Assessing the relationship between corticospinal excitability and mechanical force generation to both arms during arm cycling: are asymmetries present?

By

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ABSTRACT

Investigations regarding asymmetries in cortical motor control during static and locomotor movements has been conducted. From this research, interhemispheric asymmetries related to movement have been identified, where excitability of the dominant cerebral hemisphere is generally greater compared to the non-dominant. During locomotor outputs like cycling, bilateral asymmetries in measures such as crank torque, power, and/or work have been identified. However, the majority of studies examining human neural control during locomotor outputs is typically available only regarding the dominant limb. Currently, it is unknown how corticospinal excitability and mechanical force generation is modulated during a locomotor output, and whether asymmetries are present. Thus, the purpose of this study was to examine corticospinal and spinal excitability with vector force generation to the dominant and non-dominant biceps and triceps brachii during arm cycling to determine whether bilateral asymmetries were present.

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List of Symbols, Nomenclature or Abbreviations

AI – asymmetry index

AMT – active motor threshold

APB – abductor pollicus brevis

CMEP – cervicomedullary evoked potential

CNS – central nervous system

CPG – central pattern generator

CSE – corticospinal excitability

D-waves – direct waves

EEG – electroencephalography

EPSP – excitatory post synaptic potential

FCR – flexor carpi radialis

FMRI – functional magnetic resonance imaging

H-reflex – Hoffman reflex

IE – index of effectiveness

I-waves – indirect waves

IPSP – inhibitory post synaptic potential

LH – left-handers

M1 – primary motor cortex

MEP – motor evoked potential

Mmax – maximal M-wave

RH – right-handers

RMT – resting motor threshold

SRC – stimulus-response curve

TES – transcranial electrical stimulation

TMS – transcranial magnetic stimulation

TMES – transmastoid electrical stimulation

1 INTRODUCTION

1.1 Overview

It can be mutually agreed the importance of hand movements in everyday human activities, many of the tasks we complete daily are done so with our hands. Object manipulation and dexterity requires motor regulation and higher-order organization. Notably, we use our hands (and limbs) in an asymmetrical manner, the dominant and non-dominant hands usually presuming a manipulative and stabilizing role, respectively (Guiard, 1987; Hammond, 2002). Handedness is a behavioural phenomenon that arises as the result of asymmetrical neural organization of human motor systems, and in relation to motor performance remains largely uncharacterized (Sainburg, 2002).

While bilateral asymmetries corresponding to neural control and in relation to handedness has been examined, much less information is available concerning bilateral asymmetries and locomotion. Locomotion is a bilateral motor output where both limbs move asynchronously in tandem with one another, but principally perform the same motor output. Much of the research examining the bilateral cycling motion has been assessed assuming symmetry in force production and kinematics of the lower limbs (Bini & Hume, 2014) however bilateral asymmetries in force and torque during pedalling has been recorded extensively (Bini & Hume, 2015; Bini et al., 2017; Bini & Hume, 2014; Carpes et al., 2007; Daly & Cavanagh, 1976; Smak et al., 1999). For example, a consistent finding throughout the literature is that the preferred (often dominant) leg generally contributes to overall propulsion to a greater degree than the non-preferred leg regardless of the cadence cycled at (Carpes et al., 2010).

The primary motor tract responsible for modulation of voluntary human locomotion is the corticospinal tract (CST) (Welniarz et al., 2017a). Excitability measurements of this corticospinal tract in humans is measured indirectly and bilateral differences have been shown (Amunts et al., 1996; Hammond, 2002). To model the neural control of human locomotion, arm cycling may be used a methodological paradigm (Carroll et al., 2006; Spence et al., 2016; Zehr et al., 2004). Arm cycling can be utilized as a locomotive model since it shares many characteristics of other human locomotor activities such as walking and running; coordinated and alternating bilateral activation of the limbs. The basic "machinery" responsible for generating these distinct rhythmic patterns demonstrated during locomotor activities primarily resides within the spinal cord (Dietz, 2003; Zehr et al., 2004), and is accompanied by descending input from the primary motor cortices (Forman et al., 2014; Petersen et al., 2001).

It is plausible that corticospinal excitability (CSE) may depend on the task and handedness of an individual (Papadatou-Pastou et al., 2020); however whether bilateral asymmetries in CSE are present during locomotor outputs are unknown.

1.2 Purpose

The primary purpose of this study is to determine if bilateral differences in CSE and/or vector force output are present in the upper limbs during arm cycling.

1.3 Hypotheses

It is hypothesized that:

1. CSE to the dominant biceps brachii will be higher than the non-dominant biceps brachii. This will likely be due to the association between CSE and force values by the dominant limb.
2. The dominant arm will contribute to greater overall force output during arm cycling compared to the non-dominant biceps brachii.

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2 REVIEW OF LITERATURE

2.1 Introduction

Humans and non-human animals both have the capabilities to locomote or move from one place to another with little conscious effort. A level of automaticity of the central nervous system (CNS) can be inferred considering the ease with which humans move throughout their surroundings. Human locomotive activities are characterized by rhythmic and alternating patterns of muscle activity, such as walking or cycling. The coordination and modulation of these rhythmic motor outputs in humans is known to be controlled (at least in-part) by spinally-located specialized interneurons known as central pattern generators (CPGs) (Dietz, 1996; Zehr et al., 2004). Notably, the initiation and continued modulation of locomotion requires descending input from the motor cortex in humans (Forman et al., 2014; Petersen et al., 2001).

The main descending motor pathway involved in the voluntary modulation of human locomotion is the corticospinal tract (CST) (Welniarz et al., 2017a). In humans, CSE is assessed through indirect measures, and has been determined to differ bilaterally, which may possibly be a reflection of use-dependent plasticity (Amunts et al., 1996; Hammond, 2002; Sawaki, 2005). Bilateral asymmetries in spinal motoneurone excitability have been confirmed via single motor unit recordings. Adam et al. (1998) demonstrated that motor unit parameters that directly influence force production differed within homologous muscles of the hands. Within the dominant hand, motor unit action potentials in the first dorsal interosseous (FDI) muscle were characterized by reduced initial and average firing rates, a shift towards lower recruitment thresholds, and muscle force production compared to the non-dominant FDI (Adam et al., 1998). To date however it is unspecified how CSE is modulated bilaterally during a locomotor output, and whether it is correlated with kinetic and kinematic measures (e.g., torque).

Arm cycling is frequently used as a model for locomotion due to its rhythmic and alternating movement pattern and similar neural control mechanisms as other forms of locomotion (Kaupp et al., 2018; Power et al., 2018). Studies mainly from our lab have investigated the effect of locomotor intensity on the modulation of CSE whilst arm cycling (Forman et al., 2015; Lockyer et al., 2018; Spence et al., 2016; Weavil et al., 2015) in addition to phase and muscle-dependent effects (Forman et al., 2019). There has yet to be a study to compare bilateral differences in CSE while cycling at a constant workload to muscles of the upper limb.

This review will first discuss the CST and the role it plays in controlling locomotor outputs, the techniques we use to examine CSE in our lab to provide the reader a basis to refer to. Secondly, this review will review the existing literature on bilateral asymmetries in studies using measures of CSE. Thirdly, the modulation of CSE and the presence of bilateral asymmetries during locomotor outputs will be examined.

2.2 The Corticospinal Tract

The CST plays a critical role in the cortical control of spinal cord activity and is the primary descending tract responsible for the modulation of human locomotion (Welniarz et al., 2017a). Thus, researchers have sought to understand how this tract is involved in modulating motor outputs. Research on this topic began on non-human mammals (Lemon et al., 1986) and has now evolved to be indirectly assessed in humans, due to a growing body of research affirming that many structures in primary motor cortex (M1) possesses corticospinal projections (Canedo, 1997; Nathan et al., 1990).

In humans, neurones within the CST originate from inferior areas of cortical layer V in the primary motor and sensory cortices (Welniarz et al., 2017a) finally terminating on spinal motoneurones (Purves, 2004). The CST forms two pyramids in tandem with the corticobulbar tract on the ventral surface of the medulla. The fibers form protuberances named the medullary pyramids, thus the entire projection is more commonly referred to as the pyramidal tract (Kandel, 2013; Purves, 2004). The M1 is comprised of six layers, each layer containing neurones responsible for different tasks. The upper motor neurons of the M1 are comprised of the pyramidal cells in cortical layer V (Betz cells) (Purves, 2004), the primary function of the upper motoneurones is to issue commands for movement to the lower motoneurones through their axons in the CST (Kandel, 2013). Upper motoneurons will largely synapse onto the lower spinal motoneurons on the contralateral side of the body as ~ 90% of these corticospinal fibers will cross at the midline of the medulla (pyramidal decussation) forming the lateral CST (Kandel, 2013). Additionally, the remaining ~ 10% of fibers will not cross until they cease at the level of the of the spinal cord, continuing down the ipsilateral side of the body known as the anterior corticospinal tract (Kandel, 2013).

Upper motoneurons travelling within the CST may either synapse onto a spinal interneuron (monosynaptic or polysynaptic connection) before synapsing onto a spinal motoneurone, or they may synapse directly onto a spinal motoneurone (Kandel, 2013; Palmer & Ashby, 1992). In general, monosynaptic connections from the M1 onto spinal motoneurons is most dense for muscles of the distal arm, hand, and digits. The ratio of polysynaptic and monosynaptic connections, however, also depends on the motoneurone pool being examined (Palmer & Ashby, 1992). For example, motoneurone connections projecting to the biceps brachii are mostly monosynaptic (Palmer & Ashby, 1992), whereas the triceps brachii is assumed to have fewer monosynaptic connections (Brouwer & Ashby, 1990). Ultimately, voluntary motor outputs are generated from descending commands passed from upper to lower motor neurons predominantly through the CST.

2.3 Techniques used to assess Corticospinal Excitability

The ‘excitability’ of the CST is never stagnant and remains in a constant flux. Excitability, in this context refers to a level of responsiveness of the CST. Excitability of the CST can be influenced by changes in many supraspinal structures, the intrinsic properties of spinal motoneurones, interneurons, and cortical neurons (Canedo, 1997; Martin et al., 2006a). To examine the excitability of the CST there are three main stimulation techniques frequently used in our lab that will be discussed in this review: transcranial magnetic stimulation (TMS), transmastoid electrical stimulation (TMES), and brachial plexus stimulation.

2.3.1 Transcranial Magnetic Stimulation

TMS was first introduced by Anthony Barker in 1985 to evaluate central and peripheral motor conduction (Barker, Jalinous, & Freeston, 1985). TMS is a non-invasive tool that can measure CSE by stimulating corticospinal neurones both directly and indirectly (Anand & Hotson, 2002). The TMS machine acts as an electrical capacitor discharging current throughout a coil. The resultant electrical current generates a transient magnetic field perpendicular to the brain, capable of depolarizing neural tissue (Rossini et al., 2015). TMS stimulation of the CST will elicit either direct waves (D-waves) or indirect waves (I-waves) (Rossini et al., 2015). Action potentials will descend the pyramidal tract and be recorded as D-waves at higher stimulation intensities. When lower stimulation intensities are used the stimulus will activate cortical interneurons which in turn activate pyramidal neurones resulting in discharge at later intervals, thereby producing I-waves (Rossini et al., 2015). I-waves and D-waves result in the depolarization or hyperpolarization of the postsynaptic cell, resulting in excitatory or inhibitory postsynaptic potentials (EPSPs or IPSPs, respectively) (Barker et al., 2012). If the summation of EPSPs and IPSPs reach threshold for action potential generation, a motor evoked potential (MEP) will be elicited and subsequently recorded from the target muscle. MEP amplitude provides a measure for overall CSE excitability, amplitude changes are influenced by cortical, spinal, and peripheral excitability (Taylor, 2006). Therefore, to distinguish where changes in excitability along the CST occur, an additional stimulation technique must be used.

2.3.2 Transmastoid Electrical Stimulation

TMES provides a measure of spinal excitability by eliciting a cervicomedullary evoked potential (CMEP) within the muscle of interest. CMEPs are elicited using electrical stimulation (via surface electrodes) placed just inferior to the mastoid processes at the level of the cervicomedullary junction. At this site, the axons of cortical motoneurones bend, making them more susceptible to stimulation. Cervicomedullary stimulation results in a single descending volley, evoking a short-latency response that can be recorded from the muscle of interest (Taylor, 2006).

TMS used in conjunction with TMES allows one to determine if excitability changes in MEP amplitude are due to supraspinal and/or spinal excitability influence given that action potentials elicited by TMS and TMES travel along the CST. For example, MEP amplitudes normalized to CMEP amplitudes removes the spinal influence from excitability changes given their common denominator, thereby providing an estimate of supraspinal excitability (Forman et al., 2014; McNeil et al., 2009; Taylor, 2006). A limitation to using TMES is that this technique may stimulate the ventral roots instead of corticospinal axons. At higher stimulation intensities, the stimulation can jump from the cervicomedullary junction to the motor root, indicative by a decrease of ~2 ms in the latency of the response recorded from muscle EMG (Taylor, 2006). Therefore, when the ventral roots are stimulated using TMES it is no longer a measure of spinal excitability, but of peripheral excitability (Taylor, 2006). Therefore, to ensure that ventral roots are not being stimulated, the latency of the CMEP (~ 8 ms to the biceps brachii) is monitored closely (Janet L. Taylor, 2006).

2.3.3 Brachial Plexus Stimulation

Brachial plexus stimulation is applied to provide a measure of peripheral excitability. When an action potential is elicited in the spinal motoneurone it will propagate down its axon located within the peripheral nerve, across the neuromuscular junction, and travel along the sarcolemma (Gardiner, 2011). Fatigue can induce changes along the neuromuscular junction (e.g. decreased neurotransmitter release) or along the muscle fibre itself, therefore MEP and CMEP amplitudes are susceptible to fatigue-induced changes

(Gardiner, 2011). M-waves (elicited via brachial plexus stimulation) are used to study fatigue-induced changes within muscle sarcolemma membrane excitability.

Since M-waves are initiated by action potentials originating from the motor axons after an electrical stimulus is applied, changes in M-wave properties are reflective of changes in neuromuscular propagation between initiation (nerve fibers) and the site of recording (muscle) (Enoka et al., 1992; Rodriguez-Falces & Place, 2018). A maximal M-wave (M_{max}) is elicited by delivering stimulation to a peripheral nerve in the brachial plexus and increasing the stimulation intensity until a plateau is reached, or the recorded amplitude decreases with an increase in stimulation intensity (Forman et al., 2014; Magladery & McDougal, 1950). MEP and CMEP amplitudes can be influenced by changes in peripheral excitability. Thus, to infer changes occurring in supraspinal and spinal measures, peripheral excitability needs to be accounted for. Accordingly, MEP and CMEP amplitudes normalized to M_{max} removes the peripheral influence, and provide information about excitability changes occurring along the CST (Taylor, 2006).

2.4 Asymmetrical Neural Control

The primary focus of this thesis will be examining bilateral asymmetries during arm cycling. However, the majority of literature related to bilateral asymmetries stems from studies related to handedness. Hence, this review will discuss literature concerning handedness and bilateral asymmetries, providing the reader with a basis for the thesis research.

It has been recognized since the middle of the 19th century that many cognitive processes, such as language, are lateralized within the brain (Broca, 1861; Dax, 1865;

Hutsler & Galuske, 2003; Oppenheimer, 1977). Ever since, researchers have made attempts to characterize functional differences in relation to structural asymmetries in the brain (Amunts et al., 1996). Early investigations of interhemispheric differences that mediate the control of complex movements were studied in patients with unilateral brain lesions (e.g., stroke) (Haaland & Harrington, 1996). More recently, investigations can utilize techniques such as brain imaging or non-invasive stimulation techniques (e.g., TMS) to investigate interhemispheric connections that may be related to asymmetry.

2.4.1 Use-Dependent Plasticity and Bilateral Asymmetries

Symmetry is an exact agreement in terms of size, shape, and form when considered along an axis. Within the human body, the deviation of symmetry along the midline would be defined as bilateral asymmetry (Maloney, 2018). As such, asymmetries will be present in physical performance and perhaps intrinsically within terms of cortical and spinal excitability. In humans, the adult brain can reorganize itself to accommodate for both environmental modifications and lost function, a process referred to as (neuro)plasticity (Barss et al., 2016; Sawaki, 2005). The possibility exists that a lifetime of training from the preferred use of the hand or limb and/or the anatomical constraints in the projections of the CST may result in different motor unit (MU)discharge properties that reflect differences in corticomotoneuronal projections within the dominant and non-dominant hands/limbs (Sander & Scheffler, 2016; Semmler & Nordstrom, 1995; Serrien & Sovijärvi-Spapé, 2015).

For example, the neuromuscular system’s practice or training can induce adaptations to the whole system as a compensatory mechanism. Resistance training will increase maximal force output capable of the muscle of interest via hypertrophy of muscle fibers (Schoenfeld, 2010). Low-intensity resistance training performed repetitively will increase aerobic capacity, fatigue resistance, and improve muscle contractile properties (Adam et al., 1998; Holloszy & Coyle, 1984; Pesta et al., 2011; Schoenfeld et al., 2016). Therefore, conceptually depending upon the use and stress a particular muscle endures, the physiological and mechanical response will change to meet new demands (Adam et al., 1998). The neural pathways that mediate and/or initiate human movement are continuously reorganized accordingly to daily use; therefore the ability to learn new motor tasks and modify existing motor behaviours is achievable through practice (Krutky & Perreault, 2007).

Evidence has suggested that continual preferential use of one limb can induce intrinsic changes in neuromuscular properties. For example, adaptations to repetitive low-intensity use of the dominant limb capable of augmenting overall force output originating from the pool of lower threshold MUs of the dominant hand may include: greater force output for low threshold MUs through hypertrophy of slow fibers, longer twitch duration times (greater twitch fusion of MUs), and a greater number of MUs recruited at low force levels (Adam et al., 1998). Although hypertrophy of muscle fibers requires increased load and will affect all muscle types (Häkkinen, 1989). It is unlikely that daily preferential use of low recruitment threshold type I fibers in the arm and digit musculature will result in selective hypertrophy of these fibers (Adam et al., 1998). Therefore, other neuromuscular adaptations to daily preferential use are more of a likely adaptation.

For instance, greater percentages of type I muscle fibers have been noted within the dominant extensor carpi radialis brevis muscle (Fugl-Meyer et al., 1982). Increased fatigue indices and increased time to peak contraction in the FDI of the dominant hand reported by Tanaka et al. (1984) indicates differential fiber composition between FDI muscle pairs. A greater number of fatigue resistant type I muscle fibers recruited to fire and increased time to peak contraction of MU's in the dominant hand may facilitate a greater capacity of that arm to perform precise motor skills. Similarly, cross-correlation analysis of the synchronization motor unit pairs during isometric contractions is greater (synchronization peaks significantly larger and broader) in the dominant arm of left handers(LH) and right-handers (RH) (Schmied et al., 1994). Thus, contralateral differences in FDI fiber type may facilitate asymmetries due to daily preferential use of one limb to a greater degree than the other.

Asymmetries in the structure of corticospinal fiber tract decussation have been recorded, with a greater number of fibers crossing to the right side in post-mortem adults (Kertesz & Geschwind, 1971; Nathan et al., 1990). Since CST neurons from both medullary pyramids largely innervate motor unit pools in the hand and spinal cord, these studies aimed to correlate the degree of decussation to handedness (Carson, 2005; Goble & Brown, 2008). No significant association between arm preference and the corticospinal organization was evident in these studies, perhaps due to the small sample of left-handers (Kertesz & Geschwind, 1971).

Anatomically, the M1 is the most well-studied area of the brain concerning hemispheric differences (Goble & Brown, 2008). For example, magnetic resonance morphometry has shown that right-handers (RH) have a deeper precentral sulcus volume in the left cerebral hemisphere than to the right (Amunts et al., 1996). A microstructural asymmetry of cortical tissue occupied by nerve cell bodies was found. Where the left hemisphere M1 occupied a smaller cortical tissue volume with nerve cell bodies and an associated larger volume fraction occupied by fibrous processes (Amunts et al., 1996; Hammond, 2002). The asymmetry concerning the depth of the central sulcus depth was described as a marker for the cortical motor hand representation area's size, which was more pronounced in RH (Amunts et al., 1996). The greater abundance of intracortical connections in the M1 of the dominant cerebral hemisphere rather than the non-dominant is hypothesized to allow for more complicated movement actions to be executed in the dominant motor hemisphere (Hammond, 2002).

2.4.2 Laterality and Cortical Excitability

It is well established that the majority of humans (90%) are right hand dominant (Corballis, 2003; Papadatou-Pastou et al., 2020). Further, investigations have shown that hemispheric dominance is tightly knit to handedness. For instance, RH motor sequencing for the use of either hand is heavily dependent on the left hemisphere, with emphasis on the premotor and parietal areas. For many, the left cerebral (motor) hemisphere activation is significantly more responsible for cognitive-motor acts is in comparison to the right hemisphere (Haaland et al., 2004; Serrien & Sovijärvi-Spapé, 2015). Currently, much less information is available in consideration for LH. Intrinsic hemispheric control of the hands is strongly influenced by the primary motor system's contralateral hemisphere, especially within the distal hand muscles (Haaland et al., 2004). This intrinsic control is more commonly referred to as laterality. The collective of research examining cortical motor control of the distal hand and upper-limb muscles displays a trend for the dominant rather than the non-dominant motor systems to be more excitable (for a more detailed review, see Hammond, 2002).

Language lateralization and hand preference can be modeled in terms of direction (left or right) and in terms of degree (strong lateral preference or more bilaterally equal) (Isaacs et al., 2006; Somers et al., 2015). The brain's cerebral hemispheres possess unique informational processing properties; an asymmetry referred to as hemispheric lateralization implies that cognitive functions are differentially represented within the brain (Josse & Tzourio-Mazoyer, 2004; O'Regan & Serrien, 2018; Vallortigara & Rogers, 2005). It is speculated that LH are atypical in hemispheric lateralization (Papadatou-Pastou et al., 2020) compared to RH.

For example, Somers et al. (2015) investigated the degree of hand-preference and degree of language lateralization. They showed that the prevalence of right hemispheric and bilateral language lateralization rises with an increasing left-handedness degree. LH often demonstrate more symmetric motor behaviour (Sainburg, 2002). Because of the differing degrees of lateralization between LH and RH, degrees of asymmetry may vary between these groups. The neural intricacies of skilled actions have been examined in RH (Serrien & Sovijärvi-Spapé, 2015). Generally, it has been proposed that LH and RH have differing activation patterns whilst performing unimanual and bimanual tasks, with LH exhibiting fewer hemispheric asymmetries (Klöppel et al., 2007; Serrien & Sovijärvi-Spapé, 2015).

2.4.3 Asymmetries in the Functional Activation of M1 and Associated Regions

The development of in-vivo functional neuroimaging has allowed the study of the neuroanatomy of the human motor system and its active manifestations to be investigated (Solodkin et al., 2001). Functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) are just two examples of techniques used to evaluate hemispheric asymmetries during motor control sequences. Several brain mapping studies have investigated the impact of handedness upon the neuronal activation of various brain regions during a variety of unilateral and bilateral hand movements (e.g., tapping, pegboard dexterity) (Dassonville et al., 1997; Kim et al., 1993; Klöppel et al., 2007; Serrien & Sovijärvi-Spapé, 2015; Singh et al., 1998; Solodkin et al., 2001; Vingerhoets et al., 2012; Volkmann et al., 1998). Thus, in vivo neuroimaging investigations can characterize the areas of the brain active during specific motor sequences (Goble & Brown, 2008).

Preliminary studies examined the effect of movement on lateralization differences in the M1 during unimanual tasks (Dassonville et al., 1997; Kim et al., 1993). In RH, larger ipsilateral activation of the M1 has been recorded (Kim et al., 1993; Singh et al., 1998) with no significant LH difference (Singh et al., 1998). Alike, asymmetries in left and right motor cortices activation has been examined in response to finger and thumb opposition movements of each hand using fMRI (Kim et al., 1993). It was found that the right M1 was primarily activated for contralateral hand movements for LH and RH. Whereas the left M1 was substantially activated during ipsilateral movements in LH and even more so in RH, highlighting the enhanced role of the left M1 activation for RH (Kim et al., 1993).

Cortical activation patterns will change in response to task complexity and movement type (unimanual or bimanual). Single and sequential finger movement tasks yield hemispheric asymmetries in M1 and sensory-motor cortices, premotor cortices, and the cerebellum activation (Solodkin et al., 2001). Single-digit movement tasks have been associated with less cortical activation but with greater laterality than sequential movements, accompanied by greater activation in several bilateral cortical activation regions. RH and LH varied in their activation pattern, sharing a pattern of activation on simple actions and differing to sequential movements (Solodkin et al., 2001). During simple movements, LH and RH were similar in the volume, the number of areas, and laterality in cortical activation regions. However, during sequential movements LH activated larger volumes and number of cortical areas compared to RH, with significantly *less* lateralization (Solodkin et al., 2001). Vingerhoets et al. (2012) showed that LH demonstrated lesser hemispheric lateralization while performing unimanual and bimanual pantomimed movements with their dominant and non-dominant hands analyzed with fMRI. LH and RH groups both demonstrated left hemispheric lateralization regardless of the task. Handedness appeared to only influence the strength (rather than the side) of lateralization, with LH showing a reduced degree of asymmetry most evident over the posterior parietal region (Vingerhoets et al., 2012).

In summary, hemispheric dominance (lateralization) has been investigated, but clear definitive trends and brain mechanisms that instigate the asymmetries are still debated. Handedness and task complexity may be factors attributing to hemispheric asymmetries of cortical association areas. Functional neuroimaging techniques have depicted cortical representations of skilled movements in LH and RH. In RH, more extensive ipsilateral activation of the M1 during unimanual movements exists (Kim et al., 1993; Singh et al., 1998; Ziemann & Hallett, 2001). In studies that have used more complex unimanual and bimanual movements, the effect of handedness on lateralized cortical activity included other cortical brain areas, including the supplementary motor area and premotor cortex (Klöppel et al., 2007; Siebner et al., 2002; Solodkin et al., 2001), calling to the importance of task complexity. It is feasible LH may experience less hemispheric asymmetries because many tools used by persons daily are designed for RH, resulting in LH utilizing their non-dominant right hand more frequently in comparison to RH (Klöppel et al., 2007). Regardless, asymmetries in cortical activity during motor outputs are shown. LH appear to demonstrate less hemispheric asymmetries in cortical activation in comparison to RH while completing unimanual and bimanual tasks (Klöppel et al., 2007; Reid & Serrien, 2012; Serrien & Sovijärvi-Spapé, 2015; Solodkin et al., 2001; Vingerhoets et al., 2012).

2.4.4 Asymmetries in Cortical Activation Evaluated with TMS

Although neuroimaging techniques provide the necessary information concerning activation of specific regions, it does not specify whether that activation is necessary for a given task. As such, TMS is often employed to investigate cortical activity during tasks. TMS applied over the M1 will elicit MEPs in the contralateral muscle, where excitability may be enhanced through contractions of that contralateral muscle or the ipsilateral homogenous muscle (Ziemann & Hallett, 2001). MEP enhancement (increase in amplitude) may occur either at the cortical or spinal level (Liang et al., 2008).

During a contraction of the target muscle, reduced intracortical inhibition of the contralateral M1 and increased excitability of spinal motoneurones (from descending volleys) will be responsible for MEP enhancement (Di Lazzaro et al., 1998; Liang et al., 2008; Ridding et al., 1995). Greater MEP amplitude within the resting muscle is likely to occur during contractions of the contralateral homonymous muscle (Stedman et al., 1998). The voluntary activation of the contralateral M1 can increase the excitability of the ipsilateral M1 (Stinear et al., 2001). Therefore, at rest, MEP excitability will be mainly modulated by the contralateral M1. Interhemispheric projections that travel between the corpus callosum may act in a facilitatory and/or inhibitory manner (Carson, 2005).

2.4.5 Mapping Asymmetries in Cortical Excitability

Current reports using TMS to assess MEP asymmetries elicited in hand, and upper-limb target muscles have no clear consensus (Hammond, 2002). TMS may be used to “map” cortical excitability; the resultant generated plot maps can be used to discern amplitude peaks, allowing estimates of threshold excitability of corticospinal neurons projecting to particular muscles (Wassermann et al., 1992). Wassermann and colleagues (1992) mapped cortical representations of four upper-limb muscles at rest: abductor pollicus brevis (APB), flexor carpi radialis (FCR), biceps brachii, and deltoid. While considering muscles across subjects to the same left and right sides, distal muscles had larger cortical representations (MEPs with larger amplitudes and lower recruitment thresholds). The larger cortical representations is presumptive to indicate a greater density corticospinal neuronal projections in the cortical model of the distal compared to the proximal musculature (Krutky & Perreault, 2007; Kuypers, 2011). Also, the number of direct projections from the M1 to motoneurones of the upper limb is greater for distal musculature (Palmer & Ashby, 1992). Thus, the degree of asymmetry may change depending on the musculature of interest. In addition, RH had a larger APB representation in the left hemisphere, and two LH had larger representation in the right-hemisphere, affirming the trend that cortical excitability is larger within the *dominant* hemisphere.

Similarly, Triggs and colleagues (1999) mapped cortical representations of the APB and FCR muscles in both LH and RH and showed evidence of a significant asymmetry between the preferred and non-preferred hands. There was no significant difference in MEPs' size elicited within the dominant and non-dominant APB or FCR. But in RH, the right (left-hemisphere) APB MEP map was *larger* than the left, but in LH the left ABP map (left-hemisphere) was *larger* than the right. These findings indicate that number of scalp stimulation sites eliciting MEPs (generated maps) to the ipsilateral cerebral cortex was larger than that of the right APB in LH, a reversal of cortical asymmetry. The same general trend was found in FCR muscles; however, the interaction between handedness and recording site did not reach significance (Triggs et al., 1999). Symmetrical cortical map areas of the abductor digiti minimi has been documented in LH and RH (Cicinelli et al., 2000). Thus, TMS mapping studies have shown evidence for a somewhat larger representation of hand musculature in the dominant M1 in RH and LH (Triggs et al., 1999; Wassermann et al., 1992) and the non-dominant hemisphere of LH (Triggs et al., 1999).

2.4.6 Motor Threshold Asymmetries

TMS used to measure the threshold for activation of the CST can reveal possible asymmetries in motor performance. Motor threshold is defined as the lowest TMS stimulus intensity needed to evoke a MEP in a target muscle (usually in at least 50% of successive trials) (Kobayashi & Pascual-Leone, 2003). The resting motor threshold (RMT) is found while the volunteer is at rest. In comparison, the active motor threshold (AMT) is found during a slight tonic contraction (~ 20% of maximal muscle strength) (Rossini et al., 2015) or during a locomotor output. A bilateral difference in the MEP threshold would indicate that the cortical systems' readiness to initiate a MEP within the hands differed between the two cerebral hemispheres. Subsequently, a difference in the cortical representation of hand muscles can facilitate physical asymmetries.

As previously mentioned, the literature on MEP threshold asymmetries is not unanimous; small asymmetries have been identified with lower thresholds for eliciting MEPs in the muscles of the *dominant* than that of the non-dominant upper-limb muscles (Hammond, 2002). At rest, lower MEP thresholds have been reported within the ADM but not the biceps brachii in RH, with no side-to-side differences detected (Macdonell et al., 1991). The thresholds for the left and right APB and biceps brachii muscles were evaluated in 30 LH and RH (Triggs et al., 1994). In RH, the MEP threshold within the right arm was less than left arm's corresponding muscles; the opposite occurred with LH. The asymmetry of threshold indicated that the dominant limb muscles had lower thresholds to elicit MEPs than muscles of the non-dominant limb (Triggs et al., 1994). Therefore, the readiness to activate the motor system projections to the dominant APB and biceps was *greater* than the non-dominant projections (Triggs et al., 1994).

A recent study investigated motor threshold variability (in the FDI at rest) across physiological and non-pathological behaviour characteristics in a large cohort (n = 115), including hemispheric asymmetries, age, handedness, and several other indices (Chagas et al., 2018). Motor threshold variability measured by TMS varied considerably across subjects and between hemispheres, with values ranging from 32% to 87% of maximum stimulator input. Repeated-measures ANOVA indicated higher motor threshold values within the *non-dominant hemisphere,* elderly people, and stressed individuals; other biological and behavioural characteristics did not influence cortical excitability (Chagas et al., 2018). Also, at rest, DeGennaro et al. (2004) compared transcallosal inhibition using paired-pulse TMS in a sample of LH and RH. LH and RH did differ concerning motor thresholds; the *dominant* ADM hand motor area had a lower threshold than the non-dominant predominately in LH, which is in line with studies comparing motor thresholds in different handedness groups (Macdonell et al., 1991; Triggs et al., 1997; Triggs et al., 1994).

Several other studies that have employed TMS to measure RMT in muscles of the upper limb have found no significant bilateral differences. Specifically, no side-to-side differences were detected in the resting motor threshold of the FDI of LH and RH (Brouwer et al., 2001; Daligadu et al., 2013; Davidson & Tremblay, 2013), and RH only (Semmler & Nordstrom, 1998). Similarly, in the APB in LH and RH (Souza et al., 2018; Triggs et al., 1999), and in RH only (Buick et al., 2016; Shibuya et al., 2017).

2.4.7 Asymmetries in Evoked Potentials

Modeling hemispheric asymmetries in corticospinal neuron activity may also be achieved by comparing the extent of activation bilaterally. For instance, Semmler and Nordstrom (1998) assessed between-hand contraction-induced facilitation of evoked MEPs. TMS and transcranial electrical stimulation (TES) gauged hemispheric differences in CSE during a voluntary contraction of the FDI in RH (Semmler & Nordstrom, 1998). Researchers quantified excitability differences by comparing the extent of facilitation of

MEPs elicited by TMS and TES delivered at a relaxed threshold intensity as the FDI abducted at various target forces.

Hemispheric excitability differences were apparent by an asymmetric pattern of facilitation of MEPs in the FDI of the two hands with TMS but not TES. TES was defined as a measure of spinal motoneuron excitability because the stimulus predominately excited corticospinal axons directly (Semmler & Nordstrom, 1998). The authors showed that with TMS, contraction-induced facilitation of MEPs was significantly larger when the non-dominant hand (left hand) abducted the FDI. Therefore, at each contraction level, the normalized MEP amplitude was larger in the left hand. When the authors compared the MEP facilitation using TMS and TES, they concluded excitability changes were not due to spinal motoneurone excitability differences because of the similarity of contraction-induced MEP facilitation using TES and since amplitude differences were apparent using TMS (Semmler & Nordstrom, 1998). The differences in MEP facilitation seen with TMS was likely reflective of greater CSE activation to the non-dominant hand during the abduction task. In terms of asymmetries, overall corticospinal drive was greater to the non-dominant hand during the abduction task compared to performing the same task with the dominant hand. The findings of Semmler and Nordstrom (1998) suggested that during a simple abduction task of the FDI, greater M1 activity was needed to complete the task with the non-dominant hand.

To further investigate the relationship between CSE and laterality during a digital dexterity task, the same research group employed LH and a more complicated manual task. Patterns of MEP facilitation in each hand were compared with precise manual tasks: finger tapping speed, Purdue pegboard, and maximal FDI strength (Brouwer et al., 2001). It was found that facilitation of MEPs patterns was not symmetrical. Subjects with extreme degrees of hand dominance (laterality quotient (LQ) ≥ 0.85) (Brouwer et al., 2001) (LH or RH) had greater MEP facilitation in the left FDI. In non-consistent RH, MEP facilitation was larger in the right FDI muscle than the left (Brouwer et al., 2001). MEP asymmetry facilitation did not yield any correlations in finger tapping speed or peg performance (Purdue pegboard), but a small correlation between asymmetry of abduction MVC force and asymmetry of MEP facilitation. MEP facilitation tended to be larger in the stronger FDI muscle pair, suggesting that CSE asymmetry is enhanced in the preferentially used FDI (Brouwer et al., 2001).

2.4.8 Stimulus-Response Asymmetries

Using TMS, stimulus-response (input-output) curves have become increasingly popular to assess corticomotor excitability. A change in the stimulus-response relationship between TMS and the evoked potential provides researchers with a measure of neuroplasticity (Carroll et al., 2001; Cicinelli et al., 2000; Devanne et al., 1997). The evoked amplitudes of MEPs and the duration of the silent period may be employed to construct stimulus response curve (SRC)'s since they are both dependent upon the TMS stimulation intensity (Carroll et al., 2001; Kimiskidis et al., 2005; Ridding et al., 1995).

The initial segment of the MEP SRC is flat and deviates from zero, corresponding to the motor threshold. The ascending portion of the curve represents a linear increase in MEP amplitude with increasing stimulus intensity (Rossini et al., 2015). At greater stimulus intensities, the SRC will plateau with no further increase in MEP amplitude despite the increased stimulus intensity. The plateau in amplitude potential corresponds with a cancellation of the descending train of motor unit action potentials (Rossini et al., 2015). MEP amplitude may also no longer increase in amplitude due to previously stimulated neurons being maximally active, and subsequent stimulation may drive recruited units into a refractory period, causing MEP amplitude to decrease. Therefore, the resultant SRC is often sigmoidal in shape partly due to cortical pathways recruited by TMS, motoneurone recruitment, descending aspects of the CST, and increased synchronization of discharged motor units at higher stimulus intensities (Forman et al., 2019). In sum, the descending excitability spikes and the progression of recruited corticospinal fibres establish the SRC.

The neural relationships underlying performance asymmetry for the hand's distal musculature in LH and RH have been assessed using SRC's by Daligadu and colleagues (2013). SRC intensities were determined from the resting threshold in the FDI of participants; stimuli were delivered in 10% increments from 90% - 150% of RMT in each hand. The slope of the linear aspect of the recruitment curve was calculated for each participant (Daligadu et al., 2013). The principal finding authors noted that the SRC slope was greater to the non-dominant hemisphere for both LH and RH compared to their dominant hands. Therefore, LH had a greater slope in their right hemisphere, whereas RH had a greater slope in their left. The results generally disagree with mapping and threshold tracking, where excitability tends to be greater to the dominant hemisphere (Hammond, 2002), but not all studies are in agreement.

The SRC slope is dependent upon excitability changes along with the CST and the general conformation of excitable interneurons in the range of TMS coil placement (Siebner & Rothwell, 2003). Due to the methodological paradigm, intrinsic excitability changes along the CST cannot be deduced from the SRC, which may contribute to the disparity of findings from other methodological paradigms. With the increased response of excitability to the non-dominant hemisphere noted and in conjunction with mapping studies, authors suggested that if the non-dominant hemisphere has greater excitability and mapping demonstrates a larger cortical representation over the dominant M1, then the non-dominant hemisphere would possess a greater excitability level in a topographically smaller region of the M1 (Daligadu et al., 2013). In contrast, the dominant hemisphere would possess a greater excitability element in a topographically smaller region of the M1. In summary, the asymmetry of SRC slopes indicated that both LH and RH, the non-dominant hemisphere may exhibit a higher level of excitation or lower inhibition level (Daligadu et al., 2013).

Cortical excitability changes in relation to CSE can be assessed in a number of manners. During movement tasks, hemispheric asymmetries can assess functional activation of M1 and associated regions via a wide range of imaging techniques. TMS can be used to create maps, SRC's, detect asymmetries in evoked potentials, and assess corticospinal readiness bilaterally through threshold tracking of particular musculature. Indeed, evidence suggests a hemispheric asymmetry in the organization and activation of the M1 exists and may be related to handedness. The motor practice of the dominant musculature could result in more effective movement representations cortically in the dominant hemisphere than the same amount of practice with the non-dominant arm and hand (Hammond, 2002). On the contrary it is arguable that excitability may be greater in the non-dominant hemisphere. This hemisphere may functionally adapt to have a higher level of excitation or lower level of inhibition in cortical circuitry as the result of lifelong experiences sensitizing the M1 (Daligadu et al., 2013).

2.5 Spinal-Motoneurone Asymmetries

The lateral CST acts as a facilitator to independently control the digits and mediate the hand’s skilled use for fine motor tasks. Asymmetrical anatomical (Amunts et al., 1996) and physiological (Macdonell et al., 1991; Triggs et al., 1994; Triggs et al., 1999) components of the M1 and CST have been related to handedness. Therefore, it is reasonable to assume that structural and functional asymmetries in cortical anatomy can translate to be reflected at the spinal-motoneurone level. Specifically, these differences provide different possibilities for interhemispheric communication, subsequently causing differences in proximal and distal arm effectors (Aune et al., 2016). Resultantly, neuromuscular indices may differ between the dominant and non-dominant arm musculature.

For example, muscle fibre composition differences between the dominant and non-dominant FDI have been documented. During a voluntary isometric contraction of the FDI, a significantly slower MU twitch rise time was evident in the dominant FDI compared to the non-dominant (Tanaka et al., 1984). Therefore, the dominant FDI MU had a greater time to fire and produce contractile strength (twitch) before reaching the stimulated motoneurones peak tension. As such, the fatiguability of the FDI muscle pairs also differed. These results represent an example of bilateral asymmetries in contractile slowing and tetanic tension properties of MU’s.

In relation, muscle fatigue can be quantified by assessing the change in the myoelectric signal frequency throughout a contraction. Progressive muscle fatigue will be evident by a leftward shift towards lower MU firing frequencies as a result of a decrease in conduction velocity during sustained contractions (De Luca, 1984). Therefore, the myoelectric signal and conduction velocity's median frequency is related to muscle fiber size and type (De Luca et al., 1986). During a constant-force abduction protocol of the FDI, De Luca et al. (1986) investigated lateral asymmetries in EMG median frequency activity. In LH, no lateral difference was evident in the FDI muscle's median frequency behaviour, which was attributed to this group’s ambidexterity. However, during the abduction protocol, RH demonstrated greater fatigue of the non-dominant hand evident via a lowered rate of decrease in the median frequency of the dominant FDI than the non-dominant (De Luca et al., 1986). Hence, the dominant FDI MU’s possessed a greater capability to continue firing during the sustained contraction in RH (median frequency decreased slower) in comparison to the non-dominant FDI. The accumulated years of preferential use of the dominant FDI may have altered the fiber type composition (De Luca et al., 1986).

Later, the same research group investigated asymmetries in the recruitment and firing rate of motor units in the FDI muscle pairs during isometric force contractions (Adam et al., 1998). The maximum voluntary force of the contractions did not differ between the hands, but the variability of force at submaximal levels was higher on the non-dominant side. This was indexed by a greater disparity of mean firing rates and force traces of the non-dominant FDI active MU’s. Participants had a greater difficulty following a target trajectory with the non-dominant hand (30% of maximum voluntary contraction) (Adam et al., 1998). In addition, lower average firing rates, lower recruitment thresholds, and greater firing rates were present in the dominant FDI.

The results by Adam et al. (1999) were interpreted to be an adaptation to daily preferential use. A histogram of recruitment threshold and firing rates displayed a shift in the dominant FDI where MU’s were more excitable and had lower average firing rates, supporting the notion that a greater number of lower threshold MU’s were recruited at low-force levels. Further, greater cross-correlations latencies between mean MU firing rate and contraction force were noted for the dominant FDI, along with a smaller coefficient of average MU interfering intervals. A cross-correlation latency peak function between mean firing rate and contraction force signals is indicative of electromechanical coupling of MU’s (rate coding) (De Luca et al., 1982). Often an increase or decrease in one unit's firing rate will be accompanied by similar changes in the firing rates of other MU’s (De Luca & Erim, 1994). Accordingly, a smaller coefficient of variation of firing rate and a greater cross-correlation peak in the dominant FDI attests to a disparity of fiber type between the hands. Together, these findings provide credible evidence of a dominant arm advantage in consideration for MU recruitment threshold, initial and average firing rates, and discharge variability at a target contraction force.

A similar trend was identified in FDI muscle pairs in LH and RH (Kamen et al., 1992). Using an in-dwelling needle electrode, FDI muscle pairs demonstrated greater firing rate cross-correlation scores in the dominant hand than in the non-dominant hand. (Kamen et al., 1992). Since cross-correlation analysis estimates the strength of common input to two motoneurones (Semmler, 2002), a greater correlation between MU recordings of the dominant hand suggests a greater synaptic input to that hand. During the voluntary contraction, fluctuations in the firing rate were greater in the dominant hand (Kamen et al., 1992). Therefore, the variability of MU force produced was greater in the dominant FDI

MU’s while performing the ramp isometric contraction task. However, Semmler and Nordstrom (1995) examined the discharge properties of FDI MU pairs in the dominant and non-dominant hands of 6 LH and RH. No differences in discharge rate or variability were evident between motor unit pairs.

Thus, some evidence of bilateral asymmetries in MU parameters such as firing rate, recruitment threshold, and contractile fatigue has been reported. Evidence has implied the corticospinal system is plastic in response to motor practice, at the level of the M1 and spinal-motoneurone processes. Trends have displayed an imbalance in spinal motoneurone excitability, with an increased readiness of the system to the dominant upper limb. A lifetime of preferred use could potentially facilitate adaptations in muscle fiber compositions, thereby increasing the mechanical efficiency and effectiveness of that limb.

2.6 Arm and Leg Cycling as a Model for Locomotor Outputs

The neural mechanisms that mediate rhythmic locomotor outputs in humans such as cycling and running has been shown to be similar in nature to quadrupeds (Zehr et al., 2007). A plethora of indirect evidence has been gathered to suggest that humans also possess spinally-mediated CPG’s that are capable of producing rhythmic locomotor outputs like leg and arm cycling (Power et al., 2018; Zehr, 2005). More recently, rhythmic leg and arm cycling training has been implemented within a chronic stroke population has induced changes to muscle activation and/or reflex modulation in all four limbs (Kaupp et al., 2018; Klarner et al., 2016). Therefore, when selecting a human-based modality to represent a rhythmic locomotor output, arm and leg cycling are ideal choices. For example, when assessing CSE, arm cycling is an ideal motor output because head stability is easy to control and efficient for the methods used to assess spinal excitability (Power et al., 2018).

Although it is very likely that the neural control of arm and leg cycling is similar, some biomechanical differences/definitions between the two cycling modalities should be mentioned. Similar to walking, cycling motor outputs have analogous joint ranges of motion, muscle activation, and neural control because they demonstrate a rhythmic and alternating pattern of flexor and extensor motoneurones (Zehr, 2005). Arm and leg cycling can be broken down into two distinct phases: flexion and extension. Although many names (e.g., power and recovery phase, upstroke and downstroke) can be attributed to these two phases, the terms flexion and extension will be used here throughout the review.

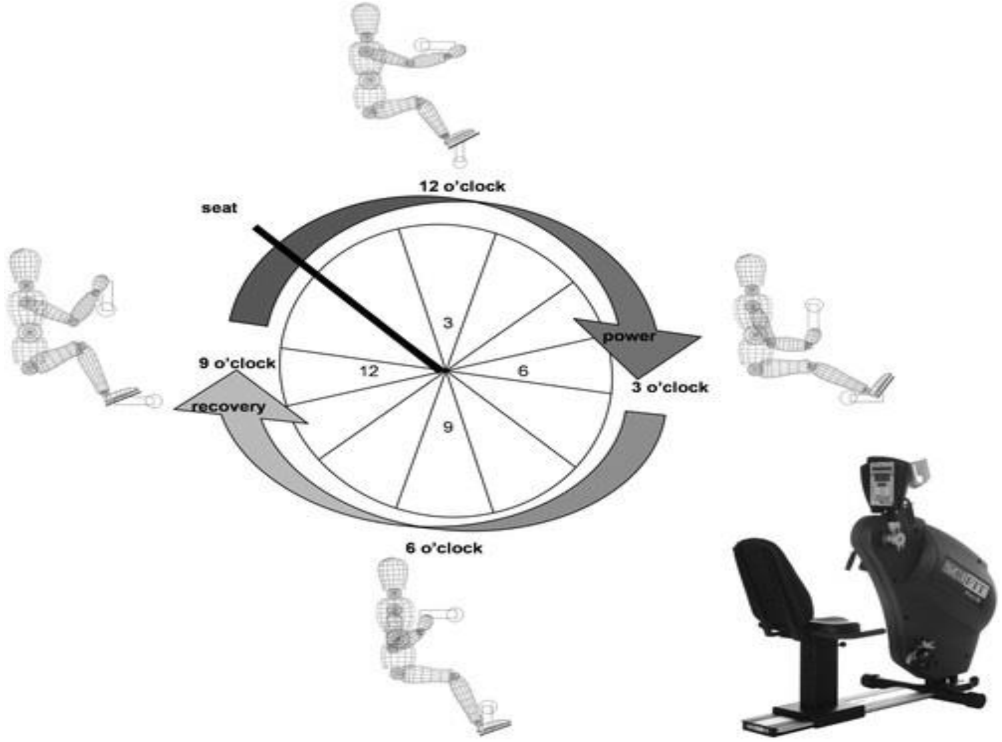

Figure 1. *Schematic of arm and leg positions corresponding to the functional positions throughout the locomotor cycle in reference to the right leg using a SCIFIT ergometer. Leg positions are labelled outside the circle with 12 o'clock as the start position. Notice that the arm crank lies 90 degrees ahead of the leg crank, therefore when the leg is at 12 o'clock the arm is at 3 o'clock. In the bottom right hand corner is an image of the equipment utilized. Figure is taken from (Balter & Zehr, 2007).*

Specific positions of arm cycling are typically either represented in degrees or relative to a clock face (Carroll et al., 2006; Forman et al., 2015, 2016; Power & Copithorne, 2013; Sidhu et al., 2009; Spence et al., 2016). During arm cycling, the flexion phase occurs as the elbow joint moves from 3 o’clock to 9 o’clock (90° to 270°), and the extension phase as the elbow joint moves from 9 o’clock to 3 o’clock (270° to 90° degrees). To compare, the “flexion” phase of leg cycling (upstroke) occurs when the knee is in full extension (180° to 0°), or as the foot and pedal moves from 6 to 12 o’clock. The “extension” phase of leg cycling (downstroke) occurs as the knee begins in flexion and moves from the 12 to 6 o’clock position (0° to 180° degrees) (Bini & Carpes, 2014). Typically, both modalities use an asynchronous form of cycling, meaning that the pedals are 180° relative to each other. For example, during leg cycling the when the left knee is in full extension (180°) the right knee will be in full flexion (0°).

2.7 The Role of the CPG During Locomotor Outputs in Humans

As previously mentioned, CPGs are neurones located within the spinal cord that in the absence of descending drive can generate the basic pattern of locomotor outputs. Graham Brown (early 20th century) was one of the first scientists to explain CPG involvement in the production of locomotion (Brown, 1910, 1913, 1915). In the cat and guinea pig he verified a stepping output pattern was not correlated with sensory or descending inputs (Stuart & Hultborn, 2008). His “half-centre” model describes the opposed pair spinal centres, one exciting flexors and inhibiting extensors, and the other with opposite functions (Stuart & Hultborn, 2008) confirming that the discrete rhythm/pattern of generating networks are responsible for producing the basic locomotor pattern seen in locomotion (Zehr, 2005). While it has been demonstrated that task- and state- dependent changes in CSE properties are present in quadrupeds, it cannot be immediately assumed these changes are evident in humans, therefore warranting analysis.

Today, indirect methods are used to assess the CPG contribution in humans. Before the onset of movement, intrinsic state-dependent changes in spinal excitability occur (Krawitz et al., 2001; Power et al., 2010). State-dependent changes refer to fluctuations in the intrinsic properties of motoneurones. During a CPG-mediated output the CNS will be employed in a state of enhanced excitability compared to rest (Power et al., 2018). Moving from the state of rest to locomotion will initiate processing of information within the CNS, including supraspinal input, sensory feedback, and spinal tracts. The CNS will also initiate descending commands to increase the excitability of spinal interneurons causing the CPG to oscillate and recruit motoneurones for the initiation of motor output (Power et al., 2018). As a collective, at the onset of a motor output, the entirety of the spinal motor system will be in an enhanced state of excitability compared to rest.

The last couple of decades has given rise to a lot of information regarding the control of CPG mediated motor outputs in various animals, however the combined cortical, subcortical, and spinal contributions that contribute to different movements in humans is far less understood (Carroll et al., 2006a; Sidhu et al., 2009). In humans, a growing body of evidence suggest that supraspinal inputs are more important to initiate locomotor outputs in comparison to quadrupeds (Petersen et al., 2001; Sidhu et al., 2009).

2.8 CSE Modulation During Arm Cycling

Assessing CSE during a locomotor output in humans needs to be accompanied by an appropriate modality. When selecting to model a human-based CPG rhythmic motor output to assess CSE, arm cycling is an ideal choice. Given that it is easy to utilize the stimulation techniques and ensure head stability (Power et al., 2018), evaluation of supraspinal and spinal excitability can be assessed with ease using TMS and TMES. Research, primarily from our lab, has determined that CSE is task-, phase-, and muscle-dependent.

2.8.1 Task-Dependent Modulation of CSE

Forman et al. (2014) assessed whether differences in CSE (supraspinal and spinal) to the biceps brachii existed during arm cycling and an intensity-matched isometric contraction. TMS and TMES were used to assess changes in MEP and CMEP responses respectively at three positions (3, 6, and 9 o'clock) relative to a clock face during both motor outputs. Results showed that CSE projecting to the biceps was larger at the beginning (3 o'clock), and middle (6 o'clock) phases of elbow flexion during arm cycling in comparison to an intensity-matched contraction, evident by greater MEP amplitudes (Forman et al., 2014). Additionally, no difference in CMEP amplitudes occurred at the 6 o'clock position, indicating the larger MEP amplitudes were due to supraspinal influence. CMEP amplitudes were larger during arm cycling only at the initiation (3 o' clock) of elbow flexion, with no differences at the 6 and 12 o'clock positions (Forman et al., 2014). In summary, supraspinal excitability projecting to the biceps increased during the flexion phase of arm cycling, and spinal excitability increased at the onset of flexion in comparison to an intensity-matched contraction. In contrast, one study recorded a decrease in MEP amplitude of the FCR in the flexion phase of arm cycling in comparison to an intensity- and position matched contraction (Carroll et al., 2006a). Therefore, indicating a reduction in the cortical influence (greater input from spinal CPG's) in the initiation of arm cycling when compared an intensity-matched tonic contraction.

Once established that CSE is modulated in a task-dependent manner *during* motor outputs, it is then intuitive to hypothesize that pre-movement CSE may be modulated similarly. In the quiet state before arm cycling, Power and Copithorne (2013) assessed supraspinal and spinal motor neuron excitability. Amplitude of MEPs initiated in the biceps brachii were greater prior to arm cycling compared with rest. No differences in CMEP amplitudes were detected at any of the three stimulation intensities between conditions. Hence, supraspinal but not spinal excitability was enhanced prior to arm cycling (Power & Copithorne, 2013). It was unclear whether the increase in MEP amplitude was due to the motor systems "priming" excitability changes prior to the onset of movement or cycling dependent.

Later, Copithorne et al. (2015) sought to determine whether differences existed between the modulation of CSE to the biceps brachii before arm cycling and an intensity-matched contraction to confirm if the previously reported results were indeed cycling-dependent. The report revealed similar pre-movement increases in CSE between arm cycling and an intensity-matched contraction. MEP amplitudes were larger with shorter onset latencies before arm cycling and tonic contractions when compared to rest, with no differences between the motor outputs. Spinal excitability measures (CMEP amplitudes and onset latencies) remained unchanged before cycling and tonic contractions in comparison to rest, concluding that pre-movement increases in CSE were due to an increase in supraspinal excitability, that was not task-dependent (Copithorne et al., 2015).

2.8.2 Intensity-Dependent Modulation of CSE

Modification of cycling cadence or power output can alter the intensity of an arm cycling task. Recently, Forman et al. (2015) assessed cadence-dependent changes in CSE to the biceps brachii while arm cycling. MEP and CMEP responses were recorded at two positions (6 and 12 o'clock) and two cadences (60 and 90 rpm). MEP and CMEP amplitudes increased with a concurrent increase in cadence during elbow flexion, CMEP amplitudes also increased with cadence during flexion (Forman et al., 2015). During elbow extension CMEP amplitudes decreased. In addition, changes in spinal excitability were phase-dependent as cadence increased, evident via an increase and decrease in CMEP amplitude during elbow flexion and extension, respectively (Forman et al., 2015).

Power-output dependent changes in supraspinal and spinal excitability to the biceps and triceps brachii has been confirmed (Spence et al., 2016). Interestingly, muscle-dependent changes in CSE were evident. Excitability projecting to the biceps brachii was higher during elbow flexion than extension and increased with a higher relative workload during arm cycling. On the other hand, no phase-dependent differences in CSE was evident in the triceps (lateral head), and spinal excitability was greater during elbow flexion than extension (Spence et al., 2016). Overall, CSE modulation of the antagonistic muscle groups differ supraspinally and spinally.

Lockyer et al. (2018) assessed the effects of cadence and power output on CSE projecting to the biceps and triceps brachii. MEPs and CMEPs elicited by TMS and TMES respectively were recorded during mid-elbow flexion (6 o'clock) and extension (12 o'clock) at two cadences (60 and 90 rpm), and three power outputs (20%, 40%, and 60% of peak power output) (E. J. Lockyer et al., 2018). Results indicated different supraspinal and spinal excitability modulation was dependent upon the how the intensity of arm cycling was altered (cadence or power output) and the effects were both muscle- and phase-dependent.

During the least active phase of cycling for each muscle, a change in power output did not significantly change spinal excitability, but an increase in cadence decreased and increased excitability to the biceps and triceps, respectively (Lockyer et al., 2018). As a collective, during the least active phases of the muscles, supraspinal excitability seems to contribute more to overall changes in CSE to the biceps, where a larger influence of spinal mechanisms is responsible modulation of CSE projecting to the triceps (Power et al., 2018).

To dive deeper into the phase-, task-, and muscle-dependence effects of CSE to the biceps and triceps brachii Forman et al. (2019) utilized TMS elicited SRCs elicited at eight different stimulus intensities (85% — 190% of MEP threshold). MEPs were recorded at two positions, mid-elbow flexion (6 o'clock) and extension (12 o'clock) and compared to an intensity and position-matched tonic contraction (12 o'clock). Participants cycled at 60 rpm during all cycling trials (Forman et al., 2019). At the 12 o'clock position, the biceps brachii SRC slope was greater during a tonic contraction than compared to arm cycling, with equal EMG activity between the two conditions. Therefore, CSE to the biceps was task-dependent during the extension phase of arm cycling. Greater CSE during rhythmic locomotor outputs may be modulated by enhanced excitability of cortical neurones which are easily stimulated by TMS (Forman et al., 2019). In addition, the biceps SRC slope was greater at the 6 o'clock position compared to 12 o'clock.

Contrastingly, CSE to the triceps brachii was not affected by task or position in this study, CSE did not differ between 6 and 12 o'clock positions. These excitability changes may be possibly due to different antagonistic muscle patterns while cycling. During arm cycling, the triceps brachii has a more complex rhythm of activation compared to the biceps brachii. For example, the biceps brachii EMG activity obeys a clear phase-dependent change, whereas the triceps brachii remains active throughout the full revolution (Forman et al., 2019). In conclusion, this study highlights CSE during rhythmic tasks is muscle specific; the biceps exhibits task- and phase- dependency, and the triceps brachii remained unchanged across conditions (Forman et al., 2019).

2.8.3 Muscle-Dependent Modulation of CSE

A growing body of evidence has revealed CSE during rhythmic locomotor outputs is muscle-dependent (Carroll et al., 2006a; E. J. Lockyer et al., 2018; Sidhu et al., 2012a; Spence et al., 2016; Weavil et al., 2015). For example, no phase-dependence (elbow flexion vs extension) was detected in the triceps brachii demonstrated by greater spinal excitability during elbow flexion (the less active phase), which is in direct opposition to the biceps brachii, with greater spinal excitability during flexion (the more active phase) (E. J. Lockyer et al., 2018; Spence et al., 2016). Another example, CSE projecting to the biceps was *higher* during arm cycling than compared to a tonic contraction (Forman et al., 2014), where CSE to FCR is *lower* during arm cycling compared to a tonic contraction (Carroll et al., 2006a).

There are likely multiple factors that influence the intermuscular differences in CSE during the less active phases of activation. Multiple descending pathways have an influence on excitability occurring along the CST, including the rubrospinal tract during locomotor outputs (Purves, 2004). In humans, *supraspinal* influence may be of greater importance in the control of flexor motor neuron pools. Capaday et al. (1999) showed in the tibialis anterior MEPS elicited during the stance phase of walking (inactive phase) were larger than compared to MEPs elicited during a plantar flexion contraction, and MEPs in the soleus were smaller during the stance phase compared to the intensity matched contraction (Capaday et al., 1999). This can be further supported by greater cortico-motoneuronal monosynaptic connections existing to the flexors rather than extensors (Brouwer & Ashby, 1990). Therefore, greater cortical control projecting to the biceps rather than triceps brachii may explain intermuscular differences in CSE (Power et al., 2018).

2.9 Evaluation of Bilateral Asymmetries During Locomotor Outputs

A common method to evaluate the central control of a rhythmic locomotor output is to compare the motor output to a tonic (isometric) contraction. This has proven useful to examine task-dependent differences in CSE (Power et al., 2018). During tonic contractions, input from CPG’s are not present, therefore tonic contractions can be used to infer the level (if at all) of CPG influence regarding the control of locomotor outputs. The lower limbs have demonstrated task-dependency (i.e. changes in amplitude and sign) during different motor tasks (Zehr et al., 2003, 2009; Zehr & Kido, 2001). Zehr and colleagues have confirmed that arm cycling is also partially modulated by CPG's (Balter & Zehr, 2007; Zehr, 2005; Zehr et al., 2016; Zehr et al., 2004). Thus, arm and leg cycling are appropriate modalities to assess CPG contribution during locomotor outputs. The literature examining bilateral asymmetries in biomechanical measures has primarily used leg cycling as a model.

Asymmetries may be quantified by examining torque modulation throughout the pedalling cycle (Bini & Hume, 2014), asymmetry indexes (AI), left-right ratios, or through statistical analyses (Carpes et al., 2010). Additionally, forces on the pedal surface is separated into three orthogonal components: normal – Fy, anterior-posterior – Fx, and medio-lateral – Fz directions (Bini & Carpes, 2014). The medio-lateral component does not contribute to overall bicycle propulsion, and therefore may not always be reported.

Total force applied to the pedals during cycling can be computed from the Fx and Fy force components. Subsequently, a percentage of the total force applied to the pedal will be concentrated perpendicular to the crank – effective force (Bini et al., 2013). The effective force (index of effectiveness) (IE) is defined as the ratio of force perpendicular to the crank (effective force) and the total force applied to the pedal (resultant force) (Bini et al., 2013). Intuitively, a higher IE translates to a cyclist maximizing force economy and/or efficiency; the ratio between mechanical energy produced and physiological demand is reduced (Bini et al., 2013; Korff et al., 2007). The following section will review the literature assessing bilateral differences in kinetic and kinematic parameters and muscle activation synergies during cycling.

2.10 Presence of Bilateral Asymmetries During Locomotor Outputs

Generally, in relation to bilateral asymmetries during locomotion, cyclists are the most investigated group. Asymmetries while cycling can refer bilateral differences in parameters such as torque and/or force. In the literature, it has been established that larger power output values whilst cycling is tightly knit to the capability to effectively apply force to the pedals. Because of the methods utilized to evaluate force and torque output, many cycling studies that are piloted are under the assumption that cyclists are pedalling symmetrically with each limb (Carpes et al., 2010). However, studies have recorded marked bilateral differences in crank torque (Bini & Hume, 2014; Carpes et al., 2007; Rannama & Port, 2015), power output (Bini & Hume, 2015; Rannama & Port, 2015), pedalling rate (Smak et al., 1999), and work (Daly & Cavanagh, 1976).

In competition situations, cyclists need to apply a precise pedalling technique to the pedals in order to maximize power and mitigate energy cost (Rannama et al., 2015). It is generally accepted that cyclists and non-cyclists exhibit a pedalling asymmetry (5-20%) (Carpes et al., 2010), but it is unclear if applying larger or more symmetrical pedal forces leads to better cycling performance (Bini et al., 2016) in comparison to cyclists whose pedal forces are more symmetrical. Indeed, the larger the effective pedal forces applied to the pedals translated to crank torque would allow cyclists to enhance power output for a given cadence (Bini & Hume, 2014). However, it should be noted that maximal cycling power will be dependent on several internal and external factors (Hug & Dorel, 2009). While cycling, movement of the lower limb is reserved to the circular path determined by the geometry of the bicycle. Cyclists can vary their pedalling technique by changing the kinematics of their lower limbs, and the activation of muscles (Bini et al., 2013). There is a small pool of research that has been conducted to quantify the relationship between symmetry in pedal forces and that influence of performance (Bini et al., 2013).

2.10.1 Influence of Limb Dominance and Pedalling Symmetry

A relationship between leg dominance and pedalling kinetics can be characterized. Generally, leg dominance is classified by the preferred leg chosen for kicking (Smak et al., 1999) or by characterization of the Waterloo inventory (van Melick et al., 2017). Several studies have found different bilateral biomechanical pedalling arrays in competitive cyclists. During pedalling, greater peak crank torque of the dominant leg has been recorded during submaximal cycling powers during incremental cycling tests (Bini & Hume, 2014; Carpes et al., 2008) and a 40-km time trial (Carpes et al., 2007). The dominant leg has also been reported to contribute greater dominant leg power and pedalling smoothness values compared to the non-dominant leg during 30 second isokinetic cycling sprints (Rannama & Port, 2015). Smak et al. (1999) determined that the dominant leg contributed significantly more to average crank power compared to the non-dominant when cycling between 60 and 120 rpm at a workload of 260W. A caveat to the studies by Smak et al. (1999) and Rannama and Port (2015) is that leg dominance was determined by kicking preference, where complete reliability of dominance cannot be stated. Additionally, reliability of leg dominance and direction of asymmetry are reportedly unrelated, and can vary significantly day-to-day (Daly & Cavanagh, 1976).

Other studies have reported bilateral asymmetries in pedalling kinetics. Bertrucci and colleagues assessed the biomechanics of master’s cyclists during an incremental test

(2012). A significant asymmetry in crank torque was observed in masters cyclists at both relatively low (100 W) to higher intensities (250 W) (Bertucci et al., 2012). The AI index quantified the crank torque difference between the legs to be 30 ± 8, 27 ± 15, 28 ± 17 and 23 ± 13 % in favour of the *dominant* leg for the power outputs of 100, 150, 200 and 250 W, respectively (Bertucci et al., 2012).

It is plausible that age may be a factor in the degree of bilateral asymmetry whilst cycling. Liu and Jenson (2012) assessed bilateral asymmetries in cycling in children and adults. Younger (5-7 years), older (8-10 years) children, and adults performed five 15-second cycling trials at five randomized cadences (40, 60, 80, 100, 120 rpm) to evaluate the effects of age and pedalling rate on cycling performance. Interestingly, children were unable to adapt to changing task demands with the same success as adults, evident by lesser performance and increased pedalling asymmetry (higher AI%). Secondly, children cycled more symmetrically compared to adults with changing pedalling rates, though asymmetry changes were unrelated to limb dominance. Thirdly, bilateral asymmetries in participants changed with pedalling rate. For all groups, the highest AI was at 40 rpm, and decreased as pedalling rate increased (Liu & Jensen, 2012a). It is possible that an age-related performance effect is possible, younger children are more variable and less accurate during cycling (Liu & Jensen, 2009). In addition, is also likely that dominance has not been solidified at younger ages.

2.10.2 Effect of Workload and Cadence on Pedal Force Effectiveness

A wide range of asymmetry indexes have been reported among studies assessing bilateral pedalling asymmetry, but the effects of cadence/power output on asymmetries is not fully understood (Carpes et al., 2010). In competitive cycling, cadence is a very important component because it is one of the few variables a cyclist can manipulate to manage performance and fatigue (Ansley & Cangley, 2009). Power output can be improved by increasing the magnitude of force (assuming near symmetric). In addition, changing the cycling technique to follow a more circular path can improve power output, but only because the effective force applied to pedals has been improved (Bini et al., 2013). A few of studies have identified that continually cycling at a lower pedalling cadence will result in an increase in the effective force and power output compared to higher cadences (Ericson & Nisell, 1988; Gregor et al., 1991; Sanderson, 1991). On the other hand, higher pedalling cadences have seen to decrease the amount of effective force (Patterson & Moreno, 1990; Sanderson, 1991). In addition, exercise intensity impacts the degree of pedalling asymmetry, an increase in workload leads to greater symmetry in crank torque produced (Carpes et al., 2007; Sanderson, 1991).

Smak et al. (1999) investigated whether bilateral asymmetry in cycling changed systemically with pedalling rate, participants cycled at 5 different pedalling rates (60, 75, 90, 105, and 120 rpm) at a constant workload of 260 W. Asymmetry was quantified for percent differences in average positive-, negative-, and average crank power. From the participants studied only the percent difference in negative power displayed a significant relationship with pedalling rate; as pedalling rate increased, asymmetry decreased (Smak et al., 1999).

Daly and Cavanagh (1976) evaluated the effects of changing cadence and resistance on the bilateral symmetry of work output while cycling. The force produced during the propulsive phase (0° to 180°) of the pedal cycle was considered, during three cadences (60, 80, and 100 rpm) at two power outputs (100 and 350 W). Although, significant differences in asymmetry occurred with changing pedalling speed, no clear trend between asymmetries, leg preference, or mechanical variables was evident (Daly & Cavanagh, 1976).

Similarly, Sanderson et al. (1991) studied the influence of power output (100 W and 235 W) and different pedalling rates (60, 80, 100 rpm) on the magnitude and orientation of applied pedal forces for recreational and experienced cyclists. No significant differences in the pedalling kinetics were evident between groups of cyclists. An IE was computed for cyclists to determine within-cycle changes in the effective force application. Little difference in the IE was present across the three pedalling rates (44% lower pedal force effectiveness changing from 60 rpm to 100 rpm, 16% lower pedal force effectiveness changing from 80 rpm to 100 rpm, and 56% greater pedal force effectiveness changing from 100 W to 235 W) (Bini et al., 2013; Sanderson, 1991). Interestingly, when power output was increased to 235 W the IE increased just before top dead centre of the cycle, indicating riders were reducing impact of negative forces during the recovery phase (Sanderson, 1991). The lack of measurable differences between groups was attributed to relatively lower power output and limited degrees of freedom of the bicycle (Sanderson, 1991).

Although no significant differences in asymmetries were evident between the two groups, both the competitive and recreational cyclists responded similar to increases in cadence and power output. Riders had a decrease in peak normal (Fy) forces and no change in the tangential component as cadence increased (Sanderson, 1991). In addition, regardless of the cadence cycled at, riders responded to an increased power output by increasing the amount of net positive angular impulse (downstroke). The calculated IE reduced as the cadence increased, noted largely in effect due to recorded forces during recovery (Sanderson, 1991). However it is worthy to note an IE computed over the entirety of the whole cycle would not be sensitive to small changes within the cycle, and also takes into account both muscular and non-muscular components (Leirdal & Ettema, 2011), and may not fully represent the riders pedalling technique (Bini & Diefenthaeler, 2010).

The effect of cadence and the resistance on bilateral pedalling asymmetries has not yielded any consistent observations. However, some trends have been identified. Smak et al. (1999) noted as the pedalling rate the cyclist worked at increased, asymmetry decreased. Daly and Cavanagh (1976) identified that the extent of asymmetry was dependent upon the pedalling rate but did not find any clear directional trends. A limitation from the previous study was that only crank torque measures were available, rather than the pedal force component measures. Sanderson (1991) found no significant differences between competitive and recreational cyclists concerning the influence of cadence and power output on the magnitude of force applied to the pedals. It was anticipated that peak forces would reflect a difference in pedalling strategies between the groups of cyclists, where competitive cyclists would orient their forces to minimize the magnitude. It was expected to see a reduction in the peak normal (Fy) and an increase in the tangential component. Normal and tangential components were higher for competitive cyclists but it was not significant (Sanderson, 1991). It is possible the power outputs (100W and 235W) cyclists performed at may have not been challenging enough for the competitive cyclists to effectively apply forces (Sanderson, 1991). In summary, contradicting evidence exists whether bilateral asymmetries are influenced by cadence and power output. Trends suggest there is an effect, though there is a high degree of variability in pedalling asymmetry among individuals

(Smak et al., 1999). Therefore, individuals may utilize different integral changes in asymmetries with pedalling rate dependent upon the parameter of interest (Smak et al., 1999).

An increase in workload will facilitate an increase of symmetry in crank torque produced for cyclists (Carpes, Mota, et al., 2010). Peak crank torque is a prevalent measure to characterize bilateral differences between the pedals, given a large percentage of force applied to the pedal along the sagittal plane is translated to crank torque during that part of the cycle (Sanderson, 1991). During a 40-km cycling time trial, the dominant leg always produced more crank torque and an increase in exercise intensity (% $VO2_{peak}$) decreased the asymmetry index (Carpes et al., 2007). Cyclists were instructed to ride the 40 km in as least time as possible, VO_2 was collected every 40 seconds and crank torque every 5 minutes during 10 consecutive crank cycles (Carpes et al., 2007) The race was split into quarters, interestingly athletes had the lowest asymmetry index (more symmetrical pedalling) in the first, and last quarters, when the intensity and physical demand is highest (Carpes et al., 2007). Thus, the degree of asymmetry changed systemically with crank torque, the pedalling asymmetry was attenuated (lower AI%) when crank torque and exercise intensity increased.

Contrastingly, no bilateral asymmetry was reported during an incremental cycling test for 11 male cyclists (Bini et al., 2007). The four stages of the incremental test aligned with 60, 75, 90, and 100% of VO_{2max}, kinematic variables and pedal forces were measured throughout. Crank torque and total work increased throughout the test, but no differences between the legs in relation to work and toque at the crank was evident (Bini et al., 2007).

Thus, the relationship between crank-torque symmetry and power-output level is unclear (Bini & Hume, 2014).

Bini and Hume (2014) compared peak crank torque between a commercial instrumented pedal and instrumented pedals to assess the effect of power output on bilateral asymmetries while cycling. 10 right-leg dominant cyclists completed an incremental test to exhaustion using each system, differences in left (non-dominant) and right (dominant) peak torque and AI was assessed using effect sizes. Asymmetries in peak torque *increased* in favour of the dominant leg at higher power-output levels (Bini & Hume, 2014), which is against the trend of asymmetries decreasing at higher workloads (Carpes, Mota, et al., 2010). Increased bilateral neural input between the motor cortices (common drive) has been hypothesized to a reason a reduction in asymmetries in crank torque is seen at higher power outputs (Carpes, Mota, et al., 2010).

An IE while cycling can quantify the economy and efficiency the cyclist is generating throughout the crank cycle. This measure can give an indicator about the technical aspects of pedalling and the ability to generate propulsive force (Candotti et al., 2007). Ericson and Nissel (1988) assessed changes in pedal force efficiency during different workloads (100 W and 240 W), pedalling rates (40, 60, 80, and 120 rpm), and saddle height. They found improved effectiveness when workload was increased (from 100 to 240 W) without concerning the effect of pedalling rate and saddle height (Ericson & Nisell, 1988), following the trend that lower pedalling cadence will increase the effective force and power output in comparison to greater cadences (Sanderson, 1991).

A decrease in the effective force has been recorded while cycling at higher cadences (Patterson & Moreno, 1990; Sanderson, 1991). A decrease in effective force can be attributed to a saturation in the force-velocity relationship (Bini & Carpes, 2014; Rassier et al., 1999). The muscle force velocity relationship will naturally be linked to the force capability of muscle shortening velocity, which are both dependent upon pedalling cadence (Bini & Carpes, 2014). Generally, the pedalling cadence requiring minimal muscle activation will be progressively greater as power output increases (MacIntosh et al., 2000). Which is in part, also due to a greater influence of inertial forces on crank torque at higher cadences, reducing muscle activation requirements (Neptune & Herzog, 2000)

Rossato et al. (2008) investigated the effects of changing cadence and workload on pedalling technique. Cyclists performed an incremental maximal cycling test, and two submaximal tests at 60% and 80% of their maximal power output. In the submaximal trials' cyclists pedaled for 10 minutes at a freely chosen cadence, then 10 minutes each at 20% above and 20% below the freely chosen cadence. The resultant and effective force, in addition to the IE was calculated during the propulsive and recovery phases (Rossato et al., 2008).

Cyclists improved their pedalling technique (13% higher effectiveness changing from 80% to 60% of maximal power output) (Bini et al., 2013) when the workload was increased, with a congruent decrease in their freely chosen cadence pedalling condition. Cyclists continually had an improvement in pedalling effectiveness at higher workloads, independent of cadence throughout the recovery phase. There were no significant changes in the effectiveness between the three pedalling cadences, suggesting cyclists could maintain a similar effectiveness index regardless of the cadence. The lack of difference was hypothesized to be attributed to the training status (elite cyclists); the test protocol may have employed workloads below the athletes normal training regime (Rossato et al., 2008).

Additionally, the effects of exercise intensity on pedalling IE has been researched. Kautz et al. (1991) recorded a 66% greater force effectiveness when cyclists changed from a workload of 100 W to 200W, and 1.5 lower effectiveness when pedalling rate increased from 50 to 110 rpm (Bini et al., 2013; Kautz & Hull, 1993). During submaximal cycling tests Zameziati et al. (2006) determined the IE during submaximal cycling tests at different intensities. Positive relationships (r = 0.79) between IE and efficiency, and IE (r = 0.66) during the recovery phase and efficiency was identified (Bini et al., 2013; Zameziati et al., 2006). Together, these studies indicate a better pedalling technique with an increase in cycling intensity.

2.10.3 Asymmetries in Muscle Activation Synergies

Asymmetries in pedalling is likely also related to differences in lower limb muscle activation and firing synergies. Like the upper-limbs, limb preference could facilitate different EMG responses between the dominant and non-dominant lower limbs while cycling. For example, a lower degree of muscle activation and greater muscle efficiency could describe preference-related advantages to the lower extremities and help elucidate to why some asymmetry is present while cycling (Carpes, et al., 2010).

Currently, there is a scarcity of research assessing the relationship between bilateral pedalling asymmetry kinetics and leg musculature EMG activity, though some studies have evaluated muscle activation synergies during unilateral cycling. Carpes et al. (2011) investigated the effects of leg preference on muscle efficiency and activation while one-legged pedalling in cyclists and non-cyclists working at the same relative workload. The average root mean square EMG activity was monitored for the vastus lateralis, biceps femoris, and gastrocnemius (medial head) muscles during unilateral cycling with the preferred and non-preferred leg (Carpes, Diefenthaeler, et al., 2010). The magnitude of muscle activation was similar for both cyclists and non-cyclists exercising under submaximal conditions (Carpes, Diefenthaeler, et al., 2010). During a 30 second sprint cycling test, leg dominance dependence in pedalling power asymmetries were related to a bilateral asymmetry of vastus lateralis muscle firing patterns (Rannama & Port, 2015). Bilateral differences in vastus lateralis activation patterns were not significant. However, pedalling kinetics asymmetry was significantly correlated with an asymmetry of vastus lateralis EMG patterns (Rannama & Port, 2015). A larger dominant side pedalling symmetry was associated with larger vastus lateralis EMG mean frequency values in the non-dominant leg, and a greater dominant asymmetry in power values was related with the same direction asymmetry in vastus lateralis normalized root mean square amplitude (Rannama & Port, 2015). These findings indicated that pedalling power patterns and leg dominance asymmetries exist, decreasing during the 30 second maximal cycling test and were related to a bilateral asymmetry of VL muscle firing patterns.

Much of the literature characterizing bilateral asymmetry for parameters such as torque and force has been examined within the lower limbs. Factors that influence the degree of asymmetry include pedalling cadence, workload, power output, and limb dominance. It appears the dominant limb is more effective at producing greater overall torque values in comparison to the non-dominant limb. Further, the degree of asymmetry for pedalling seems to be greatest at submaximal intensities and decreases near maximal output.

2.11 Cycling Asymmetries and Performance

Pedalling asymmetries, whether during arm or leg cycling will result in a degree of instability considering the context. It has been suggested that bilateral asymmetries may be detrimental to physical performance, but research has not fully addressed the relationship between asymmetry and performance, as well as in association to injuries (Carpes et al., 2010; Maloney, 2018).

The appreciation of balance can be applied to a practical perspective when evaluating pedalling asymmetries and injury. Researchers have proposed that large bilateral asymmetries in peak forces should be avoided. Asymmetrical cyclists may apply larger joint forces to one leg, leading to overuse injuries (Bini et al., 2017). Injured cyclists have displayed up to 400% differences in left to right pedal forces (Carpes et al., 2010; Hunt et al., 2003). It would be within an individual's interest to reduce pedalling asymmetries. A lower asymmetry could enhance performance by more evenly sharing the intensity between the leg musculature (Bini et al., 2017). However, it is worthy to note that even masters cyclists have significant asymmetries during pedalling at a variety of power outputs (Bertucci et al., 2012).

2.11.1 Pedalling Retraining to Reduce Bilateral Asymmetries

It is suggested that cyclists that adopt a more symmetrical cycling pattern will be at lower risk for overuse injuries (Carpes et al., 2010). A few studies have assessed pedalling training intervention effects on the reduction of asymmetries in cyclists (Bini et al., 2017; Kell & Greer, 2017). Kell and Greer (2017) demonstrating using a Wattbike ergometer that cyclists who had an asymmetry index within a normal range (5-20%) could significantly improve bilateral pedalling symmetry with the use of visual feedback. Similarly, Bini et al. (2017) enrolled twenty male cyclists (many with competitive experience) into a one-session pedalling intervention to reduce bilateral asymmetry in pedal forces. Cyclists (n = 10) who demonstrated a bilateral asymmetry greater than 20% completed 12 trials pedalling retraining using visual feedback, and audio cues to increase force to their weaker leg and vice-versa to their “stronger leg” from the researchers. In line with the results from Kell and Greer (2012) cyclists reduced their force asymmetry with verbal and visual feedback of pedal forces. Cyclists who presented with larger asymmetry indexes prior to pedalling retraining were the cyclists with the largest improvement (Bini et al., 2017). Evidence has shown that bilateral asymmetries in force generation can be minimized with training interventions while cycling. However, whether a similar regime applied to arm cycling to reduce bilateral asymmetries concerning force generation would be effective is unknown. Future studies could implement a pedalling retraining protocol to investigate this.

2.12 Conclusion

This review has examined functional asymmetries in M1 excitability and the subsequent motor representations in the muscles of the upper-limb. The current body of knowledge suggests that handedness may be related to bilateral asymmetries in motor performance. An asymmetry in cortical motor control of the hands and upper-limb muscles has been identified, where generally excitability of the dominant cerebral hemisphere is greater compared to the non-dominant. Studies examining bilateral pedalling assessments has cyclists displaying frequent asymmetries. Asymmetries in crank torque, power and/or work appears to be influenced by exercise intensity. Higher asymmetries indexes are present at submaximal intensities and decrease (become more symmetric) at higher workloads. In addition, the dominant kicking limb generally contributes more to overall crank torque regardless of the cadence cycled at. However, it remains unclear whether bilateral asymmetries in CSE measures are present during a locomotor output, and whether these measures are correlated with torque production while arm cycling. The following study will examine bilateral differences in neuromechanical measures while arm cycling at a set workload.

2.13 **References**

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3 Assessing the relationship between corticospinal excitability and mechanical force generation to both arms during arm cycling: are asymmetries present?

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Running Head: Bilateral assessment of CSE and force generation during arm cycling

Key words: locomotion, bilateral asymmetry, MEP, CMEP, stimulus-response, transcranial, transmastoid

3.1 Abstract

No research has examined corticospinal excitability (CSE) bilaterally during a locomotor output. The aim of this study was to investigate CSE and vector force generation bilaterally to muscles of the upper limb during arm cycling. Using transcranial magnetic stimulation (TMS) and transmastoid electrical stimulation (TMES) generated stimulus-response curves (SRCs), supraspinal and spinal excitability were assessed at seven different experimental intensities, respectively (90 – 150% of motor evoked potential (MEP) or cervicomedullary evoked potential (CMEP) threshold). TMS-evoked MEPs and TMES-evoked CMEPs were recorded at the 6 o'clock position from the biceps and triceps brachii bilaterally while arm cycling at 60 RPM and 25 W. Vector force at the 6 o'clock position was also collected bilaterally. CSE did not differ between the dominant and non-dominant biceps ($p = .740$) or triceps ($p = .497$) brachii. Force generation was significantly greater in the dominant limb compared to the non-dominant limb (Dominant: 23.4 ± 9.04, Non-Dominant: 14.6 ± 3.41 N, $P = .028$). Collectively, this data suggests that CSE projecting to the biceps and triceps does not significantly differ between the dominant and non-dominant limbs, and vector force generation at the 6 o'clock position is greater for the dominant upper limb.

3.2 Introduction

Human gait can be described as a smooth coordinated pattern of regular and repeating cyclical movements of the arms and legs (Abu-Faraj et al., 2015; Cappellini et al., 2006). This synergetic pattern of locomotion seemingly requires little thought to initiate, however, a substantial amount of neural effort and coordination is actually required to execute such maneuvers (Power et al., 2018). Locomotion, and similar rhythmic movements, such as cycling, demonstrate bilateral rhythmic and alternating coordination of the limbs. Within the spinal cord, circuitries of neurones, known as central pattern generators (CPG's), are capable of enabling the primary pattern of locomotive motor outputs in the absence of afferent input or descending drive (Grillner, 2011; Steuer & Guertin, 2019; Zehr et al., 2004) with accompanying descending input from the primary motor cortex (Petersen et al., 2002). Ultimately, supraspinal structures will activate motor circuitry within the brainstem and spinal cord to eventually activate spinal motoneurones, which will project and activate skeletal muscle to generate movement (Power et al., 2018).

Recently, researchers have sought to understand how supraspinal and spinal motor systems are modulated during locomotor outputs. Using indirect methods, the excitability of the corticospinal tract (CST) in humans can be measured. The corticospinal tract plays a key role in the cortical control of spinal cord activity in humans (Welniarz et al., 2017b). To model locomotor movements, often arm (Carroll et al., 2006; Copithorne et al., 2015; Forman et al., 2014; Forman et al., 2019; Lockyer et al., 2018; Power & Copithorne, 2013; Spence et al., 2016) and leg (Sidhu et al., 2012b; Weavil et al., 2015) cycling are used.

To indirectly measure excitability of the corticospinal pathway, transcranial magnetic stimulation (TMS) and transmastoid electrical stimulation (TMES) is often employed. In recent years, it has become more common to assess corticospinal excitability (CSE) during locomotion. However, when CSE is assessed during locomotor outputs, it is usually only examined in one limb, often to the dominant limb (Alcock et al., 2019; Carroll et al., 2006; Forman et al., 2014; Forman et al., 2019, 2019; Lockyer et al., 2018; Lockyer et al., 2019; Zehr et al., 2003; Zehr & Kido, 2001). This is an important consideration because bilateral asymmetries in CSE have been documented, albeit these investigations are typically done at rest or during tonic contractions. For example, Daligadu and colleagues (2013) showed an asymmetry of neural drive between the dominant and non-dominant hemispheres for both left- and right-handed participants using a TMS stimulus-response technique. The slope of the stimulus-response curve (SRC) showed a greater increase in the activation of the non-dominant motor hemisphere when compared to the dominant in both handedness groups. Meaning, there was an asymmetry in cortical motor control, where the non-dominant motor hemisphere was the more excitable area (Daligadu et al., 2013).

While some research is available on bilateral asymmetries at rest and during tonic contractions, how CSE is modulated bilaterally during locomotion remains largely unknown. Indeed, CSE is different between the conditions of rest and locomotion, considering CSE and spinal excitability is modulated in a phase-, intensity-, and state-dependent manner (Carroll et al., 2006; Forman et al., 2014; Forman et al., 2019; Lockyer et al., 2018; Power et al., 2018; Spence et al., 2016).

Although CSE has predominately been assessed in one limb during arm cycling, asymmetries in force and torque production during cycling have been recorded (Bini & Hume, 2015; Bini & Hume, 2014; Carpes et al., 2007; Daly & Cavanagh, 1976). During cycling, the dominant leg normally contributes more to overall propulsion than the non-dominant leg (Carpes et al., 2010). Given this information, it is unknown if a relationship (if at all) exists between CSE and force generation during cycling.

The primary purpose of this thesis was to investigate whether a bilateral difference in CSE was present to the biceps brachii while arm cycling. Secondly, we sought to determine if vector force output differed between the upper limbs and whether measures of CSE and force production were correlated. We hypothesized that: (1) CSE and spinal excitability would be greater in the dominant biceps brachii and (2) the dominant arm would contribute more to overall force output than the non-dominant arm.

3.3 Methods

3.3.1 Ethical Approval

Prior to data collection, all procedures were verbally explained to participants. Any participant concerns or questions were addressed prior to providing signed informed consent. The study was conducted in accordance with the Helsinki declaration and all study protocols approved by the Interdisciplinary Committee on Ethics in Human Research at Memorial University of Newfoundland

(ICEHR No. 20201309-HK). Tri-council guidelines were adhered to and all risks were disclosed to participants.

3.3.2 Participants

Seven (4 males and 3 females; 5 right-hand dominant, 2 left-hand dominant) volunteers were recruited to participate within the study. Participants were excluded from the study if they had any known neurological impairments screened via a magnetic stimulation safety checklist (Rossi et al., 2009). Participants were also screened for any contraindications to exercise, evaluated by completing a Physical Activity Readiness Questionnaire (PAR-Q+) (Warburton et al., 2011). To determine hand dominance, participants completed a Edinburg inventory handedness questionnaire (Oldfield, 1971). Seven participants received TMS and 6 also received TMES, one participant consistently evoked cervical root stimulation (Taylor, 2006) and therefore only received TMS.

3.3.3 Experimental Set-up

A one-group within subject experimental design was used. This study was conducted over two separate days; a familiarization session and a testing session interspersed by a minimum of 48 hours.

3.3.3.1 Familiarization Session

During the familiarization session, participants were familiarized with the stimulation techniques and the experimental setup. Participants received TMS, TMES, and brachial plexus stimulation to ensure they were comfortable receiving stimulations during the experimental protocol. Participants were also introduced the arm cycle ergometer and asked to cycle at 60 RPM at a workload of 25 W to ensure they could complete the experimental protocol.

3.3.3.2 Testing Session

Arm cycling trials were completed on an arm cycle ergometer (SCIFIT, model PRO2 Total Body, Tulsa, OK, USA) with the arm cranks affixed in a neutral handgrip position (180 degrees out of phase). The height of the ergometer seat was adjusted to have participants shoulder joint horizontally aligned with the arm cranks axis of rotation. The seat distance from the arm cranks was adjusted so that participants had no undue reaching or trunk rotation. During arm cycling trials, participants wore wrist braces to limit wrist flexion and extension to reduce heteronymous reflex connections that lie between the wrist flexors and extensors (Manning & Bawa, 2011).

In this study, measurements were taken at the 6 o’clock position relative to a clockface (bottom dead centre; mid-elbow flexion). Stimuli were automatically triggered when the assigned arm being assessed (dominant or non-dominant) passed the 6 o’clock position. The six o’clock position for measurements was selected because it is the position during the cycling movement where the biceps brachii (the main muscle of interest) is maximally, or near maximally, activated (Forman et al., 2014). Data measurements were taken bilaterally from the biceps and triceps brachii during arm cycling with the arm being assessed first having been randomized. Seven trials were recorded per arm, for a total of 14 cycling trials. Participants were asked to cycle at a constant power output of 25W at 60 rpm (Forman et al., 2014).

This power output and cadence was selected as it allows cycling without inducing fatigue and sufficient electromyography (EMG) responses from the muscles of interest (Forman et al., 2014).

3.3.4 Electromyography Recordings

EMG recordings were taken bilaterally from the biceps and lateral head of the triceps brachii of the dominant and non-dominant arms using Ag-AgCl surface electrodes (Kendall^{TM} 130 Foam Electrodes conductive adhesive electrodes, Covidien IIC, Massachusetts, USA). EMG was recorded using a bipolar configuration with an inter-electrode distance of 20 mm. Ground electrodes were placed on the lateral epicondyle of each arm.

To obtain the best signal-to-nose ratio of EMG, prior to placement of the electrodes the skin at the recording site was prepared to reduce impedance. The electrode site was shaved, abraded (using abrasive pads) to remove dead epithelial cells, and sanitized with isopropyl alcohol. EMG was collected on-line at 5 kHz using a CED 1402 interface and the associated Signal (version 5.11) software (Cambridge Electronic Design (CED) Ltd., Cambridge, UK). EMG signals were amplified (gain = 300) and filtered with a 3-pole Butterworth filter with cut-off frequencies of 10 –1000 Hz with the CED 1902 amplifier.

3.3.5 Stimulation Techniques

TMS, TMES, and brachial plexus stimulation was used to elicit responses from the biceps and triceps brachii whilst arm cycling. Motor responses from the dominant and non-dominant limbs were recorded on the same session. Stimulation intensities were set as participants cycled at a workload of 25 W and a cadence of 60 RPM. Participants completed seven arm cycling trials per arm (14 total), once stimulation intensities were set for one limb participants completed seven cycling trials for one limb before moving onto the other. Seven experimental intensities (90, 100, 110, 120, 130, 140, and 150% of MEP and CMEP active motor threshold (AMT)) were calculated for the 6 o'clock position to create a SRC. AMT was defined as the lowest percent maximum stimulator output (MSO) resulting in a clearly discernable MEP or CMEP from background biceps brachii EMG in 50% of cycling trials (4 out of 8), The order of stimulation intensity trials was completed in a randomized order. Dominant and non-dominant limb responses were completed in a counterbalanced order.

In addition, stimulation intensities for brachial plexus stimulation, TMS, and TMES were set relative to the biceps brachii. The stimulations were triggered automatically as the assigned arm crank passed the 6 o'clock position. For instance, for a right-handed participant completing the dominant arm responses, stimulations were triggered as the right arm crank passed the 6 o'clock position.

3.3.5.1 Transcranial Magnetic Stimulation

A Magstim 200 (Magstim, Whitland, Dyfed, UK) stimulator was utilized to elicit MEPs at the stimulation site (motor vertex) using a circular coil (diameter = 13.5 cm). Motor vertex was defined as the intersection of the midpoints between the nason and inion, and the midpoint between the tragi (Forman et al., 2014; Forman et al., 2019; Power & Copithorne, 2013). The position of the TMS coil was held tangent to the skull of the participant. The coils current direction (based on handedness) was optimized to preferentially activate either the left- or right- motor cortex. For example, while recording the dominant limb responses of a right-handed participant the direction of the coil was optimized to activate the left motor cortex.

While arm cycling at 25W and 60 RPM AMT was determined for participants. The TMS stimulation intensity began at 25% MSO and was gradually increased until AMT was reached. Seven experimental intensities (90, 100, 110, 120, 130, 140, 150% of MEP AMT) were calculated to create a SRC.

3.3.5.2 Transmastoid Electrical Stimulation

TMES stimulations were delivered slightly inferior to the mastoid processes using adhesive Ag-AgCl electrodes. Using a second Digitimer stimulator, the stimulus duration was fixed at 200 μs in duration (DS7AH, Digitimer Ltd., Welwyn Garden City, Hertfordshire, United Kingdom). First, CMEP threshold was determined. The stimulator intensity was slowly increased until a discernable CMEP was visible from the background biceps brachii EMG in 50% of cycling trials (4 out of 8). Once determined, seven experimental intensities (90, 100, 110, 120, 130, 140, 150% of CMEP AMT) were calculated to create a stimulus response curve to be used in the cycling trials.

To ensure only the corticospinal tract was stimulated and not the ventral roots, the latency of the elicited CMEP was monitored closely. The appropriate latency to ensure that only the corticospinal axons are stimulated during experiments is ~ 8 ms to the biceps brachii. When the ventral roots are stimulated a decrease of the recorded CMEP of ~2 ms will occur, as the duration for transmission between the descending axons and spinal motoneurones is absent (Taylor, 2006).

3.3.5.3 Brachial Plexus Stimulation

At Erb's point, electrical stimulation was used to elicit maximal action potentials (M_{max}) using a Digitimer constant current stimulator (model DS7AH, Digitimer Ltd., Welwyn Garden City, Hertfordshire, UK). Electrical pulses were 200 μs in duration. Stimulating electrodes were placed on the acromion process (anode) and the supraclavicular fossa (cathode). While arm cycling at 25 W and 60 RPM, the stimulator intensity was set to begin at 25 mA and was gradually increased until M_{max} of the biceps brachii was determined. Visually, M-wave amplitude was monitored until a plateau in peak-to-peak amplitude was achieved or began to decrease. To ensure that M_{max} was elicited consistently throughout the experimental protocol stimulation intensity was increased by 20% above that used to elicit M_{max} and remained constant throughout the cycling trials (Forman et al., 2014; Power & Copithorne, 2013).

3.3.6 Experimental Protocol

Following the experimental stimulation setup, the experimental protocol could begin. Prior to the participant beginning the protocol, stimulation intensity trial order and the limb from which recordings were made was randomized. Participants completed 14 cycling trials total (7 per arm). Each cycling trial was 70 seconds in duration. During each cycling trial participants received TMS, TMES, and brachial plexus stimulation. The order of the stimulations was randomized throughout the trial and were evoked approximately ~ 5 seconds. In each cycling trial, participants received 8 MEPs, 4 CMEPs, 1 M-wave, and 1 blank frame (14 frames per trial). One blank frame was given to participants to mitigate stimulation anticipation. Between cycling trials participants were given time to rest if they chose.

3.3.7 Measurements

Data was analyzed off-line using Signal 5.11 software (CED, UK) after the experimental protocol was completed. Peak-to-peak amplitudes of evoked potentials (MEP, CMEP, and M-wave) were recorded from the initial deflection of the voltage trace to the return of the trace back to baseline EMG. MEPs and CMEPs were then normalized to the amplitude that elicited the largest average of 8 MEPS and 4 CMEPS within each condition (Forman et al., 2019). Amplitudes of the evoked potentials were normalized this way in order to better examine the slope of each condition relative to its own maximum excitation (Forman et al., 2019). All measurements were taken from the all the averaged files of 8 MEPs, 4 CMEPs, and 1 M_{max}.

The pre-stimulus EMG, defined as the mean rectified EMG prior to the stimulus artifact, was measured from the virtual channels created for each muscle. Using a custom script, the mean rectified pre-stimulus EMG was measured 50 ms prior to TMS and TMES evoked stimuli for each muscle. All EMG was then normalized as a percentage of $M_{max.}$

SRCs were generated manually off-line by normalizing MEP and CMEP evoked potential amplitudes of the stimulation intensity used to elicit the largest MEP or CMEP within each cycling trial (Forman et al., 2019). Next, the average data for each participant was then graphed. From there, the slope of each SRC was manually calculated along the linear portion of the curve (between AMT threshold and SRC plateau (or peak amplitude if a plateau was not present) as the net change in MEP or CMEP amplitude (normalized) over the net change in stimulation intensity relative to MEP or CMEP threshold (Forman et al., 2019).

$$\text{Slope} = \frac{\text{MEP}_{\text{Plateau}} - \text{MEP}_{\text{Threshold}}}{\text{SI}_{\text{Plateau}} - \text{SI}_{\text{Threshold}}}$$

$$\text{Slope} = \frac{\text{CMEP}_{\text{Plateau}} - \text{CMEP}_{\text{Threshold}}}{\text{CMEP}_{\text{Plateau}} - \text{CMEP}_{\text{Threshold}}}$$

During arm cycling trials, bilateral force recordings were measured from the cycle ergometer arm cranks in the x and y directions, from which the overall force vector (z) was calculated. The vector force in each limb at the 6 o’clock position was then identified. The average vector force measure was taken from an average of seven output values from each stimulus intensity (90 – 150% of motor threshold).

3.3.8 Statistics

Statistical analyses were performed using IBM® SPSS® statistics version 27 (IBM, Markham, Ontario, Canada). Tests of sphericity were examined with

Mauchly’s test, and if violated, the appropriate corrections to the degrees of freedom were made (Field, 2017). A two-way (2x7) repeated measures ANOVA with factors of “limb” and “intensity” was used to determine if statistically significant differences in MEP or CMEP amplitudes (normalized to the largest amplitude), or pre-stimulus EMG occurred as a main effect of limb dominance. When a significant effect was found, repeated pairwise comparisons with a Bonferroni correction was used (Field, 2017).

To assess differences the slope of MEP and CMEP SRCs between the limbs, a Wilcoxon-Sign rank test was conducted in place of a t-test due to non-parametric data. The difference scores were approximately normally distributed, which was assessed with a histogram with a superimposed curve.

A paired-samples t-test was used to determine if a statistically significant mean difference in vector force produced at 6 o’clock was present between the dominant and non-dominant limbs. One outlier was detected that was greater than 1.5 box-lengths from the edge of the box within a boxplot. Inspection of the outlier value did not reveal the case to be extreme, and therefore was kept in the analysis. Additionally, a paired-samples t-test was also used to assess if a statistically significant mean difference in pre-stimulus EMG at the 6 o’clock position was present between the dominant and non-dominant limbs. All analysis was performed on group data with a significance level of $p < .05$.

3.4 Results

Data is reported in Table 1. Table 1 displays raw and normalized data from the “dominant” and “non-dominant” limb during arm cycling. All data is reported in text as means ± standard deviation (*SD*) and illustrated in figures below as ± standard error (*SE*).

3.4.1 Biceps Brachii

3.4.1.1 MEP Slope

For the biceps MEP SRC slope, the Wilcoxon-signed rank test indicated that the slopes were not statistically different between the limbs (dominant biceps (Mdn = 1.89) and non-dominant biceps Mdn = 1.64); z = -1.01, $p = .310$).

3.4.1.2 MEP Amplitude

For the biceps brachii, group data demonstrated no significant effect for the interaction between limb and stimulation intensity ($F_{(2.515,15.087)} = 1.16$, $p = .349$). In addition, no significant main effect of limb was present ($F_{(1,6)} = .740$ $p = .740$), indicating the MEP amplitudes were similar between the limbs. A significant main effect was found for stimulation intensity ($F_{(2.202,13.214)} = 142.8$, $p < .001$) signifying mean MEP amplitude increased with increased stimulation intensity. Pairwise comparisons indicated that mean MEP amplitudes were significantly different for each stimulation intensity greater than 90% ($p < .05$ for all comparisons), with the exception of no significant mean differences between 110% and 120% stimulus intensities ($p = .76$), 130% and 140% stimulus intensities ($p = .253$), and between 140% and 150% stimulus intensities ($p = .127$).

Pre-stimulus EMG MEPs. No significant main effect for limb ($F_{(1,6)} = .17$, $p = .691$), stimulation intensity ($F_{(6,36)} = .90$, $p = .505$), or interaction between limb and stimulation intensity ($F_{(2.207,\ 13.245)} = 1.5$, $p = .260$) was present indicating similar levels of bEMG between the biceps brachii.

3.4.1.3 CMEP Slope

The Wilcoxon-Sign rank test indicated that the CMEP SRC slopes were not significantly different between the limbs (non-dominant biceps ($Mdn = 1.83$) and dominant biceps ($Mdn = 1.72$); $z = -.94$, $p = .345$).

3.4.1.4 CMEP Amplitude

No significant main effect of limb ($F_{(1,5)} = 1.85$, $p = .232$), or the interaction between limb and stimulation intensity was identified ($F_{(6,30)} = .581$, $p = .743$). A significant main effect of stimulation intensity was identified ($F_{(6,10.212)} = 60.7$, $p < .001$), indicating the mean CMEP amplitude increased with increasing stimulation intensity. Pairwise comparisons revealed that CMEP amplitudes at 140 and 150% of AMT were significantly greater than MEP amplitudes at 90, 100, 110, and 120% of AMT ($p < .05$ for all comparisons).

Pre-stimulus EMG CMEPs. No significant interactions were identified for limb ($F_{(1,5)} = 1.03$, $p = .355$), stimulation intensity ($F_{(6,30)} = 1.28$, $p = .295$), or the interaction between stimulation intensity and limb ($F_{(6,30)} = 1.09$, $p = .390$).

3.4.2 Triceps Brachii

3.4.2.1 MEP Slope

Group data for the triceps MEP slope is illustrated in Figure 6A. For the triceps MEP SRC no significant difference between the slopes was evident ($z = -1.01$, $p = .310$).

3.4.2.2 *MEP Amplitude*

For the triceps brachii, group data indicated no significant effect for limb ($F_{(1,6)} = .523$, $p = .497$), and the interaction between limb and stimulation intensity ($F_{(1.889,11.333)} = 1.49$, $p = .266$). A significant effect for stimulation intensity ($F_{(6,36)} = 164.0$, $p < .001$) was identified. Pairwise comparisons revealed that mean MEP amplitudes were significantly different between each stimulation intensity greater than 90% ($p < .05$ for all comparisons), with the exception of no significant differences between 90 and 100% ($p = .126$), 120 and 130% ($p = .998$), and between 140 and 150% stimulation intensities ($p = .949$).

Pre-stimulus EMG for MEPs. No significant effects were found for limb ($F_{(1,6)} = .34$, $p = .583$), stimulation intensity ($F_{(2.240,13.441)} = .57$, $p = .599$), or the interaction between the two factors ($F_{(1.586,9.518)} = .43$, $p = .621$).

3.4.2.3 *CMEP Slope*

In figure 4B, group CMEP SRC for the triceps at the 6 o'clock position is shown. Group mean CMEP slope is presented Figure 6B. No significant difference between the limbs was evident (non-dominant triceps (*Mdn* =1.79) and dominant triceps (*Mdn* = 1.72); $z = -.734$, $p = .463$).

3.4.2.4 *CMEP Amplitude*

Group data indicated no significant effect for limb ($F_{(1,6)} = 1.65$, $p = .253$), a significant effect of stimulation intensity ($F_{(6,30)} = 96.6$, $p < .001$), and no significant interaction between limb and stimulation intensity ($F_{(6,30)} = 1.38$, $p = 2.52$).

Pre-stimulus EMG CMEPs. As a group, there was a significant effect of limb ($F_{(1,5)} = 8.08$, $p = .036$), no main effect of stimulation intensity ($F_{(6,30)} = 1.34$, $p = .269$), and a significant interaction between the two ($F_{(6,30)} = 3.47$, $p = .01$). The group data is presented in Figure 6D. Pairwise comparisons indicated that means were significantly different at 100, 110,130, and 140% stimulation intensities ($p < .05$ for all comparisons), but not at 90% ($p =.789$), 120% ($p = .077$), or 150% ($p = .202$).

3.4.3 Vector Force

The dominant arm produced significantly more force at the 6 o'clock position compared to the non-dominant arm, ($t_{(6)} = 2.87$, $p = .028$) indicated by the paired-samples t-test (dominant arm (21.5 ± 9.04 N) vs non-dominant (14.6 ± 3.41 N; Figure 7).

3.4.4 bEMG at 6 o'clock

At the 6 o'clock position there was no significant differences in bEMG between the dominant and non-dominant biceps brachii ($t_{(6)} = 1.36$, $p = .223$) or triceps ($t_{(6)} = -1.83$, $p = .116$) indicated by the paired-samples t-test. Pre-stimulus EMG at 6 was 1.27 ± 1.16 and 0.65 ± 0.76 %M_{max} and 0.64 ± 0.38 and 0.93 ± 0.59 %M_{max}, for the biceps and triceps, respectively.

3.5 Discussion

There were two main observations from this study. First, during arm cycling, corticospinal and spinal excitability projecting to the dominant and non-dominant biceps and triceps brachii did not differ. Second, at the 6 o'clock position the dominant arm produced significantly more force compared to the non-dominant during arm cycling.

3.5.1 Bilateral modulation of corticospinal and spinal excitability

At the 6 o'clock position it was found that corticospinal (MEP) and spinal (CMEP) excitability projecting to the biceps and triceps brachii did not differ between the dominant and non-dominant limbs (representative MEP and CMEPs; Figures 1 and 2) during arm cycling.

Significant effects of intensity for MEPs and CMEPs were found for the biceps and triceps brachii ($p < .001$ for all comparisons), indicating that mean MEP or CMEP amplitude increased as stimulus intensity increased. Since our constructed SRC's using MEP and CMEP amplitudes started at 90% of AMT and increased in 10% increments until 150% of AMT, it is predictable that mean amplitude would increase in a similar fashion. We observed no significant interaction effects between limb and intensity were detected for either muscle for MEP or CMEP amplitude. The slopes of the SRC's were also compared bilaterally using a Wilcoxon-signed rank test, no observed differences between the limbs were present for either the biceps or triceps.

The finding of similar MEP and CMEP amplitudes and lack of significant differences between the SRC slopes the results of this study inferred that CSE projecting to the limbs is equal, a finding that disagreed with our initial hypothesis. We hypothesized that CSE would be greater to the muscles of the dominant limb compared to the non-dominant. The consideration for this hypothesis stems from plasticity of the human motor system in response to long-term motor sequences. For example, previous work has found motor units in the dominant FDI have been shown to be more excitable, characterized by lower recruitment thresholds and lower average firing rates (Adam et al., 1998). Lower recruitment thresholds for eliciting MEPs in the dominant biceps brachii and abductor pollicis brevis have been shown in left and right-handers (William J. Triggs et al., 1994). On the other hand, using a similar stimulus-response technique, Daligadu and colleagues (2013) demonstrated a greater slope to the non-dominant motor hemisphere for elicited MEPs in the first dorsal interosseous for left and right-handers. An important distinction is the previously aforementioned results were determined while participants were at rest, performing isometric contractions, or simple manual performance tasks, which differ significantly compared to an asynchronous locomotor task like arm cycling. (Forman et al., 2014).

With regard to our comparison of CSE measures bilaterally, no measurable differences were found between the limbs. One possible influence as to why asymmetries were not present between the limbs could be the intrinsic influence of the CPG during a rhythmic motor output like cycling. At the onset of locomotion, descending commands increase the excitability of spinal interneurons causing them to oscillate and recruit motoneurons to produce rhythmic motor output (Klarner & Zehr, 2018; Power et al., 2018). The CPG will likely play a larger operational role during cycling compared to a tonic contraction. Specifically, the degree of excitatory input needed to recruit and maintain motoneurone firing to produce the locomotor motion is likely less during cycling. The activation of these networks is substantially reduced, or even absent during non-locomotor tasks (Power et al., 2018). Given this, the task (arm cycling) may have influenced our results. It could be hypothesized that the increased CPG contribution during a rhythmic locomotor task like arm cycling could decrease the likelihood of side-to-side differences given the increased intrinsic excitability during cycling. For instance, at the 6 o'clock position during arm cycling it has been shown that MEP and H-reflex amplitudes were significantly smaller than when compared to a position and intensity-matched contraction (Carroll et al., 2006b). At the 3 o'clock position, H-reflexes were larger during a tonic contraction compared to cycling, and MEPs remained unchanged. Thus, these findings demonstrated a decrease in the motor cortex's influence during arm cycling in comparison to performing a tonic contraction (Carroll et al., 2006b) likely due to the spinal CPG influence during arm cycling (Power et al., 2018). However, it is unclear whether arm cycling had any influence on the lack of bilateral differences in CSE between the dominant and non-dominant limbs.

In relation to bilateral asymmetries during locomotion, cyclists are a widely researched group. The methods used to examine torque and/or force output in most studies is done so under the assumption that performance is symmetric between the legs (Carpes, Mota, et al., 2010). In our study, we demonstrated that the dominant arm (figure 6) contributed significantly more to overall power output at the 6 o'clock position compared to the non-dominant, with no observed significant differences in CSE. One potential reason no observed bilateral difference in CSE was not seen could be due to our low cycling workload (25 W). Generally, MEP and CMEP amplitudes will increase in size until a peak during isometric contractions (Martin et al., 2006; Taylor et al., 1997), we have also shown this during arm cycling across multiple power outputs (Lockyer et al., 2019). It is possible the workload our participants cycled at was not demanding enough to detect any significant differences in CSE measures between the limbs.

Interhemispheric cortical communication is another putative mechanism that may explain our lack of bilateral differences in CSE between the limbs. In cycling studies, when pedaling workload is increased there is an improvement in pedaling symmetry (F. P. Carpes et al., 2007; Felipe P. Carpes, Diefenthaeler, et al., 2010; Liu & Jensen, 2012b; Sanderson, 1991; Sanderson et al., 2000). This symmetry is likely related to the influence of fatigue on motor unit recruitment, where muscle fatigue coinciding with incremental exercise leads to a common bilateral input (Boonstra et al., 2008). The increase in common bilateral input is due to facilitated excitability (Glass, 2001) through interhemispheric cortical communication (Carpes, Diefenthaeler, et al., 2010; Carpes, Mota, et al., 2010) which is among factors minimizing larger lateralized differences (Anguera et al., 2007; Seidler & Noll, 2008; Teixeira & Caminha, 2003). Although, a common bilateral input resulting in less lateralized differences is unlikely to have occurred in our study due to the relatively easy cycling workload at 25 W. Perhaps this may be due to the differing degree of bilateral coupling between the arms and legs concerning the neural regulation of rhythmic movement, where coupling between the arms is not as strong compared to the legs (Klarner & Zehr, 2018).

3.6 Differing bEMG level between the triceps

Given the observation of similar CSE measures between the limbs, it is useful to assess pre-stimulus EMG to the musculature to gauge the level of muscle activity. In this study, MEP and CMEP pre-stimulus EMG was measured 50 ms prior to the stimulus. Equal levels of background EMG were present for each comparison with one exception, CMEP pre-stimulus EMG significantly differed between the dominant and non-dominant triceps brachii. Figure 6A illustrates that bEMG was significantly greater to the non-dominant triceps brachii. From this, it can be inferred that background activity of the non-dominant triceps brachii was greater despite no mean difference in CMEP CSE between the triceps.

The difference in CMEP pre-stimulus to the dominant and non-dominant triceps brachii can perhaps be explained by a difference in motor coordination between the triceps. At the 6 o'clock position the triceps brachii is relatively inactive, whereas the biceps brachii is most active (Lockyer et al., 2018). To propel the arm cranks forward during arm cycling both limbs will need to work in an asynchronous fashion. The results of this study suggest that the non-dominant triceps had increased musculature activity at the 6 o'clock position. In comparison to the dominant limb, it could be inferred that the non-dominant triceps was not as efficient.

Manual asymmetries can stem from anatomical asymmetries within the brain (Amunts et al., 1996; Annett, 2002). Concerning cortical representations, the dominant hand has been shown to occupy a larger representation, compared to the non-dominant (Hammond, 2002; Volkmann et al., 1998). Regarding motor control processes two chief hypothesis posited included: 1) processing feedback of the dominant hand is more efficient compared to the non-dominant hand, 2) motor output of the dominant hand is less variable compared to the non-dominant (Richard G. Carson, 1989). For example, rapid finger tapping is a motor task that has been commonly used for the assessment of motor control. A consistent finding is an asymmetry between the hands; tapping is faster and less variable in the dominant hand (Carlier et al., 1993; Hammond et al., 1988; Hubel et al., 2013; Schmidt et al., 2000). Therefore, if greater efficiency and speed is expected in the dominant triceps it is possible that less neural input is required to perform the same motor output in comparison to the non-dominant triceps.

There are likely several factors contributing to the disparity of level of activity between the triceps, however it is likely connected to long-term plasticity of the motor system. Greater habitual use of the dominant arm (triceps) could prompt use-dependent plasticity in the corticospinal tract (Holland et al., 2015; Sawaki, 2005) and greater motor efficiency of that limb compared to the non-dominant. Additionally, we only measured from the lateral head of the triceps brachii a monoarticular muscle, not regarding the influence of the long and medial head of the triceps brachii (Spence et al., 2016). In previous work from our lab we have also shown a dissociation between EMG and CSE regarding the triceps (Spence et al., 2016). Spence et al. (2016) noted no phase-dependent difference in CSE between elbow flexion and extension despite a significant phase-dependent difference in pre-stimulus EMG amplitude (larger during elbow extension). This finding suggests that changes in overall CSE relates to a difference in central motor command rather than changes in central motor drive where TMS-evoked MEP amplitudes may not necessarily relate to changes in triceps activity (Spence et al., 2016). Although no differences in CSE were seen in the triceps despite a difference in bEMG, it is important to note that this study did not include a full sample (n = 7).

3.7 Vector Force – CSE

The results from the current study show that during arm cycling at the 6 o’clock position the dominant limb produced a greater vector force than the non-dominant limb (Figure 7), with no bilateral differences in CSE. This result suggests that the dominant limb had a greater pushing and/or pulling motion during the locomotor output. This finding agreed with one of our initial hypotheses, where it was expected the dominant limb would contribute more to overall force output compared to the non-dominant. Despite that the dominant limb produced an overall greater vector force we questioned; “why did CSE measures not show the same trend?”

The relationship between CSE and force will be heavily dependent upon the type of task performed. Specifically, spinal motoneurone properties will behave differently whether the motor output is rhythmic and alternating, or tonic in nature (Power et al., 2018). Generally, it is agreed that CSE will increase as the strength of an isometric contraction increases (evident via enhancement of MEPs) until a plateau is reached, follow by a consequent decrease in excitability as maximal isometric contraction strength is reached, a similar pattern is seen with spinal excitability with the modulation of CMEPs (Gelli et al., 2007; Lévénez et al., 2008; Martin et al., 2006b; Oya et al., 2008; Taylor et al., 1997; Todd et al., 2003).

For instance, at submaximal contraction intensities there appears to be a linear relationship between MEP amplitude and force (Oya et al., 2008; Pearcey et al., 2014). However, in the aforementioned studies isolated contractions of a specific muscle in either the upper- or lower limb. A relationship between CSE and force can certainly be concluded during an isometric task, but this begs the question: does force and CSE share a similar relationship during a locomotor output?

Compared to a tonic contraction, force at the 6 o’clock position during arm cycling is not constant. Thus, it would be expected that force would be more variable during arm cycling assuming EMG activity is recorded from the biceps brachii. In this study, EMG activity was collected only from the biceps and the lateral head of the triceps brachii, and vector force was modeled from the entirety of the upper limb. Therefore, these results must be interpreted with some limitations in mind. First, arm cycling is a whole-body systemic exercise, and a complicated muscle-joint movement. Many muscles are active to produce the cycling motion in addition to the biceps and lateral head of the triceps brachii including: brachioradialis, latissimus dorsi, stabilizers (Chaytor et al., 2020). Thus, we are limited to only the data provided by EMG activity of the biceps and triceps brachii. Second, given the complex relationship that CSE exhibits during locomotion with factors such as workload, intensity, and the muscles examined all influencing its modulation, it should be stressed that the strength of a relationship between force output and CSE during locomotion may not be very strong.

A secondary objective to this project was to identify whether a relationship between CSE and force was evident during arm cycling. Differences in the mechanical efficiency between the dominant and non-dominant limbs is a putative mechanism that could explain why no concurrent increase in CSE was seen with greater vector force in the dominant arm. To gain better insight, bEMG at the 6 o'clock position was determined (average of 14 frames) for the biceps and triceps and normalized to M_{max}.

A paired t-test indicated no significant difference in pre-stimulus EMG at the 6 o'clock position for either the biceps or triceps (Figure 7). However, for the biceps brachii it can be seen that bEMG was ~ 65% greater for the dominant bicep, however for the triceps brachii bEMG was ~ 37% greater to the non-dominant triceps. In the case of the biceps, the greater bEMG values were accompanied with greater vector force for that arm. Thereby, implying that the dominant agonist muscle (biceps) during the pulling phase of the arm cycle movement had twice as much activity compared to the antagonist (Figure 7). The opposite was found for the triceps, where the non-dominant triceps brachii had greater activity at the 6 o’clock position during arm cycling. Together, these findings suggest a bilateral asymmetry in the production of the arm cycling movement. At the 6 o’clock position during arm cycling it appears the biceps brachii of the dominant arm, and the triceps brachii of the non-dominant arm are antagonistic in terms of central drive required to produce EMG levels.

3.8 Methodological Considerations

A couple of factors should be considered in the assessment of the results from this study. First, our data is gathered from a sample of n = 7, rather the intended sample of n = 12 participants. Resultantly, we have decreased statistical power from the data set (Field, 2017), and therefore limitations are present concerning observations that can be made about the results. In addition, it is important to note the small sample set may not be fully representative of the population. The second factor that should be considered is how the vector force – CSE relationship is classified in this study. Vector force classification is modeled as the total force applied to the left and right arm cranks while cycling at 25W and 60 RPM. However, we only measured CSE from the biceps brachii and lateral head of the triceps brachii. This can be problematic for a couple of reasons. For example, we are limited to only comparing the vector force (z), excluding the other orthogonal components; the normal – Fy and anterior-posterior – Fx. In addition, CSE is represented only by the muscles we chose to measure from, while there are numerous other muscles in the upper limb that contribute to arm cycling. Thus, our vector force – CSE relationship is not all encompassing.

Another factor that should be considered is evoked potential amplitudes at a sub-threshold stimulation intensity. If you refer to figures 3 and 4 it will be noticed that at 90% AMT there were recorded evoked potentials. Meaning, our SRC curves were likely closer to AMT (100%) at this intensity. However, our statistical analyses for slope calculations did not include measures at 90% AMT and therefore had no influence concerning SRC slope analyses.

3.9 Conclusion

This present study demonstrates that CSE projecting to the biceps and triceps brachii did not differ between the dominant and non-dominant limbs during arm cycling. Vector force generation at the 6 o'clock position was significantly greater to the dominant limb compared to the non-dominant. Whether a relationship between CSE and force generation during arm cycling remains unknown, the results of this study suggest not. Future studies should explore bilateral assessment of CSE and torque production during arm cycling in x, y, and z directions during a range of workload and cycling intensities.

3.10 FIGURE LEGEND

Figure 1. Representative MEP and CMEP amplitudes from the biceps brachii at the 6 o'clock position during arm cycling (*n* = 1). Average MEPs (top row) and CMEPs (bottom row) traces from the dominant and non-dominant sides at 110% of threshold intensity. **(A)** MEP amplitudes were 7.8% and 10.7% of maximum for the dominant and non-dominant sides, respectively. **(B)** CMEP amplitudes were 10.7% and 14.7% of maximum for the dominant and non-dominant sides, respectively.

Figure 2. Representative MEP and CMEP amplitudes from the triceps brachii at the 6 o'clock position during arm cycling (*n* = 1). Average MEPs (top row) and CMEPs (bottom row) traces from the dominant and non-dominant sides at 140% of threshold intensity. **(A)** MEP amplitudes were 68.0% and 100% of maximum for the dominant and non-dominant sides, respectively. **(B)** CMEP amplitudes were 100% and 100% of maximum for the dominant and non-dominant sides, respectively.

Figure 3. Group SRC data during arm cycling at the 6 o'clock position for (A) MEP amplitude SRC for the biceps brachii (mean ± SE, n = 7), and (B) CMEP amplitude SRC for the biceps brachii (mean ± SE, n = 6). The x-axis represents the stimulation intensity, which is made relative to the participants motor threshold, where 100% represents either MEP or CMEP threshold. The y-axis represents MEP or CMEP amplitude as a percentage of the maximum recorded. The black curve represents MEPs or CMEPs elicited from the dominant limb, while the grey curve from the non-dominant limb during arm cycling.

Figure 4. Group SRC data during arm cycling at the 6 o'clock position for (A) MEP amplitude SRC for the triceps brachii (mean ± SE, n = 7), and (B) CMEP amplitude SRC for the triceps brachii (mean ± SE, n = 6). The x-axis represents the stimulation intensity made relative to the participants motor threshold, were 100% is either MEP or CMEP threshold. The y-axis represents MEP or CMEP amplitude as a percentage of the maximum amplitude recorded. The black curve represents MEPs or CMEPs elicited from the dominant limb, while the grey curve from the non-dominant limb during arm cycling.

Figure 5. Group data during arm cycling at the 6 o'clock position for (A) MEP SRC slopes of all muscles examined (mean ± SE, n = 7), (B) CMEP SRC slopes for all muscles examined (mean ± SE, n = 6), (C) MEP pre-stimulus EMG (mean ± SE, n = 7) for all muscles examined, and (D) CMEP pre-stimulus EMG (mean ± SE, n = 6). * denotes a significant difference between the dominant and non-dominant limb.

Figure 6. Group data (mean ± SE, n = 7) for the vector force output from the dominant and non-dominant limb. The y-axis represents the limb force output measured in Newtons. *denotes a significant difference between the dominant and non-dominant limb.

Figure 7. Group data (mean ± SE, n = 7) for background EMG (all frames) at the 6 o'clock position during arm cycling for the dominant and non-dominant biceps and triceps brachii. Background EMG is represented as a percentage of M_{max}.

3.11 List of Tables

Table 1. Raw and normalized data for the biceps brachii, and triceps brachii at the 6 o'clock position during arm cycling.

	Biceps Brachii		**Triceps Brachii**	
	Dominant	Non-Dominant	Dominant	Non-Dominant
MEP				
- **peak-to-peak, mv**	11.38 ± 5.23	13.54 ± 9.18	5.26 ± 1.49	4.36 ± 1.76
- **Peak-to-peak, mv**	2.84 ± 2.45	3.0 ±2.42	0.52 ± 0.38	0.57 ± 0.38
- **SRC Slope**	1.98 ± 0.26	1.80 ±0.32	1.72 ± 0.09	1.62 ± 0.26
- **Pre-stimulus EMG, mv**	0.128 ± 0.01	0.127 ± .009	0.03 ± .002	0.03 ± .001
- **Pre-stimulus EMG, % of M$_{max}$**	1.44 ± 0.08	1.53 ± 0.01	0.77 ± 0.06	0.84 ± 0.03
CMEP				
- **Peak-to-peak, mv**	1.93 ± 1.78	2.03 ± 1.66	0.52 ± 0.42	0.53 ± 0.34
- **SRC slope**	1.71 ± 0.12	1.74 ± 0.35	1.65 ± 0.21	1.80 ± 0.27
- **Pre-stimulus EMG, mv**	0.123 ± 0.01	0.120 ± .007	0.03 ± .002	0.03 ± .003
- **Pre-stimulus EMG, % of M$_{max}$**	1.42 ± 0.18	1.24 ± 0.14	0.59 ± 0.06	0.78 ± 0.09
Force				
	Dominant			Non-Dominant
- **Vector Force, N**	23.4			14.6

3.12 LIST OF FIGURES

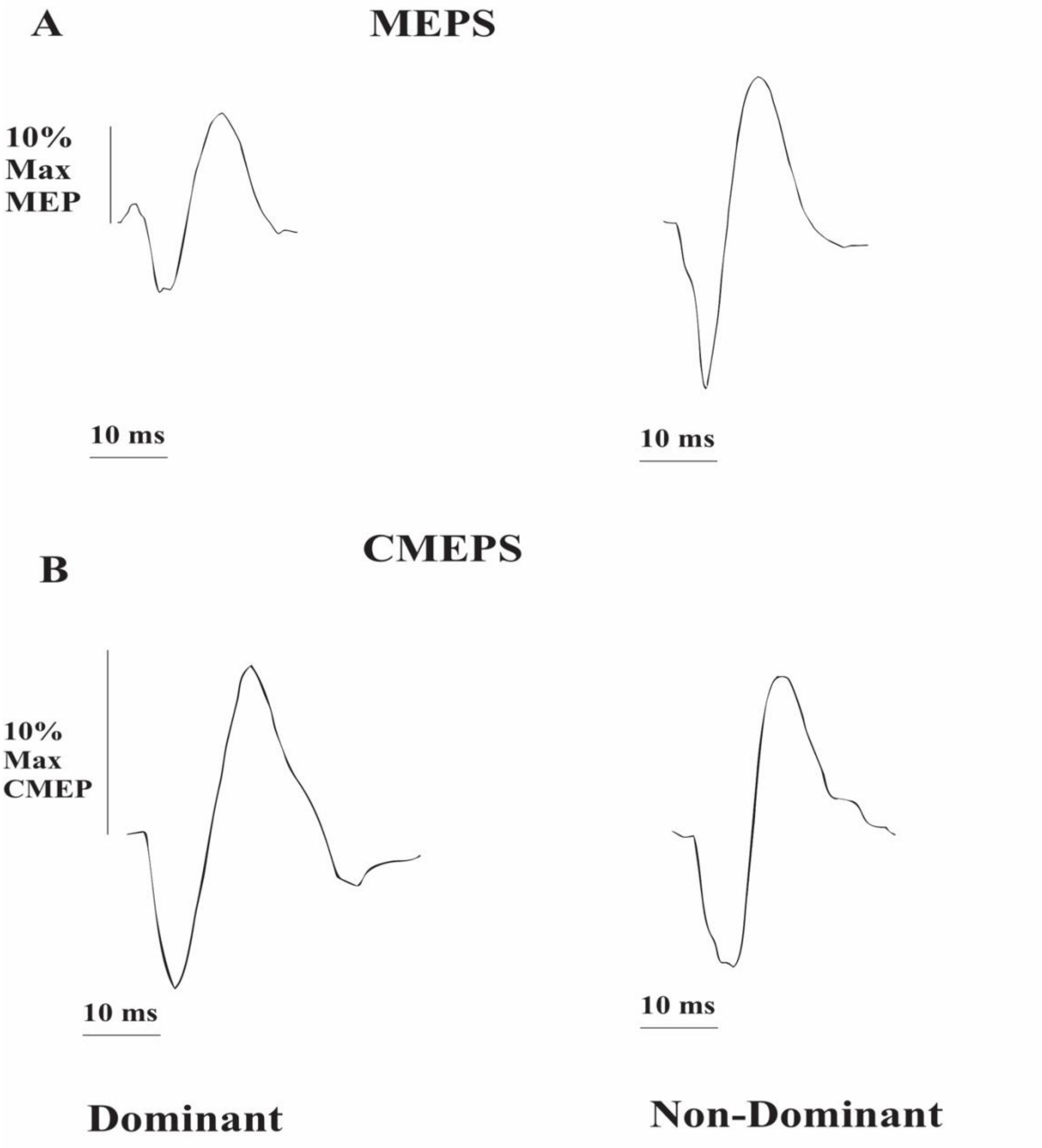

Figure 1. Representative MEP and CMEP amplitudes from the biceps brachii at the 6 o'clock position during arm cycling (n = 1). Average MEPs (top row) and CMEPs (bottom row) traces from the dominant and non-dominant sides at 110% of threshold intensity. ***(A)*** *MEP amplitudes were 7.8% and 10.7% of maximum for the dominant and non-dominant sides, respectively.* ***(B)*** *CMEP amplitudes were 10.7% and 14.7% of maximum for the dominant and non-dominant sides, respectively.*

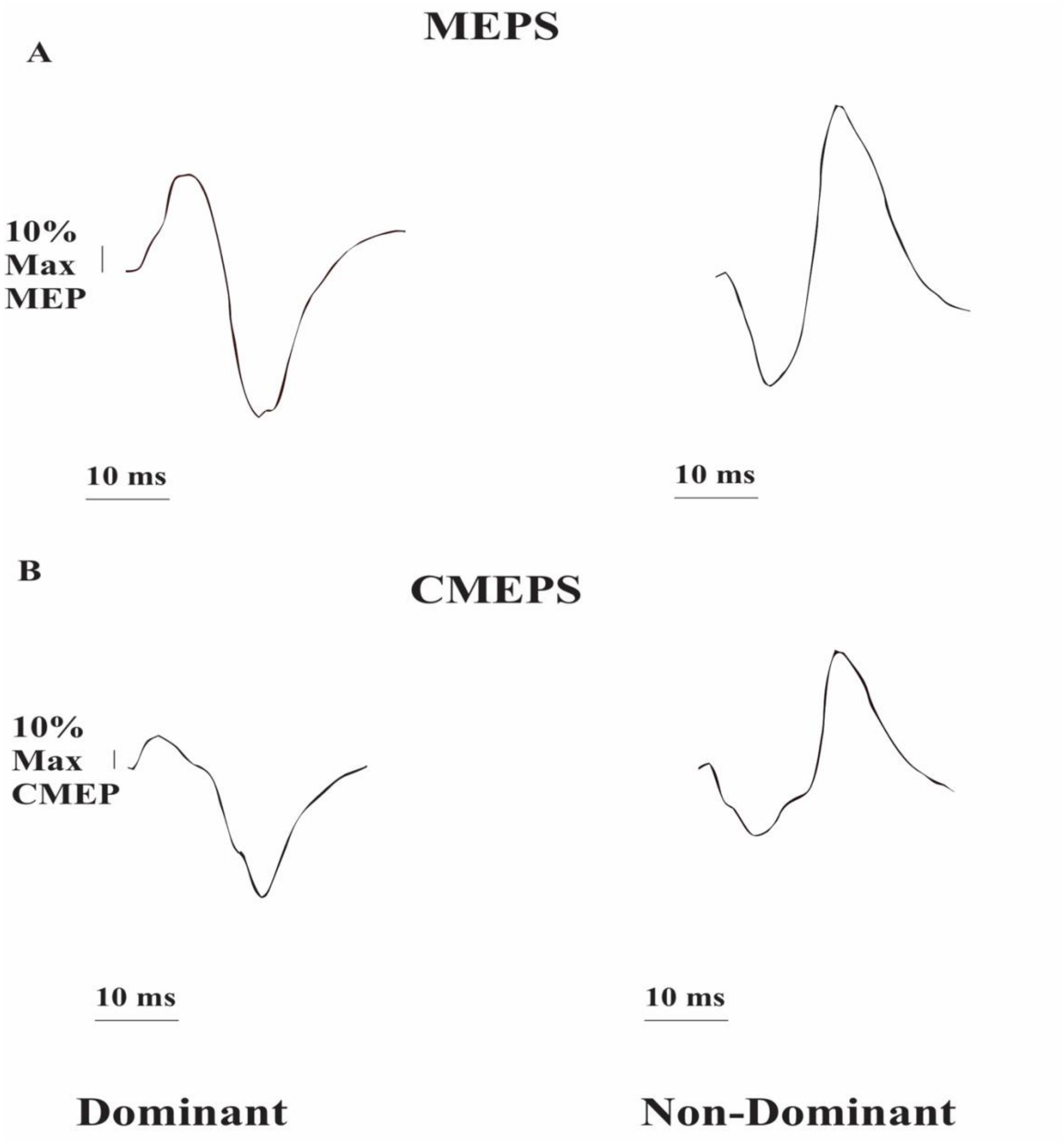

Figure 2. Representative MEP and CMEP amplitudes from the triceps brachii at the 6 o'clock position during arm cycling (n = 1). Average MEPs (top row) and CMEPs (bottom row) traces from the dominant and non-dominant sides at 140% of threshold intensity. (A) MEP amplitudes were 68.0% and 100% of maximum for the dominant and non-dominant sides, respectively. (B) CMEP amplitudes were 100% and 100% of maximum for the dominant and non-dominant sides, respectively.

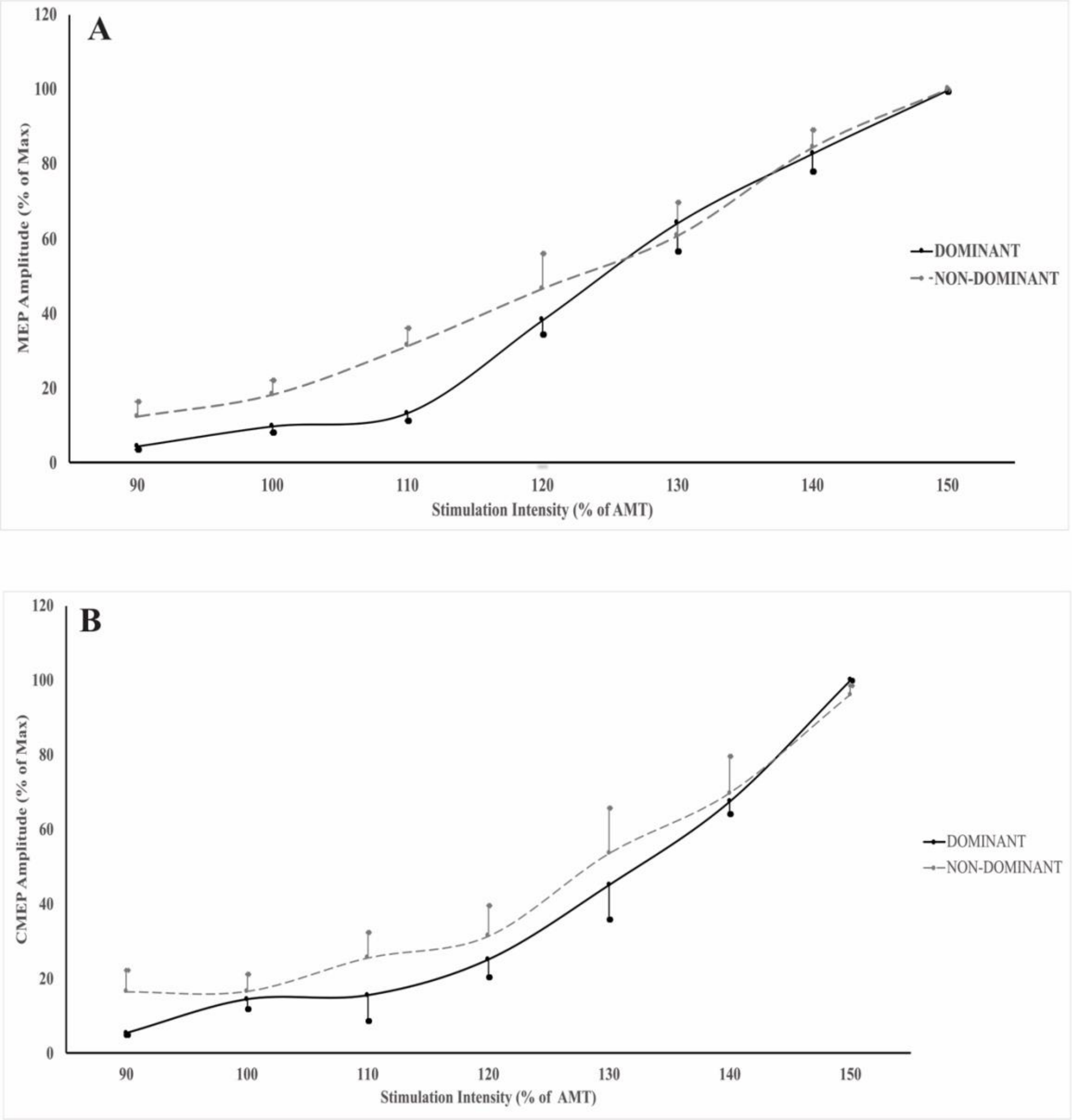

Figure 3. Group MEP (mean ± SE, n =7) and CMEP (mean ± SE, n = 6) SRC during arm cycling at the 6 o'clock position for the biceps brachii.

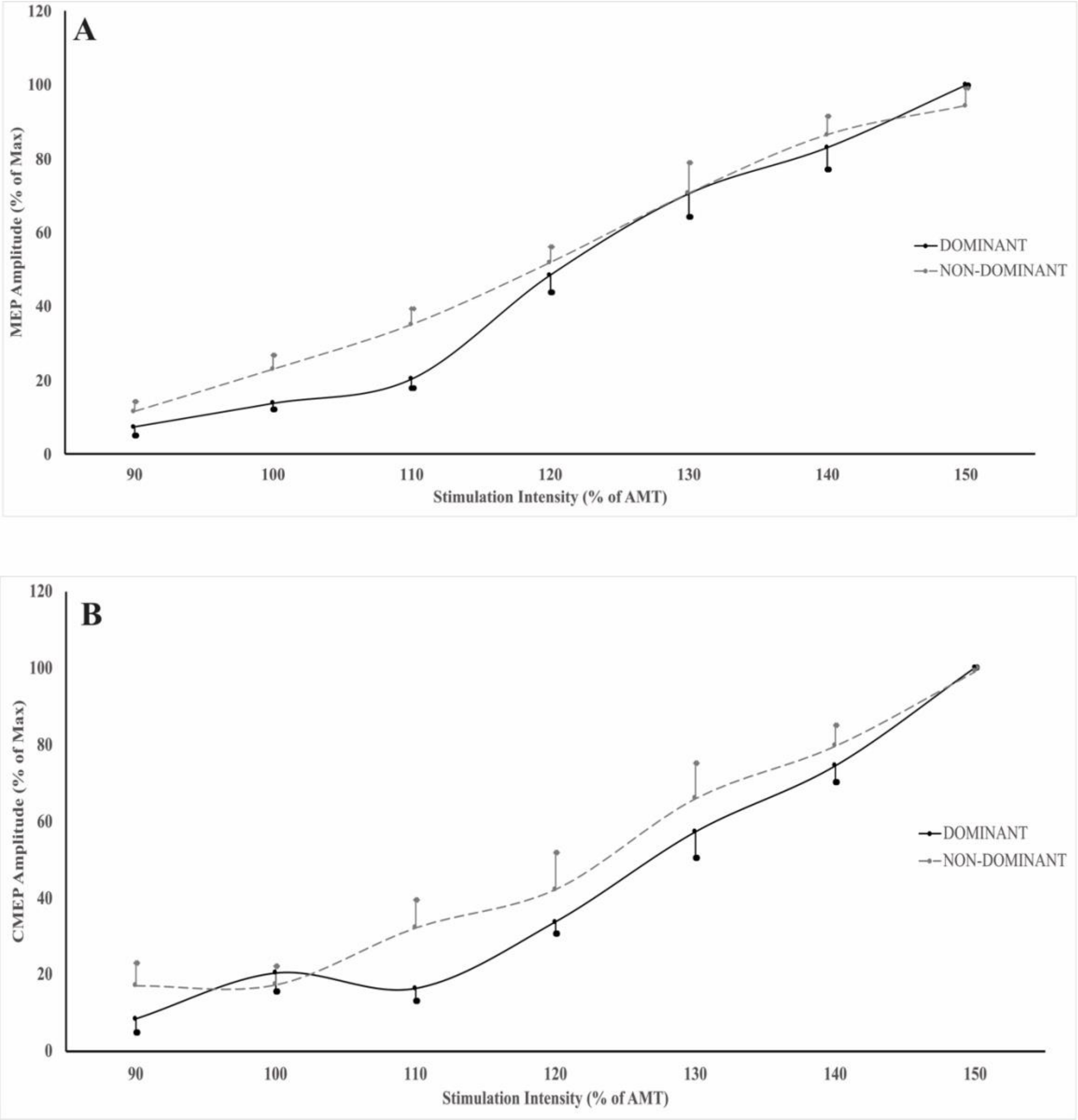

Figure 4. Group MEP (mean ± SE, n =7) and CMEP (mean ± SE, n = 6) SRC during arm cycling at the 6 o'clock position for the triceps brachii.

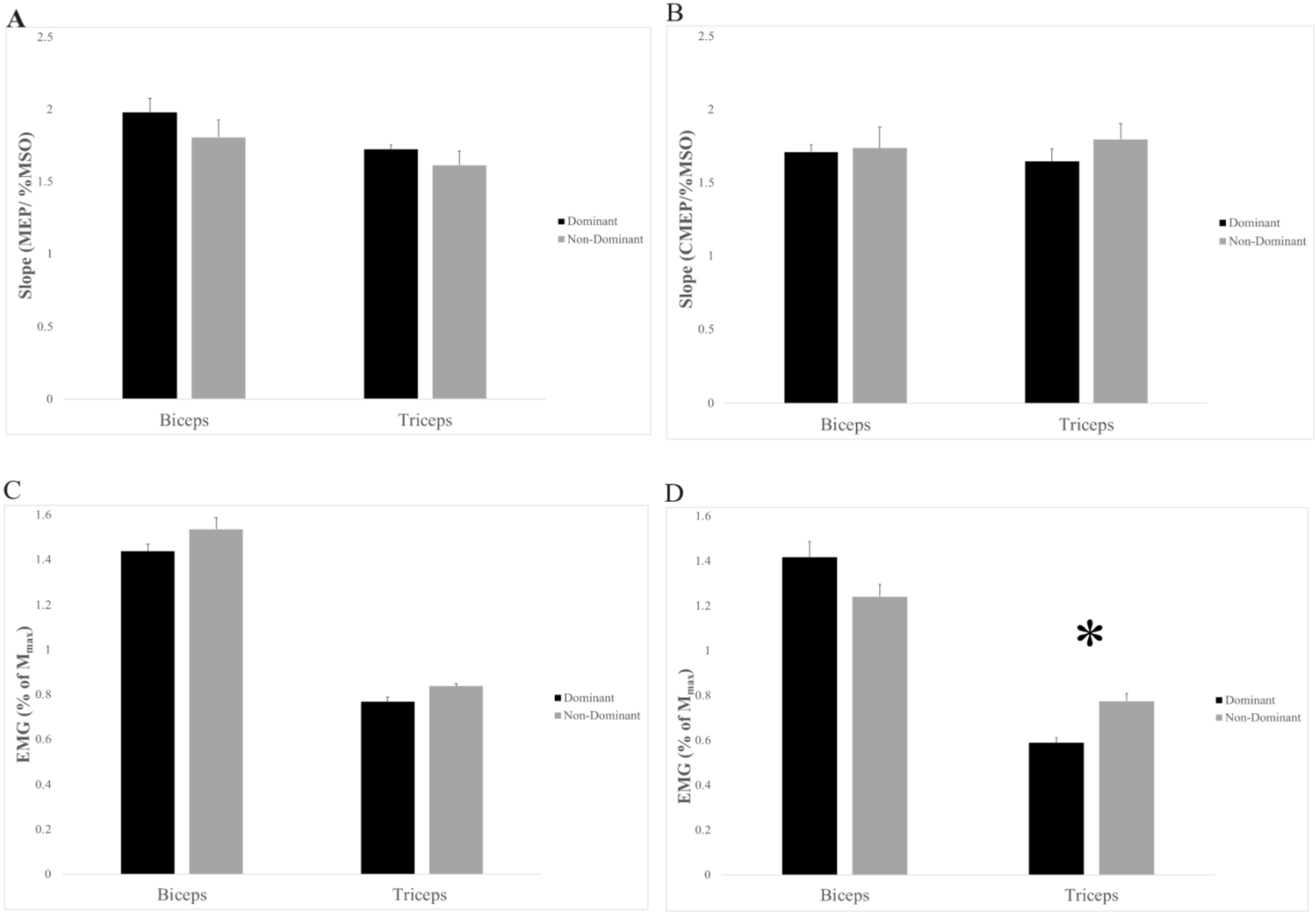

Figure 5. Group slope and pre-stimulus EMG for MEPs and CMEPs during arm cycling at the 6 o'clock position.

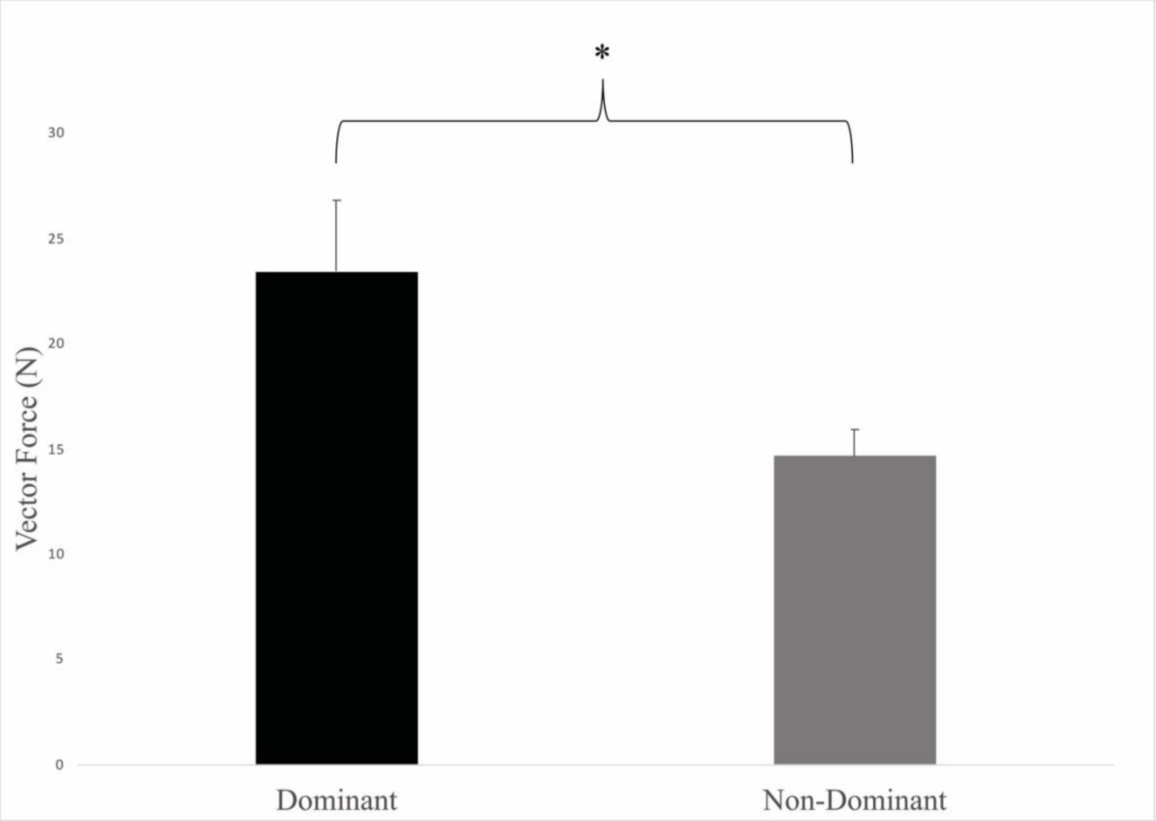

Figure 6. Group vector force output for the limbs during arm cycling at the 6 o'clock position.

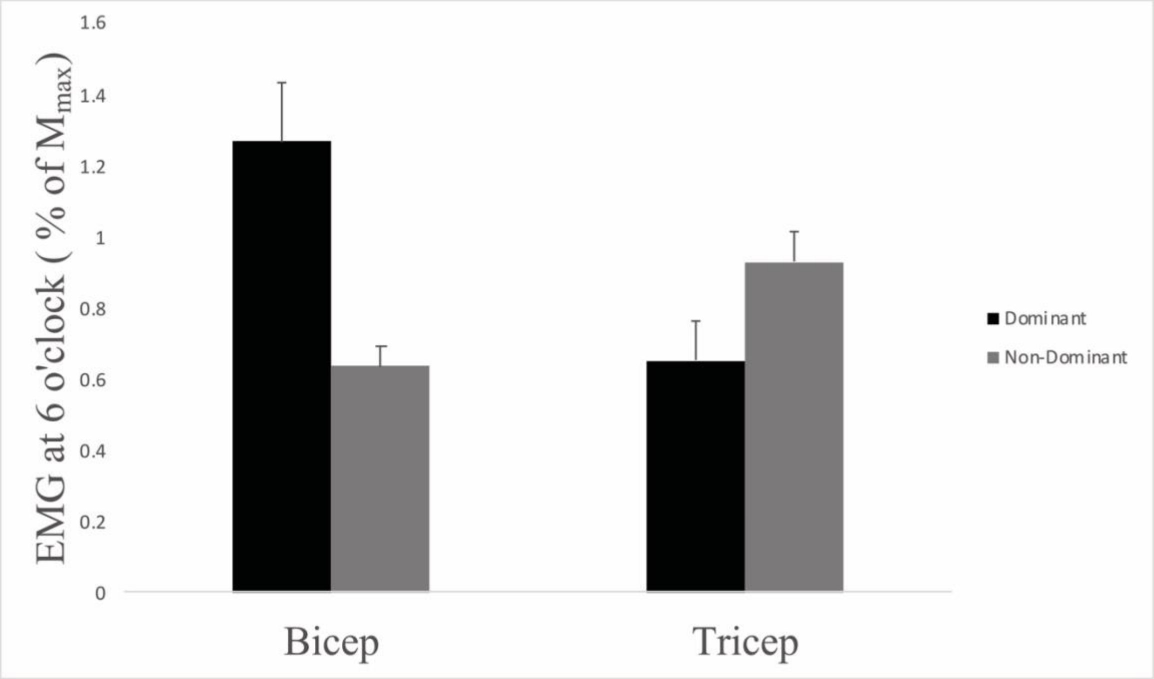

Figure 7. bEMG at the 6 o'clock position during arm cycling for the biceps and triceps brachii.

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4 Future Directions

Research examining how the brain and spinal cord contribute to the production of locomotor outputs in humans is not only important for the advancement of our understanding of bipedal locomotion but may also have clinical applications in the field of rehabilitation and performance. In the present study, we examined corticospinal excitability bilaterally to muscles of the upper limbs while arm cycling. The findings of this study add to our understanding of bilateral interactions in corticospinal excitability and mechanical force generation during a locomotor output. Future works should attempt to characterize bilateral interactions between force generation and corticospinal excitability measures during rhythmic locomotor outputs. This may include assessment of different muscles, various workloads, and cadences during cycling. This type of research could provide a better understanding of a potential relationship between corticospinal excitability and force generation as well as the bilateral modulation of corticospinal excitability during locomotor output, which remains largely uncharacterized. This research has clinical applications in the field of neurorehabilitation, where techniques and rehabilitation strategies may be developed for those with central nervous system disorders. Application of this research may also be beneficial for coaches and athletes in terms optimal force effectiveness during cycling. For example, pedalling retraining using augmented feedback of pedal forces can help increase overall force effectiveness on the efficiency and performance of the athlete (during bicycling).

The present study had limitations in terms of our understanding of bilateral assessment of corticospinal excitability and vector force generation. In our current data set not all the data was available. In this thesis, our sample size included an n = 7. Currently, more data collection is currently underway to help strengthen and enhance our statistical power. Once the sample size is enhanced, we aim to investigate whether corticospinal excitability and force generation is correlated during arm cycling. This would also include examining force in the x and y directions in addition to the vector force. The strength study could have also benefitted from measuring from more than one position than just 6 o'clock. From this, we are limited to inferring what is occurring during mid-elbow flexion, rather than extension as well. Thus, future work is warranted to gain a better understanding of bilateral modulation of corticospinal and spinal excitability during arm cycling.