SHORT-INTERVAL INTRACORTICAL INHIBITION TO THE TRICEPS BRACHII DURING ARM CYCLING

By

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Abstract

Non-human animal work shows the existence of a network of spinal cells called central pattern generators (CPGs) that partially control locomotion. Indirect evidence shows that CPGs also contribute to human locomotion. However, humans require the integration of descending input from cortical motor-related areas for the generation and control of locomotive outputs. Unfortunately, the cortical circuits that modulate the excitability of the motor cortex during locomotor outputs are not well understood. Short-interval intracortical inhibition (SICI) is one circuit thought to help inhibit the motor cortex. The majority of work done to understand SICI has utilized isometric contractions, but evidence suggests that cortical circuits are modulated differently during locomotor outputs. Our lab has shown the presence of SICI to the biceps brachii during arm cycling, but did not investigate SICI to the triceps brachii, another vital muscle required for arm cycling. Examining SICI to the triceps may improve knowledge translation to neurological rehabilitation programs that utilize arm cycling.

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List of Abbreviations

AMT – Active motor threshold

CMEP – Cervicomedullary evoked motor potentials

CPG – Central pattern generator

CS – Condition stimulation

CST – Corticospinal tract

D-wave – Direct waves

EMG – Electromyography

FDI – First dorsal interosseous muscle

GABA – Gamma-Aminobutyric acid

$GABA_A$ – Gamma-Aminobutyric acid receptor subtype A

ICF – Intracortical facilitation

IHI – Interhemispheric inhibition

ISI – Interstimulus interval

I-wave – Indirect waves

LICI – Long-interval intracortical inhibition

MC – Motor cortex

MEP – Motor evoked potential

ppTMS – Paired-pulse transcranial magnetic stimulation

RMT – Resting motor threshold

SICF – Short-interval intracortical facilitation

SICI – Short-interval intracortical inhibition

TMES – Transmastoid electrical stimulation

TMS – Transcranial magnetic stimulation

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Chapter 1 Introduction

1.1 Overview

Our ability to locomote is an essential facet of human life. It consists of alternating rhythmic activity between flexors and extensors that causes displacement of the body (Dietz, 2002; Zehr et al., 2004). There are several forms of locomotion, such as walking, jumping, swimming, leg, and arm cycling. Indirect evidence suggests that human locomotion is partially controlled by specialized spinal cell networks known as central pattern generators (Capaday et al., 1999; Zehr et al., 2004; Zehr et al., 2009). Human locomotion also requires the integration of descending input from motor-related cortical regions to generate and control locomotion (Capaday et al., 1999; Petersen et al., 2001). Unfortunately, the control of these cortical regions during locomotion is not well understood. Arm cycling can be used as a model to investigate the cortical control of locomotion.

There are several cortical circuits within the cortical motor related areas that help modulate motor output. One circuit of interest is short-interval intracortical inhibition (SICI), which has been shown to exert its effects within a hemisphere (Kujirai et al., 1993). This cortical circuit allows each motor cortex to inhibit itself (Kujirai et al., 1993) and is thought to help with the selective activation of different muscles (Zoghi, Pearce & Nordstrom, 2003). SICI activity is investigated using transcranial magnetic stimulation (TMS) (Kujirai et al., 1993). Using TMS, SICI is predominantly investigated during isometric contractions of upper body musculature (Kujirai et al., 1993; Ridding et al., 1995; Fisher et al., 2002; Roshan et al., 2003) with very little known about SICI modulation during locomotive outputs. Our lab has previously demonstrated the presence of SICI to the biceps brachii during arm cycling (Alcock et al., 2019). However, Alcock et al. (2019) did not investigate the presence of SICI to the triceps brachii, another vital muscle required to produce arm cycling. The findings of SICI to the biceps cannot be applied to

the triceps brachii because SICI appears to demonstrate muscle specificity (Ridding et al., 1995; Zoghi et al., 2003). The thought of SICI being muscle-dependent is possible given the muscle dependency of corticospinal excitability, which is composed of supraspinal (cortical) and spinal input, during arm cycling (Spence et al., 2016). Spence and colleagues (2016) showed that the biceps brachii demonstrated phase-dependent modulation of corticospinal excitability, but the triceps brachii did not. This difference in phase-dependent modulation suggests that the triceps and biceps have different central control (Spence et al., 2016). In other words, since corticospinal excitability is composed of cortical and spinal input, changes to it could be a result of changes to cortical excitability due to the action of cortical circuits like SICI. The same study showed that although no phase-dependent modulation was noted for the triceps brachii, the spinal excitability was higher during elbow flexion (triceps are in a lengthened position) than elbow extension (triceps are in a shortened position) (Spence et al., 2016). This suggests that the increase in spinal excitability acts to compensate for inhibited cortical excitability during the elbow flexion phase of an extensor muscle (Spence et al., 2016). Extending this thought, it may be possible that cortical excitability to the triceps brachii will be more inhibited during elbow flexion, when the muscle is lengthened, compared to elbow extension, when the muscle is shortened during arm cycling to reduce unwanted movement. As such, this study aims to examine the modulation of SICI to the triceps brachii during arm cycling.

1.2 Purpose

The purpose of the proposed study is to investigate if SICI is present to the triceps brachii using arm cycling as a model of locomotion. Further, if SICI is present, this study hopes to investigate potential phase-dependent modulatory effects of SICI to the triceps brachii during an arm cycling revolution (i.e., during elbow flexion or extension when the triceps brachii lengthened and then shortened).

1.3 Research Hypotheses

It is hypothesized that:

1. SICI will be present to the triceps brachii during arm cycling.
2. SICI will be stronger at the point of lower triceps brachii muscle activity (i.e., SICI activity will be highest during elbow flexion, the point of lower triceps brachii activity)

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2.0 Review of Literature

2.1 Introduction

We are all born with the instinct to want to move from one location to another, or in other words, locomote. Initially, our movements are unstable, but we soon learn to crawl, walk, run, jump, swim, cycle, and so much more. Some of these movement outputs appear seemingly effortless and can often be done while engaging in other activities such as conversation. This suggests that the central nervous system has evolved to automate the process of locomotion to some degree. There is evidence to show that human locomotion involves the use of rhythmic alternation between flexors and extensors (Dietz, 2002; Zehr et al., 2004). This rhythmic movement is in part controlled by a specialized network of cells in the spinal cord known as central pattern generators (Capaday et al., 1999; Zehr et al., 2004; Zehr et al., 2009). Non-human animal work has shown that central pattern generators are capable of producing basic locomotor output patterns devoid of descending cortical input (Jordan, 1998). This is not the case for humans. Initiation of human locomotion requires descending input from the cortical areas (Capaday et al., 1999; Petersen et al., 2001). While much work has been done to understand the spinal contribution, very little is known about cortical control involved in locomotion.

Through years of work, we now have a general understanding of the cortical map and its functional regions. The primary motor cortex, premotor cortex, supplementary motor area, and sensory cortex are the orchestrators of producing descending input to elicit motor outputs (Reis et al., 2008). A study using functional magnetic resonance imaging has shown that the motor cortex plays a predominant role in controlling human cycling (Mehta et al., 2009). Input from cortical motor production areas travels down descending motor pathways. The pathways consist of cortical motor neurons that synapse onto descending tracts to affect motor output. Of the descending pathways, there are several descending tracts involved in the transfer of information, for example,

the reticulospinal (Matsuyama & Drew, 2000), rubrospinal (Yang et al., 2011), and corticospinal tracts (Welniarz et al., 2017). The corticospinal tract, for example, travels contralaterally, carrying information from cortical regions to muscles of the opposite side of the body. This review focuses on the corticospinal pathway, as it is thought to be one of the most prominent pathways involved in controlling human locomotion (Taylor et al., 2016; Welniarz et al., 2017).

The efficacy at which the corticospinal pathway communicates information from cortical regions to effector muscles is corticospinal excitability (Weavil & Amann, 2018). Corticospinal excitability consists of contributions from supraspinal and spinal regions. Considering supraspinal contributions, alterations in the cortical circuits may lead to potential modulation of corticospinal excitability. That is, decreases or increases to corticospinal excitability may be a result of decrease or increase motor cortex excitability (Weavil & Amann, 2018). In fact, a study from our lab investigating corticospinal excitability to the biceps brachii showed that it is higher during arm cycling than an intensity- and position- matched isometric contraction (Forman et al., 2014). By utilizing two stimulation techniques, transcranial magnetic stimulation (TMS) and transmastoid electric stimulation (TMES), the authors were able to compare supraspinal and spinal contributions, respectively, to the higher corticospinal excitability shown during cycling. They determined that higher corticospinal excitability during arm cycling was partly due to supraspinal mechanisms, though possible involvement of different cortical circuits were not examined (Forman et a., 2014). Other prior work utilizing TMS-induced motor evoked potentials (MEPs) reported changes in amplitudes during gait (Schubert et al., 1997, Capaday et al., 1999) and leg cycling (Pyndt & Nielsen, 2003). Changes in peak-to-peak MEP amplitude provides information regarding corticospinal excitability, where increases in amplitude represent increases in corticospinal excitability and decreases in amplitude represent decreases in corticospinal

excitability (Power et al., 2018; Weavil & Amann, 2018). Since MEPs involve cortical synapse, the authors above, Schubert et al. (1997), Capaday et al. (1999), and Pyndt & Nielsen (2003), speculate that changes in MEP amplitude may be related to changes in cortical excitability. As such, descending motor input that travels down the corticospinal pathway is modulated by cortical circuits and these circuits determine cortical excitability levels.

Cortical excitability reflects the responsiveness of cortical neurons to a perturbation and is a cumulative process of the excitation or the inhibition of cortical neurons (Badawy et al., 2012; Ly et al., 2016). The formation of cortical circuits is possible given the immense number of neuronal connections in cortical centers. Cortical interneurons synapse onto further interneurons and so on to create a large, interconnected network. Given the density of neurons and neuronal connections, the possibility of having a large number of cortical circuits is high. So far, cortical circuits have been classified as either excitatory or inhibitory and exist within (intracortical) or across hemispheres (interhemispheric) (Ni & Chen, 2008). The following discussion will focus on intracortical circuits, which can be classified as either intracortical facilitatory or intracortical inhibitory circuits (Lee et al., 2007). Intracortical inhibitory circuits are further classified as either short-interval intracortical inhibition (SICI) or long-interval intracortical inhibition (LICI) (Lee et al., 2007). As the name suggests, intracortical inhibitory circuits work to decrease cortical excitability (Lee et al., 2007). Comparatively, intracortical facilitation (ICF) circuits work to increase cortical excitability (Lee et al., 2007). During locomotor outputs, excitatory and inhibitory neurons that compose these cortical circuits in the motor cortex are active to different extents within the hemispheres (Li & Moult, 2012).

The activity of inhibitory and excitatory intracortical circuitry during isometric or locomotive outputs can be examined using paired-pulse TMS (ppTMS) (Kujirai et al., 1993; Lee

et al., 2007; Di Lazzaro & Ziemann, 2013; Sidhu et al., 2013; Alcock et al., 2019). Of interest to this review is the intracortical inhibitory circuit SICI, which is one of the circuits that assists the motor cortex in inhibiting itself (Kujirai et al., 1993). It is also thought to be a circuitry involved in the muscle's selective activation during motor output (Zoghi et al., 2003; Qian et al., 2019). It is one of the most widely examined cortical circuits, yet a majority of the work utilizes isometric contractions. Unfortunately, work done using isometric contractions likely cannot be used to describe the behaviour of SICI during locomotive outputs. The two types of motor outputs differ in the neural control (Carroll et al., 2006; Zehr & Duysens, 2004; Forman et al., 2014; Forman et al., 2016), and since SICI is a cortical circuit, the modulation may differ between the two motor outputs. Due to locomotion being such a pertinent aspect of human life, it is essential to investigate the role of SICI during locomotion.

In the past decade, only a few authors have explored the activity of SICI during locomotor outputs such as walking (Garnier et al., 2019), rhythmic arm activity during walking (Barthelemy & Nielsen, 2010) and leg cycling (Yamagushi et al., 2012; Sidhu et al., 2013; Sidhu & Lauber, 2020). Recently our lab demonstrated that SICI is present in the biceps brachii during arm cycling (Alcock et al., 2019). The ability to arm cycle is made possible due to flexion of the biceps and the extension of triceps brachii. However, Alcock and colleagues (2019) did not explore the modulation of SICI to the triceps brachii. The SICI findings to the biceps cannot be applied to the triceps brachii for several reasons. First, both muscles have different functions during arm cycling. In forward arm cycling, the biceps brachii pulls the arm cranks towards the individual and the triceps brachii pushes the arm cranks away from the individual. Studies from our lab demonstrate that corticospinal excitability is muscle dependent, with the biceps brachii showing phase-dependent modulation of corticospinal excitability, which is not present to the triceps brachii

(Spence et al., 2016; Power et al., 2018). So, it is logical to assume that if corticospinal excitability modulation is different between biceps and triceps brachii, then the cortical circuits that influence it may be differentially activated. Second, the electromyography (EMG) activity to the biceps and triceps brachii is different during arm cycling (Chaytor et al., 2020). Biceps brachii activity is strongest during flexion to pull the arm crank in, with little to no activity during the extension phase. This is expected as the anatomical function of the biceps is flexion. The same thought was applied to triceps brachii, since anatomically, it is an extensor. Highest EMG activity was detected during the extension phase as expected, but unlike the biceps, the triceps remained active during the flexion phase (Chaytor et al., 2020). This EMG activity during what is expected to be the "off period" for the triceps brachii could be explained by considering its actions as a stabilizer to the biceps brachii during arm cycling. Chaytor and colleagues (2020) did not utilize TMS to examine corticospinal excitability, however, differential modulation of the cortical circuits could alter the descending input to the motoneuronal pools of the biceps and triceps brachii that EMG detects. The third reason SICI in the biceps cannot be used to explain potential SICI in the triceps is related to the first two reasons. Biceps and triceps brachii are antagonistic muscles, with differences in intrinsic motoneuronal properties (Wilson et al., 2015). As such, the findings of SICI modulation in the biceps brachii from Alcock et al. (2019) may not apply to the modulation, if any, to the triceps brachii.

Although the findings from the biceps cannot be applied to the triceps, perhaps findings from other extensor muscles can be used to gauge SICI activity in the triceps brachii. For example, the knee extensors are to the lower body what the triceps brachii is to the upper body. Sidhu et al. (2013) and Sidhu & Lauber (2020) noted the presence of SICI in the knee extensors during cycling. Both studies also observed a difference in the strength of SICI depending on the task and phase of

the knee extensors (Sidhu et al., 2013; Sidhu & Lauber, 2020). On the other hand, Garnier et al. (2019) noted no phase-dependent change in SICI to the knee extensors while walking.

This review will discuss the findings from the few locomotor studies and those done with isometric contractions to understand SICI and its potential modulation in triceps brachii. Investigating how SICI is modulated to both prime movers can lend insight into cortical excitability during arm cycling. To the best of my knowledge, there are no known studies examining the activity of SICI to the triceps brachii during arm cycling. This information will add to the growing body of knowledge examining cortical excitability during locomotion and may have implications for rehabilitation purposes. Thus, the aim of this literature review is to gather information for a study interested in determining if SICI is present to the triceps brachii during arm cycling. First, this review will examine cortical excitability and intracortical communication. Secondly, it will discuss the corticospinal pathway in relation to its role as a conduit for descending motor information that is in part controlled by cortical circuits such as SICI. Thirdly, the method of eliciting SICI will be discussed. Finally, it will discuss some of the factors that modulate SICI.

2.2 Cortical Excitability

Cortical excitability is important for every aspect of our behaviour and is facilitated by the millions of neurons that form cortical circuits. The levels of excitability of these cortical circuits are mediated by neuronal communication as a result of interactions between neurotransmitter and their respective receptors (Badawy et al., 2012). Cortical excitability considers the whole cortex, whereas intracortical excitability focuses on one hemisphere. Intracortical excitability is maintained by a delicate balance between excitatory and inhibitory cortical circuitry, which then modulates cortical output (Ni & Chen, 2008). Simply put, intracortical communication is the propagation of action potentials down a neuron within a hemisphere to affect another neuron via neurotransmitter release (Roland et al., 2014). These neurons may exert an excitatory or an

inhibitory effect. Cortical neurons are constantly being given input that could easily overwhelm cortical circuitry if not kept in check. As a result, inhibitory neurons play a dynamic role in ensuring the efficient processing of information. A review by D'Souza and Burkhalter (2017) suggests that the maintenance of excitation and inhibition is different within each layer of the cortex. Studies suggest that there is a greater amount of inhibition in superficial layers compared to deeper layers, and this is largely due to the function of cells within each layer (Bastos et al., 2015; Michalaread et al., 2016).

The motor cortex is traditionally divided into six layers. The neurons found in layer five are of interest because, in primate models, this layer is responsible for the formation of the corticospinal pathway (Anderson et al., 2020). In non-human animal models, it has been shown that layer five, in particular, contains long-range neural projections to other cortical areas, making it a prominent layer in neural communication and motor control (Veinante et al., 2000; Hattox & Nelson, 2007). Some suggest that the motor cortex connectivity can be described by two interconnected circuits instead of six distinct layers (McColgan et al., 2020). The first circuit comprises layers two to five, and the second circuit comprises layers five and six. The first circuit is thought to receive excitatory input that then projects to the second circuit. This suggests that corticospinal neurons in layer five receive input from layers two and three (McColgan et al., 2020). This is further supported by studies examining the mechanism of TMS as described in the sections below, where TMS activates interneurons in the superficial layers (two and three) that synapse onto corticospinal neurons in the deeper layers (Aberra et al., 2020).

The excitability of each motor cortex is dictated by the activity of the intracortical faciliatory and inhibitory circuits. At any given instance, there are multiple cortical circuits acting to modulate excitability. In general, intracortical facilitation (ICF) within the motor cortex causes

an increase in TMS evoked MEP amplitude (Kujirai et al., 1993). Comparatively, intracortical inhibition causes decreased MEP amplitude (Kujirai et al., 1993). However, in both cases there can also be no change in MEP amplitude as no circuit works independently. For example, Garnier et al. 2019 noted an increase in MEP amplitude in the vastus lateralis during downhill walking, but this increase did not affect the ratio between conditioned and unconditioned MEPs. Therefore, they were unable to note any changes in SICI between the modes of walking, although the corticospinal excitability increased during downhill walking (Garnier et al., 2019). This illustrates that cortical excitability is not as simple as noting increases or decreases in MEP amplitude and requires an awareness of the synergistic cortical circuitry effects.

The two forms of intracortical inhibition, LICI and SICI, are thought to be mediated by gamma-Aminobutyric (GABA) neurons (Jones 1993; Chen et al., 2021). However, they are two independent systems with different GABA receptors mediating their activity (Tokimura et al. 1996; Ziemann et al. 1998b; Chen & Garg, 2000). In the motor cortex, layers two to three have the largest concentration of GABAergic neurons with vertical projections that synapse onto cortical CST neurons (Jones 1993; Keller 1993). Thus, activation of these GABAergic interneurons through ppTMS may result in the inhibitory effects being stronger than faciliatory effects on the corticospinal pathway. This may result in MEP amplitude inhibition.

2.3 The Corticospinal Pathway

The corticospinal pathway is relevant to this discussion as descending motor-related information travels down from cortical representation areas to the spinal cord to influence muscle activation. The motor output of the corticospinal pathway is in part regulated by inhibitory interneurons in the motor cortex, which indirectly projects on the corticospinal neurons (Chen, 2000; Rossini & Rossi, 2007; Brownstein et al., 2020). The corticospinal pathway has been an area of interest for more than a century, with thoughts of it dating back to 1853 (Lassek, 1995). Much

has been done to understand this pathway's anatomy and physiology, although most of the work employs non-human animal models (Nudo & Masterton, 1990). However, advances in technology have been able to describe the anatomy and physiology of the corticospinal pathway in humans more accurately. As such, it is now known to be important in voluntary motor control (Jang, 2009).

The tract portion of the pathway originates within the motor and sensory cortices, with other motor areas contributing to it as well (Seo & Jang, 2013; Welniarz et al., 2017). About 37% of the axonal population to the tract arises from the motor cortex, with approximately 32% from the sensory cortex and the remaining 32% from other motor-related areas (Seo & Jang, 2013). About 80 - 90% of the tract decussates at the medulla, giving rise to the tract's lateral portion. The remaining portion (10-20%) remains ipsilateral, creating the tract's ventral portion, which largely provides input to axial muscles (Welniarz et al., 2017). Depending on the muscle of interest, the corticospinal pathway makes monosynaptic or polysynaptic connections (Maeda et al., 2015). Monosynaptic connections are thought to exist for small muscles that require extremely fine motor control, such as the muscles found in the hand (Lemon et al., 2002; Lemon, 2008). The biceps brachii, a primary mover in arm cycling, has been shown to be innervated by mostly monosynaptic corticospinal connections (Peterson et al., 2001). Polysynaptic connections occur when corticospinal neurons synapse with spinal motoneurons through two or more interneurons (Kamiyama et al., 2015). Polysynaptic connections are thought to be reserved for larger muscles involved in gross movement (Kamiyama et al., 2015). For example, the triceps brachii is predominantly innervated by polysynaptic connections (Brouwer & Ashby, 1990). Ultimately this path serves to connect cortical motor neurons with lower motoneurons to carry information that produces locomotor output.

2.4 Measuring Motor Cortex Excitability

2.41 Transcranial Magnetic Stimulation (TMS)

TMS was first introduced in the UK by Anthony Barker as a painless method of stimulating the human cortex using electromagnetic waves (Baker, Jalinous, & Freeston, 1985). It has since been used to non-invasively investigate cortical and corticospinal physiology (Pascual-Leone et al., 1998). It can be used to study many cortical areas, but for the purpose of this review, the use of TMS is discussed in the context of the motor cortex. There is a range of TMS paradigms used to highlight different aspects of cortical and corticospinal excitability. As such, a single-pulse TMS paradigm over the motor cortex is used to investigate corticospinal excitability (Kobayashi & Pascual-leone, 2003). Whereas ppTMS is used to investigate intercortical and intracortical circuitries, which contributes to motor cortex excitability (Kujirai et al., 1993). To study intracortical circuitries, two coils are used to carry out the ppTMS paradigm (Ferbert et al., 1992). Alternatively, a single coil connected to a BiStim module can be used to produce the ppTMS paradigm to study intracortical circuitries (Schäfer et al., 1997; Hanajima et al., 2002). Regardless of the paradigm, the stimulation intensity and location of the coil play a role in determining the cortical regions activated (Edgley et al., 1990).

TMS acts by producing magnetic pulses from a coil placed over the scalp through which current is passed (Kobayashi & Pascual-Leone, 2003). The magnetic field acts perpendicular to the current flow. The magnetic field force can be hampered by extracerebral tissues, such as the scalp and the meninges (Klomjai et al., 2015). When the coil is held tangential to the scalp and a single pulse stimulation is given, there is preferential activation of presynaptic corticospinal interneurons, causing a descending volley of indirect waves (I-waves) to travel down the corticospinal pathway resulting in an evoked potential at the muscle of interest (Day et al., 1989; Burke et al., 1993; Kobayashi & Pascual-Leone, 2003; Di Lazzaro et al., 2004; Kolmjai et al.,

2015). Essentially, I-waves occur because of the transsynaptic activation of corticospinal neurons that create the CST (Wagle-Shukla et al., 2009). There are early and late I-waves, denoted as I_1, I_2, and I_3. Early waves are thought to result from monosynaptic connections and late waves are thought to be a result of polysynaptic connections (Terao & Ugawa, 2002). As TMS intensity increases, I_3-waves are recruited first, followed by I_2, then I_1 waves (Kolmajai et al., 2015). At higher stimulation intensities, TMS can directly active corticospinal neurons causing direct (D) waves (Wagle-Shukla et al., 2009; Kolmajai et al., 2015). These descending volleys cause muscle activity that can be detected using EMG.

In this review, I will discuss a ppTMS paradigm used to investigate intracortical circuits. ppTMS involves the use of a conditioning stimulus (CS) preceding a test stimulus (TS) at a specific interstimulus interval (ISI) over the motor cortex of interest (Hallett et al., 2000; Chen et al., 2008). There are two common stimulation protocols using ppTMS that involve different CS and TS intensities. The first method involves using a suprathreshold CS and suprathreshold TS, which is used to investigated LICI (Chen, 2004). This method will not be discussed. The other method of interest to this review involves a subthreshold CS and a suprathreshold TS and can be used to investigate ICF and SICI (Kujirai et al., 1993; Ridding et al., 1995c; Chen, 2004).

Subthreshold stimulations are given below the threshold for producing a MEP in a muscle of interest (Kujirai et al., 1993; Ridding et al., 1995c). In contrast, suprathreshold stimulations are given above the known threshold to cause a response in the muscle of interest (Ridding et al., 1995c). The CS causes modulation of the TS MEP amplitude compared to when the TS is given alone (Hallett, 2000). The CS is thought to have a cortical effect because it is not high enough to produce an evoked muscle response but modulates the TS evoked MEP amplitude (Ridding et al., 1995c). The subthreshold CS is thought to activate low threshold inhibitory interneurons that

project to cortical motoneurons (Nakamura et al., 1997; Orth et al., 2003). This causes a reduction in TS-induced MEP amplitude. To confirm that ppTMS activates intracortical inhibition, Kujirai et al. (1993) investigated the effect of moving the coil that produced the CS relative to the maintained position of the TS coil. By moving the CS coil in an anterior or posterior direction over the motor strip, they noted a more inhibited test response in one location. Thus, they concluded that there is some level of locality of the inhibitory circuit being tested. Similarly, Ashby et al. (1999) showed intracortical inhibition could be evoked when subdural electrodes were spaced 1cm apart, but any greater distance produced no inhibition.

The ISI between the CS and the TS is essential in targeting the correct intracortical cortical circuit. ICF causes MEP amplitude facilitation and is noted using ISIs of 8-30ms (Ziemann et al. 1996; Nakamura et al. 1997). Another faciliatory intracortical circuit, known as short-interval intracortical facilitation, develops over a period of 1-5ms (Chen & Garg, 2000; Van den Bos et al., 2018). For SICI, an ISI of approximately 1-5ms is used (Kujirai et al., 1993). Some reports use an ISIs of 1-4ms (Roshan et al., 2003), 1-6ms (Chen, 2004), and 2-5ms (Boroojerdi et al., 2000). The use of TMS does not directly activate the inhibitory neurons that cause the MEP suppression (Chen et al., 2021). Instead, TMS activates interneurons that synapse onto inhibitory GABAergic neurons to produce SICI (Chen et al., 2021). It also appears that the different I-waves are affected differently in the presence of SICI, where I_3 has the highest susceptibility, and I_1 has the lowest susceptibility (Hanajima et al., 1998).

Another critical factor to consider when studying SICI is the intensity of the CS (Kobayashi & Pascual-leone, 2003). The CS is intended to suppress the MEP caused by the TS by activating lower threshold inhibitory neurons that involve $GABA_A$ receptors (Ibanez et al., 2020). CS intensity can be determined when the muscle of interest is at rest or during an active state. Studies

that investigate SICI during a resting state or during an isometric contraction have used CS intensities between 60-80% of the resting motor threshold (RMT) (Kujirai et al., 1993; Schäfer et al., 1997). RMT is obtained when the muscle of interest is at rest and is characterized by the minimum amount of stimulation required to elicit a MEP during half of the trials (Orth et al., 2003; Borckardt et al., 2006). Work has shown that the inhibition that arises with CS intensity of 80% RMT is due to cortical mechanisms instead of spinal mechanisms because no changes in spinal excitability were observed (Kujirai et al., 1993; Chen et al., 1998; Chen et al., 2021). Studies using arm and leg cycling as a model of locomotion determine CS intensity based on the active motor threshold (AMT). The AMT is characterized by a stimulation intensity that produces clearly distinguishable MEPs from the background EMG signal during movement for half of the trials (Orth et al., 2003; Sidhu et al., 2013; Alcock et al., 2019; Sidhu & Lauber, 2020). Alcock and colleagues (2019) used CS intensities of 70% and 90% of the AMT and showed that both intensities were equally effective at inducing SICI to the biceps brachii during arm cycling. Yamaguchi et al. (2012) chose to use 80% of AMT to elicit SICI in the tibialis anterior and soleus during a leg pedalling study. Sidhu et al. (2013) tested CS intensities between 70-95% of the AMT during leg cycling. In a similar study, Sidhu & Lauber (2020) used 70% of the AMT during the same leg cycling task. The comparison between isometric and rhythmic locomotor outputs shows that, in general, the CS has to be increased during locomotor outputs. This increase in intensity may be due to the increase in supraspinal excitability during locomotor outputs compared to isometric contraction (Forman et al., 2014). An increase in excitability may decrease the responsiveness of inhibitory interneuron. As such, slightly higher intensity is required to achieve the same response from the CS.

Orth et al. (2003) suggest that CS intensities should be expressed as a percentage of individual thresholds for SICI compared to the AMT to control for within- and between-subject variability. Using the first dorsal interosseous muscle, Peurala et al. 2008 demonstrated a correlation between ISI and the chosen CS intensity, adding a layer of complexity to measuring an already complex cortical circuit. They showed that if the ISI and CS were not chosen carefully, then the experimental protocol is at risk of contaminating SICI with short-interval intracortical facilitation (SICF). They tested several ISIs (1.54, 1.97, 2.61, 3.50, 4.25ms) where SICF has been previously demonstrated and used CS intensities ranging from 50% to 120% AMT. They maintained the TS intensity so that it elicited a 1mV MEP when given without the CS. They found that SICI demonstrated a sigmoidal curve with increasing CS intensity at 1.54 and 1.97ms and was the strongest at 1.97ms. At other ISI's they noted the amount of SICI represented more of a U-shaped curve as the CS intensity increased, which suggests an ideal CS intensity range for testing at other ISIs. A commonly used ISI when testing SICI is approximately 2.5ms. They show that at ISI of 2.61ms, the amount of SICI increases at low CS intensities but decreases past CS intensities 90% of the AMT (Peurala et al., 2008). As such, it is recommended that when using an ISI of 2.5ms, the CS should be no greater than 90-95% AMT (Peurala et al., 2008).

Regarding the TS, it is set at an intensity that elicits a MEP peak-to-peak amplitude of 1mV when given alone (Kujirai et al., 1992; Sanger et al., 2001). However, the study's that use 1mV as a target threshold typically use isometric contractions. Work using leg cycling as a model of locomotion set the TS intensity to elicit a MEP amplitude between 2-3mV in the vastus lateralis, which was approximately 140% of the AMT (Sidhu et al., 2013). Another study using arm cycling as a model of locomotion set the TS intensity at 120% of the AMT (Alcock et al., 2019). The authors chose to use 140% and 120% AMT, respectively, to match it to the average MEP amplitude

achieved during cycling and to ensure that SICI measurements were not affected by size-dependent differences of the test-MEP (Alcock et al., 2019).

In order to quantify the amount of SICI present to a muscle, the MEPs obtained from ppTMS (CS-TS) have to be made relative to the MEPs obtained from using the TS intensity alone (Sidhu et al., 2013; Alcock et al., 2019; Sidhu & Lauber, 2020). If the MEP amplitude obtained from ppTMS is similar to the MEP amplitude obtained from TS alone, then this reflects reduced SICI (Brownstein et al., 2020). SICI is also reported as a ratio ($i.e.$ $\frac{ppTMS\ MEPs}{TS\ MEPs}$) expressed as a percentage (Sidhu et al., 2013; Alcock et al., 2019; Sidhu & Lauber, 2020). Percentages less the 100% indicate cortical inhibition with MEP amplitude reduction present, whereas anything greater than 100% indicates cortical facilitation, with MEP amplitude increases present (Sidhu et al., 2013).

2.42 Electromyography (EMG)

In neurophysiological studies, researchers need a method of quantifying the effect stimulations, such as TMS, have on the corticospinal pathway. As such, responses are often detected at the muscle of interest by using EMG. There are several types of EMG with numerous applications. However, for this review, only surface EMG will be discussed.

Unlike other methods of EMG, surface EMG is a non-invasive tool that is used to record muscle's electric activity in humans (DeLuca, 1997). EMG detects the cumulative electrical input made by a motor unit, defined as a single motoneuron and all the muscle fibres it innervates (Farina et al., 2004). It is a measure of global motor unit activity that takes into account peripheral and central properties (Farina et al., 2004). EMG records these signals through the use of electrodes placed on the surface of the skin (DeLuca, 1997). Typically, electrodes are placed parallel to the muscle fibres and over the muscle belly (DeLuca, 1997). There are several options for electrode arrangement, all of which have advantages and disadvantages. The most common form of

electrode placement is in a bipolar fashion. Two electrodes are placed over the muscle belly and a ground electrode is placed further away on a non-active component such as a bony protrusion (Merletti & Parker, 2004; Corneal et al., 2005). The details of the factors that affect EMG, such as the interelectrode distance, electrode size, placement of electrodes, the amount of tissue separating the muscle and the skin, and cross talk will not be discussed in this review (Farina et al., 2004; Merletti & Parker, 2004).

Nonetheless, the EMG signal seen on a computer screen is generated by the electrical activity of the muscles (Farina et al., 2016). Action potentials travel down motoneuronal axons and cross the motor endplate to generate endplate potentials. These potentials usually exceed the voltage threshold of the muscle fibre, causing muscle fiber depolarization. It is generally thought that when TMS is given over the motor cortex during resting states, it causes the motor units to be recruited in the same manner as volitional activity recruitment (Bawa & Lemon, 1993; Rothwell, 2007). Based on previous assumptions that all the fibers in a motor unit get activated, then properly placed electrodes should result in the best summation of motor unit action potentials (Garcia et al., 2017). As such, in some arm cycling studies, electrodes are placed over the "muscle belly" or "midline" of the triceps and biceps brachii (Forman et al., 2014; Forman et al., 2015; Spence et al., 2016; Alcock et al., 2019).

These responses are detected as a voltage and must be converted to a digital signal to be compatible with a computer. Electrical signals from the muscle are very small and as such, the signal is amplified. Additionally, the signal is filtered to remove any background noise and reduce the impact of the 60 Hz hum (DeLuca, 1997). It can then be analyzed by using commercially available software. The choice of analysis is up to the researcher's discretion and the demands of the research question.

2.5 Arm Cycling as A Model of Locomotion

Arm cycling is used as a rehabilitation tool for individuals living with impairments following a stroke or spinal cord injuries, with the intent of fostering neuroplasticity and maintaining functional locomotor-like outputs (Chaytor et al., 2020). Similar to all non-human quadrupeds, arm and leg activity appears to be coupled during locomotor outputs (Zehr, 2005; Zehr et al., 2007; Zehr et al., 2009). This coupling is thought to be controlled by a "common core" (Zehr, 2007) that is composed of CPG's which are able to control rhythmic motor outputs (Calancie et al., 1994; Dimitrijevic et al., 1998; Zehr et al., 2004; Zehr, 2005; Solopova et al., 2016). Zehr and colleagues (2004, 2005, 2016) show that arm cycling is similar to leg cycling in that they are both partially mediated by CPGs. These studies provide support for the contribution of spinal regions to arm cycling. Human locomotor outputs, however, are more reliant on cortical areas than non-human animals (Nielsen, 2003; Yang & Groassini, 2016). Direct cortical contributions have been shown in studies involving both leg (Sidhu et al., 2012) and arm cycling (Carroll et al., 2006; Forman et al., 2014; Forman et al., 2015).

Further, arm cycling is the chosen model of locomotion as our lab has used it for several years to investigate locomotor output. Thus, it makes sense to use this design. Secondly, much of the literature investigating SICI has chosen to do so using upper body musculature. Hence, it would be more plausible to continue to investigate SICI to the upper limbs. Thirdly, Barthelemy & Nielsen (2010) have shown that SICI is present in the upper limb musculature during locomotion and our lab has demonstrated the presence of SICI during arm cycling (Alcock et al., 2019). Naturally, this review is aiming to build on the work conducted by Alcock and colleagues (2019). Arm cycling also enables better head stability and increases the ease at which the ppTMS paradigm can be applied compared to other locomotor outputs such as walking and leg cycling. As such, arm cycling is the chosen model.

2.6 Interactions Between Cortical Circuits

It would be naïve to assume that one circuit acts to modulate motor cortex excitability devoid of influence from the other circuits. The following section will briefly discuss potential interactions between circuits, specifically relating to SICI. Eliciting the three predominantly studied intracortical circuits (SICI, LICI, ICF) and interhemispheric inhibition (IHI) involves the use of ppTMS. So, studies examining the different interactions between the circuits rely on changing the ISI and the TS intensity.

2.61 SICI and other Inhibitory Circuits

Sanger et al. (2001) tested the hypothesis that different cortical circuits mediate LICI and SICI by changing the TS intensity. They indicated that if the two inhibitory processes had different reactions to changing the TS intensity, then they are mediated by two different circuits. They noted different reactions of SICI and LICI, with no correlation between the extent of SICI and LICI. The neurons responsible for SICI were more susceptible to higher TS intensities than the neurons responsible for LICI. As such, they provided evidence to suggest two different neuronal circuits (Sanger et al., 2001). Pharmacological studies have corroborated that LICI and SICI are mediated by different GABA receptors (Hanajima et al., 1998; Werhahn et al., 1999). Research shows that SICI has no effect on LICI, but this relationship might not be the same in reverse as LICI may act to inhibit SICI (Chen, 2004). In some cases, LICI may negate SICI altogether during resting state (Sanger et al., 2001). Daskalakis et al. (2002) also examined the interaction between SICI and interhemispheric inhibition (IHI). IHI is related to contralateral neurons that exert their inhibitory effect on the opposite homologues cortical area (Daskalakis et al., 2002; Chen et al., 2004). Daskalakis and colleagues (2002) found that IHI significantly reduced SICI, but SICI had no effect on IHI. Unlike the effects of LICI on SICI, IHI reduced SICI but did not completely negate its presence. IHI may have a milder effect on SICI than LICI because it involved inhibition from the

other motor cortex. Comparatively, LICI is inhibition within the same hemisphere similar to SICI. Nonetheless, other inhibitory phenomenon work to decrease SICI.

2.62 SICI and Faciliatory Circuits

SICI's interaction with faciliatory circuits is rather complex, particularly with short-interval intracortical facilitation. Short-interval intracortical facilitation is due to the summation of I-waves of the corticospinal neurons, resulting in MEP facilitation. It has the highest activity at three different peaks (ISI of 1.5, 2.9, and 4.5 ms) (Ziemann et al., 1998; Wagle-Shukla et al., 2009). Comparatively, SICI is thought to exert the opposite behaviour, resulting in the suppression of I-waves to decrease MEP amplitude (Wagle-Shukla et al., 2009; Shirota et al., 2010). If the ppTMS is not carefully administered, the effects of SICI may be contaminated with short-interval intracortical inhibition, as they interfere with each other (Peurala et al., 2008; Wagle-Shukla et al., 2009; Shirota et al., 2010). Either a reduction of SICI is noted, or the presence of short-interval intracortical facilitation is seen. Experiments by Wagle-Shukla et al. (2009) show that as the TS intensity increases, SICI also increases while ICF and short-interval intracortical facilitation decrease. However, with increasing CS intensities up to 90% AMT, short-interval intracortical facilitation appeared to be stronger in the presence of SICI than alone. Thus, Wagle-Shukla and colleagues (2009) suggest that SICI facilitates short-interval intracortical facilitation, although they remain unsure about the mechanisms and warn that the results may be due to contamination of the cortical circuits. Peurala et al. (2008) would agree with this conclusion as they highlight the importance of accounting for ISI in avoiding contamination, a factor Wagle-Shukla did not consider.

The exact mechanisms of all the cortical circuits are yet to be determined. However, each cortical circuit has a distinct pathway based on its interaction with changing CS and TS intensities, along with changes in ISI. Additionally, pharmacological studies using Lorazepam, a $GABA_A$

receptor agonist, noted enhanced levels of SICI (Ziemann et al., 1996b; Di Lazzaro et al., 2000; Ilić et al., 2002) indicating that SICI $GABA_A$ receptors (Ziemann, 2004). Comparatively, short-interval intracortical facilitation utilizes glutamate and is reduced by drugs that increase $GABA_A$ activity (Hanajima et al., 1998; Werhahn et al., 1999; Wagle-Shukla et al., 2009). Nonetheless, it cannot be denied that these cortical circuits interact with each other to some extent, and it is a balance between them that determines the final impact on all motor outputs. As such, investigating SICI during locomotive outputs, such as arm cycling, will add to the growing field of understanding cortical circuitry.

2.7 A Cortical Circuit: Short-Interval Intracortical Inhibition (SICI)

2.71 Functional Significance of SICI

Inhibition within motor-related areas was first demonstrated in non-human animal studies, where authors noted stimulation to the exposed cortex resulted in reduced excitability of neurons (Krnjevic et al., 1966 a, b, c). Kujirai et al. (1993) were one of the first groups to replicate these results in conscious man and demonstrate the presence of inhibitory circuits in man. In healthy subjects, when a motor task requires selective activation of a muscle, the intracortical inhibition of the surrounding cortical representation areas increases to prevent unwanted movement (Beck et al., 2008). SICI being an inhibitory cortical circuit contributes to the selective activation of different muscles (Zoghi et al., 2003). SICI is mainly thought to occur in the motor cortex and possibly other motor-related areas rather than the subcortical or spinal levels (Nakamura et al., 1997; Di Lazzaro et al., 1998; Hanajima et al., 1998) for the following reasons. 1) Inhibition of MEP amplitude was not present when the TS was evoked using electrical stimulation. Electric stimulation, unlike TMS, results in the opposite descending volley wave order (D-waves followed by I-waves). MEPs that arise from electrical stimulation consist mainly of D-waves that are not subject to changes in cortical excitability because they are thought to originate deep in the

subcortical white matter instead of the cortical grey matter (Rothwell et al., 1994; Terao & Ugawa, 2002). Essentially, D-waves arise from the direct activation of the neurons of the motor cortex instead of the transsynaptic neurons responsible for I-waves. 2) Although CS is a subthreshold stimulus, it causes EMG suppression but does not inhibit the spinal H-reflex (Kujirai et al., 1993). This suggests that the CS used in the ppTMS paradigm to elicit SICI affects cortical activity but not spinal motoneurons. 3) Additionally, a positron emissions tomography monitoring the cerebral blood flow changes during ppTMS of the motor cortex noted differences in blood flow when the ISI was 3ms (activation of SICI). A positive correlation was obtained between blood flow and the amount of inhibition observed in the motor cortex (Strafella & Paus, 2001).

Most studies treat SICI as one entity. However, some research demonstrates two distinct phases of SICI, one at approximately 1ms and the other at approximately 2.5ms (Fisher et al., 2002; Hanajima et al., 2003; Roshan et al., 2003). The study conducted by Fisher and colleagues (2002) used TMS threshold tracking, an alternate method of investigating SICI not discussed in this review as our lab does not utilize this technique. To validate these findings of two different phases, Roshan et al. (2003) used ppTMS and obtained similar results to Fisher et al. (2002). In collaboration with other works, both studies provide punitive mechanisms to explain SICI being strongest at 1ms and 2.5ms.

The mechanisms of the first phase have yet to be understood but it is thought that intrinsic properties of the neurons, such as the refractory period, may play a role (Fisher et al., 2002). The second phase of SICI may be related to synaptic inhibition (Fisher et al., 2002). Pharmacological investigations show that SICI, specifically at an ISI of 2.5ms, is modulated by $GABA_A$ receptors (Ziemann et al., 1996b; Di Lazzaro et al., 2000; Ilić et al., 2002). However, it is not known why maximum SICI occurs at 1ms and 2.5ms. It has been postulated that at 1ms, the TS activates

neurons one synapse away from neurons activated by the CS. The increase of SICI at 2.5ms might be due to the TS activating neurons two synapses away from neurons activated by the CS (Roshan et al., 2003). Another potential mechanism is that 2.5ms represents the time for which the excitability of the low-threshold neurons have recovered sufficiently from the CS to be activated again by the TS (Roshan et al., 2003). This explanation suggests that increasing the TS intensity should reduce the ISI at which a maximum SICI is noted. However, Roshan et al. (2003) did not observe any changes in MEP amplitude when they increase TS intensity. Nonetheless, there is speculation that the second phase of SICI more accurately represents intracortical inhibition than the first phase (Fisher et al., 2002; Hanajima et al., 2003; Roshan et al., 2003). In a previous study conducted by our lab examining SICI, an ISI interval of 2.5ms was used (Alcock et al., 2019). As such, the study this review hopes to inform will also utilize ISI of 2.5ms to target synaptic inhibition compared to the neuronal refractory period.

SICI is not a "one size fits all" phenomenon. It demonstrates high individual variability (Awiszus et al., 1999). There is evidence to suggest that SICI is greater in older individuals compared to their younger counterparts at rest (McGinley et al., 2010). SICI exhibits differences in neurological cases. Studies show that it is reduced in Parkinson's (Ridding et al., 1995a), Tourette's disease (Ziemman et al., 1997), dystonia (Ridding et al., 1995b), Alzheimer's (Liepert et al., 2001), and schizophrenia (Daskalakis et al., 2002). Additionally, SICI is reduced during a contraction compared to resting states (Ridding et al., 1995c). No matter the demographic, population, or activity state of the individual, the decrease in SICI is thought to represent a "release" in cortical representation areas to allow for ease of movement (Floeter & Rothwell, 1999). The following section will discuss the modulation of SICI during rest and contraction and potential task, phase, and muscle-dependent effects of SICI.

2.72 SICI During Resting and Contracting States

Prior to 1995, most work conducted to investigate motor cortex excitability elicited the activity of inhibitory cortical circuits during rest (Kujirai et al., 1993). Compared to resting states, voluntary contractions increase the excitability of the corticospinal pathway (Forman et al., 2014; Forman et al., 2015). As such, Ridding and colleagues (1995c) wanted to determine if SICI activity differed between rest and voluntary motor output (i.e., isometric contraction of the hand muscles). They chose to study SICI during resting and active states of the FDI. They noted that compared to rest, unilateral contraction of the FDI resulted in less suppression of the TS-induced MEP during a ppTMS paradigm. In other words, during a slight contraction (5% of maximum voluntary contraction), SICI is reduced compared to when the FDI is at rest. These findings regarding the impact of volitional contraction were confirmed by other authors investigating SICI to small muscles in the upper body (Fisher et al., 2002; Roshan et al., 2003; Zoghi et al., 2003; Zoghi & Nordstrom, 2007; Jaberzadeh et al., 2007). Although, Ortu and colleagues (2008) showed that SICI is reduced during volitional contractions only when the CS is greater than 80% of the AMT. At CS of 70% AMT, they noted the amount of inhibition was similar during active and rest conditions.

It is thought that, perhaps, downregulation of inhibitory neurons causes a reduction in SICI during active states (Ridding et al., 1995c). These inhibitory neurons project onto neurons of the motor cortex that are responsible for the intended contraction. Thus, reduced activity of inhibitory neurons results in decreased GABA release and, thus, lower concentrations. Hence, the amount of SICI present decreases, enabling ease of movement (Ridding et al., 1995c; Reynolds & Ashby, 1998). Contrary to this thought, some propose that the activity ICF is greater during volitional contractions, which counteracts the effect of SICI, reducing the overall amount of inhibition (Ortu et al., 2008). Evidence suggests that SICI and ICF, specifically SICF, interact with each other, although they have distinct pathways and mechanisms (Ortu et al., 2008).

To this day, SICI has been predominantly investigated during unilateral isometric contractions, with only a few studies examining its modulation during locomotion. This is partly the case as the added factor of rhythmic movement increases the variability and complexity of observing SICI. As it stands, studies by Boroojerdi et al. (2000) and Orth et al. (2003) show that SICI is highly variable between subjects and within subjects at different time points. Orth et al. (2003) noted that the variability for SICI was greater than the variability for ICF between subjects. Much of this variability arises from the ppTMS paradigm used to investigate SICI, as discussed above. Further, a majority of these isometric contractions only consider the FDI muscle. Primarily because of the ease of eliciting a response in FDI muscles and the hand representation area in the motor cortex is well understood. Additionally, the motoneuronal pool for the hand muscles receives strong direct projection (Clough et al., 1968). Yet, this creates a gap in knowledge where very little of SICI's modulation during locomotion and its behaviour to other muscles is understood.

2.73 SICI During Locomotor Outputs

Cortical excitability increases as the activity of the muscles increases (Reynolds & Ashby, 1999), as such, cortical excitability should increase as the motor output changes from rest, to isometric contraction to locomotion due to the increase in the number of muscles involved. Isometric contractions are often unilateral and only involve a single joint tonic contraction (Fisher et al., 2002; Zoghi et al., 2003), whereas locomotor outputs require multiple joints and are a bilateral movement (Sidhu et al., 2013; Alcock et al., 2019). This increased excitability is supported by a concurrent decrease in inhibition. By extension, it can be assumed that SICI will be reduced in locomotor outputs than isometric or resting conditions. To the best of my knowledge, there are only a few studies examining the modulation of SICI during locomotive outputs (Barthelemy & Nielsen, 2010; Yamaguchi et al., 2012; Sidhu et al., 2013; Ito et al., 2015; Alcock

et al., 2019; Garnier et al., 2019; Sidhu & Lauber, 2020). These studies indicate that SICI was indeed present to the muscle of interest during the variety of locomotor outputs tested (Barthelemy & Nielsen, 2010; Yamaguchi et al., 2012; Sidhu et al., 2013; Ito et al., 2015; Alcock et al., 2019; Garnier et al., 2019; Sidhu & Lauber, 2020).

Barthelemy & Nielsen (2010) were one of the first known authors to show the activity of SICI during a locomotor output. They investigate the role of cortical input to the arm muscles (anterior and posterior deltoids, biceps brachii, triceps brachii, flexor capri radialis, and extensor carpi radialis), which demonstrate rhythmic activity during walking. Although they recorded EMG from a variety of muscles, they only used ppTMS to evoke MEPs in the shoulder muscles since the posterior deltoids had consistent EMG activity throughout the gait cycle. They had participants walk on a treadmill at speeds ranging from 3.4 to 4km/h. They demonstrated that in fourteen subjects, SICI contributions were present to the posterior deltoids (Barthelemy & Nielsen, 2010). Although they highlight that the level of SICI was dependent on the phase of the muscle (discussed below). They also report that the triceps brachii, similar to the posterior deltoid, exhibits consistent EMG activity through the gait cycle. However, they did not examine SICI to this muscle and did not provide an explanation of their choice. The consistent EMG activity might suggest that the triceps brachii has a role even during gait and is worth an investigation.

Three other studies examined SICI to the lower body during leg cycling (Yamaguchi et al., 2012; Sidhu et al., 2013; Sidhu & Lauber, 2020). Although not related to the triceps brachii, these studies can still provide insight into SICI activity during locomotion. Yamaguchi et al. (2012) recruited ten participants to examine SICI modulation to the tibialis anterior and the soleus muscle. They had participants cycle at 60 RPM with 5Nm of resistance. Their choice of cycling parameters was used to consider patients with severe paresis who have been shown to perform a low resistance

pedaling task. Either way, their results showed a reduced amount of SICI to both muscles compared to baseline measurements (Yamaguchi et al., 2012). Similarly, Sidhu et al., 2013 reported the presence of SICI to the knee extensors during leg cycling. They collected responses from the vastus lateralis from 10 participants, who cycled at 80 RMP with a workload of 100W. SICI appeared to be present only during the deactivation phase of the knee extensors and not the activation phase during leg cycling (activation phases were based on EMG activity) (Sidhu et al., 2013). The knee extensors appeared to demonstrate phase-dependent modulation of cortical inhibition similar to the posterior deltoids on Barthelemy & Nielsen's (2010) study.

Further work by Sidhu & Lauber (2020) confirmed that SICI is present to the knee extensors during knee extension. Both works from Sidhu and colleagues (2013, 2020) examined the modulation of SICI to an extensor muscle during locomotor outputs. Although the knee extensors, specifically the vastus lateralis is a much larger muscle than the triceps brachii, extensors throughout the body have similarities in their motoneuronal properties and cortical control (Wilson et al., 2015). The knee extensors work to extend the leg and the triceps brachii work to extend the arm. Extrapolating this thought suggests that SICI may be a potential cortical circuit that modulates triceps as well. Finally, Alcock et al. (2019) investigated SICI as a potential cortical circuit responsible for the modulation of corticospinal excitability to the biceps brachii noted by Forman et al. (2014). They recruited twelve participants, whom they collected EMG data from the triceps and biceps brachii. They had participants arm cycle at a cadence of 60 RPM with a 25W workload. They evoked MEPs using ppTMS to the dominant biceps brachii. The authors showed that SICI to the biceps brachii was indeed present during arm cycling. Since triceps is known to be active during arm cycling, although differently from the biceps brachii activity profile as discussed in the introduction, it is plausible then that SICI may also be present to the triceps.

In summary, it appears that SICI is present during locomotive outputs as described by the studies above. Although it appears that SICI may have task-dependent modulation. Additionally, it appears that within locomotive outputs, SICI is stronger during certain phases of the contraction. These effects are explored in the following sections.

2.74 SICI Task-dependency

Discussing task-dependent effects require the use of findings from isometric studies to substantiate findings from locomotor studies. Previous work has determined that corticospinal excitability behaves in a task-dependent manner (Forman et al., 2014; Forman et al., 2019). Since cortical input contributes to corticospinal excitability, any task-dependent modulation may be a result of changes in cortical circuits, such as SICI.

Opie et al. (2015) investigated the task-dependent differences in SICI to the FDI muscles during an isometric unilateral abduction and a precision gripping task. They found that SICI was reduced for both active conditions compared to rest. When comparing the isometric unilateral abduction task to the precision gripping task, they noted a greater reduction of SICI in the precision gripping task (Opie et al., 2015). Similarly, Kouchitr-Devanne et al. (2012) also examined an isolated FDI contraction compared to a precision finger-thumb gripping task. They also noted that SICI was less prominent in the precision gripping task than the isolated FDI contraction (Kouchitr-Devanne et al., 2012). Prior to that, Devanne et al. (2002) examined a pointing task that required co-activation of arm muscles. They noted that through the pointing task, extensor carpi radialis MEPs were facilitated possibly due to decreased SICI activity compared to an isolated contraction of the extensor carpi radialis (Devanne et al., 2002). They concluded the MEP facilitation was due to a lack of cortical inhibition instead of changes to the motoneuron pool because of the lack of task-dependent change to the H-reflex (Devanne et al., 2002). These studies appear to illustrate that as the task increases in complexity, unilaterally, SICI activity decreases. If this is the case,

then one might assume that SICI to the biceps or triceps brachii might be diminished during arm cycling (a more complex motion) than an intensity- and position-matched isometric contraction. However, the above studies compared an isometric, unilateral contractions to another isometric unilateral contraction that required other muscles to be involved. The levels of cortical inhibition noted in this type of motor output may not apply to that of a bilateral locomotor output. As with Alcock et al. (2019), they noted SICI activity to the biceps brachii, although not different than an intensity-and position-matched isometric contraction. In this case, the type of motor output may dictate if task-dependent modulation to SICI occurs.

Alternatively, in lower body musculature, Yamagushi et al. (2012) showed that SICI to the tibialis anterior and soleus differed between the active cycling task mentioned in the previous section and repetitive, isometric, dorsiflexion of the ankle (there was reduced SICI during active pedalling). However, SICI did not differ between passive cycling and repetitive dorsiflexion. Nor were there significant changes from baseline to the amount of SICI present to the tibialis anterior and the soleus during passive cycling and repetitive dorsiflexion (Yamagushi et al., 2012). The decrease in SICI during the active pedaling may be due to the disinhibition of the cortical representation areas (Pascual-Leone et al., 1995). Comparatively, during passive cycling, the participants were not required to make the intentional decision to move the pedals, so the extent of disinhibition to the cortical leg representation areas was much less (Yamagushi et al., 2012). The authors conclude that the results of their study and previous work in the area indicate that intentional activities increase the task specificity of the motor cortex (Christensen et al., 2000; Pyndt & Nielsen, 2003; Yamagushi et al., 2012). To this point, Ito et al. 2015 were interested in the cortical control of the tibialis anterior and soleus during three different types of walking that required different volitional control and patterns of muscle activity. Each gait pattern differed in

the left to right stance ratio (i.e.: walk 1 had a ratio of 1:1, walk 2 had a ratio of 1:2 and walk three had a ratio of 2:1). The authors show that SICI was modulated differently between the three locomotor tasks with significant increases in inhibition for walk 1 compared to the others. Walk 1 was considered the normal walking gait pattern, as such the authors suggest that less "release" of the cortical representation area was required because a healthy individual uses this gait pattern every time they walk (Ito et al., 2015). In other words, a novel task or a task not practiced as often may require more cortical facilitation, thus, a decrease in inhibition (Ito et al., 2015).

Sidhu et al. (2013) demonstrated that SICI was also present in the knee extensors during a static contraction. Unfortunately, they did not directly compare results to those obtained during cycling, so they were unable to comment on the task dependency of SICI modulation. However, Sidhu & Lauber (2020) compared leg cycling at a fixed cadence and at a freely chosen cadence. Their results showed that SICI was reduced to a greater extent during the freely chosen cycling (approximately 72 RPM) compared to the fixed cadence cycling (70 RPM) (Sidhu & Lauber, 2020). A study from our lab showed that as the cadence of arm cycling increased, corticospinal excitability also increased (Forman et al., 2015). Although, this finding has phase-dependent modulation where corticospinal excitability (both spinal and supraspinal influences) increases were consistent during the elbow flexion phase. Comparatively, during elbow extension, increases in corticospinal excitability to the biceps brachii were largely related to increases in supraspinal factors (Forman et al., 2015). However, the cortical control mechanisms remained unclear, though a study using fMRI noted increased activity in the motor cortex as the pedalling cadence increased (Christensen et al., 2000). Sidhu & Lauber (2020) suggest that at higher cadences, seen in freely chosen cycling, the influence of ICF is much greater, which may contribute to the increase in

corticospinal excitability and decreased SICI. They compared the balance between ICF and SICI and show that SICI influence is stronger at lower cadences (Sidhu & Lauber, 2020).

It is thought that this modulation of SICI during a task is due to the effects of GABAergic neurons (Opie et al., 2015). During voluntary contraction, there is a reduction in GABA release to increase the facilitation of the cortical representation areas involved in the motor output (Matsumura et al., 1991; Matsumura et al., 1992). There is evidence to suggest that GABAergic inhibition differs between tasks that require different muscle activation patterns, perhaps to help increase activation of all the cortical representative areas of muscles involved in the task (Opie et al., 2015). So, although no task difference SICI modulations were noted to the biceps brachii, these results may be impacted by the set workload and cadence chosen by the authors (Alcock et al., 2019). As such, these findings cannot be applied to triceps brachii during arm cycling.

2.75 SICI Phase-dependency

Corticospinal excitability has been shown to behave in a phase-dependent manner (Power et al., 2018). It is possible that modulation of cortical circuits such as SICI contributes to the noted phase-dependent effect on corticospinal excitability. Spence et al. (2016) found significant phase-dependent effects of corticospinal excitability to the biceps brachii between flexion and extension, where MEP amplitude was greater for flexion than extension during arm cycling. This increase may have been partially due to increased cortical excitability, although they were unable to comment on the potential mechanisms at the time of this paper. Unlike biceps brachii, corticospinal excitability to the triceps brachii did not show phase-dependent modulation between extension and flexion (Spence et al., 2016). However, prior to stimulation, the EMG showed significant phase-dependent effects between flexion and extension of triceps brachii. The authors suggest that these differing results to the triceps might be due to the nature of TMS-evoked MEPs (Spence et al., 2016). Garnier et al. (2019) investigated the change in corticospinal excitability of the knee

extensors between concentric and eccentric contraction phases. They noted increased corticospinal excitability during the eccentric phase but not during the concentric phase. Although they could not detect any phase-dependent changes to SICI, they proposed that overall intracortical inhibition was reduced to facilitate excitability. Interestingly, Spence et al. (2016) note an increase in corticospinal excitability to the biceps brachii during the flexion or concentric phase. Comparatively, Garnier et al. (2019) saw an increase in corticospinal excitability to the knee extensors during the eccentric or extension phase. This suggests that perhaps the phase-dependent effects of corticospinal excitability may be muscle-dependent. However, it cannot be said if the opposing results are due to differences in cortical circuit changes, as that was not the aim of the study conducted by Spence et al. (2016). Both Spence et al. (2016) and Garnier et al. (2019) examined extensor muscles but were unable to confirm if corticospinal excitability or SICI is phase-dependent, although changes were noted.

In contrast, Barthelemy & Nielsen (2010) noted that the SICI activity to the posterior deltoid was phase-dependent. SICI was diminished during higher bursts of EMG activity toward the maximal forward and maximal backward position of the shoulder during arm swing (Barthelemy &Nielsen, 2010). So, the strongest SICI activity was noted during the middle of the forward swing, where the EMG activity was lowest (Barthelemy & Nielsen, 2010). Similarly, Sidhu et al. (2013) noted that SICI was reduced or even abolished during the activation phase of the vastus lateralis compared to the deactivation phase. Again, this supports the notion that SICI diminishes during higher levels of muscle activity to enable ease of movement. It can then be said that the excitability of the cortical cells is higher during specific phases, such as the activation phase. The reduction in inhibition increases cortical excitability to help facilitate movement.

2.76 SICI Muscle Dependency

The thought of SICI being muscle-dependent is plausible given that CSE has been shown to behave as such (Power et al., 2018). There is evidence to show the intrinsic hand muscles have a greater degree of intracortical inhibition, although the inhibitory circuit was not specified, than proximal upper limb muscles (biceps brachii) (Abbruzzese et al., 1999). These differences are attributed to the organization of the corticospinal neurons, where the hand muscles receive a greater portion of input for fine motor control (Palmer & Ashby, 1992). Another study examining cortical excitability across a variety of resting muscles noted that SICI was greater from the abductor pollicis brevis, and the tibialis anterior muscles compared to the trapezius muscle (Menon, Kiernan & Vucic, 2018). They determined that cortical inhibition varies across body regions with greater inhibition to limb muscles compared to axial muscles. The authors suggest that similar cortical organization of corticospinal neurons for the limb muscles (abductor pollicis brevis and tibialis anterior) compared to the trapezius may contribute to the results (Menon et al., 2018). They also highlight that the bilateral cortical representation along with contributions from smaller diameter corticospinal neurons for the trapezius muscle could contribute to decreased SICI (Menon et al., 2018). As such, the corticospinal neurons' representation and organization may have possible contributions to the amount of SICI detected in a muscle.

Ridding et al. (1995c) showed significant changes in inhibition when participants contracted the muscle of interest, FDI. However, when they asked participants to contract the biceps brachii (proximal to the FDI), they noted no significant changes to SICI levels of the FDI. Since the contraction of a proximal muscle had no effect on the amount of SICI to the FDI, they suggest that perhaps SICI is muscle specific. The specificity may be related to the role the muscle has in the task; the biceps brachii had no role in the contraction of FDI muscle. To explore the muscle-dependent effects of SICI within the same muscular region, Zoghi et al. (2003) examined

the modulation of SICI to synergistic hand muscles (abductor pollicis brevis, FDI, and abductor digiti minimi). They noted that selective activation of one of those muscles resulted in less SICI to the active muscle but not the muscles at rest. Although they chose to assess synergistic muscles, it was only the active muscle that experienced SICI modulations (Zoghi et al., 2003). Alternatively, there is evidence to suggest that even though SICI decreases in the active muscle, it increases above resting levels to the non-active synergistic muscles to prevent unwanted movement (Stinear & Byblow, 2003). Nevertheless, these studies support the notion that SICI is differentially modulated between muscles during isometric contractions.

Similarly, the few locomotor studies also indicate muscle dependency (Bartherlemy & Nielson, 2010; Sidhu et al., 2013; Spence et al., 2016). Sidhu et al. (2013) noted that the amount of SICI to the knee extensors was less than that of the posterior deltoid during walking, as determined by Bartherlemy & Nielsen (2010). This again highlights a potential muscle-dependent modulation of SICI. Also of interest, both these studies examined extensor muscles, while the study by Alcock et al. (2019) examined the biceps brachii, a flexor muscle. There are documented differences between the motoneuron pools that innervate flexors and extensors (Cotel et al., 2009; Wilson et al., 2015). For example, elbow extensors and flexors appear to have differences in intrinsic excitability (Wilson et al., 2015). These differences indicate that perhaps cortical control is different between extensors and flexors (Wilson et al., 2015). So then, not only may SICI be muscle dependent but may also demonstrate differences between flexors and extensors. Wilson et al. (2015) provide evidence to show that there is greater cortical control to the extensor motor units compared to the flexor motor units in the upper limb. Non-human animal work supports these results by showing higher neuronal excitability to the extensors in decerebrated cats (Hounsgaard et al., 1988) and rats (Cotel et al., 2009). In order to produce higher excitability to the extensors,

SICI activity has to reduce to allow for more excitatory input. The next steps in understanding SICI during locomotive outputs are to investigate its modulation to the triceps, as the results collected from the biceps (Alcock et al., 2019) cannot be applied to the triceps brachii.

2.77 Summary of SICI

SICI is a cortical circuit that is thought to have a role in motor output and the modulation of corticospinal excitability. It is reflective of GABAergic inhibition in the motor cortex. It decreases as the muscle of interest becomes more active to potentially assist with the ease of performing the task. As such, SICI appears to decrease as the muscle of interest becomes more active. However, factors such as the task can modulate the level of SICI present. The literature suggests potential phase-dependent effects that should be considered for the muscle of interest (eg: flexion compared to extension). Unfortunately, SICI has been examined only to a few muscles during locomotor outputs. The literature highlights the probable muscle-dependent modulatory effects of SICI. As such, the findings from one muscle cannot definitively be applied to another. The next step in understanding SICI during locomotion is to investigate its presence in the triceps brachii during arm cycling.

2.8 Conclusion

As it currently stands, it is known that the cortical control of locomotion is modulated by input from cortical areas such as the motor cortex. However, much less is known regarding the cortical circuits involved in controlling motor cortex excitability. Research within the past two decades has highlighted the existence of many cortical circuits. One specific cortical circuit that contributes to cortical inhibition, SICI, exerts inhibitory effects, through $GABA_A$ receptors, on to descending motor pathways such as the corticospinal pathway. Recent research has investigated the modulation of SICI during resting and isometric contractions, with only a few studies examining its effect during locomotion. As illustrated by our lab, supraspinal excitability is higher

to the biceps brachii during arm cycling than an intensity- and position-matched isometric contraction. As such, our lab sought to investigate the cortical circuits involved in the modulation of corticospinal excitability and found the presence of SICI to the biceps brachii during arm cycling. However, arm cycling involves the use of the triceps brachii as well, and little is known regarding the cortical control to this muscle. This project aims to explore the cortical control to the triceps brachii by investigating the presence and potential modulatory behaviour of SICI to the triceps during arm cycling.

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Chapter 3 Short-Interval Intracortical Inhibition to the Triceps Brachii During Arm Cycling

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Running head: Examining Short-Interval Intracortical Inhibition During Am Cycling

Key words: SICI, MEP, EMG, arm cycling, triceps brachii

3.0 ABSTRACT

Corticospinal excitability to the triceps brachii is not phase-dependent, yet spinal excitability is higher during elbow flexion compared to elbow extension. This suggests that supraspinal excitability is lower during elbow flexion, though the mechanisms are currently unknown. Thus, the purpose of this study was to investigate if short-interval intracortical inhibition (SICI) was present to the triceps brachii during arm cycling, and if so, if the amount of SICI present was phase-dependent. SICI was assessed using a conditioning stimulus (CS) of 90% of active motor threshold (AMT) and a test stimulus of 120% AMT with an interstimulus interval (ISI) of 2.5ms. SICI was elicited at mid-elbow flexion and mid-elbow extension (6 and 12 o'clock, respectively, relative to a clock face). SICI was present at both positions during arm cycling with motor evoked potential (MEPs) amplitudes reduced by 50.7% ($p < 0.001$) at 6 o'clock and 57% ($p = 0.001$) at 12 o'clock. There was no significant difference in the amount of SICI present between 6 and 12 o'clock ($p = 0.671$). This data is the first to demonstrate the presence of SICI to the triceps brachii during arm cycling. However, the lack of phase-dependent modulation suggests that SICI of the triceps brachii is not the likely inhibitory mechanism contributing to the inhibition of supraspinal excitability at the 6 o'clock position relative to that at 12 o'clock.

3.1 INTRODUCTION

The ability to produce locomotor outputs, such as leg and arm cycling, is partially credited to specialized spinal interneurons known as central pattern generators (CPGs) (Dietz, 2002; Zehr et al., 2004). Non-human animal work has demonstrated that the CPG is capable of generating the basic pattern of locomotor outputs without significant cortical or sensory input (Jordan, 1998). Although CPGs play a role in human locomotor outputs, humans require the integration of information from cortical regions, such as the motor cortex (Capaday et al., 1999; Petersen et al., 2001; Reis et al., 2008; Mehta et al., 2009). Descending input from the motor cortex is influenced by cortical excitability, which can be modulated by various cortical circuits, such as short-interval intracortical inhibition (SICI) (Kujirai et al., 1993; Badawy et al., 2012). Research shows that SICI occurs in cortical structures (Kujirai et al., 1993; Nakamura et al., 1997; Di Lazzaro et al., 1998; Hanajima et al., 1998) and is a $GABA_A$ mediated circuit (Ziemann et al., 1996; Di Lazzaro et al., 2000; Ilić et al., 2002). This intracortical inhibitory circuit plays an important role in motor output. For example, SICI is thought to be one of the circuits that assists the motor cortex in inhibiting itself (Kujirai et al., 1993) as well as aiding in muscle's selective activation during motor output (Zoghi et al., 2003; Qian et al., 2019). Further, it appears to have a role in suppressing corticospinal excitability during volitional muscle activation (Ridding et al., 1995).

SICI is investigated using paired-pulse transcranial magnetic stimulation (ppTMS), involving a subthreshold condition stimulus (CS) that precedes a suprathreshold test stimulus (TS) by approximately 1-5ms (Kujirai et al.,1993). The use of ppTMS causes the motor evoked potential (MEP) amplitude to be inhibited compared to if a TS was given independently (Kujirai et al.,1993, Alcock et al., 2019). Not surprisingly, much of the work done to understand this

intracortical inhibitory circuit has been during resting states or isometric, unilateral, contractions (Kujirai et al., 1993; Ridding et al., 1995; Fisher et al., 2002; Roshan, Paradiso & Chen, 2003; Zoghi et al., 2003; Zoghi & Nordstrom, 2007; Jaberzadeh et al., 2007). The role SICI plays in modulating cortical excitability during these states cannot be applied to locomotor outputs since they have been shown to have different neural control (Carroll et al., 2006; Zehr & Duysens, 2004; Forman et al., 2014; Forman et al., 2016).

Only four studies have examined SICI during locomotor outputs (Barthelemy & Nielsen, 2019; Sidhu, Cresswell, Carroll, 2013; Alcock et al., 2019; Sidhu & Lauber, 2020). Barthelemy & Nielsen (2010) showed that SICI is active in the arm muscles during human walking. They noted that the amount of SICI present was inversely correlated with muscle activity detected by electromyography (EMG), where SICI was increased at low levels of muscle activity and decreased during high levels of muscle activity (Barthelemy & Nielsen, 2010). The influence of SICI has been shown to be present in the knee extensors during leg cycling (Sidhu et al., 2013; Sidhu & Lauber, 2020). Sidhu et al. (2013) observed that the amount of SICI to the knee extensors depended on the activation phase of the muscle, such that SICI was decreased during the activation of the knee extensors and increased during the deactivation of the knee extensors during leg cycling. The findings from both studies suggest that SICI may depend on the level of muscle activity, where it is reduced with high muscle activity, and the phase of muscle activation, such that it is reduced during the activation phase (Barthelemy & Nielsen, 2010; Sidhu et al., 2013).

Previous work from our lab demonstrated that corticospinal excitability to the biceps brachii measured through TMS-evoked MEPs is dependent on whether the muscle is flexing or extending the elbow during arm cycling (Spence et al., 2016). The same phase-dependency was

not noted in the antagonistic triceps brachii. Instead, using transmastoid electrical stimulation to elicit cervicomedullary motor evoked potentials, the authors noted that spinal excitability to the triceps brachii was higher during elbow flexion compared to elbow extension (Spence et al., 2016). A lack of phase-dependency in corticospinal excitability, with the noted changes in spinal excitability, suggests that supraspinal excitability is suppressed during the elbow flexion phase of arm cycling to the triceps brachii. This work, along with the above studies, provides support for the possibility that the amount of SICI present during arm cycling is phase-dependent. A study from our lab examined SICI to the biceps brachii in response to phase-dependent modulation of corticospinal excitability noted by Spence et al. (2016) (Alcock et al., 2019). Alcock et al. (2019) determined that SICI existed to the biceps brachii, but they did not assess the same circuit to the triceps brachii, a muscle that demonstrated potential supraspinal excitability suppression in Spence et al. (2016) and is an equally important muscle in the production of arm cycling. The findings from Alcock et al. (2019) cannot be applied to the triceps brachii for the following reasons. First, there is some evidence to suggest that SICI modulation is muscle-dependent (Abbruzzese et al., 1999; Menon, Kiernan & Vucic, 2018). Second, findings from our lab demonstrate that the triceps and biceps brachii have different EMG activity profiles during arm cycling, where triceps brachii remain active throughout the arm cycling revolution and the biceps brachii displays phase-dependent activity (Chaytor et al., 2020). These reasons suggest that the triceps and biceps brachii are under different corticalspinal control and should be investigated separately.

The purpose of the current study was to determine (1) if SICI is present to the triceps brachii (dominant arm triceps brachii) during arm cycling and (2) to determine if SICI showed phase-dependent modulation if present. It was hypothesized that: (1) SICI will be present to the

triceps brachii during arm cycling and (2) SICI will be the decreased during the highest level of muscle activity to the triceps brachii (during mid-elbow extension) and will be increased during the lowest level of muscle activity to the triceps brachii (during mid-elbow flexion).

3.2 METHODS

3.2.1 Ethical Approval

Prior to commencing data collection, all participants were informed of all potential risks and benefits of the study via verbal and written explanation and were given an opportunity to ask questions. All participants then gave written informed consent. This study was conducted in accordance with the Helsinki declaration and all protocols were approved by the Interdisciplinary Committee on Ethics in Human Research at Memorial University of Newfoundland (ICEHR No. 20220230-HK).

3.2.2 Participants

Seventeen healthy volunteers between the ages of 18 and 40, with no known neurological impairments, participated in the study (23.3 ± 4.4 years of age, one left hand dominant). Following the completion of the informed consent, participants completed a safety checklist to screen for contraindications to magnetic stimulation delivered via TMS (Rossi et al., 2009). Participants also completed a Physical Activity Readiness Questionnaire (PAR-Q+) to ensure they could safely perform physical activity (Canadian Society for Exercise Physiology, 2002). Hand dominance was determined using the Edinburg Handedness Inventory (Veale, 2014). Additionally, participants completed a COVID-19 questionnaire upon entering the laboratory.

3.2.3 Experimental Setup

All cycling trials were conducted using an arm cycle ergometer (SCIFIT ergometer, model PRO2 Total Body). Participants were seated upright in a comfortable position at a distance from the arm cranks such that they did not need to lean forward or rotate their torso

while cycling. The seat height was adjusted to fit each individual so that the arm crank was approximately in line with the participant's shoulders. The arm cranks on the ergometer were fixed 180° out of phase to enable asynchronistic cycling. Participants cycled in a pronated grip position, as was done in previous work from our lab (Alcock et al., 2019). Their wrists were stabilized with a wrist brace to prevent unwanted flexion or extension of the wrists. This was done to limit the influence of heteronymous reflex connections between the wrist flexors and the biceps brachii (Manning & Bawa, 2011).

The position of the arm cranks are made relative to a clock face in respect to the dominant arm, with "top dead centre" at 12 o'clock and "bottom dead centre" at 6 o'clock (Forman et al., 2014; Forman et al., 2015; Lockyer et al., 2018; Alcock et al., 2019). For example, 12 o'clock occurs when the right hand is at the "top dead centre" position for a right-handed individual. The triceps brachii is the primary muscle of interest, so elbow extension happens as the arm crank moves from 9 o'clock to 3 o'clock. At the 12 o'clock position, the elbow is in mid-elbow extension, the point at which triceps brachii activity is the highest and biceps brachii the lowest (Chaytor et al., 2019). In contrast, elbow flexion happens as the arm crank moves from 3 o'clock to 9 o'clock. At the 6 o'clock position, the elbow is in mid-elbow flexion, where triceps brachii activity is lower than at the 12 o’clock position and biceps brachii is at maximum or near-maximum activity (Chaytor et al., 2019). TMS was triggered automatically when the dominant arm passed 12 o'clock and 6 o'clock. For all trials, participants cycled at a constant workload of 25 watts (W) and 60 revolutions per minute (RPM) based on previous studies conducted by our lab (Forman et al., 2014; Alcock et al., 2019; Benson et al., 2020).

3.2.4 Electromyography

EMG activity was recorded from the dominant triceps brachii (specifically the lateral head) and biceps brachii using Ag-AgCl surface electrodes (MediTraceTm 130 Foam Electrodes with conductive adhesive hydrogel, Covidien IIC, Massachusetts, USA). The electrodes were placed in a bipolar configuration (2-cm interelectrode distance), in-line with the muscle fiber direction of the triceps (lateral head) and biceps brachii muscle belly. In addition, a ground electrode was placed over the lateral epicondyle. Prior to the placement of the electrodes, the participant's skin was shaved to remove fine hair, then abraded and cleaned with an isopropyl alcohol swab to reduce EMG recording impedance. EMG recordings were collected from the triceps brachii at 6 o'clock (mid-flexion, low activity) and 12 o'clock (mid-extension, high activity). Additional background EMG recordings were collected from the biceps brachii. EMG recordings were collected at a frequency of 5 kHz using a CED 1401 and Signal 5 software program (Cambridge Electronic Design, Cambridge, UK). Signals were amplified and band-pass filtered using a three-pole Butterworth filter (10-1000Hz). The high frequency is to prevent noise from the radio station and generators located near our laboratory.

3.2.5 Transcranial Magnetic Stimulation

Motor evoked potentials (MEPs) were elicited from the dominant arm triceps brachii lateral head via TMS using a Magstim 200 stimulator (Magstim, Whitland, Dyfed, UK) applied to the contralateral motor cortex (i.e., dominant motor cortex) during arm cycling. A circular coil (13.5cm diameter) was held 1cm lateral to the vertex, parallel to the floor, and the current flow direction preferentially activating the dominant motor cortex (Alcock et al., 2019). The vertex is defined as the intersection point of the halfway marks (Forman et al., 2014; Copithrone et al., 2015). Vertex was located by measuring nasion to inion and tragus to tragus, marking the

location on the scalp halfway between them. This method has previously been used in our lab to measure SICI from the biceps brachii (Alcock et al., 2019). There were two stimulation conditions used in this study, a single-pulse TMS condition, which consisted of the test stimulus (TS) alone, and ppTMS condition, which consisted of the TS and conditioning stimulus (CS).

3.2.6 Active Motor Threshold

Active motor threshold (AMT) was defined as the minimum stimulation intensity at which a MEP is clearly discernible from the background EMG (bEMG) in 50% of the arm cycling trials (Sidhu et al., 2013; Forman et al., 2018). AMT was determined at two different positions (6 o'clock and 12 o'clock) while the participant's cycled at 25 W and 60 RPM and was collected pre- and post-experimental protocol. Randomization determined which position was tested first. AMT was needed to calculate TS and CS intensities.

3.2.7 Test and Condition Stimulus Intensities

TS intensity was defined as a suprathreshold TMS pulse. Based on previous work examining SICI, the TS was set at 120% AMT (Alcock et al., 2019). The amount of SICI present is influenced by the test MEP, so to prevent any test MEP size-dependent differences, TS was set at 120% AMT (Sanger, Garg & Chen, 2001; Roshan et al., 2003; Sidhu et al., 2013; Alcock et al., 2019). The CS intensity was defined as a subthreshold TMS pulse. Based on Alcock et al. 2019, the CS was set at 90% AMT. The CS was delivered to the dominant motor cortex 2.5ms prior to the TS. Participants received 12 TS and CS while cycling. Participants also received TS alone (120% AMT at the 6 o'clock and 12 o'clock positions) while cycling, which acted as a control. During this stimulation procedure, they received 12 TS alone every 7 seconds while cycling.

3.2.8 Experimental Protocol

On the day of testing, participants first completed a familiarization session to ensure that participants were comfortable with TMS and arm cycling. Participants were then given the option to continue with the rest of the testing protocol or to take time to consider their level of comfort with the protocol. Sixteen of the seventeen participants felt comfortable continuing with the testing protocol. One participant came back a week later to complete the testing protocol.

Prior to beginning data collection, the order at which position the stimuli were delivered (6 o'clock or 12 o'clock) and the order in which stimulation protocol occurred first (single pulse or ppTMS) were randomized. Participants were informed if they would receive single pulse or ppTMS. However, the ISI was too short for participants to notice a difference between trials. Once the order was determined, participants sat at the arm cycling ergometer and began cycling at 60 RPM and 25W. Following this, participants were given TMS beginning at 25% of the maximum stimulator output (MSO) and increasing in intensity until MEPs could be detected. This served as their familiarization to TMS and the arm cycling protocol. After verbally confirming that they felt no ill effects, the AMT at the first position was determined. For example, if 6 o'clock was the first position, then the AMT at 6 o'clock was determined. Similar to Alcock et al. 2019, participants were exposed to two experimental stimulus conditions at both positions: TS alone and ppTMS. Following the determination of AMT, the TS and CS intensities of the MSO were determined for the first position. After this, both the TS alone and ppTMS conditions were delivered at the first position while participants cycled at 60 RPM and 25W. For the stimulation conditions, if, for example, ppTMS was determined to be first, then it was delivered while the participant cycled. The participant then paused cycling while the TMS settings were changed to deliver the TS alone. Finally, post-AMT was determined for each

position. After obtaining AMT, delivering both single-pulse and ppTMS conditions, and measuring post-AMT at one position, the procedure was repeated at the other position.

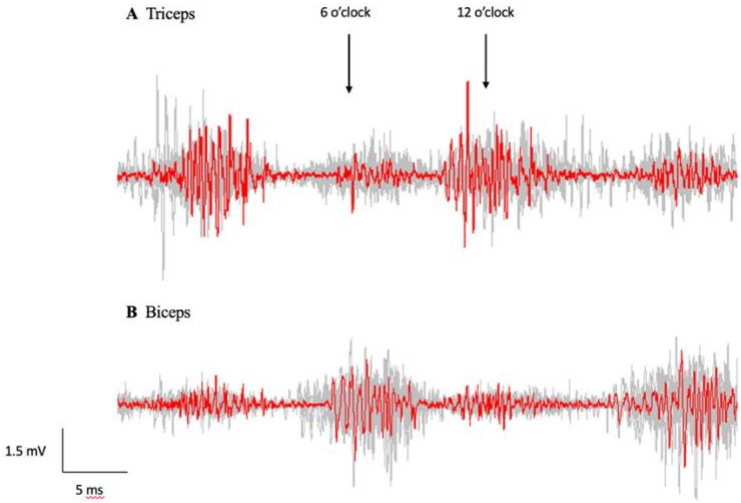

Figure 6 EMG trace from one participant (n=1) for (A) triceps brachii and (B) biceps brachii activity, with arrows indicating activity at positions 6 and 12 o'clock where stimulation was delivered. The grey trace indicates previous cycling trials with stimulation and the red trace indicates the current trial with stimulation. The best trial was chosen to represent EMG traces for 6 and 12 o'clock.

3.2.9 Data Analysis

The average peak-to-peak MEP amplitudes of the dominant arm triceps brachii at 6 and 12 o'clock was assessed using Signal 5.08 data collection software. Averaged peak-to-peak amplitude for the 12 MEPs elicited via ppTMS were compared and made relative to the averaged peak-to-peak amplitude of 12 MEPs obtained during TS alone from single pulse TMS. Additionally, pre-stimulus EMG was measured from the rectified virtual channel created for the triceps and biceps brachii. A 50ms window was used immediately prior to the stimulation artifact.

3.2.10 Statistical Analysis

SICI was presented as a ratio of conditioned MEP amplitude (obtained from ppTMS) over test MEP amplitude (obtained from TS alone) and then multiplied by 100 to give a percentage. All statistical analysis was completed using IBM's SPSS statistics (IBM SPSS

Statistics for Mac OS, Version 27.0. Armonk, NY: IBM Corp). Paired t-tests were employed to compare the conditioned MEPs obtained at 6 o'clock and 12 o'clock. Previous work from our lab has shown phase-dependent activity in pre-stimulus EMG for the triceps and biceps brachii (Spence et al., 2016). As such, the mean rectified bEMG using a 50ms window at both positions for the triceps and biceps brachii were compared using a paired t-test. Finally, paired t-tests were used to determine if MEP amplitudes elicited using AMT stimulation intensities changed throughout the experiment (pre to post protocol). All statistical analyses were performed on group data, and a significance level of $p<0.05$ was used. Data are presented and shown in figures as mean ± SD.

3.3 RESULTS

3.3.1 Active motor threshold (AMT)

The AMT was used to determine the test and conditioning stimulation intensities for all trials. Following the experimental protocol, AMT was replicated to ensure that any changes to MEP amplitudes during the protocol are related to cortical changes (i.e., SICI) and not changes to AMT. AMT obtained pre- and post-protocol at the 6 o'clock position were not significantly different (p = 0.232, d = 0.0946, t = 1.254) nor was it significantly different at the 12 o'clock position (p = 0.174, d = 0.283, t=1.422) (see Table 1). AMT between pre 6 o'clock and pre 12 o'clock were not significantly different (p =0.486, d = 0.335, t = 0.717) nor was it significantly different between post 6 o'clock and post 12 o'clock (p =0.643, d = 0.153, t = 0.472).

AMT	6 o'clock	12 o'clock
Pre (mV)	0.309 ± 0.154 (n=17)	0.402 ± 0.262 (n=17)
Post (mV)	0.287 ± 0.117 (n=17)	0.305 ± 0.150 (n=17)

Table 3 Mean AMT MEP amplitudes immediately pre and post cycling protocol for 6 o'clock and 12 o'clock

3.3.2 Stimulation intensities

Conditioning stimulation (CS) intensities used in ppTMS at the 6 o'clock and 12 o'clock positions ranged from 19 to 40% and 23 to 48% of the maximum stimulator output (MSO), respectively. On average, the CS intensity used at the 12 o'clock position was higher than that used at 6 o'clock. There was a significant difference between positions for CS intensities (p = 0.001, d =3.45, t = 4.081). Test stimulation (TS) intensities ranged from 25 to 53% and 30 to 60% of the MSO at 6 o'clock 12 o'clock, respectively. The TS intensities used were significantly higher at the 12 o'clock position than at the 6 o'clock (p = 0.00129, d = 4.73, t =3.896). The MEPs elicited using TS alone were on average larger at 12 o'clock compared to 6 o 'clock (0.795 mV compared to 0.576 mV) (see Table 2). However, the MEP amplitudes were not significantly different between the 6 and 12 o'clock position. Thus, direct comparisons between the two positions can be made (p =0.208, d = 0.688, t = 1.31).

Condition	6 o'clock	12 o'clock
120% TS	38.7 ± 7.96 (n=17)	43.2 ± 8.78 (n=17)
90% CS	29.1 ± 5.99 (n=17)	32.5 ± 6.60 (n=17)
TS MEP amplitude (mV)	0.576 ± 0.236 (n=17)	0.795 ± 0.634 (n=17)

Table 4 Mean percent MSO used at 6 o'clock and 12 o'clock for each cycling trial. Mean MEP amplitude (mV) using test stimulation intensity at 120% is shown

3.3.3 SICI

SICI is shown as a ratio of the conditioned MEP amplitude compared to the test MEP amplitude. As such, values less than 100% demonstrate inhibition of MEP amplitude, and values above 100% demonstrate facilitation of MEP amplitude. Figure 2 shows an example of test and conditioned MEP traces obtained at 6 and 12 o'clock from a single participant. All participants

demonstrated intracortical inhibition at the 6 o'clock position. At the 12 o'clock position, fifteen participants demonstrated inhibition, but two participants demonstrated facilitation. At 6 o'clock, participants demonstrated 50.7% inhibition, and at 12 o'clock, participants demonstrated 57.0% inhibition. The amount of SICI present between both positions was not significantly different (p = 0.671, d = 59.9, t = 0.433) (Figure 3).

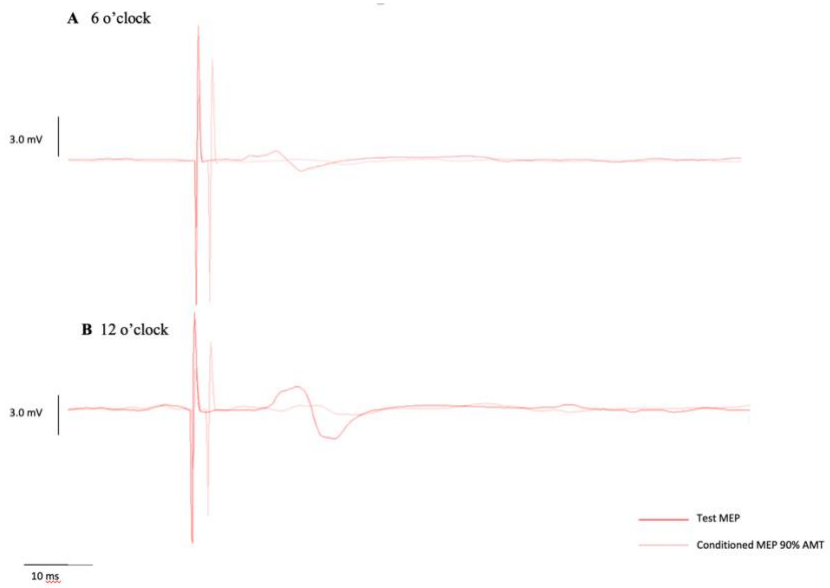

Figure 7 Average (A) test (120% AMT) and conditioned (90% AMT) MEP traces at (A) 6 o'clock where the test MEP amplitude was reduced from 0.42mV to 0.12mV and (B) 12 o'clock where the test MEP amplitude was reduced from 0.74mV to 0.16mV to the triceps brachii during arm cycling from one participant (n=1)

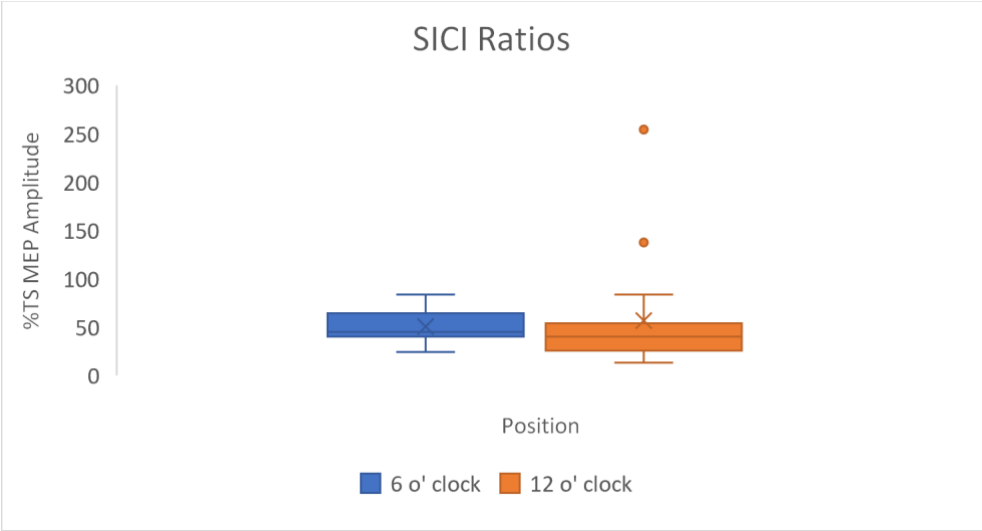

Figure 8 Conditioned MEP amplitudes as a percentage of test MEP amplitudes to the triceps brachii at 6 o'clock and 12 o'clock during arm cycling (n=17)

3.3.4 Background EMG (bEMG)

3.3.4.1 Triceps Brachii

The bEMG activity was significantly greater to the triceps brachii at 12 o'clock compared to 6 o'clock during the ppTMS protocol (p = 0.00466, d =0.125, t = 3.28). Similarly, there was significantly greater bEMG activity at 12 o'clock during the TS alone protocols (p = 0.00101, d = 0.0104, t = 4.012) (Figure 4).

3.3.4.2 Biceps Brachii

The bEMG activity was significantly higher at 6 o'clock than 12 o'clock position during the ppTMS protocol (p = 0.002, d = 0.133, t = 3.731). Similarly, there was significantly greater bEMG activity at 6 o'clock than 12 o'clock during the TS alone protocol (p = 0.00182, d = 0.134, t = 3.731) (Figure 5). As expected, there was no significant activation difference in bEMG of the triceps and biceps at the same position between the stimulation conditions, given that the role of the muscles remained the same.

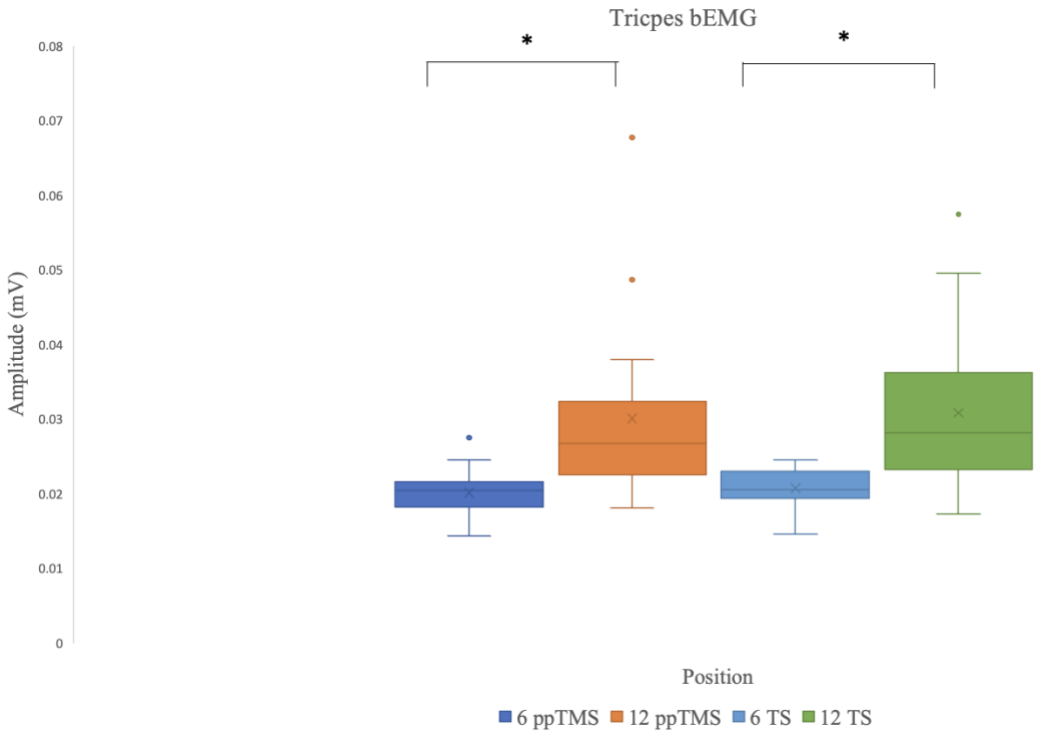

Figure 9 Background EMG for the triceps brachii during arm cycling at 6 and 12 o'clock positions during the experimental stimulation conditions (n=17)

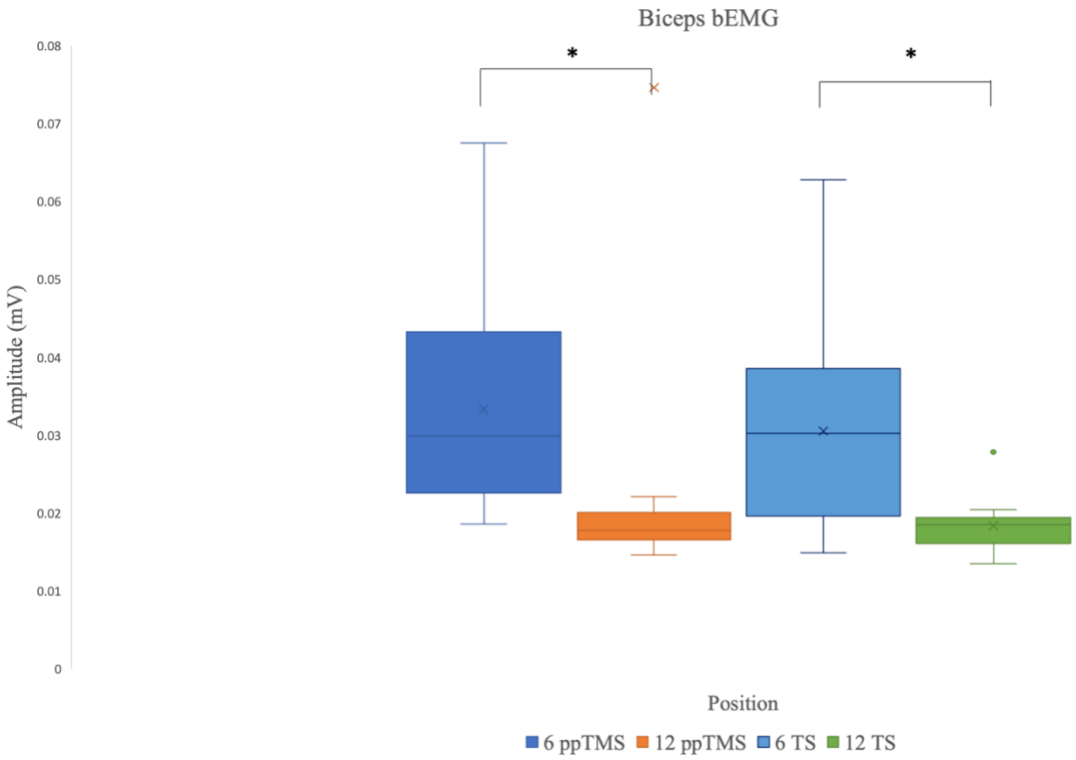

Figure 10 Background EMG for the biceps brachii during arm cycling at 6 and 12 o'clock positions during the experimental stimulation conditions (n=17)

3.5 DISCUSSION

The two main purposes of this study were to (1) determine if SICI exists to the triceps brachii during arm cycling and (2), if present, to determine if there was phase-dependent modulation of SICI to the triceps brachii. This study was the first to show that (1) SICI is present to the triceps brachii during arm cycling, and (2) there was no significant phase-dependent modulation of SICI to the triceps brachii during arm cycling.

3.5.1 SICI is present to the triceps brachii during arm cycling

Spence et al. (2016) examined the phase-dependent modulation of corticospinal excitability to the triceps brachii. Their results showed no overall phase-dependent modulation of corticospinal excitability. However, they noted that spinal excitability was greater during elbow flexion than elbow extension, contrary to what was expected for an extensor muscle. Increased spinal excitability during flexion in conjunction with no phase-dependent modulation of overall

corticospinal excitability suggests that supraspinal excitability was lower to the triceps brachii during elbow flexion (Spence et al., 2016). A possible mechanism for reduced supraspinal excitability to the triceps brachii during arm cycling could result from higher activation of intracortical inhibitory circuits such as SICI. Past work has examined SICI to the arm musculature during walking (Barthelemy & Nielsen, 2010), to the knee extensors during leg cycling (Sidhu et al., 2013; Sidhu & Lauber, 2020), and to the biceps brachii during arm cycling (Alcock et al., 2019). Alcock et al. (2019) did not examine SICI to the triceps brachii, an equally important muscle to the production of arm cycling. Thus, to investigate the results from Spence et al. (2016), we sought to examine the presence of SICI to the triceps brachii during arm cycling.

In line with previous works from Barthelemy & Nielsen (2010), Sidhu et al. (2013), Alcock et al. (2019), and Sidhu & Lauber (2020), the current study demonstrates that SICI is present to the triceps brachii. The influence of intracortical inhibition to active muscles suggests that there are neural mechanisms in place to reduce muscle activity (i.e., decrease activity to the motoneuron pool associated with a particular muscle) and assist in selective muscle activation (Liepert et al., 1998; Zoghi et al., 2003; Qian et al., 2019). This may serve as a protective mechanism and may help modulate the force production needed for the required movement. The amount of SICI present, however, is not the same across all muscles. Sidhu et al. (2013) highlighted that the level of SICI from the knee extensors during leg cycling was much less than that observed to the posterior deltoids during walking (Barthelemy & Nielsen, 2010). Importantly, however, the actions of these muscles are quite different during each task. The knee extensors are among the primary force-producing muscles during leg cycling, whereas the posterior deltoids are not primary movers during walking. Less SICI would be expected in

primary force-producing muscles as the cortical excitability to the muscles of interest would be higher than if the muscles were axillary to the movement. Reduction in SICI may enable greater excitation of cortical circuitry to facilitate descending cortical input to the motoneuronal pool of the muscle of interest to ensure sufficient force generation.

Sidhu et al. (2013) determined that SICI appeared to be related to the phase of muscle activation. They noted that SICI was reduced during the activation phase of the knee extensors, which corresponded to rising EMG activity. Comparatively, SICI was increased during the deactivation phase, which corresponded to decreasing EMG activity of the knee extensors. This implies that the effectiveness of the inhibitory circuits was depressed during a period where greater excitability is required to ensure adequate force production (Sidhu et al., 2013). Additionally, Barthelemy & Nielsen (2010) noted that the level of SICI present appeared to be inversely related to the amount of background EMG present. That is, the greater the muscle activity noted, via EMG, the less SICI present and vice versa (Barthelemy & Nielsen, 2010).

In the current study, background EMG was significantly different for both the triceps and biceps brachii between the positions. As expected, there was greater EMG activity detected for the triceps brachii at 12 o'clock because at this position, it is performing its anatomical function of elbow extension. As such, it is possible that greater cortical excitability is required to increase motoneuronal recruitment and firing frequency to ensure appropriate activation of the triceps brachii to push the arm crank away from the body. This increased EMG activity corresponded to less SICI at 12 o'clock (approximately 6% less than at 6 o'clock). The potential phase-dependent modulation of SICI modulation to the triceps brachii is discussed below.

3.5.2 SICI to the triceps brachii is not phase-dependent during arm cycling

There was no phase-dependent modulation of SICI to the triceps brachii in this study. This suggests that SICI is not primarily responsible for the lack of phase-dependent effects on

corticospinal excitability in the triceps brachii found by Spence et al. (2016). Other intracortical inhibitory neural circuits such as long-interval intracortical inhibition may play a bigger role in the lack of phase-dependent modulation of corticospinal excitability noted in Spence et al. (2016). It is also important to acknowledge that no circuit functions independently. The net result of cortical excitability is determined by the synergistic product of all circuits that are known and yet to be discovered. Thus, the potential decrease in supraspinal excitability at flexion (as noted by the lack of change in corticospinal excitability and increase in spinal excitability) may be due to the cumulative influence of multiple inhibitory circuits that work to decrease excitability.

Reduced SICI was expected at 12 o'clock because at this position, the triceps brachii is at mid-elbow extension, its most active position throughout the cycle where EMG activity is increased. Increased motoneuronal activity detected by EMG at 12 o'clock can be partly attributed to the influence of descending input resulting from increased cortical excitability. Increased cortical excitability can occur in two ways, the first of which being that intracortical inhibition (SICI) decreases and the second being that inhibition remains relatively constant while intracortical facilitation increases via faciliatory circuits. The present study did not measure intracortical facilitation.

Another possible explanation for a lack of change in SICI could be because the study examined SICI to the lateral head of the triceps brachii, which is a mono-articular muscle, only crossing the elbow joint. Thus, during extension, the lateral head may act to extend the elbow, but during flexion, it may act to stabilize the elbow joint (Chaytor et al., 2020). This activity may contribute to increased EMG levels during the elbow flexion phase, preventing the lateral head from having an "off" period where cortical inhibition may increase to reduce movement/activation. There is some evidence to suggest that SICI is reduced as co-activation

increases during a unilateral pointing task (Devanne et al., 2002). It is possible that the amount of SICI noted at the 6 o'clock position might have been greater had we examined a different head of the triceps brachii. Chaytor et al. (2020) discuss the anatomical role of the triceps heads during arm cycling and note that the long head most likely acts to extend the shoulder during the flexion phase suggesting that it may contribute less than the lateral head to elbow stabilization. As such, SICI may behave differently in the long or medial head.

At the 6 o'clock position, the triceps brachii had significantly less EMG activity than the 12 o'clock position, similar to the pre-stimulus EMG activity noted by Spence et al. (2016). At 6 o'clock, the triceps brachii is not at an optimal length to perform its anatomical function of elbow extension. Thus, it stands to reason that more cortical inhibition would be present at this position to limit the excitability of corticospinal neurons to the triceps brachii. Alcock et al. (2019) examined SICI from the biceps brachii at the 6 o'clock position and noted more inhibition at this position compared to the triceps brachii (approximately 40% SICI ratio). Although, it appears from the results of Alcock et al. (2019) that the biceps brachii has greater inhibition at the 6 o'clock position, where the highest EMG activity is reported (Alcock et al., 2019). The SICI results from the triceps brachii in this study, however, cannot be compared to the biceps brachii from Alcock and colleagues (2019). First, as mentioned before, the corticospinal excitability and the EMG activity to the triceps and biceps brachii differ, whereby the triceps brachii lack phase-dependent modulation (Spence et al., 2016; Chaytor et al., 2020). Second, previous studies suggest that SICI may be muscle-dependent (Abbruzzese et al., 1999; Ridding et al.,1995; Menon, Kiernan & Vucic, 2018). Possible differences in intracortical inhibition have been attributed to the organization of corticospinal neurons, where some muscles receive a greater portion of input to enable finer control of movement (Palmer & Ashby, 1992).

Further, most participants had never experienced arm cycling, making this a new motor task. Although an informal familiarization session was provided to ensure there were no ill effects to the stimulation, participants were not given an opportunity to practice the arm cycling consecutively over several days. Thus, it is unlikely that neural rearrangement and adaption due to the informal familiarization occurred. Ito et al. (2015) examined the modulation of SICI before and after completion of various walking tasks with gait patterns that were natural (i.e., a participant's normal gait pattern) and novel to participants. The authors suggest that tasks that are novel require greater facilitation and excitability to perform compared to tasks practiced more often (Ito et al., 2015). Therefore, since this was the first time most participants performed arm cycling, SICI noted at both positions may be reduced to allow increase excitability compared to participants with prior arm cycling experience. However, the modulation of cortical excitability may depend on the complexity of the motor task as other studies have observed decreases in SICI following motor training (Liepert et al., 1998; Perez et el., 2004). Both these studies utilize non-locomotor like tasks such as repetitive thumb movements (Liepert et al., 1998) and ankle dorsi- and plantarflexion (Perez et al., 2004) that may contribute to the differences in noted results. Yet, it is important to note the time frame of the current study. The session lasted approximately 60 minutes. It is possible that some neural adaptation throughout the session occurred which may have contributed to the study's results, although that was not the study's primary outcome measure.

There was a significant difference in CS intensities used between the positions with higher intensities required at 12 o'clock to elicit the same inhibitory response. The CS is intended to suppress the MEP amplitude of the test stimulus (TS) by activating lower threshold inhibitory neurons to increase the release of GABA into the cortical region (Nakamura et al.,

1997; Orth et al., 2003). However, as the muscle increases in activity, cortical neurons increase in excitability. Prior work has shown that the triceps brachii is most active at the 12 o'clock position during arm cycling (Chaytor et al., 2020), so to counteract increases in cortical excitability and apply an inhibitory effect, the CS intensity must be increased. In other words, the inhibitory interneurons that compose the intracortical inhibitory circuit SICI were not as responsive to stimulation at 12 o'clock compared to 6 o'clock. This adds support to show that the effectiveness of SICI was reduced and suggests that cortical excitability to the triceps brachii was increased at the 12 o'clock position.

Other work has also considered the possible phase-dependent modulation of intracortical inhibition. Garnier et al. (2019) showed phase-dependent modulation of corticospinal excitability to the knee extensors during walking, where it was increased during downhill walking. They were unable to determine if SICI specifically resulted in this modulatory effect of corticospinal excitability. Nevertheless, they did suggest an overall decrease in the effectiveness of intracortical inhibitory circuits to enable increased facilitation during downhill (eccentric contraction) walking (Garnier et al., 2019). However, a study examining SICI to the first dorsal interosseus during a precision gripping task showed that it was phase-dependent. The authors showed that SICI was reduced during active and passive cyclical wrist flexion compared to wrist extension (Gagne & Schneider, 2008). Although, Gagne & Schneider (2008) utilized a synergistic unilateral contraction (precision gripping task) and manipulation of a proximal joint, which is different from the current study's experimental design. In another study, the authors examined SICI modulation to the hand muscles when the shoulder was in full horizontal adduction or abduction. Their results demonstrated that SICI to intrinsic hand muscles on the dominant side is dependent on the position of the shoulder (Geed et al., 2021). Although

position-dependent effects to SICI are noted, these authors modified the position of a proximal joint to observe effects at more distal muscles during isometric contractions (Geed et al., 2021). Unlike Geed et al. (2021), the shoulder position in the current study changes from 0 to 90 degrees of flexion as participants go through an arm cycling revolution instead of adduction and abduction. Even though the range of motion is different, the possibility of the shoulder position contributing to some of the non-significant differences noted in SICI to the triceps brachii in the present study should not be ignored.

3.5.3 Methodological considerations

There are several factors that should be considered when interpreting this study's results. First, we recorded from only the lateral head, which is a monoarticular muscle, and excluded the long and medial head of the triceps brachii as well as the anconeus muscle. Our results may not necessarily reflect the amount of SICI present to all the muscles that contribute to elbow extension as SICI has been shown to be muscle dependent (Zoghi et al., 2003; Spence et al., 2016; Menon et al., 2018). Second, this study was done at a set workload and cadence, so although non-significant phase-dependent modulation was noted in this study, the results cannot be applied to other intensities. Ortu et al. (2008) highlighted that SICI is intensity-dependent, and thus, it is plausible that other cadences and workloads may yield alternate results.

Thirdly, this study utilized a circular coil and did not hotspot for the triceps brachii motor representation region. This study also used a single CS intensity (90% AMT). However, some evidence suggests that different CS intensities can yield different amounts of SICI being present even during the same resting task (Ibáñez et al., 2020). Alternatively, Alcock et al. (2019) found no significant difference between using CS intensities of 70% and 90% AMT. Finally, there are many intracortical inhibitory circuits that are active during a motor output. During tonic

contractions, these circuits have been shown to interact with each other and, thus, influence the effectiveness of each circuit (Daskalakis et al., 2002; Chen et al., 2004; Rossini et al., 2014). However, it is still unclear how these circuits interact with each other during a locomotor output.

3.6 CONCLUSION

This was the first study to examine the presence of SICI to the triceps brachii during arm cycling, as well as to examine if any phase-dependent modulatory effects existed. This study showed that SICI is indeed present to the triceps brachii during arm cycling at workload and intensity of 25W and 60 RPM. There was no significant phase-dependent effect in the amount of SICI present (6 vs 12 o'clock), though a non-significant reduction in SICI was noted at 12 o'clock, where EMG activity was the highest during mid-elbow flexion. Future studies should investigate the effect of other cortical circuits on cortical excitability during arm cycling and other locomotor activities.

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Chapter 4 Summary and Future Directions

This research was inspired by previous work conducted by the Human Neurophysiology Lab (HNL) at Memorial University of Newfoundland and Labrador. The HNL aims to piece together how the central nervous system produces and controls locomotor outputs in humans. Since its creation, the HNL lab has conducted several investigations to understand the modulation of corticospinal excitability during arm cycling using TMS and TMES. As mentioned through this thesis, work done in 2016 showed that corticospinal excitability is differentially modulated to the biceps and triceps brachii. The results of this study were unexpected regarding the triceps brachii. Although the triceps brachii showed no phase-dependent corticospinal excitability modulation, unlike the biceps brachii, they did exhibit higher spinal excitability during elbow flexion than extension. Additionally, other work from our lab in 2020 highlighted that the biceps and triceps brachii have different EMG profile activities throughout an arm cycling revolution. The biceps brachii appear to have distinct "on" and "off" periods that coincide with elbow flexion and elbow extension. The triceps brachii, on the other hand, appear to be "on" throughout the arm cycling revolution, although greater activity was detected at mid-elbow extension. In 2019 our lab examined the presence of SICI to the biceps brachii to determine if it contributed to the phase-dependent modulation of corticospinal excitability to the biceps brachii. However, the presence of SICI to the triceps brachii was not investigated during that study.

The differential modulation of corticospinal excitability as well as the EMG activity between the biceps and triceps brachii and the gap left by Alcock et al. (2019) led to the inception of this thesis. This thesis is the third project completed by the HNL to examine cortical excitability and the first to examine the presence of SICI to the triceps brachii. This thesis had

two purposes: first to determine if SICI to the triceps brachii is present and second if present to determine if there was phase-dependent modulation between elbow flexion and extension. Using ppTMS and single-pulse TMS, SICI in this study was reported as a ratio of conditioned MEPs over unconditioned MEPs and then expressed as a percentage. Notably, the results of this thesis showed that SICI is indeed present to the triceps brachii during arm cycling at 25W and 60 RPM. However, to the second purpose, this study found no significant phase-dependent modulation of SICI to the triceps brachii.

Future studies should compare SICI to the triceps brachii during arm cycling and tonic contractions to ensure that the results are due to the locomotor output of interest. As well, SICI should be examined at different workloads and cadences of arm cycling. Additionally, future work should consider the effect of grip position (i.e., neutral, supinated, and pronated grip) and direction of arm cycling on the amount of SICI present. Further investigation of cortical mechanisms will develop a more robust understanding of the control and production of locomotor outputs in humans. Continuing this line of research may aid in improving neurorehabilitation programs for persons with neurological impairments such as stroke and Parkinson's patients.

Appendix A: Ethical Approval

MEMORIAL UNIVERSITY

Interdisciplinary Committee on
Ethics in Human Research (ICEHR)

St.John's, NL Canada A1C 5S7
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ICEHR Number:	**20220230-HK**
Approval Period:	June 11, 2021 – June 30, 2022
Funding Source:	
Responsible Faculty:	Dr. Kevin Power School of Human Kinetics and Recreation
Title of Project:	*Short interval intracortical inhibition projecting to the triceps brachii during arm cycling*

June 11, 2021

Nehara Herat
School of Human Kinetics and Recreation
Memorial University of Newfoundland

Dear Nehara Herat:

Thank you for your correspondence of June 2, 2021 addressing the issues raised by the Interdisciplinary Committee on Ethics in Human Research (ICEHR) for the above-named research project. ICEHR has re-examined the proposal with the clarifications and revisions submitted, and is satisfied that the concerns raised by the Committee have been adequately addressed. In accordance with the *Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans (TCPS2)*, the project has been granted *full ethics clearance* for **one year**. ICEHR approval applies to the ethical acceptability of the research, as per Article 6.3 of the *TCPS2*. Researchers are responsible for adherence to any other relevant University policies and/or funded or non-funded agreements that may be associated with the project. If funding is obtained subsequent to ethics approval, you must submit a Funding and/or Partner Change Request to ICEHR so that this ethics clearance can be linked to your award.

The *TCPS2* **requires** that you **strictly adhere to the protocol and documents as last reviewed** by ICEHR. If you need to make additions and/or modifications, you must submit an Amendment Request with a description of these changes, for the Committee's review of potential ethical concerns, before they may be implemented. Submit a Personnel Change Form to add or remove project team members and/or research staff. Also, to inform ICEHR of any unanticipated occurrences, an Adverse Event Report must be submitted with an indication of how the unexpected event may affect the continuation of the project.

The *TCPS2* **requires** that you submit an Annual Update to ICEHR before **June 30, 2022**. If you plan to continue the project, you need to request renewal of your ethics clearance and include a brief summary on the progress of your research. When the project no longer involves contact with human participants, is completed and/or terminated, you are required to provide an annual update with a brief final summary and your file will be closed. All post-approval ICEHR event forms noted above must be submitted by selecting the ***Applications: Post-Review*** link on your Researcher Portal homepage. We wish you success with your research.

Yours sincerely,

Kelly Blidook, Ph.D.
Vice-Chair, Interdisciplinary Committee on
Ethics in Human Research

KB/bc

cc: Supervisor – Dr. Kevin Power, School of Human Kinetics and Recreation