Assessment of Corticospinal Excitability during Synchronous and Asynchronous Arm Cycling

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A Thesis submitted to the

School of Graduate Studies

In partial fufilment of the requirement for the degree of

Master of Science in Kinesiology

School of Human Kinetics and Recreation

Memorial University of Newfoundland and Labrador

December 2023

St. John's, Newfoundland and Labrador

ABSTRACT

Arm cycling is a rhythmic locomotor output which has a wide range of use both in clinical and for research purposes. In most cases, asynchronous arm cycling mode is usually used. In recent researches, there are direct and indirect evidences to show that arm cycling, like other forms of human locomotor output, is produced by supraspinal inputs, spinally located specialized set of neurons called the central pattern generators (CPGs) and somatosensory inputs. The excitability of the corticospinal tract during arm cycling has been investigated when there are changes in cadence and load, but none has investigated corticospinal excitability during asynchronous and synchronous arm cycling. Given that corticospinal excitability has been shown to be task dependent, there is possibility that neural control mechanisms during asynchronous arm cycling might not be the same during synchronous arm cycling. Also, previous experimental researches done in rhythmic non-locomotor output have hinted that rhythmic movement might be biased towards the synchronous mode as cadence or frequency of movement increases. Hence, the primary aim of this research is to investigate changes in corticospinal excitability during asynchronous and synchronous arm cycling at different cycling cadences.

Land Acknowledgement

We respectfully acknowledge the territory in which we gather as the ancestral homelands of the Beothuk, and the island of Newfoundland as the ancestral homelands of the Mi'kmaq and Beothuk. We would also like to recognize the Inuit of Nunatsiavut and NunatuKavut and the Innu of Nitassinan, and their ancestors, as the original people of Labrador. We strive for respectful relationships with all the peoples of this province as we search for collective healing and true reconciliation and honour this beautiful land together.

Acknowledgement

My sincere gratitude goes to God Almighty for making this work a success and granting me the grace to complete my programme in this prestigious university. He saw me through the bitter and pleasant times, may all glory, honour and adoration be unto Him.

My sincere appreciation goes to my parents; Prof & Dr (Mrs) J.O. Ogolo and my siblings for their care, advice, sacrifices, encouragement and support morally, financially and spiritually. Thank you for everything, I will forever be grateful to you.

I want to express my profound gratitude to my supervisor, Professor Kevin Power, for his support, love, patience and commitment throughout the course of this study. Despite his busy schedule, he still found time to supervise my research work. I would miss your friendly gestures and unending camaraderie. It has been a priviledge working with you, and I look forward to working with you again in the nearest future.

Futhermore, I will like to show my deep appreciation to my lecturers; Duane Button (Ph.D), Greg Pearcey (Ph.D), Shahab Alizadeh (Ph.D), John Cullen and Evan Lockyer (Ph.Dc), thank you all for the unending love, support and the knowledge you have impacted on me. Also, I want to thank the departmental secretary, Mrs Parsons Peggy-Ann for her support when I was processing my admission into the department of Kinesiology.

Finally, I will like to appreciate all the co-authors of this research; Evan Lockyer, Kate Rait and Farahmand Fattaneh, your support on this project cannot be overemphasized.

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Figure 2.

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LIST OF ABBREVATIONS

TMS- Transcranial Magnetic Stimulation

TMES- Transmastoid Electrical Stimulation

MEP- Motor Evoked Potential

CMEP- Cervicomedullary Motor Evoked Potential

EMG- Electromyography

CPG- Central Pattern Generators

RMT- Resting Motor Threshold

CST- Corticospinal tract

SD- Standard deviation

SE- Standard error

RPM- Revolutions per minute

mV- millivolts

ms- milliseconds

CHAPTER 1 Introduction

1.0 Overview

Arm cycling is employed in research, rehabilitation, sport (i.e. wheelchair) and as a model of locomotion in experimental studies (Zehr, 2005). Research and rehabilitation tend to employ an asynchronous (arms moving in opposite directions - one arm pulls the crank towards the body while the opposing arm pushes the crank away from the body) form while persons with spinal cord injury that self-propel using a manual wheelchair tend to employ a synchronous (arms moving together) form. While most studies have focused on cycling efficiency, and cardiovascular changes that occur during these two cycling modes (Dallmeijer et al., 2004; Hopman et al., 1995; Mossberg et al., 1999), none has compared neurophysiological changes such as corticospinal (brain and spinal cord) excitability using these cycling forms.

Previous experimental studies involving non-locomotor tasks have shown that spontaneous transitions exist between modes of coordination (symmetrical and asymmetrical) while performing rhythmic motor tasks, with symmetrical movements being performed more reliably (Carson, 1995; Kelso et al., 1981; Kelso, 1984; Klapp, 1979; Riek et al., 1992). A study conducted by Cohen (1971) where 12 subjects were asked to perform bimanual wrists movements first synchronously and then asynchronously shows that there is high precision in the coordination of bimanual non-locomotor output when homologous muscle groups are activated simultaneously, compared to when non-homologous muscle groups are activated. The result from this study suggested the existence of a unitary coupling mechanism which facilitates simultaneous action of homologous muscles of the upper limbs (Cohen, 1971). It has also been shown that different areas of the cerebral cortices are activated when performing these different modes of rhythmic motor task. When moving in synchrony (easy rhythm) maps of radial current densities across the scalp indicated activations of the two primary motor cortices (MI). However, when bimanually tapping different rhythms, there

was not only an activation of MI cortices, but a very large activation of the mesial, central cortex was observed (Lang et al., 1990). Locomotor tasks, however, are under a different neural control strategy involving spinally located central pattern generators (CPG) (Barbeau & Rossignol, 1987; Brown, 1911; Forssberg et al., 1980; Sherrington, 1910). In quadrupeds, gait patterns can abruptly change from a less stable "out-of-phase (asymmetric) mode" to a more stable "in-phase (symmetrical) mode" when they move from a "trot" to a "gallop"; to select the best spatiotemporal pattern for muscle activity (Kelso, 1984). Indirect evidence suggests that humans also possess a spinally located locomotor CPG (Calancie et al., 1994; Dimitrijevic et al., 1998; MacKay-Lyons, 2002) that is also active during arm cycling (Power et al., 2018; Zehr et al., 2012). It is presently unclear whether differences in cortical activation or corticospinal excitability differs between symmetrical and asymmetrical modes of arm cycling.

Corticospinal excitability is the overall excitability of the corticospinal pathway. The corticospinal tract is important for the production of voluntary movements in humans and has been shown to be task and cadence specific (Forman et al., 2014; 2015). A study conducted by Forman and colleagues (2014) investigated corticospinal excitability to the biceps brachii during rhythmic motor output (arm cycling) and an intensity matched tonic contraction. They showed that corticospinal excitability was higher during arm cycling than during an intensity matched tonic contraction state (Forman et al., 2014). Subsequent to the above findings, Forman and colleagues (2015) also showed the effect of cycling cadence on corticospinal excitability. In this study, participants were allowed to perform asynchronous arm cycling task at different cadences (30, 60 and 90 rpm) and a fixed workload of 25W. During each cycling trial, corticospinal excitability was measured using transcranial magnetic stimulation (TMS) which recorded motor evoked potential (MEP) from corticospinal neurons, and transmastoid electrical stimulation (TMES) which measured cervico-medullary motor evoked potential (CMEP) from spinal neurons. In this study,

recordings were taken from the biceps brachii at two separate positions corresponding to the elbow flexion and extension phases (6 and 12 'o' clock relative to a clock face, respectively). The results indicated that there was an overall increase in corticospinal excitability to the biceps brachii throughout arm cycling as cadence increased (Forman et al., 2015). No known studies have investigated whether asynchronous and synchronous arm cycling modes are similar or different tasks. Thus, it remains unknown what effect changing arm cycling modes can have on corticospinal excitability. This represents a gap in the literature that is very important to investigate, as it will contribute to our current understanding of how corticospinal excitability is modulated when homologous and non-homologous motor areas of both cerebral hemispheres are activated during rhythmic locomotor tasks.

Determining which mode of cycling results in greater excitability of the corticospinal tract would be beneficial, especially for neuro-rehabilitation where the goal is to increase functional abilty, i.e. to enhance the ability of the nervous system to undergo changes and thus potential functional gains. This study will be the first comparing corticospinal excitability in synchronous and asynchronous forms of arm cycling exercise.

1.1 Purpose of the study

The purpose of this study is to investigate corticospinal excitability during asynchronous and synchronous arm cycling at three different cycling cadences.

1.2 Reseach hypotheses

1. Corticospinal excitability will be greater during synchronous rather than asynchronous arm cycling

2. Corticospinal excitability would increase in both cycling modes as cadence increases

1.3 References

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CHAPTER 2 Review of Literature

2.0 Introduction

Humans engage in different forms of motor activities on a daily basis, such as walking, running and cycling. These activities are considered normal by the human population. As simple as these tasks are, studies have revealed that they are actually mediated by complex spinal and supra-spinal activities (Lockyer et al., 2021; Pearcey & Zehr, 2020). It has been shown that a complex interraction of electrical and chemical (neurotransmitters) actions occur within the brain to stimulate motor circuitry within the brainstem and spinal cord, thus, leading to the overall electrical activation of skeletal motor neurons, thereby causing these seemingly simple tasks to occur (Barter et al., 2014; Fan et al., 2012; Sherrington, 1906). In an attempt to understand this rather complex aspect of human physiology, several experiments have been performed on animals, some of which has proven the involvement of central pattern generators (CPG) present in the spinal circuitry as playing a major role in the mediation of rhythmic activities in animals (Barbeau & Rossignol, 1987; Brown, 1911; Forssberg et al., 1980; Sherrington, 1910). Similarly to animals, some indirect evidences suggest that humans have spinally situated CPG that helps to mediate rhythmic motions such as walking and cycling (Calancie et al., 1994; Dimitrijevic et al., 1998; Klarner & Zehr, 2018; Solopova et al., 2016).

2.1 Corticospinal pathway

The corticospinal pathway is one of the most important tracts present in descending motor pathways responsible for the production of controlled voluntary movement in humans (Nathan & Smith, 1955), and originates in broad regions of the cerebral cortex. Other parts of the descending motor pathways include the rubrospinal, reticulospinal and vestibulospinal tracts which are all known to originate from nuclei in the brainstem. They are assumed to receive inputs from the

corticofugal neurons which are believed to coordinate their activities (Canedo, 1997). The bulk of the corticospinal tract is believed to originate from the precentral gyrus, mainly in its upper two-thirds, and also the paracentral lobule. These cells when excited cause stimulation of the upper limbs (Ferrier, 1876). According to some studies, about 30 percent of the tract originates from the primary motor cortex, about 30% from premotor and supplementary motor areas, while the remainder is thought to arise from non-motor areas such as the somatosensory areas and the parietal cortex (Canedo, 1997). This bundle of close to a million fibers (corticospinal) form an important aspect of the crus cerebri located in the midbrain, and also make up a major part of the posterior limb of the internal capsule. The long axons that run in the cerebrospinal tract descend into the brainstem as part of large fibre bundles called the cerebral peduncles. The long axonal tract continues down into the medulla region of the brain stem where it forms two large collections of axons known as the pyramids; the pyramids create traceable ridges on the external surface of the brainstem. Close to the region of the medulla, about 75 to 90 percent of the descended tract decussate or cross over to opposite sides of the brainstem via the pyramidal decussation (Kamson et al., 2014; Nathan & Smith, 1955; Welniarz et al., 2017).

The decussated tracts are referred to as the lateral corticospinal tract. This tract continues into the spinal cord and tends to cause movement to limbs opposite to the side of the cortex from which it originate. For example, right tract would cause movement on the left limb and vice versa. The remaining 10 percent of the tract that does not decussate is referred to as the anterior (ventral) corticospinal tract. This tract continues down the ipsilateral side of the spinal cord and sends fibres mainly to the trunk and axial muscles (Javed et al., 2023). They have also been observed to finally decussate just before they synapse to the lower motor neurons. Lateral corticospinal tracts have been shown to control the muscles of the opposite limbs while anterior corticospinal tract tend to control the muscles of the trunk, shoulders and neck (Bear et al., 2001; Crossman & Neary, 2004).

The majority (about 55 percent) of the corticospinal fibres terminate at the cervical level, 25 percent terminate at lumbosacral levels while 20 percent terminate at the thoracic level (Crossman & Neary, 2004).

The corticospinal tract helps in the control of motor output by allowing for the passage of information between the brain and the spinal cord. Studies have shown that the corticospinal tract in humans have both polysynaptic and monosynaptic connections with spinal neurons. In the case of monosynaptic, the corticospinal tract connects directly to spinal motor neurons, while in the case of polysynaptic, the corticospinal tract first of all joins to the spinal interneurons (association neurons) before synapsing on the spinal motor neuron (Palmer & Ashby, 1992). The variations in the number of types of these synapses per muscle have been shown to exist as there are more monosynaptic connection in the biceps brachii of the upper limb compared to the triceps brachii (Brouwer & Ashby, 1990; Petersen et al., 2002).

2.2 Assessment of corticospinal excitability

A generalized and effective way of determining the influence or effect of cycling modes on overall motor output is by investigating the excitability of the corticospinal pathway. The corticospinal pathway is a complex interaction of the motor cortex and spinal motor neurons which form a major descending tract that is involved in the voluntary control of human motor outputs (Canedo, 1997; Nathan & Smith, 1955). The corticospinal pathway is composed of spinal and supra-spinal motor neurons or tracts which helps to regulate voluntary motor actions. Corticospinal excitability can be assessed using the TMS. While using a TMS, a MEP is recorded. Measuring the amplitude of the MEP gives an overview of the excitability mediated by the entire corticospinal pathway.

TMS is delivered using a bi-directional electromagnetic coil which generates a magnetic field that passes through the cranium. The coil is placed tangentially to the vertex (midpoint) of the head. Once a charge of appropriate intensity is delivered, cortical interneurons are activated which in turn activate the cortical motoneurons. These cells constitute the starting point of the descending corticospinal tract which synapse either to the spinal interneurons or directly on to the spinal motoneurons. In cases of polysynaptic pathways, spinal interneurons might synapse with more than one interneuron before finally synapsing on to the spinal motoneurons. The spinal motor neurons send action potentials along the peripheral nerves that run directly into the muscle to which it innervates (Klomjai et al., 2015). This constitute the synaptic pathway to which a muscle is activated when induced by electromagnetic impulses from TMS. The peak-to-peak amplitude of the MEP generated is used to estimate corticospinal excitability (Klomjai et al., 2015).

In this study, we expect to carry out different tasks, i.e. synchronous and asynchronous cycling, and investigate their effects on corticospinal excitability using TMS. If there are any effect, we intend to note them and discuss various reasons for the observed changes. This study would be the first of its kind and would be investigating some concepts that have never been investigated in human motor neural control.

2.3 Why use arm cycling?

The majority of human motor control investigations are usually conducted in an isometric or rest state. This is understandable because according to the famous Russian scientist Nikolai Bernstein, who is considered to be the father of modern-day motor control research, he noted that a person never performs a movement the same way twice, this he summarized in his “Bernstein’s sentiment of repetition without repetition” (Bernstein, 1996). This dynamics in human movement he considered to be as a result of variability in the neural control of movement. The change itself is

good for humans because it allows us to perform movements at various limited conditions and environment, i.e. because of this inherent ability, we tend to devise new and optimum motor control skills to an appropriate motor problem. However, the variability in the neural control creates complexities for researchers while trying to investigate and understand neural motor control. In most cases, during experimentation, this observation (i.e. large variability in neural motor control in humans) create a significant level of background noise (i.e. random disturbance to the electrical signals observed during data collection) which tend to impair the results of the experiment (Lockyer et al., 2021). Thus, in order to mitigate this challenge, researchers in this area of specialization always prefer to carry out experiments while participants are at rest or during isometric exercises, as this tends to limit the observed level of background noise. As good as this may sound, this tends to limit our understanding of the neural control of human movement.

Overall, human movement is considered to be dynamic. In order to really understand locomotive movement in humans, we would need to simulate a relative rhythmic pattern of movement which would tend to limit background noise and overall variability during experimental sessions. In humans, from a neural control perspective, the control of all rhythmic movements can be summed up to be the complex interaction of three basic neural controls, namely spinal central pattern generators, somatosensory feedback from moving limbs and supra-spinal inputs (Pearcey & Zehr, 2020). This tripartite control system is common to all rhythmic motor task, thus, an investigation of a task such as locomotion can be generalized to all other tasks such as swimming, running, crawling and cycling (Lockyer et al., 2021; Zehr, 2005; Zehr et al., 2016). The fact that a core neural component is general to all makes movement neuroscience researchers confident that the result obtained from studying a rhythmic task could be generalized to all other rhythmic motor tasks (Lockyer et al., 2021). In many of the researches done on corticospinal excitability in our lab, we have proven that arm cycling can be used as a model for human locomotion. Zehr and colleagues

have also shown from their studies for the past 20 years that arm cycling can be used to explain rhythmic motor output such as locomotion in humans (Zehr et al., 2016).

Arm cycling has also been used in several researches to study neural control of rhythmic motor output in persons with neurological impairments (Kaupp et al., 2018; Zehr et al., 2012; Zhou et al., 2018). Its usefulness in training people with neurological impairments has also made it good to be used for research purposes. Lockyer and colleagues also indicated that one major reason why arm cycling is advantageous over walking in studying neural control is its relative ease of use for people with neurological impairments such as hemiparesis (in which case the weak hand could be strapped to the wheel and allowed to move passively), and also that it could be performed under various conditions (i.e. various loads and cadences) where the head, neck and torso remain relatively still, minimizing the effect of background noise on the overall result. They however pointed out that a major limitation to using arm cycling as a model of human locomotion is that walking necessitates propulsion from the leg to ensure forward progression during upright balance preservation whereas arm cycling do not, thereby reducing demand for neural resources to maintain balance during arm cycling. This limitation is noted, but would however not cancel out several advantages and relatable characteristics that exist between cycling and walking with the major one being the fact that they are both mediated by the complex interaction of the three basic neural controls (Lockyer et al., 2021; Zehr, 2005; Zehr et al., 2016).

2.4 Synchronous vs asynchronous arm cycling

Asynchronous arm cycling mode (i.e. arms moving in opposite directions - one arm pulls the crank towards the body while the opposing arm pushes the crank away from the body) is the

most common arm cycling mode used both for training people with neurological impairments (especially for cardiorespiratory purposes) and also for research purposes (Celli, 1994; D. Forman et al., 2014; D. A. Forman et al., 2015; Hardison et al., 1987; Power et al., 2018; Powers et al., 1984; Weissland et al., 1997; Zehr, 2005; Zehr et al., 2012; Zehr & Duysens, 2004). In clinical setting, when arm cycling is used to rehabilitate patients with neurological impairments (i.e. in cases of stroke and spinal cord injury), one of the goals is to increase corticospinal excitability as this has been linked to increased intra-cortical activities (reduced intra-cortical inhibition) and ultimately improved functional abilities (Liepert et al., 2000; Tatemoto et al., 2019; Ziemann, 2001). However, there is been no studies to show that asynchronous cycling mode generates a higher corticospinal excitability compared with synchronous cycling mode. The utilization of asynchronous movement pattern during arm ergometry investigations could most likely result from the fact that arm cycle ergometers emerged from modified leg cycle ergometers (Mossberg et al., 1999). This cycling mode is considered innate due to the fact that a toddler begins crawling in an asynchronous manner immediately from infancy. Also, the natural walking mode in humans is done in an asynchronous form, a manner in which opposite legs performs opposite actions in opposite directions at the same time. Many researches that aim to study the basic neural controls involving human locomotion tend to simulate human rhythmic motor output using this cycling mode.

The majority of the investigations carried out using synchronous movements have been done using rhythmic non-locomotor output such as bilateral finger tappings and wrist movements (Baldissera et al., 1991; Cohen, 1971; Haken et al., 1985; Kelso, 1981, 1984; Lang et al., 1990; Riek et al., 1992). Most of this works in behavioural sciences which aim to investigate the action of the brain in maintaining stability. For example, in a study conducted by Kelso (1981a), participants were asked to rhythmically oscillate their index fingers in an horizontal plane (i.e. adduction-abduction) using one of two modes, i.e. in-phase or anti-phase. In the in-phase mode,

homologous muscle groups were activated simultaneously while in the anti-phase mode, the muscles contract in an alternating form. Participants were asked to follow a pacing metronome whose oscillating frequency was systematically increased from 1.25Hz to 3.50Hz in steps of 0.25Hz which lasted up to about 10secs. They were asked to produce one full movement cycle with each finger for each beat of the metronome. In this study, it was observed that when participants began with the anti-phase mode, there was spontaneous change to the in-phase mode at a certain critical frequency of oscillation. This change was observed not to revert even when the oscillating frequency was reduced (i.e. participants continued in the symmetrical in-phase mode of oscillation even when frequency was reduced). There was no change observed when participants started with the in-phase mode of oscillation. They hypothesized that a "switch mechanism" which has neural origin but currently still poorly understood was involved in the phase transition that occurred. In their conclusion, they noted that coordinated transistion appeared to have occurred because of the continuous scaling influence (increased oscillatory frequency) that rendered the previous movement mode (anti-phase) unstable, then at a critical point (frequency), bifurcation occurred and a new stable (and perhaphs energetically more efficient) mode arose (Kelso, 1981, 1984).

2.4.1 Corticospinal excitability during arm cycling

Corticospinal excitability has been assessed during various motor outputs, including arm cycling and has been shown to be task and phase dependent (Forman et al., 2014; Kalmar, 2018; Power et al., 2018). For example, a study conducted by Forman and colleagues where they investigated supra-spinal and spinal excitability to the biceps brachii during rhythmic motor output (arm cycling) and an intensity matched tonic contraction showed that corticospinal excitability was higher during arm cycling than during an intensity matched tonic contraction state. In this study, they also noted that supra-spinal excitability were higher at the onset of elbow flexion, mid flexion and elbow extension phase while spinal motoneurone excitability increased only during the onset

of elbow flexion and was not significantly different from tonic contraction during mid elbow flexion and elbow extension phases. From this study, they concluded that corticospinal excitability is task and phase dependent (Forman et al., 2014).

Corticospinal excitability has also been shown to be muscle dependent (Forman et al., 2019; Spence et al., 2016). For example, in a study conducted by Spence and colleagues (2016), they noted that there was phase dependent modulation of corticospinal excitability to the biceps brachii muscle while there was no change observed in the corticospinal excitability both in the flexion and extension phases of the triceps brachii muscle. They suggested that the observed difference might suggest that these antagonistic muscles might be under different neural control mechanism during arm cycling (Spence et al., 2016). Even though few studies have shown the impact of task, phase and muscle groups on the modulation of corticospinal excitability during rhythmic locomotor output (arm cycling), there is however a dearth of experimental study on the influence of cycling modes on corticospinal excitability in rhythmic locomotor output.

Given that arm cycling is a bilateral, rhythmic motor output, one must consider how the limbs influence each other. It has also been known for some time that limbs do not operate independently, as there is influence of one on the other; an example of such interlimb neural connections is the cross extension reflex (Sherrington, 1910). The concept of crossed facilitation has been established even though it's mechanism of action is not yet fully understood. It has been shown that activation of a musculature during voluntary tonic contraction on one limb leads to increased excitability of contralateral homologous motor pathway (Carson et al., 2004; Cernacek, 1961; Hortobágyi et al., 2003). Given the fact that corticospinal excitability is considered to be task specific, a study was conducted in our lab by Lockyer and colleagues in which the influence of activity on one limb on corticospinal excitability to the contralateral limb during a rhythmic locomotor output was examined. In this study, it was observed that there reduced corticospinal

excitability during bilateral arm cycling compared to when the dominant limb was at rest. This suggested the possibility of crossed inhibition during bilateral (asynchronous) arm cycling as opposed to crossed facilitation that might have occurred when the dominant arm of participants was kept at a state of rest (Lockyer et al., 2020). If bilateral asynchronous arm cycling resulted in the activation of intra-cortical inhibitory neurons, should we also assume that this would be the case when cycling both arms synchronously? Hence the reason for this study. There is evidence to support that rhythmic non-locomotor movement modes (i.e. either synchronous or asynchronous) can have effect on corticospinal excitability (Stinear & Byblow, 2002), but no known study has been done to investigate corticospinal excitability using both modes in arm cycling exercise (i.e. rhythmic locomotor output).

2.5 Intensity-dependent cycling

The intensity of arm cycling can be adjusted by making changes in the cadence and/or load output (i.e. cadence and workload together make up power output). Cadence has been shown to play a major factor in the somatosensory processing of information during human locomotion (Capaday & Stein, 1987; Ferris et al., 2001; Simonsen & Dyhre-Poulsen, 1999) and when cycling is used as a form of human locomotive motor output (Staines et al., 1997). The use of a fixed cadence during experiments helps to retain concentration in participants (i.e. they have to observe their cadence on the ergometer monitor). This is a form of directed visual attention which has been shown to increase neural activity in the brain, as evidenced in functional magnetic resonance imaging (Kastner et al., 1999). Majority of studies on arm cycling performed in our lab are usually done using fixed cadences and workloads. However, there have also been times when workload and/or cadence were changed for experimental purposes (Forman et al., 2015; Lockyer et al., 2018, 2020; Spence et al., 2016). Changes in cadences have been shown to affect stretch reflex (i.e. H-

reflex). A study conducted by Ferris and colleagues reported suppression of H-reflex gains during running compared to walking (Ferris et al., 2001). Also, increase in leg cycling cadences tends to suppress the amplitude of somatosensory evoked potential and H-reflex (Staines et al., 1997). In addition, an increase in leg cycling cadence has also been shown to have effect on muscles, i.e., increasing load and pedaling rate led to inhibition in EMG activity of the soleus muscle. This likely reflects the need of reducing inhibition of the soleus muscle motoneurons to ensure a sufficient activation of the muscle during bicycling. (Pyndt et al., 2003).

Forman and colleagues (2015) showed the effect of cycling cadence on corticospinal excitability. In this study, participants were allowed to perform asynchronous arm cycling task at different cadences (30, 60 and 90 rpm) and a fixed workload of 25W. During each cycling trial, corticospinal excitability was measured using TMS which recorded motor evoked potential (MEP) from corticospinal neurons, and TMES which measured cervico-medullary motor evoked potential (CMEP) from spinal neurons. Also, muscle excitability was measured using peripheral nerve stimulation. In this study, recordings were taken from the biceps brachii at two separate positions corresponding to the elbow flexion and extension phases (6 and 12 ‘o’ clock relative to a clock face, respectively). The results indicated that there was an overall increase in corticospinal excitability to the biceps brachii throughout arm cycling as cadence increased. However, the changes that occurred in spinal excitability as cadence increased were noticed to be phase dependent, i.e., it increased during elbow flexion and decreased during elbow extension. This they suggested might be due to the fact that there is decreased reciprocal inhibition to the biceps brachii during elbow flexion (i.e. increased motoneurone excitability) and increased reciprocal inhibition to the biceps brachii during elbow extension, leading to reduced spinal motoneurone excitability (Forman et al., 2015). Spence and colleagues (2016) investigated corticospinal excitability to biceps and triceps brachii while increasing workload during asynchronous arm cycling. The result from this study shows that there

is an overall increase excitability in the corticospinal and spinal motoneurons in both muscle groups with an increase in workload intensity. In this study, it was observed that even though corticospinal excitability was higher during the flexion phase of the biceps brachii compared to the extension phase (i.e. phase dependent), it was not phase dependent in the triceps brachii muscle. Another rather interesting observation made in this study was that spinal motoneuron excitability to the triceps brachii was higher during the flexion phase of cycling compared to the extension phase. This is termed unusual considering the fact that the triceps brachii muscle is more active during the extension phase of arm cycling compared to the flexion phase. In this study, several putative mechanisms thought to be responsible for the observed variations in the triceps brachii muscle were discussed, including the idea that during the flexion phase, the triceps brachii muscle is stretched, leading to the activation of persistent inward currents (PICs) (Wilson et al., 2015) which in turn amplifies synaptic inputs to the spinal motoneuron pool, thus, reducing the need for supra-spinal input to the muscle. The result from this study further corroborate the fact that corticospinal excitability is intensity and muscle dependent (Spence et al., 2016). Also, a study conducted by Lockyer and colleagues (2018) where he made changes to cadence and workload (i.e. power output) revealed that intensity type (either cadence or power output) differentially modulate spinal and supra-spinal excitability in a manner that is phase and muscle dependent (Lockyer et al., 2018).

There has been no known study to investigate the effect of different cycling intensities during synchronous cycling mode, neither has there been any form of comparison between the two cycling modes. The previous evidences shown in the work of Spence et al (2016) and Forman et al (2015) that increasing cycling intensity tend to increase overall corticospinal excitability cannot be generalized, as these studies were done while only considering asynchronous cycling mode.

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CHAPTER 3: Assessment of Corticospinal Excitability during Synchronous and Asynchronous Arm Cycling

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3.0 ABSTRACT

This is the first study to assess corticospinal excitability during synchronous and asynchronous arm cycling modes. Corticospinal excitability to the biceps and triceps brachii was assessed using transcranial magnetic stimulation (TMS) of the motor cortex. Motor evoked potentials (MEPs) were evoked during the mid-flexion position of arm cycling across two modes; (1) synchronous (Sync) and (2) asynchronous (Async) cycling at three different cadences; 30, 60 and 90rpm. The power output was kept constant at 30watts throughout the cycling trials. In the biceps brachii muscle, TMS-induced motor evoked potential (MEP) amplitudes were significantly higher during the synchronous mode compared to the asynchronous arm cycling mode ($F_{(1,10)}$ = 12.18, $p < 0.05$). However, MEP amplitudes were not significantly different between both modes in the triceps brachii muscle at the mid elbow flexion phase of arm cycling. There was also no significant difference in the corticospinal excitability to both muscles between the two modes as the cycling cadence increased from 30 to 90rpm (i.e. no interaction effect between mode and cadence). In line with our previous studies, we observed that MEP amplitudes increased as the cycling cadence increased from 30 to 90rpm in both the biceps brachii ($F_{(2,20)}$ = 12.92, $p < 0.01$) and triceps brachii ($F_{(2,20)}$ = 6.314, $p < 0.05$). We suggest that the observed higher corticospinal excitability observed during sync mode in the biceps brachii might be due to increased interhemispheric facilitation (cortical spread) or reduced interhemispheric inhibition at the cortical level.

Key words: MEP, motor cortex, transcranial magnetic stimulation

3.1 Introduction

Arm cycling is used to study the neural control of rhythmic motor output in healthy humans (Power et al., 2018; Zehr, 2005) and persons with neurological impairments (Kaupp et al., 2018; Zehr et al., 2012; Zhou et al., 2018). The use of arm cycling in neuro-rehabilitative medicine cannot be over-emphasized as it has been shown that arm cycling has both neurological and cardiorespiratory benefits (Dallmeijer et al., 2004; Hopman et al., 1995; Klarner et al., 2014, 2016; Mossberg et al., 1999). Research and rehabilitation tend to employ an asynchronous (arms moving in opposite directions - one arm pulls the crank towards the body while the opposing arm pushes the crank away from the body) form (Celli, 1994; Hardison et al., 1987; Kaupp et al., 2018; Power et al., 2018; Powers et al., 1984; Weissland et al., 1997; Zehr, 2005) while persons with spinal cord injury that self-propel using a manual wheelchair tend to employ a synchronous (arms moving together) form. In the clinical setting, when cycling is used to rehabilitate patients with neurological impairments (i.e. in cases of stroke and spinal cord injury), the goal is to improve overall functionality. It has been shown that skillful cycling induced a significant reduction in short interval intracortical inhibition (SICI) in the lower extremity motor cortex area, and this could be used to improve gait function in neurorehabilitation (Tatemoto et al., 2019). In addition, it has also been shown that arm cycling improves walking, physical performance and neurophysiological integrity after stroke (Kaupp et al., 2018). However, no studies have been done to compare synchronous with asynchronous arm cycling, and thus, we currently don't know whether the basic neural control between these two modes differ or not. Also, we do not know which of the two modes would be more beneficial in terms of neuro-rehabilitation.

Previous experimental studies involving non-locomotor tasks have shown that spontaneous transitions exist between modes of coordination (synchronous and asynchronous) while performing rhythmic motor tasks, with symmetrical movements being performed more reliably (Carson, 1995;

Kelso et al., 1981, 1984; Klapp, 1979; Riek et al., 1992). In a study conducted by Kelso (1981a), participants were asked to rhythmically oscillate their index fingers in a horizontal plane (i.e. adduction-abduction) using one of two modes, i.e. synchronous (in-phase) or asynchronous (anti-phase). In the synchronous mode, homologous muscle groups were activated simultaneously while in the asynchronous mode, the muscles contract in an alternating form. It was observed that when participants began with the asynchronous mode, there was spontaneous change to the synchronous mode at a certain critical frequency of oscillation. He hypothesized that a "switch mechanism," which has neural origin but still poorly understood, was involved in the phase transition that occurred. In his conclusion, he noted that coordinated transition appeared to have occurred because of the continuous scaling influence (increased oscillatory frequency) that rendered the previous movement mode (anti-phase) unstable, then at a critical point (frequency), bifurcation occurred and a new stable (and perhaps energetically more efficient) mode arose.

Although the cause of the change in coordination is not well understood, Kelso (1981a) likened this observed phenomenon to what is usually observed in quadrupeds when they change from a "trot" to a "gallop",i.e. walking to running. When quadrupeds increase movement speed, there is usually a gait transition from asynchronous (anti-phase) to synchronous (in-phase) mode. He suggested that this observed gait transition in quadrupeds might be related to the activation of central pattern generators (CPGs) which are spinally located and help select the best spatiotemporal pattern for muscle activities during rhythmic movements (Kelso, 1981, 1984). However, even though index-finger oscillation test performed by participants in the study is rhythmic, it cannot be considered to be a locomotor output, thus, the observed phase transition from asynchronous (anti-phase) to synchronous (in-phase) movement mode as oscillatory frequency increased might not have been due to the activation of spinal CPGs, as these specialized neural cells are usually activated during rhythmic locomotor outputs.

In a study where 12 neurologically intact participants were asked to perform arm cycling movement at different cycling frequencies using an uncoupled hydrodynamic arm ergometer, it was observed that as cycling frequency increased, there tend to be a shift from an asynchronous cycling to a synchronous arm cycling mode. The concept of inter-arm coupling mechanism (where synchronous cycling provides a greater neural coordination compared to asynchronous arm cycling) was suggested, and the possibility that this mechanism tried to restore the stability which had been perturbed by the continuous scaling frequency by changing the cycling mode to a more stable synchronous arm cycling was discussed. However, it was suggested that more research is needed in this area to further ascertain the activities of rhythmic locomotor neural control mechanisms in selecting the best movement pattern for a given locomotor output (Vasudevan & Zehr, 2011).

Corticospinal excitability, which is the overall excitability of the corticospinal pathway, is responsible for the production of voluntary movements in humans and has been shown to be task and cadence specific (Forman et al., 2014; 2015). A study conducted by Forman and colleagues (2014) investigated corticospinal excitability to the biceps brachii during rhythmic motor output (arm cycling) and an intensity matched tonic contraction. They showed that corticospinal excitability was higher during arm cycling than during an intensity matched tonic contraction state (Forman et al., 2014). Subsequent to the above findings, Forman and colleagues (2015) also showed the effect of cycling cadence on corticospinal excitability. In this study, participants were allowed to perform asynchronous arm cycling task at different cadences (30, 60 and 90 rpm) and a fixed workload of 25W. During each cycling trial, corticospinal excitability was measured using transcranial magnetic stimulation (TMS) which recorded motor evoked potential (MEP) from corticospinal neurons, and transmastoid electrical stimulation (TMES) which measured cervico-medullary motor evoked potential (CMEP) from spinal neurons. In this study, recordings were taken from the biceps brachii at two separate positions corresponding to the elbow flexion and

extension phases (6 and 12 ‘o’ clock relative to a clock face, respectively). The results indicated that there was an overall increase in corticospinal excitability to the biceps brachii throughout arm cycling as cadence increased (Forman et al., 2015). No known studies have investigated whether asynchronous and synchronous arm cycling modes are similar or different tasks. Thus, it remains unknown what effect changing arm cycling modes can have on corticospinal excitability. This represents a gap in the literature that is very important to investigate, as it will contribute to our current understanding of how corticospinal excitability is modulated when homologous and non-homologous motor areas of both cerebral hemispheres are activated during rhythmic locomotor tasks.

Research examining the influence of arm cycling modes on corticospinal excitability has not been conducted. In this study, we investigated corticospinal excitability (using transcranial magnetic stimulation) while participants cycled; (1) asynchronously (2) synchronously, each at three different cadences (30, 60 and 90 rpm). We hypothesized that (1) corticospinal excitability to the biceps brachii muscle would be higher during synchronous compared to the asynchronous mode at the elbow flexion phase of arm cycling (2) corticospinal excitability would be significantly different between both cycling modes as cadence increased.

3.2 METHODS

3.2.0 Ethical approval

The procedures of the experiment were verbally explained to each volunteer prior to the start of the session. Once all questions were answered, written consent was obtained. The study was conducted in accordance with the Helsinki declaration and approved by the interdisciplinary Committee on Ethics in Human Research at Memorial University of Newfoundland (**ICEHR no.**

20230109-HK). Procedures were in accordance with the Tri-Council guideline in Canada, and potential risks were fully disclosed to participants.

3.2.1 Participants

Eleven healthy volunteers (10 males, 1 female; ten right-hand dominant, one left-hand dominant; 25.8±6.2 years of age, height = 175.4 ± 7.6 cm, weight = 82.5 ± 24.7 kg) partook in this study, participants had no known history of neurological impairments or injury. Prior to the experiment, all volunteers completed a magnetic stimulation safety checklist to screen for contraindications to magnetic stimulation (Rossi et al., 2009). Edinburg Handedness Inventory was used to determine hand dominance of participants (Veale, 2014). Also, the Physical Activity Readiness Questionnaire (PAR-Q) was used to screen participants for any contraindication to physical activity (Warburton et al., 2011).

3.2.2 Experimental setup

Participants who had not participated in any of our prior studies in the lab went through a familiarization session prior to the experimental session. Day 1. The familiarization session was used to expose potential participants to the stimulation paradigms (peripheral nerve stimulation and TMS) to ensure they were comfortable with the protocols. Day 2 was the testing/experimental day. A complete description of the protocols and consent form was administered prior to the experimental session.

During the experimental session, participants were asked to perform arm cycling using an arm cycle ergometer (SCIFIT ergometer, model PRO2 Total Body, Tulsa, Oklahoma, USA), maintaining a comfortable distance from the hand pedals so as to avoid undue reaching and changes in trunk posture during cycling. The seat height was adjusted so that the shoulders of each individual were approximately the same height as the center of the arm crank shaft. Participants wore wrist braces so as to limit the amount of wrist flexion and extension during cycling thereby reducing the

influence of heteronymous reflex connections that exist between the wrist flexors and the biceps brachii (Manning & Bawa, 2011). Each Participant was strapped securely to the ergometer seat with straps placed over the chest so as to ensure that posture was maintained throughout all trials. Participants gently gripped the ergometer handles with the forearms in a neutral position.

As with our previous work (Forman et al., 2015; Lockyer et al., 2018; Spence et al., 2016), we define positions during arm cycling relative to the face of a clock with reference to the dominant arm. Hence, movement from 3 o' clock to 9 o' clock defined the elbow flexion phase while from 9 o' clock to 3 o' clock defined the elbow extension phase. In relation to this study, all measurements were taken from the dominant arm while it was at the 6 o' clock position relative a clock face, which is also referred to the "bottom dead center". This position during arm cycling coincides with the mid-elbow flexion, where the biceps brachii is most active and there is minimal activity from the triceps brachii.

Participants in this study were required to cycle in two distinct modes (asynchronous and synchronous) at three distinct cadences (30, 60, and 90rpm) each while maintaining a constant workload of 30W. Six distinct trials were performed with measurements taken at the 6 o'clock position. The order of these trials were randomized and responses were automatically created as the arm crank passed by the six o'clock position of arm cycling.

3.2.3 Electromyography (EMG) recordings

Participants underwent EMG preparation i.e. light skin abrasion for the removal of dead epithelial cells (using shaving stick) and cleansing with an isopropyl alcohol swab. After undergoing EMG preparation, pairs of disposable Ag-AgCl surface electrodes (MediTrace 130 Foam Electrodes with conductive adhesive hydrogel; Covidien IIC) were used to record EMG signals from the biceps and triceps brachii of the dominant limb. These electrodes were positioned

on the belly of the biceps brachii and on the lateral head of the triceps brachii. A ground electrode was positioned on the lateral epicondyle of the dominant arm. EMG was collected at 5 KHz using CED 1401 interface and Signal 5 [Cambridge Electronic Design (CED) Ltd., Cambridge, United Kingdom] software program. Signals were amplified (gain of 300) and filtered using a 3-pole Butterworth filter with cutoff frequencies of 10-500Hz.

3.2.4 Stimulation conditions

3.2.4.1 Brachial plexus stimulation

Participants were given a constant current stimulation which caused an electrical stimulation of the brachial plexus at Erb's point (stimulator model DS7AH, Digitimer Ltd., Welwyn Garden City, Hertfordshire, United Kingdom). The stimulation intensities ranged from 100 to 300mA using 200μs pulse duration. This was used to elicit compound muscular action potentials (M-waves) during the course of the study. The anode was placed on the acromion process, and the cathode in the supraclavicular fossa. The initial stimulation intensity was set at 25mA and gradually increased until maximum M-wave (M-max) was achieved. Because M-max can alter within the course of an experiment (Crone et al., 1999), the stimulation intensity was increased by 20% to ensure that M-max was evoked throughout the course of the investigation. After the experiment, the M-max was used to normalize the MEP amplitudes during each trial so as to account for potential changes in peripheral neuromuscular propagation (Taylor, 2006).

3.2.4.2 Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation (TMS) of the motor cortex via a circular coil (13.5cm outside diameter) of Magstim 200 (Magstim Company, Dyfed, UK) was used to generate motor evoked potentials (MEPs). The circular coil was placed tangentially to the vertex of the head. The vertex was determined by measuring the midpoint position between the participant's nasion and inion, and the midpoint between the participant's tragi. The intersection of the these two points was

measured, marked and defined as vertex (Forman et al., 2015; Lockyer et al., 2018). The direction of the coil was adjusted depending on the dominant arm. Stimulation intensity of magnetic stimulator output was gradually increased until a MEP amplitude value that ranged between 15-25% of the M-max amplitude was obtained. At this point the TMS stimulation intensity value that obtained a MEP amplitude between 15-25% of the M-max value was used throughout the course of the experiment for the same participant.

3.2.5 Experimental protocol

Once stimulation intensities for the brachial plexus (M-max) and TMS were determined, the six different cycling trials (synchronous and asynchronous modes, each at 30, 60 and 90rpm) were performed. The total length of each cycling lasted approximately 3min. The arm ergometer was set at a constant workload of 30W and participants were instructed to cycle at a fixed cadence which they were able to monitor via a screen directly in front of them on the SCIFIT ergometer during each cycling trial. The order of cycling was randomized, and each in each cycling trial, a total of 12 TMS evoked MEPs and 2 M-waves were recorded from the biceps brachii of the dominant limb (at the 6 o' clock position of arm cycling). The order of the stimulations was randomized throughout the trial, and stimulations were separated by approximately 6-7s. Two frames without stimulations were added in order to further reduce anticipation of the stimulations.

3.2.6 Measurement

Data were analyzed off-line using Signal 5.11 software (CED, UK). The peak-to-peak amplitudes of MEPs and M-max recorded from the biceps brachii were measured and averaged across each cycling trial. The peak-to-peak amplitudes for all evoked potential were measured from the initial deflection of the voltage trace from the baseline of EMG to the point where it returned back to the baseline. Considering the fact that changes in M-max can cause changes in MEP

amplitude, MEPs were normalized to the M-max evoked during the same cycling trial. Pre-stimulus EMG was measured from a rectified channel of the biceps brachii. The length of window was determined by the cadence of the trial; 30rpm, 100ms; 60rpm, 50ms; 90rpm, 33.3ms (Forman et al., 2015; Lockyer et al., 2020). Measurements were taken from the averaged files of 12 MEPs and 2 M-max for each trial.

3.2.7 Statistics

The Data was analyzed using IBM SPSS statistics version 28. Descriptive statistics of data was used to determine the general characteristics of participants. Mauchly's test was employed to assess the assumption of sphericity for repeated measures analysis. If sphericity was violated, the appropriate correction was applied (i.e., Greenhouse Geisser or Huynh-Feldt) and the degrees of freedom were adjusted. The amplitude of the MEP (normalized to the M-max) was measured for each cycling mode and intensity. All statistics were run on group data and statistical significance level set at $p < 0.05$. Separate two-way repeated measure ANOVAs (MODE X CADENCE) were performed to determine whether statistically significant difference exist in MEP amplitudes as well as average pre-stimulus EMG across the conditions. Where significant difference occurred, repeated pairwise comparison using Bonferroni post hoc tests were used to determine where exactly the differences existed within the conditions. Data is reported in text as mean ± SD.

3.3 RESULTS

3.3.0 Mode and cadence-dependent changes in excitability to the biceps brachii.

As a group, there was no significant interaction effect between MODE and CADENCE ($F_{(2,20)} = 1.22$, $p = 0.316$; Fig. 2C). However, there were significant main effects for MODE ($F_{(1,10)}$

= 12.18, p = 0.006; Fig. 2A) and CADENCE ($F_{(2,20)}$ = 12.92, p = 0.001; Fig. 2B). Posthoc comparisons revealed that MEP amplitudes (normalized to M-max) were higher during synchronous cycling mode compared to the asynchronous cycling mode (8.8%± 2.5%, p = 0.006). The result also revealed higher MEP amplitude as cadence increased. A significant difference in MEP amplitude (normalized to M-max) was obtained between 30rpm and 60rpm mode (8.1% ± 2.5%, p = 0.025), and also between 30rpm and 90rpm mode (17.0% ± 3.6%, p = 0.003). However, there was no significant difference between the MEP amplitude obtained between 60rpm and 90rpm mode (8.9% ± 3.9%, p = 0.133). The MEP amplitudes (normalized to the M-max) for the Modes and Cadences are represented in box and whiskers plots below. Figure 1 shows the average of 12 MEPs expressed as a percentage of M-max taken from one participant at 60rpm while cycling synchronously and asynchronously. In this example, MEPs expressed as percentage of M-max were 34.9% during synchronous and 19.7% during asynchronous cycling mode.

Pre-stimulus EMG for MEPs. Figures 2D, E and F given below report averaged group data for pre-stimulus EMG from the biceps brachii muscle arranged in the order of mode, cadence and interaction effect. There was a main effect for CADENCE ($F_{(2,20)}$ = 18.123, p = 0.0001; Fig. 2E) but there was no significant main effect for MODE ($F_{(1,10)}$ = 4.320, p = 0.065; Fig. 2D) neither an INTERACTION between them ($F_{(2,20)}$ = 2.082, p = 0.162; Fig. 2F). Posthoc comparisons revealed that pre-stimulus EMG was higher significantly at 90 rpm compared to 30 rpm (192.8μV ± 44.4 μV, p = 0.004; Fig. 2E) and 60 rpm (131.7 μV ± 29.5 μV, p = 0.004; Fig. 2E), also higher significantly at 60rpm compared to 30rpm (61.1μV ± 19.4 μV, p = 0.031; Fig. 2E).

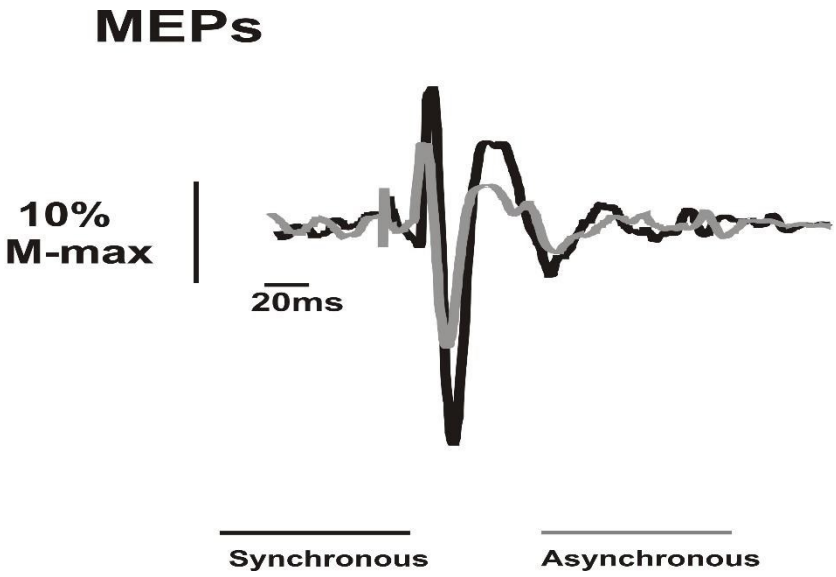
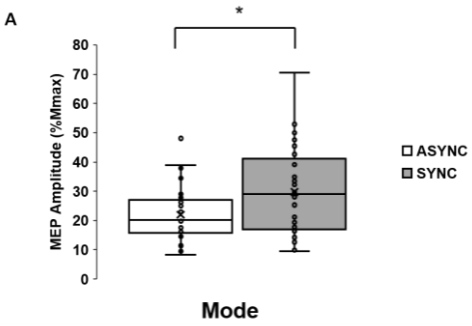
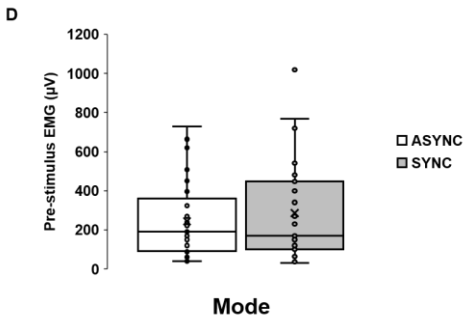
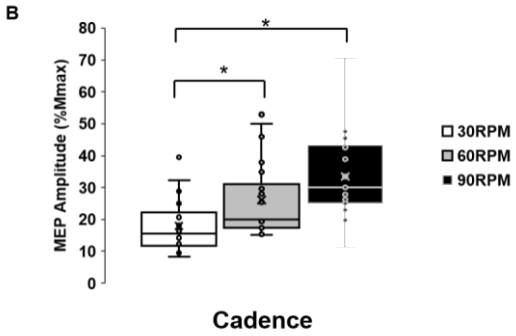
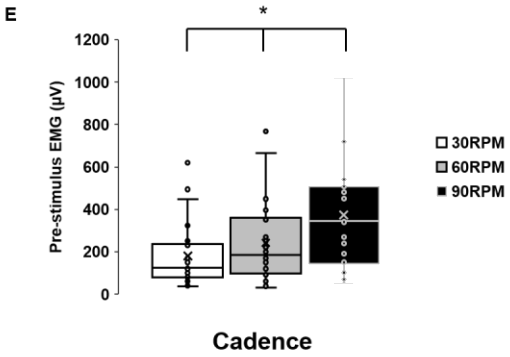


Fig 1. Average motor evoked potential (MEP) traces in the biceps brachii following 12 stimulations during synchronous (solid black lines) and asynchronous (solid gray lines) arm cycling at the 6 o' clock position. Amplitudes are expressed as a percentage of maximal M-wave (M-max).









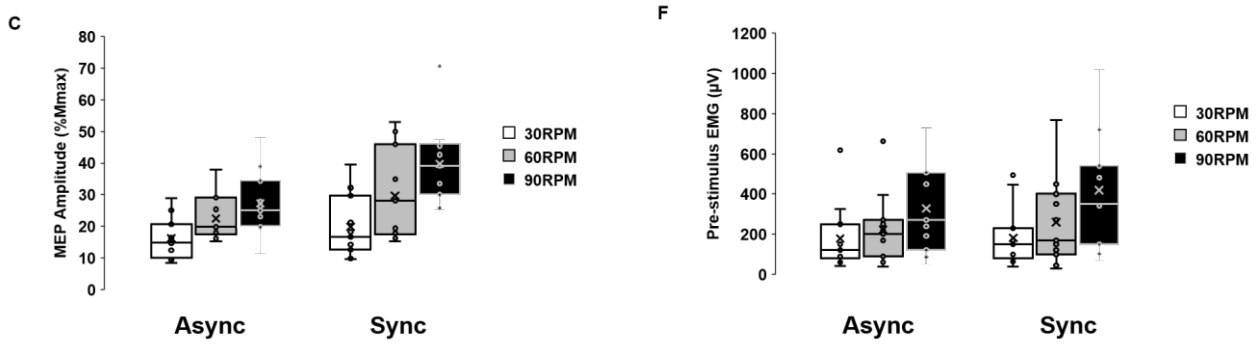


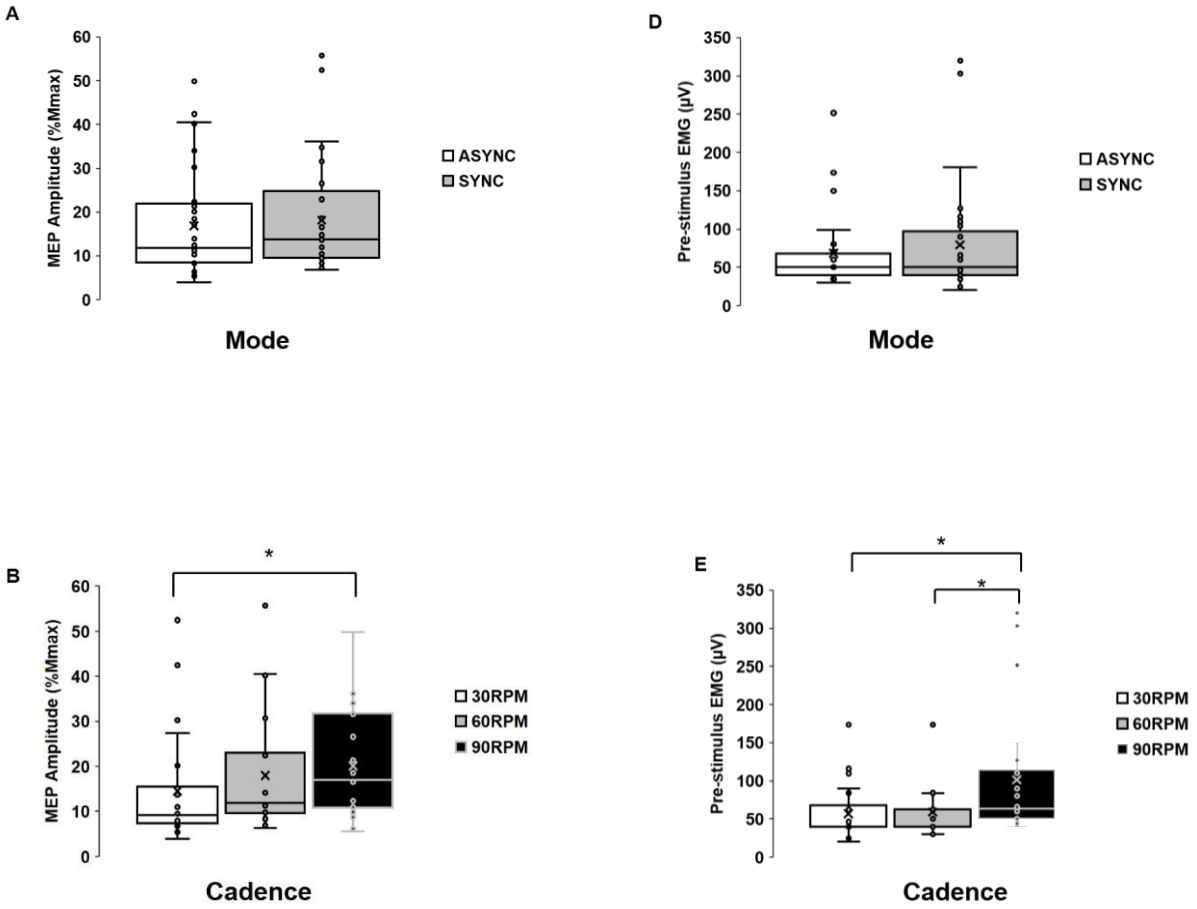
Fig. 2. (**A**) Group data (mean ± SE, n= 11) for MEP amplitude recorded from the biceps brachii at the 6 o' clock position of flexion during asynchronous and synchronous arm cycling modes. (**B**) MEP amplitude as cadence increases. (**C**) MEP amplitude in cadence separated by cycling modes. (**D**) Mean pre-stimulus EMG (i.e. prior to TMS) separated by cycling task (**E**) and cadence (**F**) Pre-stimulus EMG in each cadence separated by cycling modes.

3.3.1 Mode and cadence-dependent changes in excitability to the triceps brachii.

Figure 3 below gives the box and whiskers representation of the MEP amplitude observed in the triceps brachii muscle during the 6 o' clock (flexion) position of arm cycling. As a group, there was a significant main effect for CADENCE ($F_{(2,20)} = 6.314$, $p = 0.007$; Fig. 3B), however, there was no significant main effect for MODE ($F_{(1,10)} = 0.767$, $p = 0.402$; Fig. 3A) neither an INTERACTION between both ($F_{(2,20)} = 0.747$, $p = 0.487$; Fig. 3C). The Posthoc comparisons revealed that there was no significant difference in the MEP amplitude (normalized to M-max) between 30 rpm and 60 rpm (3.472% ± 1.390%, $p = 0.095$), neither between 60 rpm and 90 rpm (2.112% ± 1.383%, $p = 0.474$). However, there was a significant difference in the MEP amplitudes between 30 rpm and 90 rpm (5.584% ± 1.926%, $p = 0.048$).

Pre-stimulus EMG for MEPs. Fig 3 D, E and F shows average grouped data for pre-stimulus EMG recorded from the triceps brachii arranged for mode, cadence and interaction respectively. The result showed significant main effect for CADENCE ($F_{(2,20)} = 10.509$, $p = 0.001$; Fig. 3E), however

there was no significant main effect for MODE ($F_{(1,10)}$ = 1.172, p = 0.257; Fig. 3D) neither was there INTERACTION between them ($F_{(2,20)}$ = 2.172, p = 0.145; Fig. 3F). Posthoc comparison revealed that pre-stimulus EMG was significantly higher at 90 rpm compared to 30 rpm (44.150 µV ± 13.009 µV, p = 0.021; Fig. 3E) and 60 rpm (37.739 µV ± 12.251 µV, p = 0.035; Fig. 3E). However, there was no significant difference in the pre-stimulus EMG at 30 rpm compared to 60 rpm (6.411 µV ± 2.364 µV, p = 0.07; Fig. 3E).



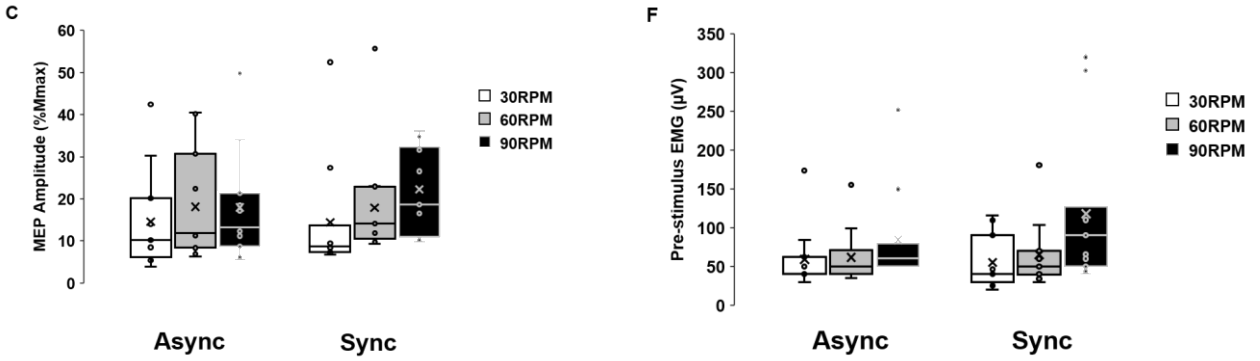


Fig. 3. (**A**) Group data (mean ± SE, n= 11) for MEP amplitude recorded from the triceps brachii at the 6 o' clock position of flexion during asynchronous and synchronous arm cycling modes. (**B**) MEP amplitude as cadence increases. (**C**) MEP amplitude in cadence separated by cycling modes. (**D**) Mean pre-stimulus EMG (i.e. prior to TMS) separated by cycling task (**E**) and cadence (**F**) Pre-stimulus EMG in each cadence separated by cycling modes.

3.4 Discussion

In this study we investigated corticospinal excitability to the arm muscles during synchronous and asynchronous arm cycling at three different cadences (30, 60 and 90rpm), specifically at the flexion phase of cycling. As we had previously hypothesized, corticospinal excitability to the biceps brachii was higher during synchronous arm cycling compared to the asynchronous cycling (Fig 2A). However, there was no significant difference in the overall corticospinal excitability to the triceps brachii muscle at the flexion (6 o' clock) phase of arm cycling while comparing the two cycling modes investigated (Fig 3A). Contrary to our original hypothesis, we showed that corticospinal excitability to both muscles (biceps and triceps brachii) did not significantly change in both cycling modes as cadence increased, i.e. no interaction between cycling mode and cadence (Fig 2C & 3C). This suggests that the excitability of the corticospinal tract to the motoneuron pools in both muscles did not significantly differ during both cycling modes as cadence increased. Also, in line with the previous studies from our lab, we observed that

corticospinal excitability to both muscles increased with increasing cadence during the flexion phase of arm cycling (Fig 2B&3B).

3.4.0 Potential mechanism for the difference in corticospinal excitability to the biceps brachii at the flexion phase of both synchronous and asynchronous arm cycling.

Corticospinal excitability to the biceps brachii muscle was higher during Synchronous cycling compared to the Asynchronous cycling at the 6 o'clock position of arm cycling (Fig. 2A). Importantly, the pre-stimulus EMG of the biceps brachii was not significantly different between the two conditions suggesting that the changes in the corticospinal excitability observed were not due to differences in motoneurone pool output (Fig. 2D, 3D). A potential explanation for the observed increase in corticospinal excitability during Synchronous mode of arm cycling could be an increase in interhemispheric facilitation. It is well-established that the distal musculature of one side of the body is controlled by the contralateral cerebral hemisphere, indicating that during bilateral limb activation, there is a corresponding activation of more motor areas in the brain (Noble et al., 2014). The two hemispheres are however connected by commissural fibers, making it possible for one hemisphere to either facilitate or inhibit the other hemisphere.

Interhemispheric facilitation has been previously demonstrated during tonic contractions. Ugawa et al (1993) investigated the interaction of the human bilateral hand motor area using two magnetic stimulators in 6 healthy subjects (aged 25 - 40years). They revealed the existence of excitatory connections between homotopic areas of the bilateral hand motor cortices. The response observed in the study showed the existence of interhemispheric facilitation in humans. Also, potentiation of motor evoked potential (MEPs) to inactive muscles by the contraction of contralateral homologous muscle has been previously researched both in non-locomotor tasks (Carson, 2005; Hortobágyi et al., 2003; Uehara et al., 2013) and in locomotor tasks (Lockyer et al.,

2020). In a study conducted by Lockyer et al, (2020) where 12 healthy volunteers (24.8 ± 4.4years) were asked to perform 3 different locomotor tasks; (1) bilateral arm cycling (BL), (2) unilateral, contralateral cycling with the ipsilateral arm moving passively (IP), and (3) unilateral, contralateral cycling with the ipsilateral arm at rest (IR). It was shown that corticospinal excitability (MEP amplitudes) was significantly lower in bilateral arm cycling compared to unilateral, contralateral cycling with the ipsilateral arm moving passively and unilateral, contralateral cycling with the ipsilateral arm at rest. In their conclusion, they stated that one potential reason for the observed higher corticospinal excitability during the IP and IR tasks is interhemispheric facilitation (cortical spread) to the inactive contralateral homologous motor area which could have led to the potentiated MEP amplitudes observed in the biceps brachii muscle during the elbow flexion phase of arm cycling (Lockyer et al., 2020). Thus, we suggest that the observed increase in corticospinal excitability during the synchronous mode of arm cycling could be due to the bilateral activation of homologous motor areas of both cerebral hemispheres which could potentially increase interhemispheric facilitation (cortical spread), thereby potentiating MEP amplitude readings observed in the biceps brachii during the elbow flexion phase (6 o' clock position) of bilateral arm cycling.

The concept of interhemispheric inhibition could be another way to explain the observed reduction in the corticospinal excitability to the biceps brachii muscle during the asynchronous mode compared to the synchronous mode of arm cycling. It is well-known that in an attempt to keep the two cerebral hemispheres working in harmony, there tends to be a degree of interhemispheric interference (either facilitate or inhibit) with the information processing and motor programming (Gazzaniga & Sperry, 1966). In a study conducted by Gazzaniga and Sperry (1966), four healthy subjects and a different four operated subjects (i.e. patients who had undergone midline section of the interhemispheric commissure) were asked to perform two different choice reaction

time tasks with each hand simultaneously. It was observed that the reaction time to do the double choice reaction was the same as the single hand task, while in the normal subjects, the reaction time was longer in the double task than for the single task. In their conclusion, they suggested that the results are in tandem with the view that the interhemispheric commissures serve to unify adjustment to the visual world and their presence tends to prevent the two halves of the brain from making discordant volitional decisions (i.e. acting incongruently), hence, there was a form of interhemispheric inhibition while performing the double task which was not present during the single task (Gazzaniga & Sperry, 1966). Interhemispheric inhibition is thought to exist in order to reduce unwanted activity in the contralateral muscles, thereby making the ipsilateral muscles function optimally (Mayston et al., 1999). In a study conducted by Ferbert et al, 1992, where they observed the EMG produced in the finger muscle (first dorsal interosseous) while paired transcranial magnetic stimulus over one cerebral hemisphere. They observed that this stimulus inhibited the contralateral corresponding motor cortical neurons, thus reducing the EMG of the muscles controlled by these neurons i.e. related reduction in the speed and force produced in these neurons (Ferbert et al., 1992).

Also, Benson et al (2020) demonstrated the existence of interhemispheric inhibition (IHI) to the biceps brachii during asynchronous arm cycling (Benson et al., 2021). This study is more relevant to the present study considering the fact that it was the only study to have investigated interhemispheric inhibition to the biceps brachii muscle at the 6 o'clock position of arm cycling using ipsilateral silent period method. A follow up study to this where 36 participants were recruited to investigate if IHI was task-dependent showed that IHI was stronger during arm cycling than an intensity- and positioned matched tonic contraction, i.e. Interhemispheric inhibition is task dependent (Compton et al., 2022). Subsequently, if we consider both synchronous and

asynchronous arm cycling as two different tasks, then we could assume the possibility that IHI during asynchronous arm cycling is much greater compared to synchronous arm cycling.

The aforementioned findings suggest the existence of interhemispheric inhibition especially while performing bilateral simultaneous movements. In relation to the present study, having established that one motor cortex can reduce cortical excitability to the contralateral motor cortex via interhemispheric inhibition both during locomotor and non-locomotor output, we therefore suggest that the activation of non-homologous muscle led to the upregulation of interhemispheric inhibition while the activation of homologous muscle groups caused a down-regulation of interhemispheric inhibition (disinhibition), leading to the observed higher MEP amplitude observed in the biceps brachii during the synchronous mode compared to the asynchronous arm cycling mode. However, this should be considered speculative, bearing in mind that this study did not measure interhemispheric inhibition that might have been generated during both cycling modes.

It is noteworthy to state here that this study did not measure spinal excitability of the corticospinal pathway. Thus, we cannot categorically declare at this point that the observed increase in MEP amplitude observed during the synchronous mode compared to the asynchronous mode was merely due to supra-spinal changes. Considering the fact that there are speculations that the spinal CPGs may likely be responsible for the rapid change of movement pattern from a less stable asynchronous movement to a synchronous movement pattern as cadence increases (Kelso, 1984), it is imperative to suggest that the observed increase in corticospinal excitability during synchronous arm cycling mode might not only be due to supra-spinal changes but also involve spinal changes. But given also that the spinal CPGs are considered to be the chief regulator of rhythmic locomotor output in humans (Dimitrijevic et al., 1998; Power et al., 2018; Zehr et al., 2012), it might not be completely out of line to speculate that the observed increase in corticospinal excitability observed during synchronous movement is primarily from supra-spinal input in an

attempt to suppress the normal rhythmic asynchronous movement chiefly regulated by the spinal CPGs. Whatever the circumstances, we cannot conclude on this at this point, as the scope of this study did not cover possible spinal changes that might have occurred during both cycling modes.

3.4.1 Corticospinal excitability in the triceps brachii during the flexion phase of synchronous and asynchronous arm cycling modes.

The results from this study showed that corticospinal excitability to the triceps brachii was not significantly different between the two modes during the flexion phase of arm cycling. This result was anticipated considering the fact that during elbow flexion, the biceps brachii is more active and the triceps brachii could be considered to have a highly reduced motoneuron pool due to the concept of reciprocal inhibition in order to allow for the optimal function of the agonist muscle (i.e. the biceps brachii). Thus, for the sake of this study, we suggest that the absence of a significant difference in CSE to the triceps brachii muscle is primarily due to the fact that reading were made at a position where the biceps brachii was more active.

Also, the fact that stimulation intensities were set using the biceps brachii muscle and not the triceps muscle might be a reason for the lack of difference observed in the CSE projection to the triceps brachii between the two modes. Additionally, this study strengthens the claim that corticospinal excitability is muscle-dependent (Spence et al., 2016), because contrary to what was observed in the triceps muscle, we observed a significant difference in the corticospinal excitability to the biceps brachii at the flexion phase of both synchronous and asynchronous arm cycling. One potential mechanism that could be responsible for this is the difference in monosynaptic projections from the brain to the motoneuron pools observed in both muscles (biceps and triceps brachii). Despite the fact that both the biceps and triceps brachii receive monosynaptic corticospinal

excitation, there are significantly more monosynaptic connections to the biceps brachii (Brouwer & Ashby, 1990; Palmer & Ashby, 1992; Petersen et al., 2002). Therefore, more excitability of motoneurons via monosynaptic pathway in the biceps brachii would infer lesser influence of spinal interneurons as compared with the triceps brachii where we have fewer monosynaptic connections. However, we propose that there might be significant difference if recordings were taken at the extension phase (12 o' clock position) of arm cycling during both cycling modes.

3.4.2 Methodological considerations

Several methodological factors should be considered in interpreting the present result. First, while setting the stimulation intensities, participants cycled at the rate of 60rpm and 25watt. However, when the main experiment began, the power output was increased from 25watt to 30 watt, this we did because we observed that while cycling at 25 watt in the synchronous cycling, participants tend to free fall from the extension phase (12 o' clock position) to the 6 o' clock position, thereby reducing the torque generated in the biceps brachii muscle. By increasing the workload from 25watt to 30 watt, the effect of free falling was limited, causing the biceps brachii to perform more work during the flexion phase of arm cycling. We do not think this could have impacted the result, given the fact that all the cycling trials were performed at a constant power output of 30watts. Lastly, in this study, spinal excitability wasn't measured and therefore, we cannot categorically ascertain that the observed changes in the corticospinal excitability between the two cycling modes are mainly due to supra-spinal inputs.

3.5 Conclusion

This is the first study to investigate differences corticospinal excitability to the arm muscles during synchronous and asynchronous arm cycling modes. Corticospinal excitability to the biceps brachii was higher during synchronous mode compared to the asynchronous mode at the flexion phase (6 o' clock position) of arm cycling. While the exact mechanism contributing to this are not yet fully understood, we speculate that increased interhemispheric facilitation or reduced interhemispheric inhibition is involved. These assumptions are still widely speculative and require further investigation.

3.6 Acknowledgements

This study was supported by NSERC Discovery Grant to K.E.P. We would like to thank the participants for volunteering to take part in this study.

3.7 Disclosures

No conflict of interest, either financial or otherwise, are declared by the authors.

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CHAPTER 4: SUMMARY AND FUTURE DIRECTIONS

For the fundamental improvement of the body of knowledge on locomotion-related studies in humans, a deeper comprehension of how the central nervous system (brain and spinal cord) work to produce locomotor outputs, such as rhythmic arm cycling, is crucial. In this study, we investigated corticospinal excitability to the biceps and triceps brachii during synchronous and asynchronous arm cycling at the elbow flexion position using various cycling cadence. We aimed to know the effect of arm cycling modes on corticospinal excitability and if this effect varies across different cycling cadences. The findings from this study shows that corticospinal excitability to the biceps brachii is higher during synchronous compared with asynchronous arm cycling at the elbow flexion phase. The result further affirm the claim that corticospinal excitability is muscle-dependent because in contrast to what was observed in the biceps brachii, corticospinal excitability to the triceps brachii was not significantly different between synchronous and asynchronous arm cycling. Although we suggested that this result might be different if readings were recorded at the extension phase of arm cycling, because we know from previous studies that corticospinal excitability is phase-dependent. Also from the result, we observed that there was no significant difference in the corticospinal excitability observed in both synchronous and asynchronous arm cycling as cadence increased. The result from this study adds to the current body of knowledge suggesting that neural control durng rhythmic lomotor outpout may be dependent on the movement pattern (i.e. whether there is simultaneous activation of biliateral homologous or non-homologous muscle groups).

However, in this study, we did not investigate spinal inputs to the overall excitability of the coricospinal tract during both synchronous and asynchronous arm cycling. Thus, we encourage future studies to investigate spinal excitability during these two cycling modes. We believe that doing this will not only help us to understand the potential neural mechanism of action during these

two arm cycling modes, but also increase the overall body of knowledge on how the central nervous system regulate rhythmic locomotor output.

Furthermore, even though this study only investigated the theoretical aspect of the neural mechanism involved in both arm cycling tasks, we encourage the use of this research knowledge in clinical settings. As previously stated, most rehabilitation clinics where arm cycling exercise is used to improve functional activities of people with neurological deficit tend to make use of the asynchronous mode of arm cycling. the result from this study suggest that the use of synchronous arm cycling mode may better improve functional abilities in people with neurological deficit compared with asynchronous arm cycling mode.

Finally, considering the fact that this is the first study to investigate corticospinal excitability during synchronous and asynchronous arm cycling, some of the methodological parameters used in this study were based on the results obtained from several pilot studies. We therefore encourage further investigations into this research area, for example, taking readings at the extension phase of arm cycling, setting stimulation parameters using synchronous arm cycling mode, and investigation of interhemispheric inhibition and/or facilitation during these arm cycling modes.

APPENDIX 1: ETHICAL APPROVAL

MEMORIAL UNIVERSITY

Interdisciplinary Committee on
Ethics in Human Research (ICEHR)

St. John's, NL Canada A1C 5S7
Tel: 709 864-2561 icehr@mun.ca
www.mun.ca/research/ethics/humans/icehr

ICEHR Number:	**20230109-HK**
Approval Period:	June 8, 2022 – June 30, 2023
Funding Source:	NSERC [RGCS# 20161819]
Responsible Faculty:	Dr. Kevin Power School of Human Kinetics and Recreation
Title of Project:	*Assessment of corticospinal excitability in synchronous and asynchronous arm cycling*

June 8, 2022

Mr. Jirho Ogolo
School of Human Kinetics and Recreation
Memorial University

Dear Mr. Ogolo:

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

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

The *TCPS2* **requires** that you submit an Annual Update to ICEHR before **June 30, 2023**. If you plan to continue the project, you need to request renewal of your ethics clearance and include a brief summary on the progress of your research. When the project no longer involves contact with human participants, is completed and/or terminated, you are required to provide an annual update with a brief final summary and your file will be closed. All post-approval ICEHR event forms noted above must be submitted by selecting the ***Applications: Post-Review*** link on your Researcher Portal homepage. We wish you success with your research.

Yours sincerely,

James R Drover

James Drover, Ph.D.
Vice-Chair, Interdisciplinary Committee on
Ethics in Human Research

JD/bc

cc: Supervisor – Dr. Kevin Power, School of Human Kinetics and Recreation
Director, Research Grant and Contract Services

APPENDIX 2: TCP CERTIFICATE

PANEL ON RESEARCH ETHICS

Navigating the ethics of human research

TCPS 2: CORE 2022

Certificate of Completion

This document certifies that

jirho ogolo

successfully completed the Course on Research Ethics based on the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2: CORE 2022)

Certificate # 0000803390 **19 February, 2022**

APPENDIX 3: MAGNETIC SAFETY CHECKLIST

Magnetic Stimulation Safety Checklist

Please read the checklist below. If the answer to any of the questions is yes please indicate that you are ineligible to participate in the study.

You are NOT required to circle a response nor are you required to provide any further information. This checklist is for safety screening only.

1. Do you suffer from epilepsy, or have you ever had an epileptic seizure? **YES/NO**
2. Does anyone in your family suffer from epilepsy? **YES/NO**
3. Do you have any metal implant(s) in any part of your body or head? (Excluding tooth fillings) **YES/NO**
4. Do you have an implanted medication pump? **YES/NO**
5. Do you wear a pacemaker? **YES/NO**
6. Do you suffer any form of heart disease? **YES/NO**
7. Do you suffer from reoccurring headaches? **YES/NO**
8. Have you ever had a skull fracture or serious head injury? **YES/NO**
9. Have you ever had any head surgery? **YES/NO**
10. Are you pregnant? **YES/NO**
11. Do you take any medication? **YES/NO**
    a. Note if taking medication, check list for contraindicated medication on next page.
12. Do you suffer from any known neurological or medical conditions? **YES/NO**

APPENDIX 4: EDINBURG HANDEDNESS INVENTORY

Edinburgh Handedness Inventory[1]

Your Initials:_____

Please indicate with a check (✓) your preference in using your left or right hand in the following tasks.

Where the preference is so strong you would never use the other hand, unless absolutely forced to, put two checks (✓✓).

If you are indifferent, put one check in each column (✓ | ✓).

Some of the activities require both hands. In these cases, the part of the task or object for which hand preference is wanted is indicated in parentheses.

Task / Object	Left Hand	Right Hand
1. Writing		
2. Drawing		
3. Throwing		
4. Scissors		
5. Toothbrush		
6. Knife (without fork)		
7. Spoon		
8. Broom (upper hand)		
9. Striking a Match (match)		
10. Opening a Box (lid)		
Total checks:	LH =	RH =
Cumulative Total	CT = LH + RH =	
Difference	D = RH – LH =	
Result	R = (D / CT) × 100 =	
Interpretation: (Left Handed: R < -40) (Ambidextrous: -40 ≤ R ≤ +40) (Right Handed: R > +40)		

[1] Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsycholologia*, *9*, 97-113.

APPENDIX 5: PHYSICAL ACTIVITY REDINESS QUESTIONNAIRE (PAR-Q)

2018 PAR-Q+

The Physical Activity Readiness Questionnaire for Everyone

The health benefits of regular physical activity are clear; more people should engage in physical activity every day of the week. Participating in physical activity is very safe for MOST people. This questionnaire will tell you whether it is necessary for you to seek further advice from your doctor OR a qualified exercise professional before becoming more physically active.

GENERAL HEALTH QUESTIONS

Please read the 7 questions below carefully and answer each one honestly: check YES or NO.	YES	NO
1) Has your doctor ever said that you have a heart condition ☐ OR high blood pressure ☐?	☐	☐
2) Do you feel pain in your chest at rest, during your daily activities of living, **OR** when you do physical activity?	☐	☐
3) Do you lose balance because of dizziness **OR** have you lost consciousness in the last 12 months? Please answer **NO** if your dizziness was associated with over-breathing (including during vigorous exercise).	☐	☐
4) Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)? **PLEASE LIST CONDITION(S) HERE:** _____	☐	☐
5) Are you currently taking prescribed medications for a chronic medical condition? **PLEASE LIST CONDITION(S) AND MEDICATIONS HERE:** _____	☐	☐
6) Do you currently have (or have had within the past 12 months) a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be made worse by becoming more physically active? Please answer **NO** if you had a problem in the past, but it ***does not limit your current ability*** to be physically active. **PLEASE LIST CONDITION(S) HERE:** _____	☐	☐
7) Has your doctor ever said that you should only do medically supervised physical activity?	☐	☐

If you answered NO to all of the questions above, you are cleared for physical activity.
Please sign the PARTICIPANT DECLARATION. You do not need to complete Pages 2 and 3.

- Start becoming much more physically active – start slowly and build up gradually.
- Follow International Physical Activity Guidelines for your age (www.who.int/dietphysicalactivity/en/).
- You may take part in a health and fitness appraisal.
- If you are over the age of 45 yr and NOT accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional before engaging in this intensity of exercise.
- If you have any further questions, contact a qualified exercise professional.

PARTICIPANT DECLARATION
If you are less than the legal age required for consent or require the assent of a care provider, your parent, guardian or care provider must also sign this form.

I, the undersigned, have read, understood to my full satisfaction and completed this questionnaire. I acknowledge that this physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if my condition changes. I also acknowledge that the community/fitness centre may retain a copy of this form for records. In these instances, it will maintain the confidentiality of the same, complying with applicable law.

NAME _____ DATE _____

SIGNATURE _____ WITNESS _____

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER _____

If you answered YES to one or more of the questions above, COMPLETE PAGES 2 AND 3.

Delay becoming more active if:

- You have a temporary illness such as a cold or fever; it is best to wait until you feel better.
- You are pregnant - talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the ePARmed-X+ at **www.eparmedx.com** before becoming more physically active.
- Your health changes - answer the questions on Pages 2 and 3 of this document and/or talk to your doctor or a qualified exercise professional before continuing with any physical activity program.

01-11-2017

APPENDIX 6: THESIS PROPOSAL

Assessment of Corticospinal Excitability during Synchronous and Asynchronous Arm Cycling

A Thesis Proposal Submitted

By

Jirho A. Ogolo

Table of Contents

LIST OF ABBREVATIONS

- TMS- Transcranial Magnetic Stimulation
- TMES- Transmastoid Electrical Stimulation
- MEP- Motor Evoked Potential
- CMEP- Cervicomedullary Motor Evoked Potential
- EMG- Electromyography
- CPG- Central Pattern Generators
- RMT- Resting Motor Threshold

INTRODUCTION

Arm cycling is employed in research, rehabilitation, sport (i.e. wheelchair) and as a model of locomotion in experimental studies (Zehr, 2005). Research and rehabilitation tend to employ an asynchronous (arms moving in opposite directions - one arm pulls the crank towards the body while the opposing arm pushes the crank away from the body) form while persons with spinal cord injury that self-propel using a manual wheelchair tend to employ a synchronous (arms moving together) form. While most studies have focused on cycling efficiency, and cardiovascular changes that occur during these two cycling modes (Dallmeijer et al., 2004; Hopman et al., 1995; Mossberg et al., 1999), none has compared neurophysiological changes such as corticospinal (brain and spinal cord) excitability using these cycling forms.

Previous experimental studies involving non-locomotor tasks have shown that spontaneous transitions exist between modes of coordination (symmetrical and asymmetrical) while performing rhythmic motor tasks, with symmetrical movements being performed more reliably (Carson, 1995; J. A. Kelso et al., 1981; J. A. S. Kelso, 1984; Klapp, 1979; Riek et al., 1992). A study conducted by Cohen (1971) where 12 subjects were asked to perform bimanual wrists movements first synchronously and then asynchronously shows that there is high precision in the coordination of bimanual non-locomotor output when homologous muscle groups are activated simultaneously, compared to when non-homologous muscle groups are activated. The result from this study suggested the existence of a unitary coupling mechanism which facilitates simultaneous action of homologous muscles of the upper limbs (Cohen, 1971). It has also been shown that different areas of the cerebral cortices are activated when performing these different modes of rhythmic motor task (Lang et al., 1990). Locomotor tasks, however, are under a different neural control strategy involving spinally located central pattern generators (CPG) (Barbeau & Rossignol, 1987; Brown, 1911; Forssberg et al., 1980; Sherrington, 1910). In quadrupeds, gait patterns can abruptly change from a less stable “out-of-phase (asymmetric) mode” to a more stable “in-phase (symmetrical)

mode" when they move from a "trot" to a "gallop"; possibly to select the best spatiotemporal pattern for muscle activity (J. A. S. Kelso, 1984). Indirect evidence suggests that humans also possess a spinally located locomotor CPG (Calancie et al., 1994; Dimitrijevic et al., 1998; MacKay-Lyons, 2002) that is also active during arm cycling (Power et al., 2018; Zehr et al., 2012). It is presently unclear whether differences in cortical activation or corticospinal excitability differs between symmetrical and asymmetrical modes of arm cycling.

Determining which mode of cycling results in greater excitability of the corticospinal tract would be beneficial, especially for neuro-rehabilitation where the goal is to increase corticospinal excitability to enhance the ability of the nervous system to undergo changes and thus potential functional gains. This study will be the first comparing corticospinal excitability in synchronous and asynchronous forms of arm cycling exercise.

Purpose of the study

The purpose of this study is to investigate corticospinal excitability during asynchronous and synchronous arm cycling at three different cycling cadences.

Hypotheses

1. Corticospinal excitability will be greater during synchronous rather than asynchronous arm cycling

1. Corticospinal excitability would increase in both cycling modes as cadence increases

LITERATURE REVIEW

Humans engage in different forms of motor activities on a daily basis, such as walking, running and cycling. These activities are considered normal by the human population. As simple as these tasks are, studies have revealed that they are actually mediated by complex spinal and supra-spinal activities (Lockyer et al., 2021). It has been shown that a slew of electrical and chemical (neurotransmitters) actions occur within the brain to stimulate motor circuitry within the brainstem and spinal cord, thus, leading to the overall electrical activation of skeletal motor neurons, thereby causing these seemingly simple tasks to occur (Barter et al., 2014; Fan et al., 2012; Sherrington, 1906). In an attempt to understand this rather complex aspect of human physiology, several experiments have been performed on animals, some of which has proven the involvement of central pattern generators (CPG) present in the spinal circuitry as playing a major role in the mediation of rhythmic activities in animals (Barbeau & Rossignol, 1987; Brown, 1911; Forssberg et al., 1980; Sherrington, 1910). Similarly to animals, some indirect evidences suggest that humans have spinally situated CPG that helps to mediate rhythmic motions such as walking and cycling (Calancie et al., 1994; Dimitrijevic et al., 1998; Solopova et al., 2016).

Why use arm cycling?

The majority of human motor control investigations are usually conducted in an isometric or rest state. This is understandable because according to the famous Russian scientist Nikolai Bernstein, who is considered to be the father of modern-day motor control research, he noted that a person never performs a movement the same way twice, this he summarized in his “Bernstein’s sentiment of repetition without repetition” (Bernstein, 1996). This dynamics in human movement he considered to be as a result of variability in the neural control of movement. The change itself is good for humans because it allows us to perform movements at various limited conditions and

environment, i.e. because of this inherent ability, we tend to devise new and optimum motor control skills to an appropriate motor problem. However, the variability in the neural control creates complexities for researchers while trying to investigate and understand neural motor control. In most cases, during experimentation, this observation (i.e. large variability in neural motor control in humans) create a significant level of background noise (i.e. random disturbance to the electrical signals observed during data collection) which tend to impair the results of the experiment (Lockyer et al., 2021). Thus, in order to mitigate this challenge, researchers in this area of specialization always prefer to carry out experiments while participants are at rest or during isometric exercises, as this tends to limit the observed level of background noise. As good as this may sound, this tends to limit our understanding of the overall human movement.

Overall, human movement is considered to be dynamic and not overly static. In order to really understand locomotive movement in humans, we would need to simulate a relative rhythmic pattern of movement which would tend to limit background noise and overall variability during experimental sessions. In humans, the control of all rhythmic movements can be summed up to be the complex interaction of three basic neural controls, namely spinal central pattern generators, somatosensory feedback from moving limbs and supra-spinal inputs (Pearcey & Zehr, 2020). According to Lockyer and colleagues, this tripartite control system is common to all rhythmic motor task, thus, an investigation of a task such as locomotion can be generalized to all other tasks such as swimming, running, crawling and cycling. The fact that a core neural component is general to all makes researchers confident that the result obtained from studying a rhythmic task could be generalized to all other rhythmic motor tasks (Lockyer et al., 2021). In many of the researches done on corticospinal excitability in our lab, we have proven that arm cycling can be used as a model for human locomotion. Zehr and colleagues have also shown from their studies for the past 20 years

that arm cycling can be used to explain rhythmic motor output such as locomotion in humans (Zehr et al., 2016).

Arm cycling has also been used in several researches to study neural control of rhythmic motor output in persons with neurological impairments (Kaupp et al., 2018; Zehr et al., 2012; Zhou et al., 2018). Its usefulness in training people with neurological impairments has also made it good to be used for research purposes. Lockyer and colleagues also indicated that one major reason why arm cycling is advantageous over walking in studying neural control is its relative ease of use for people with neurological impairments such as hemiparesis (in which case the weak hand could be strapped to the wheel and allowed to move passively), and also that it could be performed under various conditions (i.e. various loads and cadences) where the head, neck and torso remain relatively still, minimizing the effect of background noise on the overall result. He however pointed out that a major limitation to using arm cycling as a model of human locomotion is that walking necessitates propulsion from the leg to ensure forward progression during upright balance preservation whereas arm cycling do not, thereby reducing demand for neural resources to maintain balance during arm cycling. This limitation is noted, but would however not cancel out several advantages and relatable characteristics that exist between cycling and walking with the major one being the fact that they are both mediated by the complex interaction of the three basic neural controls (Lockyer et al., 2021; Zehr, 2005).

Synchronous vs asynchronous arm cycling

Asynchronous arm cycling mode is the most common arm cycling mode used both for training people with neurological impairments (especially for cardiorespiratory purposes) and also for research purposes (Celli, 1994; Hardison et al., 1987; Powers et al., 1984; Weissland et al., 1997). In clinical setting, when arm cycling is used to rehabilitate patients with neurological impairments (i.e. in cases of stroke and spinal cord injury), the goal is to increase corticospinal excitability as this has been linked to increased intra-cortical activities (reduced intra-cortical inhibition) and ultimately improved functional abilities (Liepert et al., 2000; Tatemoto et al., 2019; Ziemann, 2001). However, there is been no studies to prove that asynchronous cycling mode generates a higher corticospinal excitability compared with synchronous cycling mode. The utilization of asynchronous movement pattern during arm ergometry investigations could most likely result from the fact that arm cycle ergometers emerged from modified leg cycle ergometers (Mossberg et al., 1999). This cycling mode is considered innate to man due to the fact that a toddler begins crawling in an asynchronous manner immediately from infancy. Also, the natural walking mode in humans is done in an asynchronous form, a manner in which opposite legs performs opposite actions in opposite directions at the same time. Many researches that aim to study the basic neural controls involving human locomotion tend to simulate human rhythmic motor output using this cycling mode.

The majority of the investigations carried out using synchronous movements have been done using rhythmic non-locomotor output such as bilateral finger tappings and wrist movements (Baldissera et al., 1991; Cohen, 1971; Haken et al., 1985; J. A. S. Kelso, 1981, 1984; Lang et al., 1990; Riek et al., 1992). Most of this works in behavioural sciences which aim to investigate the action of the brain in maintaining stability. For example, in a study conducted by Kelso (1981a), participants were asked to rhythmically oscillate their index fingers in an horizontal plane (i.e.

adduction-abduction) using one of two modes, i.e. in-phase or anti-phase. In the in-phase mode, homologous muscle groups were activated simultaneously while in the anti-phase mode, the muscles contract in an alternating form. Participants were asked to follow a pacing metronome whose oscillating frequency was systematically increased from 1.25Hz to 3.50Hz in steps of 0.25Hz which lasted up to about 10secs. They were asked to produce one full movement cycle with each finger for each beat of the metronome. In this study, it was observed that when participants began with the anti-phase mode, there was spontaneous change to the in-phase mode at a certain critical frequency of oscillation. This change was observed not to revert even when the oscillating frequency was reduced (i.e. participants continued in the symmetrical in-phase mode of oscillation even when frequency was reduced). There was no change observed when participants started with the in-phase mode of oscillation. He hypothesized that a "switch mechanism" which has neural origin but currently still poorly understood was involved in the phase transition that occurred. In his conclusion, he noted that coordinated transistion appeared to have occurred because of the continuous scaling influence (increased oscillatory frequency) that rendered the previous movement mode (anti-phase) unstable, then at a critical point (frequency), bifurcation occurred and a new stable (and perhaphs energetically more efficient) mode arose (J. A. S. Kelso, 1981, 1984).

Corticospinal excitability has been assessed during various motor outputs, including arm cycling and has been shown to be task and phase dependent (D. Forman et al., 2014; Kalmar, 2018; Power et al., 2018). For example, a study conducted by Forman and colleagues where he investigated supra-spinal and spinal excitability to the biceps brachii during rhythmic motor output (arm cycling) and an intensity matched tonic contraction showed that corticospinal excitability was higher during arm cycling than during an intensity matched tonic contraction state. In this study, he also noted that supra-spinal excitability were higher at the onset of elbow flexion, mid flexion and elbow extension phase while spinal motoneurone excitability increased only during the onset of

elbow flexion and was not significantly different from tonic contraction during mid elbow flexion and elbow extension phases. From his study, he concluded that corticospinal excitability is task and phase dependent (D. Forman et al., 2014).

Corticospinal excitability has also been shown to be muscle dependent (D. A. Forman et al., 2019; Spence et al., 2016). For example, in a study conducted by Spence and colleagues (2016), he noted that there was phase dependent modulation of corticospinal excitability to the biceps brachii muscle while there was no change observed in the corticospinal excitability both in the flexion and extension phases of the triceps brachii muscle. He suggested that the observed difference might suggest that these antagonistic muscles might be under different neural control mechanism during arm cycling (Spence et al., 2016). Even though few studies have shown the impact of task, phase and muscle groups on the modulation of corticospinal excitability during rhythmic locomotor output (arm cycling), there is however a dearth of experimental study on the influence of cycling modes on corticospinal excitability in rhythmic locomotor output.

Given that arm cycling is a bilateral, rhythmic motor output, one must consider how the limbs influence each other. It has also been known for some time that limbs do not operate independently, as there is influence of one on the other; a phenomenon considered as cross extension reflex (Sherrington, 1910). The concept of crossed facilitation has been established even though it's mechanism of action is not yet fully understood. It has been shown that activation of a musculature during voluntary tonic contraction on one limb leads to increased excitability of contralateral homologous motor pathway (Carson et al., 2004; Cernacek, 1961; Hortobágyi et al., 2003). Given the fact that corticospinal excitability is considered to be task specific, a study was conducted in our lab by Lockyer and colleagues in which the influence of activity on one limb on corticospinal excitability to the contralateral limb during a rhythmic locomotor output was examined. In this study, it was observed that there reduced corticospinal excitability during bilateral

arm cycling compared to when the dominant limb was at rest. This suggested the possibility of crossed inhibition during bilateral (asynchronous) arm cycling as opposed to crossed facilitation that might have occurred when the dominant arm of participants was kept at a state of rest (Lockyer et al., 2020). If bilateral asynchronous arm cycling resulted in the activation of intra-cortical inhibitory neurons, should we also assume that this would be the case when cycling both arms synchronously? Hence the reason for this study. There is evidence to support that rhythmic non-locomotor movement modes (i.e. either synchronous or asynchronous) can have effect on corticospinal excitability (Stinear & Byblow, 2002), but no known study has been done to investigate corticospinal excitability using both modes in arm cycling exercise (i.e. rhythmic locomotor output).

Intensity dependent cycling.

The intensity of arm cycling can be adjusted by making changes in the cadence and/or load output (i.e. cadence and workload together make up power output). Cadence has been shown to play a major factor in the somatosensory processing of information during human locomotion (Capaday & Stein, 1987; Ferris et al., 2001; Simonsen & Dyhre-Poulsen, 1999) and when cycling is used as a form of human locomotive motor output (Staines et al., 1997). The use of a fixed cadence during experiments helps to retain concentration in participants (i.e. they have to observe their cadence on the ergometer monitor). This is a form of directed visual attention which has been shown to increase neural activity in the brain, as evidenced in functional magnetic resonance imaging (Kastner et al., 1999). Majority of studies on arm cycling performed in our lab are usually done using fixed cadences and workloads. However, there have also been times when workload and/or cadence were changed for experimental purposes (D. A. Forman et al., 2015; Lockyer et al.,

2018, 2020; Spence et al., 2016). Changes in cadences have been shown to affect stretch reflex (i.e. H-reflex). A study conducted by Ferris and colleagues reported suppression of H-reflex gains during running compared to walking (Ferris et al., 2001). Also, increase in leg cycling cadences tends to suppress the amplitude of somatosensory evoked potential and H-reflex (Staines et al., 1997). Increase in leg cycling cadence has also be shown to have effect on muscles (Pyndt et al., 2003).

Forman and colleagues (2015) showed the effect of cycling cadence on corticospinal excitability. In this study, participants were allowed to perform asynchronous arm cycling task at different cadences (30, 60 and 90 rpm) and a fixed workload of 25W. During each cycling trial, corticospinal excitability was measured using TMS which recorded motor evoked potential (MEP) from corticospinal neurons, and TMES which measured cervico-medullary motor evoked potential (CMEP) from spinal neurons. In this study, recordings were taken from the biceps brachii at two separate positions corresponding to the elbow flexion and extension phases (6 and 12 'o' clock relative to a clock face, respectively). The results indicated that there was an overall increase in corticospinal excitability to the biceps brachii throughout arm cycling as cadence increased. However, the changes that occurred in spinal excitability as cadence increased were noticed to be phase dependent, i.e., it increased during elbow flexion and decreased during elbow extension. This he suggested might be due to the fact that there is decreased reciprocal inhibition to the biceps brachii during elbow flexion (i.e. increased motoneurone excitability) and increased reciprocal inhibition to the biceps brachii during elbow extension, leading to reduced spinal motoneurone excitability (D. A. Forman et al., 2015). Spence and colleagues (2016) investigated corticospinal excitability to biceps and triceps brachii while increasing workload during asynchronous arm cycling. The result from this study shows that there is an overall increase excitability in the corticospinal and spinal motoneurons in both muscle groups with an increase in workload intensity. In this study, it was observed that even though corticospinal excitability was higher during the

flexion phase of the biceps brachii compared to the extension phase (i.e. phase dependent), it was not phase dependent in the triceps brachii muscle. Another rather interesting observation made in this study was that spinal motoneuron excitability was higher during the flexion phase of the triceps brachi compared to the extension phase. This is termed unusual considering the fact that the triceps brachii muscle is more active during the extension phase of arm cycling compared to the flexion phase. In this study, several putative mechanisms thought to be responsible for the observed variations in the triceps brachii muscle were discussed, including the idea that during the flexion phase, the triceps brachii muscle is stretched, leading to the activation of persistent inward currents (PICs) (Wilson et al., 2015) which in turns increase synaptic inputs to the spinal motoneuron pool, thus, reducing the need for supra-spinal input to the muscle. The result from this study further corroborate the fact that corticospinal excitability is intensity and muscle dependent (Spence et al., 2016). Also, a study conducted by Lockyer and colleagues (2018) where he made changes to cadence and workload (i.e. power output) revealed that intensity type (either cadence or power output) differentially modulate spinal and supra-spinal excitability in a manner that is phase and muscle dependent (Lockyer et al., 2018).

To the best of our knowledge, there has been no known study to investigate the effect of different cycling intensities during synchronous cycling mode, nor comparison between the two cycling modes. The previous evidences shown in the work of Spence et al (2016) and Forman et al (2015) that increasing cycling intensity tend to increase overall corticospinal excitability cannot be generalized, as this study was done while only considering asynchronous cycling mode.

Corticospinal Pathway

The corticospinal pathway is one of the most important tracts present in descending motor pathways responsible for the production of controlled voluntary movement in humans (Nathan &

Smith, 1955), this tract has been shown to originate in broad regions of the cerebral cortex. Other parts of the descending motor pathways include the rubrospinal, reticulospinal and vestibulospinal tracts which are all known to originate from the nuclei in the brainstem. They are assumed to receive inputs from the "corticofugal neurons" which is believed to coordinate their activities (Canedo, 1997). The bulk of the corticospinal tract is believed to originate from the precentral gyrus, mainly in its upper two-thirds, and also the paracentral lobule. These cells when excited cause stimulation of the upper limbs (Ferrier, 1876). According to some studies, about 30 percent of the tract originate from the primary motor cortex, about 30% also arise from premotor and supplementary motor areas while the remainder is thought to arise from non-motor areas such as the somatosensory areas and the parietal cortex (Canedo, 1997). This bundle of close to a million fibers (corticospinal) form an important aspect of the crus cerebri located in the midbrain, and also make up a major part of the posterior limb of the internal capsule. The long axons that run in the cerebrospinal tract descend into the brainstem as part of large fiber bundles called the cerebral peduncles. The long axonal tract continues down into the medulla region of the brain stem where it forms two large collections of axons known as the pyramids; the pyramids create traceable ridges on the external surface of the brainstem. Close to the region of the medulla, about 75 to 90 percent of the descended tract decussate or cross over to opposite sides of the brainstem via the pyramidal decussation (Kamson et al., 2014; Nathan & Smith, 1955; Welniarz et al., 2017).

The decussated tracts are referred to as the lateral corticospinal tract. This tract continues into the spinal cord and tend to cause movement to limbs opposite to the side of the cortex from which it originate from. For example, right tract would cause movement on the left limb and vice versa. The remaining 10 percent of the tract that did not decussate is referred to as the anterior (ventral) corticospinal tract. This tract continue down the ipsilateral side of the spinal cord. They have also been observed to finally decussate just before they synapse to the lower motor neurons.

Lateral corticospinal tracts have been shown to control the muscles of the opposite limbs while anterior corticospinal tract tend to control the muscles of the trunk, shoulders and neck. (Bear et al., 2001; Crossman & Neary, 2004). The majority (about 55 percent) of the corticospinal fibers terminate at the cervical level, 25 percent terminate at lumbosacral levels while 20 percent terminate at the thoracic level (Crossman & Neary, 2004).

The corticospinal tract helps in the control of motor output by allowing for the passage of information between the brain and the spinal cord. Studies have shown that the corticospinal tract in man has both polysynaptic and monosynaptic connections with spinal neurons. In the case of monosynaptic, the corticospinal tract connects directly to spinal motor neurons, while in the case of polysynaptic, the corticospinal tract first of all joins to the spinal interneurons (association neurons) before synapsing on the spinal motor neuron (Palmer & Ashby, 1992). The variations in the number of types of these synapses per muscle have been shown to exist as there are more monosynaptic connection in the biceps brachii of the upper limb compared to the triceps brachii (Brouwer & Ashby, 1990; Petersen et al., 2002).

Assessment of corticospinal excitability

A generalized and effective way of determining the influence or effect of cycling modes on the overall motor output is by investigating the excitability of the corticospinal pathway. The corticospinal pathway is a complex interaction of the motor cortex and spinal motor neurons which form a major descending tract that is involved in the voluntary control of human motor outputs (D. A. Forman et al., 2015). The corticospinal pathway is composed of spinal and supra-spinal motor neurons or tracts which helps to regulate voluntary motor actions. Corticospinal excitability can be assessed using the TMS. While using a TMS, a MEP is recorded. Measuring the amplitude of the MEP gives an overview of the excitability mediated by the supra-spinal neurons.

TMS is delivered using a bi-directional electromagnetic coil which generates a magnetic field that passes through the cranium. The coil is placed tangentially to the vertex (midpoint) of the head. Once a charge of appropriate intensity is delivered, cortical interneurons are activated which in turns activate the cortical motoneurons. These cells constitute the starting point of the descending corticospinal tract which synapse either to the spinal interneurons or directly on to the spinal motoneurons. In cases of polysynaptic pathways, spinal interneuron might synapse with more than one interneurons before finally synapsing on to the spinal motoneurons. The spinal motor neurons then further synapse onto the peripheral nerves that run directly into the muscle to which it innervates (Klomjai et al., 2015). Motor units are recruited in an orderly sequence from the smallest to the largest according to the size principle (Henneman & Mendell, 1981). This constitute the synaptic pathway to which a muscle is activated when induced by electromagnetic impulses from TMS. The peak to peak amplitude of the MEP generated is used to estimate corticospinal excitability (Klomjai et al., 2015).

In this study, we expect to carry out different tasks, i.e. synchronous and asynchronous cycling, and investigate their effects on corticospinal excitability using TMS. If there are any effect, we intend to note them and discuss on various reasons for the observed changes. This study would be the first of its kind and would be investigating some concepts that has never been investigated before in human motor neural control.

METHODOLOGY

Ethical approval

Prior to recruiting participants, ethical approval will be sought from the Interdisciplinary Committee on Ethics in Human Research (ICEHR) at Memorial University of Newfoundland. The protocols

will be carried out in accordance with the Tri-Council Guidelines in Canada and all potential risks fully disclosed to all participants.

Participants

A total of about 10-15 participants will be recruited for this study, and they will be required to participate in two lab sessions.

Participants will be excluded if:

- They have had an upper body injury within the last 6 months
- Have a medical condition that prevents them from exercising
- Have any form of neurological disease or impairment

Participants will consist of graduate students, faculty and undergraduate students. They will be contacted directly by the principal investigator to ask if they wish to participate. The study will be fully explained to them and they will be repeatedly reminded that they are free to choose whether they wish to participate in the study. They will be also reminded that failure to participate in the study will not in any way, now or ever, negatively impact either their grade in a course, performance in a lab, reference letter recommendations and/or thesis evaluation. Only information on those that participate in the study will be known. The identities of persons' not wishing to participate will not be discussed. The consent form will be distributed prior to day of data collection to ensure that participants are fully aware of the study methods prior to attending. Written consent will be obtained in the lab immediately before data collection begins and after any/all questions from the participant have been adequately addressed. After consent of participants has been given, they will be asked to fill out three questionnaires;

1. Magnetic Safety Checklist this is to screen for contraindications to magnetic stimulation (Rossi et al., 2009).

2. Physical Activity Readiness Questionnaire (PAR-Q) which is to screen for contraindication to physical activity (Canadian Society for Exercise Physiology, 2002).
3. Edinburg Handedness Inventory which will be used to determine hand dominance of participants (Veale, 2014). This is important because differences has been observed in the neural control to a dominant and non-dominant limb (Daligadu et al., 2013).

Experimental Setup

The study will be an experimental study, and will require two days of participation, with Day 1 lasting approximately 1 hour and Day 2 approximately 2 hours.

Day 1 will be used as a familiarization day to expose potential participants to the stimulation paradigms (Mwave and TMS) to ensure they are comfortable with the protocols.

Day 2 will be the actual testing/experimental day provided the participants are still willing to participate. A complete description of the protocols and consent form will be administered prior to Day 1.

Protocol

Day 1 will be used to familiarize the participants with all of the afore-mentioned stimulation techniques.

DAY 2 will be used to assess corticospinal excitability (brain and spinal cord) during arm cycling with various modes and intensities. Participants will undergo EMG preparation i.e. surface electrodes will be placed on four of the participant's muscles (biceps brachii and triceps brachii of

the dominant arm) following light skin abrasion and cleansing with an alcohol swab. EMG refers to the electrical signals produced and recorded from the muscles.

Participants would be asked to perform arm cycling using an arm cycle ergometer (SCIFIT ergometer, model PRO2 Total Body, Tulsa, OK). Cycling modes (i.e. synchronous and asynchronous) will be randomized. They will be allowed to seat comfortably in an upright position and also at a reasonable distance to the hand pedals to ensure absence of trunk variations or stretching during cycling (Lockyer et al., 2018). The Participants will wear wrist braces so as to limit the amount of wrist flexion and extension during cycling thereby reducing the influence of heteronymous reflex connections that exist between the wrist flexors and the biceps brachii (Manning & Bawa, 2011). They will cycle with forearm fixed in a neutral position.

Muscular responses (EMG) will be assessed at a single location of the rhythmic movement – i.e. arm position at the 6 o'clock (flexion) position relative to a clock face during two cycling modes and at three separate cycling cadences.

Electromyography

After undergoing EMG preparation, pairs of disposable Ag-AgCl surface electrodes (MediTrace 130 Foam Electrodes with conductive adhesive hydrogel; Covidien IIC) will be used to record EMG signals from the biceps and triceps brachii muscles of the dominant limb. These electrodes would be positioned on the belly of the biceps brachii muscle and on the lateral head of the triceps brachii muscle. A ground electrode will be positioned on the lateral epicondyle of the dominant arm.

Brachial Plexus Stimulation

Every participant will be given a continuous current stimulator which will cause an electrical stimulation of the brachial plexus at Erb's point. This will be used to elicit compound muscular action potentials (M-waves) during the course of the study. The anode end of the stimulator will be placed on the acromion process, and the cathode end in the supraclavicular fossa. The stimulus strength of the stimulator will be steadily raised until maximal M-wave (M-max) is achieved. Because M-max can alter within the course of an experiment (Crone et al., 1999), the stimulation intensity will be adjusted by 20% to ensure that M-max is evoked throughout the investigation.

Transcranial Magnetic Stimulation

The transcranial magnetic stimulator (TMS) would be used to generate motor evoked potentials (MEPs). The stimulation would be generated using an electromagnetic coil which would be placed tangentially to the vertex of the coil. The vertex would be determined by measuring the midpoint position between the participant's nasion and inion, and the midpoint between the participant's tragi (D. A. Forman et al., 2015; Lockyer et al., 2018). The direction of the coil would be adjusted depending on the dominant arm. Stimulation intensity would be gradually increased until a resting motor threshold (RMT) is achieved. A resting motor threshold (RMT) is the minimum stimulation intensity at which a visible motor evoked potential (MEP) is observed. After a resting motor is recorded, the threshold is then increased by 15-20%, this is to ensure that a motor evoked potential is observed throughout the course of the experiment.

Randomization

The order of stimulation techniques (TMS and M-wave) will be randomized and performed within each trial. The order of cycling modes will also be randomized. The background and evoked EMG recordings during arm cycling will be recorded from the target muscles. In total, participants

will be asked to complete 16 arm cycling trials lasting 3 minutes each. Recording would be made at a 6 'o' clock position (flexion) x 2 cycling modes (synchronous and asynchronous) x 3 cycling intensities (30rpm, 60rpm and 90rpm).

Data Analysis

Independent variables:

1. cycling modes (synchronous and asynchronous)
2. cadences

Dependent variables:

1. MEP amplitude
2. Mwave amplitude
3. EMG amplitudes

The data would be analysed using IBM SPSS. Descriptive statistics of data would be used to determine the general characteristics of participants. The amplitude of the MEP (normalized to the Mmax) would the measured for each cycling mode and intensities. Separate two way repeated measure ANOVAs (MODE X CADENCE) will be performed for each variable. If a significant difference is observed, a repeated pairwise comparison using Bonferroni post hoc test would be used to determine where exactly the difference exist.

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