FACTORS INFLUENCING CORTICOSPINAL EXCITABILITY DURING ARM CYCLING

by

A Dissertation submitted to the

School of Graduate Studies

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Faculty of Medicine

Memorial University of Newfoundland

October 2024

St. John's Newfoundland

Abstract

Humans can effortlessly navigate their environments and perform a variety of motor tasks, yet the neural processes underlying these movements are complex. The corticospinal pathway, a major descending pathway involved in the voluntary control of human movement, can be assessed non-invasively using various stimulation techniques. However, despite continued advancements in neurophysiology, our understanding of the corticospinal pathway's role in dynamic, functional movements remains limited. This is partly because most research has focused on corticospinal excitability during static or minimally demanding tasks, leaving a substantial gap in our knowledge of its role during more natural, rhythmic motor outputs. In our lab, we use arm cycling, which resembles other forms of locomotion, to study the modulation of corticospinal pathway excitability under different conditions. This dissertation aims to advance our understanding of the neural control of arm cycling in healthy participants, specifically examining some of the factors that influence descending corticospinal drive and spinal motoneurone excitability during arm cycling.

Chapter 2 presents an invited review paper outlining methodological considerations for studying corticospinal excitability during dynamic locomotor outputs, providing a foundation for the subsequent experiments. Chapters 3 to 5 contain studies published in peer-reviewed journals, each addressing specific research questions. In Chapter 3, we investigated whether focusing on maintaining a specified cadence during arm cycling would affect corticospinal excitability and found no significant effect. Chapter 4, explored how varying cycling and stimulation intensities would influence corticospinal and spinal

excitability, revealing that both increased with cycling intensity up to a plateau, with differences observed by stimulation intensity. At high cycling intensities, we suggested that greater contributions from supraspinal centres may occur to produce the motor output. Chapter 5 examined the effects of a two-week arm cycling sprint interval training intervention on corticospinal and spinal excitability during arm cycling. The results showed enhanced spinal excitability post-training, with no change in corticospinal excitability. Given that no changes occurred in controls, we suggested that the increase in spinal excitability post-training represented a neural adaptation to training. Collectively, these findings enhance our understanding of the corticospinal pathway's role during locomotor outputs and highlight the need for future work.

General Summary

The neural control of human movement is fascinatingly complex. Yet, researchers have a rudimentary understanding of the precise mechanisms that underlie the performance of many human movements. Simply, voluntary movement occurs when excitatory 'signals' from the brain are transmitted to the muscle, resulting in muscle contraction(s) and subsequent joint movement. These 'signals' are transmitted through the central nervous system and to the muscle via conduits called tracts. In humans, one of the primary tracts involved in producing voluntary movement of the limbs is the descending corticospinal tract. Over the past few decades, researchers have used various non-invasive stimulation techniques to probe the *excitability* of the corticospinal tract to understand better how this tract contributes to human movement.

Interestingly, however, most of this work has come from studies assessing corticospinal excitability changes during tasks requiring little movement. Thus, if we wish to understand the corticospinal control of human movement, we must start assessing changes in excitability during more functional, dynamic tasks. In our lab, we use arm cycling, as a model of human locomotion, and have shown that corticospinal excitability is influenced by several factors, including the task being performed, phase, direction, mode, and intensity of the motor output. Moreover, the effects of exercise training and various attentional demands have been suggested as important factors in modulating corticospinal pathway excitability. The current thesis explores factors influencing corticospinal excitability during a dynamic locomotor output, arm cycling.

Chapter 2 comprises a published invited review paper highlighting many methodological factors that must be considered when examining potential changes in corticospinal excitability during dynamic motor outputs in humans. This review provides much of the groundwork for the information in subsequent chapters of this thesis. Study #1 (Chapter #3) examines how maintaining a specified arm cycling cadence affects corticospinal excitability. Study #2 (Chapter #4) investigates the effects of varying arm cycling and stimulation intensities on corticospinal and spinal excitability of upper limb muscles. Lastly, Study #3 (Chapter #5) looks at whether corticospinal and spinal excitability is altered following an intense, but relatively short, aerobic exercise training intervention.

COVID-19 Impact Statement

The COVID-19 pandemic had and continues to have massive impacts globally. Like many other graduate students, I was forced to modify my initially proposed PhD research plan due to the COVID-19 restrictions/shutdowns at Memorial University during the pandemic. The following provides a brief description of my proposed research plan prior to the COVID-19 shutdowns and how I changed this plan to complete my dissertation since the pandemic.

Prior to the Pandemic:

Prior to the pandemic, I had proposed to include three separate research projects in my dissertation all centring around the short- and longer-term effects of aerobic exercise training on the modulation of corticospinal and spinal excitability during arm cycling. My three proposed projects were to: 1) examine the effects of a single session of aerobic exercise on corticospinal and spinal excitability, 2) investigate the influence of 2 weeks of arm cycling sprint interval training (SIT) – a form of aerobic exercise training – on corticospinal and spinal excitability, and 3) investigate potential differences in corticospinal and spinal excitability between chronically-aerobic exercise-trained and untrained individuals. These projects all involved face-to-face data collection with healthy, neurologically intact human participants, which was not permitted at various times throughout the COVID-19 pandemic. Before the pandemic, I started data collection for Project #2 because it involved much more data collection and participant/researcher time commitment. The rationale was to get the most technically challenging study completed first. When the pandemic hit, I was over 75% of the way through data collection on Project

#2, and I was prevented from doing any data collection for approximately eight months. Once restrictions were loosened, I was able to get back in the lab and complete the data collection for this project. This project is included as Chapter 5 in my dissertation and has been published in the *Journal of Applied Physiology*. Unfortunately, Projects #1 and #3 were not completed (despite having ethics approved for Project #1). In August of 2021, based on the recommendation of my PhD committee, we decided to alter the scope of my dissertation research to ensure I could complete my PhD during the unknowns of the pandemic.

Changes due to the Pandemic:

When the COVID-19 pandemic hit, my committee and I met and decided that I would include other projects I had worked on throughout my PhD into my dissertation, instead of the initially proposed projects. Projects #1 and #2 in my dissertation now differ from the original proposal but still involve arm cycling and the modulation of corticospinal excitability. The rationales and aims of the included projects were not directly linked as those in my initial plan, resulting, perhaps, in a less linear connection between studies.

Project #1 (Chapter 3) examined whether maintaining a specified arm cycling cadence influenced corticospinal excitability recorded from the biceps brachii. Project #2 (Chapter 4) explored how different stimulation intensities and cycling workloads altered corticospinal and spinal excitability during arm cycling. Project #3 (Chapter 5) assessed the influence of 2 weeks of high-intensity arm cycling training on corticospinal and spinal excitability projecting to the biceps brachii when assessed during arm cycling following

training. Thus, despite the lack of direct linkage between chapters, the overarching aim of my thesis was to enhance the understanding of the factors influencing corticospinal pathway excitability during arm cycling.

In addition to the three projects in my thesis, I included an invited review paper (Chapter 2), which we published in the *Journal of Neurophysiology* in 2021. This review provides much of the groundwork for the subsequent chapters in this thesis and discusses some of the methodological considerations for assessing the corticospinal pathway during locomotor outputs. This review serves as a foundational paper for future studies examining the corticospinal control of human movement.

The COVID-19 pandemic substantially disrupted the linear progression of my projects, necessitating flexibility and constant adjustments. Although the journey was not as straightforward as initially proposed, it enriched my research experience and helped me develop a more comprehensive expertise.

Co-Authorship Statements

The Interdisciplinary Committee on Ethics in Human Research (ICEHR) at Memorial University of Newfoundland granted ethics approval for all original research studies presented in this thesis.

Chapter 1. Chapter one was written by Evan Lockyer and edited by Dr. Power.

Chapter 2. Chapter two is an invited review paper published in the *Journal of Neurophysiology*: Lockyer EJ, Compton CT, Forman DA, Pearcey GE, Button DC, Power KE. **Moving forward: Methodological considerations for assessing corticospinal excitability during rhythmic motor output in humans.** *J Neurophysiol*. 2021**,** 126(1), 181-194. doi: 10.1152/jn.00027.2021 (copyright license #: 5824191465500). This review was a collaborative effort between Evan Lockyer, Chris Compton, Dr. Greg Pearcey, Dr. Davis Forman, Dr. Duane Button, and Dr. Kevin Power of which Evan is the co-first author. Evan Lockyer helped conceive the sections included in the review, wrote extensive sections of the review, was responsible for creating both figures, and assisted with the editing process. All authors approved the final version.

Chapter 3. Chapter three involves Study #1 of the thesis. The ICEHR approval certificate number for this study is ICEHR #20171250. This chapter was published in *Brain Sciences*: Lockyer EJ, Nippard AP, Kean K, Hollohan N, Button DC, Power KE. **Corticospinal Excitability to the Biceps Brachii is Not Different When Arm Cycling at a Self-**

Selected or Fixed Cadence. *Brain Sciences*. 2019; doi: 10.3390/brainsci9020041. Permission to use this manuscript in this thesis was not required as the journal is open access. Evan Lockyer and Dr. Power designed the experimental protocols. Anna Nippard (graduate student), Nicole Hollohan and Kaitlyn Kean (undergraduate students) were students that Evan mentored, and they assisted Evan with the data collection for this project by helping with participant preparation and aspects of the data collection. Evan Lockyer performed all data extraction and analysis and completed the statistical analyses, drafted the manuscript, and was responsible for all figures. Evan Lockyer, Dr. Duane Button, and Dr. Power edited the manuscript, and all authors approved of the final version.

Chapter 4. Chapter four focuses on Study #2 of the thesis. The ICEHR approval certificate number for this study is ICEHR #20181196. This chapter was published in *Brain Sciences*: Lockyer EJ, Hosel K, Nippard A, Button DC, Power KE. **Corticospinal-Evoked Responses from the Biceps Brachii during Arm Cycling across Multiple Power Outputs.** *Brain Sciences*. 2019; doi: 10.3390/brainsci9080205. Permission to use this manuscript in this thesis was not required as the journal is open access. Evan Lockyer and Dr. Power conceived and designed the experimental protocols described in this chapter. Katarina Hosel (undergraduate student) and Anna Nippard (graduate student) were students in Dr. Power's Lab who Evan mentored, and they assisted with participant preparation and aspects of the data collection. Evan Lockyer performed all data extraction and analysis and completed all statistical analyses, drafted the manuscript, and was

responsible for all tables and figures. Evan Lockyer, Dr. Duane Button, and Dr. Power edited the manuscript, and all authors approved the final version.

Chapter 5. Chapter five focuses on Study #3 of the thesis. The ICEHR approval certificate number for this study is ICEHR #20191993. This chapter was published in the *Journal of Applied Physiology*: Lockyer EJ, Alizadeh S, Compton CT, Power KE. **Two weeks of arm cycling sprint interval training enhances spinal and reduces supraspinal excitability to the biceps brachii.** *J Appl Physiol.* 2023 Apr 27. doi: 10.1152/japplphysiol.00367.2022 (copyright license #: 5824211476823). Evan Lockyer and Dr. Power conceived and designed the experimental protocols described in this chapter. Evan Lockyer conducted the data collection, with assistance from Shahab Alizadeh (post-doc) and Chris Compton (graduate student). Evan Lockyer performed all data extraction and analysis and completed all statistical analyses, drafted the manuscript, and was responsible for all tables and figures. Evan Lockyer and Dr. Power edited the manuscript, and all authors approved the final version.

Chapter 6. Chapter six was written by Evan Lockyer and edited by Dr. Power.

Acknowledgements

The completion of this doctoral dissertation would not have been possible without the steadfast support of many important people in my life. First and foremost, I would like to express my sincere appreciation to my supervisor, friend, and mentor, Dr. Kevin Power. Kevin, I am deeply appreciative of your decision to take me under your wing as a master's student many moons ago and for putting up with me ever since! Your consistent encouragement, recognition of my potential, and gentle pushes (and memes) when needed have been invaluable. I am forever indebted to you for the opportunities and wisdom you have bestowed upon me. You truly epitomize what it means to be an exemplary supervisor and I look forward to a lifetime of friendship. My official departure from the Human Neurophysiology Lab (HNL) will certainly be a bittersweet one.

I would also like to thank my sincere gratitude to Dr. Duane Button, my co-mentor and friend. Duane, your constructive feedback and mentorship have been instrumental in my growth, both academically and personally, over the years. I am grateful for your generous invitations to join your lab group on several research projects and for permitting me the opportunity to present some of this work at national and international conferences. Thank you for providing me with countless hours of advice (life and research-related). You have no idea the amount of respect and appreciation I have for you.

Furthermore, I extend my thanks to committee members Drs. Xihua Chen and Matthew Parsons for their guidance and contributions throughout my doctoral journey. Your scientific insights and encouragement have been invaluable amidst the challenges that I have faced during this wild ride.

To my fellow lab mates, both past and present – I extend my deepest gratitude for your friendship and unwavering support throughout the years. Despite being the longest-serving student in the HNL, I cherish the connections I've forged with each of you, and I wish you all the brightest future ahead. To all members of the HNL who contributed, in any capacity, to the work presented in this dissertation (along with the multitude of side projects I've been involved in), I offer my heartfelt thanks. Your dedication and hard work have been indispensable, and this dissertation would not have been possible without your contributions.

I am also indebted to the various funding agencies that have generously supported my PhD journey. My sincere appreciation goes to the F.A. Aldrich Fellowship at Memorial University of Newfoundland, the Natural Sciences and Engineering Research Council, and the Faculty of Medicine's Dean Fellowship Award for their financial assistance over the past seven years.

Lastly, but certainly not least, I extend my deepest gratitude to my family and friends. To my parents, Debbie and Neil, I owe everything I am to your love and guidance throughout the years. Your selflessness and sacrifices have shaped me in many ways, and I am endlessly grateful. This dissertation would not have been possible without your unwavering support. I am truly blessed to have the best parents in the world. To my sisters, Erika and Emily, thank you for your love and support. I am incredibly proud of your accomplishments and wish you both continued successes. To my friends, your love and support have been instrumental. I look forward to many more years of love and friendship.

Finally, to my wife Natasha Buckle, I honestly don't know where I would be if it were not for you. You inspire me every single day with your work ethic, determination, and your passion for bettering yourself and others. The completion of this dissertation is a direct

testament to your continuous work ethic that has undoubtedly influenced me. I am incredibly proud of the person you are, and I cannot wait to see what our future together holds. I cannot wait to see you be the best mother ever to our baby boy, Jack, when he enters the world. You are already the best mawma to our fur-child, Gallagher! We are so lucky!

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List of Abbreviations

AE – aerobic exercise

ADL – activities of daily living

ANOVA – analysis of variance

AMT – active motor threshold

AUC – area under the curve

Ag-AgCl – silver-silver chloride

bEMG – background EMG

CMEP – cervicomedullary motor evoked potential

cm – centimetres

CNS – central nervous system

CPG – central pattern generator

CTL – control

EMG – electromyography

EPSP – excitatory postsynaptic potential

FC – Fixed cadence

FDI – first dorsal interosseus

GABA – gamma aminobutyric acid

HIIT – high-intensity interval training

HR – heart rate

ICF – intracortical facilitation

IHI – interhemispheric inhibition

iSP – ipsilateral silent period

kg – kilograms

LICI – long-interval intracortical inhibition

MEP – motor evoked potential

M_{max} – maximum compound muscle action potential

MSO – maximal stimulator output

mV – millivolts

MVC – maximal voluntary contraction

M1 – primary motor cortex

NMDA – N-methyl-D-aspartate

PICs – persistent inwards currents

PMC – premotor cortex

PNS – peripheral nerve stimulation

PO – power output

RMT – resting motor threshold

RPE – rating of perceived exertion

RPM – revolutions per minute

SCCR – spontaneous chosen crank rate

SD – standard deviation

SE – standard error

SICI – short-interval intracortical inhibition

SIT – sprint interval training

SMA – supplementary motor area

SRC – stimulus-response curve

SSC – self-selected cadence

TMS – transcranial magnetic stimulation

TMES – transmastoid electrical stimulation

TTE – time-to-exhaustion

W – watts

μV – microvolts

Chapter 1: INTRODUCTION AND OVERVIEW

1.1 Neural Control of Human Movement

As humans, we perform a variety of dynamic and coordinated movements daily with different goals, but generally little conscious thought. The ability to perform finely controlled motor outputs reflects the efficiency of our neuromuscular system, which is mediated by a complex interaction of inputs between the central (i.e., brain and spinal cord) and peripheral (i.e., neuromuscular junction, peripheral nerves, and sensory receptors) nervous systems. Although the precise mechanisms that produce human motor outputs are not fully understood, approximately two centuries of research have provided us with a relatively detailed depiction of many of the processes through which human movement is generated. Although tremendously over-simplified, voluntary movement is essentially produced after 'signals' from the cerebral cortex are sent to skeletal muscles, which ultimately leads to muscle contraction. These signals are transmitted to and from the muscles via bundles of neuronal axons, referred to as tracts or pathways. In humans, one of the major tracts involved in producing motor outputs is the descending corticospinal tract, though other descending tracts (e.g., propriospinal, reticulospinal, vestibulospinal, and rubrospinal) and sensory inputs also contribute to voluntary motor output performance (for review of these descending and sensory inputs, see Lemon, 2008). In this thesis, the corticospinal tract will be primarily discussed (see section **1.2 Overview and History of the Corticospinal Tract** below). A simplistic diagram of the neuromuscular system and some important sites and pathways of input processing are portrayed in **Figure 1.1**. A

superficial description of the neural control of human movement can be described as follows:

i. Voluntary movement typically originates from higher-order cortical areas involved in motor planning, such as the premotor cortex (PMC) and supplementary motor area (SMA). Once the plan for movement has been created, depolarization of neurones within the primary motor cortex (M1), a lower-order cortical area, occurs.
ii. This depolarization leads to the activation of upper motoneurones within the M1, which comprise some of the origins of the *corticospinal tract*.
iii. Upon depolarization, action potentials travel down the axons of the upper motoneurones, either crossing over at the pyramidal decussation or continuing ipsilateral, and synapse either directly or indirectly onto large spinal/ lower motoneurones within the anterior horn of the spinal cord.
iv. For rhythmic locomotor outputs, the descending inputs activate complex networks of interneurones within the spinal cord, known as *central pattern generators* (CPGs) prior to activation of the spinal motoneurones. This CPG activity helps regulate the oscillating activation of spinal motoneurones for flexor and extensor muscles of the limbs, which underlies the rhythmic and alternating pattern of locomotor behaviour.
v. The spinal motoneurone acts as the final common path that all inputs must travel through to produce movement given its direct innervation of skeletal muscle. The spinal motoneurone soma integrates all the excitatory and inhibitory inputs (afferent and motor) to determine whether action potentials are generated.
vi. If generated, action potentials travel down the axons of the spinal motoneurones (motor nerves) to the neuromuscular junction to recruit skeletal muscle fibres. The motoneurone and the muscle fibres that it innervates is known as a motor unit.

vii. At the neuromuscular junction, the action potentials signal the release of acetylcholine into the synaptic cleft, which binds to nicotinic acetylcholine receptors on the motor end plate of the muscle cell membrane, triggering an action potential.

viii. The resultant action potential triggers a sequence of events that ultimately leads to contraction of the skeletal muscle fibres.

ix. Throughout the execution of the movement, afferent feedback loops to both the spinal cord and supraspinal centres plays an essential role in monitoring and adjusting movement parameters in real-time.

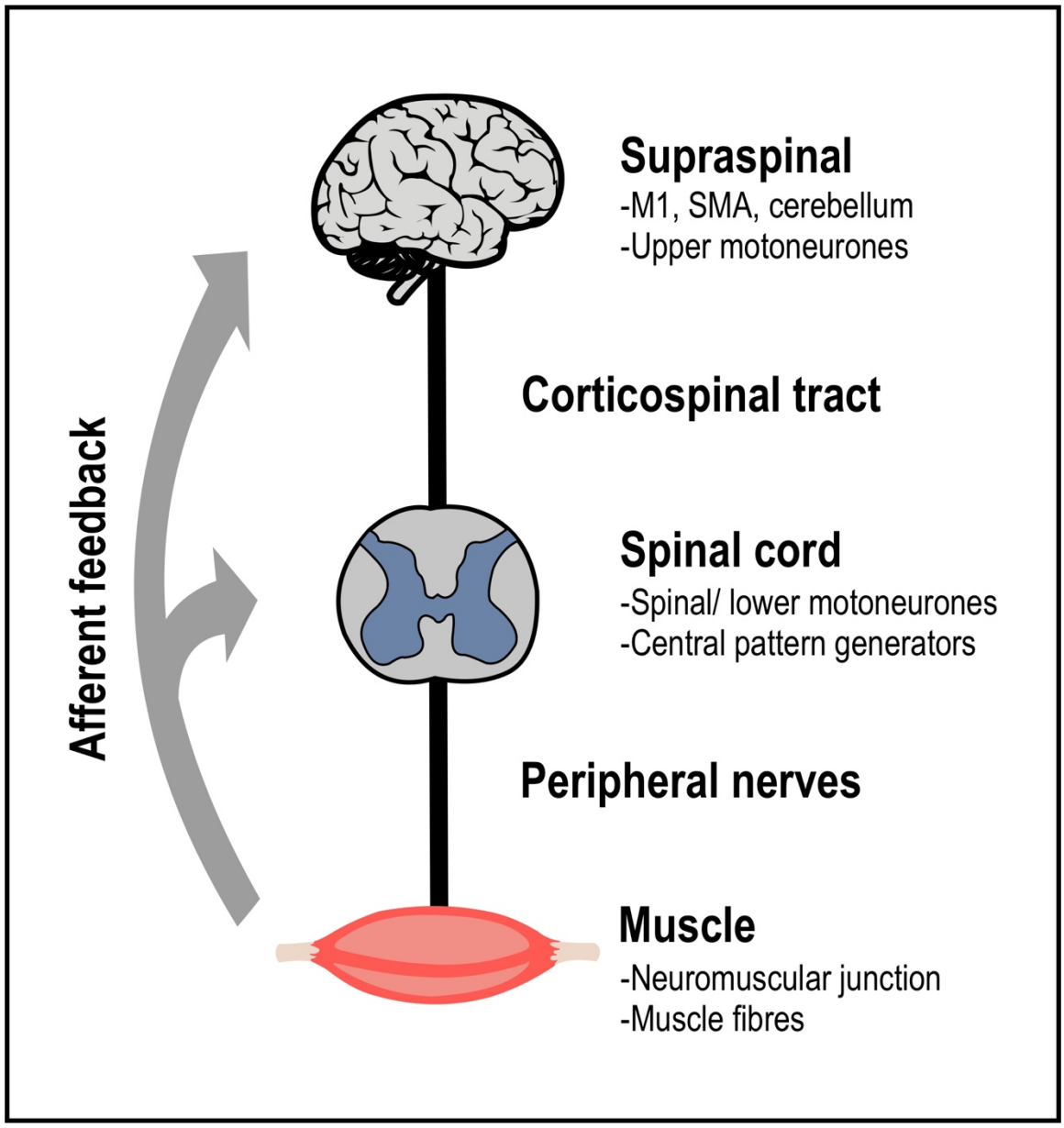

Figure 1.1. Diagram of some of the sites and inputs influencing human movement

Note: The black vertical line does not indicate specific axons, but rather indicates that all three sites (i.e., brain, spinal cord, and muscle) are connected. The exact synaptic efferent and afferent connections are not indicated for simplicity.

1.2 Overview and History of the Corticospinal Tract

The corticospinal tract is essential for the execution of voluntary motor outputs in humans, ranging from the most intricate finger manipulations to broader limb actions (Heffner & Masterton, 1975; Heffner & Masterton, 1983; Lemon, 2008; Lemon et al., 1986; Nathan & Smith, 1955). Neurones of the corticospinal tract (commonly referred to as upper motoneurones) arise from various regions of the cerebral cortex and have axons that terminate either directly (i.e., monosynaptic) or indirectly (i.e., polysynaptic) onto α-motoneurones (also referred to as lower motoneurones) within the spinal cord (Lemon, 2004; Lemon, 2008; Maier et al., 1997; Welniarz et al., 2017). As such, the corticospinal tract serves as the primary conduit through which motor signals from the cerebral cortex are transmitted to motoneurones in the spinal cord, which ultimately innervate and lead to contraction of skeletal muscles (Davidoff, 1990; Martin, 2005; Welniarz et al., 2017). The current knowledge of the corticospinal tract and its course throughout the central nervous system in humans is due, in large part, to post-mortem anatomical mapping and histological staining discoveries by many key scientists in the field of neuroscience. A brief history of some of these findings related to the corticospinal tract in humans are discussed in the following paragraphs.

Early descriptions of the corticospinal tract can be traced back to the late 17th century with the pioneering observations described by anatomist Thomas Willis (1621-1675). In his seminal work, “Cerebri Anatome”, published in 1664, Willis provided an early description of the medullary pyramids and the nerve fibres coursing through them, which formed a tract that descended from the cerebral cortex to the spinal cord (Nathan & Smith, 1955). As such, the tract was initially named the pyramidal tract (Davidoff, 1990; Nudo &

Masterton, 1990a). Subsequent work traced the nerve fibres inferiorly from the medulla and provided important details of the organization of the tract, including the decussation of many of the fibres at the base of the pyramids (called the pyramidal decussation). However, it was not until 1851 that an adequate delineation of the distal tract was described (Nathan & Smith, 1955). Australian neurologist Ludwig Türck (1810-1868) was the first to describe two separate tracts distal to the pyramidal decussation (now known as the lateral and anterior corticospinal tracts; see below), though he did not make the connection that the tracts were divisions of the same pathway. This connection was made approximately 15 years later by French physicians Charles-Joseph Bouchard (1837-1915) and Jean-Martin Charcot (1825-1893). The cells of origin of the tract remained a mystery for many years until some light was shed in 1874 with the discovery of giant pyramidal neurones located in layer V of the primary motor cortex (M1) by Ukrainian histologist Vladimir Betz (1834-1894) (Kushchayev et al., 2012). These neurones, now named after Betz, have axons that extend from the cortex to the spinal cord and, therefore, were initially thought to be the exclusive origin of the pyramidal tract (Nathan & Smith, 1955; Nathan et al., 1990; Nudo & Masterton, 1990a). Later studies disproved this suggestion, however, since Betz cells account for only a small percentage of the total fibres comprising the pyramidal tract (Davidoff, 1990; Lassek, 1940). In light of these discoveries, the pyramidal tract became known as the "corticospinal tract", as it reflected a more accurate representation of the pathway's anatomical origins and terminations; the motor cortex and the spinal motoneurones (Nathan & Smith, 1955). Although still sometimes referred to as the pyramidal tract, the pathway will be referred to as the corticospinal pathway for the remainder of this thesis.

Since the early investigations of the corticospinal pathway in humans, advances in experimental techniques and evidence from non-human animal models (specifically primates) have vastly improved our understanding of the tract's organization and connectivity (Dum & Strick, 1996; Kuypers, 1963, 1964, 1978, 1987; Lawrence & Kuypers, 1968; Seo & Jang, 2013). We now know that the corticospinal tract emerges from diverse cortical areas, including the M1, the premotor and supplementary motor areas, as well as the somatosensory areas, and terminates widely throughout the brainstem and spinal cord (Lemon, 1988; Lemon, 2008; Maier et al., 2002; Seo & Jang, 2013; Zilles et al., 1995). While variations in the numbers exist across studies and species, approximately 60% of corticospinal tract fibres originate from neurones in the motor cortex, with approximately 30% from the M1 and another 30% from the premotor and supplementary motor areas. The remaining 40% arise from the primary somatosensory cortex (Canedo, 1997; Davidoff, 1990; Dum & Strick, 1991; Nudo & Masterton, 1990a; Seo & Jang, 2013). The axons of these neurones comprise the corticospinal tract itself, which follows a relatively well-established path through the nervous system to the spinal motoneurones (Kuypers, 1964; Lemon, 2008; Nathan et al., 1990).

As the axons of corticospinal neurones descend from the various regions of the cerebral cortex, they converge to form a dense bundle of fibres that courses through the internal capsule and cerebral peduncles before reaching the brainstem (Armand, 1982; Nudo & Masterton, 1990a). The axons then travel through the white matter of the brainstem, forming the pyramids, as they continue through the midbrain, pons, and medulla. At the base of the medulla, the majority (~75-90%) of the descending corticospinal axons decussate and descend in the contralateral white matter of the spinal

cord, as the lateral corticospinal tract (Brouwer & Ashby, 1990; Davidoff, 1990; Nathan et al., 1990). Axons of the lateral corticospinal tract travel the entire length of the spinal cord and synapse onto specific spinal motoneurones ipsilateral to the side which they have decussated (Dum & Strick, 1996; Nathan et al., 1990; Welniarz et al., 2017). A smaller percentage (~10-25%) of the corticospinal axons remain ipsilateral and descend the spinal cord, forming the anterior corticospinal tract (Davidoff, 1990; Lassek & Evans, 1946; Lemon, 2008; Martin, 2005). Axons of the anterior corticospinal tract traverse the spinal cord ipsilaterally, but cross over and synapse with motoneurones at their termination sites, predominantly within the cervical and upper thoracic regions of the spinal cord (Lemon, 2008; Nathan & Smith, 1955; Nathan et al., 1990). Consequently, the anterior corticospinal tract plays an important role in controlling axial and proximal muscles, whereas the lateral corticospinal tract is predominantly involved in producing fine motor outputs of the distal extremities (Brinkman & Kuypers, 1973; Nathan & Smith, 1955; Nathan et al., 1990). Importantly, despite following divergent paths, both the lateral and anterior corticospinal tracts exert their influence on spinal motoneurones located contralateral to their origin. Thus, corticospinal neurones originating from the left hemisphere, for instance, traverse the right side of the spinal cord, ultimately innervating muscles of the right limbs. Conversely, corticospinal neurones originating from the right hemisphere navigate the left side of the spinal cord, innervating muscles of the left limbs.

One of the main features of the corticospinal tract that makes it phylogenetically unique to humans and our ancestral cousins, the primate, is the existence of direct (i.e., monosynaptic) connections between corticospinal neurones and spinal motoneurones (Bernhard & Bohm, 1954; Bernhard et al., 1953; de Noordhout et al., 1999; Kuypers, 1964;

Palmer & Ashby, 1992). Through these "cortico-motoneuronal" synapses, the motor commands generated in the cerebral cortex are efficiently transmitted to the spinal cord, resulting in the precise and rapid activation of specific muscle groups (Nudo & Masterton, 1990b; Porter & Lemon, 1993). Consequently, these direct connections have long been suggested as an evolutionary adaptation in primates to subserve finger dexterity and allow for more direct cortical control for fine-skilled motor outputs (Bernhard et al., 1953; Lemon et al., 1986; Maier et al., 1997; Porter & Lemon, 1993). Notably, these monosynaptic cortico-motoneuronal synapses do not exist in other mammals such as rats or cats (Alstermark et al., 1991; Alstermark et al., 2004; Yang & Lemon, 2003). It is important to note, however, that the exact number and extent of direct cortico-motoneuronal connections in humans is not fully elucidated, but there is some evidence to suggest that they may vary between different motoneurone pools (Brouwer & Ashby, 1990, 1992; Fetz & Cheney, 1980; Palmer & Ashby, 1992; Petersen et al., 2003). For example, motoneurones innervating distal muscles exhibit stronger monosynaptic corticospinal connections than proximal muscles of the upper limb, while within the upper limb, the biceps brachii displays greater monosynaptic connections than the triceps brachii (Palmer & Ashby, 1992). While the function of monosynaptic projections to the distal musculature is thought to underlie the skilled performance of the hands and fingers in primates (Porter & Lemon, 1993), the functional difference between flexor and extensor muscles of proximal muscles is not as well-understood.

Another notable characteristic of the direct cortico-motoneuronal pathway in primates is the fact that the axon terminals of the descending corticospinal fibres are not prone to conventional presynaptic inhibition (Jackson et al., 2006; Nielsen & Petersen,

1994). This is unique to corticospinal fibres, as the terminals of other fibres (e.g., afferent fibres) that synapse with spinal motoneurones are indeed influenced by inhibitory interneuronal connections (Hultborn et al., 1987). This lack of presynaptic inhibition permits descending motor commands from the cortex to reach the spinal motoneurones with minimal modification, allowing the cortex to exert direct control over muscle force output.

While direct cortico-motoneuronal synapses are present and certainly contribute to motor output in humans, they are not the sole means for descending motor commands to be conveyed to the spinal motoneurones (Isa et al., 2007). Instead, many corticospinal projections make indirect (i.e., di- or polysynaptic) connections to the spinal motoneurones involving activation of one or more spinal interneurones (Alstermark et al., 1999; Isa et al., 2007; Isa et al., 2006; Sasaki et al., 2004). These spinal interneurones act as intermediaries between the corticospinal neurones and the spinal motoneurones and might form part of a spinal circuit, such as the propriospinal system (i.e., a network of interneurones within the spinal cord that connect segments of the spinal cord to each other) (Alstermark et al., 1999; Burke et al., 1994; Isa et al., 2007; Pierrot-Deseilligny, 2002; Sasaki et al., 2004). Although there is less direct evidence for these pathways in humans, evidence from primates has shown that C_3-C_4 propriospinal interneuronal connections play an important role in integrating sensory feedback and modifying the performance of complex bilateral motor outputs, especially of the upper limbs (Burke et al., 1994; Maier et al., 1998; Pierrot-Deseilligny, 2002). Accordingly, the current suggestion is that these polysynaptic propriospinal connections integrate a variety of inputs from descending corticospinal projections and ascending sensory afferents, and then distribute these signals onto various

motoneurone pools on both sides of the spinal cord, thus allowing for more flexible and adaptable motor control of complex bilateral motor tasks, like locomotion or reaching (Isa et al., 2007).

Spinal motoneurones represent the final common path through which all inputs must travel to produce motor output (Sherrington, 1906). As such, spinal motoneurones do not only receive inputs from descending corticospinal neurones. They receive inputs from a variety of other sources that collectively influence their responsiveness to discharge action potentials, also known as "excitability". These inputs include signals from other descending tracts (e.g., propriospinal, rubrospinal, reticulospinal and vestibulospinal) and sensory afferents (e.g., groups I-IV afferents) acting either directly or indirectly on the spinal motoneurones (Gandevia, 2001; Isa et al., 2013; Lemon, 2008; Riddle et al., 2009). Some of these inputs are excitatory (e.g., corticospinal neurones), while others have inhibitory effects on the motoneurone (i.e., most interneuronal connections) (Milner-Brown et al., 1975). Moreover, the intrinsic properties of the motoneurone itself will also influence its excitability. Ultimately, it is the sum of all the synaptic inputs and intrinsic properties that determines how excitable a spinal motoneurone is at a given moment in time.

1.3 Stimulating the Brain and Motor Pathways: A Brief History

The discovery of the electrical excitability of the cerebral cortex is considered one of the most influential findings in the history of movement neuroscience (Nathan & Smith, 1955). Following the discovery of the link between electricity and animal muscle in the

late 1700s by the Italian physicist Luigi Galvani (1737-1798) ("An Account of the Experiments and Discoveries of Lewis Galvani," 1792; Piccolino, 1998), many scientists shifted their focus to the electrical excitability of the brain. In 1870, German researchers Gustav Fritsch (1838-1927) and Edvard Hitzig (1838-1907) demonstrated that electrical stimulation to specific regions of the exposed cerebral cortex in dogs produced observable involuntary movement of the contralateral limbs (Gross, 2007; Hagner, 2012; Millett, 1998; Nathan & Smith, 1955). These pioneering experiments provided the first concrete evidence that: 1) the cerebral cortex is involved in the performance of motor output, 2) neurones within the cerebral cortex can be examined via electrical stimulation, and 3) stimulation to specific regions of the cortex produced consistent twitch responses in specific muscles (Gross, 2007). Collectively, these key findings from Fritsch and Hitzig inspired subsequent researchers and served as a catalyst for much of the research that would follow over the next century. For instance, just three years after the observations of Fritsch and Hitzig, Scottish neurologist David Ferrier (1843-1928) replicated their experiments in a variety of animals, including dogs, cats, monkeys, rabbits, and guinea pigs, and found similar results across species (Ferrier, 1873; Millett, 1998). He soon after suggested that the electrical stimulation of the cortex activated localized neurones of the corticospinal tract and proposed that a topographic “motor map” existed within the non-human animal cerebral cortex (Ferrier, 1873; Millett, 1998; Nathan & Smith, 1955).

In humans, initial experiments testing the excitability of the cerebral cortex were restricted to applying stimulating electrodes to various regions of the exposed cortex through surgical interventions (Bartholow, 1874; Hallett, 2000; Penfield & Boldrey, 1937; Rossini et al., 1994). The first researcher to use this method in humans was neurosurgeon

Roberts Bartholow (1831-1904). In 1874, he directly inserted stimulating electrodes into the brain of a young woman who had a cancerous hole in her skull and observed limb movements on the opposite side of the body upon stimulation (Bartholow, 1874). This experiment provided the first demonstration in a human being of the motor excitability of the cerebral cortex due to activation of the corticospinal pathway. Approximately 50 years later, neurosurgeons Wilder Penfield (1891-1976) and Edwin Boldrey (1906-1988) applied similar electrical stimulation techniques to a variety of brain regions in patients and used their findings to create the first somatotopic map of the human brain, now commonly known as a "motor homunculus" (Milner-Brown et al., 1975; Penfield, 1947; Penfield & Boldrey, 1937). While the method of directly stimulating the exposed cerebral cortex certainly provided important information regarding the electrical connectivity and mapping of motor regions within the cortex, the invasive nature of the technique restricted its use mainly to non-human animal models and clinical populations for many years (Rossini et al., 2015).

That is, however, until 1980, when scientists Merton and Morton created a high-voltage electrical stimulator and showed that the device could activate motor areas of the cerebral cortex through the intact scalp in conscious humans (Merton & Morton, 1980). Specifically, they showed that brief, high-voltage electric stimulation applied through electrodes placed over the M1 could evoke twitch-like responses in muscles on the opposite side of the body (Merton & Morton, 1980). This technique, now commonly known as transcranial electrical stimulation (TES), was revolutionary at the time as it provided neuroscientists with the first non-invasive method to assess the excitability of the cerebral cortex and associated motor pathways in humans. While the utility of TES was obvious to

the field, one of its major drawbacks was that it is painful (Chen, 2000; McNeil et al., 2013; Rossini et al., 2015). Given the high resistivity of the skull and scalp protecting the brain, TES requires a high stimulation intensity to activate the underlying neuronal tissue, and this high electrical current is painful due to the activation of sensory nerve endings and electrically induced contraction of scalp muscles (Rothwell, 2018). Fortunately, five years after the creation of TES, Barker et al. (1985) demonstrated that it was possible to painlessly stimulate different regions of the intact human brain using magnetic stimulation, now referred to as transcranial magnetic stimulation (TMS). Consequently, the use of TES declined rapidly, while the application of TMS became much more mainstream (Rossini et al., 2015; Rothwell, 2018). TMS is now widely used in research and clinics to examine brain physiology and the function of the descending corticospinal pathway.

1.4 Assessing the Excitability of the Corticospinal Pathway

Several non-invasive stimulation techniques now exist to examine the corticospinal pathway and its function during movement in humans. Each technique has its own advantages and limitations (for thorough reviews of methods, see McNeil et al. (2013); Rossini et al. (2015); Taylor (2006); Taylor and Gandevia (2004)). In this thesis, TMS of the motor cortex and transmastoid electrical stimulation (TMES) of corticospinal axons will be discussed in detail as these are the techniques used to examine changes in corticospinal pathway excitability in Chapters 3-5. These techniques enable investigations into how the corticospinal pathway influences motor output and how changes in excitability correspond to alterations in motor behavior.

1.4.1 Transcranial Magnetic Stimulation

Since Barker and colleagues created the technique in 1985, TMS has emerged as a commonly used technique to non-invasively stimulate the brain and examine corticospinal excitability in humans (for excellent reviews, see Groppa et al. (2012); Petersen et al. (2003); Rossini et al. (2015); Valero-Cabre et al. (2017)). At its core, TMS operates on the principles of electromagnetic induction established by Michael Faraday (1791-1867). In short, TMS involves a rapidly changing high-intensity electrical current being passed through a tightly wound and insulated coil of copper wire, which is held over a particular region of a participant's skull (Barker, 1991; Barker et al., 1985; Hallett, 2000). When the high electrical current is passed through the coil, it generates a powerful magnetic field perpendicular to the direction of current flow, which is capable of passing painlessly through the skull and inducing electrical currents in superficial brain tissue (Rossini et al., 2015; Rothwell et al., 1999; Rothwell et al., 1991; Siebner & Rothwell, 2003). These electrical currents can subsequently cause the depolarization of cell membranes and initiate action potentials in cortical neurones. Thus, despite being often referred to as "magnetic stimulation", the neurones within the cortex are not actually activated by the magnetic field itself but rather the electrical currents that are induced by the magnetic field (Barker, 1991).

The electrical currents produced by single-pulse TMS frequently activate neurones of the corticospinal pathway indirectly rather than directly exciting the cell bodies of the corticospinal tract (Berardelli, Inghilleri, Rothwell, et al., 1991; Day et al., 1989; Di Lazzaro, Oliviero, et al., 1998; Maccabee et al., 1993; Rothwell et al., 1991). This indirect

activation is due to transsynaptic activation of the corticospinal neurones via excitatory interneurones that synapse onto the corticospinal neurones. The result is the production of a series of action potentials (i.e., volleys) along the corticospinal pathway, known as indirect waves or I-waves, that can be recorded from epidural recordings of the cervical spinal cord (Di Lazzaro et al., 2018; Rossini et al., 2015; Rothwell et al., 1991). However, when the stimulation intensity is high enough, TMS can activate the corticospinal neurones directly by exciting the corticospinal axons at or beyond the axon initial segment (Day et al., 1989; Nakamura et al., 1996; Patton & Amassian, 1954). Direct activation of corticospinal axons induces descending volleys in the corticospinal pathway that are known as direct waves or D-waves, which can be differentiated from I-waves by their shorter latencies (~1-2 ms) (Edgley et al., 1997; Patton & Amassian, 1954; Rothwell et al., 1991). It is important to note, however, that I- and D-waves are generally not elicited in a mutually exclusive manner. In many cases, the TMS pulse elicits temporally spaced out corticospinal volleys involving a combination of I- and D-waves, and it therefore said that TMS induces multiple descending volleys within the corticospinal pathway (Di Lazzaro, Oliviero, et al., 1998; Thompson et al., 1991). Ultimately, when applied to the motor cortex and delivered at sufficient stimulation intensities, the multiple corticospinal volleys produced by the TMS pulse summate to evoke a motor response (i.e., compound muscle action potential) that is recordable from the surface EMG trace of a contralateral target muscle, known as a motor-evoked potential (MEP; Hallett, 2000; Rossini et al., 2015).

While researchers can assess many parameters of the MEP response, the size (i.e., peak-to-peak amplitude or area) is commonly used to indicate the magnitude of corticospinal excitability at the time of stimulation and it provides insight into the

functional integrity of the entire corticospinal pathway – from brain to muscle (Di Lazzaro, Oliviero, et al., 1998; Di Lazzaro & Rothwell, 2014; Hallett, 2000; Rossini et al., 2015). Researchers can track MEP amplitudes over a variety of experimental conditions to determine if corticospinal excitability is altered (Rossini et al., 2015). Essentially, an increase or decrease in the MEP amplitude during or following a condition reflects an increase or decrease in corticospinal excitability, respectively. In other cases, researchers may be interested in determining the minimum stimulation intensity required to excite corticospinal neurones and induce visible MEP responses. This parameter is known as 'motor threshold' and can be determined at rest (i.e., resting motor threshold [RMT]) or during active muscle contraction (i.e., active motor threshold [AMT]; Groppa et al., 2012; Rossini et al., 2015). Increases in the motor threshold indicate a higher stimulation intensity is required to produce a response and therefore suggests a reduction in corticospinal pathway excitability, whereas reductions in motor threshold reflect the opposite.

Single-pulse TMS can also be used to examine the strength of excitatory neurotransmission by creating stimulus-response curves (SRCs; Devanne et al., 1997; Rossini et al., 1994). By plotting MEP amplitudes as a function of TMS intensity, the SRC characterizes the input-output properties of the corticospinal pathway and provides a more comprehensive profile of corticospinal excitability than a single TMS intensity. As such, the SRC is commonly referred to as the 'Gold Standard' for assessing corticospinal excitability, though its use may not be practical in every experiment (see **Chapter 2**). Typically, a shift in the slope of the SRC or a change in the area underneath the curve (AUC) is quantified to provide an index of corticospinal excitability (Carson et al., 2013;

Devanne et al., 1997; Lulic et al., 2017), and is often used to compare corticospinal excitability under various conditions, such as before and after exercise (see **Chapter 6**).

Regardless of the parameter examined, responses evoked by single-pulse TMS are influenced by the excitability of the entire corticospinal pathway, including the excitability of: 1) the corticospinal and intracortical neurones activated by the TMS pulse at the cortex, 2) the interneurones interposed between the corticospinal neurones and spinal motoneurones, 3) the spinal motoneurones themselves, as well as 4) peripheral factors (e.g., neuromuscular junction efficiency, sarcolemma excitability; Rossini et al., 2015). As such, it is not possible to tease out the locus of change in corticospinal excitability if only single-pulse TMS is used (Burke et al., 1993; Hallett, 2000; Taylor et al., 2002). To circumvent this issue, researchers often pair single-pulse TMS with other non-invasive stimulation techniques to help discern whether a change in the MEP may be related to supraspinal or spinal mechanisms (Carroll et al., 2011; McNeil et al., 2013). One such stimulation technique that is often paired with TMS of the motor cortex to provide spinal mechanistic insights is transmastoid electrical stimulation (TMES; see section 1.4.2 below).

1.4.2 Transmastoid Electrical Stimulation

Transmastoid electrical stimulation (TMES), also referred to as brainstem or cervicomedullary junction stimulation, is a non-invasive method to subcortically stimulate the descending corticospinal tract in humans (Ugawa et al., 1995; Ugawa et al., 1991). Initially described by Ugawa et al. (1991), TMES involves a high-voltage electrical current sent between surface electrodes fixed to the skin in the occipital grooves, near the mastoid processes at the base of the skull (Taylor & Gandevia, 2004). The

electrical current at this site produces a single descending volley (Berardelli, Inghilleri, Rothwell, et al., 1991; Rothwell et al., 1994) that activates corticospinal axons coursing through the brainstem at the level of the cervicomedullary junction. This site is where most of the corticospinal fibres bend to cross over at the pyramidal decussation (see section 1.2 above). It has been suggested that the corticospinal fibres are preferentially activated at this location, given that thresholds for exciting nerve fibres are generally at their bends (Amassian et al., 1992). The result of the single descending volley is the production of a compound muscle action potential that can be recorded from the surface EMG signal of several arm and leg muscles during a variety of tasks, including at rest or during voluntary muscle contraction (Taylor et al., 2002). While there are many names for the stimulation itself, the muscle response produced is typically referred to as a cervicomedullary motor evoked potential (CMEP) (McNeil et al., 2013). The amplitude or area of the CMEP response can be used to provide inferences into the excitability of the corticospinal pathway at a spinal level (known as 'spinal excitability').

There are many properties of the CMEP response that make it currently the most appropriate comparison to TMS-evoked MEPs to help delineate complex changes in the human corticospinal pathway at a spinal level (Martin et al., 2008; Taylor & Gandevia, 2004). First, perhaps the main advantage of pairing TMES with single-pulse TMS in the same experiment is that the TMES current activates many of the same descending corticospinal axons to recruit the same motoneurones as that of the TMS pulse (McNeil et al., 2013). Convincing evidence from collision experiments suggests that the CMEP response predominantly reflects motoneurone activation caused by the excitation of large-diameter corticospinal axons (Ugawa et al., 1991). When appropriately timed with

either electrical (Day et al., 1987; Rothwell et al., 1994) or magnetic stimulation of the motor cortex (Berardelli, Inghilleri, Cruccu, et al., 1991; Taylor et al., 2002), the antidromic volleys produced by the TMES current have been shown to largely occlude the orthodromic volleys from stimulation of the motor cortex, indicating that the same pathway is being readily stimulated by both techniques. Secondly, the CMEP reflects a primarily monosynaptic motoneuronal response to electrical stimulation of corticospinal axons (Petersen et al., 2002). This largely monosynaptic pathway is evidenced by the relatively stable response latency to the biceps brachii (~8 ms) at rest and during voluntary muscle contraction (Petersen et al., 2002). Importantly, this monosynaptic pathway is not prone to conventional presynaptic inhibition due to activation of Ia afferents (Jackson et al., 2006; Nielsen & Petersen, 1994). As such, the CMEP is thought to provide one of the best ways to measure spinal motoneurone excitability in humans (Martin et al., 2008), though recent advances in high-density surface EMG and decomposition algorithms may provide greater insight into motoneurone firing characteristics (De Luca et al., 2015; Farina et al., 2016).

Like TMS-evoked MEPs, an increase or decrease in the amplitude or area of the CMEP indicates an increase or decrease in spinal excitability, respectively. For instance, the CMEP response increases during voluntary contraction compared to responses in a relaxed muscle state, indicating that spinal excitability is enhanced (Taylor, 2006). Changes in the CMEP response can reflect several mechanisms at the spinal level, including altered: 1) spinal motoneurone excitability, 2) corticospinal transmission at the corticospinal-motoneuronal synapse, and 3) excitability of interneurones interposed between the descending corticospinal fibres and the motoneurones (other than those

involved in conventional presynaptic inhibition) (Gandevia et al., 1999). Thus, changes in the CMEP response throughout an experiment can indicate mechanisms other than alterations in the intrinsic properties of the spinal motoneurone.

While the use of TMES is certainly beneficial for obtaining valuable insights into changes in the corticospinal pathway that may occur at the spinal level, the technique does have some limitations (Taylor, 2006; Taylor & Gandevia, 2004). First and foremost, the stimulus from TMES is inherently painful. Magnetic stimulation at the cervicomedullary junction has been proposed to circumvent this issue, but in our experience during arm cycling, the stimulation intensity required at this site to elicit discernible CMEPs with the magnetic coil is quite high, often disrupting the ongoing cycling movement. Moreover, even at maximal stimulator output intensities, CMEPs elicited via magnetic stimulation are often difficult to obtain in some individuals. For these reasons, TMES is used for the experiments included in this thesis. At the site of stimulation, the electrical current from TMES activates local skin afferent fibres, which can induce temporary discomfort. Moreover, depending on the exact location of the stimulating electrodes, the technique can also activate nearby peripheral nerves of the head and neck that can cause rapid and relatively intense contraction of muscles in this region (Taylor & Gandevia, 2004). Most participants will be able to endure this transient discomfort, but others will not. Thus, when using TMES, it is imperative that participants are accustomed to the stimulation and the sensation of the technique prior to collecting data.

Another limitation to the technique is that in some instances at sufficient intensities, the current from a TMES pulse can bypass the motoneurone soma and directly activate

the axons of the spinal motoneurone (i.e., peripheral nerve roots) as they exit the spinal cord (Petersen et al., 2002; Taylor & Gandevia, 2004). In such an occurrence, there is a brief reduction in the onset latency of the resultant response by approximately 1-2 ms, usually seen as a "step" or a "foot" in the EMG trace (Petersen et al., 2002). This resultant response can no longer be used as a measure of spinal excitability since it is now contaminated with peripheral nerve components, making its interpretation challenging (McNeil et al., 2013). Activation of nerve roots with TMES can occur for a few reasons, including incorrect placement of the stimulation electrodes, high stimulation intensities, or alterations in head and neck position (Taylor, 2006; Taylor & Gandevia, 2004). However, even with proper placement of the stimulating electrodes on the skin, acceptable CMEPs cannot be obtained in some participants.

Nonetheless, even with its limitations, when combined with TMS, TMES can help identify the locus of change in the corticospinal pathway that may occur throughout an experiment or following an intervention. For instance, if TMS-evoked MEPs are increased following an intervention but CMEPs do not change or are reduced, it can be logically deduced that supraspinal mechanisms likely account for the increase in overall corticospinal excitability. In contrast, if, following an intervention, both MEPs and CMEPs increase, it can be deduced that at least part of the change in overall corticospinal pathway excitability is related to spinal mechanisms. In the chapters that follow in this thesis (specifically Chapters 4 and 5), this method of deductive reasoning will be used to tease out potential mechanisms that might underlie changes in corticospinal excitability during arm cycling following different interventions.

1.5 The Corticospinal Pathway and Human Movement

In the prior sections, the corticospinal pathway and some of the techniques that are commonly employed to examine its excitability during human movement are discussed. Ironically, however, most of the research that has examined the role of the corticospinal system during human "movement" does so by involving very little movement. As discussed in Chapter 2 below, most studies that have examined corticospinal pathway excitability in humans have measured excitability when the participant is either at rest or during the performance of relatively simple, single-joint isometric contractions. These conditions are selected as they are thought to ensure greater experimental consistency and reproducibility and are therefore suggested to offer better mechanistic insights to the study in question. While this may be true, the main limitation of using resting or isometric measures is that they do not reflect the complex and dynamic states of neurones and their synapses during multi-joint, purposeful movement. As such, the findings from the motor system at rest or during single-joint isometric contractions are likely very different from the motor system during multi-joint, dynamic motor outputs (Kalmar, 2018; Lockyer et al., 2021; Power et al., 2018). This is not to discredit the information we have obtained regarding the corticospinal system from studies that have been performed at rest or during isometric contractions. However, it is argued that if we truly wish to obtain a greater understanding of the corticospinal system during human movement, we need to start assessing the corticospinal system *during* dynamic and functional motor outputs, like locomotor outputs such as walking, running, or cycling.

1.6 Locomotion and The Corticospinal Pathway

For most individuals, walking is considered a relatively rudimentary motor skill involving limited conscious control or effort. However, the reality is that walking, like any rhythmic locomotor output, is rather complex. It involves the use of large muscle groups bilaterally to produce coordinated flexion and extension movements of the limbs, while also ensuring balance is maintained as the body's centre of mass moves with each step forward. As such, despite its relative ease to perform, the neural control of locomotor outputs is reasonably intricate.

Much of the current knowledge on the neural control of human locomotion arises from studies performed on non-human reduced animal preparations. Seminal experiments by Sir Charles Sherrington in quadrupeds demonstrated for the first time that the basic rhythmic walking pattern could be generated without descending input from the brain (Sherrington, 1906). In his experiments, Sherrington showed that dogs and cats with complete spinal transection at the level of the brainstem could produce rhythmic limb movements resembling locomotion when either electrical or mechanical stimulation was delivered to the animal's skin. Moreover, he noted that the degree of movement could be altered by the sensory feedback from the periphery. Collectively, these findings led Sherrington to conclude that the production of the basic pattern of locomotor-like behaviour was likely driven by afferent feedback (Sherrington, 1906). Following this work, Sherrington's student, Thomas Graham Brown (1911) performed additional experiments aimed at understanding the locomotor pattern in the absence of descending drive. He performed similar transections of the spine but also performed transections of the hindlimb afferents, thereby effectively removing the descending drive and the afferent input,

respectively (Brown, 1911). Using this method, Brown observed rhythmic bursting of flexor and extensor muscle activity in the hindlimb of the animal, indicating that the basic pattern of the locomotor output could be achieved in the absence of both descending and afferent input (Brown, 1911). This finding provided the first compelling evidence that the circuitry responsible for the basic locomotor pattern was located in the spinal cord (Brown, 1914). Brown proposed that this circuitry could be explained by what he referred to as a flexor-extensor "half-centre" model (for a modified version, see **Figure *1.2*** below). It is now known, from work using intracellular recording techniques, that this basic locomotor pattern in quadrupeds is generated by networks of oscillatory neurones within the spinal cord, now referred to as spinal central pattern generators (CPGs) (Grillner, 1975; Grillner & Wallen, 1985). While the precise architecture of spinal CPGs is not yet fully elucidated, several theoretical models have been proposed, building upon the half-centre model proposed by Brown in the early 1900s (for detailed reviews see (McCrea & Rybak, 2008; Rybak et al., 2015; Zehr, 2005). Regardless of the model used, the current belief is that CPGs exist in vertebrates and that these networks can generate the basic locomotor activity in the absence of descending or ascending input (Grillner, 1975; Rybak et al., 2015). Moreover, it is postulated that spinal CPGs exist for each of the four limbs, and they communicate with each other (likely via propriospinal and commissural connections) to facilitate the coordinated rhythmic and alternating flexor-extensor pattern of activity (Klarner & Zehr, 2018). Importantly, these spinal CPGs are not active during non-rhythmic motor outputs (e.g., tonic contractions) (Grillner et al., 2007; Power et al., 2018).

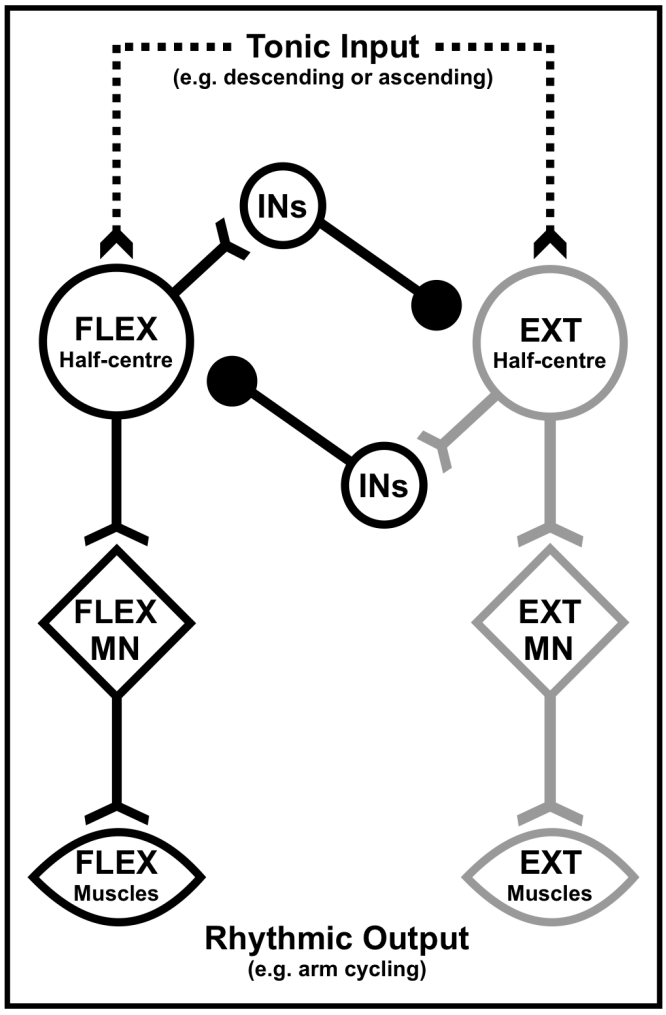

Figure 1.2: Schematic of Brown's (1911) flexor-extensor half centre model of the basic circuitry underlying rhythmic motor outputs (modified from Zehr 2005).

INs, interneurones; FLEX, flexor; EXT, extensor; MN, motoneurone pool.

While spinal CPGs in non-human animals can generate the basic flexor-extensor pattern and rhythm of locomotion in the absence of ascending or descending signals, aspects of functional locomotor outputs require inputs from supraspinal centres and afferent feedback (Armstrong, 1986; Grillner & Dubuc, 1988). Specifically, supraspinal

inputs are important for the initiation and termination of movement (Armstrong, 1986; Jordan et al., 2008), for changing speeds (Shik et al., 1966), responding to perturbations (Amos et al., 1989; Marple-Horvat et al., 1993), and for precision stepping (Beloozerova & Sirota, 1993), while somatosensory inputs help shape and modify the movements with relation to the environment (Frigon et al., 2021; Rossignol et al., 2006; Van de Crommert et al., 1998). These inputs are incorporated into the spinal CPG to ensure the smooth and coordinated locomotor pattern.

In humans, it is obviously not possible to perform the same type of experiments to confirm the existence of spinal CPGs as those performed in reduced animal preparations, given the invasive and direct nature of the recording techniques required *in vivo*. However, accumulating indirect evidence suggests that humans possess similar spinal locomotor CPGs (Burke, 2001; Calancie et al., 1994; Duysens & Van de Crommert, 1998; Frigon, 2012; Klarner & Zehr, 2018; Zehr et al., 2004), though compared to quadrupeds, greater contribution from supraspinal centres is required for functional human locomotor outputs (Eidelberg, 1981; Fedirchuk et al., 1998; Nielsen, 2003). As such, the neural control of locomotor outputs in humans is often described by a tripartite system consisting of a combination of supraspinal, spinal (i.e., CPG and interneurones), and sensory (i.e., afferent) influences (Pearcey & Zehr, 2020; Zehr, 2005) that interact with one another to ensure an optimal control under all circumstances.

In quadrupeds, the corticospinal tract is not essential to produce the basic pattern of locomotion, given that it can be generated in decerebrate animals (Armstrong & Drew, 1984; Grillner & Dubuc, 1988). However, this should not be interpreted to mean that the corticospinal tract is not important in ensuring functional coordinated output. Indeed, prior

to and throughout functional locomotor outputs in the intact cat, neurones of the corticospinal tract are active, and their firing frequencies are rhythmically modulated depending on the phase and frequency of movement (Armstrong & Drew, 1984). For example, by inserting flexible microelectrodes into the motor cortex of the animal, Armstrong and Drew (1984) were able to measure discharge rates of pyramidal tract neurones (i.e., neurones of the corticospinal tract) during locomotion and while the animal was at rest. During slow walking, the researchers observed higher pyramidal neurone discharge rates compared to when the animal was at rest, and noted that as the speed of walking increased, there was an approximately linear increase in pyramidal neurones discharge rates (Armstrong & Drew, 1984). Moreover, when walking over an obstacle or on uneven ground, activity of corticospinal neurones is increased (Drew, 1988; Drew et al., 2002). Taken together, these findings and findings from others (Amos et al., 1989, 1990; Armstrong & Drew, 1985), support the suggestion that the corticospinal pathway is involved in animal locomotion although it may not be necessary in all circumstances. Corticospinal input is likely important in non-human animals for initiating and adapting the locomotor pattern both in anticipation and in response to various motivational and environmental conditions (Armstrong, 1988).

In humans, the motor cortex and the corticospinal pathway are thought to play a more essential role in the neural control of locomotor outputs (Lemon & Griffiths, 2005). Notably, impairments resulting from lesions of supraspinal motor pathways tend to be more severe and long-lasting in humans compared to cats (Barthelemy et al., 2011; Nathan, 1994; Nielsen, 2003). Moreover, evidence from limited studies utilizing TMS during human walking further supports the important role of the motor cortex and corticospinal

pathway in the neural control of locomotor outputs (Bonnard et al., 2002; Capaday et al., 1999; Petersen et al., 2001; Schubert et al., 1999; Schubert et al., 1997).

For instance, cortical neurones projecting to lower limb motoneurones exhibit greater excitability during walking compared to rest or tonic contractions of the same intensity and muscle group (Capaday et al., 1999; Petersen et al., 1998). Furthermore, Petersen and colleagues (2001) provided more direct evidence of the corticospinal influence during locomotion. They observed notable suppression of ongoing EMG activity from the tibialis anterior during the swing phase of walking when applying subthreshold TMS to the motor cortex. This suppression, attributed to activation of intracortical inhibitory mechanisms by the weak TMS pulse (Di Lazzaro, Restuccia, et al., 1998b), suggests a reduction of corticospinal drive to the muscle and provides clear evidence of the involvement of the motor cortex and corticospinal pathway during human walking (Petersen et al., 2001). Various imaging techniques of the motor cortex during walking have revealed similar findings (Fukuyama et al., 1997; Petersen et al., 2012).

While the motor cortex and corticospinal pathway play important roles in human locomotion, their specific contributions to movement patterns remain elusive. This challenge stems partly from technical obstacles in studying the corticospinal pathway during locomotion. One considerable issue is that participants are usually in motion during locomotor tasks, making it difficult to measure corticospinal excitability accurately. Even in controlled settings like treadmill walking or running, precise measurements of corticospinal excitability are hindered by the continuous movement of the individual's head and body, as their centre of mass shifts with each step. To address some of these challenges, researchers have utilized both leg and arm cycling paradigms (Sidhu et al., 2013a; Sidhu

et al., 2012; Zehr et al., 2004), where movement of the head and trunk are relatively limited, to further investigate the neural control of human locomotor outputs. Cycling paradigms are used for a variety of reasons (see Chapter 2). Particularly, not only do they produce rhythmic coordinated limb movements and muscle activities akin to that of locomotion, but they are also thought to share a common neural control framework (Zehr, 2005; Zehr et al., 2004; Zehr & Kido, 2001). Indeed, both leg and arm cycling are believed to be mediated, at least in part, by activation of similar spinal CPGs that are responsible for generating the fundamental rhythmic motor patterns observed in tasks such as walking and running (Zehr & Duysens, 2004).

Consequently, it has been hypothesized that the neural control underlying all forms of rhythmic motor outputs in humans shares a 'common core', with the CPG serving as the foundational building block (Zehr, 2005). As such, researchers can use cycling paradigms as models of human locomotion and obtain insights into how the corticospinal pathway may be involved in the locomotor output with relative ease (Carroll et al., 2006; Power et al., 2018; Sidhu et al., 2012). While there are obvious differences between walking and cycling tasks, notably the greater importance of balance in overground walking, throughout this thesis, cycling paradigms are viewed as "locomotor-like" outputs.

1.7 Arm Cycling as a Model of Human Locomotion

Arm cycling, also known as arm ergometry or arm cranking, involves repetitive and coordinated flexion and extension movements of the upper limbs, producing a cyclical motion of the arms akin to the legs during leg cycling. Typically performed on an ergometer, arm cycling is commonly used as an exercise modality for individuals with

lower limb impairments, such as spinal cord injury. However, over the past 25 years, arm cycling as a model of human locomotion has emerged as a valuable way to obtain insights into the neural control of dynamic locomotor-like outputs. Dr. Paul Zehr's lab has contributed much to this research, wherein they have demonstrated that spinal reflexes undergo transient modulation throughout the arm cycling revolution, producing similar patterns of reflex modulation to that observed during the gait cycle (for reviews, see (Klarner & Zehr, 2018; Zehr et al., 2016). Moreover, spinal reflexes are modulated differently depending on the phase and intensity of the arm cycling movement being performed (Hundza et al., 2012; Hundza & Zehr, 2009; Palomino et al., 2011). Over the past decade, our lab has built upon this research and used arm cycling to obtain insight into the involvement of the motor system – the corticospinal pathway – in producing the locomotor-like output.

During arm cycling, like other locomotor outputs, the movement of the limbs throughout a revolution can be divided into phases. While the names given to these phases can vary between research groups, we refer to the cycling revolution as being comprised of two phases about the elbow: 1) flexion – movement of the hand towards the body from a fully extended limb position, and 2) extension – movement of the hand away from the body from a fully flexed limb position (Forman et al., 2014). Due to the asymmetrical nature of the arm cycling, when one arm is in the flexion phase, the other is in the extension phase. When assessing corticospinal and spinal excitability using TMS and TMES, respectively during locomotor outputs, responses must be evoked at the same position during each locomotor cycle to compare between trials. Our lab uses a magnet system to ensure stimuli are delivered at the same position (see **Figure *2.2*** below). When the

crankshaft of the ergometer passes a magnet at a predetermined position, a stimulation is automatically triggered within milliseconds, and the resultant response is observed from the muscle of interest. Our lab has measured corticospinal evoked responses at various positions of the crankshaft during the cycling revolution (Forman et al., 2014; Forman et al., 2019; Lockyer et al., 2018; Spence et al., 2016), however, most of our studies have examined the mid-elbow flexion position, or the 6 o'clock position made relative to the face of a clock.

In chapters 3-5 of this thesis, all experiments involved evoking corticospinal and spinal excitability responses during arm cycling as the dominant arm passed the 6 o'clock position (i.e., mid-elbow flexion). This phase of the movement was chosen as this position represents the period throughout the revolution where biceps brachii muscle activity is typically the highest (Chaytor et al., 2020). Therefore, it is worth noting that the findings in the subsequent chapters are potentially restricted to the mid-elbow flexion phase of arm cycling, given the previous findings that corticospinal excitability is differently modulated by the phase of the movement (Capaday et al., 1999; Forman et al., 2019; Forman et al., 2015; Lockyer et al., 2018; Pyndt & Nielsen, 2003; Spence et al., 2016).

1.8 Factors Influencing Corticospinal Excitability During Locomotor Outputs

The excitability of the corticospinal pathway is influenced by many factors (Rossini et al., 2015). This is true when the muscle of interest is at rest or during an isometric contraction but is amplified even more during dynamic locomotor outputs, like arm cycling, where descending commands and afferent inputs are in constant flux as the arms

move through the cycling revolution. As alluded to in section **1.5** above, most of the current understanding regarding the factors that influence corticospinal excitability has come from studies using isometric contractions. However, recent work has started recognizing factors that influence corticospinal excitability during locomotor outputs. While not an exhaustive list, corticospinal excitability is modulated differently depending on the motor task, the phase of the movement, the intensity of the motor output, the muscles examined, the stimulation parameters used, and various characteristics of the study population examined (i.e., age, various neurological conditions) (Kalmar, 2018; Lockyer et al., 2021). Moreover, there is growing evidence to suggest that corticospinal excitability is influenced by different forms of attentional processes, such as directed visual attention (Wright et al., 2018), alertness (Rothwell, 2018), motor imagery (Mouthon et al., 2015) and differing forms of directed attentional cues (Matsumoto et al., 2024; Matsumoto et al., 2022). Furthermore, the brain and corticospinal pathway appear to undergo neuroplastic changes following periods of heightened activity, such as in response to various forms of both acute (Singh et al., 2014; Singh & Staines, 2015; Smith et al., 2014) and longer term exercise training (Lulic et al., 2017; Nicolini et al., 2019; Pearcey et al., 2021). Thus, while many factors can influence corticospinal excitability, the extent and how they influence excitability during arm cycling still need to be fully established.

Understanding the many factors that influence the excitability of the descending corticospinal pathway during locomotor-like outputs is important for advancing our comprehension of how the central nervous system governs movement. Gaining insight into these factors may have implications across several domains, including optimizing rehabilitation, informing neurological disorders, and enhancing athletic performance. The

following chapters of this thesis will examine the impacts of directed attention, motor output intensity, stimulation intensity, and exercise training on corticospinal excitability during arm cycling. The ensuing sections of this chapter will outline the current understanding of each of these variables and their influence on corticospinal excitability. These sections will provide much of the theoretical framework for the experimental studies that follow.

1.8.1 Attention and corticospinal excitability

Attention is a cognitive process that involves selectively prioritizing and focusing on specific aspects of information or stimuli while disregarding other competing stimuli (Buschman & Kastner, 2015). While definitions of attention in cognitive neuroscience are plentiful, it is established that information processing in the brain is a core component (Lindsay, 2020). Attention can be directed toward stimuli based on numerous factors, including the physical properties of the stimuli (e.g., brightness, colour, speed), specified instructions, or features of the stimuli that are important for the task being performed (Buschman & Kastner, 2015). Despite being primarily considered a cognitive process, there is now growing evidence suggesting that manipulation of attention can modulate activity within the motor system (Naish et al., 2014; Rossini et al., 1991; Song, 2019).

Indeed, different attentional situation conditions can alter the neural activity in various motor regions of the brain (Binkofski et al., 2002; Kastner et al., 1999; Zentgraf et al., 2009) and have been shown to modulate the excitability of the corticospinal pathway (Fadiga et al., 1995; Matsumoto et al., 2024; Mouthon et al., 2015; Roosink & Zijdewind,

2010; Wright et al., 2018). For example, simply thinking about specific movements can increase corticospinal excitability (Izumi et al., 1995; Kiers et al., 1997; Rossini et al., 1991). Using a rest versus think about contracting versus contract paradigm, Kiers et al. (1997) found that thresholds for TMS were lower and MEP areas were larger for muscles of the hand when participants were instructed to visualize contracting their hand without subsequent contraction compared to when at rest (Kiers et al., 1997). MEPs were largest when participants actively contracted their muscles (i.e., abductor pollicus brevis or flexor carpi radialis). The authors attributed the facilitation of corticospinal excitability (i.e., larger MEP size and reduced thresholds) during the think condition to primarily an increase in cortical excitability, given the lack of change observed in the spinally-mediated H-reflex (i.e., measure of presynaptic inhibition of primary muscle spindle afferents and spinal motoneuronal excitability) during the think versus rest conditions (Kiers et al., 1997). Evidence from other motor imagery studies has further added to the understanding that attention can influence corticospinal excitability. For instance, Mouthon and colleagues (2015) had participants complete a series of attention-demanding conditions, some of which involved closing their eyes and imagining performing a static or dynamic balance task. During these mental imagery conditions, MEPs from TMS and H-reflexes from peripheral nerve stimulation were recorded from the soleus muscle. The authors reported that the mental imagery condition induced significant facilitation of the soleus MEPs, but not H-reflex responses, compared to passively observing the balance task (Mouthon et al., 2015). Thus, the authors suggested that motor imagery may facilitate corticospinal excitability, and this facilitation is likely to be primarily mediated by supraspinal factors, rather than spinal ones.

Action observation tasks also influence corticospinal excitability. For example, when emphasis is placed on directing visual attention towards specific features of an observed action, corticospinal excitability is enhanced (Fadiga et al., 1995; Leonetti et al., 2015; Puglisi et al., 2017; Wright et al., 2018). Fadiga and colleagues (1995) were among the first to explore the modulation of corticospinal excitability during action observation in humans. They found that MEPs evoked by TMS were more prominent in muscles involved in grasping when the participants observed grasping actions than when they were shown stationary objects or dimming lights. The authors interpreted this increase in MEP during grasping observation to indicate activation of the mirror neurone system, which they speculated led to enhanced excitability of the M1 and, thus, larger MEP responses recorded from the muscle (Fadiga et al., 1995). Since this study, many studies have examined corticospinal excitability during action observation and have revealed similar findings (for review, see (Naish et al., 2014). However, it appears that the features of the observed actions matter. For instance, Donne and colleagues (2011) explored the influence of a meaningless thumb-tapping task and a goal-directed pen-grasping task on corticospinal excitability during action observation and found that observations of the meaningless task did not facilitate corticospinal excitability compared to a control condition (Donne et al., 2011). However, during observation of the goal-directed action, corticospinal excitability was enhanced, suggesting that relevant features of the observed action may influence the degree of facilitation in the corticospinal pathway (Donne et al., 2011). Moreover, increases in motor output complexity, which theoretically would increase the attentional demands of the task, have been shown to increase corticospinal excitability. During treadmill walking, for example, corticospinal excitability is enhanced in muscles around

the ankle when emphasis is placed on stepping on targets compared to normal walking (Schubert et al., 1999).

Furthermore, growing evidence suggests that the type of attentional focus instructions provided prior to and during a task can modulate intracortical (Kuhn et al., 2017; Marinovic, 2017) and overall corticospinal excitability (Matsumoto et al., 2024; Matsumoto et al., 2022). These instructions, typically classified as either internal focus (IF) or external focus (EF) instruction strategies, entail directing the participant's attention to specific aspects of the movement being performed. Internal focus conditions involve directing attention towards the movement of specific body parts or muscles during a task. In contrast, EF instructions involve directing attention towards the outcome of the participant's actions on external objects or the environment. Adopting an EF strategy has consistently been shown to increase motor performance across a variety of motor tasks, including balance (Mouthon et al., 2015), precision (Zachry et al., 2005), and strength training (Neumann, 2019), though factors related to the performer, such as attentional cue preference (Weiss et al., 2008) and level of expertise (Singh & Wulf, 2020), along with task attributes such as difficulty and complexity (Becker & Smith, 2013; Raisbeck et al., 2020; Wulf et al., 2007), play a role in shaping the attentional focus effect. Studies investigating the effects of attentional focus on corticospinal excitability have revealed that adopting an external focus tends also to increase corticospinal excitability, whereas an internal focus generally results in decreased excitability (Kuhn et al., 2017; Matsumoto et al., 2024; Matsumoto et al., 2022). While the mechanisms underlying these findings are not well-established, the constrained action hypothesis has been suggested as one theory to explain the differences between IF and EF conditions (Law & Wong, 2021; Wulf, 2013).

This hypothesis posits that focusing internally on movement of the limbs or muscles during a task causes the individual to direct their attention and attempt to control the otherwise automated motor processes, which obstructs the automatic processing and ultimately leads to impairments in performance and reduced overall corticospinal excitability (Law & Wong, 2021). In contrast, adopting an EF strategy is thought to facilitate automatic information processing, which enhances the motor performance and overall corticospinal excitability (Wulf, 2013).

Taken together, the above findings suggest that simply changing the attentional demands of a task can influence motor performance and the excitability of the corticospinal pathway. For most of the studies from our lab, we instruct participants to arm cycle at 60 revolutions per minute (rpm) by observing their cadence on the ergometer screen. This cadence is chosen as it is relatively easy for participants to maintain, and it limits the development of excessive fatigue during the movement. Moreover, using a standardized cadence across studies allows for more consistency in the experimental conditions and better comparison of results between studies. However, given the abundance of evidence suggesting that variations in attentional factors can modulate corticospinal excitability, it is therefore possible that instructing our participants to focus on maintaining a constant cadence of 60 rpm during our studies may be in and of itself influencing our measurements of corticospinal excitability. The experiment in Chapter 3 of this thesis was designed with this idea in mind, as we sought to investigate whether instructing participants to maintain a specified cadence (thereby directing their attention) versus a self-selected cadence would differentially modulate corticospinal excitability.

1.8.2 Motor output intensity and corticospinal excitability

Another factor that substantially influences corticospinal excitability is the intensity of the motor output being performed. Most of this understanding has come from studies that have examined the modulation of corticospinal excitability during isometric contractions of varying contraction strengths (Gelli et al., 2007; Martin, Gandevia, et al., 2006; Rothwell et al., 1987; Taylor et al., 1997). From this work it is well-established that corticospinal and spinal excitability are lowest when in a relaxed or resting state but drastically increase immediately prior to (Cheney & Fetz, 1980; Power & Copithorne, 2013; Rothwell et al., 1987) and during the performance of slight voluntary contractions (Di Lazzaro, Restuccia, et al., 1998a; Rothwell et al., 1987). During voluntary contractions, descending input from the motor cortex and other brain regions causes excitation of the motoneurone pool, which can lead to repeated firing of some motoneurones while bringing other motoneurones closer to the threshold for firing action potentials (Taylor & Gandevia, 2004). Thus, relative to a muscle at rest, when muscles are in a contracted state, the motoneurones are more excitable and can fire action potentials with much less additional synaptic input.

Moreover, during low force isometric contractions, MEP and CMEP amplitudes have been shown to increase in a relatively linear manner, a finding that has been attributed to a combination of enhanced central motor drive to the active muscles and increased motor unit recruitment and firing frequency (Goodall et al., 2009; Martin, Gandevia, et al., 2006; Tallent et al., 2017). However, at higher contraction intensities, these increases in corticospinal and spinal excitability are not continuous. Typically, MEPs and CMEPs

increase with contraction strength up until a plateau is reached, after which a progressive decline in excitability occurs as the strength of contraction approaches maximal (Martin, Gandevia, et al., 2006; Oya et al., 2008; Todd et al., 2003). This pattern of modulation, found in a variety of upper (Martin, Gandevia, et al., 2006; Taylor et al., 1997; Todd et al., 2003) and lower limb (Goodall et al., 2009; Oya et al., 2008) muscles during isometric contractions, is thought to be mediated predominantly by spinal mechanisms. Specifically, the reduction in response amplitudes following the plateau stems from the failure of some motoneurones to generate action potentials in response to the excitatory stimulation at the higher contraction intensities (Gelli et al., 2007; Todd et al., 2003).

During dynamic locomotor outputs, much less is known regarding the pattern of corticospinal pathway modulation as motor output intensity increases. This is partly due to the lack of studies that assess corticospinal excitability during locomotor outputs, but it may also be due to the fact that the intensity of locomotor outputs can be altered in various ways. For example, during cycle ergometry, motor output intensity can be modified relatively simply by manipulating either the cadence or the resistance applied to the crankshaft during the cycling revolution (Larson et al., 2006; Pyndt et al., 2003). This allows researchers the opportunity to manipulate motor output intensity in different manners and examine the effects on motor system output.

Recent work from our lab and others have started to consider this idea during cycling tasks (Forman et al., 2015; Lockyer et al., 2018; Spence et al., 2016; Weavil et al., 2015). In separate studies from our lab, we have examined the influence of motor output intensity on the modulation of corticospinal excitability during arm cycling and have revealed that corticospinal and spinal excitability are both cadence- (Forman et al., 2015)

and workload-dependent (Lockyer et al., 2018; Spence et al., 2016). Importantly, however, these studies were performed at relatively low cycling workloads and therefore cannot provide information on the modulation of corticospinal pathway excitability during cycling when the intensity of the motor output is closer to maximal.

During leg cycling over a wide range of resistances (i.e., 100, 200, 300, and 400W), Weavil and colleagues (2015) found that corticospinal and spinal excitability to the vastus lateralis and rectus femoris increased with increasing intensity of cycling in a manner that closely resembled the pattern of modulation observed in isometric studies as contraction intensity approaches maximal. Specifically, the authors noted that both MEPs and CMEPs from the vastus lateralis progressively increased with cycling intensity up until a plateau in the responses was reached at approximately 300W, suggesting that this increase in MEP is mainly driven by spinal mechanisms (Weavil et al., 2015). Interestingly, however, this pattern of modulation varied slightly per muscle examined, as no plateau in responses was observed in rectus femoris across the cycling intensities examined, suggesting that this finding might be muscle dependent (Weavil et al., 2015). Given that the modulation of corticospinal pathway excitability is muscle and task specific (Kalmar, 2018; Lockyer et al., 2021), it remained to be seen whether similar findings from Weavil et al. (2015) would be observed during arm cycling over a wide range of cycling intensities. Thus, the experiment presented in Chapter #4 of this thesis was designed to obtain this insight.

1.8.3 Exercise training and corticospinal excitability

In addition to motor output intensity, the excitability of the corticospinal pathway can also be modulated in response to a variety of motor training experiences, such as following various types of exercise training (El-Sayes et al., 2019; Gabriel et al., 2006). Indeed, there is now extensive evidence indicating that participating in and performing different types of resistance and aerobic exercise (AE) can induce adaptations along the corticospinal pathway, which are believed to contribute to improvements in motor learning and performance (Pearcey et al., 2021; Singh & Staines, 2015), and provide evidence of exercise-induced neuroplasticity. The current evidence suggests that corticospinal adaptations can occur following acute (i.e., single session) or longer-term (i.e., multiple sessions to multiple weeks) forms of training, though the precise mechanisms, extent of change, and site(s) of adaptation are not fully elucidated.

1.8.3.1 Evidence from resistance training.

During resistance training, also known as strength or weight training, it is well-documented that improvements in strength occur within the first 2-4 weeks of training without substantial changes in muscle hypertrophy, suggesting a neural component (Carroll et al., 2011; Sale, 1988). Initial evidence for this notion of neural adaptations following resistance training came from studies using surface EMG, wherein following the early stages of resistance training, the amplitudes of the EMG signal were increased in line with the increase in muscle force production (Hakkinen et al., 1998; Moritani & deVries, 1979). Increased EMG amplitudes following training led to the conclusion that resistance

training was associated with increased neuronal drive to the muscles (Sale, 1988). However, given that surface EMG signals provide only a crude measure of neural drive to skeletal muscle during contraction (Farina et al., 2014), drawing specific conclusions on the neural mechanisms involved following training was not possible. Since these initial experiments, advances in EMG recording and decomposition techniques, including intra-muscular and high-density surface EMG methods, have permitted a more detailed understanding of some of these neural mechanisms (Skarabot et al., 2021). For instance, using these techniques, several studies have displayed motor unit adaptations (i.e., decreased recruitment thresholds and increased discharge rates) following resistance training (Del Vecchio et al., 2019; Van Cutsem et al., 1998; Vila-Cha et al., 2010), indicating neural adaptations at the level of the spinal motoneurones. Other studies, involving non-invasive stimulation techniques, like the H-reflex and volitional wave (V-wave; i.e., measure of the neural drive from the spinal motoneurone to the muscle during active contraction) (McNeil et al., 2013) have provided further evidence that adaptations to resistance training include a spinal component (Aagaard et al., 2002; Vila-Cha et al., 2012). Furthermore, recent work by Orssatto and colleagues (2023), using a relatively novel technique of paired motor unit analysis to measure persistent inward currents (PICs, i.e., an intrinsic property of spinal motoneurones that influence the overall excitability and sustained firing characteristics of the motoneurone) in humans, found that PICs were increased in older adults following six weeks of high-intensity resistance training, suggesting that changes in the intrinsic properties of the spinal motoneurone occurred with training. The authors implied that enhanced PICs following resistance training might serve as a neural mechanism underpinning the observed improvements in strength and motor

function following training (Orssatto et al., 2023). Interestingly, despite the evidence that spinal motoneurones might be more excitable following resistance training, studies employing electrical stimulation of corticospinal axons have revealed no changes in CMEPs (Nuzzo et al., 2017) or lumbar evoked potentials (Ansdell et al., 2020) following short-term resistance training paradigms. Taken together, the growing evidence suggests that neural adaptations to resistance training likely involves changes at the spinal motoneurone, though research to date is not exhaustive.

Studies employing TMS of the motor cortex have provided evidence of neural adaptations along the corticospinal pathway and associated supraspinal networks (Kidgell & Pearce, 2011; Siddique et al., 2020). Using single-pulse TMS, some studies have shown that as little as a single session of resistance exercise can increase corticospinal excitability (Hendy & Kidgell, 2014; Latella et al., 2017; Leung et al., 2015; Nuzzo, Barry, et al., 2016a), while others have suggested that overall corticospinal excitability is decreased (Giboin et al., 2018; Latella et al., 2016) or not altered (Coombs et al., 2016; Selvanayagam et al., 2011). Following longer-term forms of resistance training, studies examining changes in overall corticospinal excitability have produced similarly inconclusive results (Kidgell et al., 2017; Mason et al., 2019; Skarabot et al., 2021). Various factors have been proposed to explain the inconsistency between studies, including differences in the length and the training program employed, the type of contraction (i.e., ballistic versus slow ramp), the stimulation paradigm, and the muscle and population studied (Pearcey et al., 2021).

Using paired-pulse TMS paradigms, however, the results are slightly more conclusive, with most studies suggesting that resistance training alters the activity of

inhibitory intracortical interneurones within the M1 (Goodwill et al., 2012; Kidgell et al., 2010; Mason et al., 2019; Weier et al., 2012). Specifically, while there are some contradictory findings (Ansdell et al., 2020; Beck et al., 2007), most studies report reductions in short-interval intracortical inhibition (SICI), an inhibitory cortical circuit thought to be mediated by gamma aminobutyric acid-A ($GABA_A$) receptors (Kujirai et al., 1993; Werhahn et al., 1999), following various forms and lengths of resistance training (Coombs et al., 2016; Goodwill et al., 2012; Kidgell & Pearce, 2010; Latella et al., 2012; Leung et al., 2015; Weier et al., 2012). Moreover, in chronically resistance-trained compared to untrained individuals, recent work from our lab showed that SICI was reduced in chronically resistance-trained individuals, potentially suggesting a long-term adaptation to training (Lahouti et al., 2019). Indeed, reductions in the activity of GABA have been proposed as an important precursor for long-term potentiation and motor learning (Bachtiar & Stagg, 2014; Butefisch et al., 2000). Subsequently, reductions in GABA-mediated inhibition (i.e., SICI) in the M1 following resistance training might serve as a potential mechanism underpinning the increases in muscle strength typically observed (Kidgell et al., 2017; Skarabot et al., 2021).

1.8.3.2 Evidence from AE training.

Aerobic exercise, also known as endurance or cardiovascular training, is an effective method for inducing plastic adaptations within the central nervous system (El-Sayes et al., 2019). Adaptations in numerous brain regions (Colcombe et al., 2006; Kramer & Erickson, 2007; Voss et al., 2013) following AE are believed to enhance cognition

(Chang et al., 2012), memory (Erickson et al., 2011), and improve both physical and mental health (Mikkelsen et al., 2017). Additionally, alterations within the spinal cord circuitry can occur as well (Adkins et al., 2006; Beaumont & Gardiner, 2003; Gardiner et al., 2006; Vera-Ibanez et al., 2017; Vila-Cha et al., 2012; Vila-Cha et al., 2010), which likely contribute to improvements in motor function and performance following AE. Given the potential for AE to influence multiple fields within neuroscience, research investigating the impact of AE on neuroplasticity has substantially increased over the past few decades. However, despite this growing work, the influence of performing AE on the corticospinal pathway and associated networks is not well-established.

In non-human animals, AE has been shown to alter the biophysical properties of spinal motoneurones, some of which render the motoneurone more excitable and fatigue-resistant post-exercise (Beaumont & Gardiner, 2002; Beaumont & Gardiner, 2003). For instance, following 12 weeks of low-intensity spontaneous wheel running for two hours per day, Beaumont and Gardiner (2002) observed a lowering of the voltage threshold required for action potential initiation and an increase in the slope of the rising portion of the action potential in lumbar spinal motoneurones in adult rats, findings that were not seen in non-exercised, cage-restricted rats (Beaumont & Gardiner, 2002). Interestingly, these adaptations appeared to be restricted to slow motoneurones that innervate slow-twitch and more fatigue-resistant muscle fibres (Gardiner et al., 2006; MacDonell & Gardiner, 2018). In a follow-up study, the same researchers used a higher intensity forced treadmill running method for 16 weeks and found similar findings in the rat motoneurones (i.e., hyperpolarized resting membrane potentials and spike trigger level) (Beaumont & Gardiner, 2003). However, these adaptations also extended to fast motoneurones,

indicating that exercise intensity likely plays an important role in modulating changes in slow versus fast motoneurones (Beaumont & Gardiner, 2003; MacDonell et al., 2012). Furthermore, these changes in rat motoneurone properties seem be specific to AE, as similar adaptations do not occur following resistance training (Krutki et al., 2017) or compensatory overload (i.e., an extreme model of increased activity where removal of a muscle occurs so that the remaining muscle must work harder) (Krutki et al., 2015) in rats. Taken together, these findings provide evidence that performance of weeks of AE can alter various properties of spinal motoneurones in non-human animals, influencing how they respond to subsequent input.

In humans, it is not possible to use techniques like those employed in non-human animals to gain insight into the modulation of biophysical properties of spinal motoneurone following AE because we cannot directly isolate and record from the motoneurone itself. Consequently, evidence for motoneurone adaptations following AE is limited. However, indirect assessment methods, primarily the examination of spinal reflexes, suggest that spinal motoneurone circuitry may be altered following AE in humans (Adkins et al., 2006). For example, H-reflex amplitudes are enhanced following various forms and durations of AE (Perot et al., 1991; Vera-Ibanez et al., 2017; Vila-Cha et al., 2012), and in AE-trained athletes compared to power-trained athletes (Maffiuletti et al., 2001) and ballet dancers (Nielsen et al., 1993). More recently, using intramuscular fine wire EMG electrodes inserted into the vastus medialis and lateralis, Vila-Chã et al. (2010) reported a decrease in motor unit discharge rates during submaximal isometric contractions following a six-week leg cycling AE regime. The authors speculated that since the output of the motoneurone pool increased (as evidenced by an increase in surface EMG amplitude) and discharge rates

decreased following exercise, the overall increase in motoneurone output was likely due to recruitment of additional motor units (Vila-Cha et al., 2010). While current evidence suggests that adaptations may occur at the spinal level following AE, the research to date is not exhaustive.

A single session of AE can also alter brain function. Specifically, intracortical receptor activity, assessed via paired-pulse TMS, is altered following acute AE (Singh & Staines, 2015). Similar to resistance training, there is compelling evidence that SICI is reduced following a single session of AE (Singh et al., 2014; Singh & Staines, 2015; Smith et al., 2014; Stavrinos & Coxon, 2017; Yamaguchi et al., 2012; Yamazaki et al., 2019). Further studies report modulation in other intracortical networks, such as reductions in long-interval intracortical inhibition (LICI; i.e., a $GABA_B$- mediated intracortical network) (Mooney et al., 2016; Singh et al., 2014) and increases in intracortical facilitation (ICF; a glutamatergic-mediated cortical network associated with NMDA receptor activity) (Singh et al., 2014) following acute AE. Collectively, these changes in inhibition and excitation have been proposed to contribute to create a cortical environment conducive for neuroplasticity following AE (Smith et al., 2014).

Studies using single-pulse TMS have produced inconsistent results, like those seen with resistance training. For example, some studies report increases in corticospinal excitability following single sessions of AE (Lulic et al., 2017; MacDonald et al., 2019; Opie & Semmler, 2019), while others show no change (Andrews et al., 2020; El-Sayes et al., 2020; McDonnell et al., 2013; Neva et al., 2017; Smith et al., 2014). This inconsistency between studies has been attributed to many factors (Ridding & Ziemann, 2010), including differences in the intensity of the AE performed (Andrews et al., 2020; MacDonald et al.,

2019). Indeed, emerging evidence suggests that higher intensity AE may be more effective and consistent at inducing neuroplasticity than traditional lower intensity AE (Andrews et al., 2020; MacDonald et al., 2019; MacInnis & Gibala, 2017; McDonnell et al., 2013; Nicolini et al., 2021; Opie & Semmler, 2019).

While acute AE has been shown to transiently modulate M1 excitability and sometimes corticospinal excitability, very little is known about changes following repeated sessions of AE training. To date, only one study has examined the effects of repeated AE interventions on corticospinal neuroplasticity in healthy, neurologically intact humans (Nicolini et al., 2019). In this study, 6 weeks of high-intensity interval training (HIIT) increased cardiorespiratory fitness by 12% without changing corticospinal excitability or SICI, but it did reduce ICF. These findings suggest that the corticospinal system may be modulated following relatively short-term AE training, though it is unclear if other forms of repeated AE training may induce similar effects. Moreover, given that no measure of spinal excitability was utilized, it remains unknown whether high-intensity AE training will induce adaptations at the spinal level, as seen in non-human animals (Beaumont & Gardiner, 2003).

An important caveat to all of the above-mentioned studies reporting adaptations within the M1 and corticospinal pathway following either acute or repeated AE is that all measures were recorded from muscles either at rest or during isometric contractions following exercise (El-Sayes et al., 2019; El-Sayes et al., 2020; Lulic et al., 2017; McDonnell et al., 2013; Neva et al., 2017; Neva et al., 2021; Opie & Semmler, 2019; Singh et al., 2014; Singh & Staines, 2015). Consequently, the changes in excitability observed in these studies may not be representative of changes that occur in muscles that are actively

engaged in the AE training or *during* performance of the AE task. For example, in the study by Nicolini and colleagues (2019), changes in excitability were recorded from the first dorsal interosseus (FDI) during performance of a slight isometric contraction prior to and following the 6 weeks of leg cycling HIIT. Thus, it is not known whether similar or different corticospinal adaptations may occur when measured from a muscle actively involved in the training (e.g., quadriceps or hamstrings) and when assessed during the motor output used for training (e.g., leg cycling). Given that corticospinal and spinal motoneurone excitability are state- (i.e., rest vs active), task- (i.e., tonic vs dynamic vs locomotor), and muscle-dependent (Lockyer et al., 2021; Power et al., 2022; Power et al., 2018), it is therefore important to examine potential changes in corticospinal pathway excitability following AE: 1) *during* the motor output used for training, and 2) from a muscle actively engaged in said motor output.

In chapter #5 of this thesis, we attempted to address this issue by examining corticospinal and spinal excitability measured from the biceps brachii during arm cycling following the performance of a high-intensity arm cycling sprint interval training (SIT) protocol. We chose the SIT protocol due to its time-efficient nature and its potency for inducing performance, metabolic, and musculoskeletal adaptations (Burgomaster et al., 2005; Gibala et al., 2006). The protocol, adapted from work from the Gibala lab for arm cycling, involved repeated "all-out" or "supramaximal" sprint bouts (<30 seconds) separated by relatively longer periods of passive or active recovery (Burgomaster et al., 2006; Burgomaster et al., 2005; Gibala et al., 2006; MacInnis & Gibala, 2017). Given that the intensity of AE has been suggested to be a key determinant of AE-induced neuroplasticity (Andrews et al., 2020), it was hypothesized that the high-intensity nature

of SIT may be a potent stimulator for adaptations along the corticospinal pathway following training.

1.9 Thesis Objectives and Hypotheses

The excitability of the corticospinal pathway is influenced by numerous factors that are important to consider when designing and interpreting studies examining the corticospinal control of human movement. This is especially true for studies involving dynamic rhythmic motor outputs where changes in descending (e.g., neural drive) and ascending sensory inputs are constantly changing. Thus, if we wish to obtain a better understanding of the corticospinal system's role during human movement, it is imperative to assess corticospinal excitability *during* dynamic motor outputs that resemble normal day-to-day human movements (see Chapter 2). Given its similarities to other forms of locomotion (see section **1.7** above), arm cycling can be used as one such dynamic motor output. As such, the main objective of this thesis was to add to the body of literature surrounding the factors that influence corticospinal excitability during arm cycling. The key questions I attempt to address in this thesis are:

1. Does focusing on maintaining a specified arm cycling cadence influence corticospinal excitability? **(Study #1)**
2. How do increasing stimulation intensity and power output alter corticospinal and spinal excitability during arm cycling? **(Study #2)**
3. Is corticospinal and/or spinal excitability modulated following a short-term AE training paradigm, such as a two-week arm cycling sprint interval training

(SIT) intervention, when assessed during the motor output used for training? **(Study #3)**

This thesis is written in manuscript style with each chapter focusing on specific objectives. Chapters 2-5 have been published in peer reviewed journals with the publication information and authorship statements located on the title page of each respective chapter. Given that my thesis scope was forced to change because of the COVID-19 pandemic (see **COVID-19 Impact Statement**), and because the chapters within this thesis are stand-alone manuscripts, there is some overlap of similar content in the Introduction and Methods sections of some of the manuscripts.

Chapter #2 (Invited Review): This chapter includes a collaborative invited review paper published in the *Journal of Neurophysiology* in 2020 where we outline many of the methodological factors that should be considered when designing and assessing corticospinal excitability during motor outputs in humans. In this review, we highlight the task-dependent nature of the excitability of the nervous system, and we propose that if the field of movement neuroscience is to truly obtain a greater understanding of the neural control of human movement, it is imperative that we start placing more emphasis on examining neural excitability *during* dynamic motor outputs. We also provide suggestions to help guide future work wishing to examine the influence of the corticospinal system during dynamic motor outputs. In many ways, this review provides a framework for the content discussed in the chapters that follow in this thesis.

Chapter #3 (Study #1): This study was developed in response to a reviewer's comment on a previously submitted manuscript from our laboratory (Forman et al., 2014). In that manuscript, corticospinal excitability (assessed via TMS and TMES) to the biceps brachii was higher during the mid-elbow flexion position of arm cycling compared to a position- and intensity-matched tonic contraction and this finding was attributed to enhanced supraspinal excitability (Forman et al., 2014). We had offered some insights into potential mechanisms for this observation, however, one of the reviewers noted that the finding of higher corticospinal excitability during arm cycling might reflect an increased attentional demand for participants to focus on maintaining a constant, specified cadence. Indeed, attentional demands have been shown to influence corticospinal excitability before (Buschman & Kastner, 2015; Duecker & Sack, 2015; Roosink & Zijdewind, 2010). Thus, the purpose of this study was to investigate if corticospinal excitability would be modulated differently depending on whether participants focused on maintaining a specified cadence (i.e., fixed cadence, FC) or if they cycled at their own self-selected cadence (SSC) without focusing on maintaining said cadence. We hypothesized, given the relative ease of maintaining arm cycling cadence at low power outputs, that corticospinal excitability would not be different between FC and SSC arm cycling.

Chapter #4 (Study #2): Research from studies using isometric contractions have provided relatively detailed information on the effects of muscle contraction intensity on corticospinal excitability (Martin, Gandevia, et al., 2006; Oya et al., 2008). In general, corticospinal (measured via MEP amplitudes) and spinal excitability (measured via CMEP amplitudes) have been shown to increase with increases in muscle contraction intensity up

until a peak, after which excitability plateaus and subsequently decreases as the contraction intensity approaches maximal (Martin, Gandevia, et al., 2006; Oya et al., 2008; Todd et al., 2003, 2004). Substantially less information, however, is available regarding the pattern of change in corticospinal and spinal excitability during dynamic motor outputs, such as arm cycling, as the motor output intensity is increased. Previous studies from our lab examined the effects of cycling intensity on corticospinal and spinal excitability but only included relatively low cycling workloads (Lockyer et al., 2018; Spence et al., 2016). Moreover, these studies only used a single stimulation intensity to examine corticospinal excitability. Given that corticospinal excitability may be modulated differently with different intensities (Bachasson et al., 2016), stimulation intensity has been proposed as an important factor to consider in designing and interpreting neurophysiological experiments. Thus, the primary objective of this study was to determine the pattern of modulation in corticospinal and spinal excitability during arm cycling over a wide range of cycling intensities. A secondary objective was to determine the influence of weaker and stronger stimulation intensities on measures of corticospinal and spinal excitability during arm cycling as motor output intensity increased. We hypothesized that: 1) using the *weak* stimulus, corticospinal and spinal excitability would increase similarly as arm cycling power outputs increased, and 2) using the *strong* stimulus, corticospinal and spinal excitability would increase but experience a plateau and subsequent decrease as cycling intensity increased towards the maximum power output examined, similar to what is observed during isometric contractions.

Chapter #5 (Study #3): While it is becoming increasingly obvious that the intensity of the motor output being performed greatly influences corticospinal excitability to muscles involved in performing the movement, there is much less known regarding the effects of longer-term periods of AE training on the corticospinal system. In recent years, it has been shown that higher-intensity AE, more so than lower intensity, may be a potent stimulator of neuroplasticity within the central nervous system (Andrews et al., 2020). To date, the effects of high intensity AE training on corticospinal excitability is not well-established, with only one other study available (Nicolini et al., 2019). In that study, the authors examined the effects of a 6-week leg cycling HIIT regime on corticospinal excitability to an intrinsic hand muscle not involved in the dynamic motor training and found that supraspinal, but not corticospinal excitability, was different between participants who performed the HIIT or a control group (Nicolini et al., 2019). The authors, however, did not include a measure of spinal excitability, thus it remains unknown whether the HIIT protocol influenced spinal excitability. Moreover, given that the responses were evoked from an intrinsic hand muscle at rest and during tonic contractions, it is possible that the modulation of nervous system excitability would be different if measured *during* the dynamic motor output used for the HIIT (i.e., leg cycling). Thus, the primary objective of this study was to examine the effects of a two-week arm cycling sprint interval training (SIT) regime on corticospinal and spinal excitability to the biceps brachii when assessed during arm cycling following training. It was hypothesized that AE performance would increase following training, with concurrent increases in both corticospinal and spinal excitability in the SIT group only compared to the non-exercising control group.

Chapter #6 (Summary and Future Directions): Chapter 6 provides a summary of the studies reported in this thesis and provides some discussion into the importance of each study and their contributions to the field of human movement neurophysiology. At the end of the chapter, a brief discussion of some potential future directions for this work are provided.

Chapter 2: MOVING FORWARD: METHODOLOGICAL CONSIDERATIONS FOR ASSESSING CORTICOSPINAL EXCITABILITY DURING RHYTHMIC MOTOR OUTPUT IN HUMANS

Co-Authorship Statement:

Chapter two is an invited review paper published in the *Journal of Neurophysiology*: Lockyer EJ, Compton CT, Forman DA, Pearcey GE, Button DC, Power KE. Moving forward: Methodological considerations for assessing corticospinal excitability during rhythmic motor output in humans. *J Neurophysiol*. 2021, 126(1), 181-194. doi: 10.1152/jn.00027.2021 (copyright license #: 5323241079194). This review was a collaborative effort between Evan Lockyer, Chris Compton, Dr. Greg Pearcey, Dr. Davis Forman, Dr. Duane Button, and Dr. Kevin Power of which Evan is the co-first author. Evan Lockyer helped conceive the sections included in the review, wrote extensive sections of the review, was responsible for creating both figures, and assisted with the editing process. All authors approved the final version.

2.1 Abstract

The use of transcranial magnetic stimulation to assess the excitability of the central nervous system to further understand the neural control of human movement is expansive. The majority of the work performed to-date has assessed corticospinal excitability either at rest or during relatively simple isometric contractions. The results from this work are not easily extrapolated to rhythmic, dynamic motor outputs, given that corticospinal excitability is task-, phase-, intensity-, direction-, and muscle-dependent (Power et al., 2018). Assessing corticospinal excitability during rhythmic motor output, however, involves technical challenges that are to be overcome, or at the minimum considered, when attempting to design experiments and interpret the physiological relevance of the results. The purpose of this narrative review is to highlight the research examining corticospinal excitability during a rhythmic motor output and, importantly, to provide recommendations regarding the many factors that must be considered when designing and interpreting findings from studies that involve limb movement. To do so, the majority of work described herein refers to work performed using arm cycling (arm pedaling or arm cranking) as a model of a rhythmic motor output used to examine the neural control of human locomotion.

2.2 Introduction

The Russian scientist, Nikolai Bernstein, is considered by many as the founder of current day motor control research. Among his many scientific contributions, Bernstein was known for his work examining motor equivalence, which states that any given movement goal can be achieved by various combinations of neural activation strategies.

Essentially, a person never performs a movement exactly the same way twice, as summarized by Bernstein's sentiment of "repetition without repetition." In other words, the neural production of human movements is inherently variable given the many degrees of freedom. This variability in the motor system is beneficial in that it ensures that human movement can be performed under different environmental constraints but increases the complexity of examining the neural control of human movement. Large variability is often viewed as a drawback or limitation because it produces variability in measurements; it is viewed as creating noise in the data, making analysis and interpretation difficult. Thus, the majority of research in our field (neural control of movement) attempts to control the many degrees of freedom associated with human movement to reduce neural variability, predominantly by assessing neural excitability with participants at rest or during isometric contractions. This methodological stringency has created a paradox, whereby we seek to understand the neural control of human *movement* but do so without using human *movement* as a model. This is not to downplay or discredit the importance of research examining neural excitability at rest or using different modes of motor output (e.g., isometric or isokinetic contractions). However, we propose that current methodologies can be improved, and new methods can be developed, to allow a detailed task-relevant assessment of neural excitability during dynamic motor outputs. To do so requires thinking critically about how we use current research techniques to understand human movement, their strengths, and limitations, while also accepting that human movement is inherently variable; ergo, the data will have a degree of variability when collected during movement.

2.3 Assessing Corticospinal Excitability: The Corticospinal Pathway

Although numerous pathways of the central and peripheral nervous systems contribute to motor outputs, this review will focus on measures of corticospinal excitability. Corticospinal excitability is defined as the excitability of the pathway from the cortical site of neuronal depolarization to spinal motoneurone depolarization. As the name suggests, *corticospinal* excitability implies that measures of excitability are influenced by changes at cortical and/or spinal levels. Following a brief description of the corticospinal pathway we provide an overview of the main techniques discussed in this review to assess corticospinal excitability; transcranial magnetic stimulation (TMS) and transmastoid electrical stimulation (TMES). For a more detailed discussion of these techniques the reader is referred to recent excellent reviews on these topics (Di Lazzaro, Oliviero, et al., 1998; McNeil et al., 2013; Rossini et al., 2015; Taylor, 2006).

The corticospinal pathway is considered the dominant descending pathway involved in the execution of voluntary movements (Cho et al., 2012; Davidoff, 1990; Heffner & Masterton, 1983; York, 1987). The corticospinal pathway is typically discussed as originating from the primary motor cortex (Martin, 2005; Oudega et al., 1994) and descending through the brainstem (Nathan & Smith, 1955) where the axons of the corticospinal tract decussate to the contralateral side of the brainstem and project down through the spinal cord. The corticospinal tract then synapses onto either spinal interneurones, which may be part of a certain spinal circuit, such as the propriospinal system (Alstermark et al., 1999; Isa et al., 2006; Pierrot-Deseilligny, 2002; Sasaki et al., 2004), or directly onto spinal motoneurones (Lemon, 2008; Lemon et al., 2002).

One goal of motor control and neurophysiology scientists is to identify not only how corticospinal excitability changes but also where the source of this change originates (i.e., supraspinal and/or spinal). In humans, the excitability of the corticospinal pathway is most commonly measured indirectly using magnetic and/or electrical stimulation techniques (**Figure 2.1**).

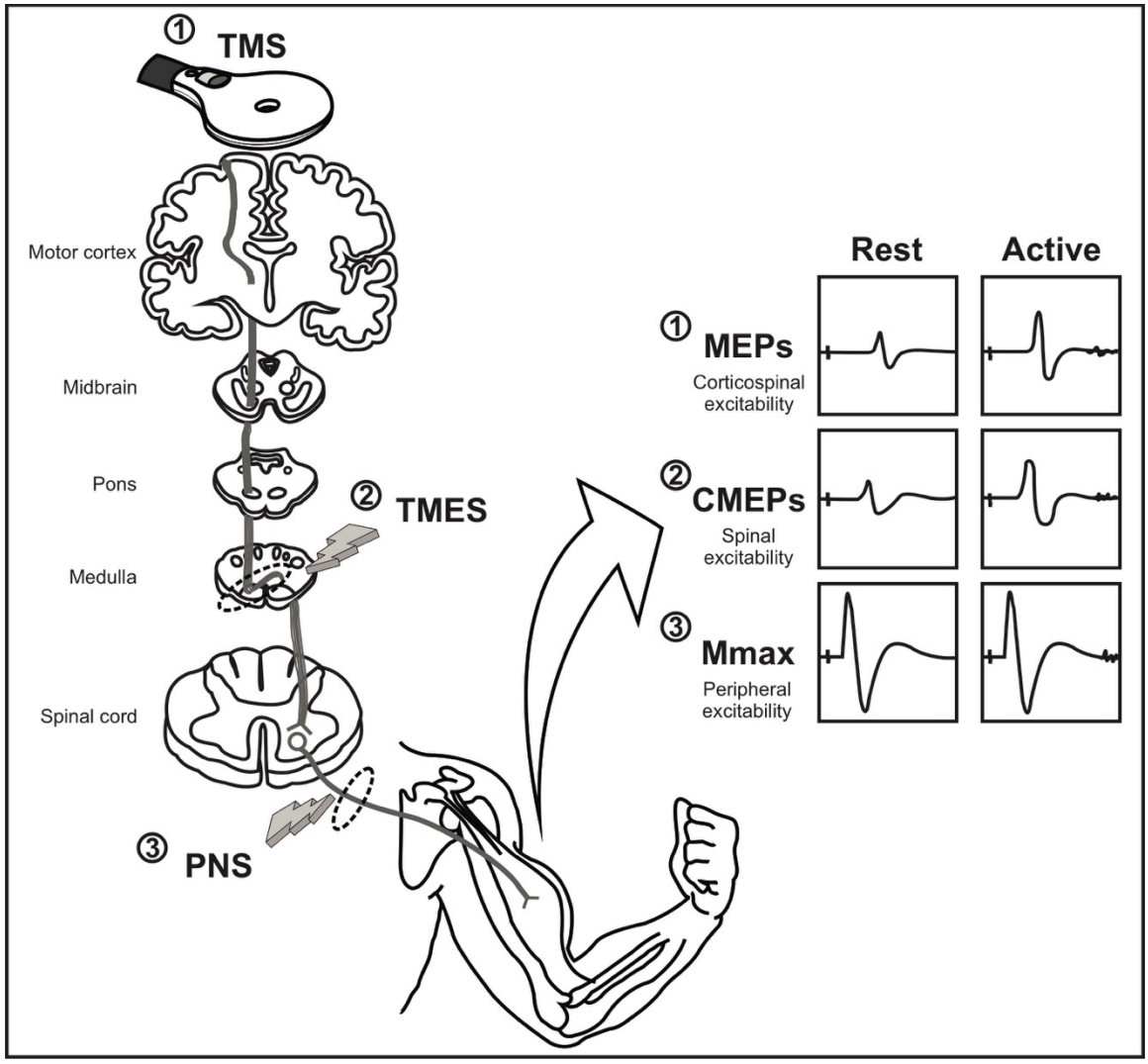

Figure 2.1: Simplified overview of stimulation techniques used to assess excitability of the corticospinal pathway (left), and the associated evoked responses to each stimulation at rest and during an active contraction (right).

1) Transcranial magnetic stimulation (TMS) elicits a response known as a motor-evoked potential (MEP), which is recorded from surface electromyography from a muscle of interest (e.g., the biceps brachii in this case) and provides a measure of corticospinal excitability. Changes in MEP size (i.e., amplitude or area) can be due to mechanisms at either the cortical, spinal, or peripheral level. As such, other techniques can be used to help identify the site of change. 2) Transmastoid electrical stimulation (TMES) involves electrically stimulating axons of the corticospinal tract at the site of the pyramidal decussation to evoke a response recorded from surface electromyogram (EMG) known as a cervicomedullary motor-evoked potential (CMEP), which provides a measure of spinal excitability. 3) Peripheral nerve stimulation (PNS) involves electrically stimulating a peripheral nerve, and when the stimulation is maximal, it evokes a response known as a maximal compound muscle action potential (M_{max}) and provides a measure of peripheral excitability. When the MEP and CMEP are evoked during an isometric contraction (active), responses are larger than those evoked when the person is at rest (rest). M_{max} is frequently used as a control measure of peripheral excitability.

2.3.1 Assessing Corticospinal Excitability: Transcranial Magnetic Stimulation

Single-pulse TMS-evoked responses (**Figure 2.1**, stimulation no. 1) are recorded from the target muscle(s) in the surface EMG as a compound muscle action potential and are referred to as motor evoked potentials (MEPs). A common means used to examine changes in corticospinal excitability is the peak-to-peak amplitude of the MEP (i.e., MEP amplitude). An increase or decrease in the MEP amplitude typically represents an increase or decrease in corticospinal excitability, respectively. As mentioned, however, the corticospinal pathway includes supraspinal and spinal segments that innervate muscle. It is therefore possible that changes in corticospinal excitability (i.e., MEP amplitude) between experimental conditions are due to changes at the supraspinal, spinal and peripheral levels, or a combination thereof. Determining the level of that change cannot be accomplished

with single pulse TMS alone as MEPs are an indicator of overall corticospinal pathway excitability. Thus, TMS is often used alongside independent measures of cortical, spinal and peripheral excitability in order to improve the interpretation of changes in MEP amplitude. Examples of such techniques are TMES and peripheral nerve stimulation.

2.3.2 Assessing Corticospinal Excitability: Transmastoid Electrical Stimulation

Transmastoid electrical stimulation (TMES) is used as a measure of spinal motoneurone excitability in humans. The technique is performed by placing surface electrodes just inferior to each mastoid process on the back of the skull, and an electric current is subsequently passed between these electrodes. The electrical stimulation excites the axons of the corticospinal tract near the cervicomedullary junction (**Figure 2.1**, stimulation no. 2), the details of which have been previously discussed (Taylor, 2006). The resulting effect is that the motoneurone pool is activated by a single descending volley transmitted by the corticospinal axons producing an evoked response (Ugawa et al., 1995; Ugawa et al., 1991) known as a cervicomedullary motor evoked potential (CMEP) and is used as a means to identify the responsiveness of the spinal motoneurone pool to synaptic activation (McNeil et al., 2013; Taylor, 2006). It is therefore used in combination with TMS to differentiate changes in corticospinal excitability as of either supraspinal or spinal in origin given that both TMS and TMES activate similar axons of the corticospinal tract (Taylor et al., 2002).

2.3.3 Assessing Peripheral Excitability: Peripheral Nerve Stimulation

When either TMS or TMES are used to elicit a response in a target muscle, there is the possibility that any changes within the conductivity (or excitability) of the motoneurone's axon, the neuromuscular junction, or the muscle fibers themselves could influence the size of these responses. In other words, TMS and TMES-evoked potentials may be impacted by peripheral transmission. Instead, this is typically accomplished by stimulating the peripheral nerve that contains efferent fibers to the target muscle (Fig 1, stimulation no. 3). When the peripheral nerve is stimulated, an evoked potential can be measured at the target muscle with surface EMG, referred to interchangeably as a compound muscle action potential (CMAP) or more commonly as an M-wave (Tucker et al., 2005). During motor outputs, a supramaximal electrical stimulus is applied to a nerve to evoke a maximal M wave (M_{max}) which represents the summation of the electrical activity of the motor units activated by the electrical stimulus (Rodriguez-Falces & Place, 2018). The main role of the M_{max} in relation to quantifying central nervous system excitability during dynamic motor outputs is for normalization purposes (Carroll et al., 2002; Collins et al., 2017; Forman et al., 2014; Forman et al., 2015; Gandevia et al., 1999; Pearcey et al., 2014; Power & Copithorne, 2013; Stefanelli et al., 2019). Because the electrical stimulus that elicits the M_{max} occurs outside of the central nervous system pathways, it should not reflect changes in excitability that occur centrally. In other words, M_{max} identifies failure distal to the site of stimulation. The absence of a change in M_{max} suggests that changes in TMS or TMES evoked potentials lie proximal to the site of peripheral stimulation in the central nervous system.

2.4 Making The Case For Moving

A challenge with using these powerful techniques, TMS in-particular, is that the measurements are often variable both within and between participants. To minimize this variability, the majority of studies assess corticospinal excitability either at rest or during a tonic contraction whereby the degree of muscle activation, joint angle, muscle length and movement are tightly controlled. Findings from these studies are not easily extrapolated to human movement because corticospinal excitability is phase-, muscle-, state-, intensity-, direction- and task-dependent (Power et al., 2018). In the sections that follow, a brief description of some factors that alter corticospinal excitability is provided.

2.5 Measuring Corticospinal Excitability At Rest

In the resting state, inputs upstream of the motor cortex involved in the planning of movement, descending extrapyramidal neuromodulatory commands and propriospinal inputs, afferent feedback (e.g., GTOs, muscle spindles, group III/IV afferents, cutaneous, joint receptors) and inputs from synergistic and/or antagonistic muscles (e.g., reciprocal inhibition) are either absent or substantially reduced. This experimental design thus assesses the motor system in a non-motor state, which may be beneficial for studies examining cortical map plasticity, for example, but raises questions as to the generalizability of these findings to human movement. The obvious solution, therefore, is to assess corticospinal excitability during a motor state.

What defines a motor state? A ‘motor state’ is certainly achieved during voluntary muscle contraction but does a muscle contraction define a motor state? Likely not. A rich

body of research has demonstrated that changes in neural excitability are evident prior to contraction onset as the motor system prepares to engage in voluntary muscle contraction (Chen & Hallett, 1999). This could be considered a compromise between measuring corticospinal excitability at rest, thus reducing measurement variability, but still raises questions about whether these data relate to human movement. For example, do premovement changes in corticospinal excitability represent what is occurring when the intended movement is engaged? In our lab we have assessed these very questions in an attempt to determine when task-dependent changes in corticospinal excitability (tonic vs arm cycling) commence (Copithorne et al., 2015; Power & Copithorne, 2013). We compared corticospinal excitability (MEPs and CMEPs) prior to intensity- and joint-position matched tonic and arm cycling motor outputs and showed that supraspinal excitability was higher preceding arm cycling as compared to tonic contraction but spinal excitability was not altered (Copithorne et al., 2015). It was thus apparent that supraspinal excitability was not task-dependent in the *pre-contraction* phase and likely represented a general priming of the motor system to engage in muscle contraction. However, we had previously shown that both supraspinal and spinal excitability were higher *during* arm cycling than tonic contraction, which raised the question as to when do task-dependent changes in corticospinal excitability become evident (Forman et al., 2014)? We subsequently assessed corticospinal excitability during the initiation and onset of both arm cycling and tonic contraction and showed that task-dependent changes were not evident at motor output onsets and were only evident upon achieving a steady-state of arm cycling (overcame movement inertia and a set cadence achieved; Forman, Philpott, et al., 2016). It

is thus apparent that corticospinal excitability prior to movement does not necessarily represent that which occurs during movement itself.

2.6 Why Use Arm Cycling As A Model Of Rhythmic Motor Output?

In non-human animals the evidence is conclusive that prior to and throughout the onset of CPG-mediated motor outputs there is a reconfiguration of spinal excitability (reflexes and motoneurone properties) that essentially creates a new functional locomotor "state" when compared to rest (Krawitz et al., 2001; Power et al., 2010). In humans, it is generally accepted that rhythmic motor outputs, such as locomotion and cycling (leg and arm), are partially generated by spinally located CPGs, thus providing a human model to assess state- and task-dependent changes in neural excitability (Klarner & Zehr, 2018; Power et al., 2018).

The basic neural elements for the control of all rhythmic behaviours in humans and non-human animals can be summarized as a complex interaction between: 1) spinal CPGs, 2) somatosensory feedback from the moving limbs, and 3) supraspinal commands (Pearcey & Zehr, 2020). This tripartite control system is common among rhythmic motor tasks, such as locomotion, and allows for the study of one task to provide inferences about the neural control of many other tasks such as crawling, running, swimming, breathing, and cycling, among others. Indeed, levels of muscle activation and joint range of motion are comparable across walking and cycling tasks (Klarner et al., 2014), and this is because rhythmic behaviours share a "common core" of neural elements responsible for the generation of the rhythmic movement (Zehr, 2005). The shared neural elements responsible for the control

of walking and cycling allows investigators to study cycling and remain confident that their findings reflect the overall neural control of other rhythmic motor behaviours. While arm cycling is not something most of us engage in, it has been used as a model of locomotion for ~20 years by Zehr and colleagues (Klarner & Zehr, 2018; Zehr, 2005; Zehr et al., 2004; Zehr et al., 2003). Most importantly, arm cycling provides a convenient model to examine neural excitability during dynamic, rather than tonic, motor output.

It is, however, important that we acknowledge the limitations when using arm cycling as a model to study the neural control of rhythmic behaviours. Walking necessitates propulsion from the legs to ensure forward progression during upright preservation of balance, whereas cycling and arm cycling do not. The reduced demand for neural resources to maintain balance during arm cycling may be viewed as a drawback, since balance-related neural resources can be diverted to the control of the rhythmic behaviour. Regardless, we believe that several advantages of cycling as a model to study the neural control of rhythmic behaviours, when compared to walking, should not be overlooked. For instance, arm cycling, in particular, can be studied in various neurological impairments due to the relative ease of use (i.e., it can be performed with no resistance or even with assistance), accommodation of hemi-paresis (i.e., one arm can be strapped on to move passively), low risk of falls, and reduced need for harnesses and/or other safety devices to mitigate the risk of falls during rhythmic movement. Indeed, arm cycling has successfully been implemented by several groups to train and study the neural control of rhythmic motor output following neurological impairment (Kaupp et al., 2018; Zehr et al., 2012; Zhou et al., 2018). Probably most pertinent to the current discussion, is that arm cycling can be performed under a variety of conditions (i.e., various loads and cadences), while the head,

neck and torso remain relatively stationary. These factors enhance our ability to measure TMS and TMES evoked potentials at various phases of arm cycling (**Figure 2.2**), which are the focus of this review.

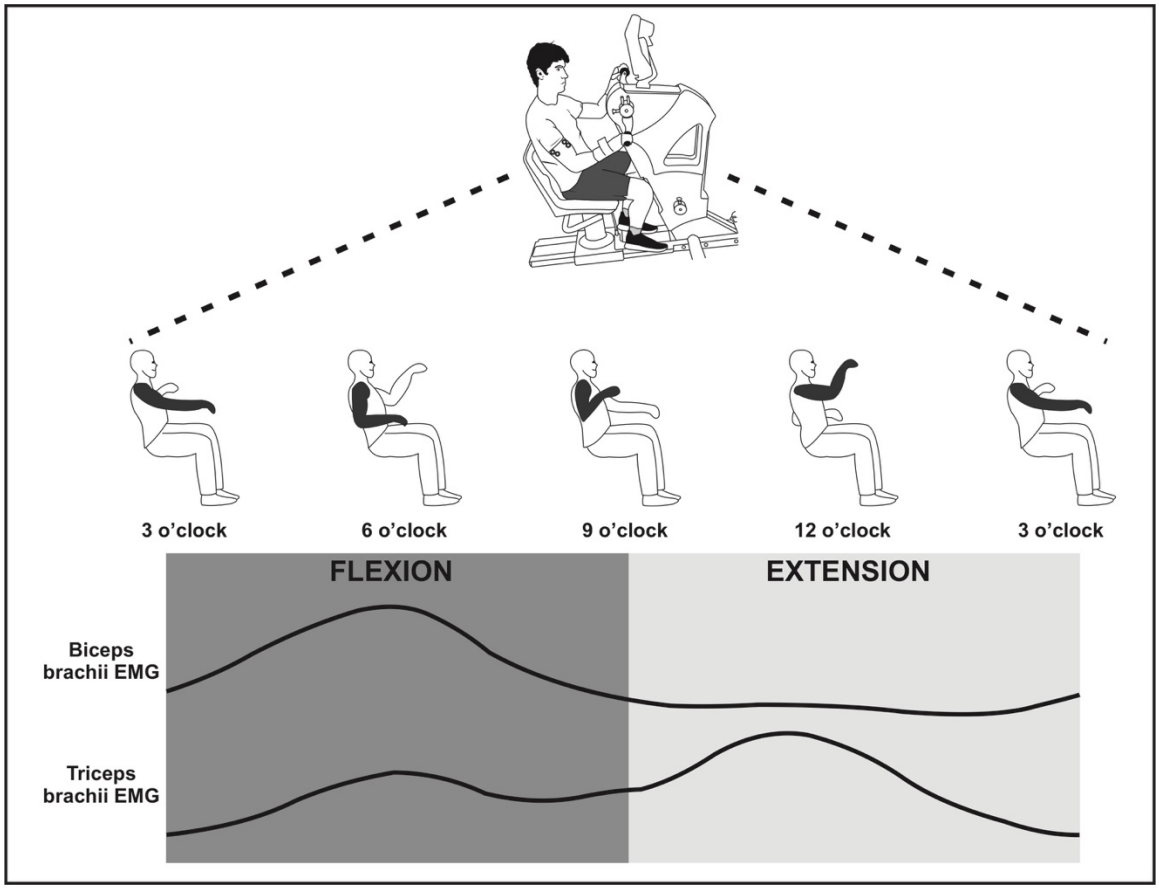

Figure 2.2: Schematic overview of the various phases of arm cycling and the associated electromyogram (EMG) profiles from the biceps and triceps brachii throughout a revolution.

A typical position of a person arm cycling is shown at the top. The right arm (darker) moves in a circular pattern in the clockwise direction. From the 3 o'clock to the 9 o'clock position, the elbow undergoes flexion and the biceps brachii are highly active, whereas the triceps brachii are only moderately active. From the 9 o'clock to the 3 o'clock position, the elbow undergoes extension and the biceps brachii are quiescent, whereas the triceps brachii are highly active.

2.6.1 Considerations For Assessing Corticospinal Excitability During Rhythmic Motor Output

While arm cycling does provide a convenient means to assess corticospinal excitability during a rhythmic task, there are factors to consider about the movement itself that likely influence data interpretation and should be considered. In the following paragraphs we provide, as examples, several important factors that we consider during experimental design and data interpretation. These factors likely apply to other rhythmic motor outputs involving multiple limbs such as jumping, rowing, walking, swimming and resistance training. Note that a detailed discussion of the mechanisms relating to the factors listed is beyond the scope of this review.

First, arm cycling is typically performed with asynchronous arm cranks; while one arm engages in elbow flexion the opposite arm performs elbow extension (see **Figure 2.2**). The limbs do not operate independently, however, with crossed influences having been documented for over 100 years (Sherrington, 1910). Thus, muscular activity in the limb contralateral to the limb being assessed may influence measures of corticospinal excitability as we recently demonstrated (Lockyer et al., 2020).

Second, arm cycling may not be performed similarly for each individual. For example, we typically collect corticospinal excitability measures from the biceps (elbow flexor) and triceps brachii (elbow extensor) during mid-elbow flexion, while the arm is in the pulling phase of arm cycling (3 o'clock to 9 o'clock) and the opposite arm engages in elbow extension or a pushing phase (9 o'clock to 3 o'clock) (Chaytor et al., 2020). In recent work from our lab (unpublished), not every participant adopted the same strategy to arm

cycle. Some participants adopted a pulling strategy, where forces were highest during the pull phase of a revolution whereas other participants performed a pushing strategy where forces were highest during the push phase of a revolution. Depending on the muscle examined this could have potential implications for the findings and thus interpretation. For example, corticospinal excitability to the biceps brachii during the pull phase (i.e., elbow flexion) of a participant who uses a pushing strategy would be relatively lower than that of a participant who uses a pulling strategy and thus more actively engages the 'pulling' muscles, including the biceps brachii.

Third, given the fixed range of motion both arms must travel during a revolution, it could be reasonably assumed that both arms contribute equally to producing the prescribed power output. This is likely not the case. Bilateral asymmetries during rhythmic tasks such as running and leg cycling, are well documented in the literature (for review see (Carpes et al., 2010) and are both cadence- (Carpes et al., 2007; Rossato et al., 2008) and workload- (Cavagna, 2006; Rossato et al., 2008) dependent. Therefore, the cadence, workload, and arm selection appear to be heavily intertwined and must be considered when designing a study and interpreting results from that study.

2.7 Factors To Consider For Assessing Corticospinal Excitability During Rhythmic Motor Output

2.7.1 Choosing Stimulation Parameters

A difficult, yet very important, decision to make when designing an experiment to examine corticospinal excitability is deciding upon the appropriate stimulation parameters

to use. This is a common challenge that is influenced by many factors intrinsic to the study itself, such as the task being performed, the stimulation type, and/or the question being addressed. As such, there is great heterogeneity in the methods used for determining stimulation parameters across studies. This topic is not well-discussed or disclosed in the literature. In this section of the review, we will outline stimulation parameters that are commonly used during both static (i.e., rest and tonic) and dynamic (i.e., limb movement) contractions, and provide some discussion of the factors that must be considered when choosing suitable stimulation parameters. Additionally, we will discuss how, although important across all human neurophysiology studies, it becomes especially important to consider the many factors influencing stimulation parameters during locomotor-like outputs given that corticospinal excitability is task-, phase-, muscle-, direction-, cadence-, load- and phase-dependent (Power et al., 2018).

2.7.2 Summary Of Methods Used To Determine Stimulation Intensities

The stimulation techniques used to assess the excitability of the corticospinal pathway does so by producing measurable EMG responses recorded from the target muscle(s). Prior to obtaining measurements, however, the intensity of each stimulation technique must first be determined, a decision that is based on several factors.

It is important to note that when we discuss the setting of stimulation intensities in the context of this review, we are primarily referring to TMS-evoked MEPs and TMES-evoked CMEPs, rather than the M_{max}. This is because the methods for determining the M_{max} are relatively similar across studies, although some of the factors that influence M_{max} are

discussed below. The primary goal for setting stimulation intensities is to produce responses that are: 1) measurable, and 2) large enough to discern the evoked response from the background EMG across the experiment (i.e., avoiding potential flooring effects), but also small enough to avoid potential saturation of the evoked responses (i.e., ceiling effects).

Stimulation intensities are often set with reference to a motor threshold of a target muscle (Groppa et al., 2012; Rossini et al., 2015). Motor threshold is assessed when the target muscle is either at rest, known as resting motor threshold (RMT; Rossini et al., 1994), or during a tonic contraction, known as an active motor threshold (AMT; Groppa et al., 2012; Rossini et al., 1994; Sidhu et al., 2012). The intensity of stimulation used to determine motor threshold reflects the overall excitability of the corticospinal pathway, whereby a higher stimulation indicates a higher threshold, and vice-versa (Groppa et al., 2012). RMT is defined as the lowest stimulus intensity that is required to elicit a discernible response from a resting target muscle in at least 50% of the trials (Chen, 2000; Groppa et al., 2012; Rossini et al., 1994; Rossini et al., 2015). The proposed standard to ensure RMT determination is to evoke a response in at least 5 out of 10 trials (Rossini et al., 1994), however, in practice, this criterion varies and can range, for example, anywhere from 3 out of 5 (Barthelemy & Nielsen, 2010; Carson et al., 2004; Sidhu et al., 2012), to 4 out of 8 (Copithorne et al., 2015; Forman et al., 2018; Forman et al., 2015; Lockyer et al., 2018), to 5 out of 10 trials (Kalmar & Cafarelli, 2004; Knikou et al., 2013; Lockyer, Hosel, et al., 2019; Power & Copithorne, 2013; Pyndt & Ridding, 2004; Sharples & Kalmar, 2012).

Similar to RMT, AMT is defined as the lowest stimulation intensity to elicit an evoked response in at least 50% of the trials, but is typically measured during tonic

contraction of a target muscle instead (Forman et al., 2018; Forman et al., 2015; Groppa et al., 2012; Pearcey et al., 2014; Rossini et al., 2015; Sidhu et al., 2012), though we have recently adapted the terminology for AMT during dynamic motor outputs (see below). When setting AMT, EMG activity will be heightened given that the muscle is contracting, making it more difficult to discern the evoked response from the ongoing EMG. As such, the stimulator intensity used to determine AMT will be gradually increased until a clearly discernible response is observed in the contracting muscle (Rossini et al., 1994). Typically, once either RMT or AMT has been determined for a given study, stimulation intensity is then increased by a certain percentage of threshold (e.g., 10-50%) as a means to ensure that the evoked responses will be consistently measurable throughout the course of an experiment (Rossini et al., 2015).

Another method that is commonly used to set stimulation intensities is to adjust the stimulation intensity so that the amplitude of the MEP and CMEP approximately match a specific value of the M_{max} (e.g., 10% Mmax; Donges et al., 2017; Nuzzo, Trajano, et al., 2016; Pearcey et al., 2014; Weavil et al., 2015, 2016). This method is often performed in studies where both MEPs and CMEPs are used together as it is presumed that responses approximately equal in amplitude would likely be activating the same portion of the motoneurone pool and would theoretically provide a convenient way to differentiate whether potential changes are occurring at the supraspinal or spinal level. Moreover, this method can be performed when the muscle is at rest or during the investigated motor output.

Finally, one can use a range of stimulation intensities to create a stimulus-response curve (SRC) at rest or during a muscle contraction to determine the stimulation intensity

used for a given experiment. SRCs can be elicited by using either absolute or relative (i.e., %RMT or %AMT) stimulation intensities and typically range from subthreshold stimulation (i.e., does not evoke a response) up to approximately two times threshold (Daligadu et al., 2013; Devanne et al., 1997; Forman et al., 2018). Whereas fixed, single intensity stimulation assesses only a specific portion of the motoneurone pool, SRCs created across a wide range of stimulation intensities may more appropriately reflect the excitability of the entire corticospinal pathway (Devanne et al., 1997) and as such may provide the most fruitful and insightful understanding of corticospinal excitability. By using the range of stimulation intensities, the input-output properties of the corticospinal pathway can be evaluated. Researchers can then select a stimulation intensity on the ascending limb of the sigmoidal SRC in order to avoid potential flooring or ceiling effects or to assess a certain portion of the motoneurone pool. Characteristics of the SRC itself, such as the slope (Daligadu et al., 2013; Devanne et al., 1997; Forman et al., 2018) and the area under the curve (AUC; Nicolini et al., 2019), are often used to detect changes in corticospinal excitability across multiple conditions. In this respect, steeper slopes or an increased gain (i.e., a leftward shift in slope from a reference slope) and/or larger AUC values are thought to reflect enhanced corticospinal excitability. One caveat to SRCs is that they are time-consuming to create and therefore may not be applicable during situations where time is of the essence for collecting data (i.e., in the presence of fatigue, during dynamic contractions or locomotor outputs).

2.7.3 Task-Dependent Changes In Corticospinal Excitability That Influence Stimulation Parameters

Using a combination of the abovementioned methods for setting stimulation intensities, it is now well-established that corticospinal excitability is influenced by the motor task (Carroll et al., 2006; Cinelli et al., 2019; Forman et al., 2014; Kalmar, 2018). As such, task-dependent changes in corticospinal excitability are important to consider when selecting stimulation parameters for a given study. We know that corticospinal excitability assessed at rest immediately prior to initiating a motor output is higher than corticospinal excitability observed at rest without a plan for movement (Chen, Yaseen, et al., 1998; Power & Copithorne, 2013; Sharples & Kalmar, 2012). We also know that corticospinal excitability is higher during a tonic muscle contraction than compared to rest (Temesi et al., 2014), and that corticospinal excitability is different during a locomotor-like task than that observed during an intensity-matched tonic contraction (Carroll et al., 2006; Forman et al., 2014; Forman et al., 2018; Weavil et al., 2015). Furthermore, as the intensity of the motor output is increased, corticospinal excitability also increases regardless of whether the task is tonic (Martin, Gandevia, et al., 2006; Oya et al., 2008; Temesi et al., 2014) or dynamic (Forman et al., 2015; Lockyer et al., 2018; Lockyer, Hosel, et al., 2019; Spence et al., 2016; Weavil et al., 2015). While many factors may underlie these task-dependent changes in corticospinal excitability, changes in spinal motoneurone excitability are at least partially involved (Forman et al., 2014; Forman et al., 2015; MacDonell et al., 2015; Weavil et al., 2015). Indeed, the excitability of the motoneurone is enhanced during performance of a motor task likely due to a combination of changes in

supraspinal drive, intrinsic motoneurone properties, neuromodulatory drive, as well as afferent feedback (Heckman et al., 2008; MacDonell et al., 2015; Power et al., 2018). However, an important question to ask is how do these task-dependent differences in corticospinal excitability influence the selection of the stimulation parameters?

The stimulation intensity required to elicit responses at rest (e.g., RMT) is typically higher than that required to evoke responses during a motor task (e.g., AMT) (Kalmar, 2018; Rossini et al., 2015; Temesi et al., 2014). This may result in participants becoming uncomfortable at higher stimulation intensities and may cause anticipatory bracing. However, setting stimulation intensities at rest allows for easier control of confounding variables such as changes in joint angle, muscle length, afferent feedback, as well as antagonistic and synergistic muscle contributions (Kalmar, 2018). While controlling for these confounding variables reduces variability in the measurement, assessing corticospinal excitability at rest provides little insight into the corticospinal control of voluntary, functional human movements. Another potential issue for setting stimulation intensities at rest arises when the resting stimulation intensity is subsequently used to measure corticospinal excitability during a motor output. This stimulation intensity may allow for recordings of MEPs during cycling phases with low levels of muscle activity (e.g., elbow extension for biceps brachii). However, this can become problematic as the stimulation intensity used will likely be suprathreshold during the motor output which may actually saturate the corticospinal pathway and result in a ceiling effect in the evoked responses during phases involving high levels of muscle activity. If this occurs, it could lead to erroneous interpretation of the results. Furthermore, it could be influenced by the

intensity of the motor output which may vary from participant to participant, unless motor output intensity is normalized to a maximum (Lockyer et al., 2018).

As a means to circumvent some of these potential drawbacks for measuring corticospinal excitability at rest, many researchers record changes in excitability during relatively low intensity (e.g., 5-50% maximal voluntary contraction) tonic contractions (Barthelemy & Nielsen, 2010; Martin, Gandevia, et al., 2006; Nuzzo, Trajano, et al., 2016; Oya et al., 2008). During tonic contractions, the stimulus intensity will be substantially lower than that needed at rest as the corticospinal pathway is now primed and engaged in a motor output (Darling et al., 2006; Rossini et al., 1994). Moreover, setting stimulation intensities during a motor output provides a greater representation of the motoneurone during an active state (Temesi et al., 2014) and the evoked potentials at AMT are typically less variable than those at RMT (Darling et al., 2006).

The decision to set stimulations at rest versus during a motor output is dependent on the question being investigated. If the rest component is not an essential part of the research question, it may be more practical to evoke responses during a motor output. If we truly wish to push towards a greater understanding of the neural control of human movement, it is imperative that we set stimulation intensities and measure corticospinal excitability *during* the motor output of interest.

2.7.4 Factors To Consider For Setting Stimulation Intensities During Rhythmic Motor Output

Unlike rest or tonic contractions, where muscle activity, joint angles, and muscle length are held relatively constant, locomotor-like outputs involve alternating phases of variable muscle activation, coupled with continuous alterations in joint angles, muscle lengths, and afferent feedback as the limb moves through its range of motion (Capaday et al., 1999; Chaytor et al., 2020; Forman et al., 2014; Petersen et al., 1998; Power et al., 2018; Schubert et al., 1997; Zehr et al., 2007). Accordingly, greater attention to how the stimulation parameters are set is necessary.

One of the main factors for consideration when setting stimulation parameters during locomotor outputs is the phase-dependent changes in corticospinal excitability. During locomotor outputs, corticospinal excitability is largely modulated in a phase-dependent manner that closely parallels the phasic modulation of the EMG (Capaday et al., 1999; Chaytor et al., 2020; Forman et al., 2014; Petersen et al., 1998; Power et al., 2018; Schubert et al., 1997; Sidhu et al., 2012; Zehr et al., 2007). In other words, when muscle activity is high during specific phases of the movement, the threshold to elicit evoked responses is generally low and the amplitude of these responses is typically large. In contrast, when muscle activity is low throughout the motor output, the threshold to elicit evoked responses is much larger and results in much smaller response amplitudes than when the muscle is more active. Understanding that corticospinal excitability is modulated in this manner across various phases of the locomotor output is important for setting stimulation intensities, as depending on the phase of the motor output investigated, the

stimulation intensity used may be too low or too high to track measurable changes. We recently experienced some of these phase-dependent challenges during assessment of the biceps brachii during the elbow extension phase of arm cycling (Forman et al., 2014). In this study, stimulation intensities were initially set to evoke MEPs and CMEPs equal to 5-10% M_{max} while participants were at rest, prior to performing an arm cycling bout at 60 rpm and 25W. MEPs and CMEPs were subsequently recorded during the mid-elbow flexion (i.e., 6 o'clock position) and mid-elbow extension (i.e., 12 o'clock position) phases of arm cycling. During cycling, MEP and CMEP amplitudes were enhanced at the 6 o'clock position but were drastically reduced at the 12 o'clock position (Forman et al., 2014). The reduction in evoked potential amplitudes meant that only the most excitable portion of the corticospinal pathway was being activated by the stimulation employed resulting in a potential flooring effect of the evoked response amplitudes, thus limiting the discussion between the main conditions being examined in the study (i.e., cycling vs tonic contraction). A higher stimulation intensity was likely required at this position to ensure evoked responses could be modulated between tasks, which was performed in subsequent studies (Forman et al., 2015; Lockyer et al., 2018).

Higher stimulation intensity is supported by work performed in spinalized cats which demonstrated that during locomotor-related motoneurone activity (i.e., fictive locomotion and scratch), inhibition via Ia inhibitory interneurons is largest in the antagonist flexor motoneurones during the inactive (hyperpolarized) phase of the movement (i.e., swing) (Geertsen et al., 2011). This 'active inhibition' during the inactive phase of the motoneurone during the motor output is thought to provide adequate activation of the motoneurones involved in maintaining stance, while also ensuring essential limb flexion

for foot clearance involved in swing (Geertsen et al., 2011). Provided a similar mechanism of active inhibition exists during the inactive phase of the intended movement in human motoneurones, greater inhibition may help explain the need for a higher stimulation intensity to evoke a measurable response during the inactive (i.e., elbow extension) phase of the biceps during arm cycling.

2.7.5 Recommendations For Setting Stimulation Intensities During Rhythmic Motor Output

Over the past several years, we have investigated the corticospinal control of arm cycling across a variety of conditions using each of the aforementioned methods for setting stimulation parameters (Copithorne et al., 2015; Forman et al., 2014; Forman et al., 2018; Forman et al., 2015; Forman, Richards, et al., 2016; Lockyer et al., 2018; Lockyer, Hosel, et al., 2019; Lockyer, Nippard, et al., 2019; Nippard et al., 2020; Power & Copithorne, 2013). For various reasons, we have utilized different methods to set stimulation intensities across different studies, which has undoubtedly contributed to the existing variability in methods utilized for setting stimulation parameters across the field of human neurophysiology. In attempts to better understand the neural control of human movement, future studies should place a greater emphasis on the many factors that influence the selection of stimulation parameters for a given study.

Based on what we have learned, along with many of the challenges we have faced when determining stimulation intensities during arm cycling, we have formulated the

following recommendations which we feel is the most 'suitable' method for setting stimulation intensities for future studies during dynamic motor outputs.

1. Set stimulation intensities during the motor task(s) of interest given that corticospinal excitability is task-dependent (Kalmar, 2018; Power et al., 2018).

2. Set stimulation intensities relative to the phase (e.g., power, recovery, flexion or extension) of the motor output when possible.

3. In acute studies, multiple stimulation intensities such as those used to create a SRC based on the AMT may be the ideal way to assess corticospinal excitability during rhythmic motor outputs. However, due to the longer timeframe required to collect data using a SRC, one must consider time-dependent effects and/or fatigue before using this approach.

4. For task-dependent comparisons ensure that the evoked potentials are matched relative to M_{max}.

5. For task-dependent comparisons ensure that joint angles and motor output intensities are matched (discussed below) when eliciting evoked potentials.

2.8 Measurement Of Peripheral Excitability During Rhythmic Motor Output

Using M_{max} for normalization purposes during dynamic motor outputs has several advantages. The amplitude of the M_{max} is reproducible both within (Aboodarda et al., 2015; Collins et al., 2017; Forman, Philpott, et al., 2016; Pearcey et al., 2014; Power et al., 2018) and between experimental days (Calder et al., 2005); during a range of isometric and dynamic contraction intensities (Aboodarda et al., 2015; Collins et al., 2017; Forman,

Philpott, et al., 2016; Pearcey et al., 2014; Power et al., 2018); prior to, during and following fatiguing contractions (Kennedy et al., 2016; Martin, Smith, et al., 2006; Nuzzo, Barry, et al., 2016b); in the presence of pain (Stefanelli et al., 2019) and in the presence of hyperthermia (Todd et al., 2005) and hypothermia (Cahill et al., 2011). Interestingly, in all of the aforementioned studies (except one, vastus lateralis) the M_{max} was elicited in the biceps brachii. There is an advantage for producing a M_{max} response in the biceps brachii compared to some of the other upper body muscles because anatomically the brachial plexus (Erb's Point) is accessible for the placement of electrodes to stimulate the musculocutaneous nerve, which is the terminal branch of the lateral cord of the brachial plexus. Eliciting a M_{max} in many of the other upper body muscles may not provide an optimal response because the nerves innervating those muscles are not as easily accessible.

The consistent magnitude of the M_{max} response in the biceps brachii is not immune to all experimental parameters. A change in joint position can alter the M_{max} response. For example, M_{max} amplitudes are substantially increased in the biceps brachii, irrespective of whether the muscle was quiescent or active, when moving the shoulder from 0° to 90° of flexion (Collins & Button, 2017). The effect of joint position on M_{max} is not only unique to the shoulder, as changes in the knee joint position alters the M_{max} amplitude of the soleus (Takahara, 2011) and changes in ankle joint position alter M_{max} amplitudes in the tibialis anterior and soleus (Frigon et al., 2007). The stimulation intensity required to evoke a M_{max} is also affected by joint position. During isometric elbow flexion contractions, the electrical stimulation required to evoke a M_{max} in the biceps brachii is altered with changes in the shoulder position (Collins & Button, 2017). Differences in the magnitude of the M_{max} and the stimulation intensity required to induce a M_{max} response may be due to movement of

the surface electrodes used to stimulate the nerve of interest, leading to a change in the area of the nerve being stimulated and an altered M_{max} response. In addition, the surface EMG recording electrodes placed over the muscle of interest may also change when the joint position is altered leading to changes in the motor units from which the action potentials are recorded and subsequently a change in the M_{max} response (Frigon et al., 2007; Takahara, 2011).

2.8.1 Recommendations For Eliciting M_{max} During Rhythmic Motor Output

1. Corticospinal excitability measures (i.e., MEPs and CMEPs) must be normalized to M_{max} to account for changes in peripheral excitability, unless a SRC is used.

2. M_{max} must be recorded at the same joint angle as the measures of corticospinal excitability to ensure accurate normalization occurs as failing to do so could lead to either an under or over estimation of corticospinal excitability.

2.9 Task-Dependent Comparisons

The question that arises following studies examining corticospinal excitability during arm cycling is, "are the observed differences due to the actual motor output of cycling or are they simply reflective of a change in excitability resulting from motor output in general?" In other words, are the findings task-dependent? This seemingly simple question is important to address but can also be technically challenging. The manner in which we have chosen to address whether our findings are cycling-dependent is based on the work of others (Carroll et al., 2006; Zehr et al., 2003). To the best of our knowledge, the details

regarding the physiological relevance behind these comparisons, in addition to their pitfalls as it relates to data interpretation, have not been described in detail. The following sections will describe the methodological rationale, strengths and limitations of said comparisons.

2.9.1 How To Make Task-Comparisons Based On Surface EMG

Although there are well-known and previously described pitfalls for interpreting EMG during dynamic contractions (Farina, 2006), they will not be covered in this review. Regardless of those pitfalls, a common means to compare neural excitability between motor tasks is to have both motor outputs produce the same level of EMG (i.e., matched EMG) in the muscle of interest at the time of stimulation (e.g., TMS, TMES). Given that surface EMG reflects the overall output of the spinal motoneurone pool activating the muscle, matched EMG amplitudes suggests that the motor outputs are being performed at a similar level of motoneurone output or neural drive. In this manner, any differences in measures of neural excitability between the tasks at matched EMG levels are attributed to task-dependent differences in neural control or excitability. If the EMG levels are not matched a comparison becomes difficult to interpret because observed differences may simply be due to the well-known influence of muscle activation intensity on various measures of neural excitability.

The EMG measurements used to match the motor outputs are often referred to as the background EMG (bEMG) or pre-stimulus EMG. Both of these terms refer to the EMG produced by the muscle immediately preceding a stimulation evoked potential. Matching the EMG of different motor outputs can be difficult to achieve due to the many degrees of

freedom, particularly during multi-joint, bilateral motor output. In our lab, the more complex movement, arm cycling, is performed first. The bEMG from the cycling trials is then measured and the average value (RMS or linear envelope) is presented as a horizontal line placed on a computer screen. The participant is then required to perform the isometric contraction such that the EMG produced in the muscle of interest matches the level presented by the target value (cycling EMG). The reason for this order is simple, trying to produce (match) a specific EMG value during cycling to that previously done during a tonic contraction is more difficult. Producing an EMG level during a tonic contraction about a single joint, however, is relatively easy and is routinely done in studies assessing neural excitability during isometric contractions (Collins et al., 2017; Forman et al., 2014; Lahouti et al., 2019; Pearcey et al., 2014; Philpott et al., 2015).

An important consideration when assessing bEMG for comparison purposes is the duration of the measurement. A standard protocol in our lab involves a cycling cadence of 60 rpm. At this cadence and the full revolution broken into 12 phases, that means that each position on the clock represents 83.3 ms. If we are to measure corticospinal excitability at the 6 o'clock position from the biceps brachii (bottom dead centre), we take a bEMG measurement from that point in time to 50 ms preceding that time. This measurement is then repeated over a number of cycling trials and an average value calculated to be used as a target value to be matched during the tonic contraction. The isometric contraction then consists of, in this particular case, an elbow flexion contraction with the shoulder, elbow and wrists at the bottom dead centre position and EMG is recorded.

Though a generally accepted method to match tasks, there are caveats and questions that must be considered in data interpretation. Rhythmic motor outputs include relatively

predictable muscle activity patterns that involve both activation and inactivation (Chaytor et al., 2020), as opposed to tonic contractions whereby the muscle actively is generally constant or performed in a controlled, ramp-like fashion. Thus, the time-window in which the EMG is measured encompasses a changing EMG pattern and raises an important question; "when during the rhythmic motor output is neural excitability examined?" During leg cycling, measures of corticospinal excitability can mirror changes in the bEMG during a set cadence and workload (Sidhu et al., 2012) though differences in cortical excitability are evident at the same EMG level when comparing the ascending and descending portion of the EMG burst during leg cycling (Sidhu et al., 2013b). Sidhu and colleagues examined a cortical circuit (short-interval intracortical inhibition; (SICI)) during three conditions at matched vastus lateralis EMG amplitudes: (1) a tonic contraction, (2) activation phase of the EMG burst during leg cycling and (3) inactivation phase of the EMG burst during leg cycling. They showed the SICI was present during tonic contraction, absent during the activation phase and present during the inactivation phase. This highlights two important factors that can alter data interpretation: task- and phase-dependent changes in SICI. The task-dependency of SICI is phase-dependent (activation versus inactivation). Thus, task-dependent changes would either be evident or not depending on the phase of cycling compared to the tonic contraction (inactivation versus activation phase of the cycle, respectively).

Changes at the spinal level are also possible. An assumption underlying the ascending limb of the EMG burst is that the increase in EMG is always linear. Yet this may not be the case given the very potent effect of persistent inward currents in spinal motoneurones that act to amplify synaptic input in a non-linear fashion, thus enhancing

excitability of the motoneurone pool (Heckman et al., 2008). Importantly, the activation of persistent inward currents is quite prevalent in locomotor outputs suggesting that this may be at play in human studies (Heckman et al., 2008). If this is the case, then measures of corticospinal excitability during a 'matched' EMG amplitude may provide significantly different results based on these underlying mechanisms. The TMS-evoked MEP amplitude, for example, would be amplified at the spinal level via enhanced motoneurone responsiveness to descending drive, an effect that would not be evident at the same EMG level during a tonic contraction provided the tonic contraction EMG is held constant as opposed to the changing EMG levels associated with ramp contractions commonly used to assess persistent inward currents in humans (Heckman et al., 2008; Kim et al., 2020; Wilson et al., 2015). This is not necessarily a limitation of this method and may instead represent persistent inward current activation during locomotor outputs that may not occur or not occur as strongly during tonic contractions of the same muscle(s). Regardless, this possibility highlights the fact that a matched EMG does not mean that the matching is necessarily produced via the exact same mechanism(s).

The ability to match motor outputs based on bEMG is also influenced by task intensity. The assumption made when the bEMG between tasks is similar is that the effort level to produce those tasks is also similar. In our experience and in-line with leg cycling work (Hautier et al., 2000), the EMG produced during arm cycling at a relatively high workload, such as 35% of maximal power output (Chaytor et al., 2020), is often greater than can be produced by the same muscle during a submaximal tonic contraction. In other words, the effort required to generate equivalent EMG during an isometric contraction as that produced during a submaximal bout of arm cycling may be substantially higher. This

would mean that at a given intensity of cycling, the tonic contraction used to match the EMG would be at a higher percentage of its own maximum (i.e., easier to produce the equivalent EMG during cycling than the tonic contraction). This would support our findings and, if anything, suggest that we may underestimate task-dependent differences and obscure them in other instances (i.e., no task-dependent difference because the tonic contraction requires more effort than the cycling task). Studies in our lab have repeatedly demonstrated that corticospinal excitability during mid-elbow flexion to the biceps brachii is higher during arm cycling than a bEMG matched tonic contraction, but these measures have been made at every low effort levels (25W). We have yet to systematically examine task-dependent changes in corticospinal excitability over a range of contraction intensities, a series of studies that will undoubtedly require an effort index, such as that generated via the ratings of perceived exertion criterion. One possibility may be to measure the maximum EMG during cycling sprints and then have participants cycle at various percentages of that EMG. Then, on a separate day measure the maximum EMG during maximum isometric contractions. Participants could then perform isometric contractions at the same relative percentage of EMG as in the cycling condition. Thus, the two tasks would be matched in terms of their percentage of the maximum muscle activity (i.e., EMG).

2.9.2 Recommendations For Making Task-Comparisons Based On Surface EMG

1. It may be easier to perform the more complex motor task first, from which the EMG to be matched is assessed.
2. Match the tasks based on equivalent EMG time windows.
3. Match EMG between tasks at similar joint angles.

4. Matched EMG should be done during a similar 'activation profile' – activation or inactivation.
5. Future studies may include measures of effort when matching tasks based on EMG.
6. Though only the EMG of the agonist may be matched it is important to record and assess antagonist EMG, particularly for task-dependent comparisons. Though not discussed in this review, this data may help provide insight into mechanism(s) (Chaytor et al., 2020).

2.10 Considerations When Assessing Cortical Excitability During Rhythmic Motor Output

Paired-pulse TMS techniques include various protocols designed to examine different cortical circuits involving intracortical, interhemispheric or intrahemispheric connections. Once activated, these circuits inhibit or excite the motor cortex. Paired-pulse TMS involves a conditioning stimulus used to activate the circuit of interest and a test stimulus that produces a measurable MEP. The conditioned MEP is then compared to a MEP produced in the absence of a conditioning stimulus and the difference in amplitudes used as a measure of cortical excitability. Several studies, including one from our lab, have assessed cortical circuits during locomotor movement (Alcock et al., 2019; Benson et al., 2020). We showed that short-interval intracortical inhibition (SICI) was present during arm cycling but was not different than a tonic contraction when assessed in the biceps brachii. SICI is a relatively easy cortical circuit to assess because the interstimulus interval is short (~2.5 ms). Thus, the conditioning and test stimuli were elicited almost at the same moment in time. During a 60-rpm cadence, 2.5 ms represents minimal joint movement and thus the muscle activity and afferent feedback were unlikely to change dramatically between the

conditioning and test stimuli as opposed to protocols used that involve longer interstimulus intervals, such as long interval intrahemispheric inhibition (LICI). Interhemispheric inhibition (IHI) is another cortical circuit that is useful to examine and is frequently assessed during isometric contractions, yet studies involving rhythmic motor output when both limbs are active are scarce.

It is generally accepted that IHI can be examined using a single pulse induced ipsilateral silent period (iSP) using TMS. Using this technique, we recently showed that IHI can be examined during arm cycling. It may be useful to examine IHI during bilateral, dynamic motor outputs as changes in the excitability of the IHI pathway may provide insight into the cortical control of these types of motor output. For example, we recently showed that supraspinal excitability was higher to the ipsilateral cortex (ipsilateral to arm from which recordings were made) at rest compared to when it was passively or actively cycled (Lockyer et al., 2020). In each of the three conditions (rest and passive or active cycling) the contralateral arm was engaged in continuous cycling. We postulated that higher supraspinal excitability to the ipsilateral limb when it was at rest (compared to cycling) may have been due to reduced IHI from the contralateral hemisphere. The task-dependency of IHI remains to be examined.

Cortical circuits, such as LICI, are more problematic to assess during rhythmic motor output compared to SICI due to a much longer interstimulus interval (i.e., 50-200 ms). To the best of our knowledge, only one study has examined LICI during a rhythmic, locomotor output (Sidhu et al., 2018) but task-dependency was not examined given it was not a goal of that work. Determining task-dependency in this case would certainly be more difficult than 'simply' matching an EMG value during a tonic contraction, as described

earlier, and would involve some caveats. During the rhythmic motor output, the first stimulus would condition the motor cortex at that particular point in time with joint angle specific afferent feedback and a particular level of EMG produced by the active muscle. The test stimulus would occur 100-200 ms later which equates to 1 to ~2.5 'clock positions.' This duration of the cycle will occur during a different degree of EMG output and potentially different activation/inactivation kinetics as well as altered afferent feedback. While perhaps not problematic by itself, comparison, in our case, to an intensity and joint-angle-matched tonic contraction becomes difficult given the aforementioned variables. Thus, though LICI can be assessed during a dynamic motor output, comparisons for task-dependency may be difficult to interpret. A potential solution may be to perform an isometric ramp contraction whereby the EMG increases and then decreases in a similar timeframe (i.e., overlaid on a rhythmic EMG pattern) to that produced during the rhythmic motor output.

2.11 Considerations For Assessing Corticospinal Excitability During Dynamic, Non-Locomotor Activities

This review has focused on assessing corticospinal excitability during rhythmic motor output with arm cycling as the model. Though certainly a complex motor output to use as a model, there is also a fixed range of motion used and the added benefit of head stability when using TMS and TMES. During freely moving activities of daily living (ADLs), however, there is an even greater variability in the parameters used to produce a movement. Given that corticospinal excitability is task-dependent, it is thus difficult to

generalize findings from studies assessing corticospinal excitability during rest, tonic contraction or arm cycling to other non-rhythmic dynamic motor outputs. A difficulty in examining corticospinal excitability during ADLs is maintaining coil position in close proximity to the skull and ensuring minimal coil movement during the motor output – factors crucial for obtaining the most valid measurements possible. One way to ensure consistent and proper coil position during ADLs may be to secure the TMS coil to the participant. This has been successfully implemented when examining corticospinal excitability during locomotion, whereby a halo type vest was constructed and worn by the participant (Schubert et al., 1997). It's also possible to make recordings during ballistic movements, such as jumping, whereby participants wore an adjustable helmet to hold the coil along with a harness to take the weight of the cable (Taube et al., 2008). A more recent study provided the details on how to make individualized helmets to hold TMS coils so that corticospinal excitability could be examined in numerous types of ADLs (Badran et al., 2020). This novel technology may also be worth considering though the time and financial commitment required may not be warranted in acute studies carried out in many lab settings whereby participants may only be used in a single study. On the other hand, this may be an ideal method when participants are involved in chronic studies with multiple testing sessions or if they frequently partake in acute studies. Thus, novel experimental set-ups should be considered and developed to enhance our ability to examine corticospinal excitability during ADLs, such as hand writing (Cinelli et al., 2019), but the many factors discussed in this review must still be considered.

2.12 Conclusion

In this review we have attempted to summarize the methods and various technical and physiological considerations that should be considered when assessing corticospinal excitability during rhythmic motor output. We have also made recommendations based predominantly on our own experiences that may be useful when experiments are designed to assess corticospinal excitability during different rhythmic motor outputs or non-rhythmic dynamic motor outputs.

2.13 Acknowledgements

This research was supported by a Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery Grant to K.E.P., a NSERC Fellowship to G.E.P. and NSERC Scholarships to E.J.L., and D.A.F. The authors express thanks to all of the trainees and study participants for their contributions to our research program.

Chapter 3: CORTICOSPINAL EXCITABILITY TO THE BICEPS BRACHII IS NOT DIFFERENT WHEN ARM CYCLING AT A SELF-SELECTED OR FIXED CADENCE

Co-Authorship Statement:

Chapter three involves Study #1 of the thesis. The ICEHR approval certificate number for this study is ICEHR #20171250. This chapter was published in full in *Brain Sciences*: Lockyer EJ, Nippard AP, Kean K, Hollohan N, Button DC, Power KE. Corticospinal Excitability to the Biceps Brachii is Not Different When Arm Cycling at a Self-Selected or Fixed Cadence. *Brain Sciences*. 2019; doi: 10.3390/brainsci9020041. Permissions to use this manuscript in this thesis was not required as the journal is open access. Evan Lockyer and Dr. Power designed the experimental protocols. Anna Nippard (graduate student), Nicole Hollohan and Kaitlyn Kean (undergraduate students) were students that Evan mentored, and they assisted Evan with the data collection for this project by helping with participant preparation and aspects of the data collection. Evan Lockyer performed all data extraction and analysis and completed the statistical analyses, drafted the manuscript, and was responsible for all figures. Evan Lockyer, Dr. Duane Button, and Dr. Power edited the manuscript, and all authors approved of the final version.

3.1 Abstract

Background: The present study compared corticospinal excitability to the biceps brachii muscle during arm cycling at a self-selected and a fixed cadence (SSC and FC, respectively). We hypothesized that corticospinal excitability would not be different between the two conditions. Methods: The SSC was initially performed, and the cycling cadence was recorded every 5 s for one minute. The average cadence of the SSC cycling trial was then used as a target for the FC of cycling that the participants were instructed to maintain. The motor evoked potentials (MEPs) elicited via transcranial magnetic stimulation (TMS) of the motor cortex were recorded from the biceps brachii during each trial of SSC and FC arm cycling. Results: Corticospinal excitability, as assessed via normalized MEP amplitudes (MEPs were made relative to a maximal compound muscle action potential), was not different between groups. Conclusions: Focusing on maintaining a fixed cadence during arm cycling does not influence corticospinal excitability, as assessed via TMS-evoked MEPs.

Keywords: motor evoked potential, MEP, arm cranking, pedalling, exercise

3.2 Introduction

It is well established that rhythmic locomotor outputs in non-human animals (e.g., cat, rat, and dog) are partially controlled by neural circuits located in the spinal cord, referred to as central pattern generators (CPGs) (Brown, 1911; Grillner & Dubuc, 1988). Evidence, albeit indirect, has shown that the CPGs also contribute to the production of rhythmic motor outputs in humans by integrating descending and afferent inputs (Zehr et al., 2016; Zehr et al., 2004); though it is believed that the descending input is of greater importance in the control of human locomotor outputs (Power et al., 2018).

Arm cycling has been introduced as a model of locomotor output for examining changes in neural excitability during rhythmic movement, with the vast majority of these studies using a set cadence and power output for each participant (Power et al., 2018; Zehr et al., 2016). While this may be necessary to maintain experimental stringency, it is also acknowledged that, first, arm cycling may be regarded as a novel task for some participants and, second, that by setting the cadence at 60 rpm, for example, participants may not be cycling at a preferred cadence. Taken together, these two factors may act to alter attentional demands, thus influencing the measures of corticospinal excitability.

When humans engage in a novel motor task, they typically focus on how to perform the said task, placing them in what is known as the "cognitive stage" of motor learning, according to the Fitts and Posner model (Fitts & Posner, 1967). This suggests that the level of cognitive effort, and thus in all likelihood the descending input, would be greater during this stage of learning. This is supported by work examining the time course of changes in corticospinal excitability when learning a novel motor task, albeit non-locomotor (Holland et al., 2015). Holland et al. (2015) showed that the slope of the transcranial magnetic

stimulation (TMS) evoked input/output (I/O) curve decreased as learning progressed, with the majority of the change occurring on the first of two training days. This suggests that as participants began the novel task, greater cognitive effort was required thus enhancing corticospinal excitability, an effect that decreased as the task lost its novelty.

Arm cycling is a motor task that may be considered novel, and a number of studies have been published that have examined corticospinal excitability during cycling in humans (Forman et al., 2014; 2015; 2016a; 2016b; 2018; Lockyer et al., 2018; Spence et al., 2016). Work from our lab has shown corticospinal excitability, assessed via TMS of the motor cortex projecting to the biceps brachii, to be higher during arm cycling in humans when the elbow was flexed (bottom dead centre) compared to an intensity- and position-matched tonic contraction (Forman et al., 2014). This effect was due to enhanced supraspinal excitability, as there were no differences in the measures of spinal excitability. In that study, participants were required to maintain a pre-determined cadence (60 rpm) throughout the trial by observing their cadence on the ergometer monitor, and it was possible that this increased the attentional demands of the task. Research has shown that directed visual attention can induce an increase in neural activity in the fronto-parietal network, as evidenced in functional brain imaging studies (Kastner et al., 1999). It is thus possible that an increase in attention may increase corticospinal excitability during arm cycling, though we hypothesized that the difference was task-dependent and not simply due to the increased attentional demands of arm cycling (Forman et al., 2014).

Several studies have examined the influence of cycling cadence on neuromuscular activation. Marias et al. (2004) examined the effects of a spontaneous chosen crank rate (SCCR) and crank rates 20% higher and lower than the SCCR during arm cycling on

integrated electromyography (iEMG) levels in the biceps brachii muscles in humans. The researchers concluded that there were no significant differences in the iEMG between the crank rate conditions of the biceps brachii, suggesting that the SCCR was not chosen to minimize the level of muscle activity and that the degree of muscle activation was similar between the two groups (Marais et al., 2004). This finding is supported by research that showed no reduction in lower extremity muscle activation at a SCCR during leg cycling (Marsh & Martin, 1995). The iEMG assessed in these studies is a measure of the electrical activity in the muscle, representing the overall output of the motoneurone pool, and does not necessarily represent corticospinal excitability (Copithorne et al., 2015; Forman et al., 2015; Lockyer et al., 2018). Therefore, it is unknown how a self-selected cadence (SSC) during arm cycling influences corticospinal excitability in comparison to a fixed cadence (FC).

The purpose of the current study was thus to determine if corticospinal excitability between SSC and FC arm cycling was different. It was hypothesized that corticospinal excitability, as assessed via the amplitude of motor evoked potentials (MEPs) elicited via TMS of the motor cortex, would not be different between SSC and FC arm cycling.

3.3 Material and Methods

3.3.1 Ethical Approval

Prior to the experiment all participants were informed of the experimental protocol and written informed consent was obtained. This study was in accordance with the Helsinki declaration, and experimental procedures were approved by the Interdisciplinary

Committee on Ethics in Human Research at the Memorial University of Newfoundland (ICEHR #20171250). All experimental procedures were in accordance with the Tri-Council guidelines in Canada, and potential risks of participation were disclosed to all participants.

3.3.2 Participants

Eleven participants (7 males and 4 females; 22 ± 2.14 years of age) were recruited from the School of Human Kinetics and Recreation (HKR) at Memorial University using a convenience sampling technique. Prior to testing, each participant completed a magnetic stimulation safety-checklist to screen for existing contraindications to magnetic stimulation (Rossi et al., 2009). To determine hand dominance, participants completed an Edinburgh Handedness Inventory questionnaire to ensure that all evoked responses were recorded from the dominant arm (Oldfield, 1971). Additionally, to screen for existing contraindications to physical activity, each participant completed a Physical Activity Readiness Questionnaire (PAR-Q+) (Bredin et al., 2013). Participants were excluded if they had any neurological deficits or contraindications to magnetic stimulation or physical activity.

3.3.3 Experimental Set-Up

A one-group within-subjects design was used. Participants attended two lab sessions with at least 24 h in between visits. The first visit was for a half-hour

familiarization session and the second was the testing session, lasting approximately 1 h. The experiment was completed on an arm cycle ergometer (SCIFIT ergometer, model PRO2 Total Body) with the arm cranks set at 180 degrees out of phase (see **Figure 3.1**). Each participant was advised to sit upright at a comfortable position from the arm cranks to ensure that they could maintain an upright posture throughout each cycling protocol. The seat height was adjusted to ensure the participant's shoulders were in line with the centre of the arm shaft. The participants were informed to lightly grip the handles with their forearms in pronation. Each participant was required to wear wrist braces to limit wrist joint movement during cycling, to reduce the effects of the heteronymous reflex connections that exist between the wrist flexor muscles and the biceps brachii muscle (Manning & Bawa, 2011).

All measurements were taken at a single position—6 o'clock relative to a clock face. This position was relative to the participants' dominant hand, such that the TMS would be triggered when the right or left hand was at the 6 o'clock position for a right- or left-handed dominant individual, respectively. We have examined this position previously (Forman et al., 2014; Forman et al., 2018; Forman et al., 2015; Forman, Philpott, et al., 2016; Forman, Richards, et al., 2016; Lockyer et al., 2018; Spence et al., 2016), as it corresponds to a period of high bicep brachii electromyography (EMG) activity during arm cycling since it occurs during mid-elbow flexion (i.e., movement from 3 o'clock to 9 o'clock).

The study required participants to cycle at two different cadences, both at a constant workload of 25 W. The cadences (FC and SSC) served as the independent variables in the study. The TMS and Erb's point stimulation were delivered at the 6 o'clock position to

elicit MEPs and maximal M-wave (M_{max}) in the biceps brachii muscle in each condition. The MEP amplitude made relative to M_{max} and bEMG (background EMG; see below), as a measure of corticospinal excitability, served as the dependent variable. The SSC trial was completed first, followed by the FC trial, and responses were triggered as the arm crank of the dominant arm passed the 6 o'clock position.

3.3.4 Electromyography (EMG) Recordings

EMG activity was recorded from the biceps brachii and lateral head of the triceps brachii of the dominant arm using pairs of surface electrodes (Kendall™ 130 conductive adhesive electrodes, Covidien IIC, Mansfield, Massachusetts, USA). The EMG was recorded using a bi-polar configuration with an interelectrode distance of 2 cm. Electrodes were placed in the middle of the muscle belly of the biceps brachii. A ground electrode was placed over the lateral epicondyle on the dominant arm. Prior to electrode placement, the skin at the recording site was shaved to remove hair, abraded using an abrasive pad to remove dead epithelial cells, and cleaned with an isopropyl alcohol swab to reduce impedance for the EMG recordings. Signals were sampled online at 5 kHz using a CED 1401 interface and Signal 5.11 software (Cambridge Electronic Design (CED) Ltd., Cambridge, UK). The EMG signals were amplified (gain of 300) and filtered using a 3-pole Butterworth band-pass filter (10−1000 Hz) using a CED 1902 amplifier.

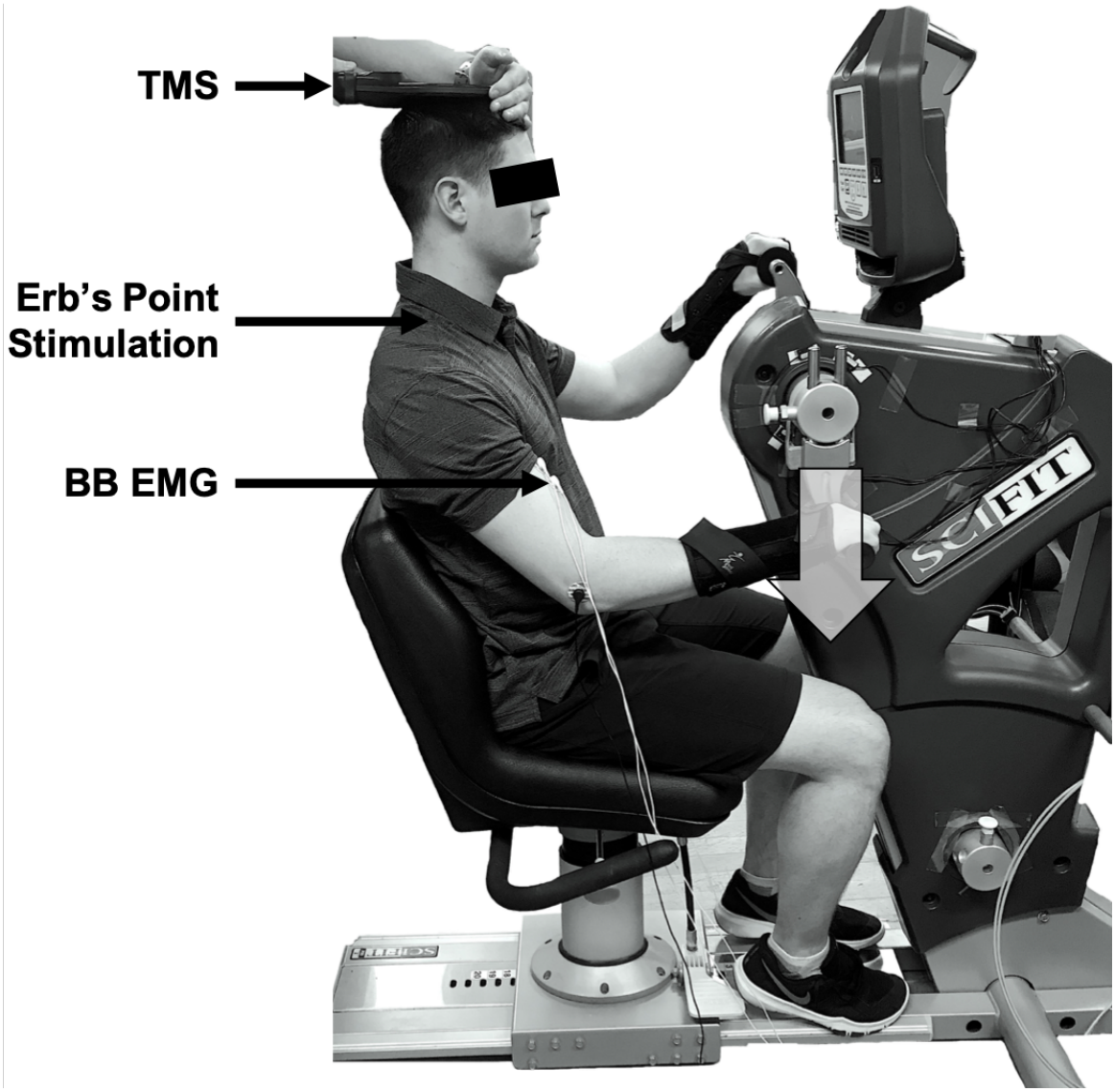

Figure 3.1: Experimental setup.

Arm cycling was performed in the forward direction, with stimulations occurring when the dominant arm passed the 6 o'clock position (i.e., bottom dead centre) when the biceps brachii was active. This position is denoted by the large, grey downwards arrow. TMS = transcranial magnetic stimulation; BB = biceps brachii; EMG = electromyography

3.3.5 Stimulation Conditions

3.3.5.1 Brachial Plexus Stimulation

Electrical stimulation of the brachial plexus at Erb's point was used to measure M_{max} (maximal M-wave; DS7AH, Digitimer Ltd., Welwyn Garden City, Hertfordshire, UK). The anode was placed on the acromion process and the cathode was placed over the skin in the supraclavicular fossa. A pulse duration of 200 μs was used and the stimulation intensity was gradually increased until the M-wave amplitude of the biceps brachii reached a plateau, referred to as M_{max}. This stimulation intensity was increased by 10% and used for the remainder of the experiment to ensure maximal M-waves were elicited during each trial (Crone et al., 1999).

3.3.5.2 Transcranial Magnetic Stimulation (TMS)

Motor evoked potentials (MEPs) were measured during both cycling trials from the biceps brachii and served as the dependent variable in the study. TMS (Magstim 200, Dyfed, UK) was used to elicit MEPs in the biceps brachii by placing a circular coil (13.5 cm outside diameter) over the vertex. TMS is a valid and reliable technique for eliciting MEPs, which are recorded from the muscle as a measure of the excitability of the corticospinal tract (Rothwell et al., 1991). The vertex was located by measuring the mid-point between the nasion and the inion and between the participant's tragi, and marks were placed for both measurements directly on the scalp. The intersection of the measurements was defined as the vertex (Forman et al., 2014; Forman et al., 2015; Pearcey et al., 2014; Taylor et al., 1997). The same researcher held the coil for each trial and was vigilant in

ensuring that the coil was held parallel to the floor and remained aligned with the vertex throughout each trial. The current preferentially activated the right or left motor cortex, depending on hand dominance. The stimulation intensity was set during cycling (60 rpm and 25W) with MEPs evoked when the dominant hand was at the 6 o'clock position. The stimulus intensity was measured as a percentage of the maximum stimulator output (MSO), and the intensity was increased until the participant's active motor threshold (AMT) was found. The AMT was defined as the lowest stimulus intensity required to evoke 5 clearly discernable MEPs (~200 μV) in 10 trials during cycling. Once the AMT was found, the MSO was increased by 10% to ensure that clearly discernable MEPs were recorded, and this stimulation intensity was then used for all trials.

3.3.6 Experimental Protocol

After the stimulation intensities were set for the TMS and Erb's point stimulation, the cycling trials were completed. The participant was first instructed to cycle forward at a comfortable pace, and the monitor displaying the cycling cadence was moved out of the participant's sight, such that the participant was blinded to their cycling cadence. When the participant reached a steady cadence, as observed by the researcher, the trial was started. A steady cadence was defined as a cadence that fluctuated no more than ±1 rpm over a 5 s period. While the participant was cycling, the researcher recorded the cadence every 5 s and calculated the average cadence over the duration of the trial. After a 1-minute break the participant was instructed to cycle forward maintaining a target cadence, as specified by the researcher, by observing their cadence on the monitor. This target cadence (FC) was equal to the average of the cadence over the duration of the SSC trial. During both trials

the arm ergometer was set to a fixed power output of 25 W. While cycling, each participant received 12 MEPs and 2 M-waves per trial, which were delivered when the dominant hand passed the 6 o'clock position. The order of the stimulations was randomized during the trial, and the stimulations were evoked every 7−8 s. To prevent anticipation of the stimulation, 2 frames without stimulation were added. The total length of cycling was approximately 2 min per trial.

3.3.7 Data Analysis

Data were analyzed off-line using Signal 5.11 software (Cambridge Electronic Design Ltd., Cambridge, UK). To determine if the central motor drive projecting to the biceps brachii was similar between the two arm cycling conditions, the mean rectified EMG 50 ms prior to the TMS stimulus artifact was measured (Forman et al., 2014). The peak-to-peak amplitude of all evoked responses (MEP and M-wave) were measured from the initial deflection of the voltage trace from background EMG to the return of the trace to the baseline level. MEP amplitudes can change as a result of changes to M_{max}, thus MEPs were normalized to M_{max} evoked during the same trial to account for potential changes in peripheral excitability. All measurements were taken from the averaged files of all 12 MEPs and 2 M-waves. All measurements were made from the dominant arm.

3.3.8 Statistical Analysis

To compare the pre-stimulus EMG between the conditions (SSC and FC), paired-samples *t*-tests were used. Additionally, paired-samples *t*-tests were used to assess whether statistically significant differences in MEP amplitudes normalized to M_{max} occurred

between the SSC and FC conditions. All statistics were completed on group data with a significance level of $p < 0.05$. All data are reported as mean ± *SE* (standard error) in the figures.

3.4 Results

3.4.1 Cycling Cadence

Figure 3.2 shows the group mean cycling cadence in revolutions per minute (rpm) during the SSC and FC arm cycling trials. The cycling cadences for each condition were not significantly different (mean cadence—SSC was 62 ± 6.4 rpm and FC was 63 ± 6.9 rpm; $p = 0.118$).

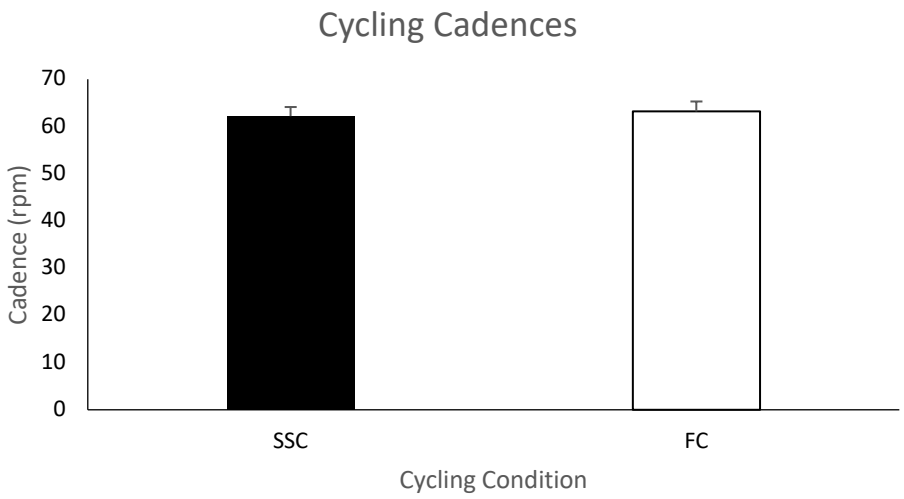

Figure 3.2: Mean cycling cadences by condition.

Mean cycling cadences for each condition (SSC = black and FC = white). Data ($n = 11$) are shown as mean ± SE.

3.4.2 MEP Amplitude

Figure 3.3A shows representative data for the MEP amplitudes from one participant for both the SSC and FC cycling conditions. **Figure 3.3B** shows the group mean MEP amplitudes expressed as a percentage of M_{max} of the biceps brachii during the SSC and FC arm cycling trials. The average MEP amplitude (normalized/standardized to M_{max}) when cycling at a SSC and a FC was 16.2% [*SD (standard deviation)* = 12.25] and 14.1% (*SD* = 11.75), respectively, with a mean difference of 2.1%. This difference was not statistically significant ($p = 0.146$).

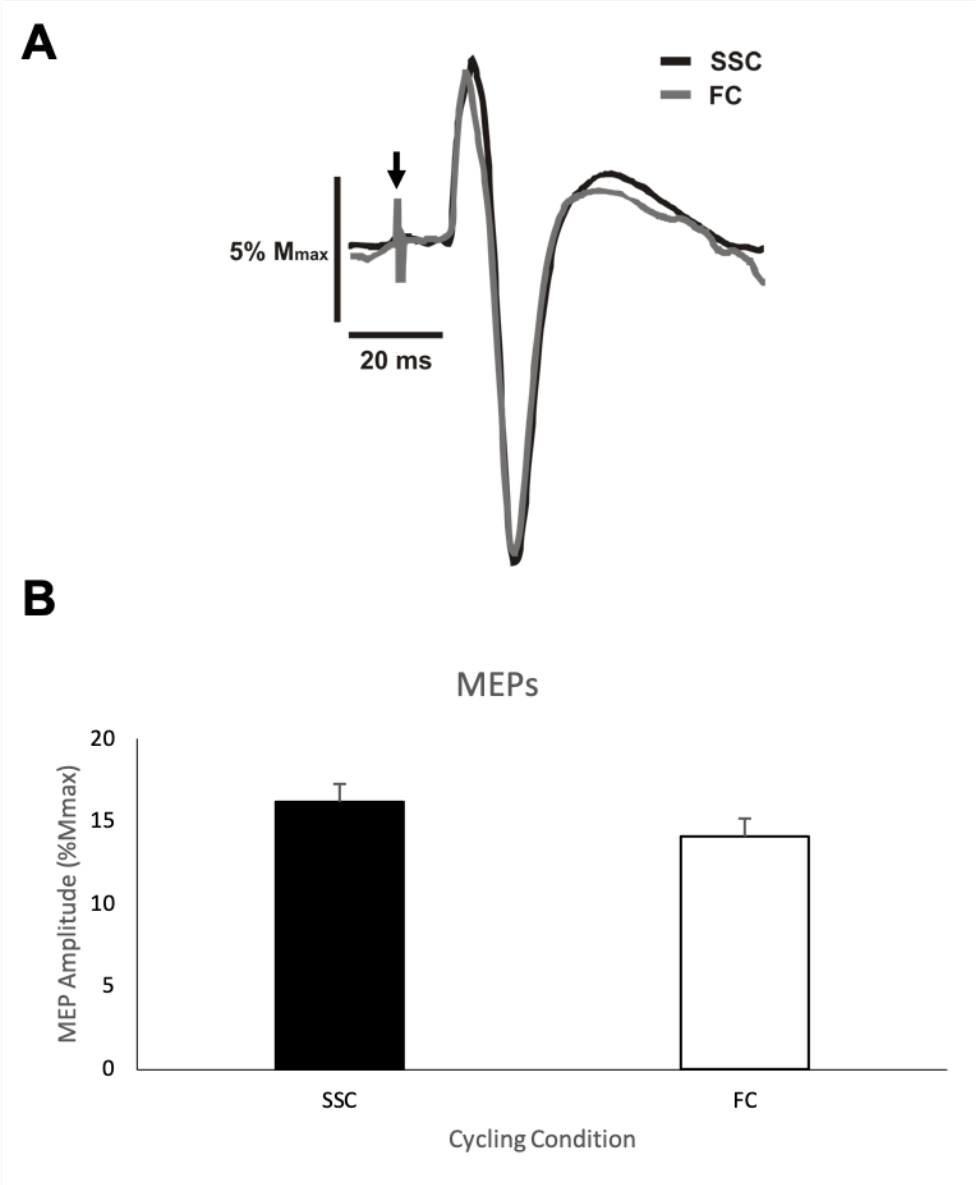

Figure 3.3: TMS-evoked MEP amplitudes during self-selected and forced cadences.

(**A**) Representative motor evoked potential (MEP) amplitudes from one participant for each cycling condition (SSC = black and FC = grey). Downward arrow indicates the location of the stimulus artifacts that have been adjusted in size for figure clarity. (**B**) Mean transcranial magnetic stimulation (TMS) evoked MEP amplitudes as a percentage of the maximal M-wave (Mmax) for each group (SSC = black and FC = white). Data (n = 11) are shown as mean ± SE.

3.4.3 Pre-stimulus EMG Of The Biceps Brachii For MEPs

The group mean (n = 11) pre-stimulus EMG of the biceps brachii prior to the TMS stimulus artifact during the SSC and FC arm cycling can be seen in **Figure 3.4**. As a group, the mean pre-stimulus EMG for the SSC and FC arm cycling trials was 30.2 ± 4.58 μV and 32.1 ± 5.82 μV, respectively. There was no significant difference between the values (p = 0.061).

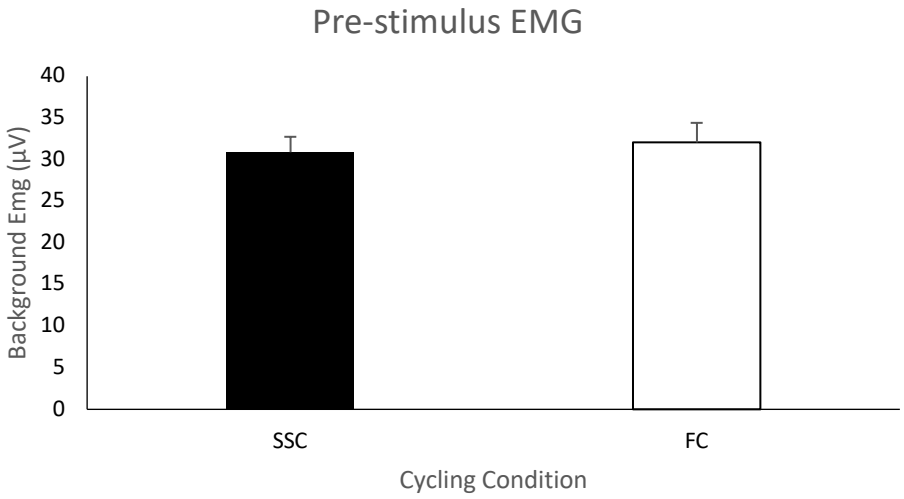

Figure 3.4: Biceps brachii pre-stimulus EMG.

Mean of the average rectified electromyography (EMG) amplitude for the biceps brachii prior to TMS-evoked MEPs for each group (SSC = black and FC = white). Data (n=11) are shown as mean ± SE.

3.4.4 Pre-Stimulus EMG Of The Triceps Brachii For MEPs

The group mean (n = 11) pre-stimulus EMG of the triceps brachii prior to the TMS stimulus artifact during the SSC and FC arm cycling can be seen in **Figure 3.5**. As a group, the mean pre-stimulus EMG for the SSC and FC arm cycling trials was 8.9 ± 2.12 μV and

9.4 ± 2.68 μV, respectively. There was no significant difference between the values (p = 0.58).

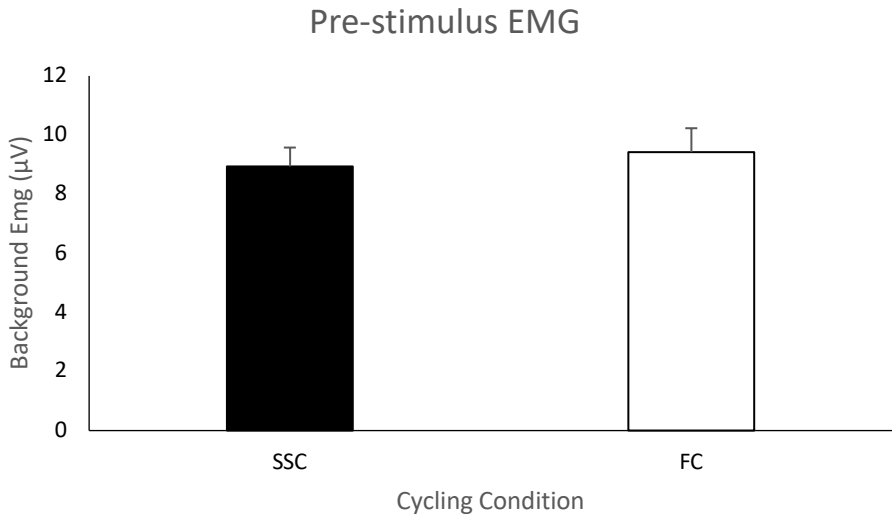

Figure 3.5: Triceps brachii pre-stimulus EMG.

Mean of the average rectified EMG amplitude for the triceps brachii prior to TMS-evoked MEPs for each group (SSC = black and FC = white). Data (n = 11) are shown as mean ± SE.

3.5 Discussion

This is the first study to compare corticospinal excitability projecting to the biceps brachii between self-selected (SSC) and fixed cadence (FC) arm cycling. There were no significant differences in corticospinal excitability, as assessed via TMS-evoked MEP amplitudes recorded from the biceps brachii, between the two arm cycling conditions. Maintaining a pre-determined cadence (FC) during arm cycling does not increase corticospinal excitability, when compared to cycling at a voluntarily chosen cadence (SSC).

A prior concern in studies from our lab and also in the work of others was that the attentional demands of maintaining a set cadence could inadvertently alter (likely increase) the measures of corticospinal excitability. The current finding that corticospinal excitability is not different between SSC and FC arm cycling lends support to our previous finding that corticospinal excitability is task-dependent and is higher during arm cycling than an intensity- and position-matched tonic contraction (Forman et al., 2015). In that study, the participants were required to maintain a pre-determined cadence (60 rpm) while arm cycling rather than a voluntarily chosen cadence (Forman et al., 2014). Thus, it was unknown if the increase in supraspinal excitability projecting the biceps brachii at the 6 o'clock position was due to the arm cycling task or if it resulted from a greater attentional demand to maintain the set cadence. The results from the current study indicate that focusing on maintaining a FC does not increase the overall excitability of the corticospinal tract, compared to arm cycling at a SSC. Thus, the increase in corticospinal excitability during arm cycling that we reported was likely to be task-dependent and not attributable to the fact that the participants had to focus on maintaining a cadence of 60 rpm (Forman et al., 2015). This is indirectly supported by prior work assessing the EMG of both arm and leg muscles during either arm (Marais et al., 2004) or leg (Marsh & Martin, 1995) cycling, respectively. In the aforementioned studies, there was no influence of the SSC or the FC on EMG amplitudes, though there were no measures of corticospinal excitability.

3.5.1 Attentional Focus and Corticospinal Excitability

Prior work has shown that visual attention modulates corticospinal excitability and directing visual attention toward the specific features of an observed action facilitates

corticospinal excitability more than passive observation (Leonetti et al., 2015; Puglisi et al., 2017). Attention can be directed to highly salient stimuli based on their physical properties (e.g., brightness, colour, and speed) or toward stimuli that are important for one's current task (Buschman & Kastner, 2015). In this study during the FC condition, participants were instructed to focus on the monitor that displayed the cadence they were cycling at and were instructed to maintain a set cadence and speed up or slow down based on the observed cadence. In contrast, during the SSC condition participants were not able to see the monitor and were not instructed to focus on any particular object in the external environment. Although participants were instructed to focus on the cadence on the monitor throughout the FC trial, corticospinal excitability projecting to the biceps brachii was not increased when compared to the SSC trial. A possible explanation for the lack of increase in corticospinal excitability during the FC trial is that it is unknown if the participant maintained their focus on the cadence displayed on the monitor throughout the entire trial, as eye tracking devices were not used. In addition, much of the literature regarding increases in corticospinal excitability with focused attention has been on the observation of human movement and the activity in the putative mirror neuron system. Notably, corticospinal excitability is facilitated during action observation and more so during goal-directed actions (e.g., grasping an object) when attention is directed to task-relevant features of the observed action (Roosink & Zijdewind, 2010). In this study, the participants were not observing an action but were rather observing numbers on a monitor that were relevant to their behavioural goal (maintaining a set cadence). Thus, the theory that corticospinal excitability is facilitated during action observation due to the increased activity in the mirror neuron system may not apply in the present study.

3.5.2 Methodological Considerations

Additional factors should be considered when interpreting the present results. This study assessed MEP amplitudes and therefore conclusions can only be made regarding the overall excitability of the corticospinal tract. In the future, research assessing spinal excitability, with TMES (transmastoid electrical stimulation) for example, to the target muscle to determine if changes in corticospinal excitability are occurring at the spinal and/or supraspinal level may be of interest (Taylor, 2006). For instance, it is possible that supraspinal excitability increased during the FC trial, and the increase was masked by a reduction in spinal excitability, resulting in no change in the overall excitability of the corticospinal tract. In order to decipher between supraspinal and spinal excitability both TMES and TMS need to be used. The reason we chose the 6 o'clock position, however, was because in our prior work we have shown that corticospinal excitability is higher during arm cycling than a tonic contraction at that position while spinal excitability is not. Thus, it is unlikely that spinal excitability was different in the present study. Additionally, some participants in this study had previous experience with arm cycling and therefore may have required less attentional focus to execute the task. However, we purposely included a familiarization session for all participants to minimize this threat to internal validity by allowing participants to practice arm cycling.

3.5.3 Conclusions

The novel finding in this study is that corticospinal excitability, as assessed by changes in MEP amplitude, projecting to the biceps brachii is not different between SSC and FC arm cycling. We can indirectly (because attention was not directly measured)

conclude that corticospinal excitability during arm cycling is independent of attentional demands, as corticospinal excitability is not different when focusing attention on maintaining a set cadence compared to cycling at a voluntarily chosen cadence.

Author Contributions: All authors participated in the data collection, analysis, and manuscript preparation. All authors have approved the submitted version of this manuscript.

Funding: This research was funded by the Natural Sciences and Engineering Research Council of Canada (NSERC), grant number (NSERC-#RGPIN-2015-05765).

Acknowledgements: This study was supported by CGS-M NSERC funding to E.J.L. as well as a NSERC Discovery Grant to K.E.P. We would like to thank Dr. Thamir Alkanani for technical support and the participants for volunteering their time.

Conflicts of Interest: The authors declare no conflict of interest.

Chapter 4: CORTICOSPINAL-EVOKED RESPONSES FROM THE BICEPS BRACHII DURING ARM CYCLING ACROSS MULTIPLE POWER OUTPUTS

Co-Authorship Statement:

Chapter four focuses on Study #2 of the thesis. The ICEHR approval certificate number for this study is ICEHR #20181196. This chapter was published in full in *Brain Sciences*: Lockyer EJ, Hosel K, Nippard A, Button DC, Power KE. Corticospinal-Evoked Responses from the Biceps Brachii during Arm Cycling across Multiple Power Outputs. *Brain Sciences*. 2019; doi: 10.3390/brainsci9080205. Permissions to use this manuscript in this thesis was not required as the journal is open access. Evan Lockyer and Dr. Power conceived and designed the experimental protocols described in this chapter. Katarina Hosel (undergraduate student) and Anna Nippard (graduate student) were students in Dr. Power's Lab who Evan mentored, and they assisted Evan with participant preparation and aspects of the data collection. Evan Lockyer performed all data extraction and analysis and completed all statistical analyses, drafted the manuscript, and was responsible for all tables and figures. Evan Lockyer, Dr. Duane Button, and Dr. Power edited the manuscript, and all authors approved the final version.

4.1 Abstract

Background: We examined corticospinal and spinal excitability across multiple power outputs during arm cycling using a weak and strong stimulus intensity. *Methods*: We elicited motor evoked potentials (MEPs) and cervicomedullary motor evoked potentials (CMEPs) in the biceps brachii using magnetic stimulation over the motor cortex and electrical stimulation of corticospinal axons during arm cycling at 6 different power outputs (i.e., 25, 50, 100, 150, 200 and 250W) and two stimulation intensities (i.e., weak vs strong). *Results*: In general, biceps brachii MEP and CMEP amplitudes [normalized to maximal M-wave (M_{max})] followed a similar pattern of modulation with increases in cycling intensity at both stimulation strengths. Specifically, MEP and CMEP amplitudes increased up until ~150W and ~100W when the weak and strong stimulations were used, respectively. Further increases in cycling intensity revealed no changes on MEP or CMEP amplitudes for either stimulation strength. *Conclusions*: In general, MEPs and CMEPs changed in a similar manner, suggesting that increases and subsequent plateaus in overall excitability are likely mediated by spinal factors. Interestingly, however, MEP amplitudes were disproportionately larger than CMEP amplitudes as power output increased, despite being initially matched in amplitude, particularly with strong stimulation. This suggests that supraspinal excitability is enhanced to a larger degree than spinal excitability as the power output of arm cycling increases.

4.2 Introduction

The influence of muscle contraction intensity on the excitability of the corticospinal pathway in humans has been well-studied during isometric contractions. Most of this research has involved the use of non-invasive stimulation techniques to assess corticospinal and/or spinal excitability to muscles of the upper (Martin, Gandevia, et al., 2006; Taylor et al., 1997; Todd et al., 2003) and, to a lesser extent, the lower limb (Oya et al., 2008) across a wide range of isometric contraction intensities. In general, the findings from these studies indicate that motor evoked potentials (MEPs) elicited by transcranial magnetic stimulation (TMS) increase in size as the 'strength' of isometric muscle contractions increases up until a peak, after which they plateau and subsequently decrease as contraction strength approaches maximal [(i.e., 100% maximal voluntary contraction (MVC)] (Martin, Gandevia, et al., 2006; Oya et al., 2008; Taylor et al., 1997; Todd et al., 2003). This modulation in MEP is accompanied by a similar change in the cervicomedullary MEP (CMEP) elicited by transmastoid electrical stimulation (TMES) of corticospinal axons, suggesting that the change in corticospinal excitability is largely mediated by spinal factors (Martin, Gandevia, et al., 2006; Oya et al., 2008).

Using a *strong* stimulus intensity [set to evoke responses equal to 65-80% the maximal compound muscle action potential (M_{max})], Martin et al. (2006) showed that MEP and CMEP areas increased linearly in size during weak isometric contractions (i.e., <50% MVC) of the biceps brachii as muscle contraction intensity increased, whereas during strong contractions (i.e., >50% MVC) MEP and CMEP areas plateaued at ~75% MVC, and subsequently decreased as the contraction intensity approached 100% MVC (Martin, Gandevia, et al., 2006). When a *lower* stimulus intensity (set to evoke responses equal to

30-50% M_{max}) was used, MEP and CMEP areas followed a similar pattern of modulation with contraction intensity, however, peak responses were not observed until ~90% MVC, after which MEP and CMEP areas decreased. Moreover, the decline in MEP and CMEP area with the lower stimulus intensity was less marked than that observed when the stronger stimulus intensity was used (Martin, Gandevia, et al., 2006). Thus, the intensity of stimulation is an important factor to consider in assessing corticospinal excitability given how it can influence the primary measurement(s) and the associated interpretation of the data.

Substantially less information, however, is available regarding the influence of muscle contraction intensity on the modulation of corticospinal excitability during rhythmic motor outputs, such as those observed during cycling (Lockyer et al., 2018; Spence et al., 2016; Weavil et al., 2015). This is an important topic to consider given that rhythmic motor outputs such as arm cycling are partially generated by spinally located networks of interneurons referred to as central pattern generators (Zehr et al., 2004; Zehr et al., 2003), and that corticospinal excitability is modulated differently during rhythmic locomotor outputs than during isometric contractions, indicating task-specificity (Forman et al., 2014; Forman et al., 2018; Weavil et al., 2015). In two separate studies from our lab, we have investigated changes in corticospinal and spinal excitability as arm cycling intensity (i.e., power output) was increased (Lockyer et al., 2018; Spence et al., 2016). However, changes in excitability were assessed across a small range of power outputs, and thus may not have observed potential changes in excitability that occurred at higher cycling intensities. Thus, it remains unknown whether a similar peak, plateau and subsequent

decline in corticospinal and spinal excitability are observed with increasing arm cycling intensity, as observed in isometric contractions.

Accordingly, the purpose of the present study was to: 1) characterize the influence of muscle contraction intensity on changes in corticospinal and spinal excitability projecting to the biceps brachii over a wide range of arm cycling intensities, and 2) assess the influence of stimulation intensity on corticospinal and spinal outputs as cycling intensity increased. Specifically, we sought to examine the effects of using a weak and a strong stimulus intensity on corticospinal and spinal excitability as power output was increased during cycling. We hypothesized that: 1) using the *weak* stimulus, corticospinal and spinal excitability would increase similarly across all arm cycling power outputs, and 2) using the *strong* stimulus, corticospinal and spinal excitability would increase but experience a plateau and subsequent decrease as cycling intensity increased towards the maximum power output examined.

4.3 Materials and Methods

4.3.1 Participants

This study consisted of a familiarization session and two experimental sessions; 1) a transcranial magnetic stimulation (TMS) session and 2) a transmastoid electrical stimulation (TMES) session (see *Protocol* below). A total of nine healthy, male volunteers (24.2 ± 5.9 years, 180.7 ± 7.8 cm, 82.2 ± 8.3 kg, 1 left-hand dominant) with no known neurological impairment participated in session one, and eight of those volunteers (1 left-hand dominant) returned on a separate day (>24 hours) to complete session two. In

accordance with the Tri-Council guidelines in Canada, all participants gave written, informed consent prior to participating in the study, and potential risks were fully disclosed. Prior to TMS, all participants were screened for contraindications to magnetic stimulation using a safety checklist (Rossi et al., 2009). To determine limb dominance, the Edinburgh handedness inventory (Veale, 2014) was used. This information was gathered because all evoked responses elicited by TMS and TMES (see *Stimulation conditions* below) were taken from the dominant arm. Additionally, all participants filled out a Physical Activity Readiness Questionnaire for Everyone (PAR-Q+; Canadian Society for Exercise Physiology (CSEP)) to screen for any contraindications to physical activity. Participants also refrained from caffeine for 12 hours and alcohol for 24 hours prior to each experimental session. All procedures were performed in compliance with the Declaration of Helsinki and were approved by the Interdisciplinary Committee on Ethics in Human Research (ICEHR no. 20181196-HK) at Memorial University of Newfoundland.

4.3.2 Experimental Setup

Many of the experimental procedures and recording techniques herein are similar to those described previously (Forman et al., 2015; Lockyer et al., 2018; Spence et al., 2016). All sessions were conducted with participants seated upright on an arm cycle ergometer (SCIFIT ergometer, model PRO2 Total Body, Tulsa, OK, USA). The seat height of the ergometer was adjusted so that participants' shoulders were approximately in line with the axis of rotation of the arm cranks and the seat distance was manipulated to a position in which participants were at a 'comfortable' distance (i.e., no reaching or trunk variation during cycling) from the hand pedals. The seat height and distance were recorded for each

participant during the familiarization session and were used for the subsequent sessions. Arm cycling trials were performed in an asynchronous cranking pattern with the forearms fixed in a pronated position. Wrist braces were worn to limit the amount of wrist flexion and extension during cycling as a means to diminish the influence of short- and long-latency reflex connections that have been shown to exist between the wrist flexors and the biceps brachii (see **Figure 4.1**) (Manning & Bawa, 2011).

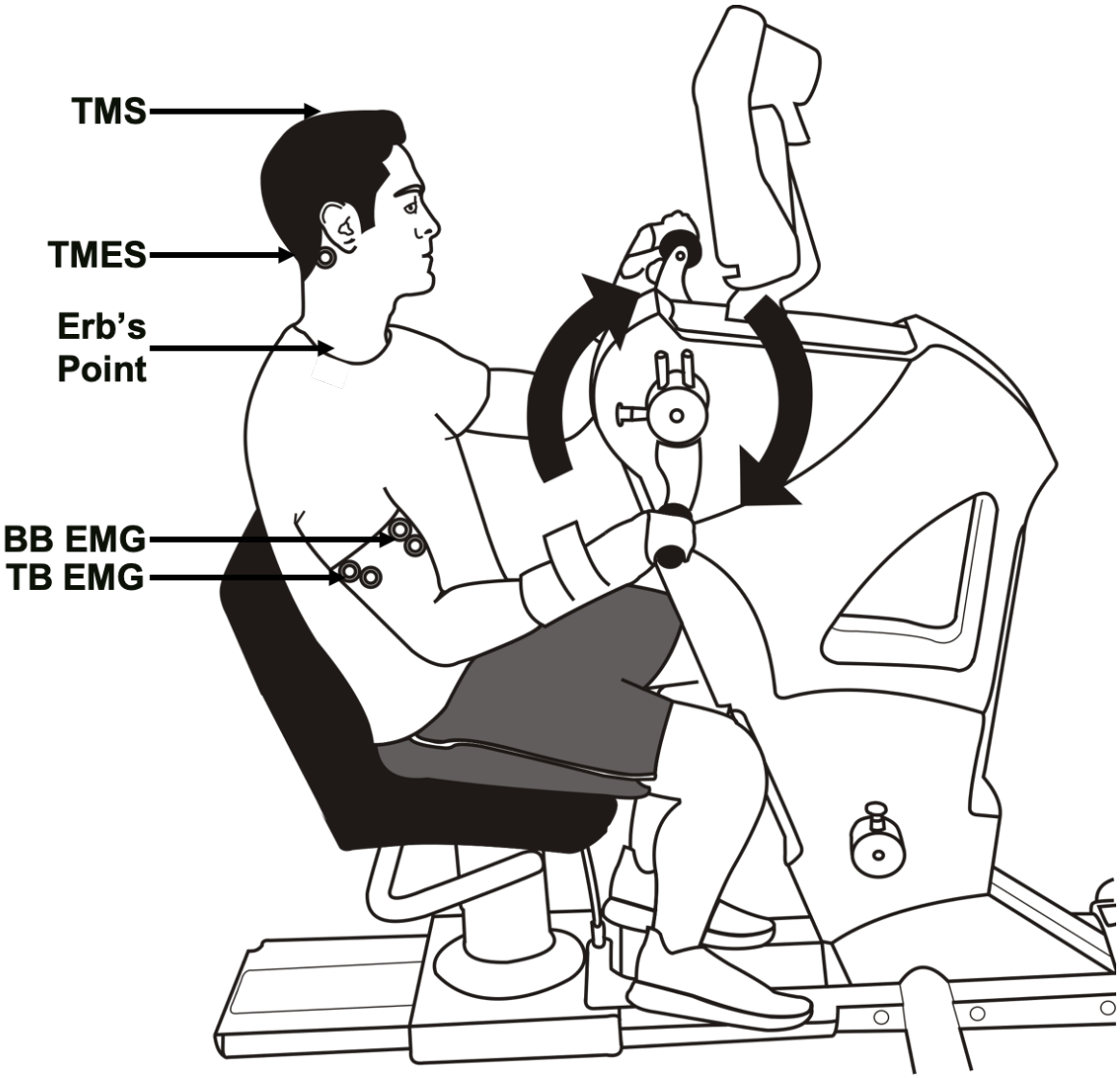

Figure 4.1: Experimental setup.

Experimental setup for arm cycling trials showing participant seated on the ergometer instrumented with surface EMG electrodes on the biceps and triceps brachii. Arrows point to the site of each stimulation technique. All arm cycling trials were conducted in the forward direction. Abbreviations: TMS, transcranial magnetic stimulation; TMES, transmastoid electrical stimulation; BB, biceps brachii; TB, triceps brachii; EMG, electromyography.

For this study, participants were required to cycle at 6 different power outputs: 25, 50, 100, 150, 200, and 250 Watts (W) all at a constant cadence of 60 revolutions per minute (rpm). These cycling conditions were repeated at two different stimulation intensities (see *Stimulation conditions* below), for a total of 12 cycling trials.

4.3.3 Electromyography Recordings

Surface electromyography (EMG) was recorded from the biceps brachii of the dominant arm using pairs of disposable Ag-AgCl surface electrodes (MediTrace^{TM} 130 Foam Electrodes with conductive adhesive hydrogel, Covidien IIC, Massachusetts, USA). Electrodes were positioned approximately 2 cm apart (centre to centre) over the midline of the biceps brachii and on the lateral head of the triceps brachii in a bipolar configuration. A ground electrode was positioned on the lateral epicondyle of the dominant arm. To reduce the impedance for EMG recordings, the skin was thoroughly prepared by removing hair (via a handheld razor), abraded to remove dead skin cells (via abrasive paper), and cleaned using isopropyl alcohol swabs prior to electrode placement. The EMG signals were amplified (x 300; CED 1902 amplifier; Cambridge Electronic Design Ltd., Cambridge, UK), and bandpass filtered using a 3-pole Butterworth filter with cut-off frequencies of 10–1,000 Hz. All analog signals were digitized at a sampling rate of 5,000 Hz and stored

on a laboratory computer for off-line analysis (CED 1401 interface and Signal 5.11 software; Cambridge Electronic Design Ltd., Cambridge, UK).

4.3.4 Stimulation Conditions

Recordings were made of the motor responses in the biceps brachii to three different stimulation techniques: 1) brachial plexus stimulation at Erb's point, 2) magnetic stimulation of the motor cortex (i.e., TMS), and 3) electrical stimulation between the mastoids at the cervicomedullary junction (i.e., TMES). Motor responses were evoked during arm cycling at the 6 o'clock position, which corresponds to the mid-elbow flexion phase of arm cycling and when biceps brachii activity is relatively the largest [for more detailed explanation of the phases of arm cycling see review by (Power et al., 2018)]. Stimulations were triggered automatically when the right hand passed a magnetic sensor on the ergometer, at either the 6 o'clock or 12 o'clock position for right-handed and left-handed participants, respectively. The intensities for all three stimulation techniques were set during arm cycling at a constant cadence of 60 rpm and power output of 25 W. For TMS and TMES, two different stimulation intensities were used: 1) a weak stimulation intensity (set to evoke responses equal to ~10% M_{max}), and 2) a strong stimulation intensity (set to evoke responses equal to ~40% M_{max}). These response amplitudes were chosen to provide insight into potential differences in excitability at different portions of the motoneurone pool as cycling intensity increased. All participants had prior experience with each of the stimulation procedures before participating.

4.3.5 Brachial Plexus Stimulation.

For both sessions, single rectangular pulses (200-μs duration; 90–275 mA) were delivered via a DS7AH constant current stimulator (Digitimer Ltd., Welwyn Garden City, Hertfordshire, UK) to the brachial plexus at Erb's point to elicit maximal compound muscle action potentials (maximal M-wave (M_{max})) in the biceps brachii. The cathode was placed in the supraclavicular fossa and the anode over the acromion process. Stimulus intensity was initially set at 25 mA and was gradually increased until the size of the M-wave plateaued (i.e., M_{max}). At this point, the stimulation intensity was increased by 10% (supramaximal) to ensure that M_{max} was elicited throughout the remainder of the study.

4.3.6 TMS.

TMS was delivered over vertex of the motor cortex to elicit MEPs in the biceps brachii using a Magstim 200^2 magnetic stimulator (Magstim, Whitland, Dyfed, UK) and circular coil (13.5 cm outside diameter). The vertex was measured and marked on the participant's scalp with a felt-tip permanent marker. One investigator ensured proper and consistent coil placement directly over vertex throughout the experiment. The coil was held firmly against the participant's skull, parallel to the floor with the direction of current flow oriented to preferentially activate either the left or right motor cortex, depending on hand dominance (i.e., "A" side up for right-handed participants, "B" side up for left-handed participants). Initially, TMS intensity was set at 25% of maximal stimulator output (MSO) and was increased until MEPs were observed in the biceps brachii equal in amplitude to ~10% M_{max}. Once found, a trial consisting of 8 TMS was performed to ensure that the

average MEPs were ~10% M_{max}. This stimulation intensity was recorded as the weak stimulation intensity and was then used for the remainder of the experiment. For the strong stimulation intensity, the same procedures were performed except the %MSO was increased until MEPs from the biceps brachii were equal in amplitude to ~40% M_{max}. Once again, a trial consisting of 8 TMS was performed to ensure that the intensity of TMS would evoke MEPs equal to ~40% M_{max}. Once determined, this intensity was recorded and then used as the strong intensity for the rest of the experiment.

4.3.7 TMES.

TMES was delivered (200 μs pulse-width duration; DS7AH, Digitimer Ltd., Welwyn Garden City, Hertfordshire, UK) to the corticospinal axons at the cervicomedullary junction to elicit CMEPs in the dominant arm biceps brachii. Self-adhesive Ag-AgCl surface electrodes were placed on the skin at the grooves between the mastoid processes and the occipital bone, with the anode and cathode on the side corresponding to each participant's dominant and non-dominant arm, respectively. Similar to the procedures for setting the stimulation intensities for TMS (see *TMS* above), the intensity of electrical stimulation was gradually increased (initially from 25 mA) until the amplitudes of the CMEPs were equal in amplitude to ~10% M_{max} (for the weak stimulation intensity) and ~40% M_{max} (for the strong stimulation intensity). Trials of 8 CMEPs were evoked at each stimulation intensity and the average was calculated. These stimulation intensities were recorded and were then used for the remainder of the experiment. The latency of responses was monitored carefully to ensure that stimulation did not activate the

corticospinal axons at or near the ventral roots, which would be indicated by a reduction in latency by ~ 2 ms (Taylor, 2006; Taylor & Gandevia, 2004).

4.3.8 Protocol

Following familiarization, participants were randomly assigned to complete either session one (TMS) or session two (TMES) first. For both sessions, the procedures were identical with the exception of the stimulation type. Following EMG preparation and ergometer modifications, stimulation intensities were determined (see above). In both sessions, M_{max} was determined first followed by the setting of stimulation intensities for the weak and strong stimulations for either TMS (session one) or TMES (session two). Once stimulation intensities were determined, participants began the 12 cycling trials consisting of six power outputs (25, 50, 100, 150, 200, and 250 W) performed at a constant cadence of 60 rpm with either the weak or strong stimulation intensity (i.e., six cycling trials at each stimulation intensity). The order of the cycling trials was randomized for each participant. While cycling, as the dominant hand passed the 6 o'clock position, one M_{max} and either six MEPs or six CMEPs (depending on the session) were evoked in a randomized order. The time between stimulations was 5–6 s. The total length of each trial was approximately 30 s. To reduce the potential influence of fatigue, one-minute rest periods were given following completion of the lower power output trials (i.e., 25, 50, 100 W), and two-minute rest periods were given after the higher power output trials (i.e., 150, 200, 250 W). Additionally, half-way through the 12 trials (i.e., after trial six), a 5-min rest period was given before the remainder of the trials were completed.

4.3.9 Data Analysis

For analysis of M_{max}, MEP, and CMEP, the averaged peak-to-peak amplitudes from each cycling trial were measured from the biceps brachii of the dominant arm. Since M_{max} is thought to represent the maximal response of the motor system (Oya et al., 2008), averaged MEPs (n = 6) and CMEPs (n = 6) from each trial were normalized to the M_{max} within each cycling trial. Response latencies of all evoked responses were carefully monitored throughout all cycling trials as well. The latency for each response was classified as the duration from the stimulus artifact to the initial deflection in the voltage trace from baseline and was averaged across the total number of stimulation trials. Additionally, since the level of voluntary muscle contraction could potentially have an influence on changes in MEP and CMEP amplitudes, pre-stimulus EMG was measured from the rectified virtual channel created for the biceps and triceps brachii as the mean of a 50 ms window immediately prior to the stimulation artifact (Forman et al., 2015). For two participants who completed CMEPs (n = 8), pre-stimulus EMG from the triceps brachii was not available due to technical error during data collection. Therefore, the final sample size for CMEP pre-stimulus EMG data from the triceps brachii was n = 6.

4.3.10 Statistical Analysis

Group data are presented as means ± SD in the text and means ± SE in the figures (with n in the legends). All statistics were performed using IBM's SPSS Statistics (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.). Mauchly's test was

employed to assess the assumption of sphericity for repeated measures analysis. In cases where sphericity was violated, the appropriate correction was applied (i.e., Greenhouse Geisser or Huynh-Feldt) and the degrees of freedom were adjusted. Separate two-way repeated-measures ANOVAs were used to assess the effects of stimulation intensity and cycling intensity (and any interaction) on the M_{max}, MEP and CMEP amplitudes (both normalized to M_{max}), the average pre-stimulus EMG, and the MEP/CMEP ratios. Post hoc pairwise comparisons were made between means using the Bonferroni correction. Additionally, because one of our aims was to examine the effects of cycling intensity on corticospinal excitability measures within each stimulation intensity (weak and strong), separate one-way repeated-measures ANOVAs were conducted for both the weak and strong stimulus on M_{max}, MEP and CMEP amplitudes (normalized to M_{max}), pre-stimulus EMG, and MEP/CMEP ratios as cycling intensity increased. If a main effect was identified, post hoc pairwise comparisons were made between means using the Bonferroni correction. Independent samples *t*-tests were conducted to compare whether MEPs and CMEPs (normalized to M_{max}) at both stimulation intensities were matched appropriately. To compare between MEP and CMEP amplitudes (normalized to M_{max}) at each power output, independent sample *t*-tests were used with a Bonferroni correction. Paired samples *t*-tests were conducted on MEP/CMEP ratios between stimulation strengths (weak vs strong) at each power output. All statistics were performed on group data and statistical significance was set at $p < 0.05$.

4.4 Results

Evoked responses (i.e., M_{max}, MEPs, and CMEPs) were recorded from the dominant arm biceps brachii at two different stimulation intensities while participants performed arm cycling bouts over a range of contraction strengths. MEPs and CMEPs (normalized to M_{max}) were evoked on separate days but were initially matched to equal 10% (weak stimulus) and 40% (strong stimulus) of the M_{max} on each day. MEPs and CMEPs were not significantly different when either the weak or the strong stimulation intensity were examined ($p > 0.05$ for both conditions), suggesting that the responses were indeed matched initially between days.

4.4.1 Biceps Brachii Evoked Responses

4.4.1.1 MEP Amplitude.

Figure 4.2 (top panel) and **Figure 4.3A** show representative and grouped data, respectively for MEP amplitudes from the biceps brachii during arm cycling across the various contraction intensities. **Figure 4.2** shows evoked potential traces from one participant during arm cycling with the weak stimulation intensity. In this example, the amplitudes of the MEPs show a progressive and generally consistent increase from the lowest (25W) to the highest (250W) arm cycling/muscle contraction intensity. Results from the two-way ANOVA on MEP amplitudes showed a significant main effect for both stimulation intensity (strong > weak; $F_{5,40} = 96.81$, $p < 0.001$) and cycling intensity ($F_{1,8} = 65.30$, $p < 0.001$). Bonferroni post hoc tests revealed that MEP amplitudes at 25W and 50W were not different from one another ($p = 0.187$) but were significantly smaller than

MEP amplitudes evoked during the 100, 150, 200, and 250W trials ($p < 0.05$ for all comparisons). Additionally, there was a significant interaction between the intensity of stimulation and the intensity of cycling on MEP amplitudes ($F_{5,40} = 65.30$, $p < 0.001$). Further analysis, through use of one-way ANOVAs for each stimulation intensity, showed a significant main effect for cycling intensity on MEP amplitudes at both the weak ($F_{5,40} = 55.61$, $p < 0.001$) and strong ($F_{5,40} = 41.28$, $p < 0.001$) stimulation conditions. Using the weak stimulation, Bonferroni post hoc tests revealed that MEP amplitudes increased as cycling intensity increased up until 200W (200W > 150W >100W > 50W > 25W; $p < 0.05$ for all comparisons) after which MEPs plateaued ($p > 0.05$). Using the strong stimulation, MEP amplitudes similarly increased with cycling intensity, however a peak was observed at 100W (100W > 50W > 25W; $p < 0.05$ for all comparisons), at a lower power output than that observed using the weaker stimulation condition (i.e., 200W). Beyond 100W, there were no further increases in MEP amplitudes ($p > 0.05$).

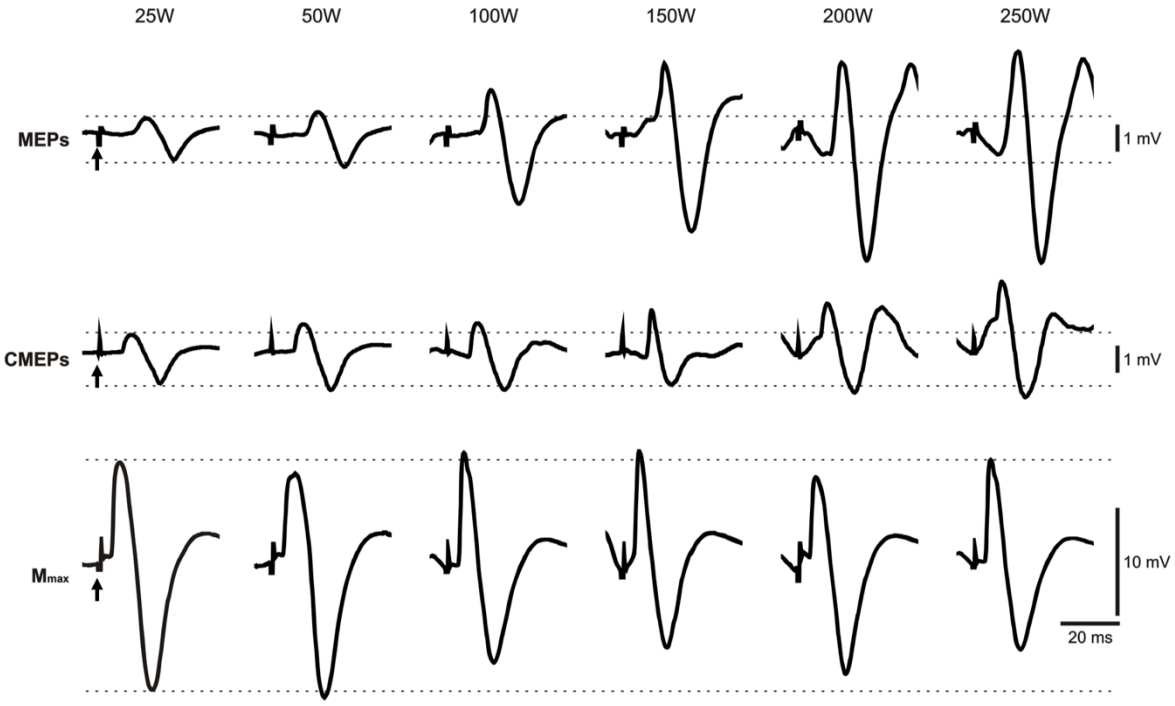

Figure 4.2: Representative evoked responses during arm cycling across power outputs.

Raw traces for MEPs (top row), CMEPs (middle row), and M_{max} (bottom row) from the biceps brachii of a single participant (n = 1) across arm cycling power outputs using the *weak* stimulation intensity. Each MEP and CMEP waveform represent the average of 6 evoked potentials. Arrows indicate the stimulus artifact, and dashed lines portray the initial amplitudes of evoked potentials with the *weak* stimulation (~10% M_{max}). In this example, MEP and CMEP amplitudes show a general progressive increase as power output increases towards 250W, while M_{max} gradually decreases.

4.4.1.2 Biceps Brachii Pre-Stimulus EMG.

Figure 4.3C shows group data for biceps brachii pre-stimulus EMG prior to MEPs during arm cycling. Results from the two-way ANOVA showed that mean biceps brachii pre-stimulus EMG in the 50 ms preceding a MEP was not different between the weak and strong stimulation intensity ($F_{1,8}$ = 1.42, p = 0.267). Therefore, the average pre-stimulus EMG was pooled between the weak and strong stimulation conditions which is represented

in **Figure 4.3C**. There was a significant main effect on biceps brachii pre-stimulus EMG for cycling intensity ($F_{1.76,14.12} = 29.33$, $p < 0.001$), but there was no interaction between stimulation intensity and cycling intensity ($F_{1.96,27.35} = 1.96$, $p = 0.137$). To further examine changes in pre-stimulus EMG with cycling intensity, one-way ANOVAs were performed. Pre-stimulus EMG increased as cycling intensity increased up until 200W (**Figure 4.3C**; $p < 0.05$), and no differences were observed between the 200W and 250W conditions ($p = 1.00$).

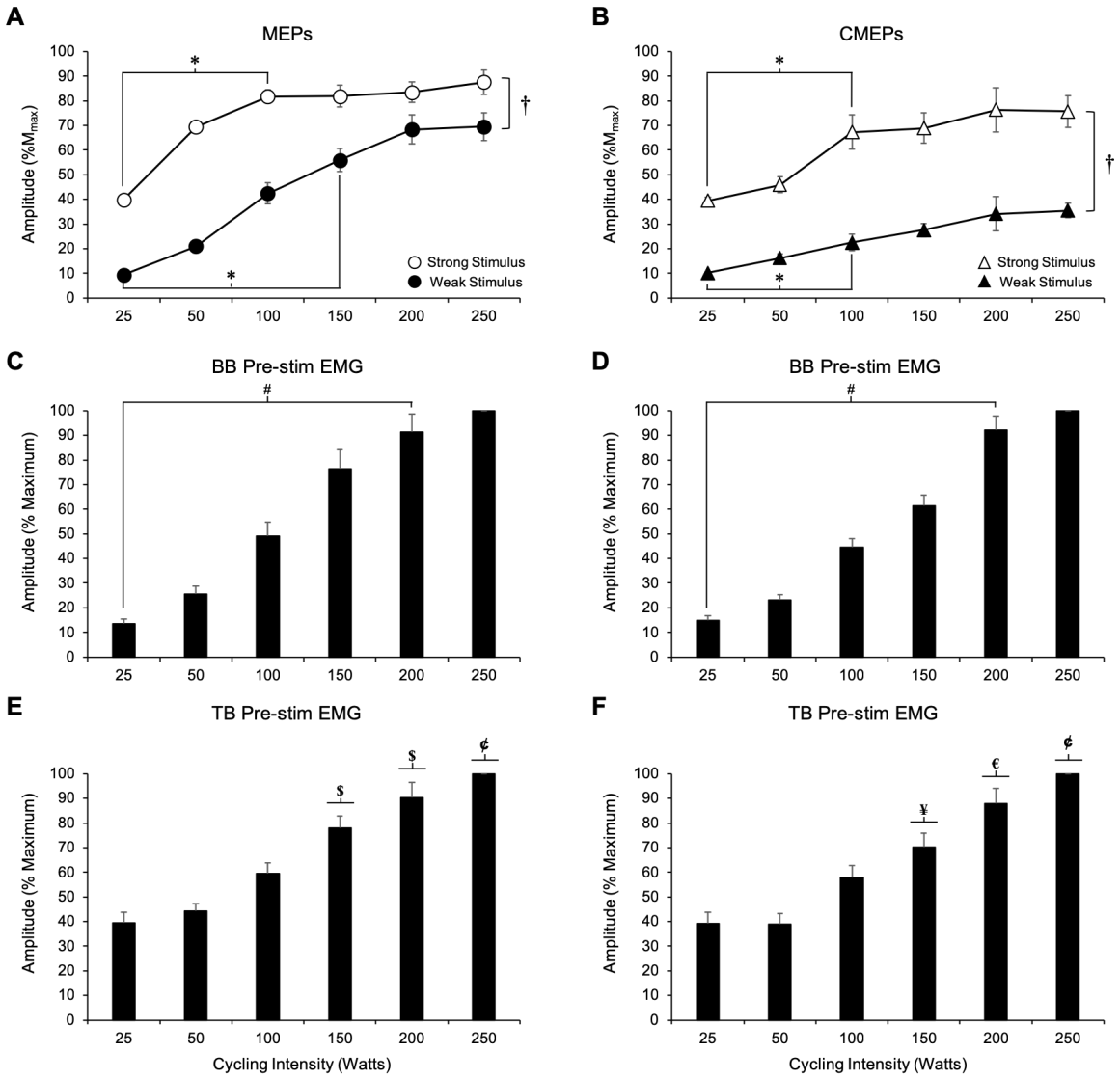

Figure 4.3: Mean evoked response amplitudes across power outputs and stimulation intensities.

(A, B) Normalized grouped data (means ± SE) of the peak-to-peak amplitudes for MEPs **(A)** and CMEPs **(B)** obtained from the biceps brachii at each power output examined. MEPs and CMEPs were normalized to M_{max} at each corresponding cycling intensity. In both A and B, filled data points represent when the weak stimulus was used, while unfilled points represent data from the strong stimulus. For clarity, circles were used for MEPs, while triangles were used for CMEPs. In some cases, data points are bigger than SE bars. *Significant difference between illustrated data points. †Significant main effect for stimulation strength ($p < 0.05$). **(C, D)** Pre-stimulus EMG (means ± SE) from the biceps brachii which has been pooled and averaged between both stimulation intensities for the TMS session **(C)** and TMES session **(D)**,

respectively. #Significant difference between all data points. **(E, F)** Pre-stimulus EMG (means ± SE) from the triceps brachii which has been pooled and averaged between both stimulation intensities for the TMS session **(E)** and TMES session **(F)**, respectively. $ denotes significant difference from all previous power outputs. ¥ denotes significant difference from the 25W condition. € denotes significant difference from the 25, 50, and 100W conditions. ¢ denotes significant difference from the 25, 50, 100, and 150W conditions.

4.4.1.3 Triceps Brachii Pre-Stimulus EMG.

Figure 4.3E shows group data for triceps brachii pre-stimulus EMG prior to MEPs. Similar to the biceps, results from the ANOVA showed no effect of stimulation intensity on triceps brachii EMG activity prior to a MEP (**Figure 4.3E**; $F_{(1,8)} = 0.100$, $p = 0.760$), but there was a significant main effect of cycling intensity ($F_{(1.62,12.94)} = 19.32$, $p < 0.001$). Also, there was no significant interaction between cycling intensity and stimulation intensity ($F_{(5,40)} = 0.803$, $p = 0.554$). To further examine the effect of cycling intensity on triceps brachii pre-stimulus EMG, one-way ANOVAs were performed using the pooled data. Results from these tests indicated that as cycling intensity increased, triceps brachii pre-stimulus EMG values were only significantly different at 150W and 200W. Specifically, triceps brachii pre-stimulus EMG was larger at 150W than at 100W ($p = 0.006$) and was larger at 200W than 150W ($p = .044$).

4.4.1.4 CMEP Amplitude.

Figure 4.2 (middle panel) and **Figure 4.3B** show representative and grouped data, respectively for CMEP amplitudes during the arm cycling bouts. **Figure 4.2** portrays data from one participant from the weak stimulation intensity condition. Similar to the MEP

amplitudes, in this example, CMEP amplitudes increase in a relatively consistent and progressive manner. The results from the two-way ANOVA on CMEP amplitudes showed significant main effects for both stimulation intensity (strong > weak; $F_{1,7} = 91.50$, $p < 0.001$) and cycling intensity ($F_{3.81,26.65} = 20.16$, $p < 0.001$), however, there was no significant interaction between the two factors ($F_{5,35} = 1.34$, $p = 0.271$). For cycling intensity, Bonferroni post hoc analysis revealed that CMEPs at 25 and 50W are smaller than those at all other cycling intensities (i.e., 100, 150, 200, and 250W; $p < 0.05$ for all comparisons). To decipher specific effects of cycling intensity within each stimulation condition, separate one-way ANOVAs for the weak and strong stimulation conditions were performed on CMEP amplitudes. The results from the one-way ANOVAs showed a significant main effect for cycling intensity on CMEP amplitudes at both the weak ($F_{5,35} = 21.11$, $p < 0.001$) and strong ($F_{5,35} = 9.95$, $p < 0.001$) stimulation conditions. For the weak stimulation condition, Bonferroni post hoc analyses revealed that CMEP amplitudes increased up until 150W (150W > 100W > 50W > 25W; $p < 0.05$ for all comparisons), after which CMEP amplitudes did not change ($p > 0.05$). When the strong stimulation intensity was used, post hoc analyses revealed that CMEP amplitudes increased up until 100W (100W > 50W > 25W; $p < 0.05$ for all comparisons), after which CMEPs plateaued ($p > 0.05$).

4.4.1.5 Biceps Brachii Pre-Stimulus EMG.

Figure 4.3D shows group data for biceps brachii pre-stimulus EMG prior to CMEPs during arm cycling. Results from the two-way ANOVA showed that mean biceps brachii

pre-stimulus EMG in the 50 ms preceding CMEPs was not influenced by stimulation intensity ($F_{1,7} = 0.02$, $p = 0.906$), thus the data was pooled between the weak and strong stimulation conditions as shown in **Figure 4.3D**. There was a significant main effect on biceps brachii pre-stimulus EMG for cycling intensity ($F_{1.49,10.41} = 43.08$, $p < 0.001$), but there was no interaction between stimulation intensity and cycling intensity ($F_{5,35} = 1.22$, $p = 0.320$). To further examine changes in pre-stimulus EMG with cycling intensity, one-way ANOVAs were performed using the pooled data. Similar to MEPs, pre-stimulus EMG for CMEPs increased as cycling intensity increased up until 200W (**Figure 4.3D**; $p < 0.05$), and there was no difference between the 200W and 250W conditions ($p = 0.885$).

4.4.1.6 Triceps Brachii Pre-Stimulus EMG.

Figure 4.3F shows group data for triceps brachii pre-stimulus EMG prior to CMEPs. Similar to above, results from the two-way ANOVA showed no effect of stimulation intensity ($F_{1,5} = 0.761$, $p = 0.423$) and thus, the data was pooled between the weak and strong stimulation intensities (**Figure 4.3F**). There was, however, a significant main effect of cycling intensity ($F_{1.31,6.55} = 14.04$, $p = 0.006$) on triceps brachii pre-stimulus EMG, but no significant interaction ($F_{5,25} = 0.961$, $p = 0.460$). To further examine the effect of cycling intensity on triceps brachii pre-stimulus EMG, one-way ANOVAs were performed using the pooled data. Results from these tests indicated that triceps brachii pre-stimulus EMG values for CMEPs were only increased at 150W, 200W and 250W compared to the 25W condition ($p < 0.05$ for all comparisons). However, triceps brachii pre-stimulus EMG was

not significantly different with increased cycling intensity from 150W to 250W ($p > 0.05$ for all comparisons).

4.4.1.7 MEP/CMEP Ratios.

Although MEPs and CMEPs were evoked on separate days, the responses were initially matched in amplitude to approximately 10% or 40% M_{max} for the weak and strong stimulation conditions, respectively ($p > 0.05$ for both stimulation conditions). Thus, MEP amplitudes were expressed relative to CMEP amplitudes and multiplied by 100% to obtain MEP/CMEP percentages for each participant (**Figure 4.4**). This was done in an attempt to isolate whether changes in overall excitability could be attributed to changes in supraspinal and/or spinal excitability. Values greater than 100% indicate that MEP amplitudes are larger than CMEP amplitudes, suggesting that supraspinal excitability may be increased. Similarly, values less than 100% indicate that MEP amplitudes are less than CMEP amplitudes, suggesting that changes in spinal excitability are important factors in maintaining excitability of the corticospinal pathway. Results from the two-way ANOVA revealed a significant main effect for stimulation intensity (weak > strong; $F_{1,7} = 6.94$, $p = 0.034$) and cycling intensity ($F_{5, 35} = 9.71$, $p < 0.001$). Bonferroni post hoc tests revealed that MEP/CMEP at 25W and 50W were not different from one another ($p = 0.413$) but were significantly smaller than MEP/CMEP at 100, 150, 200, and 250W trials ($p < 0.05$ for all comparisons). As well, there was a significant interaction effect ($F_{5, 35} = 8.18$, $p < 0.001$) between stimulation intensity and cycling intensity on MEP/CMEP ratios. To examine changes in MEP/CMEP with increased power output, one-way ANOVAs were

conducted within each stimulation intensity. Results from the one-way ANOVAs showed a significant main effect for cycling intensity on MEP/CMEP ratios at both the weak ($F_{5,35}$ = 9.44, $p < 0.001$) and strong ($F_{5,35}$ = 4.60, p = 0.003) stimulation conditions. When the weak stimulation was used, Bonferroni post hoc analysis revealed that MEP/CMEP were only significantly larger than that at 25W at 150W (p = 0.037), and 200W (p = 0.05). When the strong stimulation intensity was used, MEP/CMEP were significantly larger at 50W than at 25W (p = 0.026) but were not different for any other comparison. To compare changes in MEP/CMEP between the weak and strong stimulation intensities, paired samples *t*-tests were performed at each power output. Thus, a total of 6 comparisons were made. The *t*-tests revealed that the MEP/CMEP ratios were not significantly different at 25W ($t_{(7)}$ = 1.22, p = 0.261) or 50W ($t_{(7)}$ = 0.52, p = 0.622) when either the weak or strong stimulus was used. However, MEP/CMEP ratios were significantly larger at 100W ($t_{(7)}$ = 2.51, p = 0.041), 150W ($t_{(7)}$ = 3.24, p = 0.014), 200W ($t_{(7)}$ = 3.03, p = 0.019), and 250W ($t_{(7)}$ = 2.41, p = 0.047) when the weak stimulation was used.

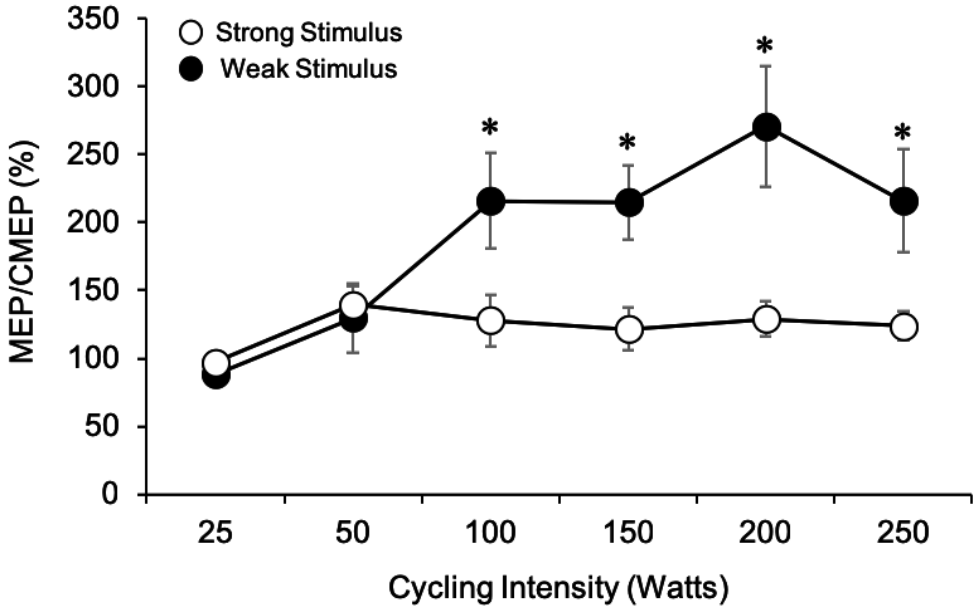

Figure 4.4: MEP/CMEP ratios across power outputs.

Comparison of MEP/CMEP ratios for the *weak* (filled circles) and *strong* (unfilled circles) stimulation intensities as power output increased from 25W to 250W. * represents significant difference between stimulation intensities at each given power output ($p < 0.05$). In some cases, SE bars were smaller than the symbols for the data points.

4.4.1.8 M_{max} Amplitude.

For both the TMS and TMES sessions, the results from the two-way ANOVA revealed similar effects on biceps brachii M_{max} amplitudes. For both sessions, there was no effect of stimulation intensity (TMS: $F_{1,8} = 0.093$, $p = 0.769$; TMES: $F_{1,7} = 1.06$, $p = 0.337$), but there was a significant main effect for cycling intensity (TMS: $F_{5,40} = 15.66$, $p < 0.001$; TMES: $F_{1,7} = 8.89$, $p < 0.001$) on M_{max} amplitudes (**Figure 4.5**). As cycling intensity increased M_{max} amplitudes decreased (**Figure 4.5A, B**). Additionally, there was no interaction observed between factors on either day (TMS: $F_{5,40} = 0.836$, $p = 0.532$; TMES: $F_{5,35} = .430$, $p = 0.825$). Since there was no effect of stimulation intensity on M_{max} values,

the averages from each stimulation condition (weak and strong) were pooled across the cycling intensities for each session (as shown in **Figure 4.5**). For cycling intensity, Bonferroni post hoc analyses indicated that M_{max} values decreased for the TMS and TMES session as cycling intensity increased from 25 to 250W.

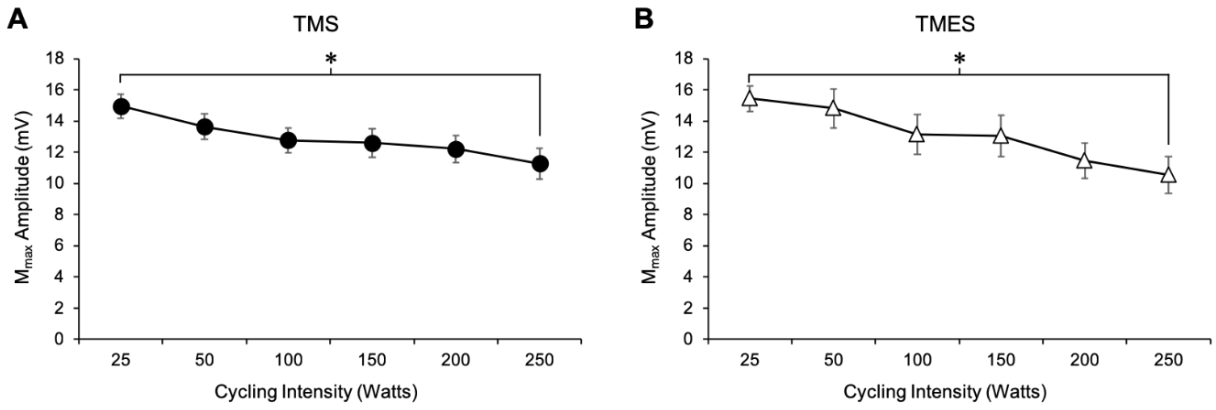

Figure 4.5: Changes in M_{max} amplitudes as power output increased.

Changes in M_{max} amplitudes with increasing power output pooled between stimulation intensities for the TMS **(A)** and TMES **(B)** session. * denotes significant main effect of power output on M_{max} amplitude. M_{max} decreased by approximately 24.9 and 31.7% as power output increased from 25 to 250W for the TMS and TMES sessions, respectively.

4.5 Discussion

This study shows that the amplitudes of TMS-evoked MEPs and TMES-evoked CMEPs increase with power output and plateau, but do not *decrease* in amplitude as has been previously shown by others during intense tonic contractions (Martin, Gandevia, et al., 2006; Oya et al., 2008). MEP amplitudes were much larger than CMEP amplitudes as power output increased regardless of stimulation strength, despite being initially matched in amplitude (**Figures 4.3A, 4.3B** and **4.4**). This finding suggests that supraspinal factors

mediate the change in overall corticospinal excitability observed during arm cycling as intensity increases. Importantly, stimulus strength had a substantial effect on MEP and CMEP amplitudes as cycling power output increased. Responses evoked by the weak stimulation (10% M_{max}) increased up to approximately 200W for MEPs (**Figure 4.3A, 4.4A**) and 150W for CMEPs (**Figure 4.3B, 4.4B**), whereas with the strong stimulation (40% M_{max}), responses reached a peak at 100W for both MEPs and CMEPs and did not change afterwards. Thus, the MEP/CMEP ratio used as a measure of supraspinal excitability was influenced by stimulation strength, which would lead to different conclusions on mechanisms of enhanced corticospinal excitability during arm cycling as power output increases.

4.5.1 Modulation Of Corticospinal And Spinal Excitability With Cycling Intensity

Past research involving isometric contractions has shown that biceps brachii MEPs and CMEPs increase up until a peak at ~75-90% MVC (Martin, Gandevia, et al., 2006; Taylor et al., 1997; Todd et al., 2003), a finding which has been attributed to the motor unit firing and recruitment characteristics of the biceps brachii during progressively stronger isometric contractions (De Luca et al., 1982; Kukulka & Clamann, 1981). Following the peak, there is a subsequent decline in responses as contraction intensity approaches 100% MVC (Martin, Gandevia, et al., 2006) which is thought to reflect the inability for some motoneurones to fire in response to artificial excitatory input at strong contraction strengths, given the high degree of voluntary input to the motoneurone pool and the associated changes in their intrinsic properties (Martin, Gandevia, et al., 2006). In the present study we did not observe a decline in corticospinal excitability as arm cycling

intensity increased to the maximum intensity employed. Instead, we observed a plateauing of responses for both MEPs and CMEPs at intensities below 250W, which were differentially influenced by stimulus strength (Figs. 3A, 3B). Our results, however, do coincide with findings from the only other study to examine corticospinal excitability changes during a locomotor-like output over a *wide range* of contraction intensities (Weavil et al., 2015). In that study, MEPs and CMEPs from the knee extensors during leg cycling increased in amplitude up to 300W, after which there was a plateauing, but no decline as cycling intensity increased to 400W (Weavil et al., 2015). Taken together, these studies suggest task-dependent changes in corticospinal and spinal excitability may be present, a finding we have previously reported (Forman et al., 2014; Forman, Richards, et al., 2016; Power et al., 2018).

In the current study, MEP and CMEP amplitudes increased at the lower, but not higher power outputs (Figs. 3A, 3B), suggesting that the increase in overall corticospinal excitability at the low intensities (i.e., 25 to 100W) is partially generated by increased spinal excitability. These finding are partially supported by biceps brachii pre-stimulus EMG values which increase for both stimulation types (Figs 3C, 3D) at the low cycling intensities but are not significantly different between the highest cycling intensities (200 and 250W). While this may explain the enhanced spinal excitability at the low power outputs, it does not explain why we observed a plateau in CMEP amplitudes beyond 150W for the weak stimulus and 100W for the strong stimulus in the present study, since EMG was still increasing beyond these power outputs. It is noted however that Weavil and colleagues showed increased EMG and workloads without changes in MEP and CMEP amplitudes. During isometric contractions, the biceps brachii is capable of recruiting

additional motor units during contractions up to and beyond 90% MVC (De Luca et al., 1982; Kukulka & Clamann, 1981), which helps to explain why CMEPs continue to increase beyond 90% MVC (Martin, Gandevia, et al., 2006). Corticospinal excitability to the biceps brachii is also task- (Forman et al., 2014; Power et al., 2018) and forearm position dependent (Forman, Richards, et al., 2016), which is an important consideration when a comparison to tonic contractions is made. However, the lack of increase in CMEP amplitudes beyond 150W and 100W during arm cycling in the current study, while MEPs and background EMG are still increasing, is unlikely to be explained by reaching the maximum motor unit recruitment of the biceps, given that these cycling intensities are not maximal, at least relative to a sprint test (Spence et al., 2016). It is possible, however, that motoneurone recruitment strategies during a rhythmic motor output such as arm cycling may be different from those observed during isometric contractions (Power et al., 2018), and therefore could cause motoneurones to be maximally recruited sooner than 90% of maximal cycling power. Work in adult decerebrate cats and rats for example, demonstrated that spinal motoneurones are characterized by changes in their electrical properties during locomotor outputs that would act to enhance their recruitment and firing (Krawitz et al., 2001; MacDonell et al., 2015; Power et al., 2010). These same changes in motoneurone excitability do not occur during tonic motor output (Power et al., 2010).

4.5.2 Modulation Of Supraspinal Excitability With Cycling Intensity

In the current study, MEP/CMEP ratios increased with power output, in particular when the weak stimulation intensity was used (**Figure 4.4**) suggesting that supraspinal excitability was enhanced to a larger degree than spinal excitability. It is plausible that

changes in the excitability of interneuronal circuits and/or interhemispheric connections may be involved. During tonic contractions, short-interval intracortical inhibition (SICI) is reduced as muscle contraction intensity increases (Kujirai et al., 1993; Ortu et al., 2008; Ridding et al., 1995), a finding that is thought to downregulate the action of the inhibitory neurons which project onto corticospinal cells involved in producing the movement. We recently showed that SICI was present during arm cycling albeit not different than a tonic contraction (Alcock et al., 2019). Thus, it is possible that reductions in SICI during arm cycling as power output increases may underlay increases in MEP amplitudes as has been shown during tonic contractions.

Another potential mechanism involves cortical spread from the non-dominant to the dominant motor cortex as we have previously hypothesized (Forman et al., 2015; Lockyer et al., 2018; Spence et al., 2016). Because arm cycling is a bilateral motor output it is possible that cortical excitation arising from the active, non-dominant motor cortex could facilitate excitability in the dominant motor cortex, which could reduce the input required to induce a MEP by a given TMS pulse. However, when the strong stimulation intensity was used the changes in MEP/CMEP ratios were less marked and did not increase as cycling intensity increased suggesting a ceiling effect in the MEP amplitudes had been reached.

4.5.3 Differences Between Stimulation Intensities

This study highlights the importance of stimulation intensity selection for experimental design during locomotor outputs. Notably, MEPs continued to increase with cycling intensity up until approximately 200W when elicited with weak stimulation

intensity (10% M_{max}), while they plateaued at approximately 100W under strong (40% M_{max}) stimulation. This led us to conclude that supraspinal excitability increases with increased power output, an effect only observed when a weak stimulus intensity was used. In contrast, using the strong stimulation intensity leads one to believe, perhaps falsely, that spinal factors were driving the change in overall corticospinal excitability as a function of power output, a conclusion also reached by Weavil and colleagues (2015) who used a strong stimulation intensity (MEPs and CMEPs were ~50% M_{max}). The use of a weak stimulation intensity yielded a more precise measure of corticospinal excitability in this specific study as MEPs were less susceptible to ceiling effects than at the strong stimulation.

4.5.4 Methodological Considerations

An important methodological consideration in interpreting the current data is that we did not make the power outputs relative to each individual as we have recently done in two separate studies during arm cycling (Lockyer et al., 2018; Spence et al., 2016). In Spence et al. (2016) we used 5 and 15% of peak power output determined by a sprint test (modified Wingate) while in Lockyer et al (2018) we used 20, 40 and 60% of peak power output determined via a standard incremental aerobic test (20W increases every two minutes; Price et al., 2007). These methods were not without limitations, however. The former used a sprint test to prescribe aerobic cycling intensity at 60 RPM and the latter incremental test resulted in most of the participants reaching a similar peak power output of ~120W. In the present study we used absolute power outputs as has been used by others (Christensen et al., 2000; Weavil et al., 2015) and all participants were able to cycle well above the aerobic

test maximum power output of 120W obtained in our prior work. We were thus able to have participants cycle at supramaximal intensities, albeit we did not quantify exertion levels. Additionally, the sample size of (n = 9) for MEPs and (n = 8) for CMEPs was not determined by a power analysis and therefore, it is unclear whether a larger sample size would have influenced the present results.

4.6 Conclusions

The present study describes the influence of stimulation strength over a wide range of cycling intensities on corticospinal and spinal excitability during arm cycling. We have demonstrated that corticospinal excitability to the biceps brachii is increased with cycling intensity during low power outputs, a finding that is partially mediated by spinal factors. As cycling intensity increases, however, it appears as though supraspinal factors may play more of a role in modulating overall corticospinal excitability. Additionally, this study highlights the importance of stimulation intensity selection to assess corticospinal excitability during motor output. It is concluded that the use of a weaker stimulation intensity provides a more precise measure of corticospinal excitability during locomotor outputs at high intensities as they are less susceptible to potential 'ceiling effects.'

Author Contributions: All authors participated in data collection, analysis, interpretation and manuscript preparation. All authors have approved the submitted version of this manuscript.

Funding: This research was funded by the Natural Sciences and Engineering Research Council of Canada, grant number (NSERC-#RGPIN-2015-05765).

Acknowledgments: This study was supported by PGS-D NSERC funding to E.J.L. as well as NSERC Discovery Grant to K.E.P. We would like to thank Dr. Thamir Alkanani for technical support and the participants for volunteering their time.

Conflicts of Interest: The authors declare no conflict of interest.

Chapter 5: TWO WEEKS OF ARM CYCLING SPRINT INTERVAL TRAINING ENHANCES SPINAL EXCITABILITY TO THE BICEPS BRACHII

Co-Authorship Statement:

Chapter five focuses on Study #3 of the thesis. The ICEHR approval certificate number for this study is ICEHR #20191993. This chapter was published in full in the *Journal of Applied Physiology*: Lockyer EJ, Alizadeh S, Compton CT, Power KE. Two weeks of arm cycling sprint interval training enhances spinal and reduces supraspinal excitability to the biceps brachii. *J Appl Physiol.* 2023 Apr 27. doi: 10.1152/japplphysiol.00367.2022 (copyright license #:5824211476823). Evan Lockyer and Dr. Power conceived and designed the experimental protocols described in this chapter. Evan Lockyer conducted the data collection, with assistance from Shahab Alizadeh (post-doc) and Chris Compton (graduate student). Evan Lockyer performed all data extraction and analysis and completed all statistical analyses, drafted the manuscript, and was responsible for all tables and figures. Evan Lockyer and Dr. Power edited the manuscript, and all authors approved the final version.

5.1 Abstract

The present study aimed to investigate whether a 2-week arm cycling sprint interval training (SIT) program modulated corticospinal pathway excitability in healthy, neurologically intact participants. We employed a pre-post study design with two groups: 1) an experimental SIT group and 2) a non-exercising control group. Transcranial magnetic stimulation (TMS) of the motor cortex and transmastoid electrical stimulation (TMES) of corticospinal axons were used at baseline and post-training to provide indices of corticospinal and spinal excitability, respectively. Stimulus-response curves (SRCs) recorded from the biceps brachii were elicited for each stimulation type during two submaximal arm cycling conditions [(25 watts (W) and 30% peak power output (PPO)]. All stimulations were delivered during the mid-elbow flexion phase of cycling. Compared to baseline, performance on the time-to-exhaustion (TTE) test at post-testing was improved for members of the SIT group but was not altered for controls, suggesting that SIT improved exercise performance. There were no changes in the area under the curve (AUC) for TMS-elicited SRCs for either group. However, the AUC for TMES-elicited cervicomedullary motor evoked potential SRCs were significantly larger at post-testing in the SIT group only (25W: p=0.012, d=0.870; 30% PPO: p=0.016, d=0.825). This data shows that overall corticospinal excitability is unchanged following SIT, while spinal excitability is enhanced. While the precise mechanisms underlying these findings during arm cycling at post-SIT are unknown, it is suggested that the enhanced spinal excitability may represent a neural adaptation to training.

NEW & NOTEWORTHY

Two weeks of arm cycling sprint-interval training (SIT) improves subsequent aerobic exercise performance and induces changes within the descending corticospinal pathway. Specifically, spinal excitability is enhanced following training while overall corticospinal excitability does not change. These results suggest that the enhanced spinal excitability may represent a neural adaptation to training. Future work is required to discern the precise neurophysiological mechanisms underlying these observations.

5.2 Introduction

In humans, indirect evidence using non-invasive stimulation techniques support the notion that aerobic exercise (AE) induces neuroplasticity. Transcranial magnetic stimulation (TMS) has emerged as a non-invasive method for probing potential insights into AE-dependent neuroplasticity within the human brain and descending motor pathways (see El-Sayes et al., (El-Sayes et al., 2019) for review). Paired-pulse TMS paradigms assess the excitability of specific inhibitory and excitatory intracortical interneuronal networks within the primary motor cortex (M1; Di Lazzaro, Restuccia, et al., 1998b; Kujirai et al., 1993) and other motor regions (Mang et al., 2016). Using paired-pulse TMS, extensive evidence shows that M1 excitability is modulated following acute bouts of AE. Specifically, many studies have demonstrated that as little as a single session of low or moderate-intensity AE can transiently reduce intracortical inhibitory networks such as short-interval intracortical inhibition (SICI; Singh et al., 2014; Singh & Staines, 2015; Yamaguchi et al., 2012) and long-interval intracortical inhibition (LICI; Mooney et al., 2016), and enhance intracortical facilitatory networks such as intracortical facilitation (ICF; Singh et al., 2014).

Single-pulse TMS provides an instantaneous measure of the excitability of the corticospinal pathway, which includes the excitability of intracortical interneurons, corticospinal motoneurones, as well as the alpha-motoneurones within the spinal cord (Rossini et al., 2015). As such, overall corticospinal excitability is influenced by the excitability of neurons at both the supraspinal and spinal level, making it difficult to determine the precise locus of change when using single-pulse TMS alone (Lockyer et al., 2021). Studies using single-pulse TMS report conflicting results, as some studies show

increases in corticospinal excitability following single sessions of AE (Lulic et al., 2017; MacDonald et al., 2019; Opie & Semmler, 2019), while others show no change (Andrews et al., 2020; El-Sayes et al., 2020; McDonnell et al., 2013; Neva et al., 2017; Smith et al., 2014). This lack of consistency between studies has been attributed to many factors (Ridding & Ziemann, 2010), including the intensity of the AE performed (Andrews et al., 2020; MacDonald et al., 2019). Specifically, emerging evidence suggests that higher intensity AE induces greater and more consistent neuroplasticity than traditional lower intensity AE (Andrews et al., 2020; MacDonald et al., 2019; MacInnis & Gibala, 2017; McDonnell et al., 2013; Nicolini et al., 2021; Opie & Semmler, 2019).

While it is becoming clear that acute high intensity AE induces neuroplasticity, substantially less information is known regarding changes that occur in these pathways following repeated sessions of AE training. To date, there is only one study that has examined the effects of repeated AE interventions on corticospinal excitability in healthy, neurologically intact humans (Nicolini et al., 2019). In this study, Nicolini and colleagues used 6 weeks of high-intensity interval training (HIIT), a form of intense AE, to investigate whether a relatively short-term lower body AE training program was capable of inducing changes in corticospinal excitability and intracortical circuitry assessed by TMS from the first dorsal interosseous (FDI) in sedentary male participants. Participants performed five 1-minute leg cycling bouts at intensities equal to approximately 105-135% of their individual peak power outputs three times per week for the 6 weeks. Following the 6-week HIIT program, the authors reported a 12% increase in cardiorespiratory fitness level, a finding that was not accompanied by changes in either corticospinal excitability or SICI. However, the authors did find a reduction in ICF following the 6 weeks of leg cycling HIIT

and suggested that the corticospinal system may indeed be modulated following relatively short-term AE training. Importantly however, this study did not include a measure of spinal excitability. Thus, it remains unclear whether changes in spinal excitability may occur following periods of repeated AE training. Given that corticospinal excitability is influenced by factors at the cortical, spinal, and peripheral levels, it is possible that changes in spinal excitability may occur following repeated AE training in the absence of changes in overall corticospinal excitability. Furthermore, whether other forms and modes of repeated AE training may induce similar neuroplastic adaptations within the corticospinal pathway remains unknown as well.

Studies that examine corticospinal adaptations following either acute or repeated AE typically record responses from a non-exercised muscle while at rest or during an isometric contraction (El-Sayes et al., 2019; El-Sayes et al., 2020; Lulic et al., 2017; McDonnell et al., 2013; Neva et al., 2017; Neva et al., 2021; Opie & Semmler, 2019; Singh et al., 2014; Singh & Staines, 2015). Very few studies have recorded changes in excitability from a muscle that was actively engaged in the previously performed AE (Yamaguchi et al., 2012). As such, the changes in excitability observed in these studies may not be representative of changes that occur in muscles that are actively engaged in the AE training or *during* performance of the AE task. This is of importance given that corticospinal and spinal motoneurone excitability are state- (i.e., rest vs active), task- (i.e., tonic vs dynamic vs locomotor), and muscle-dependent (Lockyer et al., 2021; Power et al., 2022; Power et al., 2018). It is therefore important to examine potential changes in corticospinal pathway excitability following AE: 1) *during* the motor output used for training, and 2) from a muscle actively engaged in said motor output.

Sprint interval training (SIT) is a form of high-intensity AE that is characterized by repeated “all-out” or “supramaximal” sprint bouts (<30 seconds) separated by relatively longer periods of passive or active recovery (Burgomaster et al., 2006; Burgomaster et al., 2005; Gibala et al., 2006; MacInnis & Gibala, 2017). Despite the much shorter time commitment and lower training volume, SIT has been shown to induce similar performance, metabolic, and musculoskeletal adaptations to more traditional low and moderate-intensity forms of AE (Burgomaster et al., 2005; Gibala et al., 2006). For example, Gibala and colleagues have reported that as little as six sessions of leg cycling SIT performed over a 2-week period induces similar improvements in exercise performance, muscle oxidative capacity, and muscle buffering capacity as traditional high volume AE training performed over the same training period (Gibala et al., 2006). It is currently unknown whether similar low volume SIT protocols are capable of inducing changes within the corticospinal pathway. However, given that the intensity of AE has been suggested to be a key determinant of AE-induced neuroplasticity (Andrews et al., 2020), it is plausible that the high-intensity nature of SIT may be a potent stimulator for corticospinal pathway adaptation following training. This has not yet been investigated.

Although less common than leg cycling, arm cycling is a frequently used form of AE that involves rhythmic contractions of muscles in both upper limbs to produce the intended motor output (Lockyer et al., 2021; Power et al., 2018; Zehr, 2005; Zehr & Kido, 2001). Over the past ~10 years, research from our laboratory has examined the influence of various forms and modes of arm cycling on the modulation of corticospinal pathway excitability (Copithorne et al., 2015; Forman et al., 2014; Forman et al., 2019; Forman et al., 2015; Forman, Richards, et al., 2016; Power & Copithorne, 2013). To date however,

no studies have examined the effects of repeated sessions of arm cycling AE training on the modulation of corticospinal pathway excitability. Thus, the purpose of the present study was to investigate whether 2 weeks of arm cycling SIT could induce changes in corticospinal excitability assessed *during* arm cycling (the trained motor output). To do this, we employed a pre- vs post-test design including an experimental group who performed 2 weeks of arm cycling SIT (i.e., SIT group) and a non-exercising control group (CTL). At baseline and post-testing, stimulus-response curves (SRCs) recorded from the biceps brachii were created using TMS and transmastoid electrical stimulation (TMES) during submaximal arm cycling to assess corticospinal and spinal excitability, respectively. We hypothesized that 2 weeks of arm cycling SIT would result in: 1) improved capacity to perform AE (i.e., improved peak power output), and 2) increased corticospinal and spinal excitability (i.e., the area under the curve (AUC) of SRCs would be greater following SIT).

5.3 Methods

5.3.1 Participants

A total of twenty-four healthy males (n = 17) and females (n = 7) volunteered to participate in this study. All participants were physically active and took part in some form of recreational exercise at least two to three times per week. Exclusion criteria consisted of having any known neurological impairment or if participants had a previous history of upper limb injury or pain that prevented them from completing vigorous exercise. Participants were screened for contraindications to magnetic stimulation using a magnetic safety checklist (Rossini et al., 2015), and for exercise using the Physical Activity Readiness Questionnaire Plus (PARQ+; Bredin et al., 2013). Hand dominance was

determined using a modified Edinburgh Handedness Inventory (Oldfield, 1971), as neurophysiological responses were measured at baseline and at post-testing from the dominant limb (see *Experimental protocol* below). Using this inventory, it was determined that 20 of the 24 participants were right-hand dominant. All testing and exercise procedures were fully explained, and participants provided informed written consent prior to starting the study. All experimental protocols conformed to the Declaration of Helsinki and were approved by the Interdisciplinary Committee on Ethics in Human Research at Memorial University of Newfoundland (ICEHR #20191993). Moreover, all procedures were performed in agreement with the Tri-Council guidelines in Canada.

5.3.2 General Experimental Protocol

This study used a pre- to post-test design using an experimental group (i.e., SIT) and a control group (i.e., CTL) to investigate whether a 2-week arm cycling Wingate style SIT program could induce changes within the descending corticospinal pathway. In general, the experimental protocol consisted of three phases (**Figure 5.1A**): (i) baseline testing (following a familiarization procedure), (ii) a 2-week period of either sprint interval training (SIT group) or no sprint interval training (CTL group), and (iii) post-testing. The testing procedures at post-testing were identical in all respects to those performed at baseline. Given that corticospinal excitability is task- and state-dependent (Lockyer et al., 2021; Power et al., 2022; Power et al., 2018), all neurophysiological data was recorded during submaximal arm cycling prior to and following training to assess whether changes

in corticospinal pathway excitability occurred. All procedures are described in more detail below.

5.3.2.1 Familiarization Procedures.

Prior to taking part in baseline measurements, all participants partook in a familiarization session to become acclimated with the testing procedures and exercise tests. The familiarization day was performed at least 24 hours prior to baseline testing. During the familiarization session, participants practiced arm cycling while maintaining a specified cadence of 60 revolutions per minute (rpm) and were given multiple stimulations from each of the three neurophysiological stimulation techniques used at baseline and post-testing (see below). Prior to leaving the laboratory, participants in the SIT group were asked to complete one or two maximal effort arm cycling sprints to ensure they were familiar with the sprinting procedures.

5.3.2.2 Baseline Testing.

At baseline, all participants completed two separate sessions in the same order: 1) a graded arm cycling time-to-exhaustion (TTE) test and 2) a neurophysiological testing session performed during submaximal arm cycling. These sessions were completed over separate days with at least 24 hours between sessions. Participants were encouraged to consume water prior to, during, and following each testing and exercise session.

The TTE test was performed on a computer-controlled, electrically braked cycle ergometer that had been modified for arm cycling (Velotron, RacerMate, WA; **Figure**

5.1B). Following a brief 3-minute warm-up at a self-selected cadence and a constant power output of 25W, participants were asked to cycle to volitional fatigue (Smith et al., 2004). Participants were situated at a comfortable distance from the crankshaft of the ergometer so that they were not reaching, and the chair was manipulated so that the participant's shoulders were approximately in line with the axis of rotation. This chair positioning was recorded for each participant and was subsequently used at post-testing. Participants were asked to cycle in an asynchronous pattern with their forearms in a pronated position and were asked to maintain a constant cadence of 70 rpm throughout the duration of the test. Visual feedback of the cadence was provided on a computer screen in front of participants. The test commenced with an initial workload of 50W and increased 1W every 6 s until participants could no longer maintain the 70 rpm (Smith et al., 2004). Participants were provided with verbal encouragement throughout the test and were told "to go as long as they possibly could". The test was terminated when the participants were unable to maintain a cadence of 70 rpm for five seconds despite encouragement from the research team to speed up. Peak power (in Watts) obtained prior to test termination as well as the duration of the test (in seconds) were recorded and used as indices of TTE performance at baseline and post-testing.

On a separate day (~24-48 hours following completion of the TTE test), stimulus-response curves (SRCs) were created during arm cycling using single-pulse transcranial magnetic stimulation (TMS) and transmastoid electrical stimulation (TMES), providing measures of corticospinal and spinal excitability, respectively. Participants were situated upright on a SCIFIT arm cycle ergometer (model PRO2 Total Body, Tulsa, OK, USA) in a manner similar to previous studies from our laboratory (Alcock et al., 2019; Forman et

al., 2014; Lockyer et al., 2018; Lockyer, Hosel, et al., 2019; Nippard et al., 2020) (**Figure 5.1C**). The chair height and distance were manipulated to ensure participants were not reaching and that their shoulders were approximately aligned with the axis of rotation of the crankshaft of the ergometer. Participants performed asynchronous arm cycling with their forearms in a pronated position and were asked to wear wrist braces as to limit flexion-extension movements about the wrist joint. Once positioned on the ergometer, the stimulation intensities for each stimulation technique (see below) were set for each participant. Next, participants completed two submaximal arm cycling conditions comprising eight trials each (16 trials total). These two cycling conditions consisted of maintaining a cadence of 60 rpm at: 1) a constant power output of 25W, and 2) a relative power output of 30% peak power which was obtained from the preceding TTE performed during baseline session #1. The 25W condition was performed as this is the standard power output employed in many previous studies from our laboratory (Forman et al., 2014; Forman et al., 2015; Lockyer et al., 2021) and the 30% PPO condition was performed to provide a relative measure for each participant. The order in which participants completed each condition (i.e., 25W vs 30% PPO) was randomized for each session. Within each condition, SRCs for TMS and TMES were created by using eight experimental stimulation intensities made relative to active motor threshold (AMT) ranging from subthreshold to almost two times suprathreshold (see below). Each trial consisted of 8 TMS, 8 TMES, and 2 M_{max}, which were elicited during arm cycling as the dominant hand passed the 6 o'clock position (Forman et al., 2014; Forman et al., 2015; Lockyer et al., 2018; Lockyer, Hosel, et al., 2019; Spence et al., 2016). Trials lasted approximately two minutes and one minute rest periods were provided between trials to limit the onset of fatigue.

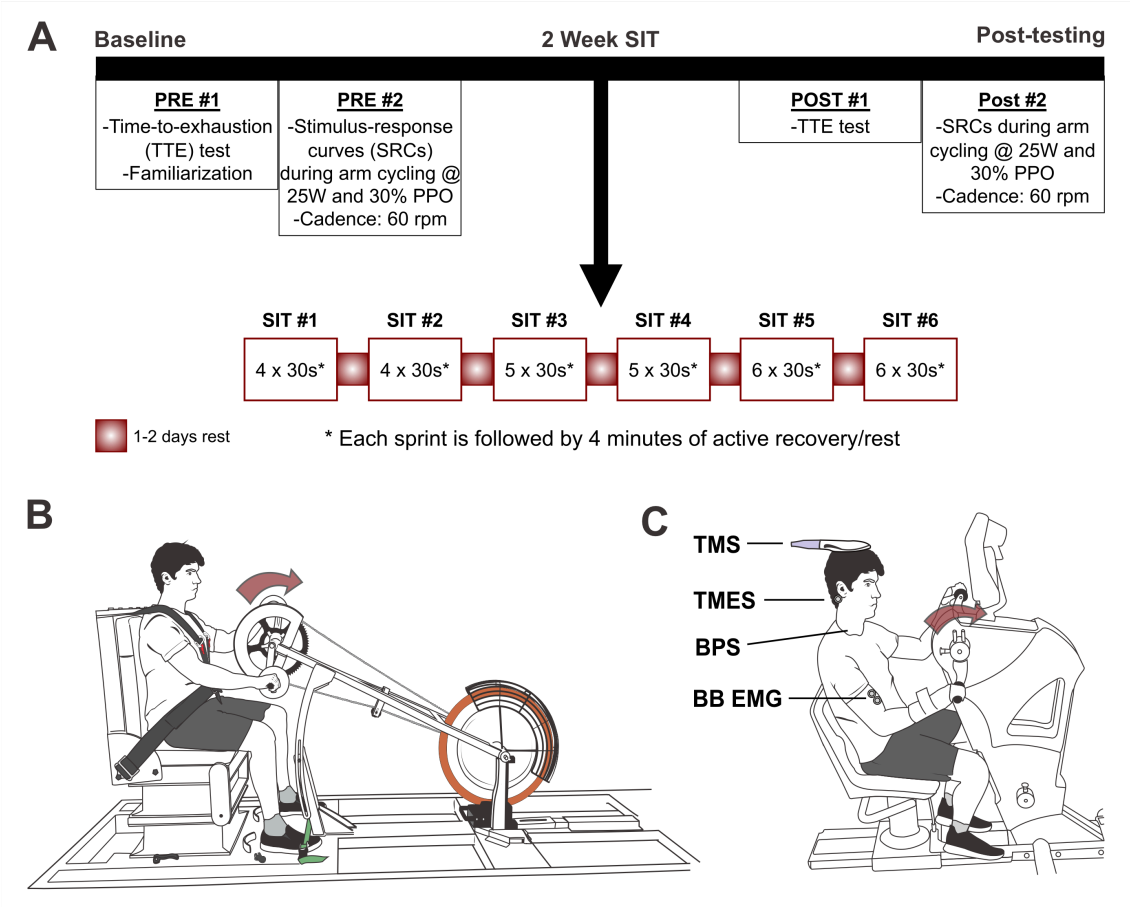

Figure 5.1: Experimental setup.

(A) Experimental timeline. **(B)** Experimental setup for the TTE at baseline and post-testing as well as the setup for the 2-week SIT program (SIT group only). **(C)** Experimental setup for baseline and post-testing day #2 where MEP and CMEP SRCs were created during arm cycling at 25W and 30% PPO.

5.3.2.3 Post-Testing.

The baseline testing procedures described above were replicated for all participants at post-testing. Post-testing sessions commenced approximately 48 hours following the 2-week training (SIT group) or no training (CTL group) period and were completed at the

same time of day (± 1 hr) as baseline testing sessions. This was done as to avoid potential fluctuations in performance and/or neurophysiological measures (Tamm et al., 2009). The 30% PPO cycling intensity used for neurophysiological testing on post-testing session #2 was taken from each participant's results on the TTE test performed at post-testing and not from baseline. This was done to account for any changes in power output that may have occurred following SIT for the SIT group and between days for the CTL group.

5.3.2.4 Electromyography (EMG).

At baseline and post-testing sessions #2, surface EMG was recorded from the dominant arm biceps brachii and triceps brachii using pairs of disposable Ag-AgCl electrodes (MediTraceTM 130 foam electrodes with conductive adhesive hydrogel, Covidien IIC, MA, USA; interelectrode distance: ~2 cm). The electrodes were positioned in a bipolar configuration over the midline of the biceps brachii and the lateral head of the triceps brachii. A ground electrode was placed on the lateral epicondyle of the dominant arm. Prior to electrode placement, the skin was shaved using a disposable handheld razor, lightly abraded using abrasive pads, and was cleansed with isopropyl alcohol swabs. EMG signals were amplified (x300; CED 1902 amplifier; Cambridge Electronic Design Ltd., Cambridge, UK), band-pass filtered using a 3-pole Butterworth filter (10-1000Hz) and were sampled at a rate of 2000 Hz using Signal 5.11 software and the analog-digital CED 1401 interface (Cambridge Electronic Design Ltd., Cambridge, UK).

5.3.2.5 Brachial Plexus Stimulation.

Prior to commencing the cycling conditions (described above), maximum compound muscle action potentials (M_{max}) were elicited via electrical stimulation to the brachial plexus at Erb's point during arm cycling at 60 rpm and a constant power output of 25W. Erb's point was electrically stimulated via self-adhesive Ag-AgCl electrodes (10 mm diameter) fixed to the skin over the supraclavicular fossa (cathode) and the acromion process (anode). Single rectangular current pulses (200-µs duration, 90–320 mA) were delivered via a constant current stimulator (DS7AH, Digitimer Ltd, Welwyn Garden City, UK) and were triggered automatically during arm cycling when the dominant arm passed the 6 o'clock (mid-elbow flexion) position. The electrical current was gradually increased until the M-wave in the biceps brachii (the main muscle of interest) reached a plateau. The stimulator intensity that elicited the plateau in the M_{max} was then increased by 20% and used for the remainder of the study to ensure that the M_{max} was truly maximal and remained maximal throughout the duration of the study (Crone et al., 1999).

5.3.2.6 Transcranial Magnetic Stimulation (TMS).

At baseline and post-testing sessions #2, TMS was applied over vertex of the motor cortex with a monophasic, single-pulse stimulator (Magstim200^2, Magstim, Whitland, UK) to elicit motor evoked potential (MEP) SRCs in the dominant limb biceps brachii. The vertex was measured and marked on the participant's scalp with a felt-tip dry-erase marker. The circular coil (13.5 cm diameter) was held firmly in place over vertex against the participant's skull and parallel to the ground, with the direction of current set to

preferentially activate the left or right motor cortex depending on participant hand dominance. The same researcher held the coil throughout the experiment. This stimulation method is commonly used for measurements taken from the biceps brachii during various types of contractions, including arm cycling (Forman et al., 2014; Forman et al., 2018; Forman et al., 2015; Taylor et al., 1997; Taylor et al., 2002). TMS intensity was set relative to AMT and was determined separately during submaximal arm cycling at 60 rpm for both the 25W and 30% PPO conditions. AMT was defined as the lowest percentage of maximal stimulator output (MSO) that could evoke visible, discernable MEPs from the biceps brachii surface EMG trace in 50% of the trials (4 out of 8). The intensity of stimulation was initially set to 30% MSO and was adjusted until AMT was determined. Once determined, TMS pulses were automatically triggered when the dominant hand passed the 6 o'clock position (i.e., mid-elbow flexion) during arm cycling when biceps brachii activity is highest (Chaytor et al., 2020). MEP SRCs were obtained during arm cycling by delivering eight TMS pulses at intensities of 85%, 100%, 115%, 130%, 145%, 160%, 175% and 190% of AMT in a randomized order (Forman et al., 2018).

5.3.2.7 Transmastoid Electrical Stimulation (TMES).

Self-adhesive surface Ag-AgCl electrodes were placed on the skin at the back of the skull, in the grooves between the mastoid process and the occipital bone (Taylor, 2006; Taylor & Gandevia, 2004; Taylor et al., 2002). Electrical stimulation (200 μs pulse-width duration; DS7AH, Digitimer Ltd., Welwyn Garden City, Hertfordshire, UK) was delivered between these electrodes to activate corticospinal axons at the cervicomedullary junction

to elicit CMEPs in the dominant arm biceps brachii. To evoke CMEP SRCs, the same procedures described above for MEP SRCs were followed at baseline and post-testing. Similar to the threshold setting for TMS, AMT for TMES was determined for both cycling intensities (i.e., 25W and 30% PPO) separately. At each cycling intensity, TMES AMT was defined as the minimum stimulation intensity that could evoke a discernable CMEP response in 50% of the trials (i.e., 4 out of 8). The intensity of stimulation was initially set to 50 mA of current and was adjusted until threshold was determined. Once determined, CMEP SRCs were created by giving eight TMES pulses at intensities of 85%, 100%, 115%, 130%, 145%, 160%, 175% and 190% of AMT in a randomized order. CMEP latencies were monitored throughout the protocol to ensure that ventral root activation (evidenced by a reduction in latency by ~2 ms) was avoided (McNeil et al., 2013; Taylor & Gandevia, 2004).

5.3.2.8 Two-week Sprint Interval Training Protocol.

For the participants in the SIT group, the training protocol started ~48 hours after completion of baseline testing session #2 and followed a slightly modified but similar protocol to those used in previous SIT studies (Burgomaster et al., 2005; Gibala et al., 2006). The training consisted of six sprinting sessions over a ~14-day period, with 24-48 hours between each session. Each sprinting session consisted of i) a 5-minute warm-up on an arm cycle ergometer (SCIFIT ergometer, model PRO2 Total Body, Tulsa, OK, USA) at a self-selected cadence and a constant power output of 40W, ii) four-to-six repeated 30-second maximal effort arm cycling sprints on the Velotron ergometer (Velotron,

Racermate, WA), and iii) a 3-to-5-minute cool-down following completion of the sprints. Each sprint was performed against a resistance equal to 5% of each participant's body weight (in Kg) (Forbes et al., 2014) and was interspersed with 4 minutes of recovery (rest or very light arm cycling against no resistance) (Burgomaster et al., 2005). The training regime was progressive in nature, in that the number of sprints increased by one every 2 sessions of training. Participants started by completing four maximal effort sprints on sprinting sessions 1 and 2, five on sprinting sessions 3 and 4, and six on sprinting sessions 5 and 6 (Burgomaster et al., 2005; Gibala et al., 2006). For all sprints, participants were given 20 seconds to "ramp-up" their cadence to 100 revolutions per minute (rpm) and were asked to hold that cadence until the sprint commenced. This "ramp-up" period was factored into the rest/recovery period following the repeated sprinting and was performed at a resistance of 10W. Participants were able to track their cadence on a computer monitor and feedback was provided from the researchers to ensure the correct cadence. Immediately prior to the start of each sprint, a member of the research team would perform a 3-second countdown and inform the participants to prepare to "go as hard and as fast as you possibly can". At the onset of the sprint, the appropriate load was applied to the braking system of the ergometer by a computer interfaced with the associated Velotron Wingate software (Racermate, Seattle, WA, USA). Participants were verbally encouraged to pedal as fast as possible throughout each 30-second effort. Heart rate and rate of perceived exertion (RPE) were recorded at rest prior to and following each sprint. Performance outcome measures, including peak and mean power, total work, and fatigue index were also recorded from each sprint using the Racermate software (data not shown).

5.3.3 Data Analysis

TTE and sprint performance measures were determined using the associated Velotron Charts and Wingate software, respectively. Peak power (in Watts) and duration (in seconds) obtained at the completion of the test was recorded for each participant and was used as a measure of TTE performance at each time point (i.e., baseline and post-testing).

Neurophysiological data was analyzed offline using Signal 5.11 software (CED). Stimulation intensities used to elicit AMT for both TMS and TMES were manually determined for each cycling intensity and were recorded for each participant. Peak-to-peak amplitudes of MEPs, CMEPs, and M_{max} of the biceps brachii were measured during each cycling trial from the initial deflection of the voltage trace from the background EMG to the return of the trace to background levels. The mean, standard deviation (SD) and coefficient of variation (CV = 100 x SD/mean) values were computed for the 8 MEP and 8 CMEP amplitudes evoked at each stimulation intensity (from 85%-190% AMT) during arm cycling for both groups. Following analysis, MEP and CMEP SRCs were constructed for each participant at each time point (i.e., baseline and post-testing) for both cycling intensities (i.e., 25W and 30% PPO). To create the SRCs for each cycling intensity, the mean peak-to-peak amplitude of MEPs and CMEPs for each trial were plotted against the eight stimulation intensities used (i.e., 85-190% AMT in 15% increments). Subsequently, the area under the curve (AUC) for each SRC was obtained by trapezoidal integration of the curve's function using Prism 9 for MacOS (version 9.2.0; GraphPad Software LLC, CA, USA) (Nicolini et al., 2019). The AUC values were then normalized to the average of

the 2 M_{max} amplitudes recorded for each cycling condition. Normalized AUC values for each cycling intensity were then compared between baseline and post-testing for both groups. This was done to observe whether the 2-week training program elicited changes in corticospinal pathway excitability (Peri et al., 2017).

Biceps and triceps brachii pre-stimulus EMG activity was recorded immediately prior to the stimulus artifact during all arm cycling trials (i.e., 25W and 30% PPO). Triceps brachii pre-stimulus EMG was recorded to determine if the amount of triceps brachii activity was similar between stimulation intensities used to create the SRCs during arm cycling. Similar to previous reports from our lab (Forman et al., 2014; Forman et al., 2015; Lockyer et al., 2018; Spence et al., 2016), pre-stimulus EMG was defined as the mean of the rectified EMG trace measured over a 50 ms window immediately prior to the stimulation artifact for each stimulation type (TMS and TMES) (Forman et al., 2015; Lockyer, Hosel, et al., 2019; Power et al., 2018; Spence et al., 2016). Raw pre-stimulus EMG data (in mV) for each stimulation intensity (85-190% AMT) was normalized to the amplitude of the M_{max} within each trial using the equation: normalized pre-stimulus EMG = raw EMG/M_{max} amplitude x 100%. These values were then averaged across all stimulation intensities within a stimulation type (i.e., TMS or TMES) to yield the collective average pre-stimulus EMG value for each stimulation type. For example, the mean rectified EMG was obtained for each stimulation intensity (8 values in total from the 85% to 190% AMT conditions) prior to TMS at 25W. These values were then averaged to yield the overall mean pre-stimulus EMG prior to TMS at 25W and were subsequently used in the analysis. The same procedures were followed to calculate the overall mean pre-stimulus

EMG for TMES and for baseline and post-testing conditions. This normalization procedure was performed to allow a comparison of pre-stimulus EMG data between days and groups.

5.3.4 Statistical Analysis

Statistical analyses were performed offline on group data using SPSS software (Version 26.0, IBM Corp., Armonk, NY). Prior to statistical comparisons, all variables were tested for normality using the Shapiro-Wilk test. All data were found to be normally distributed. Homogeneity of variance was checked using Levene's test and was assumed for each variable. At baseline, independent sample *t*-tests with Welch's correction were performed on participant characteristics and TTE performance outcome measures (peak power and duration) to assess whether there were differences between groups prior to starting the study. Hedge's *g* was computed to determine the effect size of significant comparisons. To examine the absolute and relative variability in evoked response amplitudes during arm cycling between groups and across stimulation intensities (85-190% AMT), we statistically compared the SDs and CVs of the eight MEP and CMEP amplitudes measured at baseline using separate two-way mixed model ANOVAs (Darling et al., 2006). To assess changes in the TTE performance, M_{max} amplitudes, AMT for TMS and TMES, MEP and CMEP AUC values, and pre-stimulus EMG values between groups from baseline to post-testing, separate two-way mixed model ANOVAs with between-group factor of GROUP (SIT vs CTL) and within-group factor of TIME (baseline and post-testing) were computed for each variable. In cases where the assumption of sphericity was violated, the

degrees of freedom were adjusted using the Greenhouse-Geisser correction. Partial eta squared (η_p^2) was used to determine the effect size of significant effects for ANOVAs (small: ≤ 0.06, medium: 0.07-0.14, large: >0.14) (Cohen, 1988). When significant interactions of both factors (GROUP x TIME) were found, paired *t*-tests with the Bonferroni correction were performed for each group between baseline and post-testing to determine where the significant difference existed. For these analyses, effect sizes were calculated from baseline vs post-testing comparisons for each group using Cohen's *d* (small: ≤0.2, medium: >0.2, large: ≥0.8) (Cohen, 1988). Correlation analyses were used to determine if there was a relationship between changes in TTE performance (i.e., percent changes in power output and duration) and neurophysiological data (i.e., percent changes in MEP and CMEP AUC values) for both groups. For all analyses, statistical significance was set at $p < 0.05$ and data are reported as means ± SD.

5.4 Results

Twenty-four participants volunteered to participate but three did not complete the entire intervention. Reasons for dropout were: i) scheduling conflicts (n = 2) and ii) an injury obtained outside of the study (n = 1). Out of the remaining twenty-one participants who completed the experiment, twelve participants were assigned to a SIT group and nine were assigned to a CTL group.

5.4.1 Baseline Measures

Table 5.1 summarizes all baseline outcome measures for each group. At baseline, Welch's t-tests revealed no significant differences in participant demographics (i.e., age, height, and weight), TTE performance (i.e., peak power output and duration), or stimulation intensities at AMT (for both TMS and TMES) between groups ($p > 0.05$ in all cases).

Table 5.1. *Characteristics for each group at baseline*

Participant Characteristics	SIT	CTL	SIT vs CTL
n (M/F)	12 (9/3)	9 (6/3)	–
Age (yrs)	24.5 ± 3.8	23.4 ± 3.3	$p = 0.504$
Height (cm)	178.1 ± 9.0	173.1 ± 8.7	$p = 0.213$
Weight (kg)	83.8 ± 10.1	81.6.1 ± 14.2	$p = 0.700$
TTE peak power output (W)	128 ± 25.0	125 ± 29.7	$p = 0.738$
TTE duration (s)	477 ± 151.6	449 ± 179.0	$p = 0.711$
TMS AMT_{25W} (%MSO)	32.3 ± 6.9	32.3 ± 6.6	$p = 0.999$
TMES AMT_{25W} (mA)	110 ± 14.1	101 ± 12.5	$p = 0.119$

TMS $AMT_{30\%\ PPO}$ (%MSO)	31.6 ± 7.1	32.0 ± 6.7	$p = 0.893$
TMES $AMT_{30\%\ PPO}$ (mA)	111 ± 14.0	101 ± 11.0	$p = 0.095$

5.4.2 Time-to-Exhaustion Performance

Results from the 2-way mixed model ANOVA revealed significant main effects of TIME on TTE peak power output ($F_{(1,19)} = 6.924$, $p = 0.016$, $\eta_p^2 = 0.267$) and TTE duration ($F_{(1,19)} = 6.017$, $p = 0.024$, $\eta_p^2 = 0.241$), as well as significant GROUP x TIME interaction effects (peak power output: $F_{(1,19)} = 12.799$, $p = 0.002$, $\eta_p^2 = 0.402$; duration: $F_{(1,19)} = 10.498$, $p = 0.004$, $\eta_p^2 = 0.356$). At post-testing, members of the SIT group produced 7.0% ($p = 0.003$, $d = 1.11$) greater peak power output and were able to last 12.1% ($p = 0.005$, $d = 1.01$) longer on the TTE test compared to baseline. In contrast, TTE peak power output and duration were not significantly different from baseline at post-testing for the CTL group (peak power output: $p = 0.271$; duration*:* $p = 0.569$) (**Figure 5.2**).

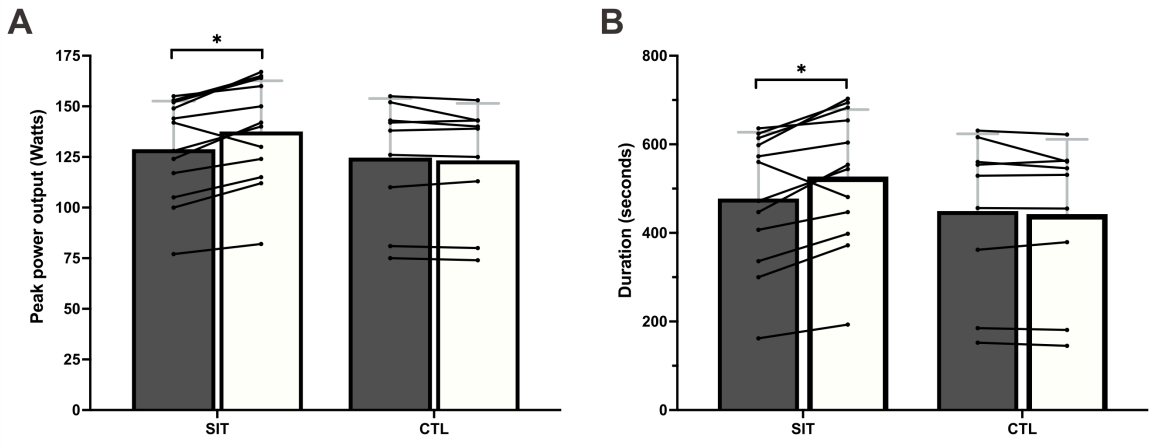

Figure 5.2: Time-to-exhaustion test performance.

Group-averaged (mean ± SD) peak power output **(A)** and duration **(B)** on the TTE test at baseline (grey column) and at post-testing (white column). For both groups, individual participant data at baseline and post-testing are portrayed by the lines. * denotes a significant difference from baseline to post-testing.

5.4.3 Active Motor Thresholds

The group-average stimulation intensities required to elicit AMT for TMS and TMES are displayed in Table 5.2 for both groups at each timepoint. Results from the two-way mixed model ANOVA revealed no significant GROUP x TIME interaction effect for the intensity of TMS required to elicit AMT at 25W ($F_{(1, 19)} = 0.038$, $p = 0.848$), or 30% PPO ($F_{(1, 19)} = 0.783$, $p = 0.387$). Similarly, there was no significant interaction effect for the intensity of TMES required to elicit AMT at 25W ($F_{(1, 19)} = 0.560$, $p = 0.463$), or 30% PPO ($F_{(1, 19)} = 0.007$, $p = 0.936$). Therefore, stimulation intensities at AMT for either stimulation type did not statistically differ between groups and was unchanged at post-testing.

Table 5.2. *Group means (± SD) for neurophysiological outcome measures between groups*

Measure	SIT group (n = 12)		
	Baseline	Post-testing	Baseline vs Post
TMS AMT_{25W} (%MSO)	32.3 ± 6.9	32.8 ± 6.7	p = 0.626
TMES AMT_{25W} (mA)	110.0 ± 14.1	114.6 ± 19.0	p = 0.282
TMS $AMT_{30\%\ PPO}$ (%MSO)	31.6 ± 7.1	32.5 ± 6.4	p = 0.272
TMES $AMT_{30\%\ PPO}$ (mA)	110.9 ± 14.0	110.2 ± 18.6	p = 0.538
MEP AUC_{25W}	29.8 ± 13.3	27.7 ± 13.1	p = 0.526
CMEP AUC_{25W}	**22.8 ± 6.1**	**34.4 ± 12.4***	***p* = 0.012, *d* = 0.870**
MEP $AUC_{30\%\ PPO}$	38.9 ± 15.4	38.5 ± 14.4	p = 0.879
CMEP $AUC_{30\%\ PPO}$	**28.3 ± 8.6**	**39.2 ± 13.7***	***p* = 0.016, *d* = 0.825**
M_{max} $amplitude_{25W}$ (mV)	11.8 ± 4.0	12.3 ± 4.6	p = 0.294
$M_{max}amplitude_{30\%PPO}$ (mV)	11.5 ± 3.9	12.2 ± 4.6	p = 0.219
	CTL group (n = 9)		
	Baseline	Post-testing	Baseline vs Post
TMS AMT_{25W} (%MSO)	32.3 ± 6.6	32.6 ± 5.3	p = 0.827
TMES AMT_{25W} (mA)	101 ± 12.5	97.2 ± 11.1	p = 0.342
TMS $AMT_{30\%\ PPO}$ (%MSO)	32.0 ± 6.7	31.7 ± 4.7	p = 0.796
TMES $AMT_{30\%\ PPO}$ (mA)	101 ± 11.0	99.0 ± 11.2	p = 0.441
MEP AUC_{25W}	29.4 ± 11.6	32.2 ± 14.9	p = 0.331
CMEP AUC_{25W}	31.4 ± 13.7	30.1 ± 10.9	p = 0.422
MEP $AUC_{30\%\ PPO}$	37.7 ± 15.3	37.2 ± 17.0	p = 0.881
CMEP $AUC_{30\%\ PPO}$	36.2 ± 13.1	32.8 ± 743	p = 0.242
M_{max} $amplitude_{25W}$ (mV)	11.6 ± 4.8	12.1 ± 5.3	p = 0.452
$M_{max}amplitude_{30\%PPO}$ (mV)	11.3 ± 4.5	11.9 ± 5.0	p = 0.519

5.4.4 MEP and CMEP Response Variability at Baseline

The average SDs and CVs for each group during 25W cycling at baseline are shown in Table 5.3. To provide insight on the absolute variability, the results from the mixed model ANOVA on SD values for MEP amplitudes revealed a significant main effect of stimulation intensity ($F_{(2.55, 48.55)} = 13.692$, $p < 0.001$, $\eta_p^2 = 0.419$), but no GROUP x STIM interaction effect ($F_{(2.55, 48.55)} = 0.197$, $p = 0.419$). Results from the mixed model ANOVA on SD values for CMEP amplitudes followed a similar pattern. There was a significant main effect of stimulation intensity ($F_{(3.75, 71.29)} = 30.0112$, $p < 0.001$, $\eta_p^2 = 0.612$), but no GROUP x STIM interaction effect ($F_{(3.75, 71.29)} = 0.970$, $p = 0.426$). For both MEP and CMEP ANOVAs, pairwise comparisons indicated that SD values were significantly smaller at the lower stimulation intensities (100 and 115 AMT, p values < 0.05), but began to increase as stimulation intensity increased (130-190% AMT, p values > 0.05). For ease of the reader, individual pairwise comparisons are not shown.

For CV values, results from the mixed model ANOVA for MEP amplitudes revealed a significant main effect of stimulation intensity ($F_{(4.29, 81.57)} = 34.541$, $p < 0.001$, $\eta_p^2 = 0.645$), but no GROUP x STIM interaction ($F_{(4.29, 81.57)} = 0.177$, $p = 0.956$). Similarly, results from the mixed model ANOVA on CV values for CMEP amplitudes revealed a significant main effect of stimulation intensity ($F_{(3.94, 74.81)} = 48.621$, $p < 0.001$, $\eta_p^2 = 0.719$), but no GROUP x STIM interaction ($F_{(3.94, 74.81)} = 0.408$, $p = 0.799$). For both MEP and CMEP ANOVAs, pairwise comparisons indicated that CV values were largest at lower stimulation intensities (100-130% AMT, p values < 0.001) and gradually decreased as

stimulation intensity increased (145-190% AMT, p values > 0.05). For ease of the reader, individual pairwise comparisons are not shown.

Table 5.3. *SD and CV for MEP and CMEP amplitudes during 25W arm cycling*

	Stimulation Intensity (%AMT)							
	85%	100%	115%	130%	145%	160%	175%	190%
SD of MEP amplitudes (mV)								
SIT	0.0	0.20	0.46	0.61	0.63	0.75	0.71	0.93
CTL	0.0	0.21	0.39	0.60	0.67	0.74	0.78	0.92
Combined	0.0	0.20	0.44	0.62	0.68	0.78	0.77	0.93
CV of MEP amplitudes (%)								
SIT	–	34.4	34.9	28.0	16.5	16.3	15.2	16.8
CTL	–	37.1	37.0	32.4	21.7	18.1	18.4	17.8
Combined*	–	35.6	35.8	29.9	18.7	17.0	16.6	17.3
SD of CMEP amplitudes (mV)								
SIT	0.0	0.15	0.47	0.55	0.67	0.65	0.84	0.63
CTL	0.0	0.16	0.45	0.65	0.69	0.68	0.64	0.70
Combined*	0.0	0.15	0.47	0.62	0.70	0.68	0.77	0.69
CV of CMEP amplitudes (%)								
SIT	–	32.7	34.2	28.8	20.2	14.5	14.0	9.6
CTL	–	27.9	34.5	28.4	20.7	15.2	12.7	12.2
Combined*	–	30.7	34.3	28.6	20.4	14.8	13.4	10.7

5.4.5 MEP Stimulus Response Curves

Figure 5.3A shows raw MEP data (normalized to M_{max} amplitude) recorded during arm cycling at 25W from a representative participant from the SIT group at each stimulation intensity at baseline (in black) and post-testing (in grey). Group-averaged (± SD) MEP SRCs for the 25W and 30% PPO condition are displayed in Figure 5.3B and 5.3C, respectively. For MEP SRC AUCs (normalized to M_{max}), the two-way mixed model ANOVA revealed no significant GROUP x TIME interaction effects for either the 25W ($F_{(1, 19)} = 1.236$, $p = 0.280$), or the 30% PPO ($F_{(1, 19)} = 0.560$, $p = 0.463$) conditions (**Figure 5.3**, **Table 5.2**).

5.4.6 CMEP Stimulus Response Curves

Figure 5.4A shows raw CMEP data (normalized to M_{max} amplitude) recorded during arm cycling at 25W from a representative participant from the SIT group at each stimulation intensity at baseline (in black) and post-testing (in grey). Group-averaged (± SD) CMEP SRCs for the 25W and 30% PPO condition are displayed in Figure 5.4B and 5.4C, respectively. For CMEP SRC AUCs (normalized to M_{max}), the two-way mixed model ANOVA revealed significant GROUP x TIME interaction effects for both the 25W ($F_{(1, 19)} = 7.626$, $p = 0.012$, $\eta_p^2 = 0.286$) and the 30% PPO ($F_{(1, 19)} = 8.194$, $p = 0.010$, $\eta_p^2 = 0.301$) conditions (**Figure 5.4**, **Table 5.2**). At 25W, CMEP AUC values were 50.9% larger at post-testing ($p = 0.012$, $d = 0.870$) in the SIT group, whereas CMEP AUC values in the CTL group were not significantly different ($p = 0.422$) between timepoints. During the 30%

PPO condition, CMEP AUC values from the SIT group were 38.2% larger at post-testing compared to baseline (p = 0.016, d = 0.825) and were unchanged in the CTL group (p = 0.242).

5.4.7 M_{max} Amplitudes

The group average M_{max} amplitudes for each cycling condition (i.e., 25W and 30% PPO) at each timepoint are displayed for each group in Table 5.2. Results from the two-way mixed model ANOVAs revealed no significant GROUP x TIME interaction effect for M_{max} amplitudes at 25W ($F_{(1, 19)}$ = 0.006, p = 0.938), or 30% PPO ($F_{(1, 19)}$ = 0.010, p = 0.921).

5.4.8 Pre-stimulus EMG

Results from the two-way mixed model ANOVAs revealed no significant GROUP x TIME interaction effect for biceps brachii pre-stimulus EMG prior to TMS at either the 25W ($F_{(1, 19)}$ = 1.049, p = 0.319; Figure 5.3F), or 30% PPO ($F_{(1, 19)}$ = 0.305, p = 0.587; Figure 5.3G) cycling conditions. Similarly, no significant GROUP x TIME interaction effect was observed for biceps brachii pre-stimulus EMG prior to TMES at 25W ($F_{(1, 19)}$ = 2.482, p = 0.132; Figure 5.4F), or 30% PPO ($F_{(1, 19)}$ = 0.028, p = 0.869; Figure 5.4G). Similar results were found for triceps brachii pre-stimulus EMG. Results from the two-way mixed model ANOVAs revealed no significant GROUP x TIME interaction effect for triceps brachii pre-stimulus EMG values prior to TMS at either the 25W ($F_{(1, 17)}$ = 0.721, p = 0.408; Figure 5.3H), or 30% PPO ($F_{(1, 17)}$ = 0.045, p = 0.736; Figure 5.3I) cycling

conditions. Likewise, no significant GROUP x TIME interaction effects were observed for triceps brachii pre-stimulus EMG prior to TMES at either the 25W ($F_{(1, 17)} = .850$, $p = 0.369$; Figure 5.4H) or the 30% PPO ($F_{(1, 17)} = .439$, $p = 0.517$; Figure 5.4I) cycling intensities.

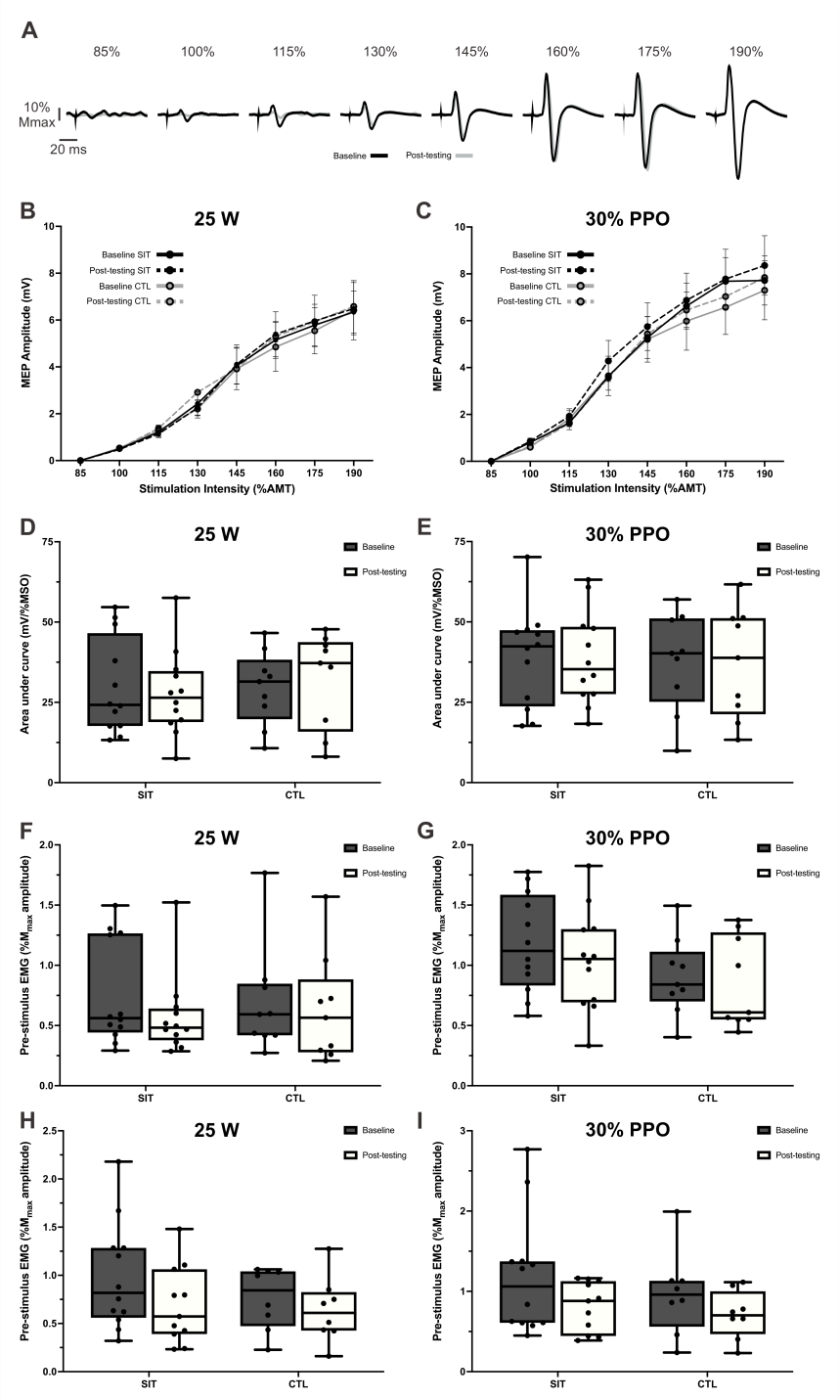

Figure 5.3: TMS-evoked MEP data.

(A) Representative example (n = 1) for biceps brachii motor evoked potentials (MEPs) from a member of the SIT group at baseline (solid trace) and post-testing (grey trace) across stimulation intensities made relative to active motor

threshold (AMT). All responses were evoked at the 6 o'clock position and are from the 25W cycling condition. In this example, MEP amplitudes at each timepoint show a general progressive increase as stimulation intensity increases towards 190% AMT. Group-averaged stimulus-response curves (SRCs) for MEP amplitudes (mean ± SE) at the 25W **(B)** and 30% PPO **(C)** cycling condition for members of the SIT group (black line) and CTL group (grey line) at baseline (solid line) and post-testing (dashed line). Group-averaged MEP SRC area under the curve (AUC) values (normalized to Mmax amplitude) at 25W **(D)** and 30% PPO **(E)** for both groups at baseline and post-testing. Group-averaged pre-stimulus EMG values (normalized to the Mmax amplitude) prior to TMS for the biceps brachii at 25W **(F)** and 30% PPO **(G)** cycling intensities. Group-averaged pre-stimulus EMG values (normalized to the Mmax amplitude) prior to TMS for the triceps brachii at 25W **(H)** and 30% PPO **(I)** cycling intensities.

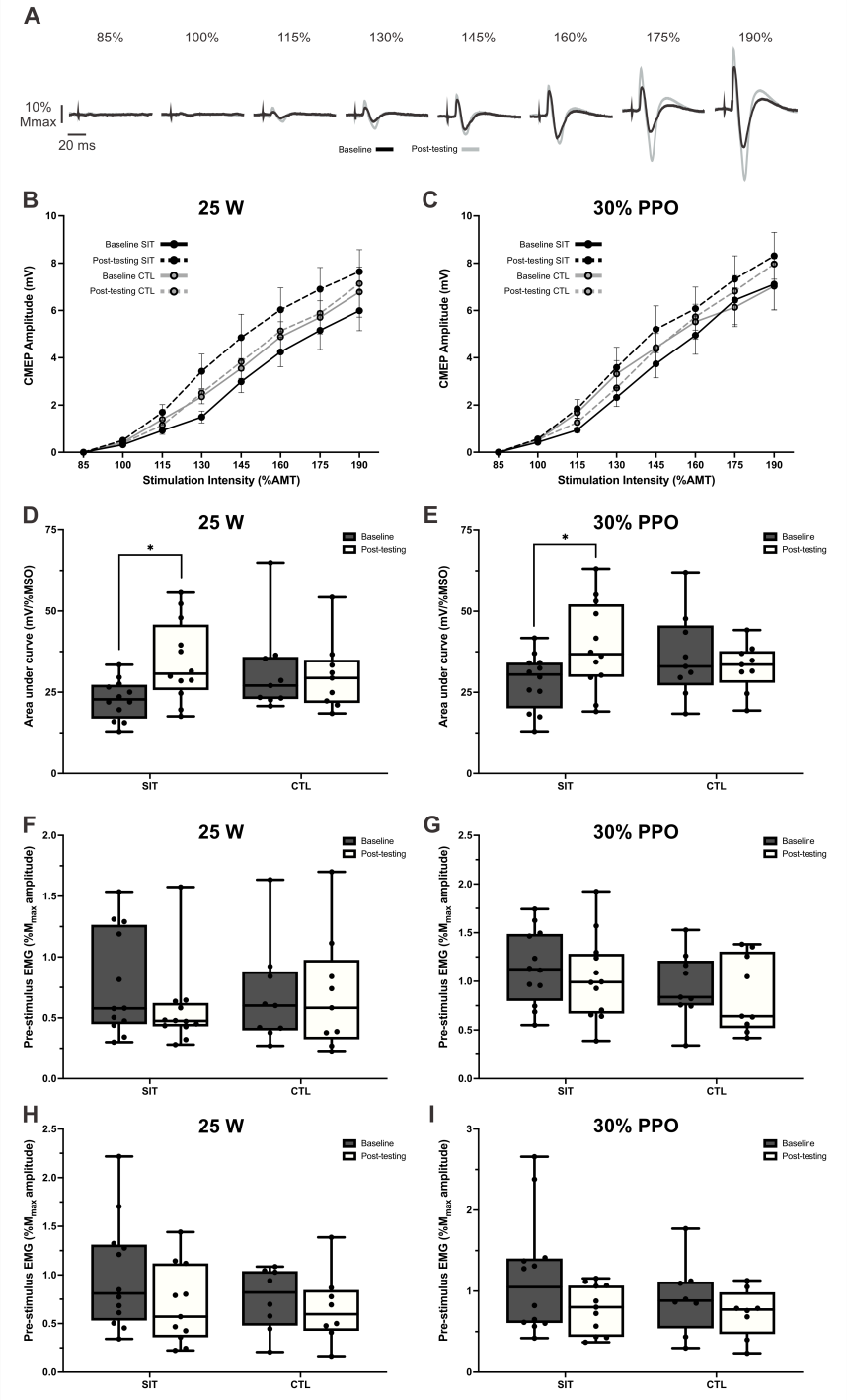

Figure 5.4: TMES-evoked CMEP data.

(A) Representative example (n = 1) for biceps brachii cervicomedullary motor evoked potentials (CMEPs) from a member of the SIT group at baseline (solid

trace) and post-testing (dashed trace) across percentages of AMT. All responses were evoked at the 6 o'clock position and are from the 25W cycling condition. In this example, CMEP amplitudes at each timepoint show a general progressive increase as stimulation intensity increases towards 190% AMT, with CMEPs at post-testing demonstrating larger responses. Group-averaged SRCs for CMEP amplitudes (mean ± SE) at the 25W **(B)** and 30% PPO **(C)** cycling condition for members of the SIT group (black line) and CTL group (grey line) at baseline (solid line) and post-testing (dashed line). Group-averaged CMEP SRC AUC values (normalized to Mmax amplitude) at 25W **(D)** and 30% PPO **(E)** for both groups at baseline and post-testing. Group-averaged pre-stimulus EMG values (normalized to the Mmax amplitude) prior to TMES for the biceps brachii at 25W **(F)** and 30% PPO **(G)** cycling intensities. Group-averaged pre-stimulus EMG values (normalized to the Mmax amplitude) prior to TMES for the triceps brachii at 25W **(H)** and 30% PPO **(I)** cycling intensities. * denotes a significant difference from baseline to post-testing.

5.4.9 Correlation of TTE Performance and Neurophysiological Data

Correlation analyses were performed to determine if there was a relationship between the percent change in TTE performance and the MEP and CMEP AUC values for each group. No correlations existed between alterations in TTE performance and the neurophysiological data, except for a significant positive relationship between TTE duration and CMEP AUC at 30% PPO ($r = 0.59$, $p = 0.045$) in the SIT group only. This significant result suggests that greater improvements in TTE duration were accompanied by greater increases in CMEP AUC values for participants who participated in the SIT intervention.

5.5 Discussion

The aim of this study was to explore whether 2 weeks of arm cycling SIT could induce modulation in corticospinal and/or spinal excitability when measured during the motor output used for training (i.e., arm cycling) and assessed from a muscle (i.e., biceps brachii) actively engaged in said motor output. Our results show that TTE performance (i.e., peak power output and exercise duration) is significantly enhanced at post-testing in the SIT group only (Figure 5.2). Accompanying this increased ability to perform AE, we observed no changes overall corticospinal excitability (i.e., MEP SRC AUCs) for either group (SIT or CTL) during cycling at either intensity (25W or 30% PPO) (Figures 5.3D and 5.3E), but there was a significant increase in spinal excitability (i.e., larger CMEP SRC AUCs) at post-testing for the SIT group only. This finding occurred during both the 25W and the 30% PPO cycling intensity conditions (Figures 5.4D and 5.4E). No changes in CMEP AUCs were observed in the CTL group. The present data therefore demonstrate that six sessions of short (30s), repeated (4-6 sprints/day) arm cycling sprints performed in an all-out manner over a 2-week period increased arm cycling AE capacity and led to enhanced spinal, but not corticospinal excitability at post-testing. Though the mechanisms underlying these observations are not fully established, we suggest that alterations in intrinsic spinal motoneurone excitability and/or alterations in the efficiency of descending drive to enhance spinal excitability may help describe the present results.

5.5.1 Time-to-Exhaustion Performance Improvements

Sprint interval training is a potent stimulator for improved aerobic capacity and performance (Burgomaster et al., 2005; Gibala et al., 2006; Gist et al., 2014) and produces similar, or even greater, physiological and performance adaptations than lower intensity forms of AE (Burgomaster et al., 2005; Harnish et al., 2017). Using a similar 2-week arm cycling SIT regime to the one used in the present study, Harnish and colleagues (2017) reported ~20% increase in AE performance following training in individuals with chronic spinal cord injury (Harnish et al., 2017). In the current study, we observed a ~7% increase in PPO and a ~12% increase in TTE duration in the SIT group following training. As expected, there were no changes in TTE performance in the CTL group at post-testing, thus confirming that the low-volume, high-intensity SIT protocol was efficacious in yielding improvements in the capacity to perform AE. While the precise mechanisms that underlie this enhanced performance are likely multifactorial, previous studies using similar sprint training protocols have suggested that alterations in skeletal muscle metabolism (Burgomaster et al., 2005), blood flow and vascular conductance (Krustrup et al., 2004), and/or improved neuromuscular factors, such as enhanced motor unit behaviour (MacInnis & Gibala, 2017) and/or central drive (Vera-Ibanez et al., 2017) may be contributing to the performance enhancement.

5.5.2 No Changes in Corticospinal Excitability After SIT

In contrast to our initial hypothesis, there were no differences in MEP SRC AUCs following the arm cycling SIT protocol, suggesting that the net excitability of the

corticospinal pathway remained unchanged following the training. Importantly, however, this lack of apparent effect on overall corticospinal excitability does not necessarily designate the absence of change entirely, as MEPs are influenced by a complex myriad of excitatory and inhibitory mechanisms within the motor cortex and the spinal motoneurones (Di Lazzaro, Oliviero, et al., 1998; Lockyer et al., 2021; Rossini et al., 2015). Thus, while the net corticospinal excitability may not have been altered, it is possible that the excitability of specific excitatory or inhibitory interneuronal networks may have been modulated following the SIT protocol. Indeed, following acute AE, several previous studies have demonstrated that the excitability of specific inhibitory and facilitatory networks within the M1 can be transiently modulated (McDonnell et al., 2013; Singh et al., 2014; Singh & Staines, 2015) for a period following exercise. Moreover, in the only other study to examine the effects of high-intensity repeated AE training on the modulation of corticospinal pathway excitability, Nicolini and colleagues (2019) reported no changes in overall corticospinal excitability (i.e., MEP SRC AUCs) following 6 weeks of leg cycling HIIT, but reported changes in interneuronal networks (Nicolini et al., 2019). Specifically, the authors reported a reduction in ICF and no change in SICI recorded from the FDI following the HIIT protocol, therefore suggesting that one of the many cortical networks is altered following a relatively short HIIT protocol. The observed reduction in ICF following HIIT was proposed to potentially serve as a mechanism to maintain excitability of the M1 and prime the release of GABAergic inhibition that has been shown to occur following a single session of AE (Lulic et al., 2017). In the present study, since we did not include a measure of cortical excitability, it is unclear whether alterations in the excitability of specific interneuronal networks such as ICF, SICI, LICI, or others, may have occurred.

However, the combined results of increased CMEP AUC values and unchanged MEP AUC values following SIT might possibly be interpreted, through deductive reasoning, as enhanced spinal excitability and reduced supraspinal excitability (Lockyer et al., 2021; Martin, Gandevia, et al., 2006). Future research should investigate the excitability of specific cortical networks following various AE training paradigms to obtain a greater understanding of potential for supraspinal adaptations to AE training.

In line with the suggestion of reduced supraspinal excitability as a potential mechanism underlying the present results, it is possible that the arm cycling SIT protocol may have induced a neural adaptation at the level of spinal motoneurone (see below) that renders the motoneurone more excitable, thereby reducing the descending drive required to activate said motoneurones to produce subsequent motor output. This, however, remains a speculative suggestion. Despite similar levels of pre-stimulus EMG at baseline and post-testing, it is possible that descending drive could still be different following training (Weavil & Amann, 2018). One way to examine whether descending drive may be influencing the enhanced spinal excitability observed following SIT, would be to assess motoneurone excitability during the silent period of a TMS-evoked MEP prior to and following training (Fuhr et al., 1991; Yacyshyn et al., 2016). Such a method would substantially reduce the confounding effects of voluntary descending drive on motoneurone excitability, and thus would provide greater insights into its potential impact following training (Fuhr et al., 1991).

5.5.3 Increased Spinal Excitability After SIT

This is the first study to examine changes in spinal excitability using TMES-evoked CMEPs in combination with measures of corticospinal excitability following a relatively short-term AE training protocol. Our results showed that AUC values from the CMEP SRCs were increased in the SIT, but not CTL group at post-testing (Figure 5.3). This was true for both the 25W and 30% PPO arm cycling intensity conditions, indicating that spinal excitability was enhanced following training regardless of cycling intensity. Importantly, this enhancement in spinal excitability was apparent when measured *during* submaximal arm cycling at least 48 hours following completion of the 2-week arm cycling SIT protocol, suggesting that the enhanced spinal excitability represents a neural adaptation to training.

Previous studies using a variety of measurement techniques have reported changes in spinal cord excitability following AE (Martinez-Valdes et al., 2017; Vera-Ibanez et al., 2017; Vila-Cha et al., 2012; Vila-Cha et al., 2010) . Most of these studies have assessed alterations in either spinal reflex responses and/or changes in motor unit firing characteristics following exercise. In particular, the H-reflex, which provides a measure of presynaptic inhibition of primary muscle spindle (Ia) afferents (Palmieri et al., 2004), is enhanced following long-term AE training (Perot et al., 1991; Vera-Ibanez et al., 2017; Vila-Cha et al., 2012). Moreover, cross-sectional studies have demonstrated that H-reflex amplitudes are larger in endurance-trained athletes compared with resistance- and power-trained athletes (Casabona et al., 1990; Earles et al., 2002; Kyrolainen & Komi, 1994; Maffiuletti et al., 2001). These results suggest that adaptations occur within the Ia afferent spinal reflex pathway following AE. However, since the H-reflex response is influenced at

pre- and post-synaptic sites, its interpretation following AE training is unclear (Vila-Cha et al., 2010). Unlike the H-reflex however, CMEPs are not prone to conventional presynaptic inhibition (McNeil et al., 2013). Since CMEP AUCs were augmented following SIT in the present study, it is suggested that the enhanced spinal excitability cannot simply be explained by changes in presynaptic inhibition and may involve changes in spinal motoneurone excitability.

Spinal motoneurone adaptations have also been demonstrated following various types of exercise training. Following traditional AE training, motor unit discharge rates are decreased while motoneurone pool output is increased (i.e., greater surface EMG) (Vila-Cha et al., 2010), suggesting that motor unit recruitment is enhanced. Conversely, Martinez-Valdes et al., (2017) recently showed that 2 weeks of HIIT induced a preferential increase in discharge rates in high threshold motor units, while 2 weeks of traditional AE training did not alter motor unit discharge rates. Despite similar improvements in cardiopulmonary fitness between training modalities, it was suggested that the HIIT and traditional AE protocols may induce specific neuromuscular adaptations which are likely related to the intensity and volume of the training protocols (Martinez-Valdes et al., 2017). In the present study, given the high intensity nature of the arm cycling SIT protocol employed, it is possible that adaptations in motor unit discharge rates and/or recruitment may occur and underlie the observed increase in TTE performance and spinal excitability.

Recently, following six weeks of resistance training in older adults, Orssatto et al. (2023) showed that intrinsic spinal motoneurone excitability is enhanced following training (Orssatto et al., 2023). In this study, estimates of motoneurone persistent inward currents (PICs) were examined using paired-motor unit analyses (to calculate delta frequency)

during isometric contractions of varying intensity prior to and following training. The authors reported enhanced PIC amplitudes following training, suggesting an increase in motoneurone excitability as a potential mechanism underlying the improvements in strength performance following training (Orssatto et al., 2023). Importantly, this study was performed on older adults, where delta frequency has recently been shown to be lower than in young adults (Orssatto et al., 2021), therefore it remains unknown whether similar findings would be observed in a population like the one examined in the present study. Similarly, following relatively long-term forms of AE training, work from non-human animals have demonstrated alterations in intrinsic properties of spinal motoneurones (Beaumont & Gardiner, 2002; Beaumont & Gardiner, 2003; Gardiner et al., 2006; MacDonell & Gardiner, 2018) and interneurons (Chen et al., 2019). Specifically, AE training enhances motoneurone afterhyperpolarization amplitude (Beaumont & Gardiner, 2003), hyperpolarizes motoneurone voltage threshold (Vth) for action potential initiation, and increases the slope of the rising portion of the action potential (Beaumont & Gardiner, 2002; Beaumont & Gardiner, 2003). Moreover, recent work from Chen et al., (2019) has also revealed that 3 weeks of treadmill training hyperpolarizes Vth, enhances PICs, and decreases rheobase for ventromedial spinal interneurons in mice (Chen et al., 2019). These adaptations would facilitate motoneurone recruitment and firing rates (Power et al., 2022).

Importantly, the aforementioned studies examined changes in motor unit properties following exercise during isometric contractions, while in the current study CMEP SRCs were elicited during submaximal arm cycling following arm cycling SIT. Therefore, motoneurone adaptations may differ when assessed during dynamic motor output following training given the task-dependence of motoneurone excitability (Power et al.,

2022). Future work should attempt to characterize potential adaptations in motor unit properties during dynamic motor outputs following training as recently proposed by Power et al., (2022) (Power et al., 2022).

5.5.4 Methodological Considerations

Throughout this manuscript and others by our laboratory (Lockyer et al., 2021; Power et al., 2022), we emphasize the importance of considering task-dependent modulation of corticospinal excitability, and specifically for the case of training, we suggest the need to assess potential changes in excitability *during* the motor output that was used for training (Power et al., 2022). Here, we employed a 2-week arm cycling SIT protocol, and we assessed excitability during submaximal arm cycling following training. While both motor outputs involved arm cycling, the SIT involved high-intensity efforts and high cadences whereas we assessed excitability during arm cycling at much lower intensities (25W and 30% PPO) and a constant cadence of 60 rpm following training. As such, we recognize that our findings may not reflect the full range of corticospinal adaptations that may have occurred should we have measured changes in excitability during arm cycling sprinting following the 2-week SIT protocol. However, we purposely chose not to do that for various reasons. Firstly, assessing changes in corticospinal and spinal excitability during sprinting is technically difficult. During all-out arm cycling sprints, there are large changes in body position, muscle activation, and power outputs that make neurophysiology recordings from TMS and TMES much more challenging. Secondly, sprinting is physically exhausting for participants. Neuromuscular fatigue occurs

early during all-out sprinting efforts (Pearcey et al., 2016) and makes discerning potential physiological mechanisms more difficult as fatigue at the central and peripheral levels must be taken into consideration. Therefore, while we acknowledge the disparity between the two tasks (i.e., sprint vs submaximal cycling), we argue that measuring changes in corticospinal excitability during arm cycling following arm cycling SIT is more task relevant than measurements made during a tonic contraction or at rest.

In addition to the disparity in cycling intensity used during post-testing compared to that during the arm cycling SIT protocol, there are other factors that may have influenced the present results. Firstly, the CTL group did not perform any AE training. Thus, it remains unknown if the observed findings are related to performing the high intensity SIT protocol or if other types of AE training paradigms might have yielded similar neurophysiological and performance outcomes. Future studies should be designed to explore changes in corticospinal excitability following various low-, moderate-, and high-intensity AE training protocols, with matched training workloads, to provide greater understanding of the impacts of AE intensity on corticospinal pathway excitability and AE performance.

Secondly, all neurophysiological measurements were taken at baseline and at post-testing during arm cycling performed at 60 rpm. However, the TTE test that participants performed as a proxy for AE capacity and performance was performed at 70 rpm. The methods of the TTE test were based off recommendations from Smith et al., (2004) for incremental exercise testing during arm cycling (Smith et al., 2004), while the use of 60 rpm for neurophysiological testing was based off previous work from our lab (Alcock et al., 2019; Chaytor et al., 2020; Forman et al., 2014; Forman et al., 2015; Lockyer et al., 2021; Lockyer, Hosel, et al., 2019; Lockyer, Nippard, et al., 2019; Lockyer et al., 2020;

Nippard et al., 2020). Regardless, given that all participants performed the same tests at the same cadence at baseline and post-testing, it is unlikely that differences in cadence can explain the observed enhanced TTE performance in the SIT group following training.

Thirdly, it is possible that the relatively low number of stimulations per stimulation type (i.e., TMS and TMES) may have impacted the present results. Although recent evidence has suggested that ~20+ MEPs per trial are needed to accurately estimate corticospinal excitability for lower limb musculature (Brownstein et al., 2018), we ultimately settled at eight stimuli per stimulation type per trial. Given the large number of trials needed to create the SRCs (eight stimulation intensities) per stimulation type (TMS and TMES) at both cycling workloads (25W and 30% PPO), we purposely chose eight stimuli per stimulation type per trial as a means to limit the potential of fatigue (whether or mental or physical) potentially impacting our results. Thus, while it is possible that the number of responses impacted our data, we suggest that this idea is unlikely to fully explain the lack of change in MEP AUC and the increase in CMEP AUC we observed following the 2-week SIT protocol. While there is inevitably variability in our data (Table 5.3), most of this relative variability (i.e., CV) comes at the lower end of the SRCs, where stimulation intensities are at or near AMT (Darling et al., 2006; Sivaramakrishnan & Madhavan, 2020). At higher stimulation intensities, where the AUC measurements would arguably be impacted the most by deviations in variability, the CVs of the response amplitude are smaller, as shown in previous reports (Sivaramakrishnan & Madhavan, 2020). Thus, we argue that response variability does not fully explain the present findings. Moreover, several previous studies have used substantially less stimulations per condition to create SRCs and have yielded usable data (Lulic et al., 2017; Nicolini et al., 2019).

Lastly, though the circular TMS coil was placed and held over vertex, which was measured and marked on the scalp and held in place by the same researcher throughout all cycling conditions, it is possible that slight modifications in coil placement could be influencing the current results. However, we suggest this is unlikely to be a major factor. In this study, we used a wide range of stimulation intensities performed in a randomized order to create SRCs with all intensities being made relative to AMT. Thus, it is likely that even if slight variations in coil position existed during arm cycling, it is unlikely to have majorly influenced the input-output relationship of the corticospinal pathway, especially at higher stimulation intensities. Moreover, during submaximal arm cycling bouts like those used in this study at baseline and post-testing, participants' head position does not move to a great extent during the movement. This is one of the advantages to using arm cycling as a model of locomotor activity (Lockyer et al., 2021). Indeed, we have used these methods in several previous experiments to examine changes in corticospinal excitability during arm cycling (Forman et al., 2018; Forman et al., 2015; Lockyer et al., 2018; Lockyer et al., 2021; Lockyer, Hosel, et al., 2019; Lockyer, Nippard, et al., 2019; Power et al., 2018; Spence et al., 2016).

5.6 Conclusion

In conclusion, two weeks of arm cycling SIT improves AE capacity (i.e., TTE performance) concomitantly with enhanced spinal excitability and no changes in overall corticospinal excitability to the biceps brachii. Importantly, these findings were measured from a muscle actively involved in the motor output used in the training regime and were

recorded *during* said motor output following training, which to the authors knowledge, is the first study to examine this effect. While the precise mechanisms underlying these observations remain to be elucidated, it is suggested that the enhanced spinal excitability observed following SIT may be related to either alterations in motor unit firing properties and/or intrinsic motoneurone properties that make the motoneurone more excitable following training. Collectively, these findings suggest that the corticospinal pathway, namely the motoneurone circuitry, can be modulated for an extended period (i.e., at least 48 hours) following a relatively short-term (i.e., 2-week) SIT program.

5.7 Acknowledgements

This study was supported by PGS-D NSERC funding to E.J.L. as well as NSERC Discovery Grant to K.E.P. We would like to thank the participants for volunteering their time.

5.8 Disclosures

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

Chapter 6: SUMMARY AND FUTURE DIRECTIONS

6.1 Summary of Thesis Findings

The main objective of this thesis was to add to the growing literature on the many factors that influence corticospinal and spinal excitability during arm cycling. Each experiment, presented in Chapters 3-5, addressed unique but relevant questions pertaining to the mechanisms underlying the modulation of corticospinal pathway excitability during arm cycling that had not been previously examined in the literature. Namely, this thesis asked the following research questions: 1) does focusing attention on maintaining a specified cadence during arm cycling influence corticospinal excitability; 2) how does increasing motor output intensity and stimulation intensity influence corticospinal and spinal excitability during arm cycling; and 3) is corticospinal and spinal excitability modulated following a short-term AE training paradigm, when assessed during the motor output used for training? In examination of these questions, several novel findings arose. The main findings of each chapter are summarized below.

In Chapter 3, focusing attention on maintaining a FC during arm cycling did not alter overall corticospinal excitability. This finding was evidenced by a lack of change in MEP amplitudes recorded from the biceps brachii between the self-selected (SSC) and FC arm cycling conditions. Our results align with the only other study to investigate the influence of focusing attention on cadence during a locomotor-like output on the excitability of the corticospinal pathway (Sidhu & Lauber, 2020). Shortly after we published the experiment presented in Chapter 3, Sidhu and Lauber (2020) employed a similar experiment procedure during leg cycling and revealed that overall corticospinal excitability recorded from the

vastus lateralis was not different between the "freely chosen cadence" or the FC conditions. Taken together, the results from both these studies suggest that focusing on maintaining a specified cadence does not influence overall corticospinal excitability during cycling tasks.

In Chapter 4, we found that corticospinal and spinal excitability projecting to the biceps brachii increased with arm cycling power output in a similar manner to that observed in the literature (Martin, Gandevia, et al., 2006; Oya et al., 2008; Weavil et al., 2015). MEP and CMEP amplitudes increased as the intensity of arm cycling increased, up until a plateau was reached, which was different for the weak and strong stimulation intensities. Beyond the plateau in responses, we did not observe a progressive decrease in MEP and CMEP amplitudes as cycling intensity continued to increase, as has been shown during isometric contractions (Martin, Gandevia, et al., 2006; Oya et al., 2008). This disparity could indicate task-dependent modulation (i.e., locomotor vs isometric contractions) in corticospinal and spinal excitability, as we have previously reported (Lockyer et al., 2021; Power et al., 2018). Nonetheless, given the similar pattern of modulation between MEPs and CMEPs, we propose that spinal mechanisms are at least partially underlying the increase in overall corticospinal excitability. However, at higher cycling power outputs, supraspinal mechanisms (e.g., increased descending motor drive) may be more involved, given that the MEPs became much larger than CMEP as the intensity of arm cycling increased (as evidenced by the MEP/CMEP ratios).

Lastly, in Chapter 5, we found that two weeks of arm cycling SIT improved time-to-exhaustion test performance (i.e., estimate of aerobic capacity) and enhanced spinal (i.e., increased CMEP SRC AUC values), but not overall corticospinal excitability (i.e., MEP SRC AUC values), in the trained group only following training. Importantly, these

observations were made ~48 hours after completion of the training paradigm and were obtained during the locomotor output (e.g., arm cycling) used for the training, albeit at submaximal intensities. No changes in performance or neurophysiological measures were observed in the control group, suggesting that the observations in the SIT group likely represent a neural adaptation to the exercise training.

Collectively, the experiments presented in this thesis represent important steps toward an understanding of the multitude of factors that influence corticospinal pathway excitability during arm cycling. Specifically, this thesis revealed that attentional focus, cycling intensity, and exercise training influence the nature and the magnitude of corticospinal and spinal excitability modulation.

6.2 Future Directions

While this thesis has helped advance the understanding of the many factors that influence corticospinal pathway excitability during arm cycling, several questions and avenues for future research remain. Some of the future directions that are of particular interest to me are discussed herein.

Firstly, the use of single-pulse TMS paradigms in the studies included in this thesis limits insights into mechanisms at the supraspinal level. Since the MEP response involves both supraspinal and spinal mechanisms, single-pulse TMS alone cannot specify potential supraspinal contributions (McNeil et al., 2013). Although combining TMES with single-pulse TMS helps identify the locus (i.e., supraspinal vs spinal) of a potential change in overall corticospinal excitability, their use together does not clarify mechanisms. One way to obtain some insight into mechanisms at the supraspinal level is to use paired-pulse TMS

paradigms. Paired-pulse TMS paradigms enable the examination of various intracortical and intercortical networks, providing insight into specific receptors and neurotransmitters that might underlie a particular finding (Chen, Tam, et al., 1998). Previous research, though not involving arm cycling, has shown that supraspinal network excitability is altered with varying attentional demands (Marinovic, 2017; Matsumoto et al., 2024; Sidhu & Lauber, 2020), contraction intensities (Hendy et al., 2019; Lahouti et al., 2019), and AE performance (Lulic et al., 2017; Singh et al., 2014; Singh & Staines, 2015; Smith et al., 2014). Whether the excitability of supraspinal networks is altered during arm cycling under similar conditions remains unexplored but is a promising opportunity for future research. Future studies should assess intracortical networks, such as SICI, ICF, LICI, as well as interhemispheric interactions, such as interhemispheric inhibition (IHI) during arm cycling under the same methodologies employed in this thesis to tease out potential supraspinal mechanisms. Recent studies from our lab, and ones that I have been involved in, have begun exploring these networks during arm cycling (Alcock et al., 2019; Benson et al., 2021; Compton et al., 2022), but further work is needed to determine how supraspinal excitability is influenced during arm cycling when focusing on cadence, increasing motor output intensity, or undergoing high-intensity AE training.

Secondly, throughout this thesis, TMES was used to measure the excitability of the corticospinal pathway at the spinal level during arm cycling. Although enhanced spinal excitability was observed with increased motor output intensity (up until a plateau; Chapter #4) and following two-weeks of arm cycling SIT (Chapter #5), the precise spinal mechanisms mediating these findings remain unclear. The CMEP response provides a global measure of spinal excitability (McNeil et al., 2013), making it difficult to pinpoint

whether increases in CMEPs are due to changes in motoneurone firing properties, corticospinal-motoneuronal synapse efficiency, or motoneurone biophysical properties (Lockyer et al., 2021; Taylor, 2006). Obviously, directly recording from motoneurones in humans is not feasible, but techniques like intramuscular and high-density surface EMG offer indirect insights into motoneurone firing characteristics. Intramuscular EMG can reveal the firing properties of active motoneurones by assessing and characterizing motor unit action potentials recorded from specific muscle fibres (Adrian & Bronk, 1929; Duchateau & Enoka, 2011), but it has limitations: namely, detecting few motor units at a time and difficulty during dynamic motor outputs due to movement of the electrode recording sites as the muscle fibres contract and shorten (Duchateau & Enoka, 2011). That said, we have recently used this technique during slow arm cycling in a collaborative project in progress with a group from London, Ontario and have yielded some promising results for the use of the technique during arm cycling (data not yet published).

Advances in high-density surface EMG grids and decomposition algorithms have provided perhaps the most promising avenue for examining potential changes in motoneurone firing properties during dynamic motor outputs in humans (Farina et al., 2016; Martinez-Valdes et al., 2017). These grids, initially restricted for isometric use (Holobar et al., 2010), have been updated for dynamic movement to permit the detection of individual motor unit action potentials along underlying muscle fibres and can be used to obtain detailed spatial and temporal information about motoneurone firing patterns during dynamic contraction (De Luca et al., 2015; Glaser & Holobar, 2019). Consequently, high-density surface EMG, combined with other techniques like TMS and TMES, presents an exciting avenue to study motor unit adaptations during dynamic motor outputs, like arm

cycling. Future studies should use this technology to characterize motor unit firing properties during arm cycling as motor output intensity is increased (Chapter #4) and following the performance of high-intensity AE protocols (Chapter #5), in order to provide deeper insight into underlying mechanisms. Indeed, tracking motor unit adaptations during locomotor outputs under various motor conditions aligns with the suggestion we recently made in our invited review in the *European Journal of Applied Physiology* (Power et al., 2022).

Lastly, in all the studies included in this thesis, the corticospinal pathway was of primary interest given its primary role in the production of smooth voluntary movement. However, it is important to highlight that the corticospinal pathway represents just one of the many descending pathways that have influence over the production of motor output in humans. The reticulospinal tract, for example, has been purported to have an important role in the production of gross bilateral motor tasks, like locomotion (Brownstone & Chopek, 2018). Arising from the pontomedullary reticular formation in the brainstem and extending across multiple spinal segments on both sides of the cord, the reticulospinal tract exerts influence over a large number of motor pools bilaterally, specifically the proximal upper limb muscles (Riddle et al., 2009), and has been implicated as a potential site of nervous system adaptation following resistance training (Glover & Baker, 2020; Pearcey et al., 2021; Skarabot et al., 2021). As such, it is plausible that the reticulospinal tract is also involved in the production of arm cycling and may be modulated with different task modifications. However, much like the assessment of corticospinal tract function in humans, direct stimulation of the reticulospinal tract in humans is not possible. Fortunately, recent work has suggested that the assessment of ipsilateral MEPs (iMEPs) from single-

pulse TMS can yield indirect insight into reticulospinal tract involvement (Maitland & Baker, 2021; Ziemann et al., 1999). This technique represents an intriguing avenue for future studies and would serve as a great opportunity to elaborate on the mechanisms that underlie the neural control of human movement.

6.3 Implications

Understanding how corticospinal and spinal excitability is modulated during dynamic locomotor outputs, like arm cycling, has value for both basic and applied neuroscience. This thesis provides deeper insight into how the excitability of the corticospinal pathway, an important neural tract for voluntary movement, is modulated during dynamic and functional movements. This understanding is fundamental for elucidating the neural mechanisms underlying human locomotion and other complex motor tasks. Moreover, the findings from this thesis also offer important methodological insights for future research in human movement neuroscience. By highlighting the need to assess corticospinal pathway excitability during dynamic tasks and by providing suggestions on methodological factors to consider (Chapter 2), this thesis will (hopefully) permit future studies to include more experimental designs that better mimic real-world motor outputs.

From an applied perspective, the type of work done in this thesis also has the potential to guide the development of more effective rehabilitation strategies for individuals with various motor impairments, such as those resulting from spinal cord injury or stroke. By identifying how factors such as attentional focus, motor output intensity, and AE training affect corticospinal and spinal excitability during motor outputs like arm

cycling, rehabilitation protocols can be tailored to include some of these factors that might serve to enhance neuroplasticity, enhancements that may strengthen transmission along the corticospinal pathway and promote voluntary movement or improvement in motor function following injury (Christiansen & Perez, 2018; Long et al., 2017; Puhl et al., 2018). For instance, Chapter 5 demonstrates, albeit in a healthy population, that performance of a two-week high-intensity arm cycling SIT regime is capable of inducing adaptations in spinal excitability that are present during arm cycling approximately 48 hours following the completion of training. While speculative, similar increases in spinal excitability in populations with spinal cord injury, for example, might be important for helping to regain motor function, representing an intriguing avenue for further research.

6.4 Concluding Statement

The neural control of locomotor outputs is complex. While this complexity has been recognized for many years, the exact nature of the mechanisms that underlie locomotor outputs remains elusive. The descending corticospinal pathway represents one important pathway involved in the production of voluntary motor outputs in humans. This thesis has made steps towards clarifying some of the factors that influence the excitability of the corticospinal pathway during a locomotor-like output, arm cycling. Specifically, in Chapter #3, focusing on maintaining a specified cadence during arm cycling did not influence overall corticospinal excitability. No measures of spinal or cortical excitability were utilized in this study, thus potential changes along the corticospinal pathway not detectable by TMS may have been missed. In Chapter #4, increasing the resistance of cycling exerted

differing modulation on supraspinal and spinal excitability, with supraspinal excitability likely contributing more to the enhanced overall corticospinal excitability at high arm cycling intensities. This effect was also influenced by stimulation intensity. Lastly, in Chapter #5, two weeks of arm cycling SIT did not exert any influence on overall corticospinal excitability, but spinal excitability was enhanced following training, suggesting a potential neural adaptation to the SIT.

In all three studies included in this thesis, the precise neural mechanisms could not be fully established due to limitations of the experimental recording techniques. Future research will be needed, perhaps using various other experimental techniques, to try and tease out greater detail on the mechanisms underlying the modulation of corticospinal pathway excitability during arm cycling. This work will aid in the understanding of the neural control of locomotor outputs, which may be used to help guide the design of optimal neurorehabilitation or exercise strategies for a variety of populations.

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Chapter 7: APPENDICES

7.1 Appendix 1: Proof of Ethics Approval for Study #1 (Chapter 3)

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:	**20171250-HK**
Approval Period:	January 18, 2017 – January 31, 2018
Funding Source:	N/A
Responsible Faculty:	Dr. Kevin Power School of Human Kinetics and Recreation
Title of Project:	*Assessing the effect of a spontaneously chosen arm cycling cadence on corticospinal excitability*

January 18, 2017

Mr. Evan Lockyer
School of Human Kinetics and Recreation
Memorial University of Newfoundland

Dear Mr. Lockyer:

Thank you for your correspondence of January 13, 2017 addressing the issues raised by the Interdisciplinary Committee on Ethics in Human Research (ICEHR) concerning the above-named research project.

The ICEHR has re-examined the proposal with the clarification 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* to January 31, 2018. 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 you need to make changes during the project, which may raise ethical concerns, please submit an amendment request with a description of these changes for the Committee's consideration. In addition, the *TCPS2* requires that you submit an annual update to ICEHR before January 31, 2018. 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 the annual update with a final brief summary, and your file will be closed.

Annual updates and amendment requests can be submitted from your Researcher Portal account by clicking the *Applications: Post-Review* link on your Portal homepage.

We wish you success with your research.

Yours sincerely,

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

KB/lw

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

7.2 Appendix 2: Proof of Ethics Approval for Study #2 (Chapter 4)

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:	**20181196-SC**
Approval Period:	December 7, 2017 – December 31, 2018
Funding Source:	**Supervisor's** NSERC (RGCS: 20161819)
Responsible Faculty:	Dr. Kevin Power School of Human Kinetics and Recreation
Title of Project:	*Differences in supraspinal and spinal excitability of the biceps brachii during various arm cycling intensities*

December 7, 2017

Miss Katarina Hosel
Department of Psychology, Faculty of Science
Memorial University of Newfoundland

Dear Miss Hosel:

Thank you for your correspondence of December 4, 2017 addressing the issues raised by the Interdisciplinary Committee on Ethics in Human Research (ICEHR) concerning the above-named research project.

ICEHR has re-examined the proposal with the clarification 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* to December 31, 2018. 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 you need to make changes during the project, which may raise ethical concerns, please submit an amendment request with a description of these changes for the Committee's consideration. In addition, the *TCPS2* requires that you submit an annual update to ICEHR before December 31, 2018. 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 the annual update with a final brief summary, and your file will be closed.

Annual updates and amendment requests can be submitted from your Researcher Portal account by clicking the *Applications: Post-Review* link on your Portal homepage.

We wish you success with your research.

Yours sincerely,

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

7.3 Appendix 3: Proof of Ethics Approval for Study #3 (Chapter 5)

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:	**20191993-HK**
Approval Period:	October 29, 2018 – October 31, 2019
Funding Agency:	Supervisor's NSERC [RGCS # 20161819]
Responsible Faculty:	Dr. Kevin Power School of Human Kinetics and Recreation
Title of Project:	*The influence of sprint interval training on corticospinal excitability to muscles of the upper limb during arm cycling*
Amendment #:	***01***

February 25, 2019

Mr. Evan Lockyer
School of Human Kinetics and Recreation
Memorial University of Newfoundland

Dear Mr. Lockyer:

The Interdisciplinary Committee on Ethics in Human Research (ICEHR) has reviewed the proposed addendum for the above referenced project, as outlined in your amendment request dated February 21, 2019, and is pleased to give approval to the additional trials and added recruitment poster, as described in your request, provided all other previously approved protocols are followed.

If you need to make any other changes during the conduct of the research that may affect ethical relations with human participants, please submit an amendment request, with a description of these changes, via your Researcher Portal account for the Committee's consideration.

Your ethics clearance for this project expires October 31, 2019, before which time you must submit an annual update to ICEHR. 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 requires contact with human participants, is completed and/or terminated, you need to provide an annual update with a brief final summary, and your file will be closed.

Annual updates and amendment requests can be submitted from your Researcher Portal account by clicking the *Applications: Post-Review* link on your Portal homepage.

The Committee would like to thank you for the update on your proposal and we wish you well with your research.

Yours sincerely,

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