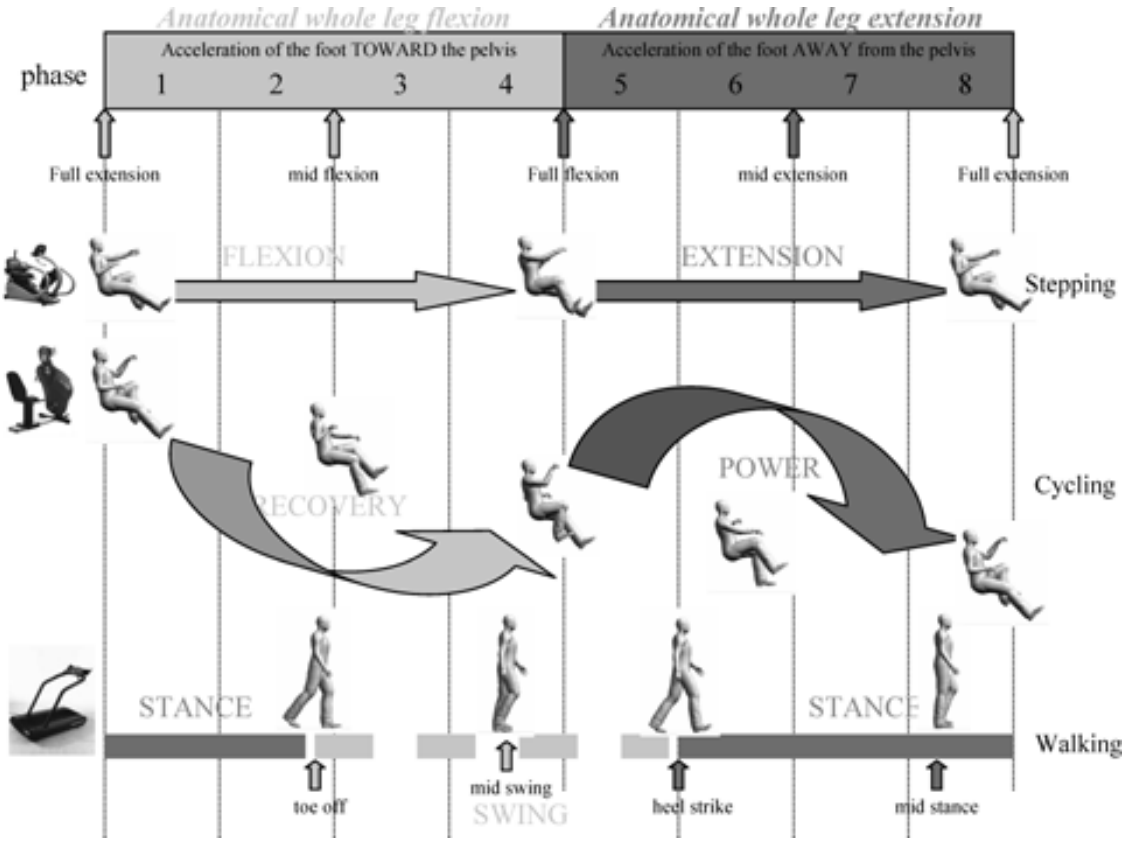
Anatomical whole leg flexion
Anatomical whole leg extension
phase
Acceleration of the foot TOWARD the pelvis
Acceleration of the foot AWAY from the pelvis
1
2
3
4
5
6
7
8
Full extension
mid flexion
Full flexion
mid extension
Full extension
FLEXION
EXTENSION
Stepping
POWER
RECOVERY
Cycling
STANCE
STANCE
Walking
toe off
mid swing
SWING
heel strike
mid stance

Figure 2.4

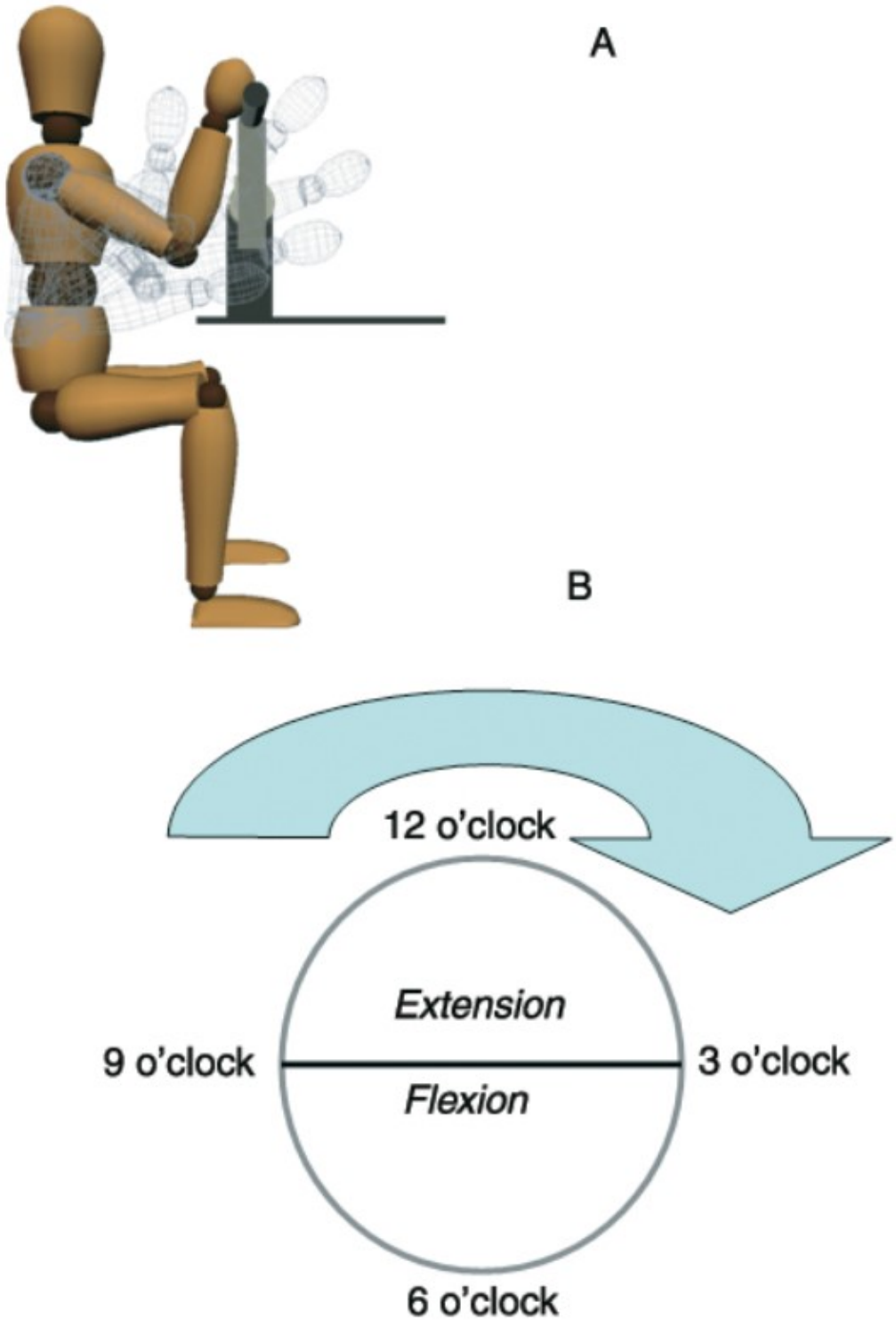

Figure 2.5

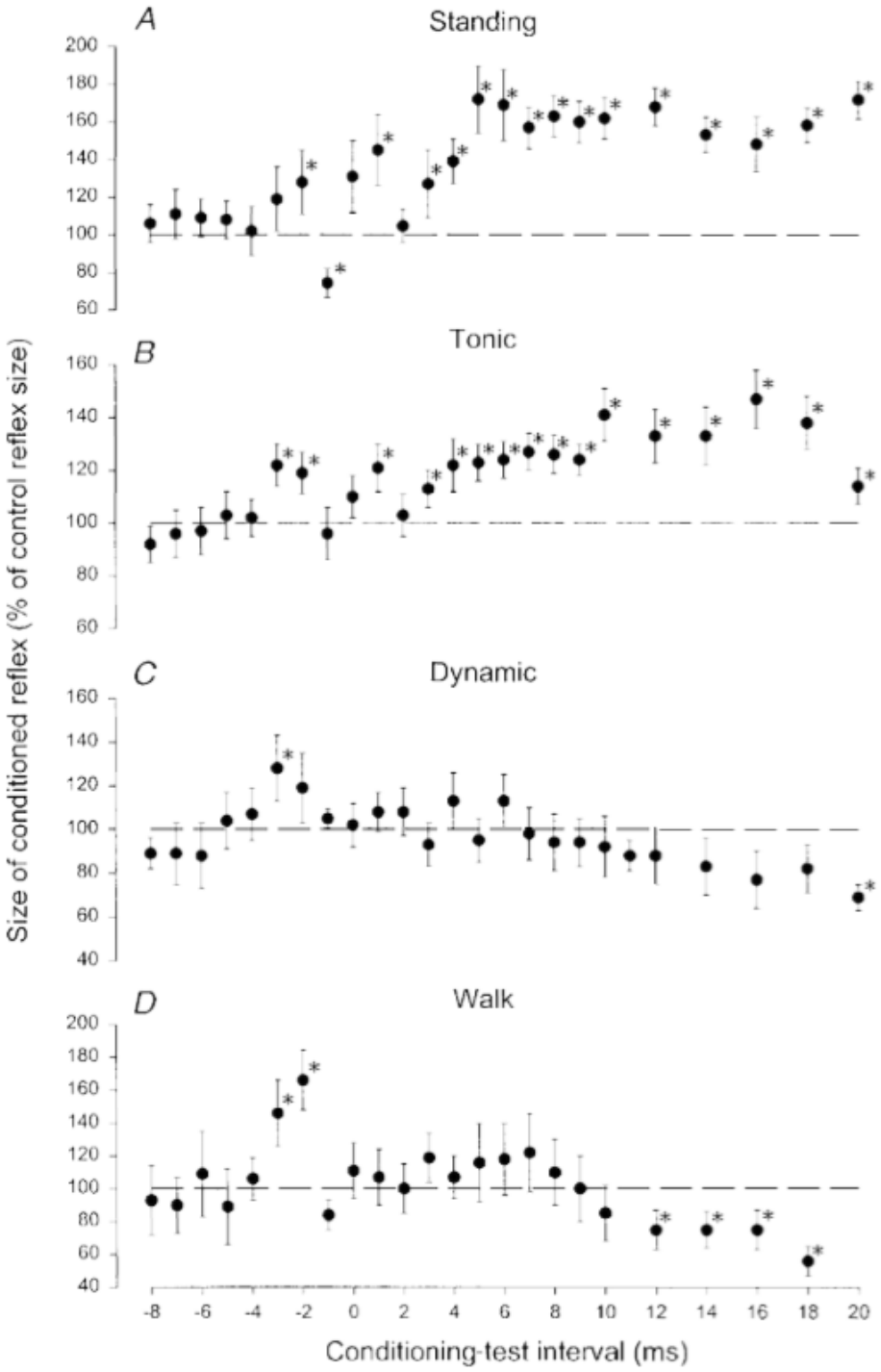
A
Standing
B
Tonic
C
Dynamic
D
Walk
Size of conditioned reflex (% of control reflex size)
Conditioning-test interval (ms)

Figure 2.6

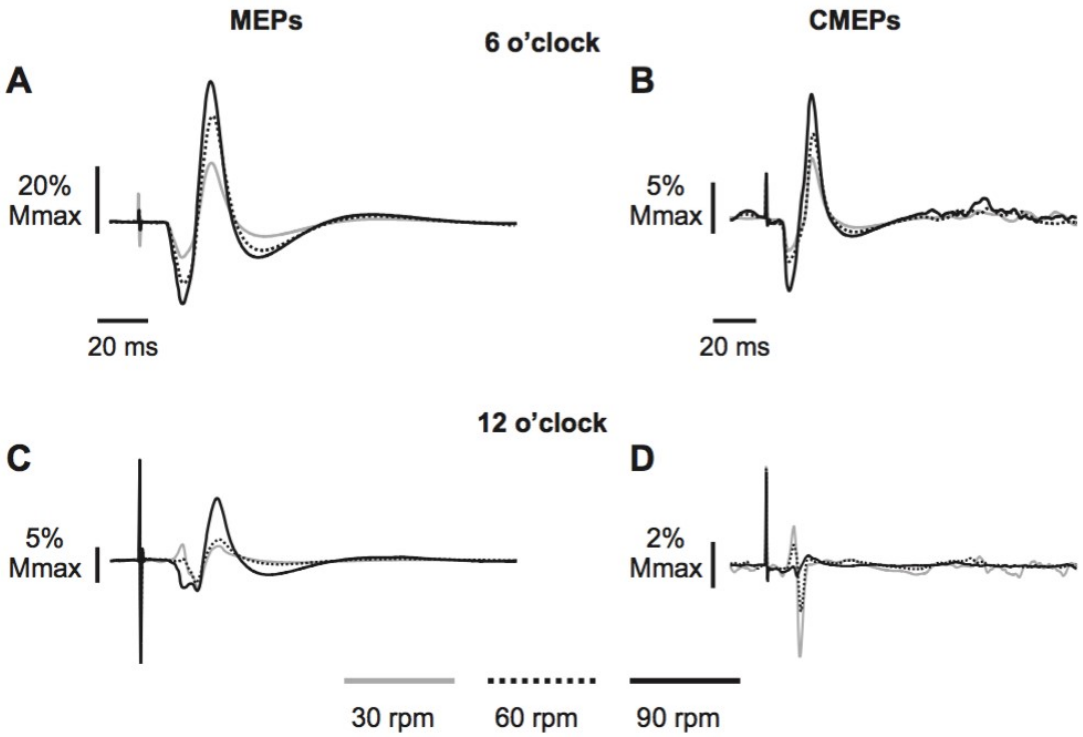
MEPs
6 o'clock
CMEPs
A
B
20%
Mmax
5%
Mmax
20 ms
20 ms
12 o'clock
C
D
5%
Mmax
2%
Mmax
30 rpm
60 rpm
90 rpm

Figure 2.7

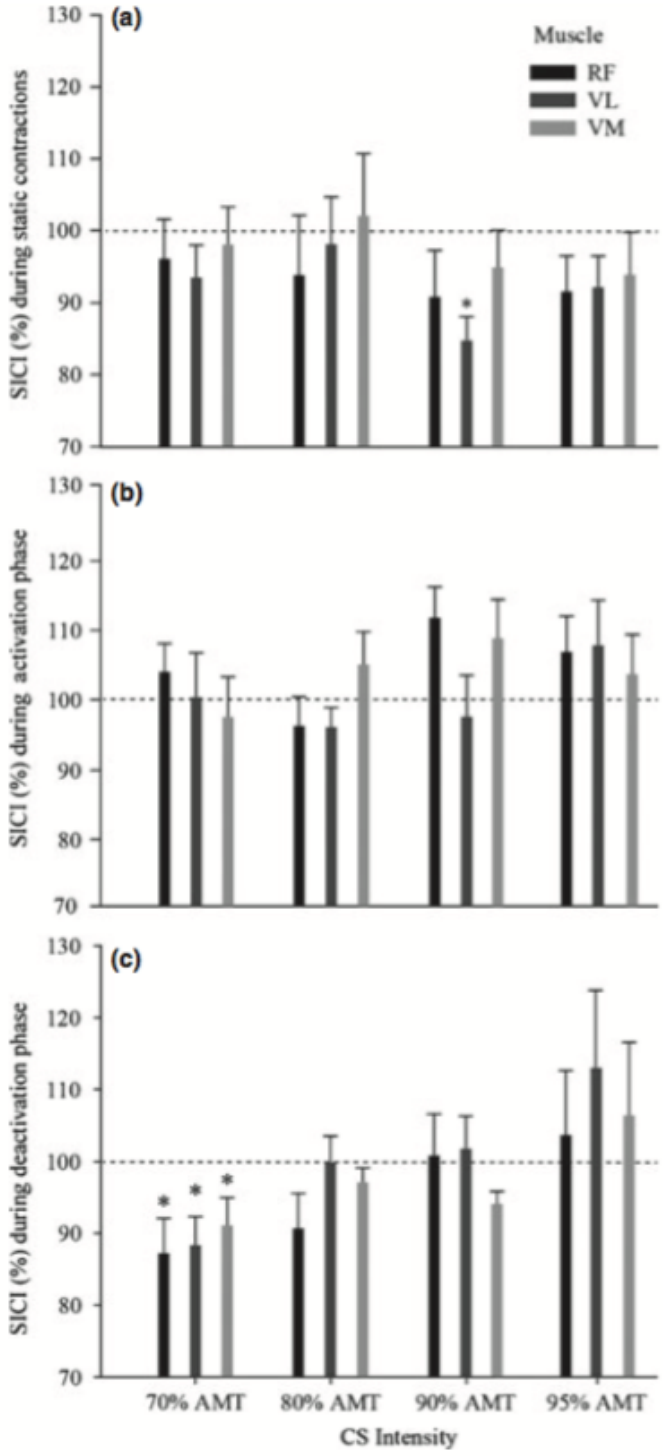
(a)
Muscle
RF
VL
VM
SICI (%) during static contractions
130
120
110
100
90
80
70
*
(b)
SICI (%) during activation phase
130
120
110
100
90
80
70
(c)
SICI (%) during deactivation phase
130
120
110
100
90
80
70
*
*
*
70% AMT
80% AMT
90% AMT
95% AMT
CS Intensity

Figure 2.8

2.6 References

Barthelemy, D. & Nielsen, J. B. (2010). Corticospinal contribution to arm muscle activity during human walking. *Journal of Physiology, 588*(6): 967–979.

Brouwer, B., & Ashby, P. (1990). Corticospinal projections to upper and lower limb spinal motoneurons in man. *Electroencephalography and Clinical Neurophysiology, 76*(6): 509–519.

Buccolieri, A., Abbruzzese, G., & Rothwell, J.C. (2004). Relaxation from a voluntary contraction is preceded by increased excitability of motor cortical inhibitory circuits. *Journal of Physiology, 558*(2): 685–695.

Burke, D., Gandevia, S. C., & McKeon, B. (1984). Monosynaptic and oligosynaptic contributions to human ankle jerk and H-reflex. *Journal of Neurophysiology, 52*(3): 435–448.

Burke, D., Hicks, R. G., & Stephen, J. P. (1990). Corticospinal volleys evoked by anodal and cathodal stimulation of the human motor cortex. *Journal of Physiology, 425*: 283–299.

Burke, D., Hicks, R., Gandevia, S. C., Stephen, J., Woodforth, I., & Crawford, M. (1993). Direct comparison of corticospinal volleys in human subjects to transcranial magnetic and electrical stimulation. *Journal of Physiology, 470*: 383–393.

Burke, D., Gracies, J. M., Mazevet, D., Meunier, S., & Pierrot-Deseilligny, E. (1994). Non-monosynaptic transmission of the cortical command for voluntary movement in man. *Journal of Physiology, 480*(1): 191–202.

Capaday, C., Lavoie, B.A., Barbeau, H., Schneider, C., & Bonnard, M. (1999). Studies on the corticospinal control of human walking. I. Responses to focal transcranial magnetic stimulation of the motor cortex. *Journal of Neurophysiology, 81*(1): 129–139.

Carroll, T.J., Baldwin, E.R., Collins, D.F., & Zehr, E.P. (2006). Corticospinal excitability is lower during rhythmic arm movement than during tonic contraction. *Journal of Neurophysiology, 95*(2): 914–921.

Chen, R., Tam, A., Butefisch, C., Corwell, B., Ziemann, U., Rothwell, J.C., & Cohen, L.G. (1998). Intracortical inhibition and facilitation in different representations of the human motor cortex. *Journal of Neurophysiology, 80*(6): 2870–2881.

Chen, R. (2004). Interactions between inhibitory and excitatory circuits in the human motor cortex. *Experimental Brain Research, 154*(1): 1–10.

Christensen, L.O., Andersen, J.B., Sinkjaer, T., & Nielsen, J.B. (2001). Transcranial magnetic stimulation and stretch reflexes in the tibialis anterior muscle during human walking. *Journal of Physiology, 531*(2): 545–557.

Cowan, J. M., Day, B. L., Marsden, C., & Rothwell, J. C. (1986). The effect of percutaneous motor cortex stimulation on H reflexes in muscles of the arm and leg in intact man. *Journal of Physiology, 377*: 333–347.

Davey, N. J., Romaiguere, P., Maskill, D. W., & Ellaway, P. H. (1994). Suppression of voluntary motor activity revealed using transcranial magnetic stimulation of the motor cortex in man. *Journal of Physiology, 477*(2): 223–235.

Di Lazzaro, V., Restuccia, D., Oliviero, A., Profice, P., Ferrara, L., Insola, A., Mazzone, P., Tonali, P., & Rothwell, J.C. (1998). Magnetic transcranial stimulation at

intensities below active motor threshold activates intracortical inhibitory circuits. *Experimental Brain Research, 119*(2): 265–268.

Edgley, S. A., Eyre, J. A., Lemon, R. N., & Miller, S. (1990). Excitation of the corticospinal tract by electromagnetic and electrical stimulation of the scalp in the macaque monkey. *Journal of Physiology, 425*: 301–320.

Edgley, S. A., Eyre, J. A., Lemon, R. N., & Miller, S. (1997). Comparison of activation of corticospinal neurons and spinal motor neurons by magnetic and electrical transcranial stimulation in the lumbosacral cord of the anaesthetized monkey. *Brain, 120*(5): 839–853.

Fisher, R. J., Nakamura, Y., Bestmann, S., Rothwell, J. C., & Bostock, H. (2002). Two phases of intracortical inhibition revealed by transcranial magnetic threshold tracking. *Experimental Brain Research, 143*(2): 240–248.

Forman, D., Raj, A., Button, D. C., & Power, K. E. (2014). Corticospinal excitability of the biceps brachii is higher during arm cycling then an intensity-matched tonic contraction. *Journal of Neurophysiology, 112*(5): 1142–1151.

Forman, D. A., Philpott, D. T. G., Button, D. C., & Power, K. E. (2015). Cadence-dependent changes in corticospinal excitability of the biceps brachii during arm cycling. *Journal of Neurophysiology, 114*(4): 2285–2294.

Graham-Brown, T. (1911). The intrinsic factors in the act of progression in the mammal. *Proceedings of the Royal Society of London, B84*(572): 308–319.

Graham-Brown, T. (1912). The factors in rhythmic activity of the nervous system. *Proceedings of the Royal Society of London, B85*(579): 278–289.

Grillner, S., & Wallén, P. (1985). Central pattern generators for locomotion, with special reference to vertebrates. *Annual Review of Neuroscience, 8*: 233–261.

Grillner, S., & Zangger, P. (1975). How detailed is the central pattern generator for locomotion? *Brain Research, 88*(2): 367–371.

Hess, A., Kunesch, E., Classen, J., Hoeppner, J., Stefan, K., & Benecke, R. (1999). Task-dependent modulation of inhibitory actions within the primary motor cortex. *Experimental Brain Research, 124*(3): 321–330.

Hunter, S. K., McNeil, C. J., Butler, J. E., Gandevia, S. C., & Taylor, J. L. (2016). Short-interval cortical inhibition and intracortical facilitation during submaximal voluntary contractions changes with fatigue. *Experimental Brain Research, 234*(9): 2541–2551.

Iles, J. F., & Pisini, J. V. (1992). Cortical modulation of transmission in spinal reflex pathways of man. *Journal of Physiology, 455*: 425–446.

Kujirai, T., Caramia, M. D., Rothwell, J. C., Day, B. L., Thompson, P. D., Ferbert, A., Wroe, S., Asselman, P., & Marsden, C.D. (1993). Corticocortical inhibition in human motor cortex. *Journal of Physiology, 471*: 501–519.

Martin, P. G., Gandevia, S. C., & Taylor, J. L. (2006). Output of human motoneuron pools to corticospinal inputs during voluntary contractions. *Journal of Neurophysiology, 95*(6): 3512–3518.

Nielsen, J., Petersen, N., Deuschl, G., & Ballegaard, M. (1993). Task-related changes in the effect of magnetic brain stimulation on spinal neurones in man. *Journal of Physiology, 471*: 223–243.

Nielsen, J., Petersen, N., & Ballegaard, M. (1995). Latency of effects evoked by electrical and magnetic brain stimulation in lower limb motoneurones in man. *Journal of Physiology, 484*(3): 791–802.

Opie, G. M., Ridding, M. C., & Semmler, J. G. (2014). Task-related changes in intracortical inhibition assessed with paired- and triple-pulse transcranial magnetic stimulation. *Journal of Neurophysiology, 113*(5): 1470–1479.

Ortu, E., Deriu, F., Suppa, A., Tolu, E., & Rothwell, J. C. (2008). Effects of volitional contraction on intracortical inhibition and facilitation in the human motor cortex. *Journal of Physiology, 586*(21): 5147–5159.

Oya, T., Hoffman, B.W., & Cresswell, A.G. (2008). Corticospinal-evoked responses in the lower limb muscles during voluntary contractions at varying strengths. *Journal of Applied Physiology, 105*(5): 1527–1532.

Pearcey, G. E. P., Power, K. E., & Button, D. C. (2014). Differences in supraspinal and spinal excitability during various force outputs of the biceps brachii in chronic- and non-resistance trained individuals. *PLoS ONE, 9*(5): e98468.

Petersen, N., Christensen, L. O., & Nielsen, J. (1998). The effect of transcranial magnetic stimulation on the soleus H reflex during human walking. *Journal of Physiology, 513*(2): 599–610.

Petersen, N. T., Butler, J. E., Marchand-Pauvert, V., Fisher, R., Ledebt, A., Pyndt, H. S., Hansen, N. L., & Nielsen, J. B. (2001). Suppression of EMG activity by transcranial magnetic stimulation in human subjects during walking. *Journal of Physiology, 537*(2): 651–656.

Philpott, D. T. G., Pearcey, G. E. P., Forman, D., Power, K. E., & Button, D. C. (2014). Chronic resistance training enhances the spinal excitability of the biceps brachii in the non-dominant arm at moderate contraction intensities. *Neuroscience Letters, 585*(1): 12–16.

Pyndt, H. S., & Nielsen, J. B. (2003). Modulation of transmission in the corticospinal and group Ia afferent pathways to soleus motoneurons during bicycling. *Journal of Neurophysiology, 89*(1): 304–314.

Reynolds, C. & Ashby, P. (1999). Inhibition in the human motor cortex is reduced just before a voluntary contraction. *Neurology, 53*(4): 730–735.

Ridding, M. C., Taylor, J. L., & Rothwell, J. C. (1995). The effect of voluntary contraction on corticocortical inhibition in human motor cortex. *Journal of Physiology, 487*(2): 541–548.

Roshan, L., Paradiso, G. O., & Chen, R. (2003). Two phases of short-interval intracortical inhibition. *Experimental Brain Research, 151*(3): 330–337

Rossignol, S. (1996). Neural control of stereotypic limb movements. In: Rowell, L. B. & Sheperd, J. T. (Eds.), *Handbook of Physiology, Section 12. Exercise: Regulation and Integration of Multiple Systems* (pp. 173–216). Oxford: America Physiological Society.

Sidhu, S. K., Hoffman, B. W., Cresswell, A. G., & Carroll, T. J. (2012a). Corticospinal contributions to lower limb muscle activity during cycling in humans. *Journal of Neurophysiology, 107*(1): 306–314.

Sidhu, S. K., Cresswell, A. G., & Carroll, T. J. (2012b). Motor cortex excitability does not increase during sustained cycling exercise to volitional exhaustion. *Journal of Applied Physiology, 113*(3): 401–409.

Sidhu, S. K., Cresswell, A. G., & Carroll, T. J. (2012c). Short-interval intracortical inhibition in knee extensors during locomotor cycling. *Acta Physiologica, 207*(1): 194–201.

Singh, A. M., Duncan, R. E., Neva, J. L., & Staines, W. R. (2014). Aerobic exercise modulates intracortical inhibition and facilitation in a nonexercised upper limb muscle. *BMC Sports Science, Medicine, & Rehabilitation, 6*:23.

Soto, O., Valls-Sole, J., Shanahan, P., & Rothwell, J. (2006). Reduction of intracortical inhibition in soleus muscle during postural activity. *Journal of Neurophysiology, 96*(4): 1711–1717.

Temesi, J. (2013). The use of transcranial magnetic stimulation in locomotor function: Methodological issues and application to extreme exercise. *Tissues and Organs.*

Zehr, E. P., Balter, J. E., Ferris, D. P., Hundza, S. R., Loadman, P. M., & Stoloff, R. H. (2007). Neural regulation of rhythmic arm and leg movement is conserved across human locomotor tasks. *Journal of Physiology, 582*(1): 209–227.

Zehr, E. P., Carroll, T. J., Chua, R., Collins, D. F., Frigon, A., Haridas, C., Hundza, S. R., & Thompson, A. K. (2004). Possible contributions of CPG activity to the control of rhythmic human arm movement. *Canadian Journal of Physiology and Pharmacology, 82*(8-9): 556–568.

Ziemann, U., Rothwell, J. C., & Ridding, M. C. (1996). Interaction between intracortical inhibition and facilitation in human motor cortex. *Journal of Physiology, 496*(3): 873–881.

CHAPTER 3

SHORT-INTERVAL INTRACORTICAL INHIBITION INFLUENCES CORTICAL EXCITABILITY TO THE BICEPS BRACHII DURING ARM CYCLING, BUT IS NOT DIFFERENT FROM AN INTENSITY-MATCHED TONIC CONTRACTION

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3.0 ABSTRACT

The motor cortex has been previously shown to play a role during spinally-mediated rhythmic and alternating locomotor outputs. The present study sought to determine if short-interval intracortical inhibition (SICI) is present during arm cycling and if so, is the amount of SICI different from an intensity-matched tonic contraction. SICI was assessed using conditioning stimuli (CS) of 70 and 90% of active motor threshold (AMT) and a test stimulus (TS) of 120% AMT at an interstimulus interval (ISI) of 2.5ms. SICI was elicited in all participants; on average (i.e. cycling and tonic contraction grouped) test MEP amplitudes were reduced by 64.2% ($p < 0.001$) and 62.8% ($P = 0.001$) following conditioning stimuli of 70% and 90% AMT, respectively. There was no significant difference in extent of SICI between tasks ($P = 0.360$). This data represents the novel finding that SICI is present during arm cycling, a motor output considered to be partially mediated by spinal interneuronal networks. The amount of SICI, however, was not different from that recorded during intensity matched tonic contractions, suggesting that SICI cannot fully explain the previously demonstrated higher levels of supraspinal excitability during arm cycling compared to tonic contraction.

3.1 INTRODUCTION

Rhythmic and alternating movements, such as locomotion, are generated and modulated via descending command from both supraspinal and spinal origins. The spinal motoneurone, or the 'final common path', translates information from descending pathways, afferent nerves, and spinal circuits, such as the central pattern generator (CPG), into signals which produce rhythmic and alternating motor outputs. Studies have suggested that rhythmic and alternating motor outputs in the upper (Carroll et al., 2006) and lower limbs (Capaday et al., 1999; Pyndt & Nielsen, 2003) are mediated largely via spinally located CPGs. However, supraspinal centres also contribute to locomotor outputs (Forman et al., 2014).

Evidence of cortical contribution to the production of locomotor tasks has been shown using several techniques. Studies have shown that subthreshold conditioning transcranial magnetic stimulation (TMS) facilitates H-reflex responses in lower limb muscles during walking and leg cycling (Capaday et al., 1999; Carroll et al., 2006; Christensen et al., 2001; Petersen et al., 1998; Pyndt & Nielsen, 2003). Similarly, subthreshold TMS is thought to activate predominantly inhibitory cortical circuits, which inhibits the descending command arising from the motor cortex. This leads to an amplitude suppression of the ongoing EMG in the active musculature (Di Lazzaro et al., 1998). In this way, the motor cortex has been shown to modulate ongoing EMG in several studies during walking and leg cycling (Davey et al., 1994; Petersen et al., 2001; Sidhu et al., 2012a).

While these studies have been conducted predominantly on the lower limb muscles, our lab has shown that supraspinal input (i.e. cortical and subcortical) likely modulates

overall corticospinal excitability during arm cycling. We demonstrated that motor-evoked potentials (MEPs) elicited through TMS were larger during the elbow flexion phase of arm cycling than during position and intensity-matched tonic contractions, indicating a higher level of corticospinal excitability during arm cycling. At the same time, cervicomedullary motor-evoked potentials (CMEPs) elicited through transmastoid electrical stimulation (TMES) of the corticospinal tract were not different between arm cycling and tonic contractions. Since the change in corticospinal excitability could not be explained via enhanced spinal excitability, we concluded that *supraspinal* excitability was enhanced during arm cycling, thus accounting for the overall increase in corticospinal excitability (Forman et al., 2014). The mechanism through which supraspinal excitability was enhanced was not examined.

There are many potential supraspinal candidates that may help explain our previous finding. Several cortical circuits, both excitatory and inhibitory for example, can be evaluated using currently available paired-pulse TMS (ppTMS) techniques. Examples include short-interval intracortical inhibition (SICI), intracortical inhibition (ICF), long-interval intracortical inhibition (LICI), and short-interval intracortical facilitation (SICF). Though commonly assessed during tonic contractions (Hunter et al., 2016; Kujirai et al., 1993; Ortu et al., 2008; Reynolds & Ashby, 1999; Ridding et al., 1995), the excitability of these cortical circuits during locomotor tasks has received limited attention. Sidhu and colleagues (2012c) assessed SICI projecting to the knee extensor motor units during different phases of leg cycling. They showed that activation of SICI occurred during leg cycling, an effect that was phase- and muscle-dependent. Importantly, though they also elicited SICI during tonic contraction of the same musculature, the two motor outputs

(cycling and tonic contraction) were not directly compared. Thus, it is unclear whether the degree of SICI was task-dependent. Furthermore, SICI has not been assessed during locomotion or arm cycling, both motor outputs thought to be partially controlled via spinally located CPGs (Capaday et al., 1999; Carroll et al., 2006; Pyndt & Nielsen, 2003).

The purpose of the current study was to expand on the current literature with respect to corticospinal excitability during arm cycling by determining: (1) if SICI is present during arm cycling and (2) if the amount of SICI between arm cycling and a tonic contraction is different. Cycling and tonic tasks are compared to determine if changes in cortical excitability are task-dependent, particularly because rhythmic and alternating movements are thought to be controlled largely by CPGs. However, SICI may modulate supraspinal excitability during arm cycling, and could possibly be a *contributing factor* for our previous finding of higher supraspinal excitability during arm cycling when compared to an intensity-matched tonic contraction. We hypothesized that SICI would be present during arm cycling and that the amount of SICI would less during arm cycling compared to a tonic contraction.

3.2 METHODOLOGY

3.2.0 Participants

Twelve healthy participants (10 males and 2 females) between the ages of 20 and 37 participated in this study. All participants completed a magnetic stimulation safety checklist (Rossi et al., 2009), a Physical Activity Readiness Questionnaire [PAR-Q+; Canadian Society for Exercise Physiology (CSEP)], and an Edinburg handedness questionnaire to identify the dominant limb for testing. Participants had no known neurological impairments. The procedure was verbally explained to the participants and written consent was obtained prior to starting the study. The experimental procedure conformed to the Helsinki declaration and was approved by the Interdisciplinary Committee on Ethics in Human Research at Memorial University of Newfoundland (ICEHR no. 20161507-HK). Procedures were in accordance with the Tri-Council guideline in Canada, with potential risks explained to participants.

3.2.1 Experimental Set-up

EMG Recordings

Electromyography recordings were taken from the dominant biceps and triceps brachii using pairs of surface electrodes (Medi-Trace 130 ECG conductive adhesive electrodes) in bipolar configuration (Ag-AgCl, 2cm interelectrode distance). Electrodes were placed over the midline of the biceps and triceps brachii (lateral head) muscle bellies. Prior to electrode placement, the skin was thoroughly prepared through shaving, abrading, and cleaning with alcohol swabs to reduce EMG recording impedance. An additional

ground electrode was placed over the lateral epicondyle. EMG data was collected online at 5 kHz using CED 1401 interface and Signal 4 software program [Cambridge Electronic Design (CED), Cambridge, UK]. Signals were amplified and filtered using a three-pole Butterworth with cut-off frequencies of 10-1,000 Hz.

Cycle Ergometer Set-up

Participants were in a seated position to perform arm cycling and tonic contraction tasks using an arm cycle ergometer (SCIFIT ergometer, model PRO2 Total Body). It was ensured that participants were in a comfortable position and at a distance from the arm cranks such that they were not leaning forward or backward and were maintaining upright trunk posture. The arm cranks on the bike were fixed 180° out of phase. Forearms were in the pronated position and stabilized with wrist braces to reduce interference from joint movement and subsequent heteronymous reflex connections between the wrist flexors and extensors and the biceps brachii (Manning & Bawa, 2011).

Crank position was made relative to a clock face with respect to the arm from which the recordings were made (dominant arm; 12, 3, 6, and 9 o'clock), with 'bottom dead centre' as the 6 o'clock position. The biceps brachii was the main muscle of interest, therefore cycling movement was defined hereafter with reference to the dominant elbow joint position. Thus, elbow flexion was defined as the movement from the 3 to the 9 o'clock position (Figure 3.1). Cycling throughout the experiment was fixed at a workload of 25 W and at a cadence of 60 rpm as per our previous work upon which the current study is based (Forman et al., 2014).

Stimulation Conditions

Motor responses recorded from the biceps brachii were elicited via (1) single-pulse transcranial magnetic stimulation (TMS) (2) paired-pulse TMS (i.e. ppTMS) and (3) brachial plexus electrical stimulation at Erb's point. During cycling, stimulation intensities were determined in reference to the dominant arm crank position and were automatically triggered as the arm crank passed the 6 o'clock position, the mid-flexion point of the dominant biceps brachii. During tonic contraction, stimulations were triggered with the dominant arm crank fixed at the 6 o'clock position as we have done previously (Copithorne et al., 2015; Forman et al., 2014; 2015).

Transcranial Magnetic Stimulation

Motor-evoked potentials (MEPs) from the dominant arm biceps brachii were elicited during cycling and intensity-matched tonic contractions using a circular coil (13.5cm outside diameter) attached to a BiStim module connected to two magnetic stimulators (Magstim 200, Dyfed, United Kingdom). The coil was held one centimeter lateral to vertex, approximately parallel to the floor, with direction of current flow preferentially activating the dominant motor cortex. Vertex was located by measuring nasion to inion and tragus to tragus; marking the location on the scalp halfway between them; and defining vertex as the intersection of the halfway marks (Copithorne et al., 2015; Forman et al., 2014; 2015).

Active Motor Threshold

Active motor thresholds (AMT), defined as the intensity at which a MEP was clearly discernible from the background EMG (bEMG) in 50% of the trials (8/16), recorded from the biceps brachii were determined using TMS in two separate conditions (1) while participants cycled at 25 W and 60 rpm and (2) while participants completed intensity-matched tonic contractions.

Test and Conditioning Stimulus Intensity

Test stimulus (TS) intensity was defined as a suprathreshold TMS of approximately 120% AMT. For cycling trials, TS was set as 120% of cycling AMT. For tonic contraction trials, TS was set as ~120% such that the MEP amplitude was matched to the average TS MEP amplitude recording during cycling. This was to ensure that SICI measurements were not affected by test MEP size-dependent differences (Sidhu et al., 2012c). Conditioning stimulus (CS) intensities of 70 and 90% of AMT (Sidhu et al., 2012c; Ortu et al., 2008; Ridding et al., 1995; Kujirai et al., 1993) were investigated during both cycling and tonic contraction trials. In all conditioned stimulations, the TS was preceded by a CS at an ISI of 2.5ms, based on previous studies which indicate an ISI of 2.5ms to activate inhibitory interneurons in the motor cortex (Figure 3.2; Ortu et al., 2008). All TS and CS stimulation intensities during cycling and tonic contractions were percentages of their respective AMT values.

Brachial Plexus Stimulation

Stimulating electrodes were placed at Erb's point (pulse duration of 200 μs), with the cathode in the supraclavicular fossa and the anode over the acromion process, in order to stimulate the brachial plexus (DS7AH, Digitimer, Welwyn Garden City, Hertfordshire, UK). Resting M_{max} of the biceps brachii was determined by increasing stimulation intensity until the M-wave reached a plateau. This stimulation intensity was then increased by 20% to ensure maximal M-waves (i.e. M_{max} stimulations) were elicited throughout the study (Forman et al., 2014). M_{max} stimulations were elicited once during each cycling and tonic contraction condition as a measure of peripheral neuromuscular excitability.

3.2.2 Experimental Protocol

Active motor threshold was first established during cycling. TMS intensity began low and increased incrementally until a MEP was clearly visible and distinct from the ongoing bEMG. When this threshold intensity was determined, the participant received sixteen stimulations at this stimulation intensity during cycling. The bEMG from the cycling period was then used to complete intensity-matched tonic contractions. bEMG activity was determined by averaging the rectified amplitude of the 50 ms window preceding stimulation during previous cycling trials and maximum EMG burst at the 6 o'clock position. Participants then performed tonic elbow flexion contractions that were intensity matched to arm cycling based on the bEMG. With the arm crank fixed at the 6 o'clock position participants were provided with visual feedback of a horizontal line on a computer screen equal to the averaged bEMG level during cycling (Forman et al., 2014). AMT was found during tonic contractions in the same manner as the cycling trials, with

stimulation administered at increasing intensities until a visible MEP was found. The participant then received eighteen stimulations at this AMT stimulation intensity during tonic contraction. Participants were always given two extra stimulations during tonic trials (i.e. 18 during tonic contraction and 16 during cycling) to account for errors in matching. This allowed two extra attempts if the participant failed to reach the predetermined intensity.

Following the determination of AMT, participants cycled for approximately one minute during which they received 10 control test stimulations (TS) at 120% AMT and one M_{max}, in random order. TS intensity (~120% AMT) for tonic contractions were determined by eliciting a MEP during tonic contraction that was size-matched to the average MEP response from the previous cycling TS control trial. Participants then completed 13 tonic contraction trials during which they received 12 control test stimulations (~120% AMT) and one M_{max} in random order. Participants were always given two extra stimulations during tonic trials (i.e. 12 during tonic contraction and 10 during cycling).

Next, participants cycled for approximately two minutes, during which they received the following conditioned stimulations in random order: 10 ppTMS stimulus with CS and TS set at 70 and 120% AMT, respectively, 10 ppTMS stimulus with CS and TS set at 90 and 120% of AMT, respectively, and 2 M_{max}. Participants then performed two-minutes of intensity-matched tonic contractions during which the participant repeated a sequence of contractions that involved active contraction for approximately 2 seconds followed by approximately 4 seconds of relaxation. They then received the following stimulations in random order: 12 ppTMS stimulus with CS and TS set at 70 and ~120%

AMT, respectively, 12 ppTMS stimulus with CS and TS set at 90 and ~120% AMT, respectively, and 2 M_{max}.

A cycling trial with sixteen stimulations at original AMT intensity was performed again upon completion of the experimental protocol. MEP amplitudes elicited via AMT stimulation intensity were then compared between pre- and post-protocol to determine whether any changes in AMT occurred throughout the experiment, which would affect the relative percent intensity of the CS. Similar comparison were made for the tonic contraction trials.

3.2.3 Statistics

All statistical analyses were performed on group data, and a significance level of $P < 0.05$ was used. Data is presented as means ± SD and shown as means ± SE in the figures.

To determine whether MEP amplitudes elicited via AMT stimulation intensities changed over the course of the experiment (pre- to post-protocol), separate paired-sample T-tests were performed for cycling and tonic conditions.

SICI is presented as a ratio of conditioned MEP amplitude over test MEP amplitude. The ratio is then multiplied by 100 to give the amplitude of the conditioned MEP as a percentage of the test MEP amplitude. A two-way (task x stimulation intensity) repeated measures ANOVA was used to determine whether statistically significant differences in SICI occurred between tasks or stimulation intensity. A two-way repeated measures ANOVA was also used to determine whether contraction intensity, as defined by bEMG, was different within or between 'task' and 'stimulation intensity'.

3.3 RESULTS

3.3.0 Active motor threshold

Test and conditioning stimulation intensities (and the MEP amplitudes they elicit) used throughout the experiment are a percentage of the AMT, therefore it is important to measure the AMT following the protocol to know if it changed throughout. MEPs elicited at AMT stimulation intensities (same stimulation intensity used pre- and post-protocol) were not significantly different for the cycling or tonic tasks (P = 0.753 and P = 0.755, respectively; see Table 3.1).

3.3.1 Stimulation Intensities

Test stimulus intensities ranged from 32 to 68% of maximum stimulator output (MSO). There was no main interaction effect of task (P = 0.113), nor was there an interaction effect between task and stimulation intensity (P = 0.934) indicating stimulator output intensity was comparable between tasks within conditions (Table 3.2). SICI results in a decrease in average test MEP amplitude when preceded by a conditioning stimulus. Therefore, it was important to match test stimulation intensities between tasks such that MEP amplitudes between cycling and tonic were not significantly different, allowing direct comparison of conditions between the two tasks. Although there was no significant difference found between tasks, a higher %MSO was often required to elicit a MEP during tonic contraction that was of similar amplitude to that recorded during cycling. This suggests that corticospinal excitability was lower during the tonic contraction, as we have previously demonstrated (Forman et al., 2014).

3.3.2 SICI

All test and conditioned MEPs were evoked using stimulation intensities relative to AMT, which was determined preceding the experimental protocol. Test MEPs were elicited using a suprathreshold stimulation intensity, which is influenced by supraspinal and spinal factors that provides an indication of the excitability of the entire corticospinal pathway. Conditioned MEPs reflect the influence of activating inhibitory and excitatory cortical circuits on corticospinal excitability and are thus representative of cortical excitability void of spinal influence. Figure 3.3 shows an example of both test and conditioned MEPs during cycling and tonic tasks using conditioning stimulation intensities of 70% and 90% of AMT. In this example, MEP amplitudes were reduced during cycling from 3.0 mV (Figure 3.3A) to 0.5 mV (Figure 3.3B) and 0.6 mV (Figure 3.3C), a reduction of 83% and 80%, respectively. During tonic contraction, MEP amplitudes were reduced from 3.3 mV (Figure 3.3A) to 0.8 mV (Figure 3.3B) and 0.7 mV (Figure 3.3C), a reduction of 76% and 79%, respectively.

The SICI ratio shows the size of the conditioned MEP as a percentage of the test MEP. Therefore, a value below 100% shows MEP amplitude reduction and a value above 100% would show MEP increase. As a group, SICI was evident in both tasks using both CS intensities (Figure 3.4). There were no main effects for 'task' ($P = 0.360$) or 'stimulation intensity' ($P = 0.301$), nor was there an interaction effect between task and stimulation intensity ($P = 0.181$).

3.3.3 Background EMG

Group data for bEMG of the biceps brachii can be seen in Figure 3.5. There were no main effects for task ($P = 0.134$) or stimulation intensity ($P = 0.744$) nor was there an interaction effect between task and stimulation intensity ($P = 0.238$). Group data for bEMG of the triceps brachii is reported in Figure 3.6. Similarly, there were no main effects for task ($P = 0.142$) or stimulation intensity ($P = 0.578$) nor was there an interaction effect between them ($P = 0.980$).

3.4 DISCUSSION

This report is the first to show that SICI is present during arm cycling, a locomotor output thought to be partially mediated by a spinal CPG. Additionally, this is the first study to directly compare the extent of SICI present between a locomotor task (i.e. arm cycling) and an intensity-matched tonic contraction. Though present during arm cycling, the amount of SICI was not different from that of an intensity-matched tonic contraction, thus showing that cortical inhibition was active during both motor outputs, but was not task-dependent. These results support our hypothesis that SICI would be present during arm cycling, but oppose our hypothesis that SICI would be less during arm cycling when compared to an intensity-matched tonic contraction.

3.4.0 SICI is present during arm cycling and tonic contractions

We have previously shown that corticospinal excitability, as assessed via TMS-elicited MEPs (single-pulse), was higher at the mid-flexion point of arm cycling (i.e. 6 o'clock) when compared to an intensity-matched tonic contraction at the same position. Given that spinal excitability as assessed via CMEPs was not different between the two motor outputs at the same position, we suggested that changes in corticospinal excitability were of supraspinal origin, though the exact mechanism(s) was unknown (Forman et al., 2014). In the present study we assessed SICI to the biceps brachii to determine if changes could partially account for our previous finding of higher supraspinal excitability during arm cycling. SICI was indeed present during arm cycling using CS intensities of 70 and 90% of AMT. These intensities were chosen based on previous research (Sidhu et al.,

2012c) which demonstrated that extent of intracortical inhibition projecting to the leg extensor motor units varied with CS intensities ranging from 70-95% of AMT. Therefore, we chose two CS intensities within this range to attempt to elicit SICI in the upper limb. Our results show that although SICI was present during arm cycling (using both CS intensities), the amount of SICI was not different from an intensity-matched tonic contraction (Figure 3.4).

3.4.1 Modulation of SICI is not task-dependent during mid-flexion of the elbow joint

This study compared the modulation of SICI during arm cycling at the mid-flexion phase to that of intensity-matched tonic contractions in the same position. Although modulation of SICI during locomotor and tonic tasks has not yet been directly compared, we expected there would be task-dependent differences between the two based on previous studies which show different amounts of SICI between resting and tonic tasks (Hunter et al., 2016; Kujirai et al., 1993; Opie et al., 2014; Ortu et al., 2008; Reynolds & Ashby, 1999; Ridding et al., 1995). Additionally, Opie and colleagues (2014) found SICI modulation to be different between tasks; a finger abduction task and a finger-thumb grip task. Although both were tonic contractions, the grip task involving synergistic contractions resulted in decreased amounts of SICI. The idea that SICI is modulated differently between tasks dependent on coactivation and varied patterns of muscle activation strengthened the expectation that there would be task-dependent differences seen between cycling and tonic contractions. This study, however, found no significant differences between the amount of SICI elicited during the two tasks (Figure 3.4). This may be due to factors such as the phase

and position of cycling and tonic tasks, muscles studied, intensity of motor output, cortical spread, or influence from other cortical circuits.

SICI has been studied in the main muscle mover during a locomotor task once before. Sidhu and colleagues (2012c) measured changes in SICI as recorded from the leg extensors during the 'activation' (i.e. during ascending EMG activity) and 'deactivation' (i.e. during descending EMG activity) phases of leg cycling. They found that SICI was enhanced during deactivation and tonic contraction of the quadriceps muscles, but not during the activation phase of cycling. Results were dependent on the muscle studied and the CS used, and amount of SICI during leg cycling trials were not directly compared to that of the tonic contraction trials. They did, however, reveal a modulation of intracortical inhibition reliant on muscle of interest and phase of cycling. During activation and deactivation phases of cycling, motor units are going through periods of recruitment and de-recruitment. One would expect less and more inhibition, respectfully, during these stages due to the requirement of more voluntary activation and, consequently, neural drive to recruit more motor units. The current study examined the biceps brachii during the point of mid-flexion about the elbow; future studies could include measurements of SICI at multiple phases of cycling in comparison to position- and intensity-matched tonic contractions, to determine if SICI-based modulation of descending drive to the upper limb muscle(s) is phase- and/or task-dependent.

The presence and extent of SICI during arm cycling has also been shown to be intensity-dependent. Cycling and tonic contractions were intensity-matched at a single standard workload; perhaps differences between tasks would become more apparent with an increase in intensity, i.e. voluntary activation, which we know to affect the amount of

SICI during tonic tasks (Hess et al., 1999; Ortu et al., 2008). Locomotor tasks which involve varying synergistic contractions, coactivation, and patterns of muscle activation (i.e. rhythmic and alternating) are likely a result of higher and more widespread cortical activation in comparison to tonic tasks. This is suggested to be modulated in part through activity-dependent changes in intracortical interneuron excitability (i.e. SICI; Opie et al., 2014). As intensity increases, the task-dependent differences between cycling and tonic contractions with respect to relative increases in cortical activation (i.e. more widespread cortical activation during cycling tasks) and resulting decreases in intracortical inhibition would be expected to become more pronounced as well. Therefore, as intensity of tasks increases, SICI may be modulated differently between tasks.

Apart from SICI there exists multiple inhibitory and facilitative circuits which contribute to recorded MEPs, and therefore a change in SICI alone may not necessarily translate to a change in overall MEP amplitude. Based on our results it is possible that although SICI may be elicited similarly between tasks, other inhibitory neural circuits such as LICI and IHI may hold more responsibility for higher supraspinal excitability previously seen during arm cycling. Alternatively, since single-pulse MEPs measure a final output reflecting a balance of inhibitory and facilitative circuits, changes in SICI could be 'masked' by facilitation from sources such as SICF and ICF. Finally, cortical spread (i.e. excitation from other parts of the motor cortex) could also potentially modulate descending input during locomotor tasks. Modulation of descending drive via these supraspinal factors and associated locomotor-dependent differences could be better understood through a more complete understanding of cortical circuits and the interactions between them.

3.4.2 Methodological Considerations

Background EMG was matched between tasks to ensure that a similar amount of muscle activity, a measure of intensity, was present during both cycling and tonic trials. This is important in order to directly compare tasks. Our results showed no significant differences between cycling and tonic tasks, and therefore can be said to be intensity-matched and can be compared. It can, however, be challenging for participants to steadily complete intensity-matched tonic contractions. So, it does appear that there is a pattern of higher bEMG during the tonic task compared to cycling (Figure 3.5), indicating a higher level of intensity during tonic contractions. Further inspection revealed that half of the participants had higher bEMG during tonic contractions, and half during cycling. Within these groups, neither those with higher bEMG during cycling *or* tonic tasks had significantly different magnitude of SICI. Therefore, although bEMG appears to have a pattern of higher activation during tonic tasks, it did not have a significant effect on the amount of SICI present.

The phase of cycling studied in this experiment was based on position, specifically mid flexion of the arm during peak activation of the biceps brachii. Cycling patterns are, however, variable to a degree between participants and, therefore, at the 6 o'clock position some participants may still be in activation phase, or may be using more force in the non-dominant arm to power the cycle. This could potentially affect the amount of SICI elicited, due to changes in inhibition during different phases of activation and deactivation. Measurements were only taken from the dominant arm, so interaction between the two limbs during this study is unknown.

Arm cycling is also a bilateral task, and although participants were instructed to push and pull with both arms during the tonic contraction task, it is still considered to be a predominately unilateral task, particularly because the visual feedback was only in relation to the dominant arm. Previous studies show that there is a difference in the amount of SICI present between completing bilateral and unilateral tasks (Chen & Rothwell, 2012; Giovannelli et al., 2009). If participants are required to complete a unilateral tonic task which is intensity-matched to a bilateral task, it is possible that they are requiring more voluntary activation to complete the action. SICI decreases as voluntary activation increases, therefore participants could be presenting with less SICI than they normally would in an intensity-matched and bilateral task. Measuring and matching force output in both limbs during cycling and tonic contractions would be extremely helpful in determining if these tasks truly are matched with respect to intensity, phase, and laterality.

These methodological considerations are important factors to consider in the interpretation of our results. Although SICI was found not modulated in a task-dependent manner, factors such as phase- and intensity-dependence, matching between tasks, and laterality can all be possible influences to be researched in future studies.

3.5 CONCLUSION

This study demonstrated the novel finding that SICI is present during arm cycling. This was also the first study to directly compare SICI during a locomotor task to intensity- and position-matched tonic contraction. We expected that SICI might be responsible in part for higher supraspinal excitability projecting to the biceps brachii during the flexion phase of arm cycling when compared to tonic contraction, which we have previously shown (Forman et al., 2014). However, SICI was not found to be task-dependent. These findings suggest that at the particular intensity and position used in this study, SICI modulates supraspinal excitability in a similar way during cycling and tonic tasks. Further research is required to determine the influence of other cortical interneurons, intensities, phases, and tasks on modulation of supraspinal excitability during locomotor activity.

3.6 TABLE LEGEND

Table 3.1: AMT MEP amplitudes immediately pre- and post-protocol for cycling and tonic tasks.

Table 3.2: Average percent MSO used throughout the experiment for each task and condition.

Table 3.1

		Cycle	Tonic
AMT	Pre (mV)	1.13 ± 0.58	0.76 ± 0.41
	Post (mV)	1.10 ± 0.53	0.78 ± 0.41

Values are in means ± SD

Table 3.2

Condition	Cycle	Tonic
TS ~120%	46.4 ± 10.0	48.7 ± 10.5
CS 70%	27.0 ± 5.7	29.2 ± 7.9
CS 90%	34.9 ± 7.6	37.5 ± 10.2

Values are in means ± SD

3.7 FIGURE LEGEND

Figure 3.1: Experimental design with participant at arm cycle ergometer. Labels indicate TMS paddle, Erb's point stimulating electrodes, biceps brachii EMG electrodes, and triceps brachii EMG electrodes. EMG trace shows bursts from biceps brachii (A) and triceps brachii (B), with an arrow indicating approximate point of stimulation during mid-flexion of the elbow joint.

Figure 3.2: Representative figure showing the paired-pulse paradigm via TMS. The first arrow indicates a conditioning pulse and the second a test pulse, resulting in a MEP with reduced amplitude.

Figure 3.3: Average test (A), conditioned using 70% of AMT (B), and conditioned using 90% of AMT (C) MEP traces after receiving stimuli during arm cycling (black lines) and tonic contraction (grey lines) from one participant.

Figure 3.4: Conditioned MEP amplitudes as a percentage of the test MEP response in the biceps brachii for both cycling and tonic tasks. No significant differences between conditions.

Figure 3.5: Background EMG during cycling and tonic contractions for all conditions in the biceps brachii. No significant differences between conditions.

Figure 3.6: Background EMG during cycling and tonic contractions for all conditions in the triceps brachii. No significant differences between conditions.

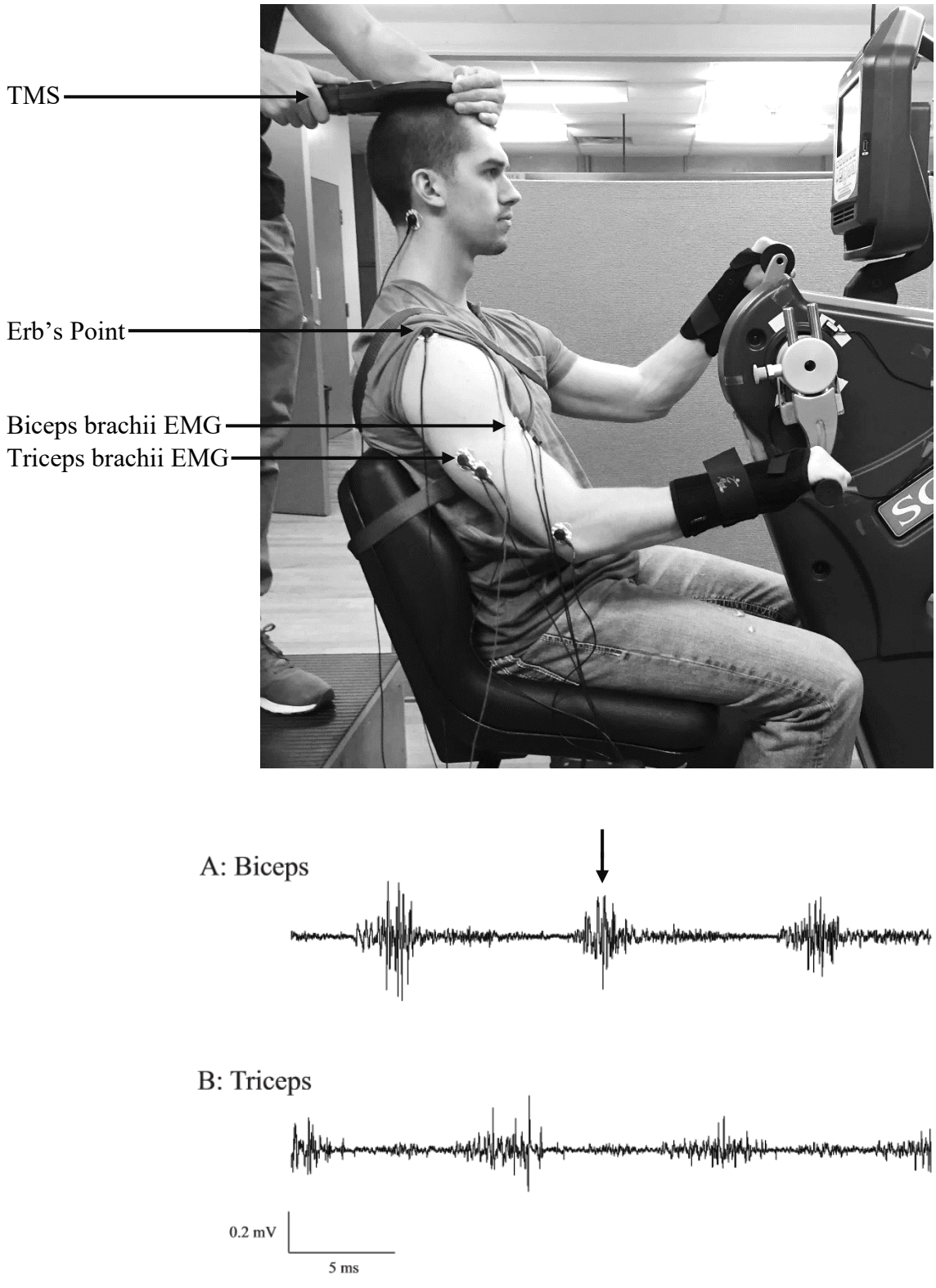
TMS
Erb's Point
Biceps brachii EMG
Triceps brachii EMG
A: Biceps
B: Triceps
0.2 mV
5 ms

Figure 3.1

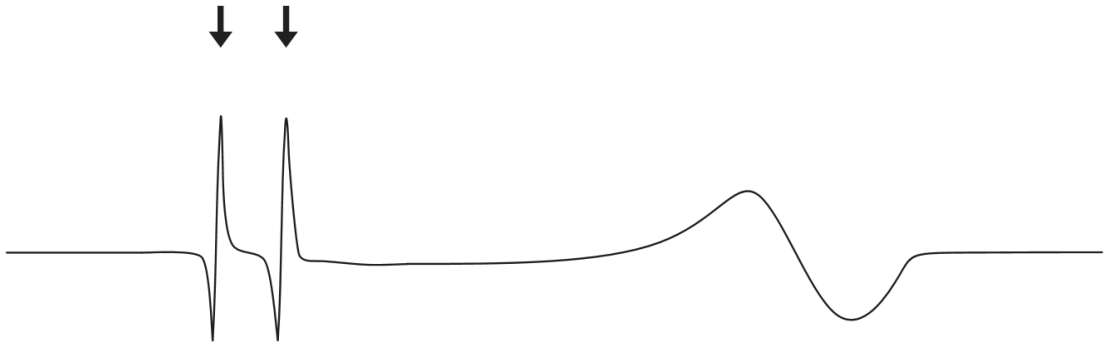

Figure 3.2

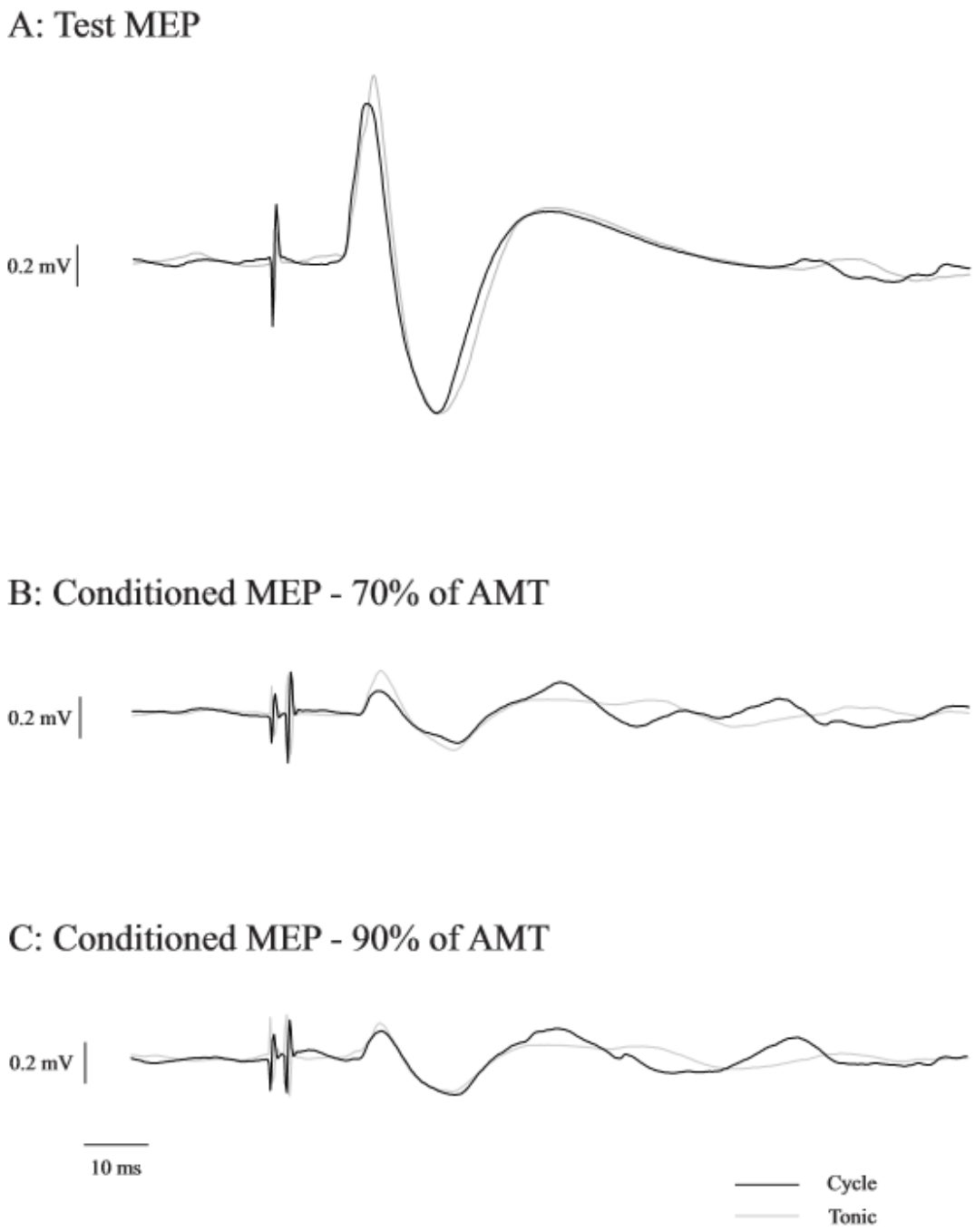
A: Test MEP
0.2 mV
B: Conditioned MEP - 70% of AMT
0.2 mV
C: Conditioned MEP - 90% of AMT
0.2 mV
10 ms
Cycle
Tonic

Figure 3.3

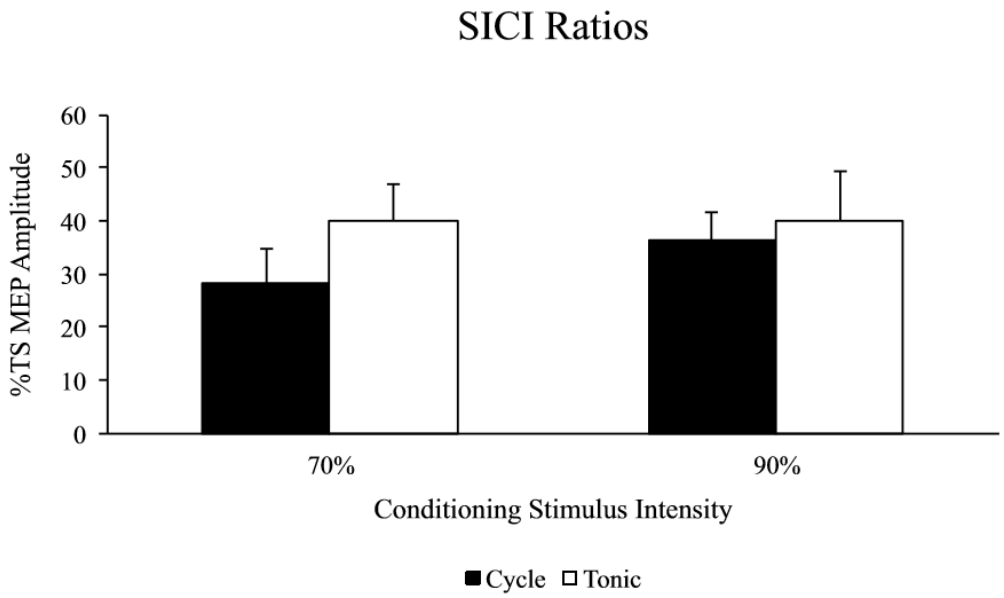
SICI Ratios
%TS MEP Amplitude
60
50
40
30
20
10
0
70%
90%
Conditioning Stimulus Intensity
Cycle
Tonic

Figure 3.4

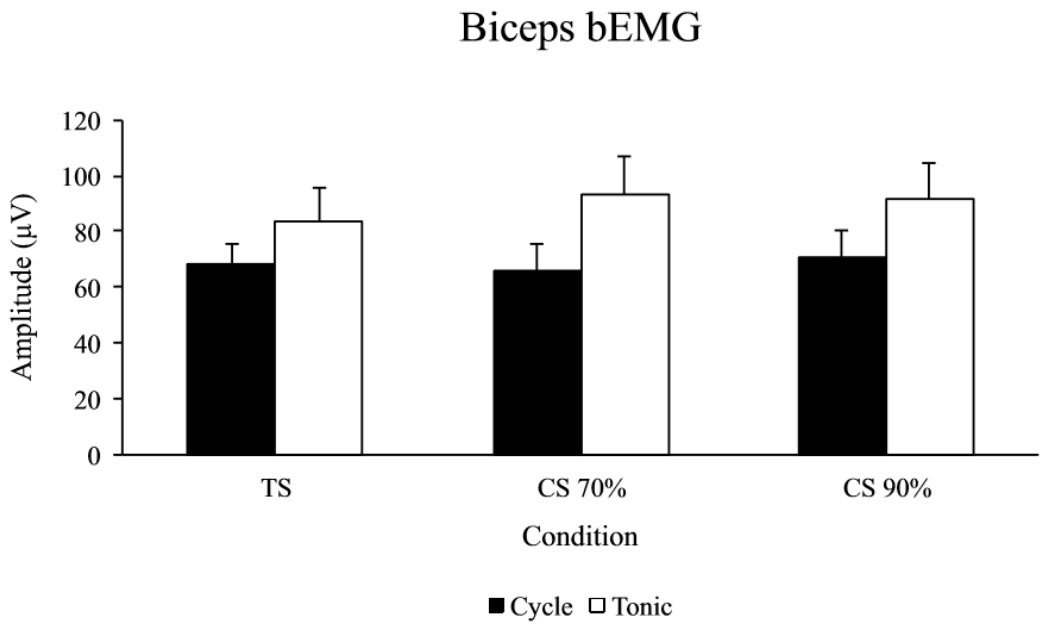
Biceps bEMG
Amplitude (μV)
120
100
80
60
40
20
0
TS
CS 70%
CS 90%
Condition
Cycle
Tonic

Figure 3.5

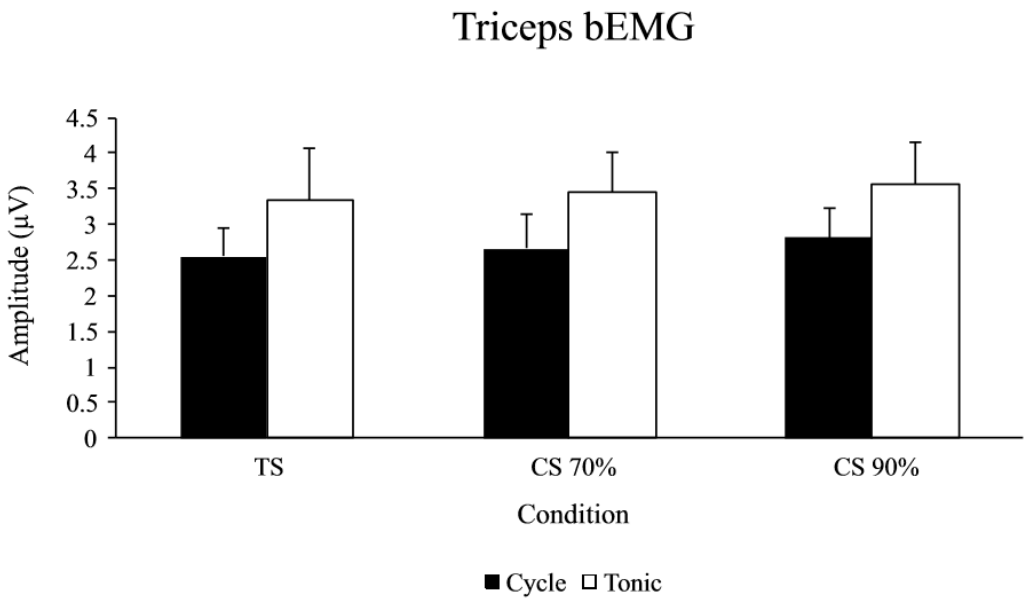
Triceps bEMG
Amplitude (μV)
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
TS
CS 70%
CS 90%
Condition
Cycle
Tonic

Figure 3.6

3.8 REFERENCES

Capaday, C., Lavoie, B.A., Barbeau, H., Schneider, C., & Bonnard, M. (1999). Studies on the corticospinal control of human walking. I. Responses to focal transcranial magnetic stimulation of the motor cortex. *Journal of Neurophysiology, 81*(1): 129–139.

Carroll, T.J., Baldwin, E.R., Collins, D.F., & Zehr, E.P. (2006). Corticospinal excitability is lower during rhythmic arm movement than during tonic contraction. *Journal of Neurophysiology, 95*(2): 914–921.

Chen, R. (2004). Interactions between inhibitory and excitatory circuits in the human motor cortex. *Experimental Brain Research, 154*(1): 1–10.

Chen, R., & Rothwell, J. (Eds.). (2012). *Cortical connectivity: Brain stimulation for assessing and modulating cortical connectivity and function*. Berlin: Springer.

Christensen, L.O., Andersen, J.B., Sinkjaer, T., & Nielsen, J.B. (2001). Transcranial magnetic stimulation and stretch reflexes in the tibialis anterior muscle during human walking. *Journal of Physiology, 531*(2): 545–557.

Copithorne, D. B., Forman, D. A., & Power, K. P. (2015). Premovement changes in corticospinal excitability of the biceps brachii are not different between arm cycling and an intensity-matched tonic contraction. *Motor Control, 19*(3): 223–241.

Davey, N. J., Romaiguere, P., Maskill, D. W., & Ellaway, P. H. (1994). Suppression of voluntary motor activity revealed using transcranial magnetic stimulation of the motor cortex in man. *Journal of Physiology, 477*(2): 223–235.

Di Lazzaro, V., Restuccia, D., Oliviero, A., Profice, P., Ferrara, L., Insola, A., Mazzone, P., Tonali, P., & Rothwell, J.C. (1998). Magnetic transcranial stimulation at intensities below active motor threshold activates intracortical inhibitory circuits. *Experimental Brain Research, 119*(2): 265–268.

Forman, D., Raj, A., Button, D. C., & Power, K. E. (2014). Corticospinal excitability of the biceps brachii is higher during arm cycling then an intensity-matched tonic contraction. *Journal of Neurophysiology, 112*(5): 1142–1151.

Giovannelli, F., Borgheresi, A., Balestrieri, F., Zaccara, G., Viggiano, M. P., Cincotta, M., & Ziemann, U. (2009). Modulation of interhemispheric inhibition by volitional motor activity: An ipsilateral silent period study. *The Journal of Physiology, 587*(22): 5393–5410.

Hess, A., Kunesch, E., Classen, J., Hoeppner, J., Stefan, K., & Benecke, R. (1999). Task-dependent modulation of inhibitory actions within the primary motor cortex. *Experimental Brain Research, 124*(3): 321–330.

Hunter, S. K., McNeil, C. J., Butler, J. E., Gandevia, S. C., & Taylor, J. L. (2016). Short-interval cortical inhibition and intracortical facilitation during submaximal voluntary contractions changes with fatigue. *Experimental Brain Research, 234*(9): 2541–2551.

Kujirai, T., Caramia, M. D., Rothwell, J. C., Day, B. L., Thompson, P. D., Ferbert, A., Wroe, S., Asselman, P., & Marsden, C.D. (1993). Corticocortical inhibition in human motor cortex. *Journal of Physiology, 471*: 501–519.

Manning, C. D. & Bawa P. (2011). Heteronymous reflex connections in human upper limb muscles in response to stretch of forearm muscles. *Journal of Neurophysiology, 106*(3): 1489–1499.

Opie, G. M., Ridding, M. C., & Semmler, J. G. (2014). Task-related changes in intracortical inhibition assessed with paired- and triple-pulse transcranial magnetic stimulation. *Journal of Neurophysiology, 113*(5): 1470–1479.

Ortu, E., Deriu, F., Suppa, A., Tolu, E., & Rothwell, J. C. (2008). Effects of volitional contraction on intracortical inhibition and facilitation in the human motor cortex. *Journal of Physiology, 586*(21): 5147–5159.

Petersen, N., Christensen, L. O., & Nielsen, J. (1998). The effect of transcranial magnetic stimulation on the soleus H reflex during human walking. *Journal of Physiology, 513*(2): 599–610.

Petersen, N. T., Butler, J. E., Marchand-Pauvert, V., Fisher, R., Ledebt, A., Pyndt, H. S., Hansen, N. L., & Nielsen, J. B. (2001). Suppression of EMG activity by transcranial magnetic stimulation in human subjects during walking. *Journal of Physiology, 537*(2): 651–656.

Pyndt, H. S. & Nielsen, J. B. (2003). Modulation of transmission in the corticospinal and group Ia afferent pathways to soleus motoneurons during bicycling. *Journal of Neurophysiology, 89*(1): 304–314.

Ridding, M. C., Taylor, J. L., & Rothwell, J. C. (1995). The effect of voluntary contraction on corticocortical inhibition in human motor cortex. *Journal of Physiology, 487*(2): 541–548.

Rossi S, Hallett M, Rossini PM, & Pascual-Leone A (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*, *120*:2008–2039.

Sidhu, S. K., Hoffman, B. W., Cresswell, A. G., & Carroll, T. J. (2012a). Corticospinal contributions to lower limb muscle activity during cycling in humans. *Journal of Neurophysiology, 107*(1): 306–314.

Sidhu, S. K., Cresswell, A. G., & Carroll, T. J. (2012c). Short-interval intracortical inhibition in knee extensors during locomotor cycling. *Acta Physiologica, 207*(1): 194–201.

Ziemann, U., Rothwell, J. C., & Ridding, M. C. (1996). Interaction between intracortical inhibition and facilitation in human motor cortex. *Journal of Physiology, 496*(3): 873–881.

CHAPTER 4 FUTURE DIRECTIONS

We presented the novel finding that SICI was present during arm cycling. This was only the second study to measure SICI in a primary muscle during a locomotor task, and was the first to directly compare it to intensity-matched tonic contractions. Surprisingly, SICI was not modulated in a task-dependent manner when compared to an intensity- and position-matched tonic contraction. SICI was likely not the main mechanism responsible for higher supraspinal excitability during arm cycling when compared to tonic contraction that we have previously demonstrated. The next steps for this research project will therefore include an attempt to discover the cortical mechanism underlying higher supraspinal excitability during arm cycling. This may include the study of other facilitative and inhibitory neural circuits such as SICF, ICF, LICI, and IHI. However, regardless of whether we are successful in discovering the responsible mechanism, the study of the interaction and relationship between cortical interneurons during arm cycling will add to the literature with respect to cortical modulation during cycling, a locomotor task, of which very little is known.

This study also brings to attention some methodological variables to be addressed in the future. For example, excitability of cortical circuits could be investigated during various intensities of arm cycling, which may influence the modulation of cortical inhibition and facilitation differently during locomotor and tonic tasks. Similarly, corticospinal excitability is known to change throughout the phases of locomotor tasks and vary across muscles involved in locomotor output. So, modulation of cortical excitability could be studied during various phases of arm cycling and from multiple arm muscles.

Finally, it would be beneficial to take measurements during truly unilateral and bilateral contractions, to determine the difference between the two, and to be able to compare more directly between locomotor and tonic contractions. This could be accomplished by introducing an arm crank force measurement during tasks.

This work gives insight into the nature of SICI during arm cycling and acts as a starting point to continue further investigation of cortical activity during locomotor tasks. This presents an opportunity to better understand the cortical influence on descending drive during locomotor tasks, which can be applied to the study of both healthy and clinical populations. It is our intention to add to the current literature with respect to cortical excitability during arm cycling, a locomotor task commonly used in a rehabilitative setting. Eventually, the end goal of better understanding cortical systems in the healthy population is to effectively study and understand when these systems are abnormal due to disease or dysfunction in the clinical population.