INTERHEMISPHERIC INHIBITION PROJECTING TO THE BICEPS BRACHII DURING ARM CYCLING

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Abstract

Indirect evidence suggests that arm cycling, along with other types of human locomotion, is partially controlled by specialized groups of spinal interneurones known as central pattern generators (CPGs). Further, it is known that the brain is directly involved in the control of arm cycling, however its specific roles are not well understood. The overwhelming majority of information regarding the brain's role in control of human motor output has come from isometric or tonic contraction, however it has been shown that the cortical input on locomotion differs from that of isometric contraction. It has been shown that inhibitory connections exist between homologous areas of the motor cortices (IHI), which have a direct influence on the motor control of isometric contraction. To date, no study has examined the existence of IHI during locomotion. Therefore, the purpose of this study was to explore the potential influence of IHI during locomotion, using arm cycling as a locomotor model.

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List of Abbreviations

- %MSO – percentage of maximal stimulator output
- CMEP – cervicomedullary evoke potential
- CNS – central nervous system
- CPG – central pattern generator
- D-wave – direct wave
- EMG – electromyography
- I-wave – indirect wave
- IHI – interhemispheric inhibition
- iSP – ipsilateral silent period
- MEP – motor evoked potential
- ms – milliseconds
- mV – millivolts
- MVC – maximal voluntary contraction
- RPM – revolutions per minute
- SD – standard deviation
- SICI – short-interval intracortical inhibition
- TMES – transmastoid electrical stimulation
- TMS – transcranial magnetic stimulation

Chapter 1 Introduction

1.1 Overview

Arm cycling is a commonly used model to research the neural control mechanisms of human locomotion. This movement possesses many similarities of other forms of human locomotor outputs, such as the bilateral, asynchronous and rhythmic activation of both flexors and extensors (Carroll, Baldwin, Collins, & Zehr, 2006; Forman, Raj, Button, & Power, 2014; Lockyer et al., 2018; Zehr et al., 2004). Previous research suggests that the basic rhythmic and alternating pattern of human locomotor output is generated, at least in part, at the level of the spinal cord by specialized groups of neurones, known as central pattern generators (CPGs) (Dietz, 2002), however, descending input from the motor cortex is also required for the generation of locomotion (Christensen, Andersen, Sinkjaer, & Nielsen, 2001; Petersen et al., 2001).

Similar to that of spinal origin, motor output can be further modulated by certain neuronal circuitry at the supraspinal level (i.e. within the cortex), however the mechanisms of their action during a locomotor output are not well understood. One supraspinal neuronal circuit of particular interest is interhemispheric inhibition (IHI), which has been shown to exist between the two motor cortices (Ferbert et al., 1992). This cortical circuit allows each motor cortex to send inhibitory impulses to one another, which has been shown to modulate the motor output of both distal (Ferbert et al., 1992; Jung & Ziemann, 2006) and proximal (Harris-Love, Perez, Chen, & Cohen, 2007; Perez, Butler, & Taylor, 2014) upper limb muscles. Researchers have used transcranial magnetic stimulation (TMS) to demonstrate the influence of IHI during unilateral (Ferbert et al., 1992) and bilateral (Perez et al., 2014)

isometric contraction of upper limb muscles. Moreover, Perez and colleagues have shown that when compared to unilateral activation, the influence of IHI is greater during bilateral activation of homologous upper arm muscles, and less during bilateral activation of antagonist upper arm muscles (Perez et al., 2014). While the recruitment patterns of arm cycling are similar to the bilateral antagonistic activation examined by Perez and colleagues, the possible existence of IHI during a locomotor output has never been examined.

1.2 Purpose

The purpose of this study is to explore the possible existence of interhemispheric inhibition during human locomotion, using arm cycling as a model. Further, this study will compare the potential influence of interhemispheric inhibition to the biceps brachii during arm cycling to that of an intensity- and position-matched tonic contraction.

1.3 Research Hypothesis

It was hypothesized that:

1) interhemispheric inhibition will be observed from the biceps brachii during arm cycling
2) the influence of interhemispheric inhibition would be greater during tonic contraction than during arm cycling

1.4 References

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Chapter 2 Review of Literature

2.1 Introduction

The ability to self-propel ourselves from one area to another, or locomote, is a necessity for human life. The instinct to move is ingrained in us from birth, as we begin crawling at a young age to explore our immediate surroundings, eventually progressing to walking, running and cycling as we reach adolescence and adulthood. The ease with which we perform these locomotor tasks suggests that our central nervous system (CNS) has evolved a certain state of automaticity; the process of placing one foot in front of the other does not require our conscious thought and effort. It has been shown that human locomotor activities rely on a characteristic rhythmic and alternating activation of bilateral flexors and extensors, and that the basic pattern of muscle recruitment during outputs such as walking, running, leg cycling, and arm cycling is generated, in part, by specialized groups of interneurones within the spinal cord, known as central pattern generators (CPGs) (Dietz, 2002; Grillner & Wallen, 1985; E. P. Zehr et al., 2004). Thus, human locomotion is thought to be, in part, an automated process mediated by interneurones in the spinal cord. While the importance of spinal interneurones is clear, much less is known about the brain's role in the control of locomotion. It is theorized that while the spinal cord has a distinct role in mediating locomotion, the action cannot be initiated without input from the brain (N. T. Petersen et al., 2001). Further, brain imaging studies using fMRI techniques have shown that the motor cortices are directly involved in the control of ongoing human cycling (Mehta, Verber, Wieser, Schmit, & Schindler-Ivens, 2009). Given the complexity of the

brain, much is still unknown about how locomotion may depend on input from supraspinal centres.

It is well known that the left motor cortex predominantly controls the right side of the body, and vice versa, however, like the spinal cord, the brain contains interneurones that connect various supraspinal regions. Interhemispheric projections have been shown to travel across the corpus callosum, allowing the two motor cortices to 'talk to each other' prior to and during motor output (for a detailed review of these interhemispheric connections, see Carson, 2005). Thus, while mainly controlled by the contralateral motor cortex, voluntary contraction of a muscle is likely indirectly affected by the ipsilateral motor cortex. It has been shown that the activation of one motor cortex (i.e. right FDI, left motor cortex) can inhibit its homologous contralateral counterpart (i.e. left FDI, right motor cortex) (Ferbert et al., 1992). This phenomenon is known as interhemispheric inhibition (IHI), as activation of one motor cortex can send inhibitory input across the corpus callosum, to the opposite motor cortex (Ferbert et al., 1992). While numerous studies have shown this phenomenon to be present during tonic contraction (Bäumer et al., 2007; Compta, Valls-Sole, Valldeoriola, Kumru, & Rumia, 2006; Harris-Love, Perez, Chen, & Cohen, 2007; Perez, Butler, & Taylor, 2014), its influence during a locomotor output has never been examined.

IHI can be grouped into an area of neuroscience research dedicated to examining cortical circuitry; the presence of interneurones in the brain which form further synaptic connections both within a single supraspinal structure, or between more distant areas of the brain. Considering the number of neurones in the brain, and how many synaptic

connections each neurone may make, the potential number of cortical circuits is clearly immense. However, one additional cortical circuit within the motor cortex known as short-interval intracortical inhibition (SICI) can be considered, and has been examined during human locomotion (Alcock, Spence, Lockyer, Button, & Power, 2019; Barthelemy & Nielsen, 2010; Sidhu, Cresswell, & Carroll, 2013). SICI exists much as IHI, a group of interneurones producing inhibitory projections within the motor cortex. SICI, however, is housed within one motor cortex, and does not cross the corpus callosum to the opposite hemisphere. Thus, SICI is the result of the one motor cortex inhibiting itself. SICI has been shown to have a direct influence on human locomotion, as inhibitory effects can be observed during walking (Barthelemy & Nielsen, 2010) leg cycling (Sidhu et al., 2013) and most recently, arm cycling (Alcock et al., 2019). While IHI and SICI act via different cortical paths and mechanisms, the premise of SICI reliably acting during various locomotor outputs may suggest that IHI may also be present during locomotion. Further, given that SICI is active during both tonic contraction and locomotor output (Alcock et al., 2019; Sidhu et al., 2013), IHI may also be present during locomotion as it has been shown in numerous studies to modulate tonic contraction (Ferbert et al., 1992; Fling & Seidler, 2012; Jung & Ziemann, 2006). Thus, similar to that observed in tonic contraction, it is possible that IHI may have a modulatory effect on locomotor output, aiding in the characteristic rhythmic activation and deactivation of bilateral musculature.

This review will first discuss the basic anatomy and physiology of the corticospinal tract and cortical circuitry, giving context for the sections that follow. Secondly, this review will characterize locomotion, including motoneurone properties taken from both animal

and human studies. Thirdly, this review will discuss the neurophysiological techniques used within the parameters of this project, and how they are used to quantify and assess corticospinal responses and IHI. Lastly, this review will discuss the literature as it currently pertains to IHI during bilateral contractions in attempt to formulate a hypothesis to this proposed research question: is IHI present in the biceps brachii during arm cycling, and if so, how will IHI's influence differ from that of a tonic contraction?

2.2 The Corticospinal Tract

At least since 1853 when Cruveilhier noted a correlation between the atrophy of medullary pyramids and impairments in movement of the contralateral limb (Lassek, 1955), the corticospinal tract has become a favoured topic of neuroscience research. The majority of the original work examining specific anatomy and physiology of the corticospinal tract was conducted in vivo, involving non-human mammals (Lemon, Mantel, & Muir, 1986; Nudo & Masterton, 1990), however there is now a strong body of evidence suggesting that numerous structures within the human cortex also possess corticospinal projections (Brouwer & Ashby, 1990; Canedo, 1997; Nathan & Smith, 1955). Thus, the corticospinal tract is considered one of the most influential descending pathways in the production of voluntary motor output in humans, and has gained increasing popularity as the subject of research aiming to better understand the neural control of voluntary motor output.

The corticospinal tract consists of approximately one million axons, of which roughly 40% arise from the primary motor cortex (Kandel, Schwartz, Jessell, Siegelbaum and Hudspeth 2013), while another 30% arise from premotor and supplementary areas (Canedo, 1997). The primary motor cortex is organized into six layers; an arrangement that

allows for increased computational efficiency of the cerebral cortex. Layers II and III contain predominantly small interneurones which project locally to subsequent neurones deeper within the cerebral cortex; a number of which synapse onto large pyramidal neurones located in layers V and VI of the neocortex. It is these pyramidal neurones in layers V and VI, which will be herein referred to as upper motoneurones, that give rise to major descending pathways including the corticospinal tract (Kandel et al., 2013). Predominantly, the axons of upper motoneurones will synapse onto lower (spinal) motoneurones on the contralateral side of the body. Approximately 90% of this pyramidal decussation will occur at the level of the medulla, giving rise to the lateral corticospinal tract. The remaining 10% of axons continue to travel down the ipsilateral side of the body, and do not crossover until they terminate at the level of the spinal cord, making up the anterior corticospinal tract (Kandel et al., 2013). Thus, both the lateral and anterior corticospinal tracts synapse with lower motoneurones on the contralateral side of the body, although they do not follow the same path.

Depending on the target muscle, upper motoneurones can make either monosynaptic or polysynaptic connections with lower motoneurones in the spinal cord. Monosynaptic connections are thought to have great influence with smaller muscle groups, specifically those specialized for more intricate movement patterns, such as individual finger movements (Kandel et al., 2013). Corticospinal axons can also make polysynaptic connections with lower motoneurones via spinal interneurones, and it is thought that these connections are vital for coordinating larger muscle groups in organized movement, such as locomotion (Kandel et al., 2013). For example, the motoneurones of the biceps brachii

receive a large excitatory input from electrical stimulation of corticospinal tract fibres, which has been found to be mostly monosynaptic (Nicolas T. Petersen, Taylor, & Gandevia, 2002). In contrast, the triceps brachii is thought to have fewer monosynaptic connections, although some monosynaptic connections exist (Brouwer & Ashby, 1990). Irrespective of the synaptic connection, it is ultimately the passage of information from the upper motoneurone to the lower motoneurone that allows for the corticospinal tract to control motor output.

2.3 Cortical Circuitry

While it is apparent that the lower motoneurone is largely influenced by descending upper motoneurones, it would be naïve to ignore the potential influence of other structures on motor output. Varying cortical regions including the cerebellum and basal ganglia, among many others, synapse directly onto upper motoneurones, and can eventually influence the lower motoneurone (Kandel et al., 2013). That is, cortical structures 'upstream' of the corticospinal tract can have a direct effect on both the upper and lower motoneurone, thus directly modulating various motor output. In addition to their connection to the upper motoneurone, interneurones in superficial layers of the motor cortex can synapse onto other interneurones in various cortical areas. These connections can have a direct or indirect effect on motor output, and will herein be known as cortical circuits. Considering the complexity of the human nervous system, describing all the potential synaptic influences on the corticospinal tract is not feasible. For the purposes of this review, I will briefly discuss select cortical circuits of the motor cortices, namely short-interval intracortical inhibition (SICI) and interhemispheric inhibition (IHI). Particular attention

will be given to IHI and its role in the modulation of motor output, as this cortical circuit was the main focus of my experiment.

2.3.1 Short-Interval Intracortical Inhibition

First described by Kujirai and colleagues in 1993, SICI (also referred to as corticocortical inhibition) of the motor cortex acts as a means for the motor cortex to send inhibitory impulses to its own upper motoneurones (Kujirai et al., 1993). Sub-threshold stimulation of the motor cortex activates a circuit of $GABA_A$ergic interneurones, which send inhibitory impulses to the upper motoneurone, decreasing its excitability (Kujirai et al., 1993). More recent studies have shown that SICI decreases during voluntary unilateral contraction (Soto, Valls-Solé, Shanahan, & Rothwell, 2006), and increases with muscle relaxation (Buccolieri, Abbruzzese, & Rothwell, 2004). Thus, the influence of SICI is dependent on the task-specifics of motor output.

Interestingly, SICI is the only cortical circuit to have been examined during human locomotor output. To date, three studies have examined the presence of this inhibitory circuit during CPG-mediated movements including walking (Barthelemy & Nielsen, 2010), leg cycling (Sidhu et al., 2013) and most recently, arm cycling (Alcock et al., 2019). While all three studies demonstrate that SICI is active during human locomotion, the specifics of such appear to vary. While Sidhu and colleagues demonstrate that SICI is greater during leg cycling than during tonic contraction (Sidhu et al., 2013), Barthelemy et al. and Alcock et al. report that SICI's influence is not different between locomotor and tonic contraction tasks (Alcock et al., 2019; Barthelemy & Nielsen, 2010). It is important to note that Sidhu and colleagues recorded SICI from muscles of the quadriceps, where Barthelemy et al. and

Alcock et al. recorded from the posterior deltoid and biceps brachii, respectively. Thus, it is likely that influence of SICI on human locomotion is muscle-dependent, potentially involving upper vs. lower limb musculature. Nonetheless, all three studies demonstrated the significance of one cortical circuitr during human locomotion, which may provide rationale to speculate the effects of other cortical circuits during locomotion, including IHI.

2.3.2 Interhemispheric Inhibition

The earliest works investigating the presence of interhemispheric connections between motor cortices was conducted in rhesus monkeys (Pandya & Vignolo, 1971). The researchers used a silver impregnation technique to examine the theorized existence of interhemispheric neural circuits, and they concluded that connections existed between homologous representations of proximal upper limb and trunk muscles, but not between distal forelimb muscles (Pandya & Vignolo, 1971). Later studies identified that the distal forelimb representations of the motor cortex in the rhesus monkey do in fact contain interhemispheric connections, however they are not as numerous as those existing in the motor cortex representations of proximal upper limb muscles (Brinkman & Kuypers, 1973; Gould, Cusick, Pons, & Kaas, 1986; Jenny, 1979; Rouiller et al., 1994). This suggests, in at least animal models, that interhemispheric connection of homologous upper limb representative areas is at least as powerful as areas devoted to distal upper limb musculature. While the abundance and strength of these connections has been observed in the rhesus monkey, its role in the modulation of functional motor output in humans remains poorly understood.

Ferbert and colleagues were the first to report inhibitory connections between the motor cortices in humans using transcranial magnetic stimulation (Ferbert et al., 1992). Using this magnetic brain stimulation technique, the researchers were able to activate the interneurones existing between homologous areas of the motor cortex, which in turn inhibited motor output of a target muscle (Ferbert et al., 1992). The specific methodology used to assess and quantify IHI is important to consider, and as such, will be discussed in a later section of this review. Nonetheless, the work from Ferbert and colleagues effectively demonstrated, for the first time, an inhibitory circuit of interneurones existing across the corpus callosum, and between the two motor cortices in humans (Ferbert et al., 1992). This proposed view was strongly supported by later studies, in which IHI was not observed in patients with agenesis or legions of the corpus callosum (Boroojerdi, Diefenbach, & Ferbert, 1996; Meyer, Röricht, von Einsiedel, Kruggel, & Weindl, 1995). While the exact mechanisms mediating IHI remains in question, there is tentative agreement on the involvement of interhemispheric glutamatergic synapses linking with upper motoneurones through GABAergic interneurons (Reis et al., 2008) (see Figure 1). Similar to that of SICI, the strength of IHI during motor output appears to be dependent on a number of factors, including the targeted muscle (Harris-Love et al., 2007; Jung & Ziemann, 2006), task specifics (Fling & Seidler, 2012), and contraction intensity (Ortu, Deriu, Suppa, Tolu, & Rothwell, 2008).

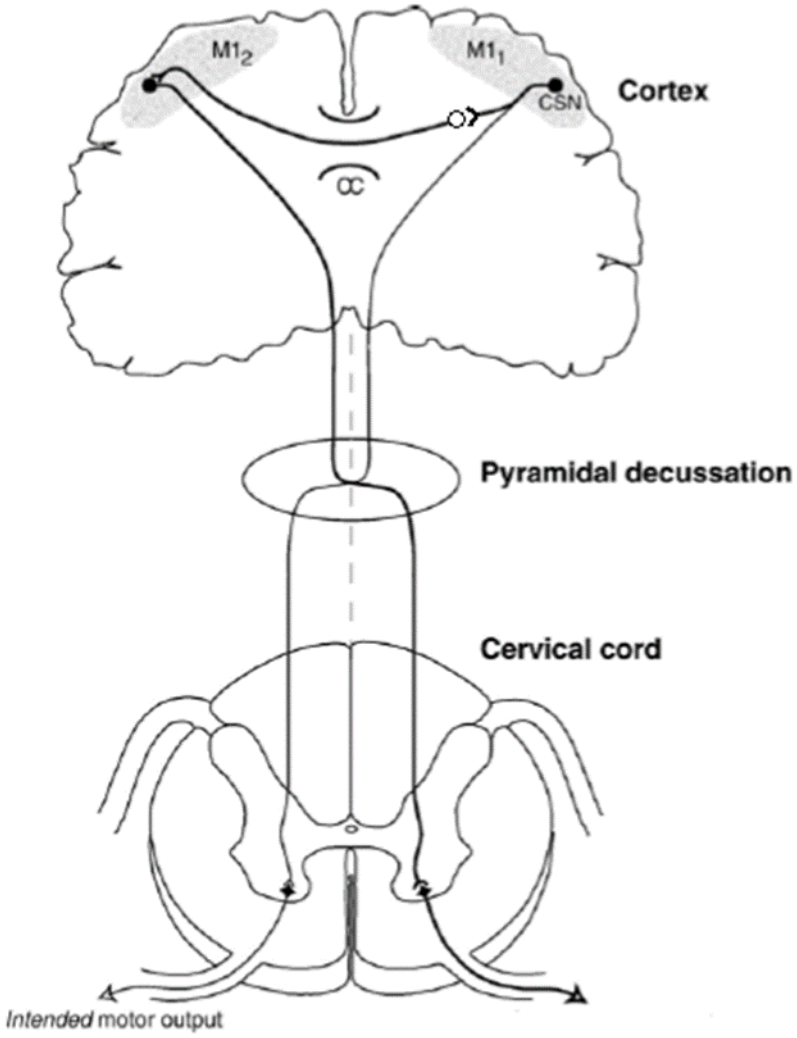

Figure 1. *A representation of the potential neural circuitry of interhemispheric inhibition between the two motor cortices. Note that the black filled neurones represent excitatory neurones, where the white fill represents inhibitory neurones. Activation of upper motoneurones of one motor cortex may project to inhibitory interneurones, which project across the corpus callosum and synapse onto upper motoneurones in the contralateral motor cortex. Figure is modified from Carson (2005).*

Given that the brain hosts nearly 100 billion neurones, the number of potential cortical circuits is incredibly vast. It is important to note that while a few select cortical circuits have been discussed, many more have been identified in the literature including intracortical facilitation (ICF) (Tokimura, Ridding, Tokimura, Amassian, & Rothwell,

1996) and interhemispheric facilitation (IHF) (Ugawa, Hanajima, & Kanazawa, 1993), and it is likely that their influence is also important for the control of human motor output. Regardless of their origin, it is ultimately the summation of both excitatory and inhibitory connections that determine whether or not the lower motoneurone will fire an action potential; a fact that prompted Sir Charles Sherrington to famously name the motoneurone "the final common path" (Sherrington, 1906). Interestingly, there is currently no information as to the influence of IHI on human locomotor output of any kind. While substantial work has been done examining the effects of IHI on muscles at rest and undergoing various types in tonic contraction, one must take caution in interpreting these results to hypothesize towards a locomotor output. Previous works have shown that even at similar joint angles and contraction intensities, muscle undergoing tonic contraction are modulated differently than muscles performing a locomotor task (Capaday, Lavoie, Barbeau, Schneider, & Bonnard, 1999; Carroll, Baldwin, Collins, & Zehr, 2006; D. Forman, Raj, Button, & Power, 2014; Sidhu et al., 2013). Further, it has been shown that supraspinal excitability is greater during arm cycling than during tonic contraction (D. Forman et al., 2014), which could potentially suggest that IHI has different effects during locomotion and tonic contraction. Thus, there is a strong need for research on the influence of IHI on human locomotion. Before these potential effects are explored, however, it is vital to clearly define locomotion, and discuss what is currently known regarding the modulation of the corticospinal tract during human locomotor output. This will be addressed in the following section.

2.4 Neural Control of Locomotion

As previously mentioned, human locomotor output is at least partially mediated by specialized interneurones in the spinal cord known as CPGs, which eventually project to motoneurones to control the characteristic pattern of rhythmic muscle activity (Dietz, 2002; E. P. Zehr, 2005; E. P. Zehr et al., 2004). However, it is important to discuss the specifics of how these CPGs modulate motoneurone properties, specifically during locomotion. The majority of works examining motoneurone excitability during these CPG mediated motor outputs have been conducted in quadrupeds, in which properties of the motoneurone have been taken following surgical interventions to isolate certain neural structures and mechanisms (Krawitz, Fedirchuk, Dai, Jordan, & McCrea, 2001; MacDonell, Power, Chopek, Gardiner, & Gardiner, 2015). While these studies provide useful information as to the basic mechanisms associated with changes in motoneurone properties, these studies do not directly tell the story of how CPG-mediated motor output may be modulated in vivo, using human subjects (Power, Lockyer, Forman, & Button, 2018). Work from our lab has begun to address this question, implementing neurophysiological techniques such as transcranial magnetic stimulation (TMS), transmastoid electrical stimulation (TMES), and surface electromyography (sEMG) to assess corticospinal and motoneurone excitability during locomotor output (Alcock et al., 2019; Copithorne, Forman, & Power, 2015; D. Forman et al., 2014; D. A. Forman, Philpott, Button, & Power, 2015; Lockyer et al., 2018; Spence, Alcock, Lockyer, Button, & Power, 2016). However, much is still unknown about the control of human CPG-mediated movement, specifically the brain's role in this modulation. The following sections will first discuss changes in motoneurone properties during CPG-mediated movement in quadrupeds, and their significance to human research.

Secondly, research regarding the modulation of CPG-mediated movement in humans and the techniques used to do so will be discussed.

2.4.1 Motoneurone Properties During CPG-Mediated Motor Output in Quadrupeds

The initiation of rhythmic motor output, including locomotion, begins with a descending command from supraspinal centres, causing spinally located CPGs to recruit the motoneurones necessary for the motor output. As a result, the oscillation of CPGs causes a rhythmic change of motoneurone excitability during locomotion, depending on whether in a flexion or extension phase. That is, at any given time point, a motoneurone may be in a different "state" of excitability. As shown in animal models, biophysical properties of the motoneurone undergo state-dependent changes throughout locomotor output, resulting in the aforementioned change in motoneurone excitability (Krawitz et al., 2001; MacDonell et al., 2015; Power, McCrea, & Fedirchuk, 2010). These changes in motoneurone properties can be considered 'state-dependent' during CPG-mediated motor output, as the motoneurones are in a more enhanced 'state' of excitability during locomotor output when compared to rest (Power et al., 2018). The following sections will discuss, in brief, two state-dependent biophysical properties of motoneurones seen in locomotor output, including changes in voltage threshold (V_{th}), and after hyperpolarization period (AHP).

2.4.1.1 Hyperpolarization of Motoneurone V_{th}

The V_{th} of a motoneurone represents the membrane potential necessary to elicit an action potential. Thus, in order to fire an action potential, the motoneurone must 'close the gap' between its resting membrane potential and its V_{th}. Modulation of the V_{th} can have a

direct effect on excitability of the motoneurone, as hyperpolarization of the V_{th} will bring it and resting membrane potential closer together. That is, following V_{th} hyperpolarization, a motoneurone will require less excitatory input to fire an action potential, thus increasing the excitability of the motoneurone. A detailed discussion of the mechanisms responsible for V_{th} hyperpolarization are beyond the scope of this review, however previous studies have examined and noted the effect of CPG-mediated motor output on motoneurone V_{th}. A select few of these studies will be discussed in brief below.

Krawitz and colleagues reported the first description of state-dependent changes in motoneurone V_{th} during CPG-mediated movement (Krawitz et al., 2001). The researchers evoked fictive locomotion in an adult decerebrate cat, and noted a V_{th} hyperpolarization of motoneurones leading to muscles in the hindlimb (Krawitz et al., 2001). Additional studies have found that V_{th} hyperpolarization occurs during other CPG-mediated movements, and in other species, and hyperpolarization of the motoneurone V_{th} was observed during fictive scratch in the adult decerebrate cat (Power et al., 2010), and fictive locomotion in the adult decerebrate rat (MacDonell et al., 2015). Further, V_{th} has been observed in varying types of motoneurones, including both fast and slow twitch (Krawitz et al., 2001; MacDonell et al., 2015; Power et al., 2010), motoneurones leading to both flexor and extensor muscles (Krawitz et al., 2001; Power et al., 2010), and whether or not the motoneurone is actively engaged in fictive locomotion (Geertsen, Stecina, Meehan, Nielsen, & Hultborn, 2011; Perreault, 2002; Power et al., 2010). Thus, it appears that during CPG-mediated motor output, all motoneurones of the spinal cord are capable of V_{th} hyperpolarization, suggesting that V_{th} hyperpolarization is an essential component of CPG-mediated motor outputs.

2.4.1.2 AHP Amplitude Reduction

Following an action potential, the motoneurone undergoes a period of hyperpolarization in which the V_{th} briefly exists below its normal resting potential. There exists a certain duration of time during the AHP in which a subsequent action potential cannot be initiated, known as the absolute refractory period of the motoneurone. Thus, if the motor output-task required muscle contraction any greater than a single twitch, it would be advantageous for the V_{th} to return to normal resting levels as quickly as possible, absolute refractory period of the motoneurone to be as short as possible. During CPG-mediated motor output, this appears to be the case. Brownstone and colleagues investigated the differences in repetitive motoneurone firing at rest, and during fictive locomotion in a decerebrate cat (Brownstone, Jordan, Kriellaars, Noga, & Shefchyk, 1992). They concluded that at rest, AHPs were significantly larger than those observed during fictive locomotion, suggesting that that this change in AHP results in an increase in motoneurone excitability during fictive locomotion (Brownstone et al., 1992). More recent work in the adult cat has also shown that AHP amplitude is reduced during CPG-mediated motor output even following a complete spinal transection, confirming that this effect is related solely to intraspinal mechanisms (Power et al., 2010). Although AHP amplitude is reduced during CPG-mediated movement, it does not appear to have an effect on the firing frequency on motoneurones during locomotor-type motor output. Brownstone and colleagues further reported that while increased current injection to the motoneurone increased motoneurone firing frequency at rest, this effect was not seen during fictive locomotion (Brownstone et al., 1992). Although the motoneurone is able to fire more frequently during CPG-mediated motor output, it is not to suggest that the motoneurone *must* fire more frequently. Thus,

while AHP amplitude is reduced during CPG-mediated motor output, it is unlikely that this has a significant effect on the modulation of locomotion.

2.5 Modulation of Corticospinal Excitability During CPG-Mediated Movement in Human

While state- and task-dependent changes in motoneurone properties during CPG-mediated movements have been repeatedly shown in quadrupeds, it is not to be assumed that these changes will also exist during CPG-mediated motor output in humans. Therefore, an investigation of corticospinal and motoneurone excitability during locomotor activity in humans is of interest. Research from our lab and others have begun to address this question, however methodological issues arise. The information gained in quadrupedal studies was conducted using invasive manipulation of the animal's nervous system. This cannot be accomplished in human subjects, for obvious ethical reasons, thus, researchers must propose a model of CPG-mediated movement to mimic the neural activity seen in fictive locomotion and scratch. Further, the stimulation and recording techniques typically used in the aforementioned quadrupedal studies also involve invasive procedures, thus alternative neurophysiological techniques must be considered when dealing with human subjects. The following sections will address both these issues, proposing and rationalizing a human model of CPG-mediated movement, as well as the stimulation techniques used to assess human subjects.

2.5.1 Arm Cycling as a Model of CPG-Mediated Motor Output

Considerable indirect evidence suggests that similar to that of quadrupeds, humans possess spinally-located CPGs capable of producing bilateral and rhythmic motor output

such as walking, leg cycling, and arm cycling (Calancie et al., 1994; Dimitrijevic, Gerasimenko, & Pinter, 1998; Solopova, Selionov, Zhvansky, Gurfinkel, & Ivanenko, 2016; E. P. Zehr, 2005; E. P. Zehr et al., 2004). For example, Dimitrijevic and colleagues were able to use a spinal stimulation technique to elicit rhythmic activity of leg musculature of patients with complete spinal cord injury (Dimitrijevic et al., 1998). In regards to upper arm musculature, Zehr and colleagues have provided substantial evidence that arm cycling, like leg cycling, is also partially mediated by spinally located CPGs (E. P. Zehr, 2005; E.P. Zehr et al., 2016; E. P. Zehr et al., 2004). Thus, both leg and arm cycling could potentially be used as a model for CPG-mediated human motor output. When selecting a model for my experiment, however, arm cycling provided some significant advantages over any other form of locomotor output. First of all, our lab has been using arm cycling as our model of human locomotion for nearly a decade, thus it made sense to continue this experimental design. Secondly, the majority of works examining IHI during tonic contraction have been in regards to upper limb musculature, so it is favorable to examine muscles that have already been shown to have interhemispheric inhibitory influence. Lastly, arm cycling provides a certain ease of experimental design, as the task provides significant head stability and ease of stimulation technique implementation. Thus, arm cycling was chosen to represent the CPG-mediated motor output typically examined in quadrupeds.

2.6 Neurophysiological Techniques to Assess the Corticospinal Tract

Output of the corticospinal tract is influenced by synapses of varying origin, each of which exist in an ever-changing state of excitability. In brief, synaptic connections arising from numerous supraspinal structures, spinal motoneurones, muscle afferents, and

other locations can have a direct influence on the output of the corticospinal tract. It is ultimately the sum of all the synaptic activity ‘upstream’ of the spinal motoneurone that will control its depolarization (Canedo, 1997; J. L. Taylor, Petersen, Butler, & Gandevia, 2002). While one can never obtain a complete understanding of the true modulation of motor output due to the complexity of the human nervous system, researchers have established a number of neurophysiological techniques in attempt to better understand each possible influencing factor. The development of techniques such as transcranial magnetic stimulation (TMS) and electromyography (EMG) have allowed researchers to generate and record responses from the corticospinal tract, providing a deeper understanding of the control of human motor output. While there are many methods and techniques used to assess corticospinal responses in humans, surface EMG and TMS will be included in this review as they were the respective recording and stimulation techniques utilized in my experiment. Particular attention will be given to TMS, and how it can be used to assess and quantify IHI.

2.6.1 Electromyography

Of the countless possible experimental parameters of neurophysiology research, the existence of an electrical gradient across muscle membranes is a common truth for all contracting muscles. In both animal and human studies, the basis of neurophysiological research relies on the ability for researchers to record this electrical potential from target muscles. Recording these responses is made possible using EMG, a group of neurophysiological techniques designed for this exact purpose. The applications of EMG are numerous; covering all the types, uses, and analysis techniques of EMG would be large

review of literature on its own. For the purposes of this review, surface EMG will be explained in brief, as this was the recording technique utilized in this experiment.

Surface EMG is the most commonly used tool to non-invasively record electrical activity of a target muscle in humans (DeLuca, 1997). The technique involves the placement of surface electrodes on the skin of a participant, usually running in parallel to the underlying muscle fibres (DeLuca, 1997). Regardless of their origin (i.e. in the motor cortex through voluntary contraction, in the lower motoneurone via nerve stimulation, etc.), action potentials cross the motor end-plate, and propagate along the muscle fibres comprised in the motor unit. Surface electrodes are able to pick-up these electrical impulses through the skin. Responses recorded from the surface electrodes are converted from analog to digital signal, usually amplified and filtered, and analyzed using EMG analysis software (DeLuca, 1997). The specifics of this recording and analysis for this experiment will be discussed in a later section.

2.6.2 Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is used extensively by clinicians and researchers to non-invasively and painlessly stimulate the human brain (Barker, Jalinous, & Freeston, 1985; Di Lazzaro et al., 1998; Terao & Ugawa, 2002). The technique is based on Faraday's Law of electromagnetic induction, in which a high electrical current is passed through an insulated coil of copper wire; this passing of current creates a magnetic field, which will be discharged perpendicular to the direction of current flow (Terao & Ugawa, 2002). When a TMS coil is placed above the head, the resultant magnetic field can pass unimpeded through the scalp and skull and activate underlying neurones in the human

cortex (Di Lazzaro et al., 2004; Rothwell et al., 1999). Depending on the placement of the coil over the scalp, TMS can stimulate numerous areas of the brain, thus having numerous research applications. For the purposes of this review, however, TMS will always be discussed in the context of application to the motor cortex.

Typically, single-pulse TMS does not directly stimulate upper motoneurones of the corticospinal tract, as these neurones are located in deeper layers of the cortex (Burke et al., 1993; Di Lazzaro et al., 2004). Instead, the induced magnetic field activates interneurones in the more superficial layers of the cortex, which project to the corticospinal tract's upper motoneurones. Thus, TMS-induced activation of the human corticospinal tract is usually indirect in nature, as upper motoneurones are trans-synaptically depolarized via interneurones. Since a single TMS pulse activates a number of interneurones, multiple descending volleys will be evoked; these can be recorded as indirect waves (I-waves) from a target muscle via surface EMG (Burke et al., 1993; Di Lazzaro et al., 2004). Under certain conditions, however, TMS may directly activate the upper motoneurones of the corticospinal tract (Di Lazzaro et al., 1998). These factors can include, but are not limited to intensity of stimulation, placement of TMS coil, existence of voluntary contraction, and individual differences. The direct activation of upper motoneurones results in descending volleys denoted as direct waves (D-waves). Since I-waves are elicited via at least one additional synapse in comparison to D-waves, researches are able to differentiate between the two responses based on the latency in which they occur. I-waves have a latency that is roughly 1-2 ms greater than that of D-waves. The descending volleys evoked by TMS can be recorded as a compound muscle action potential in an ongoing EMG trace, and are

commonly referred to as motor evoked potentials (MEPs) (Burke et al., 1993; J. L. Taylor et al., 2002). Although there are many properties of a MEP that can be assessed across various experimental protocols, it is typically changes in MEP peak-to-peak amplitude that best quantify changes in corticospinal responsiveness (Di Lazzaro et al., 1998). It is notable that an observed increase or decrease in MEP peak-to-peak amplitude represents an increase or decrease in corticospinal excitability, respectively. MEP amplitude can be influenced by several factors, including but not limited to changes in arousal, the amount of background activity of motoneurones, and the task-specificity of ongoing contraction (Capaday et al., 1999; Carroll et al., 2006; D. Forman et al., 2014). It is important to note that the pathway followed by a MEP involves the entire corticospinal tract, that is, synapses at the cortical and spinal level, as well as the neuromuscular junction; the size of the MEP depends on the excitability of cortical and spinal neurones as well as the muscle fibres involved. Thus, although the stimulation necessary to evoke a MEP occurs at the cortical level, one cannot attribute changes in MEP amplitude to changes in cortical excitability alone. To differentiate between changes in excitability in at either the supraspinal or spinal level, a second stimulation technique known as transmastoid electrical stimulation (TMES) is commonly used (Janet L. Taylor, 2006; J. L. Taylor et al., 2002; Ugawa et al., 1993). In brief, TMES is applied at the point of the pyramidal decussation, and activates the axons of upper motoneurone, thus removing any potential input from supraspinal centres. TMES, in combination with TMS techniques, can give an indication of spinal excitability. It is acknowledged that these subsequent techniques must be used in order to denote the location of change in corticospinal excitability, however they will not be discussed in detail for the purpose of this review.

2.7 Assessing Interhemispheric Inhibition Using Transcranial Magnetic Stimulation

Recall that TMS typically activates interneurones in the more superficial layers of the motor cortex, which can have direct connections to upper motoneurones of the contralateral motor cortex. Thus, TMS can be used to activate the circuit of neurones responsible for IHI between the two motor cortices. Researchers have developed two TMS paradigms to examine IHI in human subjects, both of with are commonly used in the literature today. The following sections will discuss the specifics of both of these methods.

2.7.1 Analysis of Interhemispheric Inhibition: Paired-Pulse Transcranial Magnetic Stimulation

The first method involves the use of two magnetic stimulators, one over each homologous muscle-representation of the motor cortices (i.e. biceps-biceps representations) (Ferbert et al., 1992). A sub-threshold stimulus, also known in this context as a conditioning stimulus, is delivered to the ipsilateral motor cortex, followed by a suprathreshold stimulus, also known as a test stimulus, to the contralateral motor cortex 4-7 ms later (Ferbert et al., 1992). The initial stimulus activates inhibitory interneurones of the ipsilateral motor cortex, which project across the corpus collosum, and eventually synapse onto upper motoneurones of the contralateral motor cortex. That is, sub-threshold stimulation of the ipsilateral motor cortex will inhibit the upper motoneurones of the contralateral cortex. This inhibitory effect can be observed in MEPs from the target muscle. The peak-to-peak amplitude of the conditioned MEP will be lesser than that of an unconditioned MEP, where the degree of inhibition will be quantified by the comparative

decrease in MEP amplitude (Ferbert et al., 1992). This method can be utilized when the target muscle is either active, or at rest.

2.7.2 Assessing Interhemispheric Inhibition: Single-Pulse Transcranial Magnetic Stimulation

The second method requires only one stimulator, and utilizes reduction in ongoing EMG to quantify IHI (Ferbert et al., 1992). It is important to note that this method demands that the target muscle be actively contracting, and cannot be utilized in any experimental conditions in which the target muscle is at rest. In a similar fashion to the previously outlined method, a subthreshold conditioning stimulus is applied to the ipsilateral motor cortex, however it is not followed by a second test stimulus. The conditioning stimulus will activate interneurones in the ipsilateral motor cortex, sending inhibitory pulses to the contralateral motor cortex, ultimately producing an observable suppression in the ongoing EMG trace of the ipsilateral limb. This suppression of EMG is referred to as the ipsilateral silent period (iSP) (Ferbert et al., 1992). To quantify the iSP, the absolute values of the entire EMG trace must be taken, as ongoing raw EMG reflects both positive and negative values averaging about zero. Thus, any suppression elicited by TMS may go unnoticed in a raw EMG trace. Once the EMG has been rectified, average EMG values are taken both during the iSP, and prior to the stimulus artifact (bEMG), and these two values are compared. Rectified iSP EMG is expressed as a percentage of average rectified bEMG and IHI is quantified by this percentage of reduction (see Figure 2).

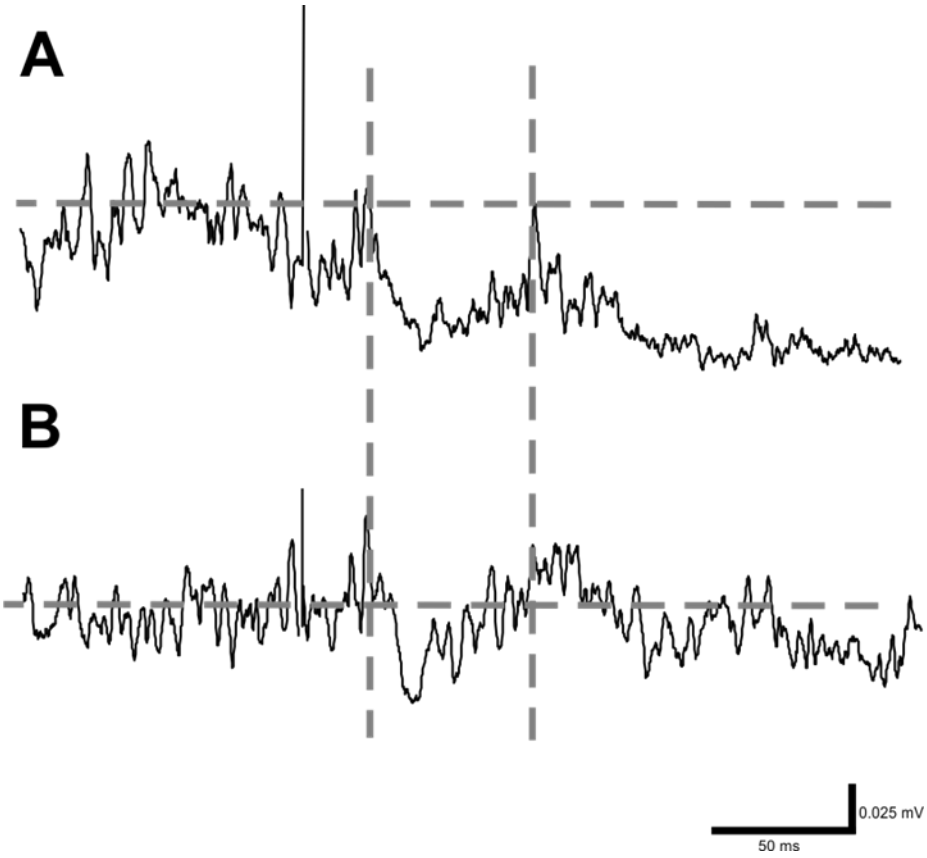

Figure 2. *A single-subject representation of the ipsilateral silent period evoked by sub-threshold transcranial magnetic stimulation, using two experimental conditions as an example. iSP was recorded from the non-dominant biceps brachii following TMS of the dominant motor cortex. The iSP onset and offset, with respect to the arm cycling condition, are denoted by the dashed vertical cursors. Average rectified EMG prior to the stimulation for each condition are denoted by the dashed horizontal cursors.*

While both the aforementioned methods can quantify IHI, the research questions must be considered when deciding which experimental protocol to use. It is important to consider the two dependent variables in question when considering both these techniques, and what they represent, respectively. A MEP generated by TMS, as discussed in the first method, is an artificially induced neurophysiological response and most closely represents excitability of the corticospinal tract. In the context of an analysis of IHI, this method would

be most beneficial when measuring IHIs influence on the overall excitability of the corticospinal tract. In contrast, ongoing EMG, as discussed in the second method, is a measure of the true output of the motoneurone pool. This method would be most beneficial when examining the influence of IHI on a specific motor task, such as measuring its role in human locomotion. Since the research questions of this project focused on the effects of IHI on two motor outputs, arm cycling and tonic contraction, the iSP method of IHI analysis was chosen.

2.8 Modulation of Interhemispheric Inhibition During Bilateral Contractions

Thus far, IHI has only been discussed with regards to its cortical configuration, or its modulation of unilateral isometric contraction. However, true human movement relies on a constant state of muscle activation from both flexors and extensors in both the upper and lower limbs. Therefore, unilateral contraction studies may not provide the best evidence to IHIs role in the modulation of real-life human movement that involve bilateral activation of multiple muscles. Recall that activation of upper motoneurones of one motor cortex can send inhibitory input to the contralateral motor cortex through interhemispheric pathways. Thus, it is likely that during bilateral muscle contraction, both motor cortices can send inhibitory influence to each other simultaneously. Past works have shown this to be the case, and have suggested that interhemispheric inhibitory connections are stronger from the dominant to the non-dominant motor cortex (Bäumer et al., 2007; Chen, Yung, & Li, 2003). Numerous studies have used measurements of bilateral muscle force production to examine IHI during bilateral contraction, however there has been very limited work implementing a TMS-paradigm to address these questions.

The earliest works on inhibitory effects observed during bilateral contractions were conducted in the absence of a TMS-paradigm, and utilized measurements in force production and perceived exertion (Herbert & Gandevia, 1996; Ohtsuki, 1983; Seki & Ohtsuki, 1990). For example, it has been reported that given the same level of perceived exertion, force is reduced during bilateral contractions for the elbow flexors and elbow extensors, when compared to unilateral elbow flexion or extension (Ohtsuki, 1983; Seki & Ohtsuki, 1990). Further, reductions in force occur with both maximal and submaximal efforts, and appear to be at least as great than force reductions observed during bilateral handgrip or thumb adduction (Herbert & Gandevia, 1996; Seki & Ohtsuki, 1990). Thus, voluntary contraction of either the elbow flexors or extensors might be expected to increase IHI to the homologous muscles of the other arm. However, this increase may not be expected with contraction of flexors of one arm and extensors of the other, as inhibitory interhemispheric connections are thought to exist between homologous muscle representations of the motor cortex, but not between other areas of muscle representation (Carson, 2005; Chen et al., 2003). It is important to note these studies did not include a TMS-paradigm, and therefore cannot directly quantify IHI.

To date, there has only been one study to use a TMS-paradigm to assess IHI in proximal arm muscles during bilateral contraction (Perez et al., 2014). Through stimulation of the non-dominant motor cortex, Perez and colleagues examined the iSP from both the dominant biceps brachii during 3 bilateral conditions: 1) flexion – rest (i.e. non-dominant biceps contracting, dominant arm at rest) 2) flexion – flexion (i.e. both biceps contracting simultaneously), 3) flexion – extension (i.e. non-dominant biceps contracting, dominant

triceps contracting). For the ease of the reader, the experimental set-up from Perez and colleagues (2014) can be seen in figure 3. The researchers implemented the TMS protocol for the analysis of the iSP as described above (see section *Analysis of Interhemispheric Inhibition: Single-Pulse Transcranial Magnetic Stimulation*. It was found that the influence of IHI on contraction of the non-dominant biceps brachii does in fact depend on the activity of the contralateral arm (Perez et al., 2014). Perez and colleagues observed that IHI has the greatest influence during bilateral contraction of homologous muscle (flexion – flexion condition), and the weakest influence during bilateral contraction of antagonistic muscles (flexion – extension condition) (Perez et al., 2014). Further, the researchers report that some participants displayed a facilitatory effect during bilateral antagonistic activation (flexion – extension) (Perez et al., 2014).

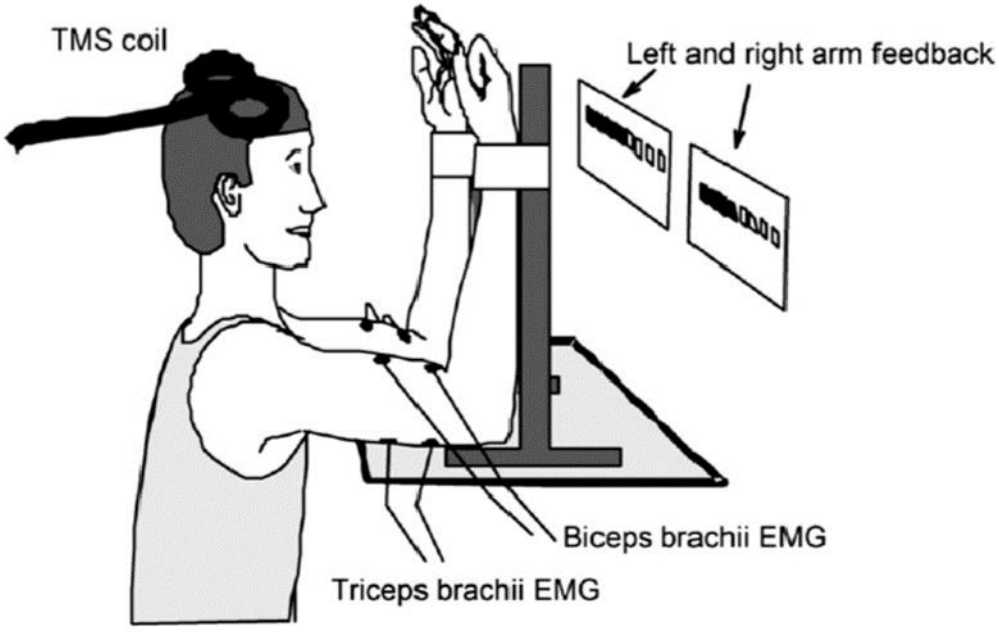

Figure 3. *Experimental design from Perez and colleagues (2014). Participants performed 3 conditions of bilateral contraction including 1) flexion – rest, 2) flexion – flexion, 3) flexion – extension, with respect to the elbow joint. Participants were provided visual feedback of the force production from each limb.*

Recall that arm cycling, our selected model of human CPG-mediated motor output, relies on the bilateral antagonistic activation of elbow flexors and extensors, similar to that of the experimental protocol used by Perez and colleagues (2014). Thus, the potential effects of IHI projecting to the biceps brachii during arm cycling can be theorized based on Perez and colleague's findings. Asynchronous arm cycling most closely mimics the flexion – extension condition from Perez and colleagues (2014), therefore it is likely that IHI will have little-to-no influence on the biceps brachii during arm cycling, however until these exact experimental parameters are examined, a direct conclusion cannot be drawn. Numerous previous works have shown that locomotor activity and tonic contraction are in fact differently modulated by the central nervous system (Capaday et al., 1999; Carroll et

al., 2006; D. Forman et al., 2014), and that the strength of IHI is dependent on the task-specifics of motor output (Fling & Seidler, 2012). Therefore, an investigation of IHI during human locomotion (using arm cycling as a model) is proposed.

2.9 Conclusion

The current understanding of the neural control of human locomotion is that the CNS is modulated by numerous descending inputs from the brain, spinal reflexes, and afferent inputs. However, much less is known as the modulatory effects of cortical circuits 'upstream' of the motor cortex. Further, it appears that each structure of the CNS has a different modulatory effect on motor output based on its specifics, including task specificity, contraction intensity, and phase of movement. While recent research has expanded our understanding of human locomotor control, there are still countless questions that remain to be answered. Specifically, the potential influence of IHI during human locomotion has never been examined. The following project will explore the potential effects of IHI to the biceps brachii during arm cycling, and if IHI is observed, will be compared to that of an intensity- and position-matched tonic contraction.

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Chapter 3 Interhemispheric Inhibition Projecting to the Biceps Brachii During Arm Cycling

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Running Head: Interhemispheric inhibition during arm cycling

Key words: arm cycling, locomotion, interhemispheric inhibition, iSP

3.1 ABSTRACT

The present study investigated the potential existence of interhemispheric inhibition (IHI) projecting to the biceps brachii during arm cycling. IHI was assessed using transcranial magnetic stimulation (TMS) of the non-dominant biceps representation of the motor cortex. TMS was delivered at 120% resting motor threshold (RMT) during the mid-elbow flexion phase of arm cycling (6 o'clock position, made relative to a clock face) and during a position-matched tonic contraction. Paired t-tests revealed that background EMG (bEMG) was different between arm cycling and tonic contraction ($p < 0.01$), therefore the two conditions could not be directly compared. IHI was observed in 9 of 13 participants during arm cycling, and in 8 of 13 participants during tonic contraction. Of the 9 participants who displayed a clear iSP during arm cycling, 6 also displayed an iSP during tonic contraction. During arm cycling, average rectified EMG observed during the ipsilateral silent period (iSP) was reduced by 32.3% ($p < 0.001$). During tonic contraction, average rectified EMG during the iSP was reduced by 24.4% ($p < 0.001$). These data suggest that human locomotor output is in part mediated by IHI existing between homologous representations of the two motor cortices.

3.2 INTRODUCTION

The basic pattern of muscle recruitment during locomotor outputs such as walking, running, leg cycling, and arm cycling is generated, in part, by specialized groups of interneurones within the spinal cord, known as central pattern generators (CPGs) (Dietz, 2002; Grillner & Wallen, 1985; E. P. Zehr et al., 2004). In non-human animal models, the characteristic pattern of locomotor muscle activation can be produced in the spinal cord by central pattern generators (CPGs) without cortical input, or sensory feedback (Brown & Sherrington, 1911). Spinal CPGs are thought to play a role in the production of human locomotion, however it is evident that locomotor output cannot be generated without descending input from the motor cortex (Petersen et al., 2001). The roles of cortical circuitry in the production of human locomotion are not well understood.

Only three studies have examined cortical circuitry during human locomotor output. Previous research has shown that short-interval intracortical inhibition (SICI) is active projecting to the arms during human walking (Barthelemy & Nielsen, 2010). Further, Sidhu and colleagues have shown that SICI is present projecting to the knee extensors during leg cycling, suggesting that cortical circuitry has a direct influence on the prime mover muscles of a locomotor output (Sidhu, Cresswell, & Carroll, 2013). Additionally, it has been shown that SICI plays a role in the control of arm cycling as well (Alcock, Spence, Lockyer, Button, & Power, 2019). These studies provide evidence as to the activity of one known cortical circuit during locomotion, however a number of other supraspinal networks exist. One such cortical network exists between homologous areas of the motor cortex via the corpus callosum, and works to inhibit a muscle during the voluntary contraction of its

contralateral counterpart (i.e. biceps-biceps) (Ferbert et al., 1992). While it is known that this neural circuit exists, its potential influence on a locomotor task has never been examined.

To examine IHI during isometric contraction, researchers have developed two transcranial magnetic stimulation (TMS) techniques (Ferbert et al., 1992). A conditioning stimulus over one hemisphere can reduce the amplitude of a test motor evoked potential (MEP) elicited from the other hemisphere across short (10 ms) or longer (40 ms) intervals (Ferbert et al., 1992). Secondly, single suprathreshold TMS can suppress voluntary electromyographic (EMG) activity creating an ipsilateral silent period (iSP), which can also be used to quantify IHI (Ferbert et al., 1992). Previous works have reported a strong inhibition of small hand muscles following stimulation of the ipsilateral motor cortex, and suggest that IHI projecting to distal upper limb musculature is both muscle- and task-dependent (Ferbert et al., 1992; Fling & Seidler, 2012; Gerloff et al., 1998; Jung & Ziemann, 2006). Most studies exploring IHI, however, have concentrated on distal upper limb muscles, whereas less emphasis has been placed on proximal arm musculature. Two studies have directly compared IHIs influence on the biceps brachii and a small intrinsic hand muscle, and both have concluded that inhibitory effects to the biceps brachii are similar to, or slightly less, than that of a small hand muscle (Ferbert et al., 1992; Harris-Love, Perez, Chen, & Cohen, 2007). While these studies demonstrate that IHI is present in the biceps brachii during tonic contraction, it is not known how IHI influence may vary during dynamic contraction, and locomotion.

Perhaps the most accurate hypothesis as to IHI to the biceps brachii during arm cycling can be drawn from Perez and colleagues. To examine IHI during bilateral contractions of proximal arm muscles, the researchers elicited iSPs in the elbow flexor muscles during voluntary contractions of the homologous and antagonist muscles of the other arm (Perez, Butler, & Taylor, 2014). That is, IHI to the biceps brachii was examined while the contralateral arm was either at rest (flexion-rest), flexing (flexion-flexion), or extending (flexion-extension) (Perez et al., 2014). They concluded that IHI was strongest during bilateral contraction of homologous muscles (flexion-flexion), and weakest during bilateral contraction of antagonist muscles (flexion-extension) (Perez et al., 2014). These findings provide strong rationale to hypothesize that IHI is present to the biceps brachii during arm cycling, as the flexion-extension paradigm used by Perez and colleagues is strikingly similar to the bilateral activation of antagonist muscles (biceps-triceps) during asynchronous arm cycling. Therefore, it is plausible that IHI will be present during arm cycling, however its strength may be less than that of a unilateral or bilateral-agonistic tonic contraction. It is important to note that these findings may allow for the speculation of IHI during arm cycling, however a direct comparison between the two tasks cannot be made. As previously mentioned, previous work has shown that IHI is dependent on both the nature of the task (Fling & Seidler, 2012) and target muscle (Ferbert et al., 1992; Harris-Love et al., 2007; Jung & Ziemann, 2006). Further, even at a matched contraction intensity and limb position, tonic contraction and arm cycling are modulated differently by the central nervous system (D. Forman, Raj, Button, & Power, 2014).

The purpose of the present study was to examine whether IHI is active during arm cycling, and to compare it to that of an intensity- and position-matched tonic contraction. To accomplish this, we will adapt arm cycling as our model for human locomotion, and the biceps brachii will be explored for potential IHI. We hypothesized that: (1) IHI would be present in the biceps brachii during arm cycling and (2) IHI would have a lesser influence on arm cycling than tonic contraction.

3.3 METHODS

3.3.1 Ethical Approval

Prior to data collection, all participants received verbal explanation of the experimental protocol. Once all questions were answered, written informed consent was obtained. This study was conducted in accordance to the Helsinki declaration and all protocols were approved by the Interdisciplinary Committee on Ethics in Human Research at Memorial University of Newfoundland (ICEHR no. 20190339-HK). Additionally, the protocols were carried out in accordance with the Tri-Council Guidelines in Canada, with the potential risks being fully disclosed to all participants.

3.3.2 Participants

Thirteen healthy, recreationally active male volunteers (22.2 ± 2.3 years of age, twelve right-hand dominant, 1 left-hand dominant), with no known history of any neurological impairment participated in this study. Following written consent, all participants completed a safety checklist to screen for any possible risks to magnetic simulation (Rossi, Hallett, Rossini, & Pascual-Leone, 2009), and a Physical Activity Readiness Questionnaire to screen for any contraindications to physical activity (Canadian

Society for Exercise Physiology, 2002). Hand dominance was determined using the Edinburg Handedness Inventory (Veale, 2014). This was done to ensure that investigations of IHI were done with respect to the non-dominant arm, as interhemispheric inhibitory connections are strongest from the non-dominant to the dominant hemisphere (Bäumer et al., 2007; Chen, Yung, & Li, 2003; Netz, Ziemann, & Hömberg, 1995).

3.3.3 Experimental Setup

All arm cycling trials were performed using an arm cycle ergometer (SCIFIT ergometer, model PRO2 Total Body, Tulsa, OK, USA) with participants cycling with a neutral forearm position (i.e. supination vs. pronation). The arm cranks were locked 180º out of phase to establish an asynchronous cycling pattern. To ensure participant comfort, participants were seated in an upright position at a comfortable distance from the hand cranks to ensure there was no flexion or rotation of the torso during cycling, and the seat height was adjusted so that participants' shoulders were approximately level with the axis of rotation of the arm cranks. Participants were asked to wear wrist braces to minimize the amount of wrist flexion and extension during cycling, as to limit the influence of heteronymous reflex connections that exist between the wrist flexors and the biceps brachii (Manning & Bawa, 2011). TMS was triggered automatically by the passing of a magnet on the right arm crank, and delivered to the dominant motor cortex when the dominant arm passed the 12 o'clock position Due to the asynchronous nature of arm cycling, this procedure would allow TMS to be delivered when the non-dominant arm passed the 6 o'clock position when the biceps brachii is most active. Similar to previous arm cycling studies, 6 o'clock was specified as the "bottom dead centre" of the cycling pattern (Balter

& Zehr, 2007; Copithorne, Forman, & Power, 2015; D. Forman et al., 2014; D. A. Forman, Philpott, Button, & Power, 2015; Lockyer et al., 2018). Participants were asked to cycle at one consistent workload of 60 revolutions per minute (RPM) and 25 watts during all stimulations of the arm cycling protocol. Participants cycled for a total of 150 seconds, over which they received a stimulation every ~ 5 seconds.

To compare IHI between arm cycling and tonic contraction, it was crucial that the intensity of the contractions be matched as closely as possible given the large influence of contraction intensity on evoked responses. To accomplish this, the background EMG (bEMG) of the biceps brachii from 50 to 0 ms before stimulation was assessed. The bEMG was rectified, and the average value of rectified bEMG served as an indication of contraction intensity. EMG was measured before the stimulation to avoid the stimulation artifact. The average of the rectified bEMG was then displayed on a computer screen via a horizontal line. The arm cranks were locked with the non-dominant arm at the 6 o'clock position, and the participant was then required to produce a tonic contraction whereby the EMG produced in the biceps brachii was equal to the horizontal line displayed on the screen. The participant accomplished this by placing both hand on the arm cranks, and pulling with the non-dominant arm. The participant was able to see the ongoing muscle activity of the non-dominant biceps, and was instructed to contract at an intensity in which the ongoing EMG matched the pre-placed horizontal line representing cycling bEMG. This method has shown success in previous works (Carroll, Baldwin, Collins, & Zehr, 2006; D. Forman et al., 2014; Pyndt, Laursen, & Nielsen, 2003). TMS was delivered to the dominant motor cortex while the non-dominant biceps brachii was producing a contraction of the

same intensity observed during arm cycling, thus, any differences in IHI could be attributed to the task. The number of stimulations was the same as that during cycling.

3.3.4 Transcranial Magnetic Stimulation

TMS to the motor cortex was applied using a Magstim 200 stimulator (Magstim, Whitland, Dyfed, UK). During both experimental conditions, a figure-eight coil was placed roughly 2 cm lateral to vertex with the handle pointing posterolaterally at roughly 45 degrees to the midline of the head. With this coil position the induced current in the brain flowed in an anterior-medial direction and probably produced D and early I wave activation of corticospinal neurons (Di Lazzaro et al., 1998). In order to isolate the biceps representation of the motor, the stimulator was turned to a suprathreshold intensity (~75% MSO) and moved around the head until the largest MEP could be evoked with the dominant biceps at rest. This location was defined as the hot spot, and was marked with a marker. To ensure an accurate marking of the hot spot, all participants wore a white swim cap to allow the researchers to easily trace around the TMS coil. To find the resting motor threshold (RMT), participants were instructed to rest with both hands on the handles of the cycle ergometer with the dominant hand at the 6 o'clock position. RMT was found by decreasing the stimulation intensity to a minimum value in which a MEP of at least 50 μV in peak-to-peak amplitude could be evoked in the dominant biceps in 4 of 8 consecutive trials via stimulation of the hot spot (Rothwell et al., 1999). Stimulation intensity was increased to 120% RMT, as this intensity has been shown to display a clear iSP without evoking a short-latency facilitation (Perez et al., 2014). TMS was applied at the same intensity in all trials.

3.3.5 Electromyography

EMG recordings were taken from the biceps brachii of both arms using pairs of Ag-AgCl surface electrodes (KendallTM 130 Foam Electrodes with conductive adhesive hydrogel, Covidien IIC, Massachusetts, USA). Electrodes were placed 2 cm apart (centre to centre) over the midline of the muscle belly, in a parallel fashion with respect to the target muscle fibres. A ground electrode was placed on the lateral epicondyle of the right limb. Prior to electrode placement, the skin was thoroughly prepared by removal of dead epithelial cells (using abrasive paper) followed by sanitization with an isopropyl alcohol swab. EMG was collected on-line and analog-to-digitally converted at a rate of 5KHz using CED 1401 interface and the associated Signal 5 (Cambridge Electronice Design Ltd., Cambridge, UK) software. All signals were amplified (x300) and filtered using a 3-Pole Butterworth filter with cut-off frequencies of 10-1000Hz. Collected data was stored on a password protected PC for further analysis.

3.3.6 Experimental Protocol

Following the determination of required TMS intensity, participants completed 2 trials (1 arm cycling and 1 tonic contraction trial). During arm cycling, TMS was delivered to the dominant motor cortex when the non-dominant arm passed the 6 o'clock position, as to elicit an iSP in the non-dominant biceps brachii during mid-elbow flexion. During tonic contraction, TMS was delivered to the dominant motor cortex while the non-dominant biceps brachii produced a tonic contraction of matched intensity to that of arm cycling. Since tonic contraction intensity were matched to the EMG observed during the arm cycling

conditions, it was necessary to perform the arm cycling condition first. During both conditions, participants received a total of 30 TMSs.

3.3.7 Data Analysis

During arm cycling trials, the iSP was measured in the biceps brachii of the non-dominant arm at the 6 o'clock position of cycling, when the biceps brachii was most active (D. Forman et al., 2014; D. A. Forman et al., 2015; Lockyer et al., 2018; Spence, Alcock, Lockyer, Button, & Power, 2016). The following iSP analysis techniques have been previously described in the literature (Perez et al., 2014; Trompetto et al., 2004). For all 30 arm cycling trials, EMG from the biceps brachii of the non-dominant arm was rectified. The mean of the rectified pre-stimulus EMG was calculated, and horizontal line was placed over the entire EMG trace at the value of the average. Using the average pre-stimulus EMG as a reference, the onset of the iSP was determined via visual examination of the EMG trace following the stimulus artifact. iSP onset was defined as the time point (following the stimulus artifact) when the rectified EMG fell below the pre-stimulus average value for minimal duration of 10 ms. Inversely, the end of the iSP was identified when the rectified EMG returned to the pre-stimulus average value. The duration of the iSP was identified as the time-interval between the onset and end of the iSP [iSP duration = (timepoint at iSP end) – (timepoint at iSP onset)]. The depth of the iSP was calculated from the average rectified EMG during the entirety of the iSP and expressed as the percentage of reduction from the average pre-stimulus EMG [iSP depth = 100 – (mean rectified iSP EMG / mean rectified pre-stimulus EMG) * 100]. Finally, the area of the iSP was calculated using the following formula [iSP area = (mean rectified pre-stimulus EMG) * (iSP duration) –

(au_iSP)], where au_iSP is the area under the rectified EMG during the iSP (Perez et al., 2014). Any trials in which short-latency facilitation was observed were removed from data analysis, as this could mask any potential inhibitory effects (Perez et al., 2014).

During tonic contraction trials, EMG was recorded from the non-dominant biceps brachii while the hand is in the 6 o'clock position. The dominant hand was resting on the opposite crank at the 12 o'clock position. The iSP onset, duration, depth, and area were calculated using the same methods as described above.

3.3.8 Statistical Analysis

All statistics were performed using Microsoft's Excel 2016. To assess whether there were differences bEMG and iSP EMG during both cycling and tonic contraction, paired-samples two-tailed t-tests were used for each condition. For the 6 participants in which IHI was observed in both conditions, paired-samples two-tailed t-tests were used to assess any differences in bEMG, iSP depth, and iSP area. For both arm cycling and tonic contraction, bEMG was correlated with both iSP depth and area, to examine any relationship between contraction and IHI.

3.4 RESULTS

Of the 13 participants tested, RMT in the dominant biceps muscle was 54.1 ± 10.3% MSO, and the intensity used to examine the iSP was 64.9 ± 12.3% MSO for both conditions (range from 51% - 90% MSO). 9/13 participants displayed a clear iSP during arm cycling ($p < 0.001$) while this was seen in 8/13 participants during tonic contraction ($p < 0.001$). 6 participants showed a clear iSP during both conditions. Figure 4 shows raw traces of the iSP in the non-dominant biceps brachii during both arm cycling (A) and tonic contraction

(B) in a representative subject. Average descriptive measurements of the iSP during both arm cycling and tonic contraction are shown in table 1. Figure 5 shows difference in bEMG and iSP EMG during arm cycling (A) and tonic contraction (B).

Table 1. *Values are means ± SD and were determined during arm cycling (n = 9) or tonic contraction (n = 8) in the non-dominant biceps brachii.*

	Arm Cycling	Tonic Contraction
bEMG, mV	0.1256 ± 0.056	0.1052 ± 0.046
iSP onset, ms	31.6 ± 3.9	36.7 ± 15.1
iSP duration, ms	45.6 ± 17.7	31.2 ± 6.3
iSP depth, % inhibition	32.3 ± 15.3	24.4 ± 6.2
iSP Area normalized to contraction	2.11 ± 1.55	0.79 ± 0.40

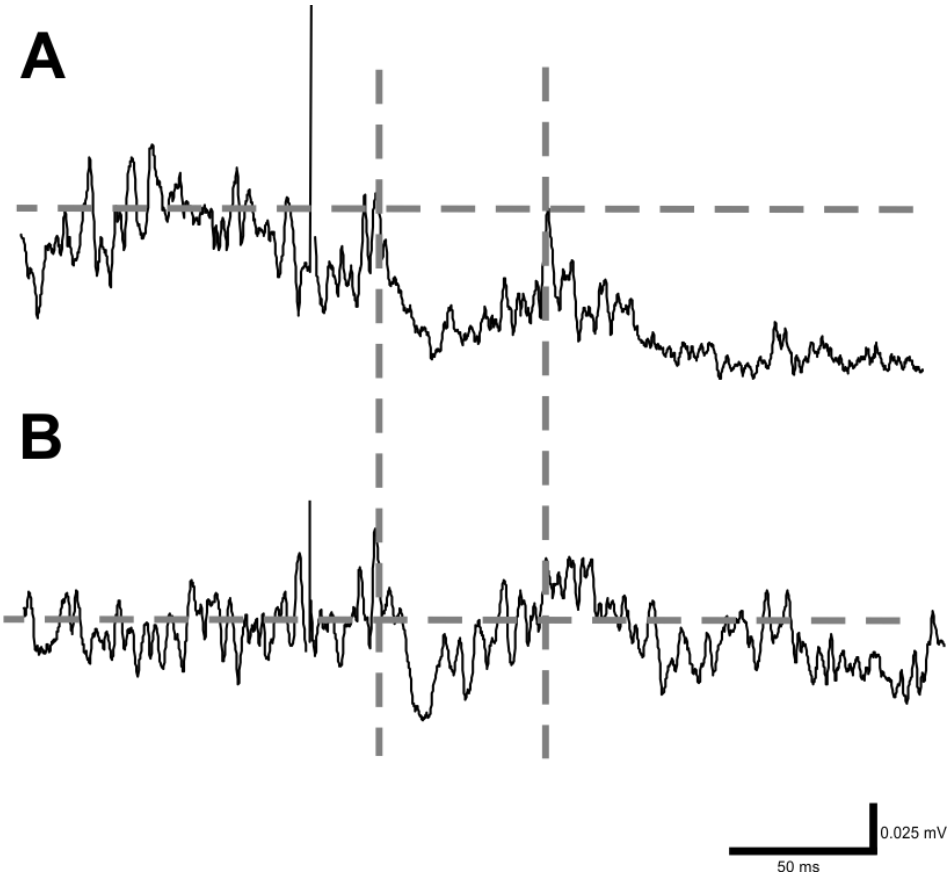

Figure 4. *EMG traces recorded from the non-dominant biceps brachii muscle in a representative subject during arm cycling (A) and tonic contraction (B) with TMS applied to the ipsilateral motor cortex. Traces show the average rectified EMG in all trials in which short latency facilitation was not observed (30 frames for both A and B). The onset and offset of the iSP are denoted by the broken vertical lines.*

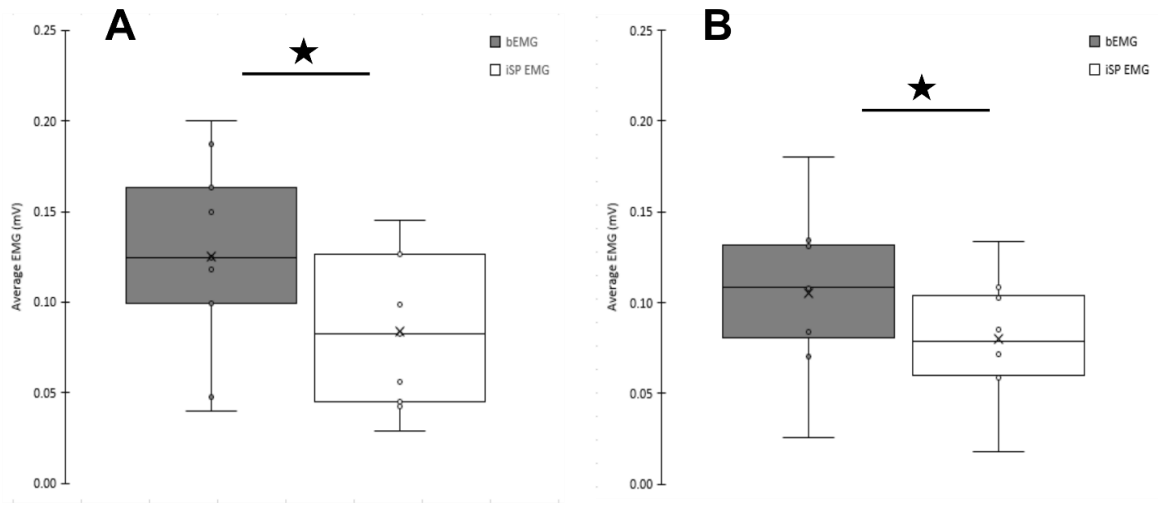

Figure 5. *Group data for bEMG and iSP EMG during (A) arm cycling (n = 9) and (B) tonic contraction (n = 8). Horizontal lines denote the minimum, first quartile, median, third quartile, and maximum values. Individual data points are represented by circles, and the group mean is represented by an x. During both conditions, iSP EMG was significantly less than bEMG (p < 0.001).*

3.4.1 Comparing Arm Cycling and Tonic Contraction

Of the 13 participants, 6 displayed a visible iSP in both arm cycling and tonic contraction. To determine the effect of task on iSP parameters, bEMG, iSP onset, duration, depth and area were compared within these 6 participants. iSP duration during arm cycling (mean = 47.8 ms) and tonic contraction (mean = 32.5 ms) appeared to be different, however this difference did not reach statistical significance ($p = 0.089$). A similar effect was observed with iSP depth during arm cycling (mean = 31.9%) and tonic contraction (mean = 32.5%) ($p = 0.202$). Paired-samples two-tailed t-tests indicated that bEMG ($p < 0.05$) and iSP area ($p < 0.05$) were different between the two conditions. Figures 6, 7 and 8 show group averages for bEMG, iSP depth and iSP area, respectively, between arm cycling and tonic contraction.

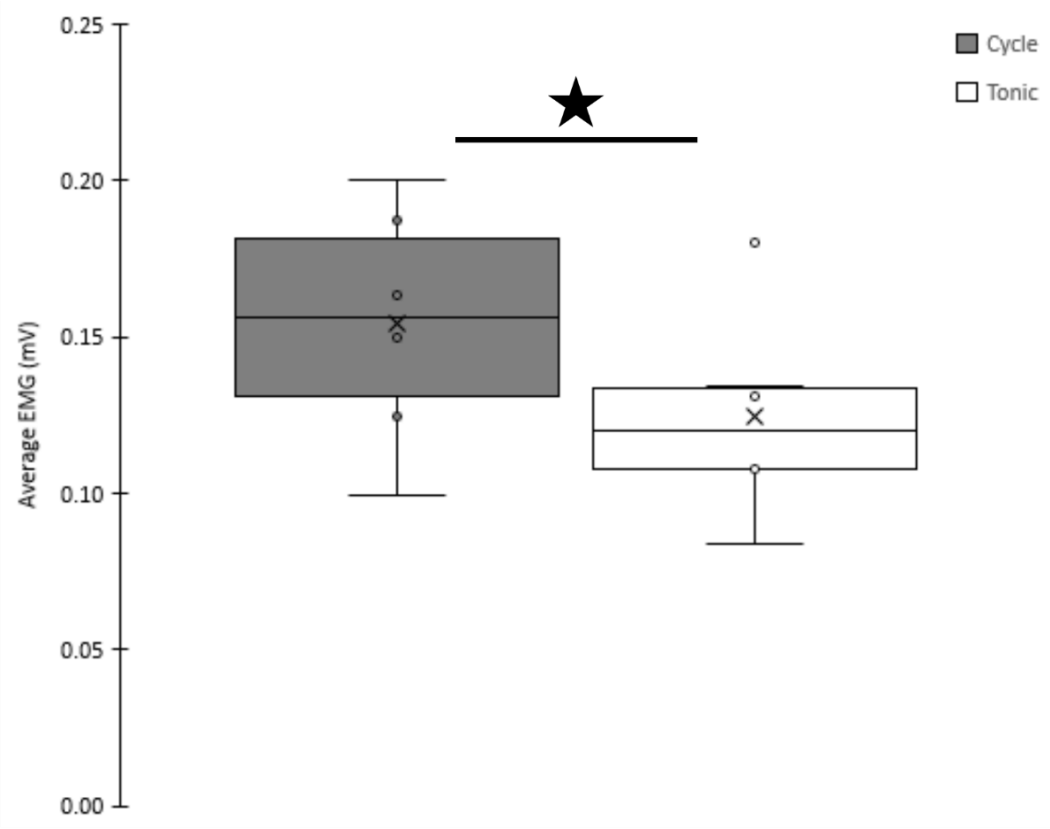

Figure 6. *Group data for bEMG during arm cycling and tonic contraction. Data is from those participants who displayed a cleat iSP in both conditions (n = 6). Horizontal lines denote the minimum, first quartile, median, third quartile, and maximum values. Individual data points are represented by circles, and the group mean is represented by an x. bEMG was significantly greater during arm cycling than during tonic contraction (p = 0.031).*

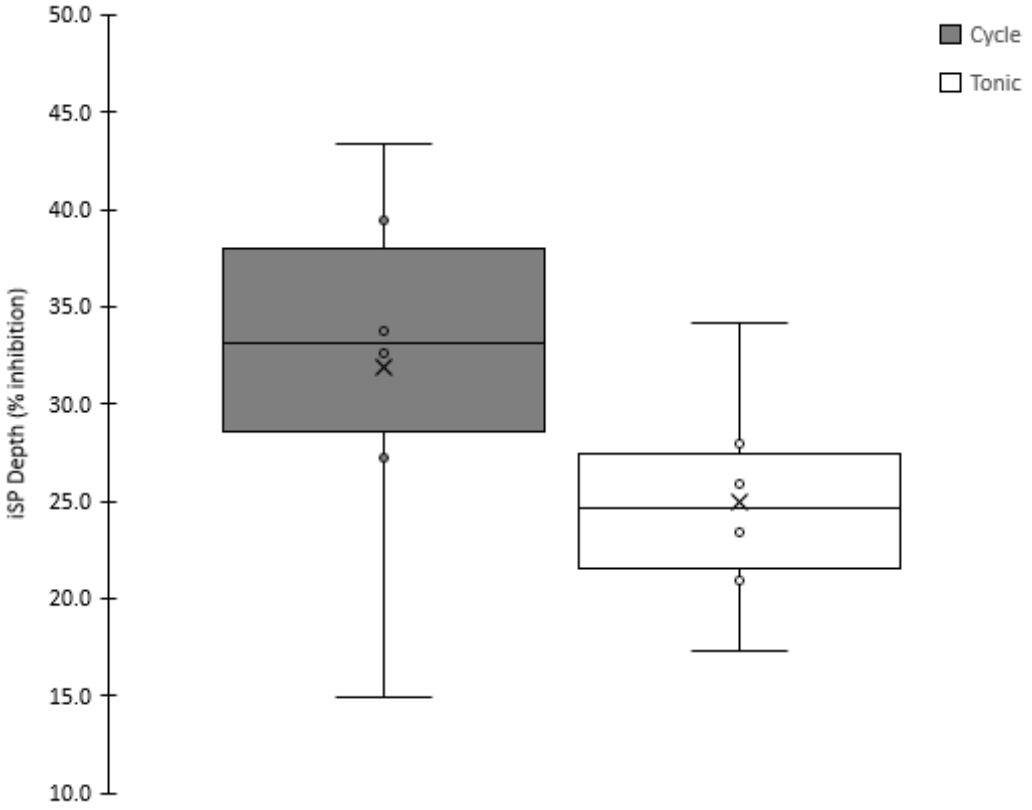

Figure 7*. Group data for iSP depth during arm cycling and tonic contraction. Data is from those participants who displayed a cleat iSP in both conditions (n = 6). Horizontal lines denote the minimum, first quartile, median, third quartile, and maximum values. Individual data points are represented by circles, and the group mean is represented by an x. iSP depth appears to be greater during arm cycling than during tonic contraction, however this difference did not reach statistical significance (p = 0.202).*

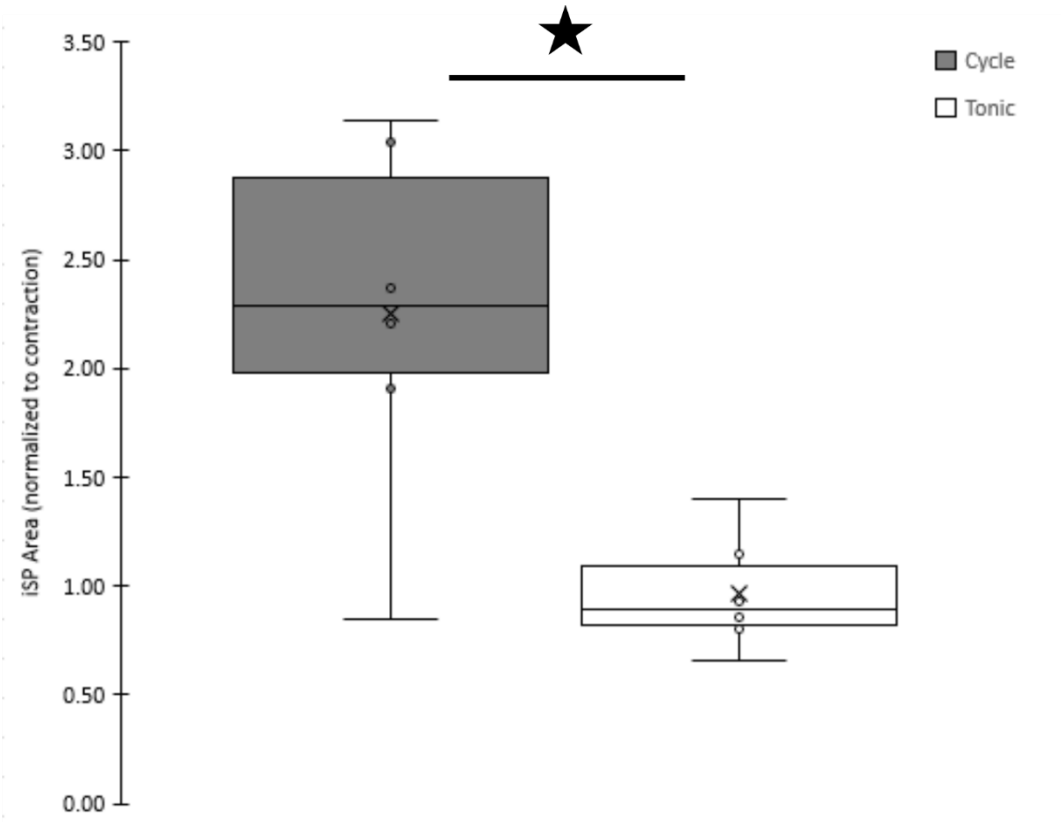

Figure 8. *Group data for iSP area during arm cycling and tonic contraction. Data is from those participants who displayed a cleat iSP in both conditions (n = 6). Horizontal lines denote the minimum, first quartile, median, third quartile, and maximum values. Individual data points are represented by circles, and the group mean is represented by an x. iSP area was significantly greater during arm cycling than during tonic contraction (p < 0.011).*

3.4.2 Contraction Intensity and iSP Properties

Since bEMG was different between arm cycling and tonic contraction, it appears that a direct comparison of iSP parameters between the two conditions cannot be made. To determine the importance of contraction intensity on IHI, however, correlation analyses were conducted between bEMG and iSP depth and area for both conditions (see Figure 9).

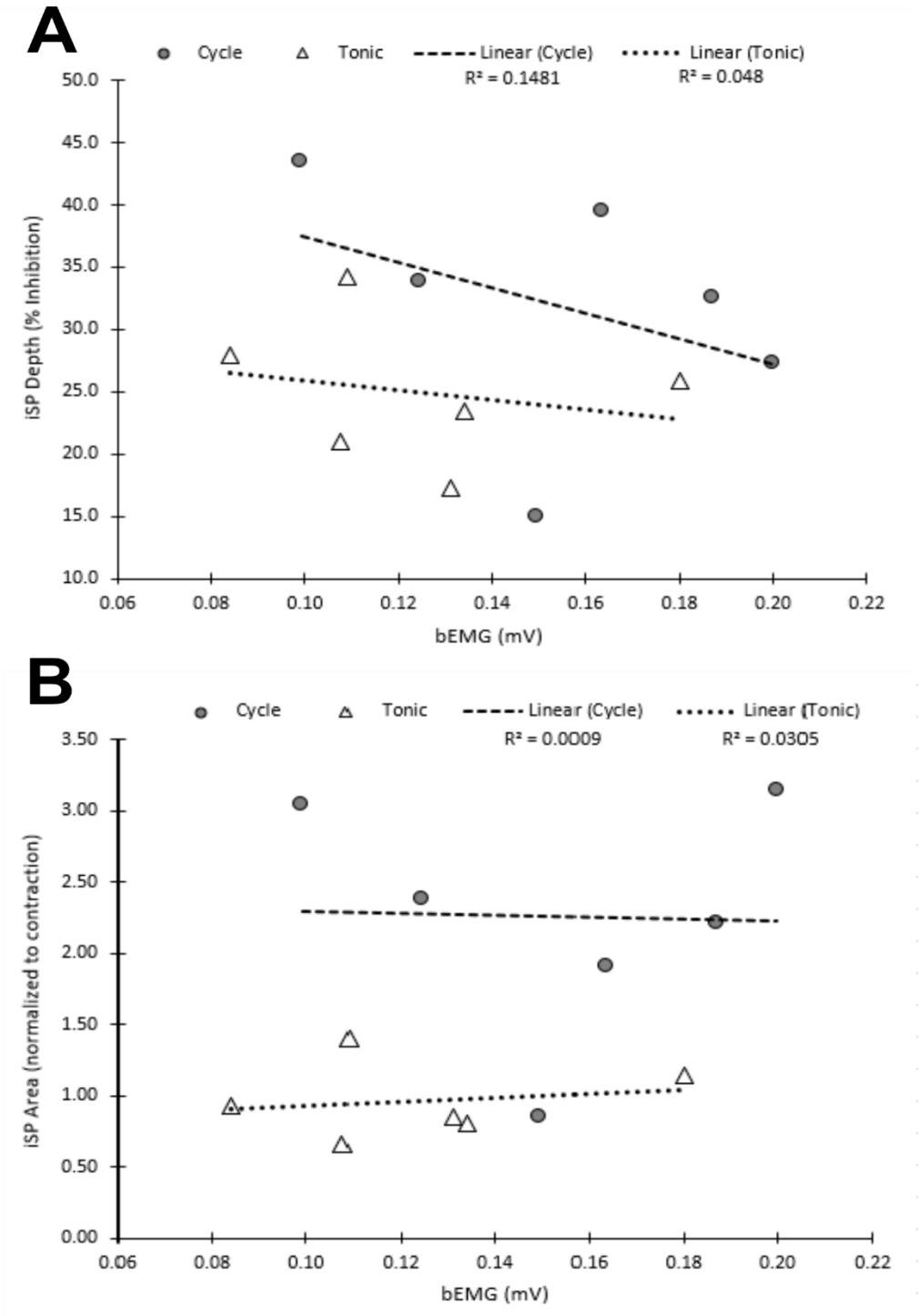

Figure 9. *A correlation analysis between the intensity of contraction (bEMG) and (A) iSP depth and (B) iSP area. Each participant (n = 6) is represented by two points with ○ representing the arm cycling condition, and Δ representing the tonic contraction condition. Note that intensity of bEMG has no correlation with iSP depth or area, regardless of condition.*

3.5 DISCUSSION

In the present study, we showed for the first time that IHI is active to the arm muscles during arm cycling, which is a CPG-mediated motor output. It is noted that due to a significant difference in bEMG, a direct comparison between arm cycling and tonic conditions cannot be made. However, possible mechanisms for differences in iSP properties between the two conditions will still be considered and discussed. Nonetheless, we report IHI during a locomotor output of any kind for the first time.

3.5.1 Biceps iSP During Arm Cycling

While numerous other studies report difficulties eliciting inhibition in the biceps brachii, we did not experience the same difficulties. In fact, from 13 participants screened we were able detect a clear iSP with no short-latency facilitation during arm cycling in 9 subjects. In contrast, Perez and colleagues report that of 45 subjects, inhibition was observed in the biceps brachii in roughly half (Perez et al., 2014), while Ferbert and colleagues report an observation of the iSP in the biceps brachii in 3 of 9 participants (Ferbert et al., 1992). The differences in our results are likely due to task-dependent changes in iSP properties. The aforementioned measurement of the iSP from Perez et al. (2014) and Ferbert et al. (1992) were taken during unilateral tonic contraction of the biceps brachii, whereas the measurements from the present study were taken during arm cycling.

When comparing arm cycling and unilateral tonic contraction, two major differences can be noted. Firstly, arm cycling is a locomotor task which is at least partially mediated by spinal CPGs (E. P. Zehr, 2005; E.P. Zehr et al., 2016; E. P. Zehr et al., 2004). It is theorized that spinal CPG input increases motoneurone excitability during arm cycling,

and this input is absent during non-locomotor outputs. It is possible, then, that spinal CPG-mediation of arm cycling may allow the motor cortex to 'relax' in this state of increased spinal motoneurone excitability, and that IHI is a primary mechanism of cortical inhibition during arm cycling. This seems unlikely, as Forman and colleagues (2014) have shown that during mid-elbow flexion (i.e. 6 o'clock position of arm cycling), supraspinal excitability is greater than that of tonic contraction. It is important to note that the present study examined the iSP from the non-dominant biceps brachii, where Forman and colleagues (2014) examined corticospinal excitability to the dominant biceps brachii. Thus, hand-dominance should be considered a potential reason for these discrepancies, as it has been shown that IHI is stronger when projecting from the dominant to the non-dominant hemisphere (Bäumer et al., 2007). It is possible that supraspinal and spinal excitability to the non-dominant biceps brachii may be modulated differently than the dominant biceps brachii as shown by Forman et al. (2014), however, this has never been researched. Further, had the iSP been examined in the dominant biceps brachii, it is possible that IHI would not be as prominent, given the results from Forman and colleagues (2014).

Secondly, arm cycling relies on a bilateral activation of upper arm musculature, whereas the aforementioned contraction paradigms used by both Perez et al. (2014) and Ferbert et al. (1992) involved unilateral contraction of the biceps brachii. Thus, it is possible that the bilateral activation as seen during arm cycling demands greater modulation of IHI. Interestingly, Perez and colleagues (2014) also examined the iSP to the biceps brachii during bilateral contraction of upper arm musculature. They found that during bilateral flexion and extension, the iSP was significantly reduced when compared to unilateral

contraction of the biceps brachii (Perez et al., 2014). This data suggests that the iSP would all but be abolished during arm cycling, however this was not the case. It is likely then, that the differences regarding the ease at which the iSP was found in the present study compared to the works by Ferbert et al. (1992) and Perez et al. (2014) is largely related to increases in supraspinal excitability during arm cycling, including that of cortical inhibitory interneurones.

3.5.2 iSP Properties Between Arm Cycling and Tonic Contraction

We observed a significant difference in iSP area between conditions, as the area of the iSP was greater during arm cycling than during tonic contraction (see figure 5). Interestingly, no significant difference was observed in iSP depth or duration between conditions, even though these are the two variables that make up iSP area (see figure 4, table 1). However, to compare iSP properties between conditions, it is vital that the intensity of contraction between arm cycling and tonic contraction be matched as closely as possible, given the large influence of contraction intensity on evoked potentials. It is noted that we observed a significant difference in bEMG between arm cycling as shown in figure 3, suggesting that a greater proportion of the biceps brachii motoneurone pool was active during arm cycling. While it has been shown that contraction intensity has a significant effect on the strength of SICI (Ortu, Deriu, Suppa, Tolu, & Rothwell, 2008), we demonstrate that there is no correlation between bEMG and iSP depth, or area (see figure 6). Thus, it is possible that differences in bEMG between arm cycling and tonic contraction may not limit our ability to interpret the present data. However, we highlight two issues when considering the present results. Firstly, a clear iSP was observed in both arm cycling and tonic contraction

from only six participants. Given such a small sample size, it is possible that the effects of contraction intensity on iSP properties has been masked. It is possible that a correlation between bEMG and iSP properties could emerge as sample size increases. Secondly, it is noted that Ortu and colleagues (2008) report changes in the strength of SICI with contraction intensities of 10%, 25%, and 50% MVC. While EMG activity cannot be directly inferred from muscle force production, it is speculated that variability of bEMG observed by Ortu and colleagues (2008) was much greater than that of the present study, as muscle force increase from 10%, 25% and 50% MVC likely demand greater increases activation of the motoneurone pool when compared to arm cycling at a set workload of 25 watts, which is relatively easy to perform. Thus, it is possible that iSP properties could also depend on contraction intensity, however variability of bEMG between conditions in the present study were on a scale small enough to mask this effect. It is suggested then, that IHI may have a stronger influence during arm cycling than during tonic contraction, however this cannot be said with full confidence given the present data. It is also noted that the biceps brachii is one of many muscles responsible for producing arm cycling, as contributions from other muscles such as the brachioradialis, brachialis, latissimus dorsi, and others also aid in the movement. It is currently not known how biceps brachii EMG correlates with increased workload of cycling.

3.5.3 Quantifying IHI; iSP Depth or Area?

An interesting question is, is IHI better represented by the depth or area of the iSP? It is important to note that in studies examining the iSP during tonic contraction, EMG of the target muscle remains relatively unchanged as the experimental protocol typically calls

for a participant to hold a contraction of a certain force output. Thus, strength of IHI in this type of study is likely best represented by the depth of the iSP. In contrast, the EMG observed from a target muscle during arm cycling is much more variable, depending on the phase of revolution (i.e. 6 o'clock vs. 12 o'clock). EMG from the biceps brachii during arm cycling closely resembles that of a sinusoidal wave, in which the greatest amount of activation is seen near the 6 o'clock position of cycling. Peak activation of the biceps brachii during arm cycling can occur slightly before or after the 6 o'clock position, increasing the variability of biceps brachii EMG with each revolution. Further, total EMG activity may vary greatly between revolutions due to small changes in factors such as trunk position and other joint angles, and recruitment of synergistic muscles such as brachioradialis. Thus, for a given window of time, iSP may be observed under different levels of output from the biceps brachii motoneurone pool. It would make sense then, that since the EMG of the target muscle is time-dependent, the variable used to quantify IHI also be time-dependent. It is suggested that during dynamic contractions such as during arm cycling, iSP area may best represent IHI, as iSP area is a factor of both the depth and duration of the iSP.

As iSP area is a function of both iSP depth and duration, it is interesting to speculate as to the different mechanisms that may relate to changes in these two variables. When considering synaptic input over durations of time, the number of synapses between the origin of input and target muscle will directly determine how much time will pass before the input is observed. The peak depth of the iSP typically occurs shortly following its onset, and essentially represents the maximal amount of inhibition sent to the target muscle. Thus,

iSP depth is most likely determined by the number of inhibitory synapses acting on the contralateral motor cortex in a relatively short time frame. In contrast, iSP duration represents the length of time that inhibitory input is acting on the contralateral motor cortex. IHI of a target muscle is likely to prolong beyond the instant in time in which the peak iSP depth is observed, suggesting that inhibitory input is still acting on the motor cortex, albeit to a lesser extent than that during peak iSP depth. Therefore, increased duration of the iSP is likely related to more polysynaptic inhibitory connections acting on the motor cortex, where the iSP duration is proportional to the number of synapses between inhibitory interneurones and the upper motoneurone. It is suggested then, that while iSP depth and duration are important in the quantification of IHI, they likely act via different cortical mechanisms.

3.5.4 Methodological Considerations

There are two of other factors we would like to highlight in the interpretation of the results from the present study. Firstly, arm cycling is a dynamic movement involving changes in muscle length, joint angles, and tendinous tension, whereas tonic contraction is a static contraction. This leads to task-dependent changes in afferent feedback, which could affect both spinal and corticospinal excitability, given that sensory feedback greatly contributes to muscle activity during movement (Nielsen, 2004). It is suggested that these sensory inputs will have a large effect on the corticospinal tract, which would have a direct effect on ongoing EMG, and thus the iSP, of a target muscle.

Secondly, when comparing arm cycling to tonic contraction, the activity of the dominant, non-tested arm must be taken into consideration. Perez and colleagues (2014)

showed that IHI is stronger during bilateral activation of homologous muscles (biceps-biceps) and weaker during unilateral activation (biceps-rest). It is likely then the activity of the contralateral, non-examined limb would have a direct effect of the iSP observed from the ipsilateral limb. During arm cycling, the upper limbs were bilaterally contracting in an antagonistic fashion, similar to that described in the 'biceps-triceps' condition from Perez et al. (2014). During the tonic contraction condition, the dominant hand was at rest at the 12 o'clock position while the non-dominant biceps produced a tonic contraction, similar to that described in the 'biceps-rest' condition from Perez et al. (2014). Interestingly, we saw greater iSP area during arm cycling (biceps-triceps) than during tonic contraction (biceps-rest) despite this difference in bilateral activation.

3.6 CONCLUSION

The present study demonstrates interhemispheric inhibition projecting to the biceps brachii during arm cycling. In agreement with previous literature, it is likely that interneurones existing through the corpus callosum act to inhibit the contralateral motor cortex during activity of the ipsilateral motor cortex. Previous literature had led us to hypothesize that IHI would be weak, if active at all, during arm cycling, however an opposite effect was observed; IHI appears to have significant modulatory effect on arm cycling. Further, the present study shows that the influence of interhemispheric inhibition is likely stronger during arm cycling than tonic contraction, although this cannot be confirmed with the current presented data. Future studies should explore the presence of interhemispheric inhibition during other locomotor tasks, including leg cycling and walking, as to further assess the speculated influence of CPG-mediation proposed in this

study. Nonetheless, the present study, for the first time, has demonstrated interhemispheric inhibition during a locomotor activity of any kind.

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Chapter 4 Summary and Future Directions

Gaining a better understanding of how the brain and spinal cord work together to produce locomotor outputs, such as arm cycling, is of significant importance for the advancement of basic human locomotor research. In the present study, we reported interhemispheric inhibition of the motor cortex during arm cycling. Moreover, this study has been the first to report interhemispheric inhibition during any type of human locomotor output. The findings from this study add to the literature suggesting that the brain's role in the control of locomotion is complex, as it is now known that the motor cortices work to inhibit each other during locomotor arm cycling. Further studies should aim to explore how interhemispheric inhibition may differ to different muscles, during different phases, and different cadences and power outputs or arm cycling. This would provide a better understanding of how interhemispheric connections may differ between various areas of the motor cortex, and how these interneurones may act differently during different specific of arm cycling. Although not conducted with a clinical population, this research could potentially help guide techniques to aid in recovery for those who use arm cycling as a rehabilitation tool for certain central nervous system disorders.

In hindsight, the present study could have benefitted from an expanded methodology in order to produce further results. Firstly, we had hoped to match bEMG between arm cycling and tonic contraction, however we were unsuccessful in our attempt. While much easier said than done, further studies should attempt a different bEMG matching technique so that interhemispheric inhibition during arm cycling can be more accurately compared to that of tonic contraction. Secondly, further stimulation techniques

could be used to provide more information to the effects of interhemispheric inhibition during arm cycling. For example, TMES and peripherical nerve stimulation could be used as a means to normalize iSP data. Further, as mentioned in a previous chapter of this thesis, interhemispheric inhibition can also be quantified using a paired-pulse TMS paradigm, which may provide additional evidence as to the strength of IHI during arm cycling. Nonetheless, the present study has been the first to demonstrate interhemispheric inhibition during a locomotor output; a significant step in understanding the brain's role in the control of human locomotor output.