Muscle Fatigue and Other Factors Influencing Forearm Muscle Activity

by

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The above committee determined that the thesis is acceptable in form and content and that a satisfactory knowledge of the field covered by the thesis was demonstrated by the candidate during an oral examination. A signed copy of the Certificate of Approval is available from the School of Graduate and Postdoctoral Studies.

Abstract

The wrist extensor muscles of the forearm exhibit relatively greater muscle activity than the wrist flexors during most hand/wrist tasks. Since the extensors operate at a greater percentage of maximum to balance wrist joint moments, this could contribute to their higher incidence of overuse injury. However, current knowledge of forearm muscle function comes primarily from isometric research or from studies examining isolated motor tasks. Conclusions derived from this work may not translate to tasks of daily living, which are typically dynamic and performed by multiple muscle actions simultaneously. Additionally, while fatigue develops more rapidly in the extensors than the flexors, the consequences of fatigue between these two muscle groups are presently unclear.

The objectives of this thesis were broken into two parts. Part 1: Quantify forearm muscle recruitment during the simultaneous execution of various handgrip and wrist forces (Chapter 3) and during dynamic wrist exertions (Chapter 4). Part 2: Characterize the effects of sustained isometric wrist flexion and wrist extension contractions on hand-tracking accuracy (Chapter 5) and investigate the underlying central mechanisms that may contribute to accuracy impairments (Chapter 6).

In Part 1, we identified that the muscle activity of the wrist flexors was highly sensitive to changes in dual-task parameters (grip and wrist exertions), while the activity of the extensors was consistently greater than the flexors during both dual-task and dynamic contractions. In some conditions, the wrist extensors exceeded flexor activity even during pure wrist flexion contractions. In Part 2, it was found that inducing fatigue separately through sustained wrist extension and wrist flexion contractions significantly impaired hand-tracking accuracy. However, there were no differences in hand-tracking

accuracy between the two methods of inducing fatigue. This was surprising, given that follow-up work demonstrated both muscle activity and corticospinal differences between the muscle groups following sustained contractions.

This thesis provides a robust examination of the factors that can influence forearm muscle recruitment. It is also the first work to document the consequences of fatigue in opposing muscle groups of the forearm. The conclusions drawn from this research are essential in furthering our understanding of overuse injury development in the distal upper-limb.

Keywords: Forearm; Muscle Activity; Performance; Fatigue; Neuromuscular Physiology

Author's declaration

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The research work in this thesis was performed in compliance with the regulations of the University of Ontario Institute of Technology's Research Ethics Board under **REB Certificate numbers** #14-046 (Chapter 3), #15044 (Chapters 4 and 5), and #15855 (Chapter 6). Ethical approval was also obtained from Brock University's Research Ethics Board for Chapters 4-6 under REB files numbers #16-263 and #18-154.

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Experimental procedures were developed by DF, GF, and MH. Data was collected by DF, GF, and JR. Data was analyzed by DF and MH. Manuscript was prepared, edited, and approved by DF, GF, RJ, and MH.

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List of abbreviations and symbols

°	Degrees
δ_l	Delta (l)/Longitudinal Component of Tracking Error
δ_n	Delta (n)/Normal Component of Tracking Error
ACh	Acetylcholine
nAChR	Nicotinic Acetylcholine Receptor
ADP	Adenosine Diphosphate
ATP	Adenosine Triphosphate
BB	Biceps Brachii
CCI	Co-contraction Index
CMAP	Compound Muscle Action Potential
CMEP	Cervicomedullary Evoked Potential
CNS	Central Nervous System
CSP	Corticospinal Silent Period
EMG	Electromyography
ED/EDC	Extensor Digitorum Communis
ECR	Extensor Carpi Radialis
ECU	Extensor Carpi Ulnaris
EP	Extensor Pollicis
EPSP	Excitatory Post-synaptic Potential
$\vec{e}$	Error
FDI	First Dorsal Interosseous
FDP	Flexor Digitorum Profundus
FDS	Flexor Digitorum Superficialis
FCR	Flexor Carpi Radialis
FCU	Flexor Carpi Ulnaris

GTO	Golgi Tendon Organ
H-reflex	Hoffmann Reflex
ICF	Intracortical Facilitation
IPSP	Inhibitory Post-synaptic Potential
ISI	Interstimulus Interval
ISJ	Integrated Squared Jerk
ITT	Interpolated Twitch Technique
JRS	Joint Rotational Stiffness
MEP	Motor Evoked Potential
M_{max}	Maximal Compound Muscle Action Potential
%MSO	Percent of Maximum Stimulator Output
MVC	Maximal Voluntary Contraction
MVE	Maximal Voluntary Excitation
MUAP	Motor Unit Action Potential
M-wave	Compound Muscle Action Potential
NMJ	Neuromuscular Junction
PCSA	Physiological Cross-sectional Area
Pi	Inorganic Phosphate
PIC	Persistent Inward Current
ROM	Range of Motion
SDN	Signal-dependent Noise
SICI	Short-interval Intracortical Inhibition
TB	Triceps Brachii
TES	Transcranial Electrical Stimulation
TMS	Transcranial Magnetic Stimulation
TMES	Transmastoid Electrical Stimulation

Chapter 1. Introduction

Background

In 1997, Hägg and Milerad reported that the wrist extensor muscles of the forearm might be more susceptible to developing fatigue than the wrist flexor muscles (see Figure 1.1 for example of wrist flexion and wrist extension movement and the muscles that drive them). In their study, surface electromyography (EMG) was collected from two wrist flexors and three wrist extensors while participants produced 25% of their maximal grip force. Grip forces were performed at three different duty cycles (grip time/rest time in seconds: 10/10, 20/10, and 30/10) on three separate sessions. In the 10/10 session, signs of fatigue (quantified by a decrease in zero crossings (similar to a decrease in median power frequency)) developed in two of the wrist extensor muscles. However, it took until the 30/10 work-to-rest cycle for signs of fatigue to develop in the wrist flexor muscles. Although gripping is executed primarily by the actions of the flexor digitorum superficialis (FDS) and the flexor digitorum profundus (FDP), the wrist extensors exhibited a much shorter onset of fatigue. In the words of the authors, "*It is remarkable that the fatigue signs generally are more pronounced on the extensor side in spite of the fact that FDS is the prime mover*" (Hägg and Milerad, 1997). This finding likely originates from the unique functions of the two muscle groups.

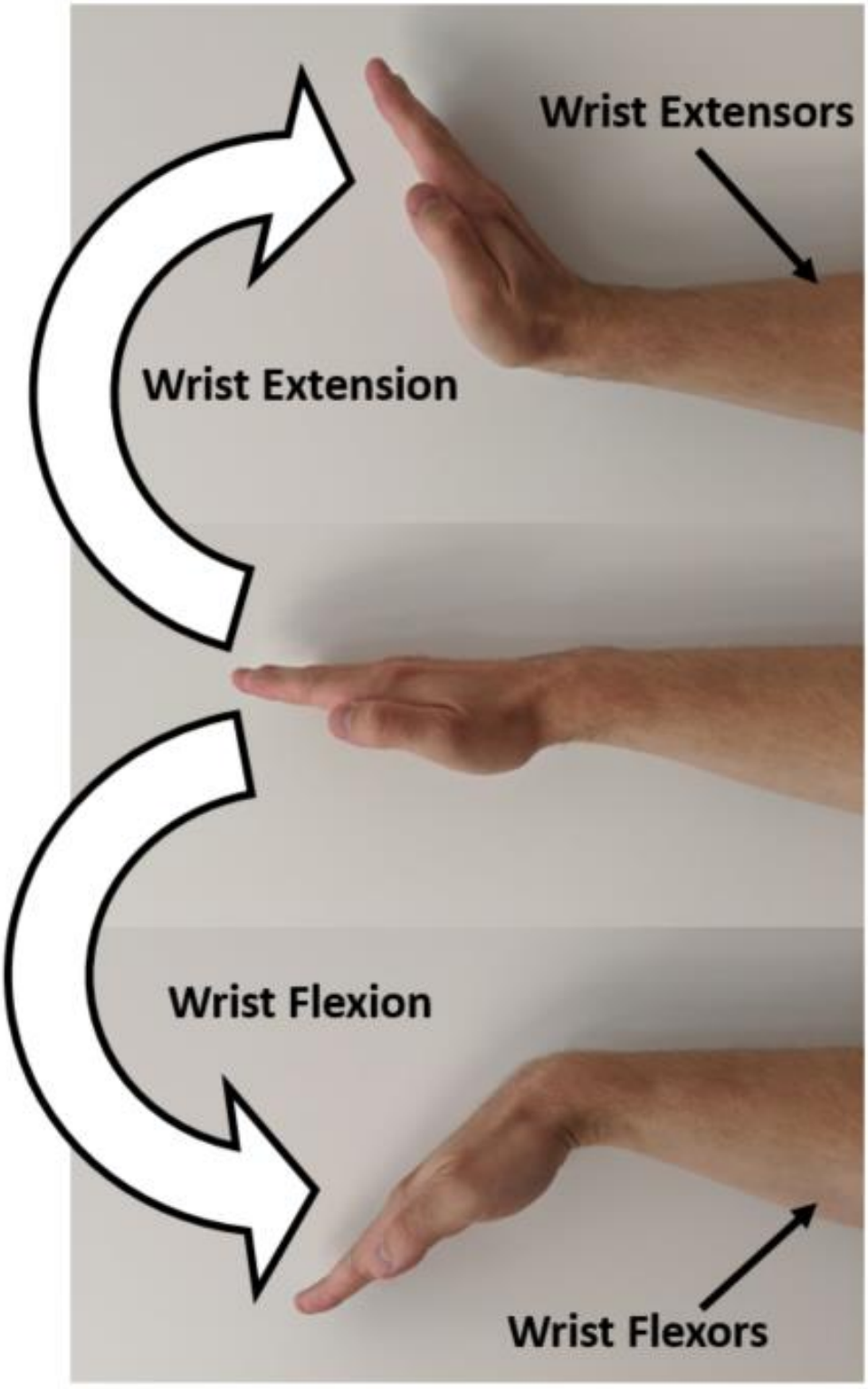

Figure 1.1. *Demonstration of wrist extension and wrist flexion movement with the associated prime movers of each movement, the wrist extensors and the wrist flexors, respectively.*

A decade earlier, researchers from the Netherlands were among the first to comment on wrist flexor/extensor functions with the use of a biomechanical model that quantified the moments generated at the wrist (Chris J Snijders et al., 1987). In this model, the authors demonstrated that grasping or pinching tasks will always result in a flexion moment at the wrist. However, in tasks of daily living, where grasping or pinching are usually performed without any movement of the wrist, there must be an equilibrium moment produced by the wrist extensors. Thus, while FDS may indeed be the prime mover during gripping, the wrist extensors must exert opposing forces to counter the ensuing wrist flexion moment. This finding, among others, led to an early notion among researchers that stabilization of the wrist joint may be a primary function of the wrist extensors. Later work would strongly support this statement.

In their second report of 1997, Hägg and colleagues examined the muscle activity of the flexor and extensor carpi radialis (FCR and ECR) in automotive workers throughout a typical work shift. Results demonstrated that the ECR exhibited a moderate but continuous level of activity during a variety of assembly-line tasks, as would be expected of a stabilizing muscle. In contrast, the FCR possessed a more dynamic pattern of activity akin to that of a prime mover, with frequent pauses in muscle activity but also higher peaks than ECR (Hägg et al., 1997). Additional research has supported these findings. Of the literature that currently exists, the following conclusions have been made regarding wrist flexor and wrist extensor muscle functions: 1) The wrist flexor muscles act as the prime movers in most tasks of the distal upper limb, particularly during gripping. As such, their activity is highly task-dependent, in the sense that changes in task parameters strongly predict their activity. 2) The wrist extensor muscles act primarily to stabilize the wrist joint

by countering the flexion moments generated by the wrist flexors. As such, they exhibit moderate-to-high levels of muscle activity during tasks of the upper-limb and are less sensitive to changes in task parameters (Duque et al., 1995; Hägg and Milerad, 1997; Hägg et al., 1997; Holmes et al., 2015; Imrhan, 1991; Kattel et al., 1996; Mogk and Keir, 2003; Chris J Snijders et al., 1987).

The need for the wrist extensors to stabilize the wrist joint is not without its challenges, given the biomechanical inequalities between the flexors and extensors. In cadaveric studies, the difference in physiological cross-sectional area (PCSA) has been reported as being approximately a 2:1 ratio in favour of the wrist flexors (Gonzalez et al., 1997; Jacobson et al., 1992; Lieber et al., 1992, 1990). This suggests that the wrist flexors are significantly stronger than the wrist extensors; PCSA is a strong predictor of muscle strength (Gonzalez et al., 1997). Modelling work has also shown that the wrist flexors cumulatively possess larger moment arms, and therefore a greater mechanical advantage, than the wrist extensors (Gonzalez et al., 1997). Since peak moment generation is derived from muscle strength and moment arm length, model estimates suggest that the wrist flexors are capable of generating peak moments in excess of 2:1 to the wrist extensors (Gonzalez et al., 1997). To compound these disparities, the wrist flexors have more direct lines of action towards wrist flexion than the wrist extensors have towards wrist extension (Bawa et al., 2000; Gonzalez et al., 1997; Loren et al., 1996). As a consequence of these collective inequalities, the wrist extensors must be active to a greater relative percentage of their maximal activation (by recruiting more motor units or discharging active units more rapidly) in order to counter the greater moments produced by the wrist flexors. This is considered to be the primary reason why the wrist extensors tend to exhibit higher levels

of muscle activity than the wrist flexors (Mogk and Keir, 2003). It is also suspected to be the leading mechanism for why the wrist extensors have an earlier onset of fatigue and develop chronic overuse injuries more frequently than the wrist flexors (Hägg and Milerad, 1997; Ranney et al., 1995; Shiri et al., 2006; Chris J Snijders et al., 1987).

Although many people experience fatigue on a daily basis without issue, particularly in sport or exercise settings, fatigue can contribute to both chronic and acute health problems. When the presence of fatigue is chronic, as is common in many occupational settings, there is a significantly greater risk of developing overuse injuries (Edwards, 2018; Lydakis et al., 2008). Sustained or prolonged muscular contractions have the potential to reduce tissue perfusion to working muscles, which is particularly problematic in isometric contractions; intracellular pressure produced by the contracting muscles can constrict capillaries (Lydakis et al., 2008). Not only does reduced perfusion limit the capacity of working muscles to clear waste by-products, but inadequate blood supply can impair tissue healing. Additionally, chronic overuse injuries develop predominantly through a combination of repetitive loading actions and insufficient rest periods (high duty cycles) to recover from previous loading cycles. Without sufficient rest, as would occur for individuals who are chronically fatigued, these loading cycles will cause a progressive accumulation of tissue damage that may eventually lead to full tissue failure (Edwards, 2018).

Fatigue can also pose concerns in the short term. Following a bout of muscular performance that induces fatigue acutely, proprioception acuity is impaired (Pedersen et al., 1999), co-contraction during precision movements is reduced, (Gribble et al., 2003; Missenard et al., 2008a), and peak contractile speed and torque generation decreases (de

Haan et al., 1989). These factors can both compromise joint stability and contribute to greater signal-dependent noise (SDN). The "signal" refers to the optimal, ideal force required by working muscles to perform a task, while "noise" indicates any deviation of force from the ideal (Missenard et al., 2008b). In other words, force variability can increase in the presence of fatigue, which subsequently reduces the accuracy of precision movements (Huysmans et al., 2008; Jaric et al., 1999; Missenard et al., 2008b). In many occupational settings, and even in certain at-home situations, reduced movement accuracy can be potentially dangerous to an individual and lead to a greater risk of suffering acute injuries (Parijat and Lockhart, 2008). Understanding how fatigue manifests acutely, and the specific ways that it impairs performance, is an important first step in mitigating its potentially harmful effects. This is particularly important in the context of the muscles of the forearm, as the hand makes the final interface with the external environment.

One additional factor that contributes to SDN is a reduction in maximal force capabilities while fatigued. With less force available, a larger relative portion of the accessible force will subsequently be required to complete tasks with absolute force requirements. This is noteworthy since force variability increases linearly with higher contractile forces (Jones et al., 2002). Fatigue-induced reductions in force were once thought to originate solely from impairments within muscle tissue. However, evidence suggests that the capacity of an individual to voluntarily activate target muscles is also reduced in the presence of fatigue (Gandevia, 2001). Perhaps the strongest support for this statement comes from studies conducted in the 90s that utilized the interpolated twitch technique (ITT), which measures voluntary activation. In some of this work, participants were instructed to maintain an initially submaximal isometric contraction (for example,

30% of maximal voluntary contraction (MVC)) until they reached *volitional* failure. The cut-off criteria stated here is important, as it means that participants stopped when they perceived they could no longer maintain the target force. However, application of the ITT revealed significant inactivation at contraction cessation (Löscher et al., 1996a, 1996b; Zijdewind et al., 1998), indicating that participants still possessed a large reserve of force despite reaching volitional failure. In these circumstances, fatigue must be at least partially the result of so-called central mechanisms.

Electrophysiology studies have provided support to this notion. As a sustained muscular contraction progresses, the discharge rates of motor units progressively decrease in two phases–first rapidly, then gradually before plateauing around 30 seconds (Bellemare et al., 1983; Bigland-Ritchie et al., 1983b; Gandevia et al., 1993; Grimby et al., 1981a; Marsden et al., 1971; Martin et al., 2006; Peters and Fuglevand, 1999; Petrofsky, 1980; Petrofsky and Lind, 1980; Woods et al., 1987). The discharge rates of motoneurons are likely inhibited through a combination of afferent pathways and decreased intrinsic excitability. However, there is also a simultaneous increase in the magnitude of electromyography (EMG) signals during sustained submaximal contractions (Bigland-Ritchie et al., 1981; DeVries, 1968; Eason, 1960; Edwards and Lippold, 1956, 1956; Hendrix et al., 2009; Lynn et al., 1978; Scherrer and Bourguignon, 1959). It is thought that EMG signals increase with fatigue as a result of increased motor unit recruitment to compensate for motoneurons that are discharging more slowly. Since the motoneurons are inhibited, any increase in recruitment must arise from supraspinal pathways. Indeed, motor evoked potentials (MEPs) elicited through transcranial magnetic stimulation (TMS), which represent changes in corticospinal excitability, increase throughout sustained submaximal

contraction (Liepert et al., 1996; Sacco et al., 1997; Samii et al., 1996; Yoon et al., 2012). This is perhaps one of the most interesting findings of fatigue-related work and central mechanisms. Larger MEP amplitudes in the presence of decreased spinal excitability suggest that supraspinal excitability increases with fatigue. The mechanisms that contribute to this increase are not well understood, given conflicting reports of changes in intracortical facilitation and inhibition (Hunter et al., 2016; Maruyama et al., 2006; Tergau et al., 2000; Vucic et al., 2011). However, what remains consistent across literature is that, in the presence of fatigue, motoneuron and motor unit discharge rates decline (at least during maximal sustained efforts), while muscle activity and corticospinal excitability increase. Continued investigations into the central mechanisms of fatigue are needed if the potentially harmful effects of fatigue are to be adequately mitigated.

Literature gaps

There are two key literature gaps that this thesis sought to address. First, as stated previously, current literature has concluded that the wrist extensors are the primary stabilizers of the wrist, while the wrist flexors are more involved in executing motor tasks as the prime movers. However, these conclusions have been drawn almost exclusively from isometric protocols or studies that have examined forearm muscle recruitment during the execution of a single task in isolation. For instance, in the 2003 study by Mogk and Keir, which is perhaps the most robust examination to date of factors that can influence forearm muscle recruitment, muscle activity of three wrist flexors and three wrist extensors was assessed while participants exerted handgrip forces in various postures. Handgrip forces ranged from 5-100% of maximal grip force, and all handgrip forces were performed in nine

different upper-limb postures. The results from this study largely supported previous work. At high handgrip forces, wrist extensor muscle activity was similar and at times greater than the muscle activity of the wrist flexors. At low handgrip forces, wrist extensor muscle activity was consistently greater. For example, when participants were instructed to simply hold the handgrip dynamometer without producing any grip force, wrist extensor muscle activity reached as high as 15% of maximal activity; wrist flexor activity never exceeded 7% (Mogk and Keir, 2003). However, not only was the motor task (hand-gripping) in this study isometric, but it also occurred in complete isolation from any other motor task. While this type of protocol may be ideal for generating strong conclusions in well-controlled laboratory settings, these findings may not necessarily translate to real-world tasks. For instance, there are almost no goal-oriented tasks of daily living that can be accomplished solely by gripping the hand in isolation. In the simple case of turning a doorknob, the doorknob must be simultaneously grasped by the hand and rotated by the forearm. Additionally, most goal-oriented tasks are accomplished not isometrically, but dynamically. Using the doorknob example again, the handle cannot not be turned without movement.

To date, the functional roles of the wrist flexors and extensors have not been sufficiently examined in experiments that more closely mimic tasks of daily living, such as those requiring multiple motor tasks to be performed simultaneously or motor tasks that are performed dynamically. While the biomechanical constraints between these two muscle groups are considerable, it is possible that the current conclusions describing wrist flexor/extensor function may not translate to these more applicable tasks. If research is to move forward and properly address the concerns of greater wrist extensor fatigability and

overuse injury risk, these conclusions regarding forearm muscle functions must be challenged under more complex experimental protocols.

Second, while evidence has shown that the wrist extensors exhibit signs of fatigue earlier than the wrist flexors, there is currently no research comparing the consequences of fatigue between these two muscle groups once it develops. Considering their unique functional roles, it is reasonable to hypothesize that fatigue of one muscle group might be more detrimental to performance metrics than fatigue in the other. For instance, since the wrist extensors are thought to provide greater stability to the wrist joint than the wrist flexors, intuition suggests that fatigue of the extensors might reduce stability of the wrist to a greater extent than the wrist flexors. If this is the case, wrist extension fatigue would likely lead to greater SDN and larger reductions in movement accuracy. In acute settings, these changes would be undesirable at the best of times and potentially harmful at the worst. However, in order to mitigate any negative effects of fatigue on forearm performance, these effects must first be characterized between the two forearm muscle groups.

Following with the previous paragraph, evidence suggests that any fatigue-induced reduction in force or movement accuracy will likely be driven by central mechanisms. As a quick summary from the *Background* section, fatigue results in a complex modulation of the central nervous system (CNS) pathways, including a reduction in motoneuron discharge rates but an increase in corticospinal excitability. However, these findings have been derived from studies that examined the consequences of fatigue either at rest or within the same motor task that was used to induce fatigue. For example, in the study by Taylor and colleagues in 2000, fatigue was induced by intermittent isometric MVCs of the elbow flexors. To quantify the effects of fatigue, TMS was used to elicit MEPs in the biceps

brachii *during* the elbow flexion MVCs. In support of previous work, results demonstrated that MEP area increased during the fatiguing protocol relative to baseline measures (Taylor et al., 2000a), indicating an increase in corticospinal excitability. While these types of protocols translate well to a number of real-world situations, whereby the consequences of fatigue can be a concern within the same task that induced fatigue, they are less applicable to others. There are many situations in occupational settings where the development of fatigue in one task can have significant consequences in a separate task. In these cases, it is currently unclear if the increase in corticospinal excitability observed during isometric elbow flexion (induced by fatiguing isometric elbow flexions) would occur in a separate motor task sharing similar muscles actions (for example, dynamic elbow flexion). In other words, the transferability of modulation in central mechanisms between motor tasks is not well understood. More specifically to this thesis, it is not clear how fatigue induced in the wrist flexors would influence corticospinal excitability in the wrist extensors, and vice versa.

Objectives and hypotheses

Chapter 3

Objective: To examine forearm muscle activity during the simultaneous performance of various handgrip forces and various wrist flexion and extension forces.

Hypotheses: Similar to previous research using isolated motor tasks, wrist flexor muscle activity will exhibit task-dependent characteristics, whereby changes in task parameters will significantly alter muscle activity. In contrast, wrist extensor muscle activity will be more static in behaviour and less sensitive to changes in task-parameters. This difference

between the two muscle groups will be noted by larger interaction effect sizes in the wrist flexors compared to the wrist extensors.

Chapter 4

Objective: To examine forearm muscle activity in the concentric and eccentric phases of dynamic wrist flexion and extension in three forearm postures.

Hypotheses: Given that forearm rotation (supination/pronation) alters forearm muscle lengths, forearm posture will influence forearm muscle activity and forearm co-contraction ratios independently of changes in movement phase or force direction. Co-contraction will also be greater during wrist flexion movement as compared to wrist extension movement, driven by greater wrist extensor muscle activity. Movement phase and force direction will interact, whereby all forearm muscles will demonstrate greater muscle activity both during the concentric phase (as compared to eccentric) and when acting as the agonist muscle (as compared to the antagonist).

Chapter 5

Objective: To examine the influence of sustained wrist flexion and extension fatiguing maximal voluntary contractions on hand-tracking accuracy metrics.

Hypotheses: Hand-tracking accuracy will be significantly impaired, as determined by all performance metrics utilized in this study, immediately after either sustained wrist flexion or sustained wrist extension MVCs (as compared to baseline measures). However, given

the stabilizing role of the wrist extensors, hand-tracking accuracy will be impaired to a significantly greater extent following a sustained wrist extension MVC compared to a sustained wrist flexion MVC.

Chapter 6

Objective: To examine the influence of sustained wrist flexion and extension maximal voluntary contractions on forearm muscle activity and corticospinal excitability to forearm muscles during low-intensity hand gripping.

Hypotheses: Given that the wrist extensors provide significant co-contraction during wrist flexion, muscle activity and corticospinal excitability of the wrist extensors will increase equally following either sustained wrist extension or sustain wrist flexion. However, because the wrist flexors are highly task-dependent, and produce little co-contraction during wrist extension, the wrist flexors will exhibit increased muscle activity and corticospinal excitability *only* following the wrist flexion fatigue session.

Chapter 2. Literature review

Review of musculoskeletal anatomy and physiology

2.1.1 Bones and bony landmarks

The human forearm is the region of the upper-limb that exists between the elbow and wrist joints and is formed by a pair of long bones: the radius, which constitutes the lateral portion of the forearm (same side as the thumb), and the ulna, which lies medial to the radius (Moore et al., 2013). Both the radius and the ulna, from their origin at the elbow to their termination at the wrist, share multiple articular surfaces; the ulna provides stabilization for the radius to pivot. At the elbow, the radius forms a joint between the head of the radius (proximal end of the bone) and the capitulum of the humerus (lateral articular surface). The ulna, via the trochlear notch (a deep, wrench-shaped hollow created by the olecranon and coronoid processes) articulates about the trochlea of the humerus (medial articular surface). The proximal radioulnar joint, lying just distal to the elbow, is the first shared articulation between the radius and the ulna, consisting of the head of the radius (medial surface) and the radial notch of the ulna (lateral surface). Moving distally, the two bones are connected via the interosseous membrane–a connective tissue sheet that joins the radius and ulna between the proximal and distal radioulnar joints. Just proximal to the wrist, the pair form a second joint known as the distal radioulnar joint–an articulation of the head of the ulna and the ulnar notch of the radius. It is at these joints that the radius may either pronate or supinate about the ulna. At the wrist itself, the radius articulates with both the scaphoid and the lunate (carpal bones).

Both the radius and the ulna contain several bony landmarks that provide origin and insertion points for muscles that act upon either the elbow or the wrist. Of the anterior elbow, the radial tuberosity and the tuberosity of the ulna (located just distal to the coronoid process) are the insertion points for the biceps brachii (BB) and brachialis, respectively. Both are flexors of the elbow. On the posterior elbow, the olecranon process of the ulna (posterior surface) serves as the insertion site for the triceps brachii (TB) (allowing for elbow extension). Moving distally along the shaft, the radius possesses a roughened site on the lateral surface that acts as the insertion for the pronator teres muscle, while both the anterior and posterior surface of the ulnar shaft have multiple sites of muscle attachments.

Continuing outwards from the forearm, the bones of the hand and wrist are divided into three distinct groups: the carpal bones, which make up the wrist joint; the metacarpal bones, which form the so called “palm” of the hand; and the phalanges, which form each of the fingers (Moore et al., 2013). While the wrist is often referred to as a singular joint (as it will be referred to throughout this thesis), it is technically a group of eight bones which form dozens of separate articulations. These eight bones are most commonly organized into two anatomical rows–proximal and distal, with the proximal and distal carpal bones articulating about one another. Situated in the proximal row (closer to the forearm) are the scaphoid, the lunate, the triquetrum, and the pisiform. The scaphoid is the most lateral of these bones (closest to the thumb side), and directly articulates with the wrist, as does the lunate which lies just medial to the scaphoid. Further medial is the triquetrum, which articulates with the articular disk. The articular disk is an oval-shaped piece of fibrocartilage that sits between the distal ulna and the medial-proximal carpal bones. Lastly, the pisiform has no direct articulation with either the radius or the articular

disk, but is instead a sesamoid bone that is embedded within the distal tendon of the flexor carpi ulnaris. Collectively, the proximal carpal bones allow for the wrist to articulate about the forearm. In the distal row, the carpal bones include the trapezium (most lateral), the trapezoid, the capitate, and the hamate (most medial). Although there is slight overlap in articular surfaces, the distal carpal bones mostly make distal articulations with a single metacarpal bone. The trapezium, trapezoid, and capitate form articulations with the first (thumb side), second, and third metacarpals, respectively, while the hamate articulates with both the fourth and fifth metacarpal. The metacarpals themselves, which correspond to each of the five fingers, make distal articulations with the most proximal phalanges of the fingers. Each finger consists of three phalanges (proximal, middle, and distal), with the exception of the thumb that has only two (proximal and distal).

2.1.2 Muscles – elbow

The function of the humero-radioulnar joint is restricted to either flexion or extension about its joint, while pronation and supination occur when the head of the radius pivots over the ulna (Moore et al., 2013). Flexion of the elbow is accomplished largely by muscles in the anterior compartment of the humerus; specifically, the BB and brachialis, although the BB is also the primary supinator of the forearm. The BB consists of two muscle heads (neither of which attach to the humerus itself). The long head and short head originate from the supraglenoid tubercle and coracoid process of the scapula, respectively, before converging into a single insertion at the radial tuberosity. The brachialis originates at the humerus (medial and lateral surfaces of the humeral shaft) and inserts at the ulnar tuberosity. Also providing flexor action is the brachioradialis, which originates on the

distal, lateral border of the humerus (supracondylar ridge) and inserts at the radial styloid process. Extension of the elbow is accomplished almost exclusively by the TB in the posterior compartment. The TB, of which there are three heads, originates at the infraglenoid tubercle (long), above the radial groove of the humerus (lateral), and below the radial grove (medial) before converging and attaching at the olecranon process. Providing additional elbow extension is the anconeus, which originates on the lateral epicondyle of the humerus and attaches to the posterior/lateral surface of the olecranon.

2.1.3 Muscles – forearm (anterior compartment)

Muscles originating, inserting, or crossing the forearm are plentiful, and so are generally divided into superficial, intermediate, or deep muscles. The superficial muscles of the anterior compartment include the flexor carpi ulnaris (FCU) and radialis (FCR), the palmaris longus (PL), and the pronator teres (Moore et al., 2013). All four muscles share a site of origin in the medial epicondyle of the humerus, although the FCU has a second origin in the medial surface of the ulna. The pronator teres also has a second point of origin located at the coronoid process of the ulna. The FCR, FCU, and PL all attach near the wrist, with the FCR inserting on lateral side at the bases of the second and third metacarpals (metacarpals which form the index and middle finger), the FCU inserting on the medial side at the pisiform carpal bone, and the PL inserting in the center on the flexor retinaculum (fibrous sheath wrapped over the carpals) of the wrist. All three serve as flexors of the wrist, while the FCR also provides radial deviation (wrist abduction) and the FCU ulnar deviation (wrist adduction). The pronator teres attaches to the lateral surface of the radius,

at approximately mid-shaft (mid-way between elbow and wrist) and serves as the main pronator of the forearm.

The intermediate compartment is occupied solely by the flexor digitorum superficialis (FDS), which is sometimes classified as a superficial muscle considering that approximately half of the muscle is located just beneath the skin (Moore et al., 2013). However, the proximal half lies beneath all four of the previously mentioned muscles, resulting in the FDS generally being termed the lone intermediate muscle of the anterior compartment. The FDS has two origin points; the medial epicondyle of the humerus, as well as a small portion of the anterior surface of the radius. Distally the FDS diverges into four separate tendons, all of which pass through the carpal tunnel (formed by the flexor retinaculum of the wrist) before attaching to the middle phalanges of the four fingers. The FDS primarily functions to flex the metacarpophalangeal joints, but can also act as a secondary flexor of the wrist.

The deep tissue of the anterior compartment is occupied by three muscles; the flexor digitorum profundus (FDP), the flexor pollicis longus (FPL), and the pronator quadratus (PQ) (Moore et al., 2013). The FDP originates from the anterior ulna and adjacent interosseous membrane before splitting into four tendons at the wrist, passing through the carpal tunnel, and attaching at the bases of the four, distal phalanges. The FDP provides interphalangeal joint flexion, as well as minor flexion force to the metacarpophalangeal and wrist joints. The FPL lies laterally to the FDP, and originates on the anterior surface of the radius and adjacent tissue of the interosseous membrane. The FPL contains a single insertion point on the distal phalange of the thumb, and serves as the primary flexor of the interphalangeal and metacarpophalangeal joints of the thumb. The PQ, located deep to the

FDP and FPL, originates at the distal end of the ulna and lies on its anterior surface. The muscle then attaches to the distal end of the radius on the anterior surface and acts in cooperation with the pronator teres muscle to pronate the forearm.

2.1.4 Muscles – forearm (posterior compartment)

The muscles of the posterior compartment of the forearm are divided only into superficial and deep categories. The superficial muscles include the extensor carpi radialis (ECR) and ulnaris (ECU), the extensor digitorum communis (EDC), and the extensor digiti minimi (EDM) (Moore et al., 2013). All four muscles originate from the lateral epicondyle of the humerus, while the ECR has a second origin point on the supracondylar ridge (lateral surface of the humerus superior to the lateral epicondyle). Each attaches at or near the wrist, with the ECR inserting at the base of metacarpals two and three, the ECU inserting at the base of the fifth metacarpal, and ED attaching to the posterior surface of the middle and distal phalanges of the four fingers, and the EDM inserting on the posterior surfaces of the phalanges of the little finger. Extension of the wrist is achieved primarily through the actions of the ECR and ECU, although contributions are also given by the ED and the EDM. The ECR also functions to radially deviate the wrist (wrist abduction) while the ECU contributes to ulnar deviation (wrist adduction). The primary function of the ED and the EDM is to extend the four fingers and the little finger, respectively, through extension of the metacarpophalangeal and interphalangeal joints.

The deep tissue of the posterior compartment consists of four muscles; the supinator, the abductor pollicis longus (APL), the extensor pollicis (EP), and the extensor indicis proprius (EIP). The supinator originates on the lateral epicondyle of the humerus

and the posterior surface of the ulna while inserting into the posterior surface of the radius. It functions along with the BB to supinate the forearm. Just distal to the supinator is the APL, which originates on the posterior surface of the interosseous membrane and the adjacent surfaces of the ulna and radius. The APL inserts into the base of the first metacarpal and functions to abduct the thumb. Lying deep to the APL is the EP, which also originates on the posterior interosseous membrane and adjacent ulnar and radial surfaces. The EP inserts onto both the proximal and distal phalanx of the thumb and functions to thumb via extension of the metacarpophalangeal and interphalangeal joints. Lastly, the EIP originates on the posterior surface of the interosseous membrane and the posterior ulna, attaching to the posterior phalanges of the index finger. The EIP serves as the primary extensor of the index finger.

2.1.5 Peripheral nerve innervation of the upper limb

Neurological innervation for nearly all limb muscles is made possible through what are known as nerve plexuses. A plexus is an interconnected network of nerves that arises from the spinal cord and branches off to form smaller peripheral nerves–which in turn, eventually innervate peripheral tissue. In the case of the upper limb, innervation is provided by the brachial plexus (one on either side of the body) (Bargalló et al., 2010). The brachial plexus, which is located just beneath the supraclavicular fossa (or just behind/above the collar bone), is formed collectively by the C5-C8 and T1 spinal nerves. To be more specific, the brachial plexus is formed by the anterior rami which originate from the C5-C8 and T1 spinal nerves. The spinal nerves themselves are formed by the merger of the dorsal roots (which enter the spinal cord) and the ventral roots (which exit the spinal cord). More

laterally, the spinal nerves branch out into either the posterior or anterior rami. It is these anterior rami of the C5-C8 and T1 spinal nerves which form the brachial plexus. Moving again more laterally, the plexus subsequently branches out into progressively smaller peripheral nerves, including the musculocutaneous nerve, which innervates the long and short heads of the biceps brachii, the axillary nerve, which innervates the triceps brachii, the radial nerve, which innervates both the triceps brachii and the posterior forearm muscles (consisting of primarily wrist extensors), and the ulnar nerve, which innervates the muscles of the anterior compartment of the forearm (consisting primarily of wrist flexors).

2.1.6 The corticospinal pathway

The predominant descending pathway involved in the control of voluntary movement in humans is the corticospinal tract. As its name suggests, this pathway primarily originates in the motor cortex and descends down through the brain and brain stem before synapsing onto spinal neurones throughout the length of the spinal cord. Specifically, the tract originates via pyramidal cells located in the 5th layer of the motor cortex. The name 'pyramidal' arises from the pyramid-like, white matter structures of the medulla; the site at which the axons of the corticospinal tract pass through just before they decussate, or cross over (Nathan and Smith, 1955). These cells have several technically-correct names, but are most often referred to as upper motoneurons in a more general sense; anatomically superior to their inferior (lower) spinal motoneurons. In this review, they will be written interchangeably as pyramidal cells or upper motoneurons. The location of upper motoneurons within the cortex varies among individuals, but more than 60% of these cells are usually found within the supplementary, premotor, and primary motor areas of the

frontal lobe (Dum and Strick, 1991; Jane et al., 1967). Additional cells have been observed in the primary sensory area and the parietal cortex (Lemon, 2008). The axons of the corticospinal tract are characterized by a relatively linear path to the brainstem, intersecting several structures of the cerebral cortex and the midbrain on the way. Here, they form the pyramids of the medulla, which occurs just rostral to the point of decussation (Nathan and Smith, 1955). The exact percentage of the tract that decussates varies between reports, but a common estimate is that 80-90% of the corticospinal tract axons cross over to the contralateral side at the medulla (Kaneko et al., 1997). At this point, the corticospinal tract branches into two separate pathways, with 80-90% of axons that crossed over forming the lateral corticospinal tract and the remaining axons forming the anterior corticospinal tract. Axons of both tracts then continue to descend before synapsing onto lower motoneurons at various levels of the spinal cord. The axons of the lateral corticospinal tract synapse directly onto spinal neurones located on the ipsilateral side in which they've travelled (contralateral to their origin within the motor cortex). The axons of the anterior corticospinal tract, once they've reached their appropriate spinal level, must first decussate to the contralateral side before they synapse onto spinal neurones (Eyre, 2003; Nathan et al., 1990). In summary, this means that while the two tracts descend on different sides of the spinal cord, they both innervate the contralateral side of the body from their point of origin in the motor cortex. Upper motoneurons travelling along both tracts will synapse onto either a spinal interneuron or directly onto a spinal motoneuron. The exact percentage that make monosynaptic connections with spinal motoneurons varies between muscles. The spinal motoneurons–which are located in the anterior horn of the grey matter at their respective spinal level–then exit the spinal cord through a ventral root. The ventral roots which

innervate the muscles of the upper limb consist of C5-C8 and T1 spinal nerves (Johnson et al., 2006) and combine to form the brachial plexus.

Review of relevant experimental techniques

2.1.7 Surface electromyography

In short, electromyography (EMG) is a technique used to measure the electrical signals produced by the membranes of muscle fibers. These signals occur as a result of muscle fiber activation via the firing of the motoneuron that innervates said fibers (Preston and Shapiro, 2013); Electromyography and Neuromuscular Disorders, 3rd ed.). Starting at the level of the spinal cord, and upon reaching the appropriate voltage threshold, the alpha motoneuron generates an action potential (a propagating, depolarizing current) that travels down the length of its axon prior to reaching the axon terminal (and subsequently, the neuromuscular junction (NMJ)). Depolarization of the terminal results in the release of the neurotransmitter acetycholine (ACh) across the NMJ, which binds with the appropriate nicotinic ACh receptors (nAChR) on the membrane surface of the sarcolemma. nAChR is both a membrane receptor and a ligand-gated channel, and once bound with ACh, permits sodium to exit the cell. This results in the activation of adjacent voltage-gated ion channels, and thus, a depolarizing potential is generated across the surface of the membrane. Subsequent, intracellular events then occur, resulting in the sliding of the actin and myosin filaments across one another, which are responsible for the contraction of the sarcomere. However, in terms of EMG, the electric potential generated across the membrane of the sarcolemma is generally large enough to be detected by recording devices. This is of special interest to researchers as patterns of muscle activation can speak to motor control strategies, sport performance, neuromuscular pathologies following disease or injury, and the efficacy of rehabilitative programs.

While surface EMG is limited in that only superficial muscles can be effectively measured (the electrical activity of deeper muscles may not reach the recording sites), it is the least invasive technique of all EMG recording procedures (Preston and Shapiro, 2013). Rather than needles or fine wire, surface EMG measures the summative electrical activity of motor unit action potentials (MUAPs) of skeletal muscles using paired, skin-surface electrodes. Two electrodes are typically recommended over one in order to reduce any electrical noise from the recorded signal (noise referring to any unwanted electrical signals that are not produced by the target muscle, such as electromagnetic fields, static electricity, etc.). When EMG is collected as both a magnitude and a vector (a signal is considered positive as it approaches the electrode, while negative as the signal retreats), the true EMG signal should appear uniquely to each of the two electrodes. Any signal recorded by the electrodes that appears the same to both electrodes must therefore be electrical noise, and can be subsequently removed from the rest of the data. This process is usually carried out by a differential amplifier, which functions both to cancel out external interference between the two electrodes and to amplify the true EMG signal. Un-amplified EMG falls in a typical range of a few microvolts-to-one or two millivolts. In most kinesiology-based research, EMG signals are amplified by a gain of 500-1000.

While paired-electrode recording techniques are effective at reducing electrical noise, they are not always enough on their own. A second strategy for improving signal quality is signal processing, or signal filtering. For surface EMG, the majority of the signals collected will be from motor units firing in a range of 10-250 Hz (Preston and Shapiro, 2013). To isolate this frequency range, a band pass filter can be utilized to remove any signals that fall outside of this breadth. A band pass filter consists of both a high pass (any

frequencies above this value will be collected) and a low pass (any frequencies below this value will be collected). The International Society of Electrophysiology in Kinesiology (ISEK) and the Surface ElectroMyoGraphy for the Non-Invasive Assessment of Muscles (SENIAM) recommend a band pass filter of 10-500 Hz for kinesiology related research studies as anything below 10 Hz will likely be a movement artifact of the electrodes/wires and anything above 500 Hz is unlikely to be biological.

Following amplification and filtering, the analog EMG signal is then converted to a digital EMG signal in order to be visually displayed and analyzed. Analog-to-digital converters (A/D boards) are characterized by their resolution (how precisely the analog signal can be converted to digital). For kinesiology-related research, a 12 bit A/D board is generally sufficient, as it provides 4095 intervals with which to convert the analog signal (4095 unique, digital values which can be assigned based on the analog signal). Unusually small signals may require higher resolution (16 bit) to be effectively measured. An additional technical item that is of great importance in terms of A/D conversion is the sampling rate used to collect the EMG signal. In order to avoid under-sampling (also known as aliasing), the Nyquist theorem states that the sampling frequency should be set to at least twice as high as the maximum expected signal frequency (1000 Hz). If sampling rates fall below the Nyquist value, there is a possibility that both the frequency and magnitude of the EMG signal will be under, or erroneously, reported. However, most kinesiology researchers recommend higher sampling rates (2000-5000 Hz), with a general rule-of-thumb being the higher the sampling rate, the better the signal.

2.1.8 Co-contraction

When an agonist muscle (or a prime mover) contracts to elicit movement of an innervated joint, antagonist muscles will simultaneously contract (although, typically to a lesser degree). This antagonistic activity is commonly referred to as co-contraction or co-activation. While some research groups consider these terms to be distinctly different, other groups use them interchangeably. In the context of this thesis, co-contraction will be defined as the muscle activity produced by an antagonist muscle in relation to the activity of an agonist muscle.

Intuitively, greater co-contraction tends to decrease net agonist torque, since the torque produced by the antagonists opposes the desired action of the prime movers (Baratta et al., 1988). On a surface level, this behaviour might seem counter productive and metabolically wasteful when executing motor tasks. However, co-contraction has long been thought to increase the stability of joints which are acted upon by the agonists. By contracting all muscle tissue that crosses a given joint, not only will the forces exerted upon said joint be more evenly distributed (and thus, reduce joint damage (Baratta et al., 1988; Solomonow et al., 1988)), but the joint itself will be more capable of resisting external torques or perturbations. From an injury risk standpoint, co-contraction is therefore potentially advantageous.

This function, however, has been challenged in recent decades by research that has shown co-contraction to decrease with resistance training and/or practice (Carolan and Cafarelli, 1992; Enoka, 1997; Häkkinen et al., 1998; Macaluso et al., 2002). The prevailing notion is that, as strength increases through training, motor pathways can more efficiently execute goal-oriented tasks without wasting energy on antagonist activity. Thus, how can

co-contraction be a beneficial quality if it is reduced by training? This question is perhaps unnecessary, given that other investigations have shown co-contraction to increase with training (Gabriel et al., 1997; Gabriel and Boucher, 2000), while others have found no change at all (Morse et al., 2005; Reeves et al., 2003). In light of these contradictory conclusions, co-contraction remains widely used as a surrogate measure of joint stability, particularly since it is associated with increases in joint stiffness (Holmes et al., 2015; van Loon et al., 2001).

Although there are numerous ways in which co-contraction can be assessed, this thesis will focus only on two of the most common methods. The first and perhaps most common method is referred to as a co-contraction index (CCI), and is given by the following formula:

$$CCI = \sum_{i=1}^{N} \left[\left(\frac{EMG_{low(i)}}{EMG_{high(i)}} \right) (EMG_{low(i)} + EMG_{high(i)}) \right]$$

where N is the total number of data points within a given measurement trial and i is a specific data point. At each specific data point, the equation uses the greater muscle activity (usually produced by the agonist) and the lesser muscle activity (usually produced by the antagonist) in an agonist-antagonist pairing. For instance, if CCI was calculated on the biceps and triceps brachii during concentric elbow flexion, the biceps brachii would almost assuredly be producing greater muscle activity. Thus, the equation would divide triceps brachii activity (low) by biceps brachii activity (high). The last portion of the equation multiplies this ratio by the sum of the triceps and biceps brachii activity, which is the

primary advantage of CCI over other methods of evaluating co-contraction. This last step allows for CCI to account for changes in overall muscle intensity along with potential changes in co-contraction. For instance, in a given trial where the triceps brachii are active to 10% of their maximum activity, but the biceps brachii are active to 20% of their maximum activity, a direct ratio would indicate a triceps brachii co-contraction value of 50%. However, if these activity values were instead 40 and 80%, respectively, the ensuing ratio would still be 50%, despite a drastic increase in task intensity and overall joint loading. That said, CCI is not without its limitations. First, the primary goal of calculating co-contraction is to assess antagonist muscle activity *relative* to agonist muscle activity. This antagonist-agonist relationship can be obscured using CCI since the ratio is multiplied by the sum of the activity of the two muscles. Second, the CCI equation establishes its fraction based on low and high muscle activity of an antagonist-agonist pairing with the assumption that antagonists will always be less active than the agonist. However, this is not always the case. For instance, in the study by Mogk and Keir (2003), whereby muscle activity of forearm muscles was quantified during various grip forces, wrist extensor activity (antagonists) often matched, or even exceeded wrist flexor (agonists) activity. Grip force is produced primarily by muscle contraction of the flexor digitorum muscles (FDS and FDP), indicating that the wrist flexors are the prime movers during this motor task. Yet, if extensor muscle activity were to exceed flexor activity while gripping, the flexors would be used as the numerator in the CCI equation. Thus, it is possible for agonists and antagonists to flip back and forth (within the fraction) over the course of a prolonged trial. This can make CCI outputs difficult to interpret.

An alternative to the CCI is a direct antagonist muscle activity/agonist muscle activity ratio, which does not take motor task intensity into account:

$$CC = \frac{Antagonist\ EMG}{Agonist\ EMG}\ x\ 100$$

In this method, the numerator and denominator are not selected based on the activity of any muscle, but rather on which muscle would mechanically drive a given motion (agonist) and which muscle would mechanically oppose a given motion (antagonist). Again referring to the work by Mogk and Keir (2003), a direct antagonist/agonist ratio would use the extensors as the numerator and the flexors as the denominator during gripping regardless of their muscle activity. The advantage of this method is that it conveys antagonist co-contraction activity relative to the activity of the agonist. However, as mentioned above, this method does not take into account the overall intensity of the motor task. It is therefore recommended that, when using direct antagonist/agonist ratios, researchers also take intensity into account with a secondary measure, such as normalized muscle activity.

2.1.9 Kinematic tracking

In precision or tracking motor tasks, accuracy can be quantified in a number of different ways. This section will discuss the methods most applicable to this thesis. Figure 2.1 shows an example tracking task. In this task, the white filled circle is travelling around

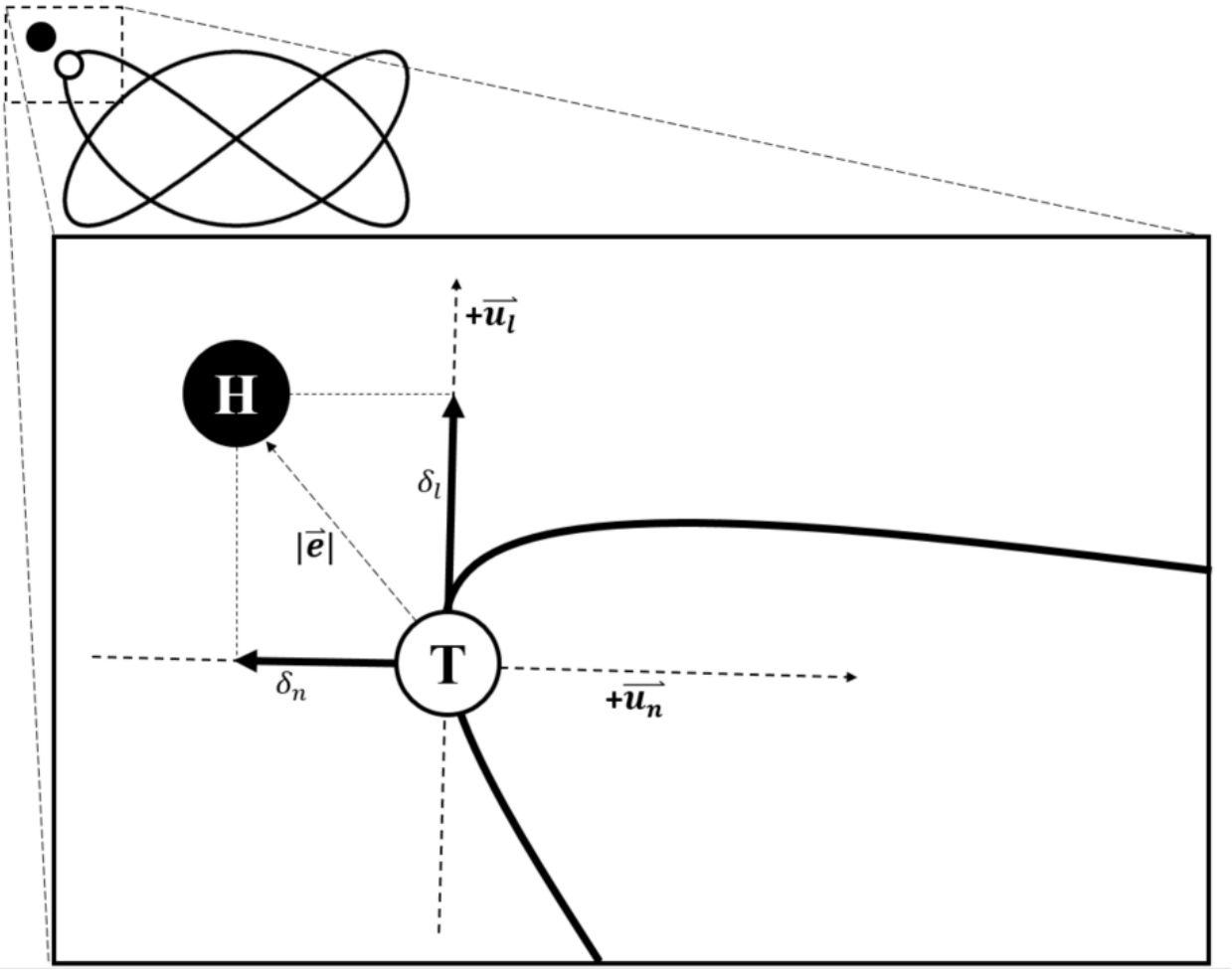

Figure 2.1. *Upper left corner: a digitally displayed target (white filled circle) moves with an upwards trajectory along a fixed path while an individual attempts to follow that target by manipulating a robotic handle (black filled circle). Center: zoomed in view of target and hand position. "H" indicates the position of the handle, while "T" is the position of target. In this circumstance, the handle is situated ahead of and to the left of the target's position.*

the Lissajous curve at a predetermined cadence. A participant is grabbing the handle of a wrist robot, which is digitally interfaced onto a computer monitor, and is trying to match their own circle (black filled circle) with the position of the target (white filled circle). At

the instantaneous moment of this figure, the target was moving with a mostly upwards trajectory (almost no lateral movement). It is visually obvious that, at this moment in time, the participant was both ahead of and to the left of the target's position. Thus, their movement accuracy was imperfect; perfect accuracy would occur only if the handle was completely covering the target's position. However, this begs the question, how best to quantify this error?

Tracking error: The simplest method of quantifying movement error (and therefore imperfections in movement accuracy) will be referred to as tracking error. Tracking error is shown in Figure 2.1 as $|\vec{e}|$ and simply represents the most direct distance between the target's position and the handle's position. This metric is simply a magnitude (not a vector) with no signed values. It is calculated as the hypotenuse formed by the error in the x-coordinate (the 'x' position of the handle minus the 'x' position of the target) and the error in the y-coordinate (the 'y' position of the handle minus the 'y' position of the target). The specific formula is displayed here:

$$|\vec{e}| = \sqrt{(H_x - T_x)^2 + \left(H_y - T_y\right)^2}$$

where $|\vec{e}|$ is the Euclidean distance, and *H* and *T* are the positions (x, y coordinates) of the handle and target, respectively. In the case of a dynamic tracking movement with multiple time points, the tracking error for each sample is typically summed and divided by the total number of samples to give mean tracking error. A large tracking error value indicates worse movement accuracy (i.e. the participant's handle is far from the position of the target). However, tracking error alone provides no information into the direction, or the consistencies, in how a participant might be missing the target. To quantify directional

error (that is, error relative to the target's trajectory), the longitudinal and normal components of tracking error must be assessed.

Longitudinal component: The longitudinal component of tracking error conveys whether the handle's position was ahead of or behind the target's position. This is determined based on the target's instantaneous trajectory. In Figure 2.1, the target's trajectory is denoted by $\overrightarrow{u_l}$ while the longitudinal component is shown by δ_l. Since this measure is based on trajectory, it is a vector quantity. The value of the longitudinal component is positive if the handle's position lies ahead of the target's position, relative to the target's trajectory. In the case of Figure 2.1, the handle is clearly ahead of the target, and therefore, δ_l would be a positive value. The full formulas to calculate both target trajectory ($\overrightarrow{u_l}$) and the longitudinal component (δ_l) are shown here:

$$\overrightarrow{u_l} = \frac{1}{\sqrt{\dot{T}_x{}^2 + \dot{T}_y{}^2}} \begin{bmatrix} \dot{T}_x \\ \dot{T}_y \end{bmatrix} = \begin{bmatrix} ux_l \\ uy_l \end{bmatrix}$$

$$\delta_l = \vec{e} \cdot \overrightarrow{u_l}$$

where $\overrightarrow{u_l}$ is the unit vector of the target's trajectory at each data point, and δ_l is the longitudinal component of the tracking error. To establish trajectory, the first derivative is taken of the target's position (given by $\dot{T}_x{}^2 and\ \dot{T}_y{}^2$), and the tangent vector of the trajectory is determined. The norm of the obtained vector is calculated. Then the tangent vector is normalized to obtain the unit vector. $\overrightarrow{u_l}$ is then multiplied against the error vector measured from earlier ($\vec{e}$, see Tracking Error) which gives either a positive (handle is ahead of the target) or negative (handle is behind the target) value.

Normal component: The normal component of tracking error conveys whether the handle's position was to the right or the left of the target's position. This is determined by taking the orthogonal value of the target's trajectory. In Figure 2.1, the target's trajectory is denoted by $\overrightarrow{u_l}$, but the orthogonal vector is shown with $\overrightarrow{u_n}$. The normal component is given by δ_n. Like the longitudinal component, this measure is a vector quantity. The value of the normal component is positive if the handle's position lies to the right of the target's position, relative to the target's trajectory. In the case of Figure 2.1, the handle is clearly to the left of the target, and therefore, δ_n would be a negative value. The full formulas to calculate both the orthogonal of the target's trajectory ($\overrightarrow{u_n}$) and the normal component (δ_n) are shown here:

$$\overrightarrow{u_n} = \begin{bmatrix} uy_l \\ -ux_l \end{bmatrix}$$

$$\delta_n = \vec{e} \cdot \overrightarrow{u_n}$$

Just like for the longitudinal component, in order to establish whether the handle is to the right or left of the target, the direction of trajectory of the target must first be established. This is given by the $\overrightarrow{u_l}$ equation described earlier. $\overrightarrow{u_n}$ is simply the orthogonal of $\overrightarrow{u_l}$ and is then multiplied by the error vector. This then gives either a positive (handle is to the right of the target) or negative (handle is to the left of the target) value.

Figural error: Even if a participant was terribly inaccurate while trying to match the position of the moving target, it is still possible that they might have followed the target's path with a high level of accuracy. In other words, they may have been unable to keep up with the target, but they still successfully recreated the shape of the Lissajous curve (Conditt et al., 1997). This type of performance cannot be quantified with the previously

mentioned metrics. Rather, this is quantified by calculating the participant's figural error (not shown in Figure 2.1) which is insensitive to time (it doesn't matter how long it takes an individual to complete the trace). To accomplish this, a single data point of the handle's position is subtracted from every single data point of the target's path. The minimum distance from this single data point of the handle is retained; this process is then repeated for the next data point. Additionally, a single data point of the target is subtracted from every single data point of the handle's movement. Again, the minimum distance is retained. Full details of the formula for figural error are shown below:

$$dist_{AB}(i) = \min_{j} \left|\left|A_i - B_j\right|\right| \quad i = 1, 2, \ldots n$$

$$dist_{BA}(j) = \min_{i} \left|\left|A_i - B_j\right|\right| \quad j = 1, 2, \ldots m$$

$$FE_{AB} = \frac{\sum_{i=1}^{n} dist_{AB}(i) + \sum_{j=1}^{m} dist_{BA}(j)}{n + m}$$

where "*A*" and "*m*" are the time series and total samples of the target trajectory and "*B*" and "*n*" are the time series and total samples of the handle trajectory. The first equation calculates the distance between a single data point of the target (denoted by *j*) and every data point of the handle before moving to the next target data point. The minimum distance of all these comparisons is then taken. **[**For example, if at sample number 100, the position of the handle was directly overlaying some portion of the Lissajous curve (this could be at any point along the target trajectory) the minimum distance would be zero.**]** The second equation is the same, but in reverse, and compares every data point of the target against a single data point of the handle. The final equation adds the sum of all the minimum distances and divides it by the sum of the two samples. A final figural error score of 0

would indicate that the handle was directly overlaying the target trajectory throughout the entire trial.

Jerk ratio: Even if a participant were to demonstrate low levels of error (for all four methods stated above), indicating that they remained close to the target at all times, these measures say nothing about how smooth the participant was able to move. This can be assessed using the jerk ratio. In the same way that velocity can be derived from displacement, jerk can be calculated by taking the third derivative of displacement. Jerk therefore indicates changes in acceleration. In the case of a jerk ratio related to a moving target with a predetermined movement and velocity, changes in acceleration are relatively small; movement is inhumanly smooth. A ratio is therefore a calculation of the integrated squared jerk (ISJ) (Platz et al., 1994) of the handle divided by the ideal ISJ of the target. ISJ is given by $\int \left(\dddot{H}_x^2 + \dddot{H}_y^2 \right) dt$ and integrated over the entire tracking trial. As the jerk ratio in this circumstance is a comparison of the handle to the target, a value of 1 would represent movement that is as smooth as possible. Any value greater than 1 would signify movement that is less smooth than the movement of the target. In studies where this method has been employed, it is not uncommon for jerk ratios to be in the 100s (Salmond et al., 2017).

2.1.10 Assessing corticospinal excitability

The electrical properties of the corticospinal tract are in constant flux. At all times, the corticospinal tract receives synaptic input from a wide range of sources, including interneuronal circuits in the cortex and spinal cord, other regions of the brain, the brain stem, and sensory feedback from the peripheral nervous system. The sum of this input, as

well as any changes in intrinsic electrical properties of the cells that compose this pathway, modulates the responsiveness of the corticospinal tract, making it more or less likely to produce a motor output. In neurophysiology, this responsiveness is referred to as *excitability*. For example, in individuals at rest, where their body is fully relaxed, corticospinal excitability is generally low. If, however, these individuals were to move their limbs, contract a target muscle, or even just consciously think about moving, corticospinal excitability would increase, meaning that the pathway has become more responsive and that a motor output is more likely. In humans, the excitability of the corticospinal tract is typically measured indirectly using either electrical or magnetic stimulation techniques. These methods apply stimulation over a specific region of the pathway, such as the motor cortex, brainstem, or spine, and measure the evoked response that manifests within a target muscle (McNeil et al., 2013). The size of the response, or how quickly the response occurs, can indicate the excitability of the corticospinal tract at the time the stimulation was delivered. Using the example mentioned above, if a stimulation of 'X' intensity was delivered to the motor cortex while a participant was at rest, it is possible that no response would be observed due to the low excitability of the corticospinal tract; neither the pyramidal neurons, nor the cortical neurons that innervate them, may have been close enough to threshold for the stimulation to induce action potentials. Under different conditions, such as a mild muscle contraction that would cause some of the pyramidal cells to begin firing (while the ones that are not firing action potentials would move closer to firing threshold), that same stimulation intensity (i.e. 'X') might result in a substantially larger response, indicating an increase in the excitability of the pathway. In other words,

the collective of neurons along the corticospinal tract (and those that act upon the pyramidal neurons) were able to fire action potentials more easily.

A multitude of techniques exist to measure corticospinal excitability in humans. While this thesis only utilized one to quantify changes in corticospinal excitability, this review will examine a total of four techniques, given the frequency in which they are reported in literature regarding fatigue. Specifically, these techniques are transcranial magnetic stimulation (TMS), transmastoid electrical stimulation (TMES), the Hoffmann reflex (H-reflex), and peripheral nerve stimulation.

2.1.11 Transcranial magnetic stimulation

TMS is a technique that works through a process known as electromagnetic induction. This is the same process that allows electric current to be generated within conductive wires (power grid) through the movement of a turbine via wind, hydro, or fossil fuel burning. In the case of magnetic stimulation, a conductive wire is repeatedly wrapped into a circle (or coil) and encased in an insulting material. When a large but brief current is passed through this coil, a magnetic field is rapidly generated, both within the center of the coil and around the coil's nearby proximity. Since human skeletal muscle and human neural tissue can conduct electricity, the discharge of the magnetic coil near either of these tissues has the capacity to generate action potentials (in neurons and in muscle fibers). When a magnetic coil is discharged over the skull (or more specifically, the motor cortex), this is referred to as transcranial magnetic stimulation (TMS) (Barker et al., 1985). Typically, this technique does not *directly* activate the pyramidal neurons of the corticospinal tract, as they are located deep within the motor cortex. Instead, TMS more commonly activates

interneurons in the upper layers of the motor cortex, which then synapse onto the pyramidal neurons of the corticospinal tract. This is referred to as trans-synaptic activation, since activation occurs across one or more cortical synapses. The number of synapses that occur before the signal reaches the corticospinal tract depends on which of the individual cells in the upper layers of the motor cortex are being activated. Therefore, the sum of the synaptic input delivered to the pyramidal neurons does not necessarily arrive at the same time (i.e. temporal summation occurs). Consequently, TMS results in the production of multiple descending volleys rather than just one synchronized evoked response. This has previously been demonstrated in practice as it is possible to observe these volleys at the spinal cord via epidural electrodes (Burke et al., 1993). These are known in literature as indirect waves (I-waves) and are the result of the trans-synaptic nature of TMS (Di Lazzaro et al., 1998a). It is possible for certain individuals, and at high enough stimulation intensities, to directly stimulate the corticospinal tract (or directly activate the pyramidal nerves themselves). These are referred to as direct waves (D-waves) and can be distinguished from I-waves in electromyography recordings (EMG) by their shortened latency of approximately 1-1.4 ms (Burke et al., 1993; Di Lazzaro et al., 1998a). Responses elicited from TMS are usually recorded from a target muscle as a compound muscle action potential–termed a motor evoked potential (MEP) (Taylor et al., 2002). The peak-to-peak amplitude, the onset latency of the evoked response, and the corticospinal silent period (CSP) (the duration of time from the onset of the stimulus artifact to when voluntary EMG returns following the evoked response) of the MEP are used to assess changes in corticospinal excitability under different experimental conditions. An increase in the MEP amplitude, a decrease in the onset latency, and a decrease in the CSP are typically interpreted as representing an

increase in corticospinal excitability. However, an important point to remember is that the corticospinal tract is composed of cortical and spinal components that ultimately innervate peripheral tissues. It is therefore possible that changes in excitability (i.e. changes in the MEPs) between experimental conditions are due to changes at the supraspinal level, the spinal level, the peripheral level, or a combination between all three. Determining the source(s) of that change is difficult with TMS alone as MEPs are an indicator of overall motor pathway excitability. Due to this limitation, TMS is often used alongside both an independent measure of spinal excitability and an independent measure of peripheral excitability in order to interpret MEPs to a greater degree. Examples of such techniques are transmastoid electrical stimulation (TMES), the Hoffmann reflex (H-reflex), and peripheral nerve stimulation.

2.1.12 Transmastoid electrical stimulation

Although its use is less common than some other methods, TMES is one of the highest quality measures of spinal excitability in humans. The technique involves an electric current being passed between surface electrodes placed on the mastoid processes on the back of the skull. Stimulation at this location activates the axons of the corticospinal tract (axons of the upper/pyramidal neurons) near the cervicomedullary junction (Taylor, 2006). This site has been determined as an optimal location for stimulation as the corticospinal tract decussates at this level and the bending of the axons provides a larger, and more readily activated surface area (Amassian et al., 1992; Maccabee et al., 1993). The resulting effect is a single descending volley in the muscles of the upper limb, and in some individuals, the lower limb (Ugawa et al., 1991, 1995a). For the upper limb, the single

volley produced by TMES proceeds down the axons of the pyramidal neurons, synapses with spinal motoneurons, and produces an electrical response at the target muscle. This evoked response is known as a cervicomedullary evoked potential (CMEP) and is used as a means to distinguish changes in spinal excitability under different experimental conditions (Taylor, 2006). An increase in the CMEP amplitude is typically interpreted as representing an increase in spinal excitability. It is therefore an appropriate choice to be used alongside TMS in order to differentiate changes in corticospinal excitability as being derived from either supraspinal or spinal sources.

An issue worth noting with TMES is that stimulation between the mastoid processes has a tendency to activate the ventral roots emerging from the spinal cord, along with the desired corticospinal tract (Ugawa et al., 1991). Ventral roots have been observed to bend upon their exit from the spinal cord, which provides a second, easily activated site following electrical stimulation (Mills and Murray, 1986; Rossini et al., 1985). If the ventral roots are indeed activated, this will likely appear in an EMG trace as a sudden decrease in the CMEP onset latency by approximately 2 ms (Ugawa et al., 1991). This can be a potential problem, as activation of the axons of the spinal motoneurons no longer represents the excitability of the motoneurons themselves. CMEP onset latency must therefore be carefully monitored when using TMES as an experimental technique.

One assumption that must be met when using different techniques to assess corticospinal and spinal excitability is that both techniques activate similar axons within the corticospinal tract. Paired TMS and TMES stimulation paradigms have demonstrated that these two techniques do indeed activate similar motor pools, as the antidromic action potentials produced by TMES appear to collide with and cancel the descending volleys

induced by TMS (Taylor et al., 2002). This finding suggests that both techniques travel along the same pathways, thus validating the use of TMS and TMES to examine corticospinal excitability.

2.1.13 Hoffmann reflex

First described in 1910 by Paul Hoffmann, the Hoffmann reflex (H-reflex) is an electrically-induced stimulation technique that mimics the same spinal pathway as the natural stretch reflex (Hoffmann, 1910). However, in contrast to a mechanically-induced stretch reflex, the H-reflex bypasses the muscle spindle by directly activating the 1a afferent neuron. Stimulation of 1a afferent neurons (typically at the site of a mixed fiber peripheral nerve) results in monosynaptic activation of the corresponding alpha motoneurons, which in turn activates muscle fibers of the agonist muscle. Recorded as EMG from the muscle, the H-reflex is thus an estimate of alpha motoneurone excitability. To elicit an H-reflex, an electric stimulation is applied to a mixed nerve that innervates a desired muscle. For example, to elicit H-reflexes from the wrist flexor muscles of the forearm, the median nerve of the forearm muscle be stimulated (Carroll et al., 2006). Bipolar surface electrodes are positioned over the median nerve at a site just proximal to the medial epicondyle of the humerus (Carroll et al., 2006). As with the other techniques discussed in this review, responses are then recorded from the target muscle as surface EMG. Generally speaking, the parameters for H-reflex stimulation are different from that of CMEPs. For CMEPs, moderate stimulation intensity (150-350 mA) and short stimulation duration (100-200 μs) are ideal, while for H-reflexes, low stimulation intensity (50-100 mA) and long stimulation duration (1 ms) are required.

A common misconception regarding the H-reflex is that it is an isolated measure of motoneuron excitability. While changes in the H-reflex amplitude can result from changes in motoneuron excitation, Ia afferents are subject to pre-synaptic inhibition (Zehr, 2002). As a brief aside, pre-synaptic inhibition occurs when an inhibitory neuron (almost always an interneuron) synapses with the axon terminal of another neuron (referred to as axo-axonal synapse), and can decrease the volume of neurotransmitter release from this second neuron. In the case of the stretch reflex, inhibitory interneurons make axo-axonal synapses with the axon terminal of 1a afferents, immediately prior to 1a afferents forming axo-dendritic synapses with alpha motoneurons. Changes in the activation of these presynaptic inhibitory neurons influences the amount of neurotransmitter release from 1a afferents to alpha motoneurons, thus indirectly modulating the excitability of the alpha motoneurons. It is thought that the purpose of these interneuronal connections is to regulate the amount of afferent information reaching the spinal motoneuron, and thus limiting or reducing any unwanted reflexes during movement (Zehr, 2002). Therefore, in the case of the H-reflex, it is possible that any changes observed may be due to either changes in the conductivity of the Ia afferents, changes in presynaptic inhibitory activity acting upon the Ia terminals, changes in intrinsic excitability of the motoneuron, or a combination of the three.

2.1.14 Peripheral nerve stimulation

When either TMS, TMES, or the H-reflex are used to elicit a response in a target muscle (which is subsequently recorded with surface EMG as an evoked potential), there is the possibility that any changes within the conductivity (or excitability) of the motoneuron's axon, the neuromuscular junction, or the muscles fibers themselves could

influence the size of these responses. A commonality between these three techniques is that none of them are capable of independently accounting for so called "peripheral" excitability. Instead, this is accomplished by stimulating (usually by electrical stimulation) the peripheral nerve that contains efferent fibers to the target muscle. Just like the previously mentioned techniques, when the peripheral nerve is stimulated, an evoked potential can be measured at the target muscle with surface EMG. In the case of peripheral nerve stimulation, this response is referred to interchangeably as a compound muscle action potential (CMAP), or more commonly as an M-wave (Tucker et al., 2005). For studies of the upper limb, particularly in the case of proximal muscles such as the biceps and triceps brachii or the brachioradialis, stimulation typically occurs at the brachial plexus. At this stimulation site, the cathode electrode is placed on the supraclavicular fossa, while the anode is placed over the acromion process (Aboodarda et al., 2015a; Copithorne et al., 2015; Forman et al., 2014; Philpott et al., 2015). Also like the previously mentioned techniques, the amplitude of the M-wave increases with greater stimulation intensity. In the case of the M-wave, the most common stimulation intensity utilized is an intensity which elicits a maximal M-wave response in a target muscle–commonly referred to as M_{max}. A maximal M-wave is desirable in many scientific investigations, since the M_{max} is widely considered to be a reliable measurement of total muscle activation (Desmedt, 1973; Hwang, 2002). Thus, by normalizing measures of corticospinal (TMS) or spinal (TMES/H-reflex) excitability to the M_{max}, it is possible to make inferences into what relative portion of the corticospinal pathway is being examined with these techniques. Additionally, since the M_{max} is a reflection of peripheral excitability (motoneuron axon, neuromuscular junction, and muscle fibers), any change in the M_{max} amplitude is likely to influence

measures of corticospinal and spinal excitability. It is therefore common for studies to present their findings of corticospinal and spinal excitability relative (or normalized) to the M_{max} elicited under the same experimental conditions (Copithorne et al., 2015; Forman et al., 2014, 2015, 2019a; Gandevia, 2001; Philpott et al., 2015). The importance of comparing other stimulus measures to the M_{max} under the same experimental conditions is vitally important. While the M-wave response to electrical peripheral nerve stimulation tends to be highly stable and repeatable, this steadiness can be compromised by certain factors. In studies where these factors have been used as independent variables, the amplitude of the M_{max} has been shown to change at different limb positions (Simonsen et al., 1995; Simonsen and Dyhre-Poulsen, 1999), during various levels of muscle contraction (Nagata and Christianson, 1995; Tucker and Türker, 2004), over the course of a long experiment (Castaingts et al., 2004; Crone et al., 1999), or at different muscle temperatures (Castaingts et al., 2004). Thus, in investigations using M_{max} to normalize their other measures of corticospinal and spinal excitability and to account for changes in peripheral excitability, the M_{max} must be elicited under as close to identical experimental conditions as possible. Otherwise, it is possible that the M_{max} could change (or remain steady) independently of changes in corticospinal excitability, and any attempt to normalize evoked potentials would result in erroneous interpretations of data.

2.1.15 Anatomical differences between the wrist flexors and wrist extensors

While the wrist flexors and the wrist extensors of the forearm are functional antagonists, their anatomical characteristics are not simply equal and opposite. In fact, there are considerable disparities between the two muscle groups. Figure 2.2 shows a cross-sectional view of the forearm and the muscles which make up its anterior and posterior

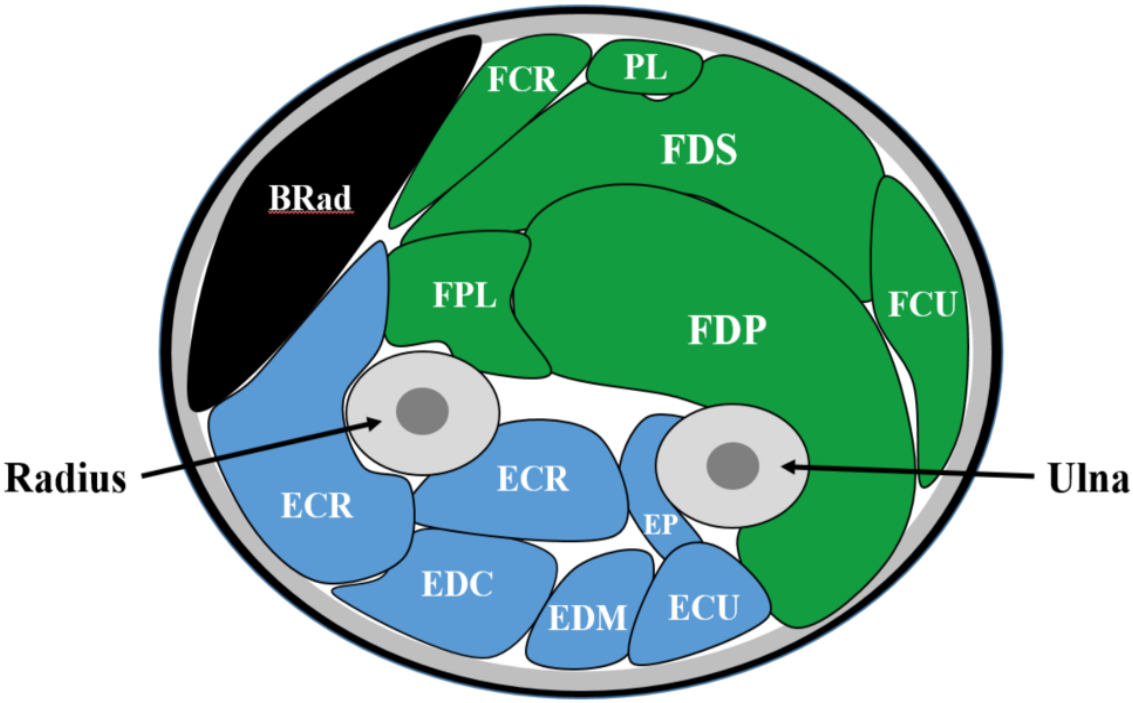

Figure 2.2. *Cross-sectional view of the radius, ulna, and the muscles of the forearm. Muscles in green reside in the anterior compartment of the forearm and act to predominantly flex the wrist and the fingers. Muscles in blue reside in the posterior compartment of the forearm and act to predominantly extend the wrist and the fingers. Note the greater size of the flexors.*

compartments. In this diagram, it is immediately obvious that there is a considerable size difference between the wrist flexors and wrist extensors. In cadaveric studies, this difference in physiological cross-sectional area (PCSA) has been reported as being approximately a 2:1 ratio in favour of the wrist flexors (Anterior compartment: ~24.8 cm^2, Posterior compartment: ~11.8 cm^2) (Gonzalez et al., 1997; Jacobson et al., 1992; Lieber et

al., 1992, 1990). The largest contributors to this difference are the FDS (6.3 cm^2) and the FDP (7.9 cm^2), which are the primary muscles involved in gripping, although they can contribute to wrist flexion moments as a secondary function. For the muscles which solely act upon movement of the wrist (FCR and FCU; ECR and ECU), the differences in PCSA are less noticeable (Wrist flexors: 5.4 cm^2; Wrist extensors: 6.8 cm^2). However, when examined cumulatively for the entire forearm, these findings suggest that the wrist flexors are significantly stronger than the wrist extensors, given that PCSA is a strong predictor of muscle strength (Gonzalez et al., 1997). This disparity is further compounded by differences in mechanical advantages. Estimated via modelling work, the wrist flexors cumulatively possess larger moment arms, both when the wrist is held in a neutral position (Wrist flexors: 1.3 cm, Wrist extensors: 1.2 cm) and when the wrist is manipulated to maximize the moment arms of each muscle group (Wrist flexors: 1.6 cm, Wrist extensors: 1.3 cm) (Gonzalez et al., 1997). Since peak moment generation is derived from muscle strength and moment arm length, model estimates suggest that the wrist flexors are capable of generating peak moments in excess of 2:1 to the wrist extensors (Gonzalez et al., 1997). As a consequence of these differences, the wrist extensors must be active to a greater relative percentage of their maximal activation (by recruiting more motor units or discharging active units more rapidly) in order to counter the greater torques produced by the wrist flexors. This is considered to be the primary reason why the wrist extensors tend to exhibit higher levels of muscle activity than the wrist flexors (Mogk and Keir, 2003). It is also suspected to be the leading mechanism for why the wrist extensors have an earlier onset of fatigue, and develop chronic overuse injuries more frequently, than the wrist

flexors (Hägg and Milerad, 1997; Ranney et al., 1995; Shiri et al., 2006; Chris J Snijders et al., 1987).

2.1.16 Muscle lines of action

With few exceptions, muscles of the skeletal system attach to bony sites via a proximal and a distal musculotendinous unit. Between these two attachment sites, the belly of the muscle will typically cross one or more joints. During muscular contraction via shortening of the muscle's sarcomeres, any joint that the muscle crosses will move/change in angle. How the angle of that joint specifically changes depends on several elements, but the most important factor is undoubtedly the geometric path between the muscle's origin and insertion points. When muscles contract/shorten, they serve to draw their origin and insertion points closer together. Most muscles shorten in a *relatively* straight path (there are numerous exceptions to this statement), and thus, movement of the joint in relation to the muscle is relatively straight as well. This characteristic is referred to as a muscle's line of action and is influential in determining how joints move. For instance, the deltoid muscle has a single insertion point on the humerus at the deltoid tuberosity, but possess three origin points in close proximity; the lateral portion of the clavicle (anterior head), the acromion process (lateral head), and the spine of the scapula (posterior head). These three unique origin points provide the deltoid with three unique lines of action, which allow the deltoid to independently flex, abduct, and extend the humerus about the glenohumeral joint. In the case of the forearm, muscle lines of action are particularly interesting. Despite the fact that a total of 14 muscles cross the wrist joint, only 5 are solely dedicated to wrist movements (although many of the remaining 9 contribute to wrist movements as secondary functions)

(Bawa et al., 2000). These muscles include the flexor carpi radialis (FCR), the palmaris longus, the flexor carpi ulnaris (FCU), the extensor carpi radialis brevis and longus (ECR), and the extensor carpi ulnaris (ECU). Although their names indicate that the FCR and FCU are wrist flexors, and the ECR and ECU are wrist extensors, work into muscle lines of action of the forearm provide conflicting evidence. In 2000, Chalmers and colleagues

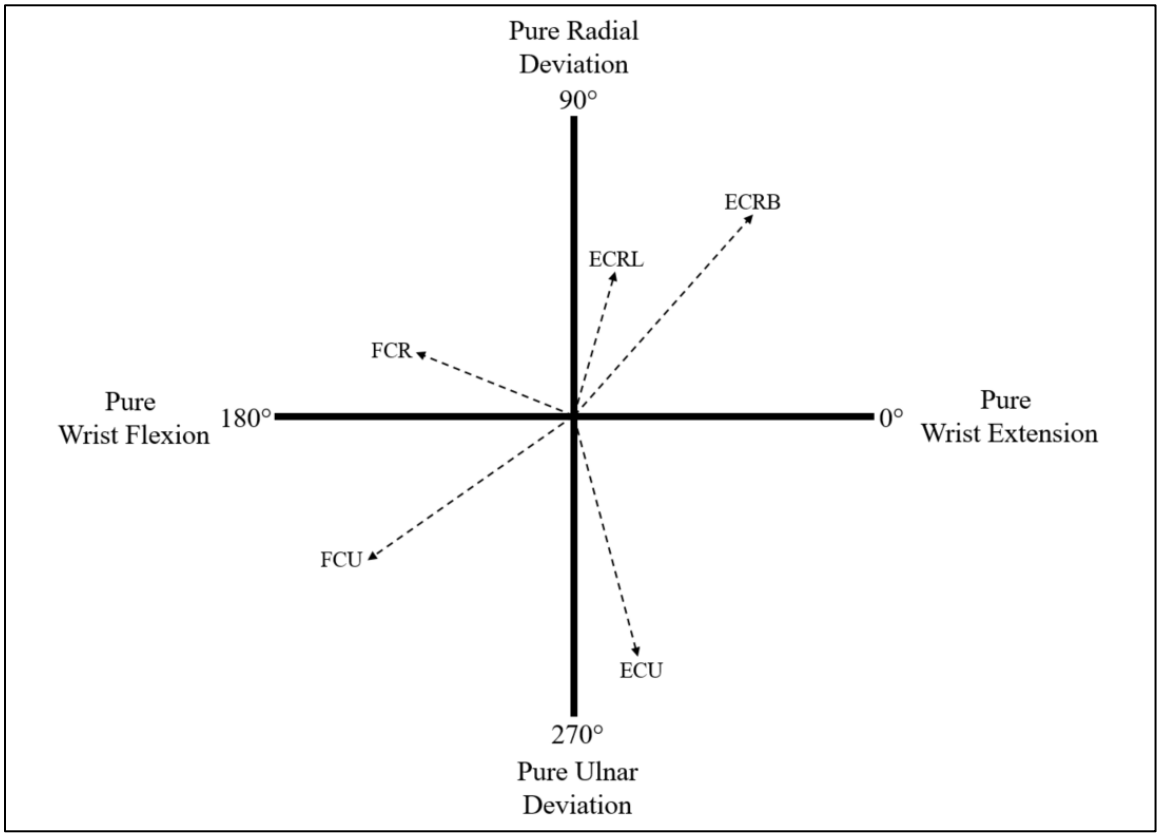

Figure 2.3. *Arrow direction depicts the line of action that each muscle would exert upon the wrist if they were to contract in isolation. For example, a line of action that were to point straight upwards would indicate a muscle whose sole function was to provide radial deviation. The length of the arrow depicts the maximal contractile isometric force of each muscle. Figure was recreated from Bawa et al. (2000) and based on data collected from Gonzalez et al. (1997) and Loren et al. (1996).*

compiled maximal isometric force data of individual forearm muscles (Gonzalez et al., 1997) and forearm muscle vectors (Loren et al., 1996) from previous studies to demonstrate the contributions of these four muscles to various wrist movements (Bawa et al., 2000). A summary of these findings can be seen in Figure 2.3. To help explain this figure, if the FCR

were to be activated in pure isolation (all other forearm, hand, and wrist muscles were perfectly relaxed), then the wrist would move mostly towards wrist flexion but also slightly towards radial deviation of the wrist. To be more specific, the FCR's line of action was reported to be 152° (only 28° away from pure wrist flexion), while the FCU's line of action was reported as 220° (30° from pure wrist flexion). This is a notable contrast with the wrist extensors, whose own lines of actions deviate substantially from pure wrist extension. For ECR longus and brevis, their lines of action are 70 and 48°, respectively (only 30 and 42° from pure radial deviation). At 289°, the ECU sits even further from wrist extension, and is only 19° from a pure ulnar deviation line of action. From a practical standpoint, this indicates that the primary wrist flexors (FCR and FCU) possess a more direct line of action towards wrist flexion than the primary wrist extensors (ECR and ECU) have towards wrist extension. It could even be argued that ECR and ECU shouldn't even be referred to as "extensors," but rather as radial and ulnar deviators, respectively. This also indicates that the wrist extensor muscles must work to a significantly greater percentage of their maximal activity when opposing the actions of the wrist flexors. Although research into the lines of action of the key phalange muscles (such FDS, FDP, and EDC, whose secondary functions can contribute to movements at the wrist) has been less studied, their lines of action are likely to be in line with pure wrist flexion and wrist extension, given their points of origin and insertion.

2.1.17 Influence of posture on force and forearm muscle activity

Variations in posture of the hand, wrist, forearm, elbow, and even more proximal structures of the upper-limb, influence the activity and force-generating capacity of

muscles of the forearm. These changes are the result of numerous neuromuscular and musculoskeletal mechanisms, including, but not exclusive to, the number of cross-bridge formations between myosin and actin filaments, the moment arms of contributing muscles, the transfer of forces through multi-articular muscles, the afferent input from muscle spindles, golgi tendon organs (GTOs), and joint receptors, and the descending input from spinal and supraspinal structures. Perhaps the most obvious of these systems are the direct, mechanical changes that occur directly at a given tissue. In the case of the forearm, any variation in wrist angle (flexion/extension, ulnar/radial deviation) will change the lengths of the crossing muscles. Indeed, the sarcomeres of the ECR significantly lengthen/shorten throughout the full wrist flexion/extension cycle (Lieber et al., 1994) and lengthen during ulnar deviation (Ljung et al., 1999). Any variation in sarcomere length will modify the volume of overlapping thin and thick filaments, which will influence the muscle's force generating capacity (Ljung et al., 1999; Walker and Schrodt, 1974). As muscle length and moment arms are intricately related, the mechanical advantage will either improve or worsen as the muscle length changes (Gonzalez et al., 1997; Loren et al., 1996), further influencing force production. These effects are easily observed during hand-grip tasks, whereby maximal grip force is significantly impaired during maintained wrist flexion (Claudon, 1998; Dempsey and Ayoub, 1996; Duque et al., 1995; Halpern and Fernandez, 1996; Imrhan, 1991; Kattel et al., 1996, 1996; Mogk and Keir, 2003). When compared to neutral and extended wrist postures, wrist flexion reduces grip force by more than 50% (Mogk and Keir, 2003). This finding is supported by modelling studies that suggest the ideal muscle length of FCR and FDS for force production is close to the middle of wrist joint range of motion, or approximately neutral (Hauraix et al., 2018). Extreme deviations

from this muscle length result in large reductions in maximal FCR and FDS force capabilities. Pronation of the forearm, as compared to a neutral or supinated posture, also reduces maximal grip force, although the magnitude is noticeably less severe (Claudon, 1998; De Smet et al., 1998; Halpern and Fernandez, 1996; Mogk and Keir, 2003; Richards et al., 1996). Neither wrist extension, as compared to a neutral wrist, nor supination of the forearm, as compared to a neutral forearm posture, appear to influence grip force (Claudon, 1998; Mogk and Keir, 2003).

Forearm posture has also been shown to influence the force of wrist exertions. In 2015, both Potvin and colleagues and Yoshii and colleagues demonstrated that maximal wrist flexion and wrist extension torques were influenced by changes in forearm rotation (La Delfa et al., 2015; Yoshii et al., 2015). In these studies, maximal wrist flexion and extension torques were assessed in three different forearm postures (supination, neutral, and pronation). Both investigations found that wrist extension generated greater peak torque in a pronated forearm posture (at least in male participants). Interestingly though, the wrist flexion peak torques differed between the two studies. In the study by La Delfa et al. (2015), peak wrist flexion torque was significantly lower in forearm supination than either of the other two forearm postures. However, in the Yoshii et al., (2015) study, wrist flexion torque peaked in forearm supination, and was significantly greater in supination than both of the other two forearm postures. Such large differences between these studies are peculiar, but they may be explained by the separate hand positions utilized in these investigations. La Delfa et al. (2015) assessed wrist torques while participants maintained an open hand (exertions were done with either the palm or back of the hand pushing against a force transducer). In contrast, Yoshii et al., (2015) required participants to exert wrist

flexion and extension torques via grasping a handle. Whether the hand is open or closed could explain these differences. At the very minimum, a closed hand would likely alter the force contributions from the FDS, the FDP, and the EDC as compared to an open palm. Such changes could influence motor control strategies, thus modifying the influence of forearm rotation on peak wrist flexion and extension torque capabilities.

Regarding rotational forearm torques, pronation torque peaks in either supinated or neutral forearm postures, while pronation torque is most impaired in a fully pronated forearm position (Gordon et al., 2004; O'Sullivan and Gallwey, 2002). Conversely, supination torque peaks in either pronated or neutral forearm positions and is weakest while held in full supination; an effect that is dependent on the angle of the elbow (O'Sullivan and Gallwey, 2002). Interestingly, the muscle activity of key forearm supinators (biceps brachii and the supinator) and forearm pronators (pronator quadratus and pronator teres) during maximal supination and pronation torques are mostly unchanged across a variety of postures (Gordon et al., 2004). However, previous reports have noted that shorter muscle lengths tend to exhibit higher levels of muscle activity; a possible compensatory mechanism of the central nervous system (CNS) to overcome a mechanical disadvantage (Buchanan et al., 1989).

Perhaps the most robust examination of posture and its influence on forearm muscle activity was conducted by Mogk and Keir (2003). In this study, surface EMG was assessed in three wrist flexors (flexor carpi radialis (FCR), flexor carpi ulnaris (FCU), and flexor digitorum superficialis (FDS)) and three wrist extensors (extensor carpi radialis (ECR), extensor carpi ulnaris (ECU), and extensor digitorum communis (EDC)). Measurements were taken during postures that varied in wrist flexion/extension and forearm

supination/pronation across a span of handgrip contractions (5-100% of MVC). Intuitively, flexor activity was highest in supinated postures, while extensor activity was highest in pronated postures. Additionally, flexor activity increased with wrist flexion while extensor activity increased with wrist extension; results similar to those who have shown that extended wrist postures increase extensor loading during typing (Keir and Wells, 2002). More recent work has demonstrated a similar increase in the mean and median frequency of the EMG signals of FCU and EDC during wrist flexion and extension, respectively (Roman-Liu and Bartuzi, 2013). Mogk and Keir (2003) also demonstrated that, as a general finding, extensor activity was higher than flexor activity at low grip forces across forearm and wrist postures; at high forces, they were relatively equal. Considering that the wrist flexors possess larger moment arms than the wrist extensors (Gonzalez et al., 1997), it is possible that the wrist extensors exhibit higher levels of activation in order to counter the larger forces generated by the flexors–a rationale that would support the concept that the wrist extensors are the primary stabilizers of the wrist joint. Indeed, in the aforementioned study, wrist extensor activity was as high as 15% of maximal activity while simply holding onto the handgrip dynamometer, while flexor activity never exceeded 7%.

2.1.18 Isometric versus dynamic contractions

A multitude of mechanical, neurological, and muscular factors can change when a muscle is contracted isometrically versus when a muscle is contracted dynamically. These factors can influence muscle recruitment patterns, which will subsequently alter measures of muscle activity. The most obvious difference between dynamic and isometric contractions is that dynamic contractions occur during movement. Movement can generally

be grouped into one of two phases: concentric contractions, which occur when the muscle is contracting and shortening, and eccentric contractions, which occur when the muscle is contracting but lengthening. Attributable to both of these phases is that the length of the muscle is constantly changing. Changes in muscle length are driven either by the contractions of individual sarcomeres overcoming external force (concentric), or external force overcoming sarcomere contractions (eccentric). Either way, changes in contracting muscle length involve continuous cross-bridge cycling of the actin and myosin filaments, which occurs to a far lesser extent during isometric contractions. Cross-bridge cycling is also unique to each phase. During concentric contractions, sarcomeres shorten by the cyclic attachment and detachment of the myosin head to actin active sites; swivel of the myosin head progressively draws the adjacent z-lines closer together (Huxley and Niedergerke, 1954; Huxley and Hanson, 1954). In contrast, eccentric contractions are executed by the continued attempt of the myosin-actin cross-bridges to resist lengthening; lengthening inevitably occurs through the forceful removal of the myosin heads from the actin active sites. This is one of the key mechanisms thought to explain why eccentric contractions result in far greater exercise-induced muscle damage than either concentric or isometric contractions (Clarkson et al., 1986; Gibala et al., 1995). This mechanism is also thought to contribute to the greater intrinsic force production of muscle fibers, along with passive tension of titin, during eccentric contractions (Edman et al., 1978; Herzog, 2014; Katz, 1939; Morgan et al., 2000). Greater intrinsic force production has direct implications for muscle activity. If a muscle is capable of maintaining high levels of force through intrinsic mechanisms, less activation of that muscle may be required. Indeed, studies have shown that muscles exhibit less activity in eccentric contractions than concentric contractions

under similar loads (Duchateau and Baudry, 2014; Kellis and Baltzopoulos, 1998; Tesch et al., 1990). As a consequence of this behaviour, it has been suggested that descending motor pathways likely control concentric and eccentric contractions with unique strategies (Enoka, 1996), which may influence measures of muscle activity.

Mechanically, changes in muscle length drive changes in joint angles, and as the angle of a joint changes, the moment arms of muscles that cross that joint can subsequently increase or decrease (Gonzalez et al., 1997). For example, at the wrist, the maximal moment arm lengths for the wrist flexors and extensors occur at approximately 40° of wrist flexion and 20° of wrist extension, respectively (Gonzalez et al., 1997). Deviation from these postures results in significant decreases in muscle moment arms. Thus, the mechanical advantage of contracting muscles constantly varies during dynamic contractions, but remains stable during isometric contractions. In line with this factor, muscle force varies with changing muscle length, and is commonly referred to as the force-length relationship. For the majority of skeletal muscles, including those at the forearm, muscle force tends to be greatest near the middle of joint range of motion, and tends to decrease as joints are taken to their end ranges (Hauraix et al., 2018). These two factors are likely the key mechanisms which explain why grip force is significantly impaired when the wrist is taken to end-range wrist flexion (Claudon, 1998; Mogk and Keir, 2003).

An additional mechanical factor that deserves mentioning is joint stiffness. As discussed in the *Co-contraction* section, the largest contribution to joint stiffness occurs through the contraction of muscles which cross that joint. Greater co-contraction is thought to provide greater stability to joints during muscle contractions. However, the capacity for muscles to stabilize joints may depend on contraction type. There is some evidence that the

ability to alter joint impedance is greater during dynamic movement than during isometric conditions, as shown through elevated levels of dynamic joint stiffness (Darainy et al., 2007). Co-contraction is also positively correlated with movement accuracy (Missenard et al., 2008a); accuracy itself is a far more important component to dynamic than isometric contractions. Thus, muscles may possess a greater capacity to provide stiffness and stability to joints when they are actively moving, which would significantly influence measures of muscle activity.

Finally, there are clear differences in peripheral receptor activity between dynamic and isometric contractions. Although the physiology of these cells will be discussed in further detail in *Central Mechanisms – The Motoneuron and the Motor Unit*, the activity of muscle spindles, joint receptors, small diameter (III/IV) afferents, cutaneous afferents, and even golgi tendon organs (GTOs) (using force detection as a surrogate assessment of muscle stretch) can be influenced by movement. The activity of these afferents have varying excitatory and inhibitory affects on both agonist and antagonist motoneurons. In most cases, their activity is likely to be much higher during dynamic than isometric contractions, and thus, could influence muscle activity.

2.1.19 Fatigue taxonomy

Traditionally, "fatigue" was defined throughout research as a reduction in the ability of a muscle to produce force, usually following a bout of exercise or a sustained period of muscle contraction. In these studies, an individual who was unable to exert as much force following a certain experimental condition was therefore said to be "fatigued." However, research has demonstrated that other performance parameters, such as speed,

balance, and accuracy can all be impaired following a “fatiguing” bout, and can sometimes occur in the absence of force decrements (Kluger et al., 2013). The term “fatigue” has also been attributed to impairments in psychological parameters, such as arousal, perception of effort, and motivation, which again can occur either with or without a reduction in force capabilities. This latter point is particularly important in neurology, where fatigue is one of the most common symptoms reported by patients across a wide variety of pathologies (Kluger et al., 2013). Thus, the term “fatigue” has been widely and inconsistently used to describe the manifestation of multiple physical and psychological phenomena. As a result, knowledge of fatigue has been fragmented and poorly classified within the field. In clinical research, treatments are frequently non-specific and target a vaguely defined symptom with disappointing outcomes (Kluger et al., 2013). This has lead to a new taxonomy, originally proposed by (Kluger et al., 2013) and later supported by (Enoka and Duchateau, 2016), in an attempt to unify the terminology of fatigue. In this work, it is proposed that “fatigue” should most accurately be described as a symptom experienced by the individual. As a symptom, fatigue manifests as a result of its two attributes: 1) perceived fatigability and 2) performance fatigability. Perceived fatigability should represent the changes in sensation that regulate the integrity (focus, attention, and motivation) of the performer (Enoka and Duchateau, 2016). In contrast, performance fatigability is an objective measure of performance carried out at a specific point in time, and encompasses measures related to peripheral (muscle contractile force, calcium kinetics, blood flow, metabolic waste, etc.) and central (voluntary activation, muscle activity, neural excitability, afferent feedback, etc.) mechanisms (Enoka and Duchateau, 2016). In addition to these new definitions, (Enoka and Duchateau, 2016) also proposed certain writing and experimental design

strategies to help ratify this taxonomy. In their 2016 paper, they wrote: "*To determine the influence of fatigue on human performance, the proposed approach involves three levels of analysis: 1) select a criterion measure of human performance that is modulated by fatigue; 2) identify a laboratory test that is a strong predictor of performance on the criterion measure; and 3) conduct mechanistic studies to determine the relative significance of the adjustments in the modulating factors (Fig. 2) that limit performance on the laboratory test*," (Enoka and Duchateau, 2016). In support of these studies, the term "performance fatigability" will be used throughout this thesis to describe decrements in physical performance which can be quantified experimentally with laboratory measures. Any mention of "fatigue" will simply be in reference to the state of the individual following prolonged exercise or a prolonged muscle contraction which induced performance fatigability. Additionally, the strategies proposed by (Enoka and Duchateau, 2016) were adopted into the studies that were completed as a part of this thesis. Regarding their first recommendation (1), the criterion of human performance to be measured included movement accuracy, movement smoothness, and maximal voluntary isometric force. (2) The laboratory tests used that were strong predictors of these human performance measures included kinematic tracking via a three degrees of freedom wrist manipulandum and force measurements via a force transducer. (3) Finally, a mechanistic study was performed utilizing surface electromyography and transcranial magnetic stimulation to determine the relative significance of certain underlying factors that may have limited performance.

2.1.20 Performance fatigability and movement accuracy

If a goal-oriented motor task possesses any element of movement (i.e. the task is not isometric), then accuracy will play at least some role in the execution of the task. Even something as simple as striking a letter on a keyboard requires a bare minimum level of accuracy in order to successfully complete. In cases where a motor task can be performed slowly and at the participant's leisure, accuracy may not be a limiting or deciding factor. In such cases, acute changes to an individual (for example, performance fatigability) that can impair certain movement parameters may not result in any loss in accuracy. In other words, the required accuracy is so minimal that compromises in force, speed, or coordination may have no effect on the execution of the task. However, if the movement is sufficiently complex–incorporating such characteristics as high speed, intensely contracting muscles, or intricate movement patterns–accuracy will be imperfect. In these cases, anything that might impair an individual's performance capabilities (again, such as fatigue) will negatively influence accuracy. No matter the complexity of a moving motor task, there is often an ideal or perfect trajectory in which that motor task should be executed. Any deviations from this ideal trajectory are frequently referred to as "error" in scientific literature.

Just as there is an ideal trajectory to complete most motor tasks, there is also an ideal level of force that muscles must exert if that trajectory is to be perfectly travelled. For example, if an individual was to try and write their name on a piece of paper with absolutely no error in pen tip movement, there would be an ideal force output that the muscles of the hand, wrist, and forearm would need to exert at precisely the right moments. This is referred to within some literature as the "signal", where signal represents the ideal or optimal force

output required to complete a motor task. However, humans are far from perfect, and muscle force outputs rarely achieve this ideal. In such cases, force deviations from this ideal are subsequently referred to as "noise", where noise represents any amount of muscle force that strays from the true signal. Interestingly, as the contraction intensity of a motor task increases, it has been reported that the level of "noise" relative to the "signal" also increases (Fitts, 1954; Harris and Wolpert, 1998; Jones et al., 2002). In other words, the contractile force of a muscle will fluctuate at a larger magnitude the more intensely that muscle contracts. This phenomenon was coined signal-dependent noise (SDN) by Harris and Wolpert in 1998 (Harris and Wolpert, 1998). Practically, this finding suggests that movement accuracy will be more precise when contractile forces are lower. SDN also increases following fatigue–a relationship that may occur independently of increasing contractile forces (Missenard et al., 2008b). This behaviour has been attributed in part to reduced force availability. A reduction in maximal force output is perhaps the most widely reported side effect of a fatigue-inducing contraction, particularly as it relates to traditionally defined "muscle fatigue." Maximal velocity and maximal torque are similarly reduced (Buttelli et al., 1996; de Haan et al., 1989; Jaric et al., 1997). If less overall force and/or velocity are available for a muscle to utilize, then motor tasks possessing an absolute amount of force to accomplish (for example, the force needed to press a button on a keyboard) will require relatively more force from the fatigued muscle (in terms of percentage (%) of maximum). Additionally, there is strong evidence that a greater number of motor units are recruited to sustain a target level of force production following fatigue, given that absolute muscle activity increases despite reductions in motoneuron discharge rates (see *Central Mechanisms – The Motoneuron and Motor Unit* for further details).

Thus, in tasks with absolute force requirements, not only is relatively more force needed from the fatigued muscles (since maximal force capabilities are reduced), but the number of active motor units is likely greater as well. These two factors may be the primary mechanisms behind the findings of Mottet and colleagues in 2008 (Missenard et al., 2008b). In this study, participants were required to perform isometric elbow flexion force matching tasks. A total of four force outputs were used (7, 13, 33, and 53% of pre-fatigue elbow flexion maximal voluntary contraction (MVC)). To induce fatigue, participants performed alternating isometric elbow flexion and elbow extension contractions at 60% of their pre-fatigue MVCs. Each contraction lasted for 20 seconds and was separated by 15 seconds of rest before participants switched to the other force direction. Cessation of the trial occurred when participants could no longer maintain the 60% workload for at least 5 seconds. Following this, the four force matching elbow flexion targets were again repeated. Results demonstrated that SDN (or force variability) increased with greater elbow flexion force, both during pre- and post-fatigue collection. However, this increase was overall greater following fatigue, suggesting that the influences of force output and fatigue on SDN are independent of one another (Missenard et al., 2008b). It is therefore possible that unique mechanisms drive these two factors.

One possible mechanism to explain the independent effect of fatigue on SDN is co-contraction. As stated in the previous *Co-contraction* section, co-contraction is typically extrapolated from measures of muscle activity. Following sustained submaximal contractions, muscle activity as measured by surface EMG typically increases due to an increase in motor unit recruitment (B. Bigland-Ritchie et al., 1986a; Enoka et al., 1989; Gamet and Maton, 1989; Person and Kudina, 1972). Depending on which co-contraction

method is utilized, this could be interpreted as an increase in co-contraction to provide greater joint stiffness, and therefore joint stability, in a fatigued state. However, there are two limitations to this statement. First, co-contraction methods typically use measures of muscle activity to predict the contractile force characteristics of the muscles they are recorded from. This assumes a constant relationship between EMG signals and muscle contractile forces. However, as stated before, the EMG-force relationship changes following fatigue, whereby greater muscle activity is exhibited to sustain the same level of absolute submaximal force. Thus, an increase in muscle activity does not necessarily indicate an increase in contractile force of the muscle. Second, the reports on muscle activity changes following fatigue have been predominantly determined during isometric protocols. Not only are investigations into dynamic protocols far less common, but a post-fatigue increase in joint stiffness is unlikely to occur during movement; an increase in joint stiffness would mean a potential and undesirable increase in limb impedance during movement. Research on this topic supports these notions. In 2008, Mottet and colleagues examined the effect of an acute bout of isometric elbow flexion/extension fatigue on rapid elbow extension reaching tasks (Missenard et al., 2008a). In this study, participants were instructed to rapidly extend their elbow from 70 to 110° of elbow extension in the span of 300 milliseconds. The difference in distance between the movement endpoint and the target location was referred to as error. EMG was collected from two flexors (biceps brachii and brachioradialis) and two extensors (long and lateral heads of the triceps brachii). Co-contraction was assessed using the co-contraction index (CCI). Results demonstrated that endpoint accuracy decreased post-fatigue; endpoint positional variability also increased. These findings were associated with a similar post-fatigue decrease in CCI, suggesting that

a decrease in co-contraction may have contributed to a loss in accuracy (Missenard et al., 2008a). This was not the first investigation to propose a relationship between co-contraction and movement accuracy. As the size of endpoint targets decreases, upper-limb joints exhibit greater co-contraction during reaching tasks (Gribble et al., 2003), supposedly to preserve endpoint reaching accuracy. This notion is supported by modelling work that has shown that increasing limb impedance through greater co-contraction (Osu and Gomi, 1999) results in less kinematic variability (Selen et al., 2005). Experimental research has revealed similar findings; when participants are instructed to consciously use co-contraction while pointing at a target, endpoint accuracy improves (Osu et al., 2004). Thus, there is compelling evidence that co-contraction (which can be impaired following fatigue) might be positively correlated with movement accuracy.

Finally, while the details of proprioception will be discussed in the subsequent section, it is important to at least mention the topic here as it relates to movement accuracy. Proprioception is widely considered to be the CNS's awareness of the body's position relative to itself in three-dimensional space; it is of the utmost importance in the completion of any goal-oriented motor task. Proprioception is produced by multiple afferent sources, including visual feedback, muscle spindles, cutaneous receptors, and tendon and joint receptors. While vision and cutaneous information is unlikely to change following fatigue, there is evidence that the behaviour of muscle spindles (detect rate and absolute length of muscle stretch) and golgi tendon organs (GTOs; detect muscle tension and contribute to perceived level of exertion) changes following fatigue (Nelson and Hutton, 1985). In particular, both muscle spindles and GTOs become more sensitive to certain types of stretch, meaning that the proprioceptive information they convey to the somatosensory

cortex may no longer be accurate. It is thought that these peripheral receptors may at least partially contribute to the observation that joint position sense is impaired following fatigue (Björklund et al., 2003; Carpenter et al., 1998; Gribble and Hertel, 2004; Pedersen et al., 1999; Roberts et al., 2003; Sharpe and Miles, 1993). Any impairment in proprioception is likely to contribute to impairments in movement accuracy, as a "sense of self" is required for the successful execution of precision motor tasks.

2.1.21 Performance fatigability and proprioception

As a field of research, the study of proprioception is considerable. However, there exists a disagreement in the literature as to its correct definition. For the sake of this review, it is pertinent to consider the historical milestones of the field. In 1887, Henry Bastian first coined the term "kinaesthesia" as a means of describing the bodily sensations directly resulting from bodily movement (Bastian, 1887). He proposed that it was kinaesthesia that was the sum of all complex sensory information that informed the brain of both position and movement of the periphery; it was ultimately kinaethesia that allowed for unconscious guidance in the performance of movement. The term "proprioception" wasn't introduced until 1906, when Sir Charles Sherrington first used the expression to describe all sensory information arising from receptors present within muscles, tendons, and joints; receptors informed the CNS of bodily position over time (Sherrington, 1906). To this day, both kinaesthesia and proprioception continue to be used in modern literature. Some research groups insist that proprioception encompasses joint position sense only, and that it is kinaesthesia that allows for the conscious perception of bodily movement (Swanik et al., 2004, 2002). While joint position sense and joint movement sense arise from quantitatively

different sensory sources (McCloskey, 1973; Proske and Gandevia, 2009), all movement corresponds with changes in joint position (Clark et al., 1985; Gregory et al., 1988; McCloskey, 1978; Taylor and Mccloskey, 1990). Thus, in functional daily tasks, joint position sense and joint movement sense accompany one another at all times (Stillman, 2002). In the scope of this review, the use of the term proprioception will therefore include both joint position sense and joint movement sense.

By following the previously described definition, proprioception is defined as the capacity of the CNS to perceive the position of the body's parts relative to itself in real time, both at rest and during movement. This also includes perceiving the speed and strength employed during movement. A substantial volume of work has demonstrated that proprioception is generated via multiple afferent sources, including visual feedback (Graziano, 1999; Plooy et al., 1998; Sober and Sabes, 2003; van Beers et al., 1999), muscle spindles (Gandevia et al., 1992; Gandevia and McCloskey, 1976; Roll and Vedel, 1982), cutaneous receptors (Voight et al., 1996), and tendon and joint receptors (Gandevia and Burke, 1992). Despite the volume of current literature, the integration of these mechanisms and their contribution to proprioceptive control remains somewhat unclear. In order to elucidate some of these mechanisms, different experimental methods have been developed. A summary of these key techniques are describe below.

Threshold to detection of passive motion: The threshold to detection of passive motion (TTDPM) method is a technique that generally utilizes an investigator-controlled apparatus to passively move a participant's limb. Upon sensation of movement, the participant then conveys to the researcher their perception of motion and states the direction of the movement (Cordo et al., 2011; Refshauge et al., 1995). If the direction that was

reported was wrong, the trial is discarded and repeated until 3-5 correct trials have been completed (Nagai et al., 2012). The measurement of interest is then the difference between the starting position and the response position, or the distance that it took for the participant to perceive the motion. A shorter distance is indicative of heightened, or improved proprioception, while a longer distance suggests proprioceptive impairment. In this type of experiment, participants are generally seated or lying down with their tested limb securely attached to the moving apparatus (usually an isokinetic machine). To isolate muscle spindles and joint receptors, participants are blindfolded, required to wear headphones, and if there is a desire to reduce cutaneous or tactile feedback, cushions or wraps can be placed over the tested part of the body. Different passive speeds are often utilized in a single experimental session, as speed has been shown to influence the onset of movement threshold onset, with slower speeds resulting in a higher movement detection threshold (Refshauge et al., 1995). Most experimenters rely on a slower movement speed, in the vicinity of 0.25 °/s, which presents one of the limitations of the TTDPM method. TTDPM studies tend to suffer from poor external validity as the speeds used in this work are often very slow (Laszlo, 1992). A speed of 0.25 °/s is generally much slower than any type of movement a person would experience throughout a normal day, and thus, the proprioception derived from such a speed may have no application to daily living. However, the TTDPM method is considered superior to something like the active movement extent discrimination assessment (AMEDA) method in terms of isolating afferent feedback.

Joint position reproduction: Joint position reproduction (JPR) is a technique that involves a participant either passively or actively reproducing a formerly-experienced

target joint angle, and can be conducted on either the ipsilateral or contralateral side of the body (Goble, 2010). Like TTDPM, participants tend to be blindfolded to prevent sight from influencing the results. In the literature, JPR is broken down into two sub-techniques. The first is ipsilateral JPR (IJPR), which involves either active or passive assessment on the ipsilateral side. A target position, determined by the researcher, is first created and experienced by the participant before returning to a starting position. In the case of passive IJPR, the researcher moves the participant to the target position and holds them there for a short period of time before returning them to the starting position. To reproduce the position, the researcher then slowly moves the body part back towards the target and the participant declares the point where they feel they have reached the target. For active IJPR, participants voluntarily move both to the target position and back to the starting position (while holding for a few seconds at the target). They then actively attempt to recreate the target and pause when they have reached what they believe to be appropriate position. The second sub-technique is contralateral JPR (CJPR) and involves joint position reproduction on the contralateral side of the body. CJPR can typically be conducted two different ways. In the first method, the participant's ipsilateral limb is moved to the target joint angle before being returned to the starting position. The participant then attempts to reproduce the same joint position with the contralateral limb. It should be noted that this technique requires memorization on the part of the participant. For the second method, the participant simply holds their ipsilateral limb at the target joint angle while attempting to match that position with their contralateral limb. This method requires no memorization as the participant can repeatedly refer to the target joint angle in real-time. Like TTDPM, JPR as an experimental technique suffers from generally poor external validity as it shares little in common with

daily, functional tasks (Lephart and Fu, 2000). In addition, most JPR techniques rely on the participant to accurately remember the location of the target body position, meaning that if memory becomes impaired during the experimental intervention, a drop in memory capacity could be mistaken as a decrease in proprioceptive proficiency. JPR is not recommended in participants with cognitive memory impairments (Goble, 2010), however, as with TTDPM, JPR is superior to AMEDA in isolating afferent feedback.

Active movement extent discrimination assessment: Active movement extent discrimination assessment (AMEDA) is an active experimental technique that relies on active discernment of an experienced joint position (Waddington and Adams, 1999). It is considered active as most AMEDA protocols require load-bearing setups on the part of the participant. Preliminary familiarization is required using AMEDA, whereby participants experience a select number of positions that vary sequentially either by displacement or joint angle (degrees). For example, in an experiment focused on the ankle, participants would stand on an adjustable platform with their tested foot. The platform would then be moved through a predetermined number of positions (for example, five joint angles ranging from 40° of plantarflexion to 40° of dorsiflexion). The participant is allowed to perceive each position multiple times and a label is given to each joint angle (positions 1, 2, 3, 4, 5). For experimental trials, the testing apparatus is randomly moved into one of the five positions for a short time, before being moved back to the starting position. Participants are then asked to identify which of the five positions they had just experienced, without any feedback being given as to whether or not they were correct in their judgement. In this context, AMEDA is a memory-dependent technique, although the importance of memory is less substantial than for JPR protocols. It is the most externally valid of all three

proprioceptive techniques, although the results of AMEDA studies are generally difficult to attribute to any one particular proprioceptive receptor.

Substantial evidence has demonstrated that fatiguing exercise results in joint position sense impairments (Björklund et al., 2003; Carpenter et al., 1998; Gribble and Hertel, 2004; Pedersen et al., 1999; Roberts et al., 2003; Sharpe and Miles, 1993), and research has identified multiple sites responsible for this decline. It is generally accepted amongst the literature of the field that muscle spindle receptors provide the greatest contribution to proprioception of all peripheral receptors (Eklund, 1972; McCloskey, 1978). Thus, any alteration in the rate of their discharge presents a significant problem in terms of joint position sense and stability. During voluntary activation, muscle spindle discharge temporarily increases before gradually decreasing over the course of a sustained contraction (Macefield et al., 1991). Following a fatiguing contraction, the Ia afferents which innervate the muscle spindles exhibit increased sensitivity to stretch, which may act as an adaptive mechanism to the reduced firing of the spindle (Nelson and Hutton, 1985). Unlike other peripheral receptors, the fatigue of muscle spindles is highly dependent upon the type of muscle contraction. In the case of shortening contractions, muscle spindle discharge rate significantly decreases, and can even be silenced completely in fast enough shortening contractions (Burke et al., 1978). However, in a contraction where the muscle is lengthened, muscle spindles fire maximally, which may worsen the fatigue-related effects. Indeed, eccentric fatiguing contractions result in worse joint position sense and force position sense measures than concentric contractions (Brockett et al., 1997). However, it should be noted that eccentric contractions produce significantly worse muscle damage than concentric contractions (Armstrong et al., 1983; Knuttgen, 1986; Newham et

al., 1986); impairment of motor function may be a compounding variable in this comparison. Other than increased discharge rate, it has been hypothesized that the myofibrillar damage associated with eccentric exercise may not be isolated to extrafusal fibers, but may also impact muscle spindles. Should muscle spindles rupture following a fatiguing bout of exercise, proprioceptive feedback would noticeably suffer. However, available research suggests that intrafusal fibers are immune to exercise-induced damage (Gregory et al., 2004).

Golgi tendon organs (GTOs), which relay information regarding the ongoing force exerted by the muscle, experience a reduced capacity once fatigued. Following high intensity contractions, the sensitivity of GTOs temporarily decreases for a period of 15-30s, and the discharge rate of individual receptors falls to as much as 50% (Nelson and Hutton, 1985). In the knee, impaired joint receptor function contributes to poor proprioception following fatigue. It has been suggested that laxity of the ligaments following prolonged exercise may alter the discharge of joint receptors (Nawata et al., 1999; Skinner et al., 1986; Sumen et al., 1999) as individuals with relaxed ligaments suffer from diminished proprioception (Barrack et al., 1984, 1983; Rozzi et al., 1999).

2.1.22 Peripheral mechanisms of fatigue

Contributions to performance fatigability through processes that extend outside of the CNS (including peripheral nerves, the neuromuscular junction, and the muscle fibers themselves) are commonly referred to as peripheral mechanisms. These are mechanisms which can cause reductions in maximal muscle force production independently to changes in voluntary drive. While any of the three sites mentioned above possess the capacity to

limit force production should their functions be compromised, research suggests that intracellular mechanisms of muscle cells are the primary cause for reduced force output related to fatigue. In some studies that have reported the maximal M-wave (M_{max}) is mostly unchanged (note: many other studies have shown the M_{max} to increase or decrease in size) following intense exercise (Billaut et al., 2013; Fernandez-del-Olmo et al., 2013; Girard et al., 2013; Hureau et al., 2014; Pearcey et al., 2015), electrically induced twitch force is significantly reduced (Billaut et al., 2013; Duffield et al., 2009; Fernandez-del-Olmo et al., 2013; Girard et al., 2013; Pearcey et al., 2015; Racinais et al., 2007). These two findings suggest that the conductivity (or excitability) of peripheral nerves, the neuromuscular junction, and the membrane of the muscle fibers remains largely unchanged following fatigue, and therefore, cannot explain a reduction in twitch force. The most likely deduction is that reduced twitch force must arise from intracellular changes within the muscle fiber. To properly consider all possible factors that might contribute to intramuscular fatigue, it is important to understand the intracellular processes that lead to muscle contraction. The following intracellular steps come from the model by Holmes and Geeves (2000). When the muscle action potential arrives at the T-tubules, the depolarizing potential activates the voltage gated Ca^{++} channels within the sarcoplasmic reticulum. The release of Ca^{++} into the sarcomere allows for the binding of Ca^{++} ions to troponin. This binding triggers a series of complex structural changes within troponin that culminate in the removal of tropomyosin from the myosin binding site on the actin thin filament. The opening of this site allows for the myosin head to bind to the actin filament, although, only once adenosine triphosphate (ATP) has been hydrolyzed and the inorganic phosphate (Pi) has dissociated from the molecule. Once bound, the myosin head executes a powerstroke (a molecular

swivel of the protein) that causes the sarcomere to contract. Myosin remains bound to the actin filament until two intracellular events take place. In order of occurrence, adenosine diphosphate (ADP) must dissociate from the bound myosin head, and the myosin head must then await for a new ATP to bind and free it from the actin filament. This waiting period is sometimes referred to as "rigor" in literature (Debold, 2012). The more rapidly the myosin head can dissociate from the actin filament, the greater the velocity of the sarcomere contraction. However, the longer the myosin head remains strongly bound to the actin filament, the stronger the contraction (at least in isometric experiments) (Debold, 2012). In other words, given the appropriate context, any change within the ADP or rigor phases separately and inversely affects force and velocity. Additionally, alterations to any one step in this cascade of events (from Ca^{++} release, to myosin binding, to duration of myosin binding) has the potential to impair force.

One of the most consistent findings within literature is that an accumulation of certain metabolites, principally H^{+} ions (acidosis), Pi, and ADP correlate with reduced force capabilities following intense muscle contractions (Dawson et al., 1978). Even without inducing fatigue voluntarily, administration of these metabolites in non-fatigued muscles similarly impairs muscle force (Cooke et al., 1988). In cases of voluntary fatiguing contractions, metabolite accumulation is partially facilitated by reduced perfusion; the intracellular pressure produced by contracting muscles (particularly in isometric states) can constrict capillaries (Lydakis et al., 2008). Not only is a reduction in oxygen delivery pertinent to the metabolism of certain muscle fibers, but reduced perfusion limits the capacity of working muscles to clear waste by-products. The accumulation of these metabolites is thought to interfere with the intracellular processes discussed previously,

which in turn impairs muscle performance. In the case of acidosis, it was known as early as the 1800s that acidity increased during prolonged muscle contractions; acidosis was thought to directly inhibit force production (Gaskell, 1880). Similarly, decreasing pH correlates with reduced muscle force (Dawson et al., 1978). More recent work has supported this finding, whereby fatiguing levels of acidosis in isolated muscles inhibit force production (Donaldson et al., 1978; Edman and Lou, 1990; Kentish, 1991; Ricciardi et al., 1994). However, this effect is seemingly mitigated at physiological temperatures (Knuth et al., 2006; Pate et al., 1995). Even more recent work has shown that acidosis might actually prevent force loss (Pedersen et al., 2004), although this statement is currently controversial (Kristensen et al., 2005). It is currently unclear whether acidosis directly influences muscle force capabilities (Debold, 2012). A finding that is less conflicting is that acidosis seems to slow actin filament velocity (Debold et al., 2008; Karatzaferi et al., 2008; Knuth et al., 2006). Research has suggested that this behaviour likely manifests due to interactions in the ADP phase of myosin binding, whereby fatigue levels of acidosis increase the duration that ADP is bound to myosin by a factor of three (Debold et al., 2008). However, while acidosis may not influence muscle force directly, evidence suggests that it can impair the sensitivity of troponin to Ca^{++} ions (Fabiato and Fabiato, 1978; Sata et al., 1995; VanBuren et al., 1995). If Ca^{++} cannot bind to troponin as readily, then fewer sites will be open for myosin to bind to actin. This effect is even more detrimental in the later stages of fatigue development, as intracellular Ca^{++} concentrations diminish, likely as a result of reduced sarcoplasmic reticulum release (Lee et al., 1991; Westerblad et al., 1991).

Inorganic phosphate (Pi) is an even stronger correlate with muscle loss than acidosis. In non-fatigued tissue, administration of Pi reduces maximal isometric force in a

dose-dependent response (Cooke et al., 1988; Cooke and Pate, 1985; Debold et al., 2006, 2004; Hibberd et al., 1985; Nosek et al., 1987; Pate and Cooke, 1989). While direct support for the underlying mechanism is scarce, it is presently thought that, at sufficiently high concentrations, Pi is capable of re-binding to the ADP-myosin complex and potentially reversing the powerstroke phase (Takagi et al., 2004). If so, this effect would significantly reduce the number of strongly bound cross-bridges during muscle contractions. Regarding muscle activation, Pi is also thought to impair Ca^{++} sensitivity similar to acidosis (Metzger, 1996; Millar and Homsher, 1992, 1990; Palmer and Kentish, 1994; Walker et al., 1992). However, the underlying mechanism is suspected to be different. Normally, when a single myosin head strongly binds with an opening on the actin filament, this facilitates the binding of neighbouring myosin heads in a positive feedforward behaviour (Gordon et al., 2000). Additionally, troponin's sensitivity to Ca^{++} increases with greater force (Gordon et al., 2000). An increase in Pi, acting to reverse the ADP-myosin complex, would reduce both of these effects. Should the powerstroke be reversed, there will be disfacilitation of additional myosin head binding. With less binding, force will decrease, which will subsequently reduce the amount of Ca^{++} binding to force-dependent troponin.

While the typical concentration of ADP in muscles that have depleted most, if not all, of their creatine-phosphate (i.e. a fatigued muscle) is somewhat contested, research has shown that even 0.5 mM of ADP can influence muscle force and contraction velocity (Greenberg et al., 2010). Evidence suggests that ADP directly inhibits myosin function (Cooke and Pate, 1985; Metzger, 1996), possibly through competing with ATP in binding at the myosin active site during the rigor state (Debold, 2012). If true, this would explain the simultaneous slowing of contraction velocity (Cooke and Pate, 1985; Metzger, 1996)

and the increasing isometric force (Cooke and Pate, 1985; Fukuda et al., 2000; Hoar et al., 1987; Metzger, 1996) associated with greater ADP concentrations. If high concentrations of ADP allow for competitive binding at the myosin active site, then the ADP-myosin complex will persist for a longer period of time. This would serve to both increase the total amount of cross-bridges (and therefore increase isometric force) and to decrease the volume of cross-bridge cycling (and therefore decrease contraction velocity). Interestingly, ADP seems to enhance troponin's sensitivity to Ca^{++} at high concentrations (Hoar et al., 1987), possibly through the same mechanism as mentioned above for Pi. If ADP is capable of competing with ATP for myosin active sites, and in the process maintains strongly bound myosin-active cross-bridges for a longer period, then isometric force will increase. This increase would subsequently facilitate the force-dependent troponin and promote additional Ca^{++} binding (Debold, 2012). However, it remains unclear how useful this mechanism is in normal exercise, given that the loss in contractile velocity likely offsets such benefits.

Lastly, while there is substantially less research into reactive oxygen species (ROS), there is some evidence that some ROS accumulate within intensely contracting muscles and might contribute to fatigue-induced force deficits (Smith and Reid, 2006). This suggestion is not without limitations, given that low concentrations of ROS may enhance force outputs (Reid et al., 1993), while high concentrations of certain species, such as H_2O_2, inhibit contractile function (Andrade et al., 1998). If ROS do contribute to contractile force loss in the presence of fatigue, it is thought that the high reactivity of these molecules may be capable of altering the structure of contractile proteins (Debold, 2012). Further research on this topic is needed.

2.1.23 Central mechanisms – voluntary activation

As early as the 19th century, it was understood by physiologists that both peripheral factors (such as red versus white muscle) and the neural pathways that controlled them could limit muscle performance (see historical review by Edwards et al., 1995). However, the underlying mechanisms that drove them were largely unknown. One of the very first investigations into the possible role of so called "central fatigue" was conducted in 1892, whereby factors which could influence voluntary contractions were explored (Lombard, 1892). The discovery was made that external variables, such as mental excitement or agitation, could improve voluntary endurance. Around the same time, it was noted by researchers that "muscle fatigue" was rarely ever complete following an exhausting task, and that the application of electrical stimulation over the muscle could provoke additional contractile force (Waller, 1892). If the muscle itself was still capable of contracting with added stimulation, then the obvious conclusion was that a central variable was a limiting factor in the presence of fatigue (Mosso, 1904). Fifty years later, this observation would be further developed. During voluntary contractions, (Merton, 1954) demonstrated that the additional force elicited by electrical stimulation (also known as a 'twitch') was inversely related to the magnitude of voluntary force (with small voluntary forces, a large twitch would be elicited, and vice versa). At exceptionally high voluntary forces, no twitch appeared at all. The subsequent suggestion was that, should stimulation fail to elicit additional force, then the stimulated muscles must already be contracting maximally. Also, given the consistent relationship between voluntary force and twitch magnitude, Merton discussed the possibility of predictive applications. Although Merton was one of the first

researchers to note this behaviour, it wasn't until the 1980s that the interpolated twitch technique (ITT) was truly refined into the method we know today (Grimby et al., 1981a, 1981b; Hales and Gandevia, 1988).

Although not without its limitations, the ITT is the most widely used method for measuring voluntary activation (or rather, inactivation), in humans. The technique involves a high intensity electrical stimulation applied either over the peripheral nerve innervating a target muscle group or over the intramuscular nerve branches of the target muscle group itself (Belanger and McComas, 1981; Shield and Zhou, 2004). When stimulation is delivered during a voluntary contraction, any motor units not already recruited, or those motor units that have been recruited but are not yet firing at their maximum rate, will generate a twitch response. This is referred to as a superimposed twitch and is observable in a force trace as a brief increase in force over the background voluntary force (Belanger and McComas, 1981; Shield and Zhou, 2004). If no twitch is observed, the assumption is that all motor units were already recruited and firing maximally; there is no additional force available for a superimposed stimulation to elicit. However, if a twitch is present, then the assumption is that the muscle (or muscle groups) was not contracting maximally. The larger the twitch force, the greater the inactivity of the target muscle groups. The extent to which a muscle is inactive must be expressed as a ratio of the superimposed imposed twitch to the maximal twitch that can be elicited by stimulation. Considering the inverse relationship between voluntary and superimposed twitch force, the maximal force of a twitch must be elicited at rest (Merton, 1954). Thus, percent inactivation is calculated as a ratio of the superimposed twitch and the potentiated twitch (a twitch elicited at rest immediately following a voluntary contraction) (Shield and Zhou, 2004).

Utilizing this technique, research has shown that voluntary activation decreases throughout a sustained contraction (Gandevia, 2001; McKenzie et al., 1997; Reid, 1927). For instance, in studies where an initially submaximal contraction of just 30% of maximal voluntary contraction is held until volitional failure, the ITT reveals large muscle inactivation (Löscher et al., 1996a, 1996b; Zijdewind et al., 1998). In other words, while participants feel that they are no longer able to maintain target force production, a superimposed stimulation suggests that they still possess a large reserve of force. Thus, failure as a result of fatigue must be at least partially the result of central mechanisms or central limits.

2.1.24 Central mechanisms – the motoneuron and motor unit

Among the earliest work that managed to tease out some of the underlying central mechanisms were Merton and colleagues (Marsden et al., 1971), who discovered that motor unit firing frequencies decreased during a sustained maximal voluntary contraction. These declines were substantial, and in the first dorsal interosseous (FDI), firing frequencies dropped from approximately 60-80 Hz at the beginning of the contraction to approximately 20 Hz at contraction cessation (Marsden et al., 1971). This decline also seemed to parallel the decline in muscle contractile speed that had already been documented at the time. Bigland-Ritchie and colleagues subsequently drew a direct association between the two phenomena, and coined the term “muscular wisdom” to describe it (Bigland-Ritchie et al., 1983b; B. R. Bigland-Ritchie et al., 1986; Marsden et al., 1971). The muscular wisdom hypothesis states that spinal motoneurons decrease their firing rates in order to match the slower rate of force production that occurs in their

innervated muscle fibers. This behavior would serve to spare the motoneuron from wastefully firing at rates which would exceed the fatigued motor unit's contractile capacity for a maximal fused tetanus (Bigland-Ritchie et al., 1979). Alternatively, it would also prevent motoneuron discharge rates from falling below the contractile capabilities of the muscle fibers, and thus, ensure sufficient activation of the muscle. Following the development of this hypothesis, numerous investigations were performed in attempts to discover a mechanism that might regulate this process. Several possibilities have since been suggested, all of which are factors that act upon the motoneuron.

Intrinsic properties: Measures of intrinsic motoneuronal properties suggest that the firing rates of the motoneuron can, and do, decrease similarly to the slowing of motor unit discharge rates even when isolated from descending and afferent inputs. When stimulated via artificial current injection, the motoneuron begins firing at an initially high rate before slowing in two distinct phases (Bayliss et al., 1997; Kernell and Monster, 1982a, 1982b; Sawczuk et al., 1995a, 1995b). The first phase is characterized by a relatively rapid drop in discharge rate, while the second consists of a slower decline that gradually plateaus around 30 seconds of sustained injection. The recovery process following cessation of current injection is also distinct when assessed independently after each of the two phases. The initial, rapid drop in discharge rates (the first phase) recovers rapidly, which is thought to allow for repeated, high-intensity contractions to be performed in fairly close succession (Gandevia, 2001). The recovery process for the second phase takes significantly longer. Across both phases, this drop in motoneuron firing frequency seems to be muscle fiber type (or rather, motor unit type) specific; in slow-twitch motoneurons, the decrease in discharge rates is less noticeable (Kernell and Monster, 1982b, 1982a; Lee and Heckman, 1998;

Sawczuk et al., 1995b; Spielmann et al., 1993). Lastly, and perhaps most interestingly, current injection studies have shown that the motoneuron enters an insensitive state following sustained activity (Sawczuk et al., 1995b). This is commonly referred to as "gain" within the neurophysiology field, and refers to the amount of input (generally a certain type of stimulus) needed to achieve a certain output (in this case, firing frequency). In this context, the gain of the motoneuron decreases with sustained firing, meaning that, while the firing rate of the motoneuron *can* increase with greater net drive to the motoneuron, that net drive needs to be significantly greater than at the beginning of sustained current injection (Sawczuk et al., 1995b). Because of this phenomena, an intrinsic factor cannot fully explain the reduction in motor unit discharge rates described by the muscular wisdom hypothesis, as greater compensation from afferent and descending pathways could theoretically overcome it.

Muscle spindles: Muscle spindles convey information regarding both the rate of muscle stretch and the current absolute length of a muscle through large diameter afferents (type Ia and II fibers). Part of this information travels through the dorsal column pathway and is transmitted to the somatosensory cortex, while the rest of this information is transmitted within the spinal cord. Forming the monosynaptic stretch reflex, Ia afferents make a direct synapse with and transmit excitatory post synaptic potentials (EPSPs) to homologous motoneurons (Lloyd, 1943). Greater activity of muscle spindles and/or type Ia and type II fibers therefore increases the excitability of the motoneuron pool to the same muscle, and thus, contributes to increased motoneuron firing rates, increased motoneuron recruitment, or both. This carries significant consequences for motoneuron function, given that sustained contractions have been shown to reduce the discharge rates in 72% of

examined spindle endings (Macefield et al., 1991). This decrease is influenced by individual spindle properties, as those spindles which fire the most rapidly at the beginning of a sustained contraction see the largest decrease in discharge rates. This loss of afferent excitation (commonly referred to as disfacilitation) almost certainly reduces the excitability of the motoneuron (Gandevia, 2001). When muscle spindles are blocked experimentally, the discharge rates of motoneurons subsequently decrease and become more irregular (Hagbarth et al., 1986; Hannerz and Grimby, 1979). Similarly, when the innervating tendon is vibrated (which effectively activates spindle endings) during a sustained MVC, force tends to increase (Bongiovanni et al., 1990; Bongiovanni and Hagbarth, 1990). This carries consequences beyond just motoneuron function, as fatigued spindles demonstrate an increased sensitivity to stretch (Nelson and Hutton, 1985; Smith et al., 1974), and yet, a reduced capacity to signal accurate muscle length changes (Pedersen et al., 1998).

Golgi tendon organs (GTOs): Of all the afferent pathways that can influence the excitability of the motoneuron, GTOs are perhaps one of the more poorly understood. GTOs are peripheral receptors that are located primarily within the musculotendinous junctions. These include the muscle and aponeurosis (or deep fascia) junctions (Golgi, 1880, 1878), which may exist throughout the full length of the muscle and not just at the proximal/distal musculotendionous ends. Only a small portion of GTOs are located within the tendon proper itself (Jami, 1992). The application of tension by the muscle is thought to tighten the finely divided collagen bundles which surround and ultimately compress the tendon organ (Bridgman, 1970). This distortion induces spike discharges by the receptor, which are transmitted via type Ib afferents to the central nervous system. Unlike the monosynaptic stretch reflex, Ib afferents influence the motoneuron indirectly through

spinal interneurons (Angel et al., 1996; Chalmers, 2002; Conway et al., 1987; Pearson and Collins, 1993; Pratt, 1995). Their effect on the motoneuron (excitatory or inhibitory) is therefore dependent upon which interneuronal pathway is preferentially activated. That said, GTOs most commonly respond to muscle tension by providing autogenic inhibition (self-inhibition) to both their source muscle and synergists (Granit and Suurosoet, 1949; Hunt, 1952) while producing an excitatory effect to antagonistic motoneurons (Lloyd and Laporte, 1951). It was traditionally thought that the purpose of this inhibitory action of the GTO was to reflexively inhibit the agonist motoneurons, and therefore the agonist muscle, during exceedingly high muscle loading (Chalmers, 2002). Theoretically, this would serve as a safety mechanism to spare the muscle from injury. However, most of the original work that described this pathway was conducted in the cat model, including anaesthetized and decerebrate experiments (Eccles et al., 1957; Granit, 1950; Nichols, 1999). The GTOs studied were primarily located within the muscles of the hind limb with a strong locomotor function; the GTO reflex function is also thought to strongly relate with locomotor outputs (Pratt, 1995). Less is known how GTOs function in non-locomotor muscles and during non-locomotor outputs. Of the scarce human data that exists, research suggests that autogenic inhibition via GTO activity may not increase with increasing muscles forces (Fournier et al., 1983). Furthermore, there is some evidence from cat models that the inhibition previously observed only manifests at the immediate onset of contraction before rapidly diminishing over the next 100 milliseconds (Zytnicki et al., 1990). Autogenic inhibition was no longer observed following this time period. It is important to note, however, that GTOs continued to fire action potentials due to the contraction stimulus, suggesting that their input into the spinal cord is almost certainly mediated by descending

or other afferent signals (Chalmers, 2002; Duysens et al., 2000; Jami, 1992; McCrea, 1986).

While the physiological function of GTOs and their Ib innervations is complex in normal conditions, it is even less clear following fatigue. There is some evidence that GTOs become less sensitive to passive length change following fatigue (Hutton and Nelson, 1986; Smith et al., 1974). Since passively increasing the length of a muscle places added stress upon the musculotendinous junction (albeit, this increase is small), GTOs can indirectly signal muscle length changes back to the CNS. However, this capacity is seemingly impaired with fatigue (Hutton and Nelson, 1986; Smith et al., 1974). Also, as stated previously, Jami and colleagues (1990, 1992) have demonstrated that the autogenic inhibitory function of GTOs and Ib afferents diminishes during a prolonged contraction (Lafleur et al., 1992; Zytnicki et al., 1990), possibly as the result of presynaptic inhibition. Thus, of the available evidence at hand, it seems unlikely that GTOs make a significant contribution to the reduced discharge rates observed in motoneurons following fatigue. It should be repeated, however, that these findings have been produced mainly from cat models, some of which were isolated specimens, and thus, void of certain descending and afferent pathways. It remains largely unclear how GTOs and Ib afferents function in humans, during exceedingly strong muscle contractions, or in contractions lasting a very long time.

Small-diameter afferents: Group III and IV muscle afferents are small myelinated and small unmyelinated sensory neurons, respectively, which innervate free nerve endings throughout the periphery, including a wide distribution throughout skeletal muscles. Unlike their type Ia, Ib, and II counterparts, which generally relay information of just one sensory

modality, group III and IV afferents are capable of discharging in the presence of many different factors. These include local mechanical stimuli (Chen et al., 2010; Hoheisel et al., 2005, 2004; Xu et al., 2010), thermal changes (Jankowski et al., 2013), and exposure to a wide variety of biochemical accumulations, such as potassium ions, lactate, histamine, arachidonic acid, and bradykinin (Kaufman et al., 1983; Mense, 1977; Mense and Meyer, 1988; Mense and Schmidt, 1974; Rotto et al., 1990; Rotto and Kaufman, 1988; Sinoway et al., 1993). Their capacity to detect changes in biochemical compounds make group III and IV afferents particularly important in cardiovascular and ventilatory reflex responses following exercise or fatiguing contractions (Craig, 1995; Kaufman and Forster, 2011). By acting through their central projections, these afferents are capable of promoting perfusion to target peripheral tissues and facilitating waste metabolite removal. For instance, when group III/IV afferent projections are blocked from the lower limb during exercise, local muscle perfusion is significantly impaired (Amann et al., 2010). The subsequent consequences are increased hypoxia, acidosis, and a reduction in oxygen delivery to working muscles. Interestingly, despite their differences in axonal diameter and conduction velocity, neither group III nor group IV afferents appear to be devoted to the detection of any one particular factor. Rather, there is tremendous overlap in their functional physiology, lending to the tendency of the two (III and IV) to be discussed as a single entity in most literature. For example, Koerber and colleagues recently performed what is perhaps the most comprehensive and robust investigation into the functional physiology of both group III and IV afferents (Jankowski et al., 2013). In this study, the right forelimb and the right spinal cord (hemisection of C7, C8, and T1) of adult mice were excised and placed in a bath of artificial cerebrospinal fluid. Sensory somata within the dorsal root ganglion were

recorded with quartz micro electrodes. To classify each sensory neuron as belonging to group III or IV, the peripheral nerves were stimulated electrically and the conduction velocity (derived from time) was determined at the soma. Neurons with a conduction velocity lower than 1.2 m/s were classified as group IV afferents, while conduction velocities ranging from 1.2 – 14 m/s were classified as group III afferents. Once the specific neuron was classified, three different stimuli were applied to the muscle of the forelimb, including mechanical contact (with von Frey hairs), thermal stimuli (hot or cold; 52° or 0°), or a low or high metabolite mixture, corresponding to a normal relaxed state or an intense ischemic contraction. Results showed that, of the 66 neurons identified, both group III and IV afferents responded to all forms of stimuli to varying degrees. For example, approximately 30% of group III and IV afferents responded to thermal stimulation. However, group III afferents did seem to be more specific to mechanical stimulation than group IVs (70% vs 27%), while more group IV afferents responded to metabolic environments than either thermal or mechanical stimulation (54% vs 33% and 27%) (Jankowski et al., 2013).

While the evidence is strong that group III and IV afferents facilitate muscle performance by enhancing local muscle perfusion, clearing metabolic waste products, and optimizing oxygen supply to working tissue, there is conflicting evidence that activity of these pathways might reflexively inhibit motoneurons. If this is true, the thought is that group III and IV afferents might limit muscle activity to prevent an adverse accumulation of metabolites during/following intense exercise (Amann, 2011; Amann et al., 2011). Following repeated fatiguing contractions in the cat, the background discharge rates of both group III and IV afferents typically increase (Hayward et al., 1991). Persistent muscle

ischemia following sustained muscle contraction maintains these increased firing rates (Adreani and Kaufman, 1998; Hayward et al., 1991; Kaufman et al., 1984a, 1984b; Mense and Stahnke, 1983; Paintal, 1960). Motoneuron firing rates are inversely related with this phenomenon, with discharges decreasing as fatigue develops and remaining reduced for as long as ischemia is maintained (B. Bigland-Ritchie et al., 1986b; Garland et al., 1988; Woods et al., 1987). In these studies, resumption of blood flow allowed these rates to return to normal. Since voluntary activation, measured via twitch interpolation during plantar flexion, remained high, the subsequent implication was that greater activity of group III and/or IV afferents resulted in reflexive inhibition of alpha motoneurons (Garland et al., 1988). Some evidence suggests that this could be carried out through presynaptic inhibition of Ia afferents (Pettorossi et al., 1999; Priori et al., 1998). However, there are some problems with this line of reasoning. If group III and IV afferents do inhibit motoneurons following fatigue, voluntary activation as measured though ITT should be reduced as well (Gandevia, 2001). In research utilizing cervicomedullary evoked potentials (CMEPs), which represent spinal excitability, CMEP amplitudes initially decrease (muscle-dependent (Giesebrecht et al., 2010)) immediately following a sustained maximal contraction (which follows with decreased voluntary activation and decreased motor unit firing rates) but recovers to baseline values 15-30 seconds into recovery (Butler et al., 2003). This rapid recovery occurs even if the exercising muscle is held ischemic post-fatigue. Thus, if group III and IV afferents do inhibit motoneurons, and are assuredly active in the presence of ischemia, spinal excitability should not have been able to recover (Gandevia, 2001). To further complicate matters, the effect of group IV afferents on flexor motoneurons of the cat may change from inhibition to excitation as stimulation duration increases (Wall and

Woolf, 1984). More recent investigations have asserted that group III and IV activity does inhibit motoneurons, although in these studies, activity of small diameter afferents has never been directly measured (Amann, 2011; Amann et al., 2011, 2009, 2008).

To summarize, motoneuron discharge rates decline similarly to the reduction in muscle contractile speed in what has been commonly referred to as muscular wisdom. The cause of this reduction in firing rates is almost certainly multifactorial, with contributions from reduced muscle spindle activity and reduced intrinsic motoneuron excitability representing two likely candidates. Contributions from GTOs and small diameter afferents are currently less clear. However, despite all these findings, the muscular wisdom hypothesis remains to be confirmed, and there have even been some calls for the hypothesis to be revaluated (Gandevia, 2001). This has primarily come about because of two reasons: 1) in studies where contractile speed and discharge rates have been examined without the influence of fatigue, a relationship between the two has not been found (B. Bigland-Ritchie et al., 1992; B. R. Bigland-Ritchie et al., 1992; Marsden et al., 1983; Vander Linden et al., 1991), 2) in the cat model, muscle contractile speed changes according to muscle fiber type. Contractile time decreases for slow twitch motor units during fatigue, but can actually increase for fast twitch motor units (Dubose et al., 1987). Thus, if the hypothesis of muscular wisdom is true, the declining firing rate of motoneurons would not be ideally matched with the contractile properties of all muscle fibers.

While the muscular wisdom hypothesis may be in need of further refinement, it is abundantly clear that motoneurons, and the motor units they contribute to, slow in their firing as maximal muscular contractions progress (Bellemare et al., 1983; Bigland-Ritchie et al., 1983b; Gandevia et al., 1993; Grimby et al., 1981a; Marsden et al., 1971; Martin et

al., 2006; Peters and Fuglevand, 1999; Petrofsky, 1980; Petrofsky and Lind, 1980; Woods et al., 1987). If the development of fatigue is severe enough, motor units may stop firing completely (Duchateau and Hainaut, 1990; Garland et al., 1988; Grimby and Hannerz, 1977; Peters and Fuglevand, 1999). In cases where a sustained contraction is maximal, this reduced discharge rate will result in gradual force loss and a reduction in overall muscle activity (B. Bigland-Ritchie et al., 1986b; Enoka, 1995). However, in the case of sustained submaximal contractions, muscle activity can increase so long as force output remains constant (Bigland-Ritchie et al., 1981; DeVries, 1968; Eason, 1960; Edwards and Lippold, 1956, 1956; Hendrix et al., 2009; Lynn et al., 1978; Scherrer and Bourguignon, 1959). This is made possible by an increase in motor unit recruitment (B. Bigland-Ritchie et al., 1986a; Enoka et al., 1989; Gamet and Maton, 1989; Person and Kudina, 1972) that ensures sufficient force production in the presence of motoneurons discharging at slower rates. Since research has repeatedly shown that the motoneuron itself is largely inhibited during the development of fatigue, any increase in recruitment is thought to arise from supraspinal pathways (see the section below for further details). Thus, when measured with surface EMG, a muscle is said to be fatigued when either the discharge rate of its motor units has decreased, its activity exceeds baseline (during submaximal contractions), or both.

2.1.25 Central mechanisms – supraspinal pathways

Since voluntary activation tends to decline with fatigue, some experts have concluded that supraspinal drive is clearly impaired following sustained or repetitive contractions (Gandevia, 2001; Sidhu et al., 2013). While this statement may be true, literature regarding fatigue and supraspinal pathways is tremendously complex, and results

between different types of measurements are often conflicting. For starters, how is muscle activity during sustained, submaximal contractions capable of increasing in the presence of both fatigue? Current understanding suggests that this is due to increased motor unit recruitment mediated by an increase in descending commands via supraspinal pathways. How is this possible given that voluntary activation is typically reduced in the presence of fatigue?

The first known study that began investigating possible supraspinal pathways that might be influenced by fatigue was conducted by Hallett and colleagues in 1993 (Brasil-Neto et al., 1993). In this study, maximal Mwaves, H-reflexes, and motor evoked potentials (MEPs) elicited by both transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (TES) were recorded with surface electromyography in the flexor carpi radialis (FCR). Prior to inducing fatigue, a set of eight responses was elicited at rest for each stimulation in the following order: Mwaves, H-reflexes, TES and TMS. Stimulations were delivered at a frequency of 0.2 Hz, meaning that a stimulation occurred once every 5 seconds within a set. To induce fatigue, participants held a 3.4 kg dumbbell while their hand hung freely over the edge of a table (forearm was supinated and supported by the table). Participants then performed dynamic, repetitive wrist flexions at a pace of one repetition per second until they were no longer capable of continuing the movement. Following fatigue, eight stimulations per stimulation technique were again delivered in the same order as baseline. Results demonstrated that only MEP amplitudes elicited via TMS decreased following fatigue; M-waves, H-reflexes, and TES-induced MEPs were not different. The authors concluded that, not only were intracortical processes involved in driving this decrease in TMS-induced MEP amplitudes, but also that TES and TMS must

clearly activate different aspects of the motor cortex (Brasil-Neto et al., 1993). Over the next six years, several other studies would confirm that TMS-induced MEP amplitudes decrease following fatigue (Gandevia et al., 1999; McKay et al., 1995; Samii et al., 1996; Zanette et al., 1995). However, it is crucially important to examine the time aspect within these studies, particularly as it relates to stimulus delivery. In the original work by Hallett and colleagues (Brasil-Neto et al., 1993), the authors stated that, "The amplitude of MEPs evoked by TMS immediately after the fatiguing task decreased." The term "immediately" requires clear definition. Because stimulations were delivered in sets of eight in a controlled order (Mwaves; H-reflex; TES; TMS), and since an interstimulus interval of 5 seconds was utilized, this means that each set took 40 seconds to complete. If no break occurred between sets (this was not stated in the article (Brasil-Neto et al., 1993)), and even if the first Mwave occurred instantaneously after the fatigue-inducing trial ceased, this would indicate that the first TMS-induced MEP was elicited 2 full minutes post-fatigue. This observation is consistent with the other studies which have observed a decrease in TMS-induced MEP amplitudes "immediately" post-fatigue. Across all four of these investigations, the first TMS was delivered 15-120 seconds post-fatigue (Gandevia et al., 1999; McKay et al., 1995; Samii et al., 1996; Zanette et al., 1995). This is noteworthy for the following reason: when TMS is delivered as close as possible to the cessation of a fatigue-inducing trial, MEP amplitudes actually increase compared to baseline (Liepert et al., 1996; Sacco et al., 1997; Samii et al., 1996; Yoon et al., 2012). These measures decrease at approximately 15 seconds and can remain reduced from baseline measures for as long as 30 minutes (Samii et al., 1996; Zanette et al., 1995). Thus, MEP amplitudes elicited after a fatigue-inducing

task are intimately time-sensitive, and any investigations reporting on these measures should clearly communicate the time-points in which they were taken.

It is strongly suspected that the initial increase in corticospinal excitability is due to an increase in supraspinal excitability, given that spinal excitability (as discussed in detail previously), measured either through motoneuron current injection (Kernell and Monster, 1982b, 1982a; Sawczuk et al., 1995a) or the use of cervicomedullary evoked potentials (CMEPs) (Taylor et al., 1996), decrease immediately post-fatigue. This is demonstrated visually in Figure 2.4. Together, these findings have produced the following conclusion: spinal excitability is reduced following a sustained contraction (which may contribute to slower motor unit discharge rates), but is compensated for by increased supraspinal excitability to ensure adequate motor unit recruitment and volitional drive (Gandevia, 2001). As mentioned before, the latter half of this statement is somewhat unclear. Given that voluntary activation tends to decrease (Löscher et al., 1996a, 1996b; Zijdewind et al., 1998), it stands to reason that volitional drive, and therefore cortical excitability (although MEPs are not an ideal indicator of the capacity of the motor pathway (Gandevia et al., 1996)), must be impaired (Gandevia, 2001; Sidhu et al., 2013). Literature of underlying

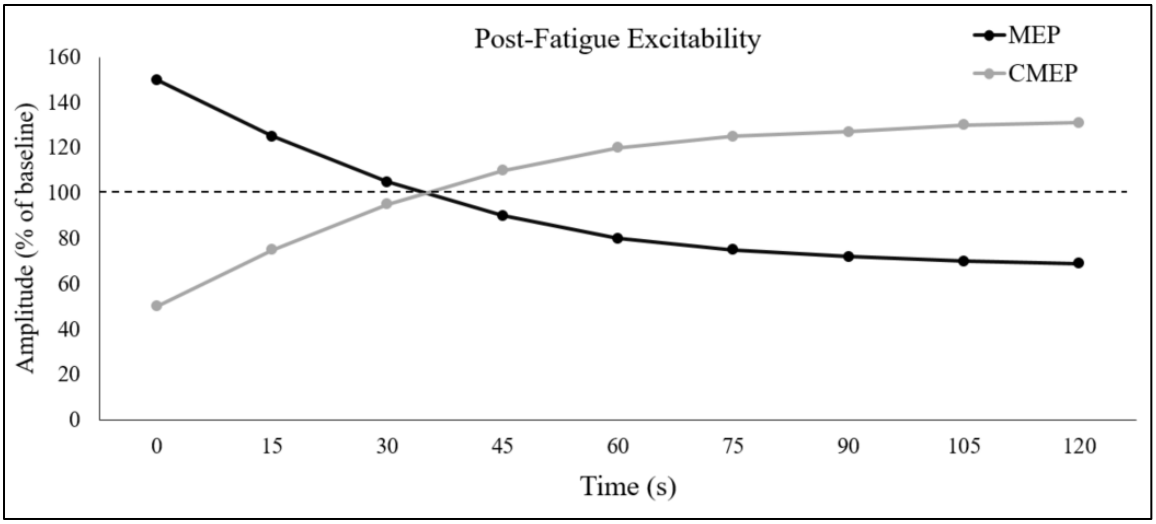

Figure 2.4. *Typical behaviour of corticospinal excitability (MEPs; black dots) and spinal excitability (CMEPs; grey dots) responses following a sustained MVC. Data (collected from a relaxed muscle) is shown as a percentage of baseline; the dashed line represents baseline (non-fatigued) responses. MEPs and CMEPs tend to increase and decrease, respectively, immediately following a sustained MVC, but over correct after approximately 15 seconds. Figure was recreated from Gandevia (2001) and Butler et al. (2003).*

supraspinal mechanisms both supports and opposes this notion. Although TMS elicits an excitatory response in neurons of the motor cortex, which transynaptically activate the pyramidal neurons of the corticospinal tract, TMS is also capable of activating cortical inhibitory pathways. After a MEP has been elicited by TMS during a voluntary contraction, there is a brief period where the EMG signal becomes nearly silent; muscle activity is virtually non-existent (Berardelli et al., 1999; Cantello et al., 1992; Fuhr et al., 1991; Holmgren et al., 1990; Merton et al., 1981; Roick et al., 1993; Triggs et al., 1993; Wilson et al., 1993). This period is known as the corticospinal silent period (CSP). If sufficiently strong stimulus intensities are utilized, CSP duration can outlast the period of reduced spinal motoneuron responsiveness, suggesting that the length of the CSP is at least partially influenced by supraspinal mechanisms (Chen et al., 1998; Fuhr et al., 1991). There is also some evidence that the recovery of intracortical inhibition, driven via $GABA_B$ receptors and inhibitory interneurons (Chen et al., 1999; Fuhr et al., 1991; Inghilleri et al., 1993;

Kang et al., 1994; Siebner et al., 1998), following TMS influences CSP duration. Thus, an increase in CSP duration is traditionally interpreted as representing an increase in cortical inhibition. When assessed following fatigue, the TMS-induced CSP duration has been shown to increase (Hunter et al., 2008; McNeil et al., 2009; Mills and Thomson, 1995; Taylor et al., 1996). Amongst the literature, this finding has been suggested to indicate that cortical inhibition increases following fatigue. However, such statements should be made cautiously. While a relationship between the size of the MEP amplitude and the duration of the CSP had been noted as anecdotal evidence since the 90s, it wasn't until 2004 that Orth and Rothwell first quantified this phenomenon (Orth and Rothwell, 2004). In this study, TMS was delivered to the first dorsal interosseous (FDI) at 6 different stimulus intensities (100, 110, 120, 130, 140, and 150% of active motor threshold). As TMS intensity increased, so too did both the size of the MEP amplitude and the duration of the CSP. The correlation between these separate increases was high ($r^2 = 0.88$) (Orth and Rothwell, 2004). Based on these findings, it was suggested that the corticospinal neurons that generate the MEP may also drive changes in the CSP. This is perhaps possible through axon collaterals from corticospinal neurons which may induce recurrent inhibition upon synergistic corticospinal neurons (Phillips and Porter, 1977). In other words, greater activity of corticospinal neurons (which will generate a larger MEP amplitude) will recurrently induce a longer CSP duration. Thus, it is possible that the increase in CSP duration that follows fatigue is not directly related to fatigue itself. Rather, it may simply be the result of the larger MEP amplitudes that also follow fatigue, and therefore, may not represent an increase in intracortical inhibitory mechanisms. However, the CSP is not the only measure that can indicate changes to intracortical inhibition.

While TMS can only elicit MEPs if its stimulus intensity is sufficient to reach, or surpass motor threshold, subthreshold TMS remains capable of activating cortical tissue. When subthreshold TMS is utilized during voluntary contractions, the EMG signal can be suppressed in target muscles (Davey et al., 1994; Petersen et al., 2001). This suppression is thought to arise from the activation of inhibitory intracortical circuits (which have a lower TMS threshold than corticospinal tract cells (Di Lazzaro et al., 1998a; Kujirai et al., 1993)) which in turn impair the excitability of pyramidal neurons acting upon motoneurons. Inhibition at the cortical level is likely to be the case, given that a test response from spinal stimulation is not suppressed at rest (when cortical contributions would be negligible), but is suppressed during voluntary contractions (when cortical contributions would likely be high) (Davey et al., 1994). The magnitude of EMG suppression is therefore thought to reflect the magnitude of cortical drive present in a given motor task; the greater the suppression, the greater the presence of cortical drive (Davey et al., 1994; Petersen et al., 2001). Although this technique has not been widely used in fatigue-related work, one study in 2010 demonstrated that EMG suppression may increase following fatigue (Seifert and Petersen, 2010). In this study, participants performed a sustained isometric elbow flexion at 30% of their maximal voluntary contraction until they could no longer maintain target force. Subthreshold TMS was delivered to the biceps brachii throughout the sustained contraction. At the beginning of the trial, the EMG signal was suppressed by ~9.5% across the group. By the end of the contraction, this suppression increased to ~15.3%. While this might indicate that greater cortical drive is present at the cessation of a sustained contraction (meaning there are more cortical neurons that are available to be suppressed), EMG suppression does not increase with increasing voluntary

force (Seifert and Petersen, 2010). Therefore, the more likely explanation is that the excitability of the inhibitory intracortical neurons increases when fatigued, and exerts greater suppression of the outgoing corticospinal signal following subthreshold TMS.

Paired-pulse TMS techniques have also offered insight into possible supraspinal pathways that might be modulated in the presence of fatigue. In these measures, TMS is delivered twice in rapid succession, with the timing between the two pulses capable of assessing the excitability of either inhibitory or facilitory cortical circuits. The first pulse is referred to as the "conditioning" stimulus, which modulates the MEP amplitude of the second and subsequent "test" response. When the interstimulus interval (ISI) between these pulses is approximately 2-5 ms, the test MEP will typically decrease in amplitude, indicating that an inhibitory cortical circuit was activated (Di Lazzaro et al., 2001, 1998b). This is referred to in literature as short-interval intracortical inhibition (SICI). Alternatively, if the ISI between pulses is approximately 10-25 ms, the test MEP will typically increase in amplitude, and indicate that facilitory cortical circuits were activated (Di Lazzaro and Rothwell, 2014; Ziemann et al., 1996). This is referred to as intracortical facilitation (ICF) in literature. In SICI, the primary mechanism behind MEP inhibition is thought to be the result of $GABA_A$ergic pathways activated by subthreshold TMS. The basis for this claim comes from findings that SICI is increased by benzodiazepines (allosteric binding that enhances the effect of GABA) such as diazepam and lorazepam (Vincenzo Di Lazzaro et al., 2006; Teo et al., 2009; Ziemann, 2013). This pathway is thought to act upon the dendrites of pyramidal tract neurons and has been found to suppress the response of later I waves in epidural recordings (although there seems to be no effect on the first I wave) (Di Lazzaro et al., 2000). Thus, greater MEP suppression is typically

attributed to enhanced activity of $GABA_A$ergic cells. In the case of ICF, underlying mechanisms are far less clear. Although MEP amplitudes are facilitated at this ISI, epidural recordings show no increase in either the size or the number of descending waves (V. Di Lazzaro et al., 2006; Ni et al., 2011). Thus, ICF may not result from excitatory circuits acting upon the pyramidal neurons themselves. Rather, it has been suggested that the activity of the underlying mechanism may recruit separate cortical circuits that are not involved in the generation of I waves. This would act to produce additional and more dispersed descending activity that may not be detectable in epidural recordings (Di Lazzaro and Rothwell, 2014).

In the presence of fatigue, both SICI and ICF have been shown to be modulated. When assessed at rest, ICF in some studies demonstrates reduced facilitation of the test MEP following fatigue (Hunter et al., 2016; Tergau et al., 2000). While this might suggest that a reduction in facilitory circuits contributes to so called "supraspinal fatigue," there are conflicting reports. In separate studies, no change in ICF has been found, while SICI also demonstrates reduced inhibition of the test MEP following fatigue (Hunter et al., 2016; Maruyama et al., 2006; Vucic et al., 2011). Thus, there have been reports of both disfacilitation and disinhibition via cortical circuits following fatigue, making interpretations on increased supraspinal excitability difficult to decipher. However, in more direct investigations, it has been communicated in studies using epidural recordings that I waves are reduced in size immediately following exercise (Di Lazzaro et al., 2003). It remains unclear how this relates to increased MEP amplitudes following fatigue.

To conclude this section, it is worth mentioning that the development of fatigue through central mechanisms is not necessarily isolated to the working muscles and the

neurological pathways which innervate them. This is in reference to the notion of "cross-over" or non-localized effects of fatigue. During a voluntary contraction, not only will the antagonist muscle(s) provide co-contraction during agonist actions (and subsequently contribute to changes in afferent, descending, and intrinsic pathways of the CNS), but strong evidence also indicates that performance fatigability can manifest globally (Halperin et al., 2014; Rattey et al., 2006; Zijdewind et al., 1998). For instance, fatigue induced in the elbow flexors modulates corticospinal excitability in the contralateral upper-limb (Aboodarda et al., 2016) and the knee extensors (Aboodarda et al., 2015b). Similarly, fatigue induced in the knee extensors modulates corticospinal excitability in the elbow flexors (Aboodarda et al., 2017; Behm, 2016). These changes are frequently attributed to central mechanisms, such as increased activity of group III/IV afferents (Amann et al., 2013)), given a lack of peripheral changes in the non-exercised muscles. An increase in activity of group III/IV afferents is likely, given increases in local and global concentrations of exercise-related metabolites; ATP, lactate, H+, etc. Stimulation of free nerve endings might then serve to alter the excitability of the entire motor pool (Amann et al., 2013). Studies inducing fatigue in "isolation" should be mindful of this phenomenon.

2.1.26 Propriospinal system

Of all the descending pathways in the CNS, the corticospinal tract is the primary pathway in which voluntary motor commands are transmitted from the motor cortex and down to the spinal cord. Throughout most of the upper limb, pyramidal neurons make monosynaptic connections with motoneurons, although the frequency of this seems to depend on the muscle (de Noordhout et al., 1999; Palmer and Ashby, 1992). In all other

cases, the corticospinal tract must exert its influence upon motoneurons through interneurons (or disynaptic/polysynaptic pathways). In the upper limb, some of these interneurons are referred to as cervical premotoneurons and are thought to be similar in physiological function to the propriospinal system in animal models (Alstermark et al., 1999; Isa et al., 2006; Sasaki et al., 2004). Anatomically, these neurons both receive and transmit information entirely within the spinal cord, meaning they neither reside in/above the brain stem nor exit the spinal cord into the periphery (Pierrot-Deseilligny, 2002). It is mostly accepted within literature that the propriospinal system in humans influences motor outputs by relaying (and subsequently altering) both descending and afferent signals to spinal motoneurons (Burke et al., 1994; Nicolas et al., 2001; Pauvert et al., 1998; Pierrot-Deseilligny, 2002, 1996). There is also evidence that the propriospinal system makes a substantial contribution to the generation of motor outputs via facilitation of descending commands through non-monosynaptic pathways (Burke et al., 1994; Mazevet et al., 1996; Nicolas et al., 2001). The activity within this system is measurable in humans. By stimulating cutaneous afferents within peripheral nerves, the on-going EMG of voluntarily active muscles is suppressed. It is unlikely that this suppression directly inhibits the motoneuron itself, since a conditioning stimulus of cutaneous afferents does not influence the H-reflex amplitude (Burke et al., 1994; Mazevet et al., 2003). Rather, the suppression is thought to arise from inhibition of the premotoneurons which carry a portion of the descending drive (Burke et al., 1994). Taylor and colleagues are one of the few groups to utilize this technique to investigate possible propriospinal mechanisms involved in fatigue (Martin et al., 2007). In this study, EMG was recorded from both the extensor carpi radialis (ECR) and the triceps brachii (TB). Electrical stimulation was applied to the superficial

radial nerve while participants produced 30% of their maximal ECR EMG in multiple, 15 second trials. The suppression of the ongoing EMG signal was subsequently measured. Fatigue was then induced by two sustained wrist extension MVCs (separated by 60 seconds of rest), which were terminated when participants could no longer maintain 60% of their pre-fatigue MVC force. Post-fatigue cutaneous stimulation followed. Results demonstrated that the suppression of ECR activity nearly doubled following fatigue as compared to baseline (Martin et al., 2007). However, suppression actually decreased following fatigue in the case of TB. These findings indicate one of two possibilities. Either the portion of the descending drive mediated by the propriospinal system increases following fatigue, and can thus be suppressed to a greater extent by cutaneous nerve stimulation, or the excitability of inhibitory interneurons acting upon the propriospinal premotoneurons increases with fatigue. Whichever of these possibilities is true, it would seem they are only present following fatigue of a prime mover (ECR) and are perhaps uniquely modulated in their innervation of coactive muscles (TB) (Martin et al., 2007).

2.1.27 Persistent inward currents (PICs)

Neurons possess a unique group of voltage sensitive Na^+ and Ca^{++} membrane channels that, following a sufficiently strong depolarizing current, inactivate slowly. Their voltage sensitive and slow inactivation characteristics set these membrane channels apart from passive leak channels and voltage-gated Na^+ and K^+ channels used in action potential generation, respectively (Heckman et al., 2008). When these channels are activated via excitatory post-synaptic potentials (EPSPs), there is a steady influx of Na^+ and Ca^{++} that further depolarizes the membrane. Since these channels inactivate slowly, this depolarizing

current lasts, often for several seconds, after EPSPs have stopped. This mechanism is referred to as a persistent inward current (PIC), and plays an especially important role in the electrical properties of spinal motoneurons. The contribution of PICs can be so strong in motoneurons that the motoneuron can continue to fire action potentials (referred to as self-sustained firing) long after synaptic input has been removed (Lee and Heckman, 1996). Functionally, this mechanism likely serves a number of roles. In has been suggested that PICs may be crucial in the maintenance of posture, whereby steady motoneuron firing can sustain steady postural forces with minimal descending input (Hounsgaard et al., 1988). There is also evidence that the majority of the PIC is generated within the dendrites, which may serve to amplify synaptic input to the motoneuron (Bennett et al., 1998; Carlin et al., 2000; Hounsgaard and Kiehn, 1993; Lee and Heckman, 1996). This mechanism is thought to lessen the burden of descending drive, whereby fewer descending EPSPs are required for a motoneuron to reach firing threshold. Once the motoneuron is no longer needed to fire, a hyperpolarizing input is capable of deactivating the PIC (Heckman et al., 2008).

Considering these functions, PICs are thought to make a significant contribution to the firing characteristics of motoneurons. Thus, during sustained firing (as would occur during a fatiguing contraction), it is possible that the physiology of PICs might change. For instance, while minimal fatigue research has been conducted regarding the function of PICs, PICs have been shown to increase in amplitude and prevalence when descending drive is reduced, as occurs following a spinal cord injury (ElBasiouny et al., 2010). While this behaviour may not be beneficial, as it occurs in a pathological state (and may contribute to spasticity), it at least demonstrates that PICs can adapt to decreases in descending drive. If descending drive also decreases following fatigue, which could be possible given reports

of fewer I waves (Di Lazzaro et al., 2003), PIC activity might subsequently increase. If so, this might serve to offset the disfacilitation of afferent inputs (Macefield et al., 1991) and the reduction in intrinsic motoneuron excitability (Bayliss et al., 1997; Kernell and Monster, 1982a, 1982b; Sawczuk et al., 1995a, 1995b) that occurs with fatigue. However, these points are largely speculative at this time and require further research.

Chapter 3. The influence of simultaneous handgrip and wrist force on forearm muscle activity

A study published in the Journal of Electromyography and Kinesiology

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Preface

The wrist flexors are approximately twice the size of the wrist extensors. The wrist flexors also possess a mechanical advantage over the extensors, meaning that their peak moment generating capacity is significantly greater (Gonzalez et al., 1997). As a consequence of these differences, the wrist extensors must contract to a higher percentage of their maximum if they are to counter the moments generated by the wrist flexors. This phenomenon is thought to be related to the functional roles of the two muscle groups, whereby the wrist flexors are responsible for executing most motor outputs of the hand and wrist as the prime movers, and the wrist extensors act chiefly as wrist joint stabilizers by balancing the ensuing flexion moments. Electrophysiological studies have provided large support for these statements. The wrist extensors provide the largest contribution to wrist joint stiffness of the forearm muscles (Holmes et al., 2015), and the wrist extensors tend to be more active than the flexors during hand-gripping at various forces and postures (Mogk and Keir, 2003). However, there is currently a large gap in this area of research in that most neuromuscular investigations examine forearm muscle recruitment during the execution of single motor tasks in isolation. This has limited applicability to real-world tasks, whereby most goal-oriented motor tasks are accomplished by multiple muscle actions performed simultaneously. Thus, the purpose of Chapter 3 was to examine how the recruitment strategies of the wrist flexors and extensors are influenced when executing two motor outputs (hand-gripping and either wrist flexion or wrist extension) simultaneously.

Abstract

The purpose of this study was to examine forearm muscle activity during the simultaneous execution of dual motor tasks–hand-gripping and wrist forces. Surface electromyography was recorded from eight muscles of the upper-limb: flexor carpi radialis, flexor carpi ulnaris, flexor digitorum superficialis, extensor carpi radialis, extensor carpi ulnaris, extensor digitorum, biceps brachii and triceps brachii. Participants were seated with their forearm supported in a neutral position with an adjustable force transducer placed on either the palmar or dorsal side of the hand (for palmar/dorsal forces). Participants performed trials of simultaneous handgrip and wrist forces of various magnitudes, ranging in intensity from 0-40% of their maximal voluntary contraction. Trials lasted 5 seconds and force and electromyography data were assessed. The wrist flexors provided greatest contributions to tasks dominated by palmar forces but exhibited very low muscle activity in dorsal dominant tasks. Wrist extensors were active at moderate-to-high levels across nearly all conditions and demonstrated greater activity than the wrist flexors during handgrip-dominant tasks. These findings suggest that the wrist extensors provide the greatest contribution to wrist stability in complex motor tasks, and highlight the importance of investigating forearm muscle recruitment strategies under dual task parameters.

Introduction

The combination of direct wrist movement (flexion/extension and ulnar/radial deviation) and rotation of the radioulnar joints (supination/pronation of the forearm) allows for an extensive range of motion at the distal upper-limb. Within this intricate system is a redundant arrangement of muscles, where several muscles are capable of the same motor task (Bawa et al., 2000; Fleckenstein et al., 1994; Loren et al., 1996). This redundancy adds a layer of difficulty when exploring motor control theories and complicates computational modeling of the distal upper limb. Further, it challenges our capacity to understand and treat neuromuscular ailments of the hand, wrist, and forearm. Part of this complexity is necessitated by the dynamic capabilities of the hand. Historically, hand strength, task demands, and workplace injury risk were established based on an individual's maximum handgrip force, determined using a force dynamometer (An et al., 1985). This approach remains valid for tasks executed purely by grasping the hand, but is inappropriate for most situations. Wells and Greig (2001) presented a modern framework to better characterize hand prehensile strength. Defined as a force and moment (rotational force) wrench, the hand can be characterized by its internal grip force, external force, and moment wrench capabilities (Wells and Greig, 2001). This approach more effectively captures the hand's tendency to stabilize an object with grip force while simultaneously transmitting torques generated by the flexors/extensors of the wrist and the supinators/pronators of the forearm (Kroemer, 1986). Wells and Greig have also highlighted the need for research to assess prehensile capabilities in multi-component, dual-task exertions that translate better to workplace settings and tasks of daily-living (Greig and Wells, 2004; Wells and Greig, 2001). However, in the ~15 years that have followed this work, minimal investigations into

dual-task protocols have been conducted. Given the importance of muscle activity as an overuse mechanism for workplace musculoskeletal disorders, understanding forearm muscle recruitment in complex hand/wrist actions is a logical continuation in injury prevention. Currently, it is unclear if an isolated strength demand of the hand or wrist generates comparable muscle demands to an effort combining multiple muscle actions.

Of the literature that has examined forearm muscle activity in single axis/uni-component exertions, the following conclusions have been produced: 1) Wrist flexor muscles are highly task-dependent, with a predominant role in producing handgrip and wrist flexion forces (Duque et al., 1995; Halpern and Fernandez, 1996; Imrhan, 1991; Kattel et al., 1996; Mogk and Keir, 2003), and 2) Wrist extensor muscles are resistant to task-dependent changes, and serve a primary role of wrist stabilization in countering the forces produced by wrist flexors (Hägg et al., 1997, 1997; Mogk and Keir, 2003). These statements are based in part by anatomical constraints, as the wrist flexors collectively possess a larger cross sectional area (CSA) and moment arm than the wrist extensor muscles (Gonzalez et al., 1997; Jacobson et al., 1992; Lieber et al., 1992). Mechanically disadvantaged, the wrist extensors must function at a higher percentage of their maximum to balance the wrist flexor moments, leaving them more susceptible to overuse injuries. Again, these findings have been generated mostly by studies investigating uni-component motor tasks (hand-gripping or wrist flexion/extensions in isolation). The roles of the forearm muscles in hand and wrist tasks with increasing complexity are not yet well understood.

It is currently unclear if the main themes of forearm muscle function derived from previous protocols are transferrable to the force and moment wrench framework proposed

by Wells and Greig (Greig and Wells, 2004; Wells and Greig, 2001). In following with the recommendations of this work, the purpose of the present study was to examine forearm muscle activity while performing a range of handgrip contractions simultaneously with a range of wrist forces. All experimental conditions summed to what was referred to as "40% combined effort", whereby combinations of handgrip forces (relative to maximum handgrip force) and wrist exertions (also relative to maximum) summed to 40%. For example, one experimental condition consisted of participants producing 10% of their maximum handgrip force while simultaneously exerting 30% maximal wrist flexion (or palmar force). Our hypotheses were three fold. 1) The wrist flexors would be highly task-dependent, in the sense that changes in contributions to the 40% combined effort would greatly alter their activity. This would be confirmed with the observation of larger effect sizes (following two-way interactions) than the wrist extensors. 2) Although the wrist extensors would be significantly influenced by changes in the contributing handgrip and wrist forces, these changes would be smaller in magnitude and exhibit smaller effect sizes than in the wrist flexors. 3) Greater co-contraction would be observed during wrist flexion (or palmar forces) trials as compared to wrist extension (or dorsal forces) trials.

Methods

3.3.1 Participants

Experimental procedures were approved by the research ethics board (REB) of the University of Ontario Institute of Technology (REB# 14-046). Written consent was obtained for all participants prior to the experiment. Twelve, right-handed males (Height: 177.8 ± 7.2 cm; Weight: 84.5 ± 12.1 kg; Age: 23.6 ± 2.2 years) were recruited for this study. Participants completed a Physical Activity Readiness Questionnaire for Everyone (PAR-Q+; Canadian Society for Exercise Physiology) to screen for any contraindications to exercise or physical exertions. Subjects were excluded if they possessed any upper-body, neuromuscular injuries.

3.3.2 Experimental setup

Participants were seated at a custom-built, table-mounted apparatus that supported the dominant forearm (Figure 3.1) atop two, foam pads: one at the distal, radio-ulnar joint and the second at the olecranon. The forearm was kept in a neutral orientation and the wrist in a neutral position (neither flexed nor extended; 0° of wrist flexion/extension) throughout the entire protocol. The forearm was held straight out from the participant (0° of shoulder abduction and 0° of lateral rotation) and while elbow extension and shoulder flexion angles weren't controlled during the study, they *were* manually assessed using a goniometer prior to the experiment (Elbow extension: 148 ± 5.4°; Shoulder flexion: 61.8 ± 9.4°). Marks, corresponding to the proper location of the foam supports, were made on each participant's forearm to ensure consistent placement. Wrist exertions were measured using a force transducer (Model: BG 500, Mark-10 Corporation, New York, USA) that was manually

positioned against either the front of the hand to assess palmar force or against the back of the hand to assess dorsal force. Specifically, the transducer contacted the posterior surface

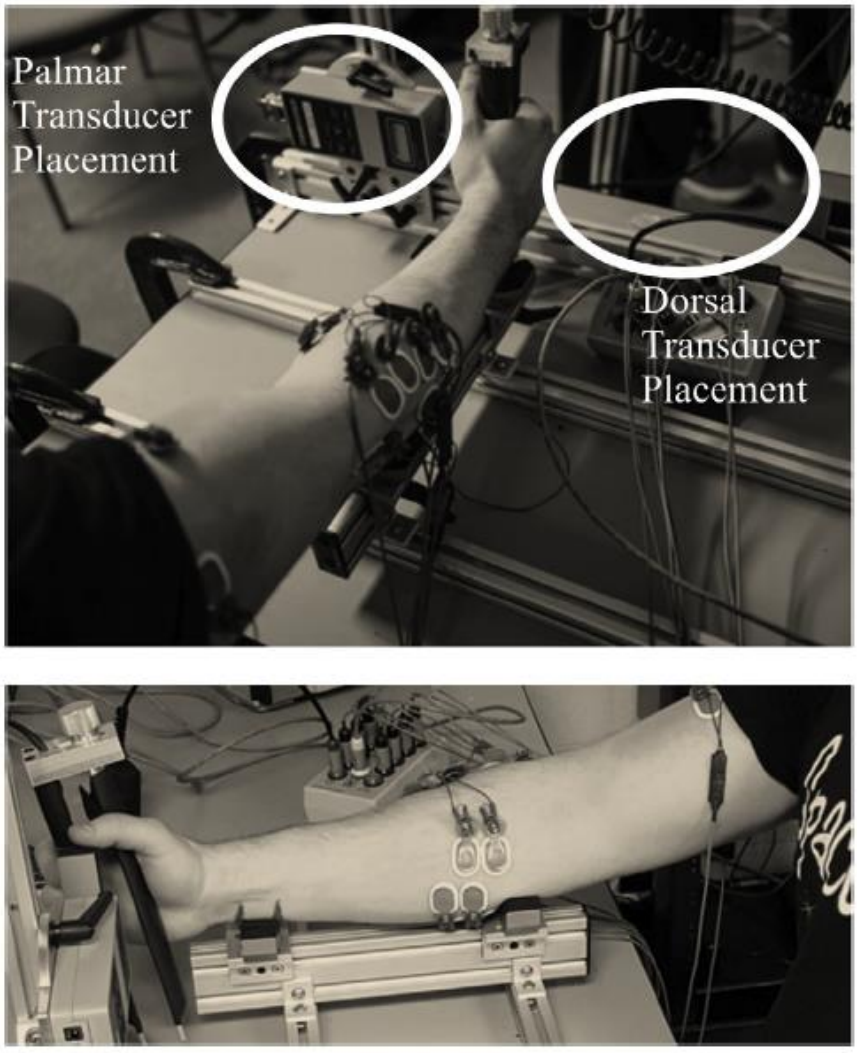


Figure 3.1. *Experimental setup. Participants' forearm supported by foam pads at both the distal and proximal radioulnar joints. Transducer in photo set for palmar force exertions. Transducer could be moved behind the hand to accommodate dorsal exertion trials.*

of the distal phalanges (closed hand) and the posterior surface of the distal metacarpal bones for palmar and dorsal trials, respectively. The force transducer was kept as close to the hand as possible to ensure that, during isometric wrist exertions, the wrist remained neutral. Participants also grasped a handgrip dynamometer (MIE Medical Research Ltd, Leeds, UK) for all experimental tasks. Hand position on the dynamometer was kept

consistent. In this setup, with the hand dynamometer grasped and the force transducer against the hand, participants performed simultaneous wrist exertions *and* handgrip contractions. The terminology used throughout this paper has been adapted from the work of Wells and Greig (Wells and Greig, 2001). Palmar and dorsal forces are in reference to the direction of force applied to a force transducer via the production of isometric wrist flexion and extension torques, respectively.

3.3.3 Electromyography

Muscle activity was recorded using pairs of surface electrodes (Blue Sensor, Ambu A/S, Denmark) from eight muscles of the dominant arm; flexor carpi radialis (FCR), flexor carpi ulnaris (FCU), flexor digitorum superficialis (FDS), extensor carpi radialis (ECR), extensor carpi ulnaris (ECU), extensor digitorum (ED), biceps brachii (BB), and the triceps brachii (TB). Electrodes were placed over the muscle belly, in-line with fiber orientation, and procedures followed previous placement guidelines (Forman et al., 2016; Holmes et al., 2015; Mogk and Keir, 2003; Perotto and Delagi, 2011). A ground electrode was placed on the lateral epicondyle of the dominant arm. Prior to electrode placement, all recording sites were shaved of hair using a disposable razor and were sanitized with an isopropyl alcohol swab. EMG was band-pass filtered (10-1000 Hz) and differentially amplified (CMRR > 100dB at 60 Hz; input impedance ~ 10 GΩ; AMT-8, Bortec Biomedical Ltd, Calgary, AB, Canada). EMG, grip force, and load cell data were sampled at 2048 Hz (USB-6229 BNC, National Instruments).

Table 3.1. *Maximal voluntary contractions (MVCs) for each of the 8 muscles assessed.*

Muscle	MVC Protocol
Flexor Carpi Radialis (FCR)	Forearm supinated, hand closed into fist, wrist flexion against manual resistance
Flexor Digitorum Superficialis (FDS)	Forearm supinated, partially opened hand grasping the hand of the researcher, combined wrist flexion and maximal grip
Flexor Carpi Ulnaris (FCU)	Forearm supinated, hand closed into fist, combined wrist flexion and ulnar deviation
Extensor Carpi Radialis (ECR)	Forearm neutral, hand closed into fist, wrist extended against manual resistance
Extensor Digitorum (ED)	Forearm neutral, hand partially opened and enclosed within the hand of the researcher, combined wrist extension and maximally opening the hand against resistance
Extensor Carpi Ulnaris (ECU)	Forearm neutral, hand closed into fist, combined wrist extension and ulnar deviation
Biceps Brachii (BB)	Forearm supinated, elbow and shoulder placed at 90° flexion, elbow maximally flexed against resistance
Triceps Brachii (TB)	Forearm neutral, elbow and shoulder placed at 90° flexion, elbow maximally extended against resistance

3.3.4 Experimental protocol

Participants performed muscle-specific, isometric maximal voluntary contractions (MVCs) to determine maximal voluntary excitation (MVE) for the 8 tested muscles. MVCs were performed against the manual resistance of one of the researchers and included specific grip and wrist actions to target individual muscle actions (Table 3.1) (Holmes et al., 2015). Participants were then seated in front of the custom-built apparatus and their dominant forearm was placed onto the foam supports (Figure 3.1). In this posture, participants performed a maximum handgrip using the hand dynamometer, and maximum wrist flexion/extension against the force transducer (order randomized). These were used to normalize both the handgrip and wrist exertion forces for the subsequent experimental conditions. Table 3.2 shows the breakdown of all 10 experimental conditions. 40%

"combined effort" was used, whereby "combined effort" was defined as the sum of the relative grip and wrist force (either palmar or dorsal). To elaborate, 40% combined consisted of participants performing a handgrip (relative to the participant's own maximum grip) in combination with either a palmar or dorsal exertion (relative to the participant's own maximum palmar/dorsal force) whose relative forces summed to 40%. While always summing to 40%, the relative contributions of the handgrip and wrist exertions were modified for each experimental condition (Table 3.2). The order of these conditions was randomized. Participants were given visual feedback on a computer monitor displayed in front of them. Two graphs displaying real-time force data were positioned side-by-side; one denoting handgrip force and the second denoting wrist force (LabVIEW 2017, National Instruments, Austin, TX, USA). Targets (with an allotted accuracy of ± 1.5%) were displayed as horizontal lines (one line representing the target and two, other lines representing ± 1.5% of the target) on each graph and represented the relative handgrip or wrist force required for that given experimental condition. For each condition, participants were instructed to simultaneously match each of the two targets on the screen and maintain the two forces for 3 seconds. A total of 3 trials were performed for each condition. To minimize the potential influence of fatigue, ample rest was given between each trial and between workloads.

3.3.5 Data analysis and statistics

EMG and force data were analyzed off-line (MatLab 2015b, Mathworks Inc., Natick, MA, USA). Signal bias was removed from both EMG and force data. EMG was full-wave rectified and digitally low pass filtered (Butterworth, dual pass, 2nd order, 3 Hz

cut-off). Force data were low pass filtered with a 10 Hz cutoff (Butterworth, dual pass, 2nd order). Muscle activity was normalized to MVCs. For each of the 3 trials for each experimental condition, a single point was manually labelled by one of the researchers where the grip force and wrist force were simultaneously matched with their respective targets. A ±0.25 second window about that point was averaged for both force and muscle activity. The values for the 3 trials were averaged into a single muscle activity and force value for each experimental condition. Co-contraction was calculated as a ratio of antagonist/agonist for all pairs of flexors and extensors (ie. FCR-ECR, FCU-ECU, FDS-ED, and BB-TB) (Damiano et al., 2000). Two-way repeated measures ANOVAs (force direction x condition; 2 x 5) were conducted to assess whether there were significant main effects or interactions of force direction and/or condition on handgrip force, muscle activity, or co-contration ratios (SPSS, V24, International Business Machines Corporation, Armonk, NY, USA). Effect sizes were evaluated using partial ETA Squared calculated as the division of the sum of squares of the effects (SS_{Effect}) by both the SS_{Effect} and the sum of squares of the error (SS_{Error}). Significance level was set at $P < .05$. Data is reported as mean ± SD and illustrated in figures as SE.

Table 3.2. *Compilation of all 10 experimental trials (% of maximum). Note: Values are displayed as a percentage of maximum grip and wrist force (palmar or dorsal). Wrist forces were repeated for both palmar and dorsal force.*

40% Combined Effort	
Grip force (% of maximum)	Wrist force (% of maximum)
0	40
10	30
20	20
30	10
40	0

Results

3.4.1 Combined handgrip & wrist forces

Figure 3.2 depicts the mean data for simultaneous handgrip and wrist forces combined to 40% of MVC. Force targets were accurately maintained, with the noted exception of the '0G' conditions, in which participants produced excess handgrip force during high wrist-only exertions. Other than '0G,' it is unlikely that any differences between the other conditions influenced the interpretation of muscle activity data. The 0G conditions produced significantly higher combined force than the other 9 conditions for both palmar and dorsal forces (both, $P < .05$). Additionally, the 30G trial during palmar force was significantly lower than the 10G trial in palmar and the 20G trial in dorsal (Palmar 30G: 40.3 ± 0.6% of MVC, Palmar 10G: 41.5 ± 0.5% of MVC, Dorsal 20G: 41.5 ± 1.0% of MVC, $P < .05$). The 30G trial of dorsal force was also significantly lower than both 10G trials (Dorsal 30G: 40.3 ± 0.6% of MVC, Palmar 10G: 41.5 ± 0.5% of MVC, Dorsal 10G: 41.7 ± 1.0% of MVC, $P < .05$).

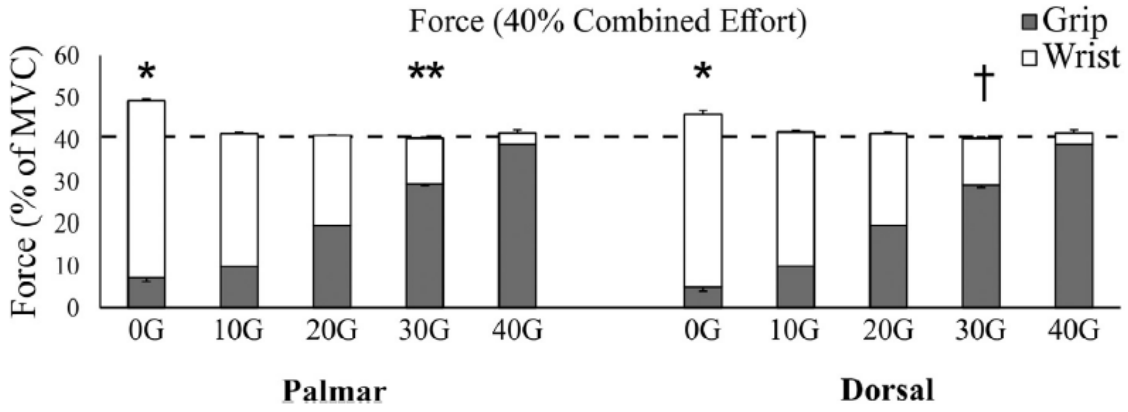


Figure 3.2. *Group averages (n = 12) of simultaneous handgrip and wrist forces summating to 40% combined effort. Grey/white bars represent handgrip/wrist force, respectively. Interaction effect investigated with post-hoc pairwise comparisons. * denotes a significant difference from all other conditions. ** denotes a significant difference from 10G Palmar and 20G Dorsal. † denotes a significant difference from 10G Palmar and 10G Dorsal*

3.4.2 Muscle activity

Figure 3.3 illustrates the mean muscle activity data during palmar and dorsal forces across the five conditions. All muscles demonstrated a significant interaction between wrist force direction and condition, with the exception of ECR (P = .08). However, ECR did demonstrate a main effect for both force direction (Palmar: 9.6 ± 1.1% of max, Dorsal: 14.3 ± 2.3% of max, $P < .05$) and condition, with muscle activity increasing as conditions became more handgrip-dominant. When the ECR data was collapsed between the two force directions, the 40G condition produced significantly greater muscle activity than the 30G and 20G conditions, with 30G also greater than 20G (40G: 15.4 ± 1.7% of max, 30G: 12.0 ± 1.6% of max, 20G: 10.2 ± 1.5% of max, $P < .05$). Table 3.3 displays both the P-values of the interaction effects as well as the effect sizes for all 8 muscles. The wrist flexors exhibited large effect sizes (particularly FCR and FCU), with muscle activity highest in conditions dominated by palmar forces (see Figures 3.3 A, C, and E). All three wrist flexors produced less than 5% of maximum muscle activity in the pure dorsal force conditions. While ED had a larger effect size than FDS, ECR and ECU had smaller effect sizes than their respective antagonists (FCR and FCU) (Table 3.3). Although the wrist extensor muscles were most active in dorsal (extension-dominant) conditions, their activity was similar if not greater than the wrist flexors in handgrip-dominant conditions. This difference is most notable between FCR (4.4 ± 2.2% of max) and ECR (15.4 ± 5.8% of max) in the pure handgrip conditions (Figure 3.3 A and B). The wrist extensors were also active in the palmar force conditions, producing 8.2 ± 5.6, 14.5 ± 7.4, and 6.7 ± 2.7% of maximum muscle activity in the ECR, ECU, and ED, respectively. The BB and TB (Figures 3.3 G and H) also exhibited interaction effects with large effect sizes. Both muscles were

significantly more active in conditions of high wrist forces compared to high handgrip forces. However, the BB contributed more to the palmar conditions, whereas the TB was more active in dorsal.

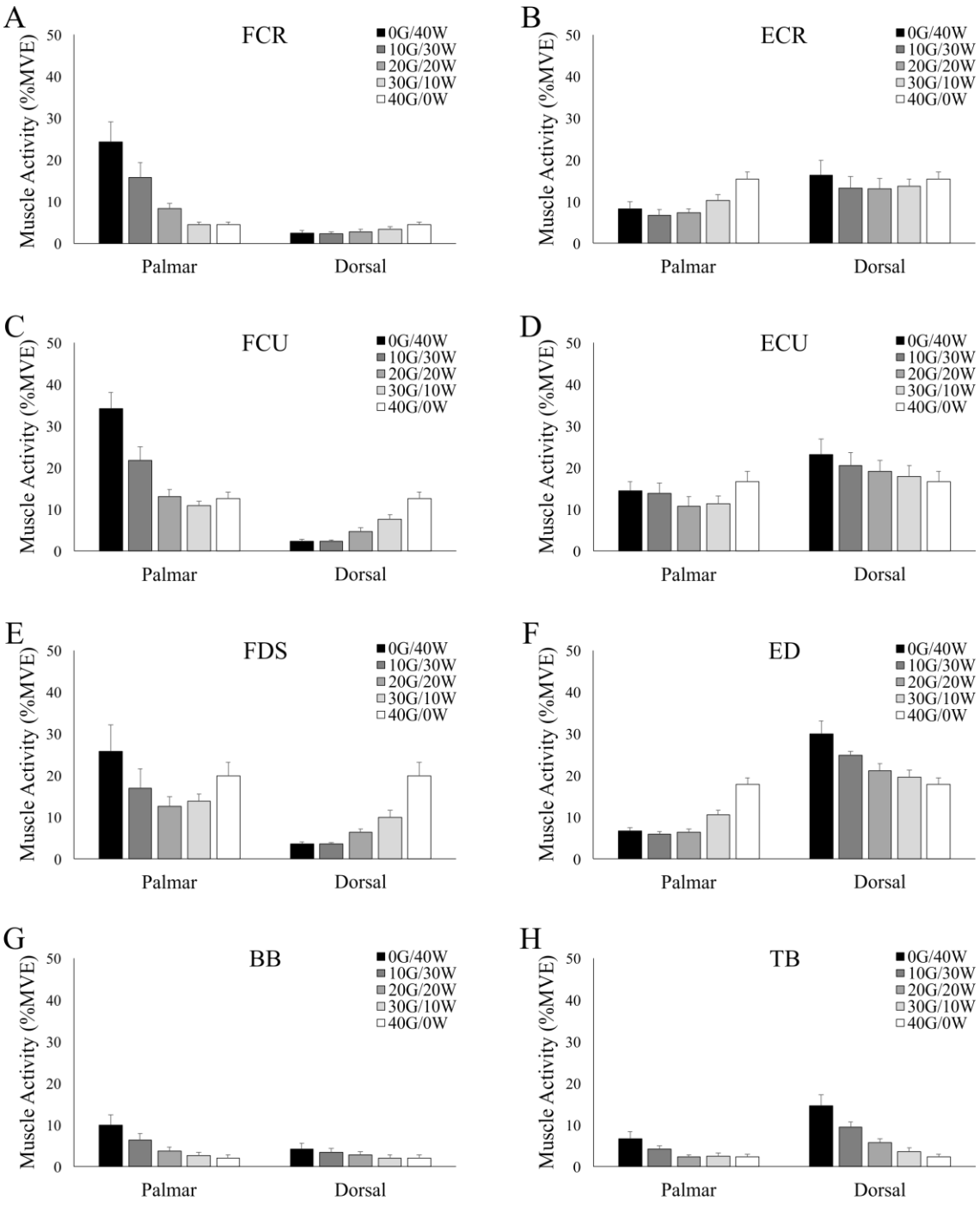


Figure 3.3. *Group averages (n = 11) of mean muscle activity (displayed as a % of maximum) during combined handgrip and wrist exertions (palmar/dorsal). Darker bars represent conditions with greater wrist force. Lighter bars represent conditions with greater handgrip forces.*

Table 3.3. *P-Values, Partial ETA Squared (η_p^2) and F-statistics on the interaction effects of two-way, repeated measures ANOVAs. * indicates a significant 2-way interaction*

	FCR	FCU	FDS
P-Value	**0.001***	**< 0.001***	**0.008***
Effect Size	0.631	0.842	0.497
F-Statistics	($F_{4,11}$ = 17.1)	($F_{4,11}$ = 53.3)	($F_{4,11}$ = 9.9)

	ECR	ECU	ED
P-Value	0.08	**0.02***	**< 0.000***
Effect Size	0.267	0.373	0.827
F-Statistics	($F_{4,11}$ = 3.6)	($F_{4,11}$ = 5.9)	($F_{4,10}$ = 43.1)

	BB	TB
P-Value	**0.03***	**0.047***
Effect Size	0.344	0.319
F-Statistics	($F_{4,11}$ = 5.3)	($F_{4,11}$ = 4.7)

3.4.3 Co-contraction ratios

Figure 3.4 illustrates the group data for antagonist/agonist co-contraction ratios. For the FCR – ECR pairing, an interaction effect was observed ($F_{(4,11)}$ = 26.4, P < .05), with significantly greater co-contraction in the palmar force direction, particularly in high handgrip conditions. Although the FCU – ECU pairing demonstrated greater co-contraction in handgrip dominant conditions for both palmar and dorsal forces, co-contraction was overall greater in the palmar direction, with main effects of force direction ($F_{(1,11)}$ = 5.9, P < .05) and condition ($F_{(4,11)}$ = 41.5, P < .05). While the FDS – ED pairing behaved similarly, only a main effect of condition as found ($F_{(4,10)}$ = 48.2, P < .05). A main effect of condition was also found for the BB – TB pairing ($F_{(4,11)}$ = 7.4, P < .05), with greater co-contraction in handgrip-dominant conditions.

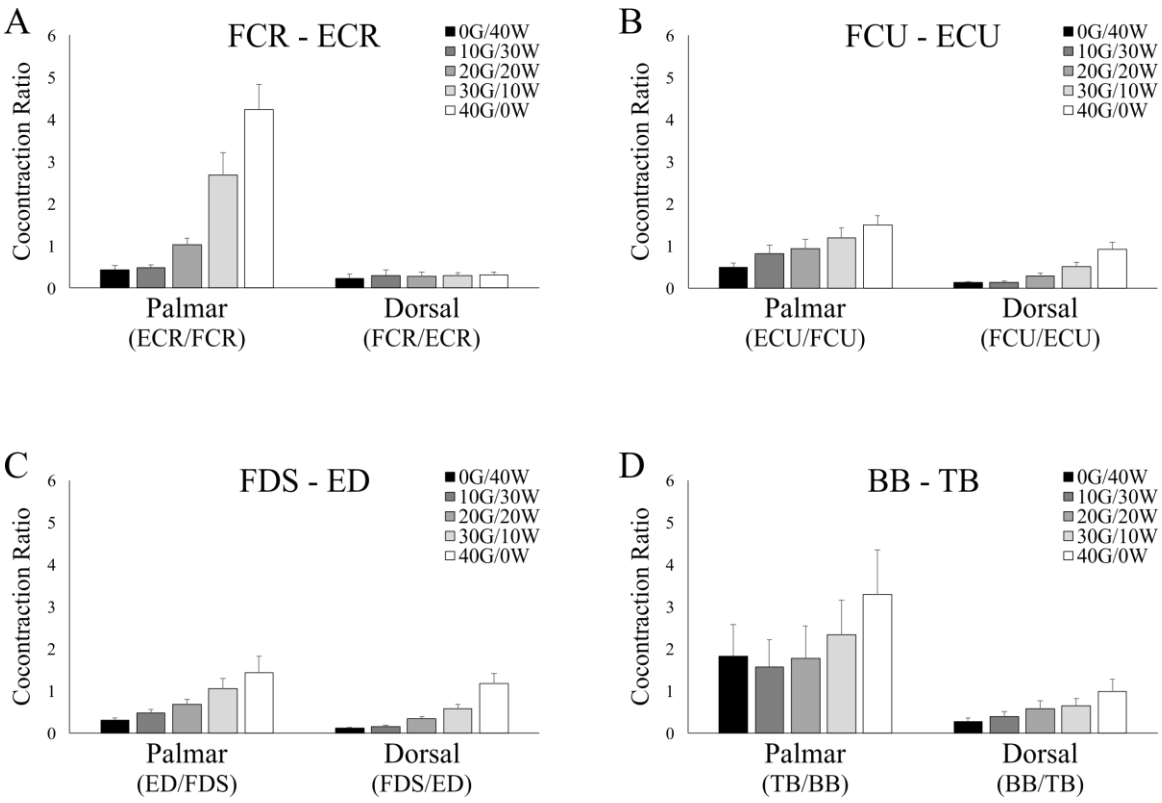


Figure 3.4. *Group averages (n = 11) of co-contraction ratios (antagonist/agonist muscle pairings). Data above palmar labels (x-axis) represent coactivation from extensor muscles. Data above dorsal labels (x-axis) represent coactivation from flexor muscles. Darker bars denote conditions with greater wrist force (palmar or dorsal). Lighter bars denote conditions with greater handgrip forces.*

Discussion

This work examined forearm muscle recruitment during simultaneous execution of handgrip and palmar/dorsal directed wrist forces to investigate motor control strategies during a dual task paradigm. Our findings indicate that the wrist flexors are highly task-dependent, in that changing task parameters significantly alters their activation. In contrast, the wrist extensors are less susceptible to variations of task demands and exhibit generally higher activity across most conditions. While the wrist flexors likely generate greater force, the wrist extensors exhibit equal, if not more activity during tasks which are dominant in hand-gripping. The results of this study suggest that, despite the added complexity of a dual-task protocol, the wrist extensors behave as joint stabilizers. This work highlights the potential vulnerability of the extensor muscles to overuse injuries in workplaces or activities of daily living that rely heavily on handgrip forces and/or wrist exertions.

3.5.1 Wrist flexors vs extensors

The novelty of the present work is that, by simultaneously modifying handgrip forces and wrist exertions across a wide array of intensities, the behavior of the wrist flexors and extensors could be examined under greater complexity than has previously been utilized. Additionally, this experimental design addresses recommendations raised by earlier investigators that ergonomic research shift towards multi-component, dual-task protocols that better translate to tasks of daily-living (Wells and Greig, 2001). However, despite the dual task methodology of the present protocol, our results are in agreement with uni-component literature. Data revealed that the wrist flexors were more task-dependent than the extensors, with effect sizes larger in most comparisons (Table 3.3). Using isolated

handgrip forces across a variety of wrist and forearm postures, Mogk and Keir (2003) showed similar findings. With no grip force, wrist extensors displayed significantly higher levels of muscle activity than the wrist flexors. Across all magnitudes of grip force, the wrist flexors demonstrated a greater postural-dependence than the wrist extensors, significantly influencing FCR muscle activity with minimal change to ECR. In agreement with our findings, Mogk and Keir (2003) demonstrated that in a neutral wrist and forearm orientation, wrist extensor muscle activity was approximately equal to flexor muscle activity (although no direct statistical analysis was performed), underlining the importance of extensors providing wrist stability. Indeed, it has been reported that wrist flexor activity only exceeds extensors at high handgrip forces, and is either equal or less active than wrist extensors at moderate-to-low handgrip forces (Claudon, 1998).

The relationship between the wrist flexors and extensors during wrist forces appears more complex. In the present study, conditions dominated by palmar exertions continued to demonstrate elevated levels of extensor activity (8.2, 14.5, and 6.7% MVE across the ECR, ECU, and ED, respectively), while conditions dominated by dorsal forces demonstrated almost negligible flexor muscle activity (2.4, 2.4, and 3.6% MVE across the FCR, FCU, and FDS, respectively). Averaged across the three flexors and extensors, this collectively represents 3.5-fold greater muscle activity in the extensors. This indicates that while substantial extensor activity is required to stabilize the wrist during palmar forces, minimal flexor activity is needed to counter dorsal forces. Of the work that exists on this matter, our findings are in agreement. In examining faciliatory and inhibitory reflex arcs to the ECR, (Fujii et al., 2007) found that FCR activity was almost non-existent in the presence of high ECR activity. Protocols examining wrist forces in combination with

various grips (power grip/pinch grip) have shown higher extensor muscle activity in stabilizing roles (Greig and Wells, 2008). This body of literature is supported by recent findings that the wrist extensors dominate the wrist stabilizing role, and whose mechanisms are driven by muscle activity, geometry, length and moment arms (Holmes et al., 2015). For both hand-gripping and wrist force production, biomechanical and anatomical factors are noteworthy. The cross-sectional area (CSA) and moment arms of the wrist flexors are larger than extensors (Gonzalez et al., 1997). The sum total CSA of the anterior compartment of the forearm is ~24.8cm^2 in comparison to 11.8cm^2 for the posterior (Gonzalez et al., 1997; Jacobson et al., 1992; Lieber et al., 1992). This manifests as a decreased force generating capacity and evidence has shown that wrist extension MVCs produce significantly less force than flexion (O. Alizadehkhaiyat et al., 2007; Omid Alizadehkhaiyat et al., 2007; Delp et al., 1996; Hallbeck, 1994; La Delfa et al., 2015; Vanswearingen, 1983; Yoshii et al., 2015). Thus, wrist extensor muscles require a greater % activation to balance flexors forces, and is the leading mechanism responsible for both the earlier onset of fatigue and development of chronic overuse injuries (Byström et al., 1991; Hägg and Milerad, 1997; Ranney et al., 1995; Shiri et al., 2006; Chris J Snijders et al., 1987).

3.5.2 Flexor-extensor muscle differences

In the present study, FCU and ECU (FCU: 12.2% MVE, ECU: 16.5% MVE, averaged across all experimental trials) demonstrated higher muscle activity than FCR and ECR (FCR: 7.2% MVE, ECR: 11.9% MVE, averaged across all experimental trials), respectively, in nearly every experimental condition. Initial interpretations suggest that

muscles located near the ulna contribute more to hand and wrist exertions than those near the radius. Anatomically, the FCU has a 41.3% greater muscle mass and a 72% larger CSA than the FCR (Lieber et al., 1990), although the FCR possesses a larger moment arm (Ettema et al., 1998). Thus, in the present study, it is possible that motor control strategies prioritize the greater strength of the FCU over the greater mechanical advantage of the FCR in generating wrist flexion. However, this explanation is inconsistent when viewed from the perspective of the extensors. Lieber et al. (1990) demonstrated that ECR brevis and ECR longus combined were 88.2% more massive with a 61.2% larger CSA than ECU. ECR also possesses a larger moment arm than the ECU (Ettema et al., 1998). Being both smaller and at a mechanical disadvantage compared to the ECR, it is therefore possible that the ECU produces greater activation in order to adequately stabilize the wrist. While these two proposed rationales may seem at odds between the flexors and extensors, this may tie in to the separate roles of each muscle group. The wrist flexors, task-dependent muscles that are typically the prime movers in nearly all hand and wrist movements (Duque et al., 1995; Halpern and Fernandez, 1996; Imrhan, 1991; Kattel et al., 1996; Mogk and Keir, 2003) may prioritize a muscle's size and strength when executing a motor task. In contrast, the wrist extensors, whose primary functions are to stabilize the wrist by balancing the considerable forces produced by the flexors (Hägg et al., 1997; Holmes et al., 2015; Mogk and Keir, 2003; Chris J Snijders et al., 1987) may be required to maintain a given level of wrist extension force. In doing so, the weaker, smaller extensor muscles will exhibit higher muscle activity.

3.5.3 Dual tasks

The present work builds on a small body of literature that has investigated simultaneous muscle actions of the hand and wrist. This work holds a distinct advancement within the field by providing insight into forearm muscle recruitment strategies during tasks relevant to workplace settings that relate more closely to the force and moment wrench behaviour of the hand (Wells and Greig, 2001). Of particular interest is the applicability of these findings to overuse injury risk; principally of the wrist extensors. It is well established that both the intensity of a muscle contraction and duration that the activity is maintained are key factors in the development of overuse injuries (Mathiassen et al., 2003; Visser and van Dieën, 2006). Recommendations have encouraged companies and job sites to reduce the loads workers are exposed to while also providing appropriate work-to-rest intervals. Ideally, work loads should be normalized to an individual's strength, and in the case of hand-dominant tasks, is typically normalized to maximum grip strength. Research by Wells and Greig propose that this approach is inappropriate in most scenarios, given that purely grasping the hand is rarely used to accomplish motor tasks (Wells and Greig, 2001). Rather than operating in a single vector, the hand should instead be viewed as a force and moment wrench, capable of both exerting grip forces and transferring torques produced at the wrist. Indeed, more recent work has shown that grip force, when used to transmit forces and moments to the environment, poorly relate with muscle activation (Greig and Wells, 2008). Our present work adheres closely to this framework. By manipulating task parameters (handgrip and wrist forces) muscle activity changed significantly. Demonstrating this issue most clearly is the FCR (Figure 3.4 A). In the pure handgrip trial, the FCR averaged 4.4% MVE, but steadily increased with added palmar forces. Any workplace settings

normalizing work loads to maximum grip, but whose tasks involve significant palmar forces, would likely underestimate the true load applied to the FCR. This task-specificity manifests not only in muscle activity, but in force outputs as well. When coupled with greater handgrip forces, wrist flexion MVCs produce significantly more force while wrist extensions MVCs are impaired (Seo et al., 2008). Collectively, this work demonstrates the need of workplace assessments to utilize dual-task or multi-component protocols, particularly when tasks involve increasingly complex hand manipulation. If only handgrip strength is chosen, estimates are likely to be erroneous.

3.5.4 Elbow flexors/extensors

In the present study, the biceps and triceps brachii demonstrated elevated levels of muscle activity during conditions dominant in palmar and dorsal forces, respectively (see Figure 3.3). Neither were highly active in the pure handgrip conditions. This suggests the biceps and triceps brachii serve a stabilizing role during wrist exertions, which is likely facilitated through multi-articular muscles spanning the humerus and forearm. This is not the first study to report a distal-proximal relationship on neuromuscular measures of the upper-limb (Forman et al., 2016; Sporrong et al., 1996). Additionally, our findings indicate that an elbow flexion moment may stabilize the forearm during palmar forces while an elbow extension moment may stabilize the forearm during dorsal forces.

3.5.5 Implications

The findings of this study solidify previous work that the wrist extensors play a stabilizing role in hand/wrist actions, exhibiting moderate-high levels of activity across all tasks. This has potential consequences for workplace design and injury prevention. A key factor in the development of chronic overuse injuries is insufficient rest intervals between periods of muscle loading. Simply varying workplace parameters throughout the day to provide episodic rest to different muscles is unlikely to benefit the wrist extensors. Any upper-limb task involving gripping or wrist exertions will result in significant extensor loading. Complete cessation of work may be required for adequate rest periods. However, it should be clarified that this investigation was still exploratory in nature, and not ergonomically focused. Tasks were also strictly isometric, and should be followed by dynamic work.

Conclusions

Despite challenges associated with executing simultaneous handgrip and wrist forces, forearm muscle recruitment matched with anatomical constraints. Findings were in agreement with previous work that has investigated forearm muscle activity under simpler motor tasks. The wrist flexors demonstrated clear task-dependency across various conditions, whereas the wrist extensors behaved as would be expected of joint stabilizers; persistently elevated muscle activity regardless of condition. The mechanisms behind these findings are rooted at least in part by the CSA, strength, and moment arms of individual muscles. These findings demonstrate the importance of assessing forearm muscle recruitment under dual task or multi-component designs. These results could have potential

implications for future work geared towards the development of chronic overuse injuries of the forearm.

Chapter 4. Characterizing forearm muscle activity in university-aged males during dynamic wrist flexion–extension movement using a wrist robot

A study published in the Journal of Biomechanics

Reference:

Forman, D.A., Forman, G.N., Avila-Mireles, E.J., Mugnosso, M., Zenzeri, J., Murphy, B., Holmes, M.W.R., 2020. Characterizing forearm muscle activity in university-aged males during dynamic wrist flexion-extension movement using a wrist robot. Journal of Biomechanics. Accepted June 2020 (#BM-D-19-01081).

Preface

In Chapter 3, it was found that the wrist flexors were highly task-dependent; changes in task parameters, such as variations in handgrip forces and/or variations in wrist flexion/wrist extension forces, altered their muscle activity to large magnitudes. In contrast, while wrist extensor muscle activity was also significantly influenced by changes in task parameters, these changes were much smaller in magnitude (their effect sizes were also smaller). The wrist extensors were consistently active to a moderate-to-high degree across all experimental conditions. Thus, while the complexity of Chapter 3's experimental protocol was greater than previous investigations that have examined single motor tasks in isolation, the key findings were largely in support of literature.

However, following this study, a significant gap remained in our understanding of forearm muscle recruitment in that nearly all investigations, including Chapter 3, have examined forearm muscle recruitment in isometric paradigms. Most tasks of daily living are accomplished using dynamic muscle contractions (with movement). Given the vast number of factors that are uniquely modulated between isometric and dynamic contractions (such as various types of afferent input (Eccles and Lundberg, 1958), co-contraction (Darainy et al., 2007), and greater cycling of cross-bridge formation (Huxley, 1957), just to name a few), it is possible that current conclusions regarding forearm muscle function might not transfer to dynamic contractions. Thus, the purpose of Chapter 4 was to characterize forearm muscle recruitment during the execution of dynamic wrist flexion and wrist extension contractions in a number of forearm postures.

Abstract

Current research suggests that the wrist extensor muscles function as the primary stabilizers of the wrist-joint complex. However, most investigations have utilized isometric study designs, with little consideration for wrist dynamics or changes in posture. The purpose of the present study was to assess forearm muscle activity during the execution of dynamic wrist flexion/extension in multiple forearm orientations (pronation/supination). In 12 healthy university-aged males, surface electromyography (EMG) was recorded from eight muscles of the dominant arm: flexor carpi radialis (FCR), flexor carpi ulnaris (FCU), flexor digitorum superficialis (FDS), extensor carpi radialis (ECR), extensor carpi ulnaris (ECU), extensor digitorum (ED), biceps brachii (BB) and triceps brachii (TB). While grasping a handle, participants performed dynamic wrist flexion/extension using a three-degrees-of-freedom wrist manipulandum. The robotic device applied torque to the handle, in either a flexion or extension direction, and in one of three forearm postures (30° supinated/neutral/30° pronated). Results indicated that forearm posture had minimal influence on forearm muscle activity, but significantly altered the activity of the biceps and triceps brachii. Movement phase (concentric-eccentric) dictated muscle activity in every muscle. Interestingly, muscle activity in the eccentric phase was equal between the two applied handle torques, regardless of whether the muscle acted as the agonist or antagonist. Co-contraction ratios were higher in the flexion conditions (flexion: 2.28 ± 2.04, extension: 0.32 ± 0.27), suggesting significantly greater wrist extensor activity–likely a contribution to wrist joint stability. This highlights the vulnerability of the wrist extensor muscles to overuse injuries in settings requiring prolonged use of dynamic wrist exertions.

Introduction

The wrist flexor muscles of the forearm are highly task-dependent and function chiefly as the prime movers in most hand-related tasks (Duque et al., 1995; Imrhan, 1991; Kattel et al., 1996). In contrast, the wrist extensor muscles balance the forces produced by the wrist flexors and function as the principal wrist stabilizers (Hägg et al., 1997; Holmes et al., 2015; C. J. Snijders et al., 1987). These conclusions have been developed in part by neuromuscular investigations of forearm muscle activity. Mogk and Keir (2003) demonstrated that average forearm muscle activity while producing handgrip forces is generally highest in pronation and lowest in supination. Additionally, wrist extensor muscle activity was significantly greater than the wrist flexors, at least during low handgrip forces. Even simply holding the grip dynamometer, extensor muscle activity was at a much higher percentage of maximum (15%) than the flexors (never exceeding 7%). As continuous activity is a known contributor in the development of chronic overuse injuries (Aarås and Westgaard, 1987; Jonsson, 1978), the study concluded that the extensors were at a greater injury risk. Supporting these findings, we recently demonstrated that the wrist flexors are highly task-dependent (their activity was dictated by task parameters) during the simultaneous execution of hand and wrist motor outputs (Forman et al., 2019). In contrast, the wrist extensors exhibited high levels of activity across all experimental conditions.

However, these conclusions regarding flexor/extensor muscle roles have arisen mostly from isometric experiments (Forman et al., 2019b; Mogk and Keir, 2003); there is a scarcity of dynamic investigations in literature. As such, it is currently unclear if patterns of forearm muscle recruitment obtained from isometric studies can be generalized to other

forms of muscle contraction. Considering the added biomechanical complexities associated with dynamic muscle mechanics (Holzbaur et al., 2005), increased muscle spindle activity (Eccles and Lundberg, 1958), and greater cycling of cross-bridge formation (Huxley, 1957), it is possible that the activity of wrist flexors/extensors might deviate from isometric work. Thus, the objective of the present study was to characterize wrist flexor and extensor function during dynamic wrist flexion/extension movement across a variety of forearm postures and movement phases. Forearm muscle activity and forearm co-contraction ratios were assessed while participants performed dynamic wrist flexion/extension exertions on a three-degrees-of-freedom wrist robot to isolate and control biomechanical variables (velocity/torque/posture). Our hypotheses were threefold. 1) Given that forearm rotation (supination/pronation) alters forearm muscle lengths (Delp et al., 2007; Holzbaur et al., 2005), it was hypothesized that forearm posture would influence forearm muscle activity and forearm co-contraction ratios. 2) In support of previous research investigating isometric protocols, it was hypothesized that co-contraction ratios would be larger during wrist flexion movement because of high, sustained wrist extensor activity. 3) All forearm muscles would demonstrate greater muscle activity both during the concentric phase (as compared to eccentric) and when acting as the agonist muscle (or prime mover).

Methods

4.3.1 Participants

Experimental procedures were approved by the research ethics boards (REB) of Brock University (REB# 16-263) and the University of Ontario Institute of Technology (REB# 15044). Written consent was obtained from all participants prior to the experiment. Twelve males (Height: 176.4 ± 6.5 cm; Weight: 75.4 ± 9.0 kg; Age: 23.8 ± 3.1 years, 11 right-handed, 1 left-handed) were recruited for this study. Participants were undergraduate and graduate students from the Brock University campus and were not selected on any anthropometric basis. Participants were excluded if they presented with any upper-body, neuromuscular injuries.

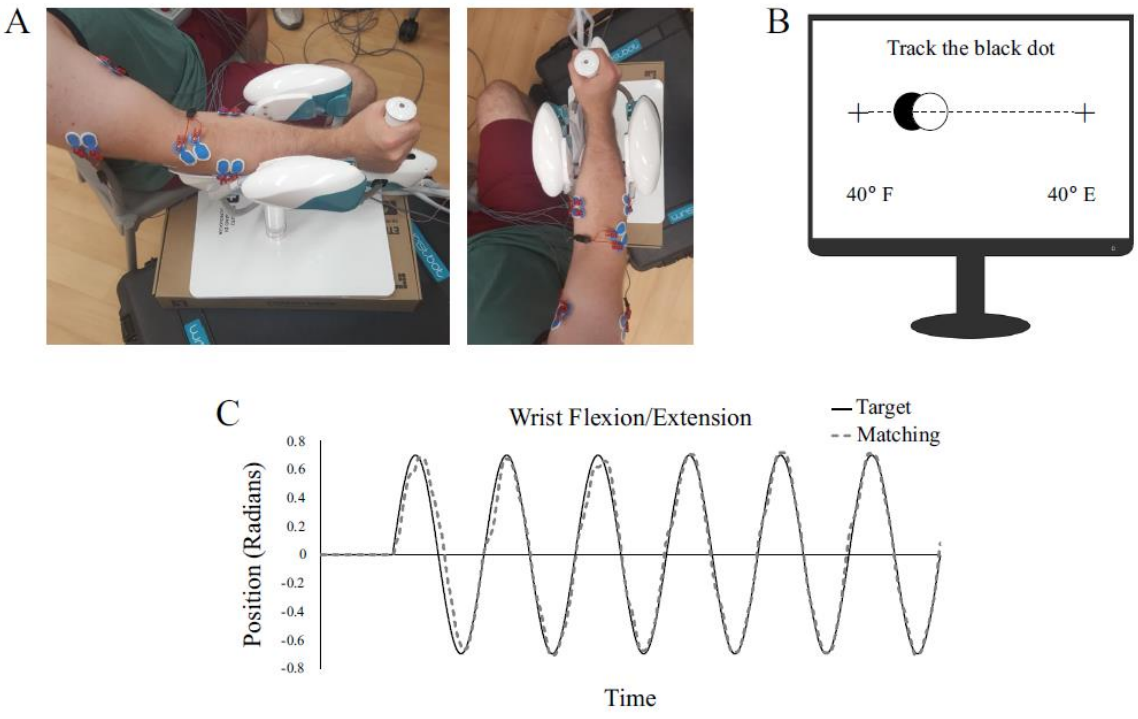


Figure 4.1. *A) Experimental setup displaying EMG placement and upper-limb position within the wrist manipulandum. B) Example of the target tracking display shown to participants ranging ±40° of wrist flexion/extension. C) Tracking proficiency shown from a single participant*

4.3.2 Experimental setup

This study was a repeated measures design that involved participants seated with their dominant forearm supported in a three-degrees-of-freedom wrist manipulandum (WristBot, Genoa, Italy; (Iandolo et al., 2019; Masia et al., 2009) and their hand firmly gripping the device's handle (Figure 4.1 A). While upper-limb position was not controlled, upper-limb joint angles *were* manually assessed using a goniometer (elbow extension: 139.7 ± 5.3°; shoulder flexion: 22.3 ± 4.5°; shoulder external rotation: 34.3 ± 4.9°). As a group, participants' grasp distance (distance from the distal wrist crease to the middle of the manipulandum's handle) was 7.1 ± 0.5 cm. The handle could be moved against an external load by flexing/extending the wrist, and the device could be rotated through various forearm postures. To control for angular velocity, the position of the handle was displayed to participants on a monitor. A circular target moved in the flexion/extension direction at a pace of 40°/sec (or 4 seconds/complete repetition) and participants were required to match that target with the robot's handle (Figure 4.1 B). This pace was selected as it allowed participants to comfortably track the target, and thus match movement speed across the sample, with minimal tracking error. An example of target matching from a sample trial can be seen in Figure 4.1 C. The manipulandum compensated for the weight and inertia of the device throughout movement in the three postures. Angular position of the handle was synchronized with measures of muscle activity.

4.3.3 Independent variables: torque direction, phase, and posture

Participants performed tracking trials against an external torque (15% of their maximal wrist extension torque; the torque was low to limit the development of fatigue)

that the WristBot applied in one of two directions. The WristBot applied either a wrist flexion torque, in which participants would oppose with wrist extension, or a wrist extension torque, in which participants would oppose with wrist flexion (± 40° wrist flexion/extension). In the presence of this applied torque, participants transitioned through two phases of movement while tracking the displayed target. Participants would concentrically contract (agonist muscles shortening) when moving their hand against the applied torque and would eccentrically contract (agonist muscles lengthening) when moving with the applied torque. Tracking trials were carried out in three separate forearm postures: 1) 30° of supination, 2) neutral, and 3) 30° of forearm pronation. These ranges of motion (ROM) (± 40° wrist/± 30° forearm) were chosen as they were well within the maximum ROMs of the study sample; ROMs were thus not taken to end-range. The study manipulated three independent variables throughout the protocol, resulting in a total of twelve separate trials (two torque directions, two movement phases, and three forearm postures). For each experimental condition, participants performed six repetitions of dynamic wrist flexion/extension.

4.3.4 Dependent variables: muscle activity and co-contraction ratios

Muscle activity was recorded using pairs of surface electrodes (Blue Sensor, Ambu A/S, Denmark) from eight muscles of the dominant arm: flexor carpi radialis (FCR), flexor carpi ulnaris (FCU), flexor digitorum superficialis (FDS), extensor carpi radialis (ECR), extensor carpi ulnaris (ECU), extensor digitorum (ED), biceps brachii (BB), and the triceps brachii (TB). Electrodes were placed over the muscle belly, in-line with fiber orientation, and procedures followed previous placement guidelines (Forman et al., 2019b, 2016;

Holmes et al., 2015; Mogk and Keir, 2003; Perotto and Delagi, 2011). A ground electrode was placed on the lateral epicondyle of the dominant arm. Prior to electrode placement, all recording sites were shaved of hair using a disposable razor and were sanitized with an isopropyl alcohol swab. EMG was band-pass filtered (10-1000 Hz) and differentially amplified (CMRR > 100dB at 60 Hz; input impedance ~ 10 GΩ; AMT-8, Bortec Biomedical Ltd, Calgary, AB, Canada). EMG data was sampled at 2000 Hz (USB-6229 BNC, National Instruments). Muscle activity was examined as a dependent variable across all three independent variables, and in addition, was used to calculate co-contraction ratios between functional antagonists. See *Data analysis and statistics* for additional co-contraction details.

Table 4.1. *Maximal voluntary contraction (MVCs) protocol for each of the 8 muscles assessed.*

Muscle	MVC Protocol
Flexor Carpi Radialis (FCR)	Forearm supinated, hand closed into fist, wrist flexion against manual resistance
Flexor Digitorum Superficialis (FDS)	Forearm supinated, partially opened hand grasping the hand of the researcher, combined wrist flexion and maximal grip
Flexor Carpi Ulnaris (FCU)	Forearm supinated, hand closed into fist, combined wrist flexion and ulnar deviation
Extensor Carpi Radialis (ECR)	Forearm neutral, hand closed into fist, wrist extended against manual resistance
Extensor Digitorum (ED)	Forearm neutral, hand partially opened and enclosed within the hand of the researcher, combined wrist extension and maximally opening the hand against resistance
Extensor Carpi Ulnaris (ECU)	Forearm neutral, hand closed into fist, combined wrist extension and ulnar deviation
Biceps Brachii (BB)	Forearm supinated, elbow and shoulder placed at 90° flexion, elbow maximally flexed against resistance
Triceps Brachii (TB)	Forearm neutral, elbow and shoulder placed at 90° flexion, elbow maximally extended against resistance

4.3.5 Experimental protocol

Participants sat at a table with a force transducer (Model: BG 500, Mark-10 Corporation, New York, USA) mounted in parallel with the surface of the table. The transducer made contact with the posterior surface of the distal phalanges (back of the knuckles; closed hand) while participants exerted maximal wrist extension force against the transducer for a single trial. The distance between the participants' wrist and the center of the transducer was measured to calculate maximum extension moment. EMG procedures followed and participants performed muscle-specific, isometric maximal voluntary contractions (MVCs) to determine maximal voluntary excitation (MVE) for all 8 muscles. MVCs were performed against the manual resistance of one of the researchers and included specific grip and wrist actions to target individual muscle actions (Table 4.1: Holmes et al., 2015). Participants then returned to the manipulandum and performed one of 6 experimental conditions against the applied torque of the WristBot. The forearm was rotated into one of 3 postures (supination/neutral/pronation), and torque was applied in one of two directions (flexion/extension). All force directions therefore refer to the agonist concentric muscle action in each condition. For each experimental condition, participants performed six repetitions of either wrist flexion or wrist extension. The order of the 3 forearm positions was first randomized. Then, within each forearm position, the order of the 2 force directions were also randomized. Two minutes of rest were provided between conditions (a condition meaning one set of 6 repetitions) to minimize the effects of muscle fatigue. A post-experiment wrist extension MVC was performed to assess if fatigue had occurred throughout the protocol.

4.3.6 Musculoskeletal modelling

Variations in forearm posture were likely to influence mechanical properties of forearm musculature. As such, a musculoskeletal model was consulted to provide quantifiable values for factors of interest. These were subsequently used to help explain any patterns present in our experimental data. These values were taken directly from the model and were not modified based on the anthropometrics of the study participants. Predictive data on muscle-tendon length, wrist deviation moment arm, and peak active fiber force in the study's three forearm postures were taken from an upper extremity model (Holzbaur et al., 2005) and implemented with OpenSim V3.3 (Delp et al., 2007). In this model (Holzbaur et al., 2005), muscle architecture and attachments were obtained from empirical evidence, and bone lengths are consistent with a 50^{th} percentile male (170 cm tall).

4.3.7 Data analysis and statistics

EMG and kinematic data of the manipulandum's handle were analyzed off-line (Matlab 2015b, Mathworks Inc., Natick, MA, USA). EMG was full-wave rectified, digitally low pass filtered (Butterworth, dual pass, 2^{nd} order, 3 Hz cut-off) and normalized to muscle-specific MVEs. For all conditions, EMG data was separated into concentric/eccentric phases determined according to the kinematic data of the manipulandum. Phases were separated based on when participants reached end-range of wrist flexion/extension. Mean muscle activity was then measured within the concentric and eccentric phases for 3 of the 6 repetitions (first 2 repetitions excluded so participants could catch up with the computer-displayed target; the final repetition was excluded in case

participants modified their tracking behaviour at the end of the condition). These measures were averaged into a single concentric and eccentric value for each condition. Co-contraction was calculated as a ratio of antagonist/agonist muscle activity for all anatomical pairs of flexors and extensors (i.e. FCR-ECR, FCU-ECU, FDS-ED, and BB-TB) (Damiano et al., 2000; Forman et al., 2019b). Assumptions of sphericity were tested with Mauchley's test of sphericity (SPSS, IBM Corporation, Armonk, NY, USA), and in cases where violated, degrees of freedom were corrected with Greenhouse-Geisser. To test our hypotheses across our three independent variables, three-way, repeated measures ANOVAs (forearm position*force direction*phase of movement) were conducted within each muscle for both mean muscle activity and co-contraction ratios (SPSS, V24, IBM Corporation, Armonk, NY, USA). In cases where interactions were observed, post-hoc simple main effects were performed with a Bonferroni correction. Effect sizes were evaluated using partial ETA Squared. Significance level was set at $P < .05$. Data are reported as mean ± standard deviation (SD) and illustrated in figures as standard error (SE).

Results

4.4.1 Muscle activity

Wrist extension MVC force was not significantly different between pre- or post-experiment measurements (Pre-experiment: 77.6 ± 19.9 N, Post-experiment: 79.1 ± 15.0 N, $P = 0.60$). Figure 4.2 depicts mean muscle activity split across concentric and eccentric phases. FCR, ECR, FDS, ED and FCU all demonstrated a 2-way interaction of force direction and phase with no influence of forearm posture. Secondary analyses revealed a significant difference between phases in the flexion force direction (Table 4.2), with greater muscle activity during concentric for the three wrist flexors (FCR, FDS, and FCU) while greater in eccentric for the two wrist extensors (ECR and ED). In extension, muscle activity was higher in the eccentric phase for FCR and FDS, while higher in the concentric phase for ECR and ED. Muscle activity during the concentric phase was also significantly different across force directions, with greater muscle activity in flexion for the three wrist flexors and greater muscle activity in extension for the two extensors. There were no differences in eccentric muscle activity between force directions. ECU, BB and TB demonstrated a 3-way interaction of posture, force direction, and movement. Subsequent analysis revealed a main effect of posture in ECU during extension, with muscle activity (averaged across phases) greater in neutral than supination ($P = 0.043$) and pronation ($P = 0.032$). Concentric muscle activity was significantly higher than eccentric during extension ($F_{(1,10)} = 13.42$, $P = 0.004$) but was not different between phases during flexion. For the BB, muscle activity was greater in flexion than extension, but only during the concentric phase ($F_{(1,35)} = 17.56$, $P < 0.001$). Also, BB muscle activity was greater during concentric than eccentric, but only in flexion ($F_{(1,35)} = 22.75$, $P < 0.001$). For the TB, muscle activity

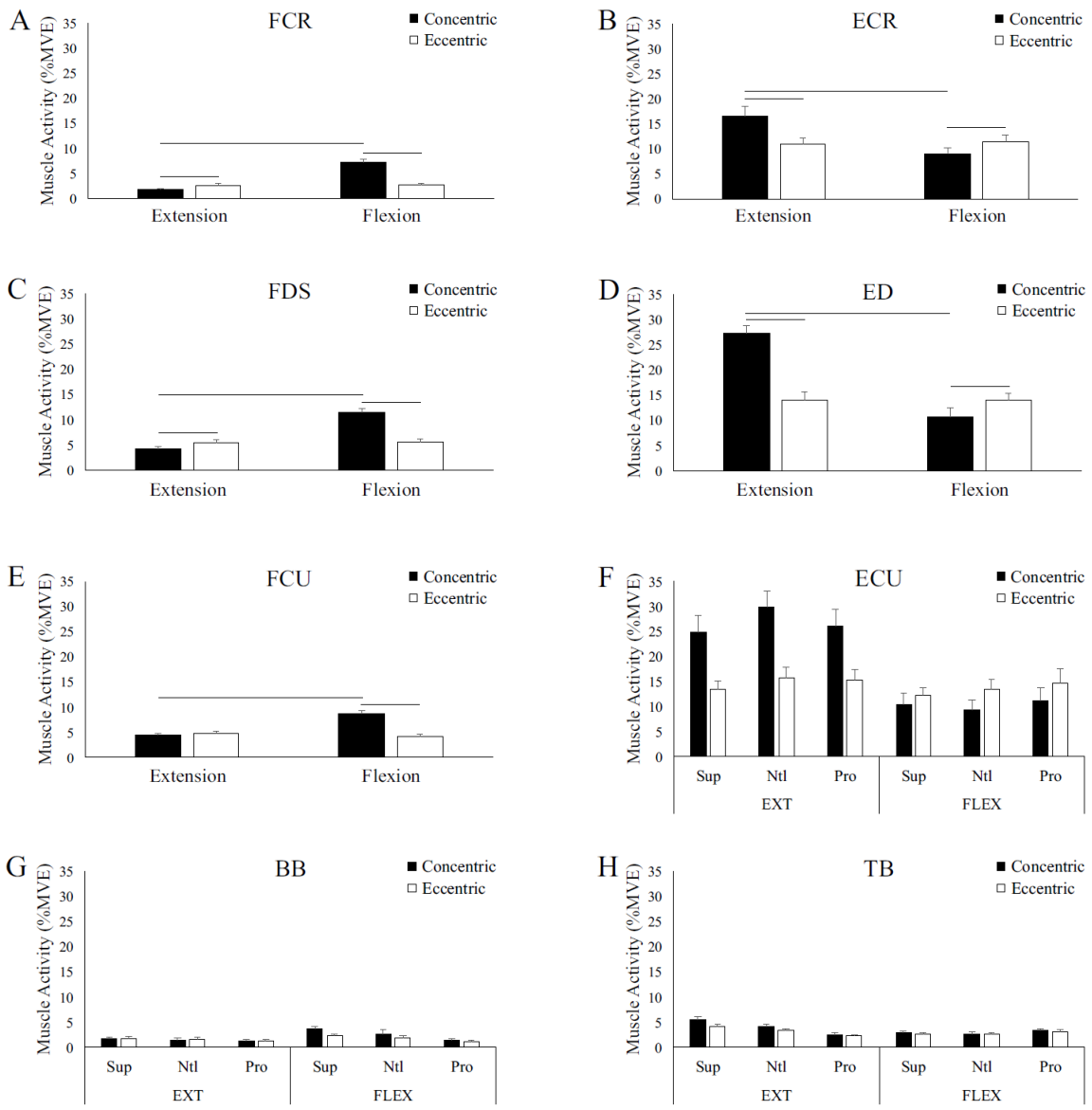


Figure 4.2: *Group averages of mean muscle activity (displayed as a % of maximum) in the concentric (black) and eccentric (white) phases. A – E depict 2-way interactions of force direction and movement phase. F – H depict 3-way interactions. Horizontal lines denote a significant difference ($P < 0.05$) between either concentric and eccentric phases within a force direction or between flexion and extension within a movement phase.*

was greater in extension than flexion for both phases ($F_{(1,11)} = 18.75$, $P = 0.001$) and greater during concentric than eccentric for both force directions ($F_{(1,11)} = 22.51$, $P = 0.001$). Posture significantly influenced muscle activity in the flexion direction for BB ($F_{(2,10)} = 9.89$, $P = 0.001$) and in the extension direction for TB ($F_{(2,10)} = 26.83$, $P < 0.001$).

Table 4.2. *Post-hoc analyses of mean muscle activity for all muscles that demonstrated a 2-way interaction of force direction and movement phase. Data was collapsed across forearm postures and main effects were conducted with a Bonferroni correction. Results are listed as P-Values, F-statistics, and effect sizes (represented by Partial ETA Squared (η_p^2)).*

		Flexion (Con vs. Ecc)	Extension (Con vs Ecc)	Concentric (Flex vs Ext)	Eccentric (Flex vs Ext)
FCR	*P*-value	**< .001***	**0.005***	**< .001***	0.661
	F-Statistic	$F_{(1,29)} = 68.69$	$F_{(1,29)} = 9.28$	$F_{(1,29)} = 85.37$	$F_{(1,29)} = 0.196$
	Effect Size	0.703	0.242	0.746	0.007
FDS	*P*-value	**< .001***	**0.029***	**< .001***	0.803
	F-Statistic	$F_{(1,29)} = 31.25$	$F_{(1,29)} = 5.29$	$F_{(1,29)} = 38.11$	$F_{(1,29)} = 0.064$
	Effect Size	0.519	0.159	0.576	0.002
FCU	*P*-value	**< .001***	0.279	**< .001***	0.093
	F-Statistic	$F_{(1,32)} = 97.33$	$F_{(1,32)} = 1.215$	$F_{(1,32)} = 58.35$	$F_{(1,32)} = 3.0$
	Effect Size	0.753	0.037	0.646	0.086
ECR	*P*-value	**0.021***	**< .001***	**< .001***	0.689
	F-Statistic	$F_{(1,32)} = 5.93$	$F_{(1,32)} = 16.38$	$F_{(1,32)} = 16.48$	$F_{(1,32)} = 0.164$
	Effect Size	0.156	0.339	0.34	0.005
ED	*P*-value	**0.047***	**< .001***	**< .001***	0.992
	F-Statistic	$F_{(1,35)} = 4.23$	$F_{(1,35)} = 38.74$	$F_{(1,35)} = 47.54$	$F_{(1,35)} = < .001$
	Effect Size	0.108	0.525	0.576	< .001

4.4.2 Co-contraction ratios

In Figure 4.3, the FCR-ECR, FDS-ED, and BB-TB pairings demonstrated 2-way interactions, with statistical results displayed in Table 4.3 and 4.4. With the exception of the BB-TB ratio, all muscle pairings showed significantly greater co-contraction in the eccentric than concentric phases (FCU-ECU: $F_{(1,9)} = 70.17$, $P < 0.001$) (see Table 4.3 for FCR-ECR and FDS-ED). There was also greater co-contraction in the flexion than extension force direction for all four muscle pairings (FCU-ECU: $F_{(1,9)} = 36.96$, $P < 0.001$). The BB-TB pairing revealed a main effect of posture during flexion, with greater co-contraction occurring towards pronation. The FCU-ECU was the only muscle-pairing to demonstrate a 3-way interaction of posture, phase, and direction ($F_{(2,9)} = 4.85$, $P = 0.021$). However, secondary analyses revealed no effect of posture on co-contraction in either force

direction (flexion: $F_{(2,19)} = 0.515$, $P = 0.61$, extension: $F_{(2,19)} = 0.941$, $P = 0.41$) or either movement phase (concentric: $F_{(2,19)} = 2.83$, $P = 0.086$, eccentric: $F_{(2,19)} = 2.29$, $P = 0.13$).

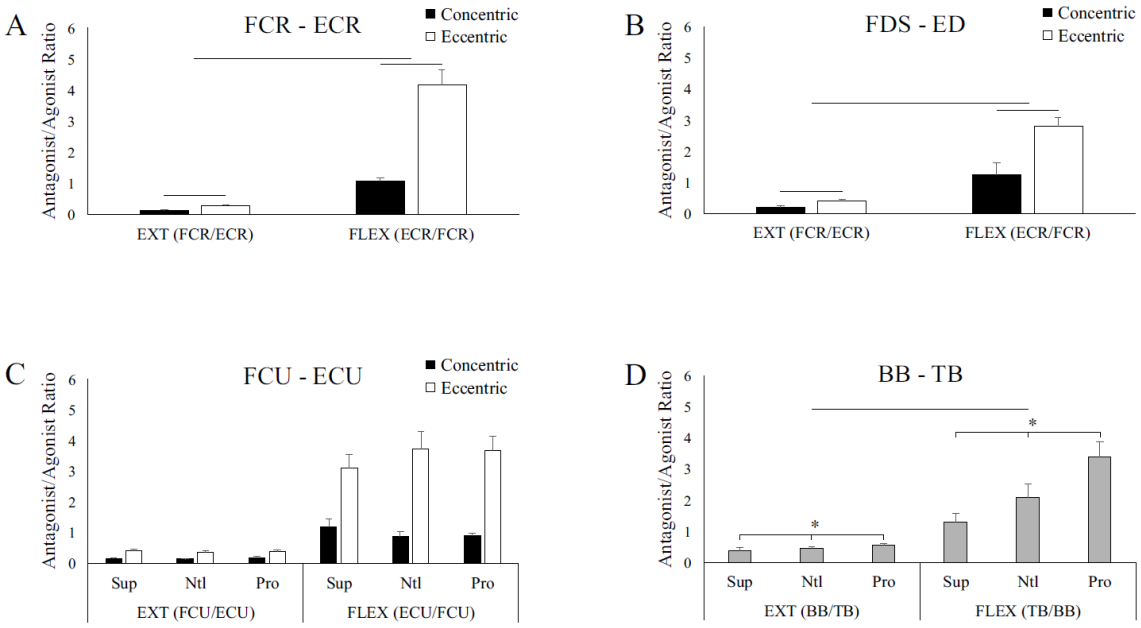


Figure 4.3. *Group averages of co-contraction ratios (antagonist/agonist muscle pairs). A and B depict 2-way interactions of force direction and movement phase (black: concentric, white: eccentric). C depicts a 3-way interaction while D depicts a 2-way interaction of posture and force direction. Horizontal lines denote a significant difference (P < 0.05) between either concentric and eccentric phases within a force direction or a difference between force directions (flexion vs extension). * denotes a significant main effect of forearm posture.*

Table 4.3. *Post-hoc analyses of co-contractions (anatomical antagonist/agonist muscle pairings) that demonstrated a 2-way interaction of force direction and movement phase. Results are listed as P-Values, F-statistics and effect sizes (represented by Partial ETA Squared (η_p^2)).*

		Flexion (Con vs. Ecc)	Extension (Con vs Ecc)	Concentric (Flex vs Ext)	Eccentric (Flex vs Ext)
FCR-ECR	*P*-value	**< .001***	**< .001***	**< .001***	**< .001***
	F-Statistic	$F_{(1,26)} = 49.878$	$F_{(1,26)} = 46.796$	$F_{(1,26)} = 60.774$	$F_{(1,26)} = 55.202$
	Effect Size	0.657	0.643	0.7	0.68
FDS-ED	*P*-value	**0.004***	**0.011***	**0.002***	**< .001***
	F-Statistic	$F_{(1,29)} = 9.606$	$F_{(1,29)} = 7.482$	$F_{(1,29)} = 11.56$	$F_{(1,29)} = 63.332$
	Effect Size	0.519	0.205	0.285	0.686

Table 4.4. *Post-hoc analyses of BB-TB co-contractions that demonstrated a 2-way interaction of posture and force direction. Results are listed as P-Values, F-statistics and effect sizes (represented by Partial ETA Squared (η_p^2)).*

		Flexion (S vs. N vs. P)	Extension (S vs. N vs. P)	Supinated (Flex vs Ext)	Neutral (Flex vs Ext)	Pronated (Flex vs Ext)
BB-TB	*P*-value	**< .001***	**0.014***	**0.002***	**0.001***	**< .001***
	F-Statistic	$F_{(2,23)} = 14.705$	$F_{(2,23)} = 4.688$	$F_{(1,23)} = 12.562$	$F_{(1,23)} = 14.567$	$F_{(1,23)} = 33.133$
	Effect Size	0.39	0.169	0.353	0.388	0.59

4.4.3 Musculoskeletal modelling

A summary of the values regarding muscle-tendon length, wrist deviation moment arm, and peak active fiber force in the three forearm postures can be found in Table 4.5. Of the forearm muscles, FCR's muscle-tendon length changed the most at 0.29 cm (representing just 0.94% of the muscle's length in supination). The forearm muscle with the largest change in peak active fiber force was FDS with a difference of only 7.5% between supination and pronation. According to the model, wrist flexion moment arms are unchanged across forearm postures. It is important to note that this model was evaluated using the supination and pronation angles used in the present protocol (30°). Had postures been taken to full supination/pronation, mechanical properties might have differed to a greater extent. For example, the same model (Holzbaur et al., 2005) predicts a muscle-tendon length change in FCR and ECR of 0.74 and 0.61 cm, respectively, throughout the full supination-pronation range.

Table 4.5. *Data obtained from the musculoskeletal model (Holzbaur et al., 2005) on muscle-tendon length, wrist flexion moment arm, and peak active fiber force. Muscle length and moment arms are reported in centimeters, while peak force is reported in newtons. Values were taken at 3 forearm postures; 30° of supination, neutral, and 30° of pronation.*

	Muscle-Tendon Length (cm)			Wrist Flexion Moment Arm (cm)			Peak Active Fiber Force (N)		
	Sup	Ntrl	Pro	Sup	Ntrl	Pro	Sup	Ntrl	Pro
FCR	30.83	30.63	30.54	1.49	1.49	1.49	71.60	70.58	70.20
FDS	40.11	39.94	39.83	1.47	1.47	1.47	48.03	50.43	51.91
FCU	30.92	30.81	30.79	1.49	1.49	1.49	114.92	112.46	111.96
ECR	30.50	30.50	30.56	-1.15	-1.15	-1.15	172.42	174.20	173.37
ED	41.24	41.26	41.30	-1.42	-1.42	-1.42	17.09	16.93	16.69
ECU	29.53	29.51	29.55	-0.63	-0.63	-0.63	92.25	92.13	92.35
BB	37.08	37.39	37.84	-	-	-	524.00	516.67	498.45
TB	18.30	18.30	18.30	-	-	-	549.87	549.87	549.87

Discussion

This work is one of the most comprehensive examinations of the interactions between forearm posture, force direction, and movement phase on forearm muscle recruitment during dynamic wrist exertions. Our findings indicated that forearm posture had minimal influence on forearm muscle activity, but significantly altered the activity of the biceps and triceps brachii. Force direction influenced muscle activity in nearly every muscle, with muscle activity levels higher in the concentric phase when muscles acted as agonists. Interestingly, muscle activity in the eccentric phase was equal across force directions, regardless of whether the muscle acted as the agonist or antagonist. Lastly, co-contraction ratios were higher in the flexion conditions, suggesting significantly greater wrist extensor activity. This highlights the vulnerability of the wrist extensors to overuse injuries in settings requiring repeated or prolonged dynamic wrist exertions.

4.5.1 Posture

In the present study, forearm posture significantly influenced muscle activity and co-contraction of the muscles acting upon the elbow joint. In flexion trials for the biceps brachii, and extension trials for the triceps brachii, muscle activity increased towards supination. However, failing to support our first hypothesis, forearm posture had almost no effect on forearm muscle activity, with only ECU influenced during extension trials. This was somewhat unexpected given literature on forearm rotation and wrist forces. Both La Delfa et al., (2015) and Yoshii et al., (2015) examined wrist force in three forearm postures and found that wrist extension generated greater force in pronation. While the wrist flexion results differed between the studies (likely due to variations in protocol: open hand (La

Delfa et al., 2015) versus gripping hand (Yoshii et al., 2015), forearm rotation influenced flexion force in both. Thus, it was expected that forearm muscle activity in the present study would have been lower in stronger postures (pronation) and higher in weaker postures (supination). However, the aforementioned studies conducted their investigations under maximal force conditions; the present study used a submaximal external load. It's possible that the interaction of posture and force might have influenced muscle activity to a larger extent had a greater load been used. Reflecting upon handgrip literature, Mogk and Keir (2003) demonstrated that forearm rotation influenced muscle activity, with lower activity in supination than pronation for most muscles and in most handgrip loads. Muscle activity was likely lower in supination than pronation as maximal handgrip forces tend to be greater in supination (Claudon, 1998; Mogk and Keir, 2003). However, the postures used in the study by Mogk and Keir (2003) were full pronation/supination, compared to the ± 30° used in the present study. Additionally, the dynamic nature of the current wrist flexion/extension task makes comparisons to isometric handgrip protocols difficult.

To help explain the minimal influence of posture in the present study, postural changes to biomechanical properties were considered (Table 4.5) (Delp et al., 2007; Holzbaur et al., 2005). Considering how little these variables changed, it is perhaps unsurprising that posture had almost no influence on muscle activity. Had ROM been taken to full supination/pronation, posture may have had a larger influence. This occurs in other joint motions, whereby changes to wrist postures (wrist flexion/extension) minimally change muscle activity unless those postures are taken to an extreme range that maximize muscle length (Delp et al., 1996). Thus, to summarize, our findings have shown that ± 30° of forearm rotation is unlikely to affect forearm demands, at least during a low external

load (La Delfa et al., 2015), but perhaps caution is needed when considering extreme ROMs (Mogk and Keir, 2003). The small changes in musculoskeletal factors (Holzbaur et al., 2005) may have also contributed to this finding. Lastly, it is possible that differences in gender, anthropometric groups, or age ranges may exhibit different effects under forearm postural changes.

4.5.2 Force direction and movement phase

Forearm muscles produced more muscle activity when functioning as agonists versus antagonists (Figure 4.2), at least in the concentric phase (i.e. flexors more active in flexion; extensors more active in extension). Confirming our third hypothesis, muscle activity was also higher in concentric than eccentric phases (only for agonists) and is a finding well supported by literature (Duchateau and Baudry, 2014; Kellis and Baltzopoulos, 1998). Evidence suggests that motor pathways employ unique control strategies for lengthening and shortening contractions (Enoka, 1996), which may stem in part from changes in muscle properties. In lengthening contractions, fewer motor units are required to reach equivalent torque as shortening contractions, given the increased intrinsic force production of muscle fibers (Edman et al., 1978; Herzog, 2014; Katz, 1939). A progressive de-recruitment of motor units (Pasquet et al., 2006) in combination with decreased discharge rate of active motor units (Del Valle and Thomas, 2005; Tax et al., 1989) is likely responsible for the reduction of eccentric muscle activity.

Interestingly, muscle activity in the eccentric phases was not different between force directions in any forearm muscle. For instance, FCR (Figure 4.2 A) demonstrated 2.6 ± 2.1% and 2.7 ± 1.5% of maximum in the eccentric phases of wrist extension and wrist

flexion, respectively. This could suggest that during dynamic contractions, forearm muscles exhibit equal activity whether they function as *lengthening agonists* or *shortening antagonists*. Given the unique protocol of the present study, it is unclear if this phenomenon has been previously reported. Considering such a relationship, there is the possibility of predictive applications. If eccentric muscle activity between flexion/extension force directions is consistent across postures (shown in the present study), loads, and movement velocity, it might be possible to make large inferences on forearm recruitment patterns with limited muscle activity data. This could also help simplify control systems for prosthetic/robotic work aimed at the distal upper extremity. For instance, prosthetic research is frequently faced with a similar degrees of freedom problem that challenges motor control specialists (such as myoelectric prostheses developers). However, if muscle activity of forearm muscles remains constant during eccentric phases, a single data point could be used to predict muscle activity levels during other periods of movement. Thus, fewer variables may need to be independently accounted for. This suggestion is largely speculative at this time; further research is needed to replicate these results under different experimental parameters.

Finally, co-contraction ratios were significantly influenced by force direction. Across all agonist-antagonist muscle pairings (Figure 4.3), there was greater co-contraction during wrist flexion than extension trials. Summed across all forearm muscles (Figures 4.3 A-C), postures, and phases, wrist extension exhibited a co-contraction value of 0.32 ± 0.27 versus 2.28 ± 2.04 in flexion. This finding is noteworthy for two reasons: 1) at ~32% the activity of the wrist extensors, the wrist flexors provided minimal co-contraction during wrist extension trials, and 2) as the antagonists during wrist flexion, the wrist extensors

provided more than twice the activity (~228%) of the wrist flexors. Despite the dynamic novelty of the present work, these results are in-line with isometric research (Mogk and Keir, 2003; Chris J Snijders et al., 1987) and support our second hypothesis that there would be greater co-contraction in flexion movement. As the wrist extensors possess both a smaller cumulative cross-sectional area and moment arm than the wrist flexors (Gonzalez et al., 1997), their force generating capacity is significantly less. Consequently, the wrist extensors must function at a higher percent of maximal activation to counteract the stronger flexors, which pose injury risks. One factor in the development of chronic overuse injuries is insufficient rest intervals between periods of loading. These results suggest that manipulating factors (i.e. posture or force direction) may be insufficient in reducing muscle activity, as the wrist extensors were never active to less than 9% of maximum in our work (activity that exceeds some recommendations for continuous work (Jonsson, 1978)).

4.5.3 Study limitations

The musculoskeletal values presented in Table 4.5 were obtained from a model (Holzbaur et al., 2005) and were not scaled for our participants. Although the cadaveric data to which this model was based on matches a 50th percentile male of 170 cm, which is similar to the average height of our sample (176.4 ± 6.5 cm), it is possible that the true musculoskeletal values of our participants were different. Thus, until experimental data on the key musculoskeletal factors discussed in this study are quantified, these values and their relation to this study's key findings should be viewed with caution.

Conclusion

This report was the first to examine forearm muscle recruitment, and the interacting factors of posture and force, during dynamic wrist exertions. Unlike previous isometric protocols, forearm posture had little influence on forearm muscle activity. The evaluation of forearm postures with larger rotation might modify mechanical properties, and subsequently muscle activity, to a greater extent. In support of literature, wrist extensors provided significantly greater co-contraction than flexors across all experimental conditions, highlighting their vulnerability to overuse. This behaviour is likely explained by anatomical and mechanical constraints.

Chapter 5. Sustained isometric wrist flexion and extension maximal voluntary contractions similarly impair hand-tracking accuracy in young adults using a wrist robot

A study published in Frontiers in Sports and Active Living – Biomechanics and Control of Human Movement

Reference:

Forman, D.A., Forman, G.N., Mugnosso, M., Zenzeri, J., Murphy, B., Holmes, M.W.R., 2020. Sustained Isometric Wrist Flexion and Extension Maximal Voluntary Contractions Similarly Impair Hand-Tracking Accuracy in Young Adults Using a Wrist Robot. Front. Sports Act. Living 2, 53. https://doi.org/10.3389/fspor.2020.00053

Preface

Although there is substantial evidence that the wrist extensors exhibit an earlier onset of fatigue than the wrist flexors (Hägg and Milerad, 1997), little is known about the consequences once these muscles are fatigued. Such information would be valuable in acute settings, where fatigue has been shown to impair the accuracy of precision movements (Missenard et al., 2008b). If accuracy is reduced, the potential for acute injuries is greater, particularly in the distal upper-limb where the hand and wrist commonly interact with the external environment.

In Chapters 3 and 4, it was found that during both the simultaneous execution of multiple isometric contractions and during the execution of dynamic contractions, wrist flexor muscle activity was highly task-dependent. In contrast, the wrist extensors consistently exhibited moderate-to-high levels of activity across all experimental conditions, which is a characteristic of muscles which function chiefly as joint stabilizers. Given such different functional roles, it was hypothesized that acute forearm fatigue would result in unique accuracy impairments of the hand and wrist between these two muscle groups. Specifically, if the extensors do indeed provide more stability to the wrist than the flexors, than fatigue of the extensors would intuitively reduce wrist joint stability to a greater degree than the flexors. Thus, fatigue of the extensors might be more detrimental to hand and wrist accuracy. This, however, has never been examined, and represents a significant gap in the literature. The purpose of Chapter 5 was therefore to examine hand-tracking accuracy using a wrist robot both before and after an acute bout of either a sustained isometric wrist flexion MVC or a sustained isometric wrist extension MVC.

Abstract

Due to their stabilizing role, the wrist extensor muscles demonstrate an earlier onset of performance fatigability and may impair movement accuracy more than the wrist flexors. However, minimal fatigue research has been conducted at the wrist. Thus, the purpose of this study was to examine how sustained isometric contractions of the wrist extensors/flexors influence hand-tracking accuracy. While gripping the handle of a three-degrees-of-freedom wrist manipulandum, 12 male participants tracked a 2:3 Lissajous curve (± 32° wrist flexion/extension; ± 18° radial/ulnar deviation). A blue, circular target moved about the trajectory and participants tracked the target with a yellow circle (corresponding to the handle's position). 5 baseline tracking trials were performed prior to the fatiguing task. Participants then exerted either maximal wrist extension or flexion force (performed on separate days) against a force transducer until they were unable to maintain 25% of their pre-fatigue maximal voluntary contraction (MVC). Participants then performed 7 tracking trials from immediately post-fatigue to 10 minutes after. Performance fatigability was assessed using various metrics to account for errors in position-tracking, error tendencies, and movement smoothness. While there were no differences in tracking error between flexion/extension sessions, tracking error significantly increased immediately post-fatigue (Baseline: 1.40 ± 0.54°, Post-fatigue: 2.02 ± 0.51°, $P < 0.05$). However, error rapidly recovered, with no differences in error from baseline after 1-minute post-fatigue. These findings demonstrate that sustained isometric extension/flexion contractions similarly impair tracking accuracy of the hand. This work serves as an important step to future research into workplace health and preventing injuries of the distal upper-limb.

Introduction

Work by Holmes et al. (2015) demonstrated that the wrist extensor muscles of the forearm contribute more to joint rotational stiffness (JRS) than the wrist flexors during external wrist perturbations. As greater JRS tends to result in a greater resistance to sudden disturbances (Brown and Potvin, 2007; Cholewicki and McGill, 1996), the wrist extensor muscles have been labeled as the primary stabilizers of the wrist. Further evidence for this hypothesis comes from studies assessing muscle activity, or from studies calculating co-contraction from muscle activity, both of which are surrogate measures for joint stiffness (Cholewicki and McGill, 1996; De Serres and Milner, 1991; Franklin and Milner, 2003; van Loon et al., 2001). The wrist extensors exhibit significantly greater co-contraction during both handgrip forces and wrist exertions than the flexors (Forman et al., 2019b). The wrist extensors also demonstrate less task-dependency; they exhibit high levels of activity regardless of task-parameters (Forman et al., 2019b; Mogk and Keir, 2003). This continuous, elevated activity predisposes the wrist extensors to an earlier onset of fatigue (Hägg and Milerad, 1997) and is likely the primary reason why they demonstrate a higher incidence of overuse injuries than the flexors (Shiri et al., 2006). For instance, the prevalence of lateral epicondylitis (which affects the wrist extensors) is approximately 1-3% in the average population (Allander, 1974; Shiri et al., 2007, 2006; Verhaar, 1994), but can vary wildly in different occupational settings. In tennis players, the prevalence is thought to be closer to 35-40%, although this number seems to increase with age (Carroll, 1981; Gruchow and Pelletier, 1979). In mild cases, lateral epicondylitis can be treated with improved rest, physical therapy, and custom braces, but in severe cases, can result in prolonged work absence and require invasive surgery. Both the prevalence and the severity

of lateral epicondylitis are worse than medial epicondylitis (affects the wrist flexors; approximate prevalence of 0.4% in the general population; Shiri et al., 2006).

Given the broad scope of fatigue as a field of study, and the inconsistency in which fatigue is defined, recent literature has proposed a taxonomy to provide clearer communication between studies (Enoka and Duchateau, 2016; Kluger et al., 2013). According to this work, fatigue should be defined as a symptom in which both physical and cognitive function may be limited through interactions of perceived fatigability and performance fatigability (Enoka and Duchateau, 2016). Perceived fatigability refers to the subjective state of the individual and thus involves subjective measures, while performance fatigability is measured through objective laboratory-based assessments characterizing the functional decline of performance (Marrelli et al., 2018). Performance fatigability (modulated by both muscle contractile function and by voluntary muscle activation, or classically termed peripheral and central fatigue; Kluger et al., 2013), can manifest experimentally as decreased movement accuracy (Missenard et al., 2008a), impaired proprioception acuity (Mugnosso et al., 2019; Pedersen et al., 1999), decreased co-contraction during precision movements (Gribble et al., 2003; Missenard et al., 2008a), and decreased peak contractile speed and torque generation (de Haan et al., 1989). These factors not only compromise joint stability but also contribute to greater signal-dependent noise (SDN; signal meaning the optimal, ideal force required to perform a task, and noise meaning any deviation from that ideal) (Missenard et al., 2008b). The result is an overall increase in force variability, which reduces the accuracy of precision movements. Greater movement error has real-world implications. While the consequences of performance fatigability can contribute to the development of chronic overuse injuries, impairments to

movement accuracy may lead to performance decrements and greater risks of suffering acute injuries (Parijat and Lockhart, 2008). Understanding how performance fatigability manifests, and the specific ways that it impairs performance, is an important step in mitigating its potentially harmful effects. This is particularly important in the context of the distal upper-limb, as the hand makes the final interface with the external environment.

However, there is currently limited research into how performance fatigability develops in the forearm, with most work centered around office mouse use (Huysmans et al., 2008). Additionally, we are aware of only one study that has examined performance fatigability between opposing muscle groups (Jaric et al., 1997). In this study, agonist muscle fatigue caused greater velocity, acceleration, and deceleration deficits in the agonist than the antagonist (minimal differences were seen whether the agonists were the elbow flexors or extensors). There is insufficient literature to conclude what influence performance fatigability of the forearm has on hand-tracking accuracy. The potential specificity of performance fatigability between forearm muscle groups is also unknown. Therefore, the purpose of the present study was to examine hand-tracking accuracy prior to and following a single bout of maximal, sustained, isometric wrist extension or wrist flexion contraction. Hand-tracking error was examined while performing on a three-degrees-of-freedom wrist manipulandum, and hand movement incorporated wrist flexion/extension and radial/ulnar deviation. Tracking error was expected to increase following sustained contractions of either muscle group. However, it was hypothesized that tracking error would be greater following wrist extension fatigue, given the evidence that the wrist extensors contribute more to wrist stability than the flexors.

Methods

5.3.1 Participants

Experimental procedures were approved by the research ethics boards (REB) of Brock University (REB# 16-263) and Ontario Tech University (REB# 15044). Written consent was obtained from all participants prior to the experiment. Twelve right-handed males (Height: 180.2 ± 7.7 cm; Weight: 77.4 ± 10.4 kg; Age: 23.9 ± 2.7 years) were recruited for this study. Participants were excluded if they presented with any upper-body, neuromuscular injuries.

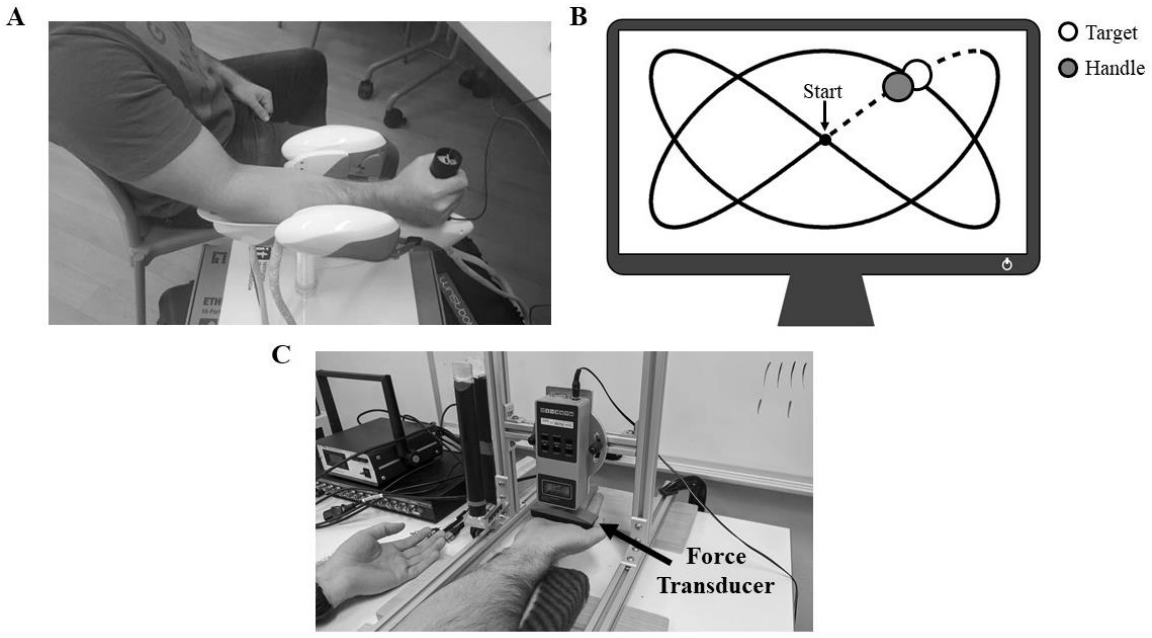


Figure 5.1. A) *Experimental setup for the tracking trials. Participant's forearm is positioned atop the WristBot support, and their hand is gripping the handle of the device.* ***B)*** *Example of the 2:3 Lissajous curve. The white circle represents the target as it moves around the curve, while the grey circle represents the real-time position of the handle. Data collected during the initial dotted-line portion was not analyzed.* ***C)*** *Experimental setup for MVCs and the sustained isometric fatigue trial. In this example, the participant was setup for wrist flexion MVCs/wrist flexion fatigue.*

5.3.2 Experimental setup

Participants were seated with their dominant forearm supported in a three-degrees-of-freedom wrist manipulandum (WristBot, Genoa, Italy; Masia et al., 2009; Iandolo et al., 2019) with their hand firmly gripping the device's handle (Figure 5.1 A). All participants had previous experience using the manipulandum (G. N. Forman et al., 2020). The manipulandum was positioned at a comfortable distance so that subjects neither leaned forwards nor sideways. While upper-limb position was not controlled between participants, upper-limb joint angles *were* manually assessed using a goniometer and matched between the two experimental sessions (elbow extension: 134.0 ± 3.4°; shoulder flexion: 33.0 ± 7.4°; shoulder external rotation: 36.0 ± 4.2°). As a group, participants' grasp distance (distance from the wrist crease to the middle of the manipulandum's handle) was 7.9 ± 0.5 cm. The position of the handle was digitally displayed to participants on a computer monitor as a blue circle that could be moved horizontally (wrist flexion/extension) and vertically (radial/ulnar deviation of the wrist) by moving the handle of the WristBot. For all tracking trials, participants were instructed to overlay their blue circle (by moving the device's handle) on the monitor with a yellow target circle that moved along a set path. This path was a 2:3 Lissajous curve that was ± 32° in the x-axis (flexion-extension) and ± 18° in the y-axis (radial-ulnar deviation). The circular yellow target took 20 seconds to complete one full cycle of the Lissajous curve (see Figure 5.1 B for an example of the monitor display). Thus, movement velocity was controlled by the target and consistent across trials. A single lap of the Lissajous curve represented a single tracking trial. The tracking trials were non-fatiguing as no resistance was provided to participants from the

manipulandum. Trials were performed both prior to and following a single bout of maximal sustained isometric contraction.

5.3.3 Experimental protocol

This experiment consisted of two separate testing sessions. Each session was separated by 7 days and consisted of either 1) maximal sustained isometric wrist flexion, or 2) maximal sustained isometric wrist extension (order was pseudorandomized across sample; 6 participants started with flexion, 6 started with extension). A visual overview of the experimental protocol can be seen in Figure 5.2.

Upon obtaining informed consent, participants were seated in front of a table-mounted force transducer (Model: BG 500, Mark-10 Corporation, New York, USA). In this same seat, the WristBot rested at the participant's right side. The transducer was raised above the table to allow participants to place their right hand underneath (Figure 5.1 C). For the wrist flexion session, the transducer made contact with the distal anterior surface of the metacarpal bones (top of the palm), while for the wrist extension session, the transducer made contact with the distal posterior surface of the metacarpal bones (back of the most proximal knuckles). This placement for both sessions was marked on the hand with a black marker to match alignment throughout the experiment. For both sessions, the angle of the wrist was maintained at neutral (neither flexed nor extended). Participants then performed two maximal voluntary contractions (MVCs) held for 3-4 seconds and separated by 1 minute of rest. For the MVCs, participants were required to maximally flex/extend (flex on flexion fatigue day/extend on extension fatigue day) their wrist upwards against the force transducer with their right hand open (phalanges extended). Participants were

instructed to maintain an open hand throughout the MVC and to keep their forearm firmly upon the support pads (to isolate wrist forces and limit any assistance from the elbow flexors). Their left hand was placed on the table beside them, supinated and palm open so as not to provide them with any additional assistance. Participants were provided with ample verbal encouragement from the researchers for both MVCs as well as visual feedback of their MVC force. The greater of the two trials was deemed their true MVC.

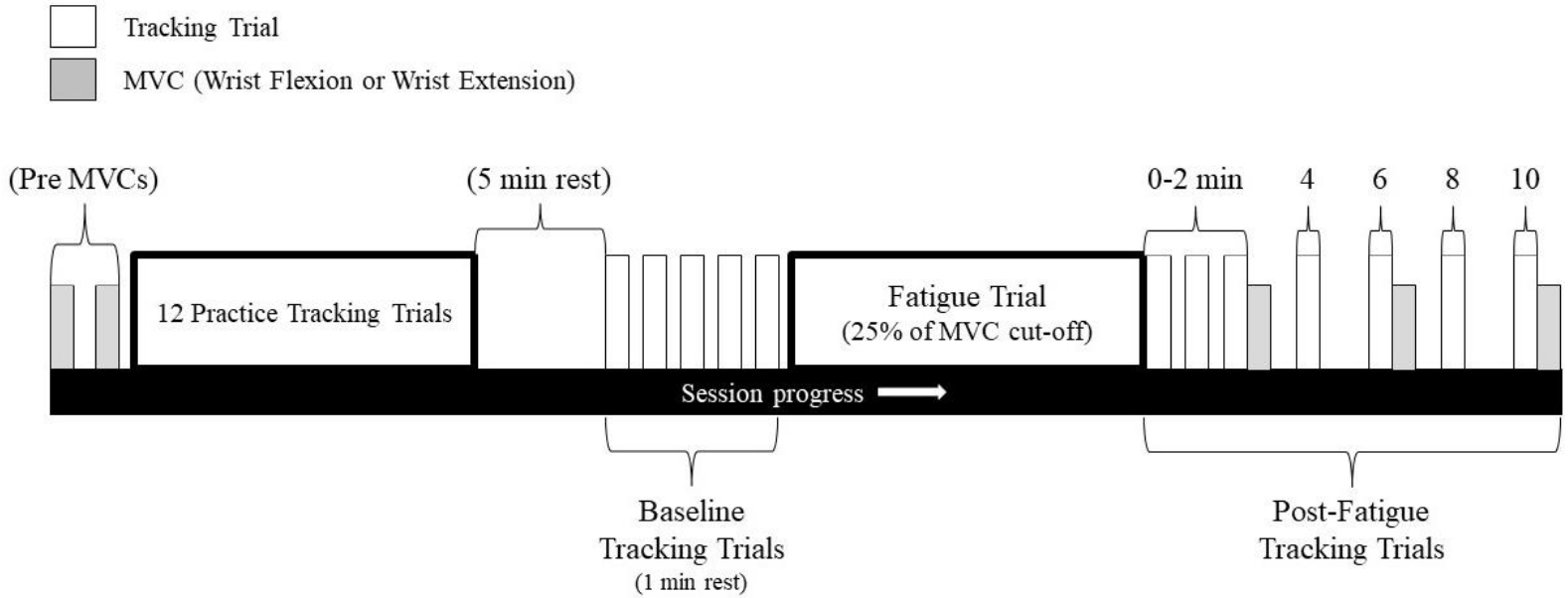
While remaining in the same seat, participants placed their right hand in the WristBot's support and grasped the handle of the manipulandum. Relevant joint angles of the upper-limb (see *Experimental setup* above) were assessed at this time. Due to the novelty of the tracking task, it was vitally important to limit the influence of motor learning on performance outcomes in the present study. To accomplish this, participants first performed 12 practice tracking trials with each trial separated by 1 minute of rest. **[**12 trials were deemed sufficient based on preliminary pilot work. In these pilot sessions, 5 participants performed 20 trials of the Lissajous curves with 1 minute of rest between trials. Mean tracking error (see *Data analysis* for explanation) rapidly decreased after the first two trials but only gradually improved after trial 3. Group tracking error did not significantly improve after trial 12.**]** Following the 12 practice trials, participants were given 5 minutes of rest. Baseline (pre-fatigue) tracking trials were then performed with a total of 5 trials separated by 1 minute of rest each.

For the fatigue-inducing trial, participants placed their right hand back underneath the table-mounted force transducer. Fatigue was then induced by a maximal sustained isometric wrist flexion/extension (on separate days) MVC. The MVC was performed following the same guidelines as mentioned above (hand open on both days). The cut-off

criteria for the sustained MVC was when participants could no longer maintain 25% of their pre-fatigue MVC force. This cut-off criteria was not disclosed to participants, who were instead told that they would be exerting maximal force for approximately 1-2 minutes. They were to relax only once the researchers (who were actively watching the force readings) told them to stop. Ample verbal encouragement was provided to participants throughout the fatigue-inducing trial.

Following the 25% cut-off, participants immediately returned their right hand to the WristBot and performed their first post-fatigue tracking trial. While the time between the end of the fatigue-inducing trial and the start of the first post-fatigue tracking trial was not measured, it is estimated that it took approximately 5 seconds to get participants back into the WristBot and begin tracking. The first tracking trial was labeled as "0" minutes post-fatigue. Additional tracking trials also occurred at 1, 2, 4, 6, 8, and 10 minutes post-fatigue. An MVC was performed immediately after the tracking trials at 2, 6, and 10 minutes post-fatigue to assess wrist flexion/extension force recovery (flexion MVCs on flexion fatigue day/extension MVCs on extension fatigue day). These MVCs were not sustained, and only lasted approximately 3-4 seconds.

Figure 5.2. *Schematic of the experimental protocol. This protocol was repeated for both the wrist flexion fatigue session and the wrist extension fatigue session (sessions separated by 7 days). Grey bars represent MVCs while white bars represent a single tracking completion of the Lissajous curve.*


Tracking Trial
MVC (Wrist Flexion or Wrist Extension)
(Pre MVCs)
(5 min rest)
0-2 min
4
6
8
10
12 Practice Tracking Trials
Fatigue Trial
(25% of MVC cut-off)
Session progress
Baseline
Tracking Trials
(1 min rest)
Post-Fatigue
Tracking Trials

5.3.4 Data analysis

Kinematic data of both the manipulandum's handle (which represents the participant's hand position) and the monitor-displayed target were sampled at 100 Hz and analyzed off-line (Matlab 2015b, Mathworks Inc., Natick, MA, USA). Because participants had to "catch-up" to the target once each tracking trial began, the initial portion of the Lissajous curve (right before the first turn; the dotted section in Figure 5.1 B) was not assessed in this study. A 6th order Savitzky-Golay filter was used to smooth the positional data in the x and y-axis (Squeri et al., 2010). The Savitzky-Golay is a polynomial fitting filter that works through the means of linear least squares. This filter is segmented in that it fits separate polynomials to a subset of data points within a predetermined window length. The window length in the present study was set to 170 ms which functions as an equivalent 11 Hz low-pass filter (Squeri et al., 2010). From this data, two groups of metrics were used to quantify performance. These include: 1) tracking error and various subtypes, and 2) movement smoothness.

Tracking error: Was calculated as the square root of the displacement between the position of the handle and the position of the target and is calculated by the following formula:

$$|\vec{e}| = \sqrt{(H_x - T_x)^2 + \left(H_y - T_y\right)^2}$$

where $|\vec{e}|$ is the Euclidean distance, and *H* and *T* are the positions (x, y coordinates) of the handle and target, respectively. The error at each data point was summed over the full tracking trial and divided by the total number of samples to give mean tracking error. To

provide additional insight into possible error patterns, we also separated tracking error into the 4 main movement directions: left, right, up, and down on the computer monitor, which was made possible primarily by flexion of the wrist, extension of the wrist, radial deviation, and ulnar deviation, respectively.

Longitudinal component: It is a measure of whether the handle is ahead of or behind the target at each data point. If the resulting value is positive, then the handle is ahead of the target relative to the target's own trajectory, and is given by the following formula:

$$\overrightarrow{u_l} = \frac{1}{\sqrt{\dot{T}_x{}^2 + \dot{T}_y{}^2}} \begin{bmatrix} \dot{T}_x \\ \dot{T}_y \end{bmatrix} = \begin{bmatrix} ux_l \\ uy_l \end{bmatrix}$$

$$\delta_l = \vec{e} \cdot \overrightarrow{u_l}$$

where $\overrightarrow{u_l}$ is the unit vector of the trajectory of the target at each data point, and δ_l is the longitudinal component of the tracking error. In order to establish whether the handle is ahead of or behind the target, the direction of the trajectory of the target must first be established. The first derivative is taken of the target displacement to find the tangent vector to the trajectory. The norm of the obtained vector is calculated. Then the tangent vector is normalized to obtain the unit vector. $\overrightarrow{u_l}$ is then multiplied against the error vector measured from earlier ($\vec{e}$, see Tracking Error) which gives either a positive (handle is ahead of the target) or negative (handle is behind the target) value.

Normal component: It is a measure of whether the handle is to the right or left of the target at each data point. If the resulting value is positive, then the handle is to the right of the target relative to the target's own trajectory, and is given by the following formula:

$$\overrightarrow{u_n} = \begin{bmatrix} uy_l \\ -ux_l \end{bmatrix}$$

$$\delta_n = \vec{e} \cdot \overrightarrow{u_n}$$

Just like for the longitudinal component, in order to establish whether the handle is to the right or left of the target, the direction of trajectory of the target must first be established. This is given by the $\overrightarrow{u_l}$ equation described earlier. $\overrightarrow{u_n}$ is simply the orthogonal of $\overrightarrow{u_l}$ and is then multiplied by the error vector. This then gives either a positive (handle is to the right of the target) or negative (handle is to the left of the target) value.

Figural error: It is a measure of how accurately the participant's trajectory adheres to the ideal target trajectory (or how well the participant recreates the target path/shape) (Conditt et al., 1997). This measure is insensitive to speed, meaning that it does not matter if an individual is ahead of or behind the target. The measure is given by the following equations:

$$dist_{AB}(i) = \min_j \left|\left|A_i - B_j\right|\right| \quad i = 1, 2, \dots n$$

$$dist_{BA}(j) = \min_i \left|\left|A_i - B_j\right|\right| \quad j = 1, 2, \dots m$$

$$FE_{AB} = \frac{\sum_{i=1}^{n} dist_{AB}(i) + \sum_{j=1}^{m} dist_{BA}(j)}{n + m}$$

where "*A*" and "*m*" are the time series and total samples of the target trajectory and "*B*" and "*n*" are the time series and total samples of the handle trajectory. The first equation calculates the distance between a single data point of the target (denoted by *j*) and every data point of the handle (in the present study, 2000 samples) before moving to the next target data point. The minimum distance of all these comparisons is then taken. **[**For example, if at sample number 100, the position of the handle was directly overlaying some portion of the Lissajous curve (this could be at any point along the target trajectory) the

minimum distance would be zero.**]** The second equation is the same, but in reverse, and compares every data point of the target against a single data point of the handle. The final equation adds the sum of all the minimum distances and divides it by the sum of the two samples. A final figural error score of 0 would indicate that the handle was directly overlaying the target trajectory throughout the entire trial.

Jerk ratio: Following filtering with the 6th order Savitzky-Golay filter, the displacement data of both the handle and the target were taken to the 3rd differential in order to obtain jerk. The jerk ratio was calculated as the integrated squared jerk (ISJ) (Platz et al., 1994) of the handle divided by the ideal ISJ of the target. ISJ was defined as $\int \left(\dddot{H}_x^2 + \dddot{H}_y^2\right) dt$ and integrated over the entire tracking trial. As the jerk ratio in the present study is a comparison of the handle to the target, a value of 1 would represent movement that is as smooth as possible. Any value greater than 1 signifies movement that is less smooth than the movement of the target.

5.3.5 Statistics

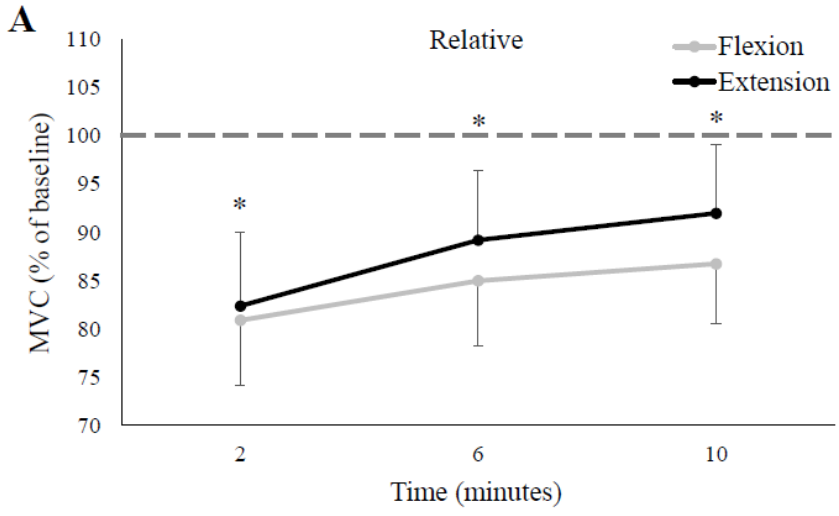
Statistical analyses were performed using SPSS software (SPSS, IBM Corporation, Armonk, NY, USA). Assumptions of sphericity were tested with Mauchley's test of sphericity, and in cases where violated, degrees of freedom were corrected with Greenhouse-Geisser. A two-way repeated measures ANOVA (fatigue day x measurement time) was conducted for MVC data, all tracking error metrics, and jerk ratio measures to identify differences between both the two fatigue sessions as well as between baseline and following sustained isometric fatigue. In cases where a main effect of measurement time

was found, post-hoc pairwise comparisons were conducted with a Bonferroni correction. Effect sizes (ES) were evaluated using partial ETA squared calculated as the division of the sum of squares of the effects (SS_{Effect}) by both the SS_{Effect} and the sum of squares of the error (SS_{Error}). Significance level was set at $P < 0.05$. Statistical analyses were performed on kinematic data in degrees (°). However, to more clearly communicate experimental findings, data has been shown in some figures as normalized to baseline measures. Group data is reported as mean ± SD.

Results

5.4.1 MVC force

Participants produced significantly more absolute force in wrist flexion than wrist extension during the pre-fatigue MVCs (Flexion: 176.1 ± 38.2 N, Extension: 157.6 ± 34.6 N, $P < 0.05$). Absolute MVC force significantly decreased following the fatigue-inducing trial, regardless of testing session, and remained significantly reduced from baseline all the way to 10-minutes post-fatigue ($P < 0.05$ for all three post-fatigue time points). Normalized to baseline pre-fatigue MVC force, Figure 5.3A shows relative MVC force in the post-fatigue recovery period. In this recovery period, there were no significant differences between the flexion or extension sessions ($F_{(3,33)} = 3.084$, $P = 0.11$, ES = 0.22), nor was there an interaction effect of session and time ($F_{(3,33)} = 2.25$, $P = 0.13$, ES = 0.17). However, there was a main effect of time ($F_{(3,33)} = 53.86$, $P < 0.05$, ES = 0.83) with relative MVC forces different from each other at all time points ($P < 0.05$ for all comparisons). This indicates that at each subsequent time point, MVC force was significantly recovering from the previous time point.



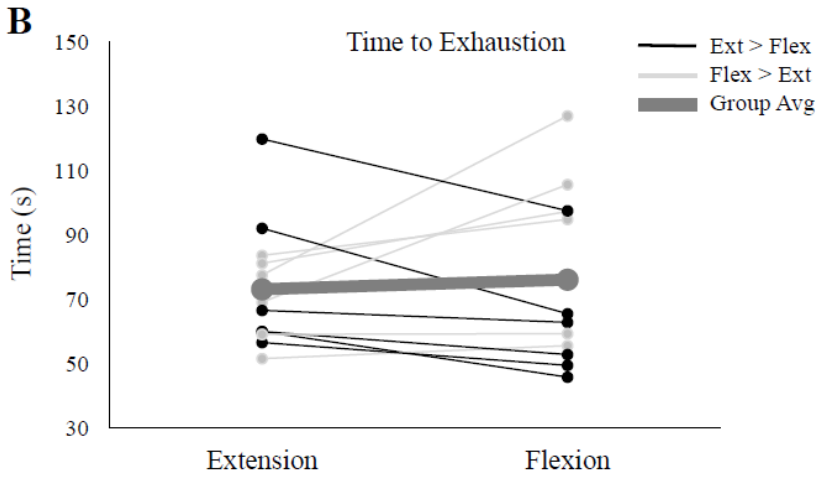


Figure 5.3. A) *Group averages of relative (% of baseline) MVC force between the wrist flexion and wrist extension sessions. Grey lines depict wrist flexion MVC force collected on the wrist flexion fatigue day, while black lines represent wrist extension MVC force collected on the wrist extension fatigue day. The x-axis denotes the time of collection; the numbers refer to time of collection after fatigue. The dotted-line represents pre-fatigue (or baseline) MVC force. * denotes a significant difference of MVC force at one time point to all other time points.* ***B)*** *Time to exhaustion for all 12 participants on both testing sessions. Black lines represent the 6 participants who took longer to fatigue on the extension day; light grey lines denote the 6 participants who took longer to fatigue on the flexion day. Lastly, the thick, dark grey line shows the group average.*

5.4.2 Time to exhaustion

Group data (Figure 5.3 B, dashed line) demonstrated that there was no difference in the time it took for participants to reach their 25% of pre-MVC force cut-off (Flexion: 76.1 ± 26.8 seconds, Extension: 73.1 ± 19.3 seconds, P = 0.65). However, there was tremendous variability across participants, with 6 participants taking longer to fatigue during extension (black lines of Figure 5.3 B) and 6 participants taking longer to fatigue during flexion (light grey lines of Figure 5.3 B).

5.4.3 Tracking error

Figure 5.4 shows group data for mean tracking error calculated over the full Lissajous curve. While statistical analyses found no difference between the extension and

flexion sessions ($F_{(7,77)}$ = 0.06, P = 0.81, ES = 0.01), there was a main effect of time on tracking error ($F_{(7,77)}$ = 12.35, P < 0.05, ES = 0.53), with error significantly worse from baseline immediately post fatigue (Baseline: 1.40 ± 0.54°, 0: 2.02 ± 0.51°, P < 0.05).

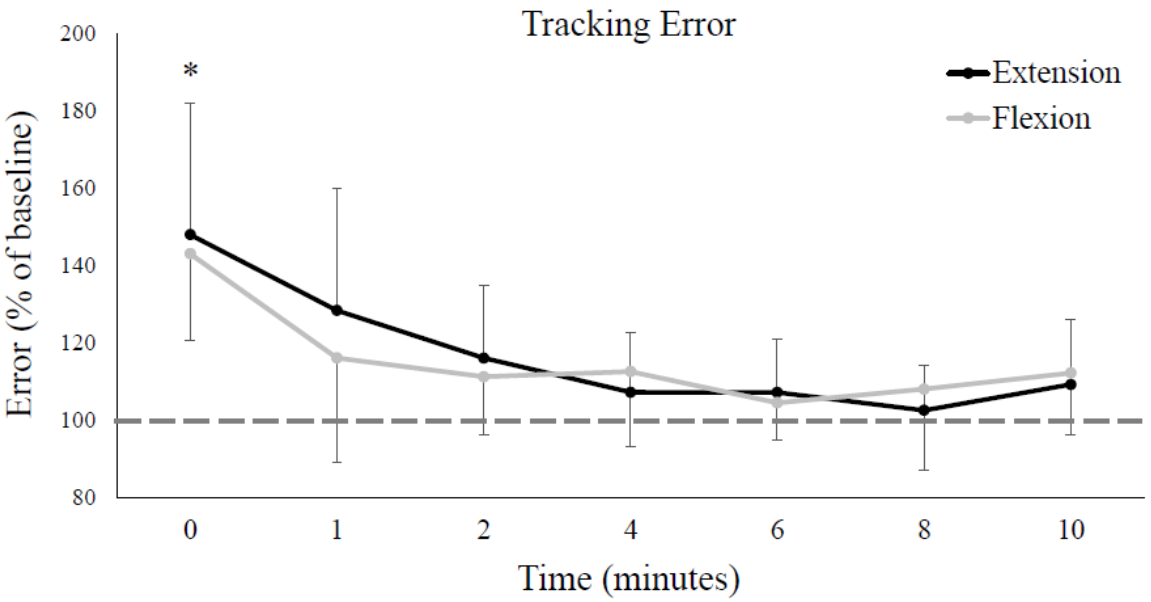
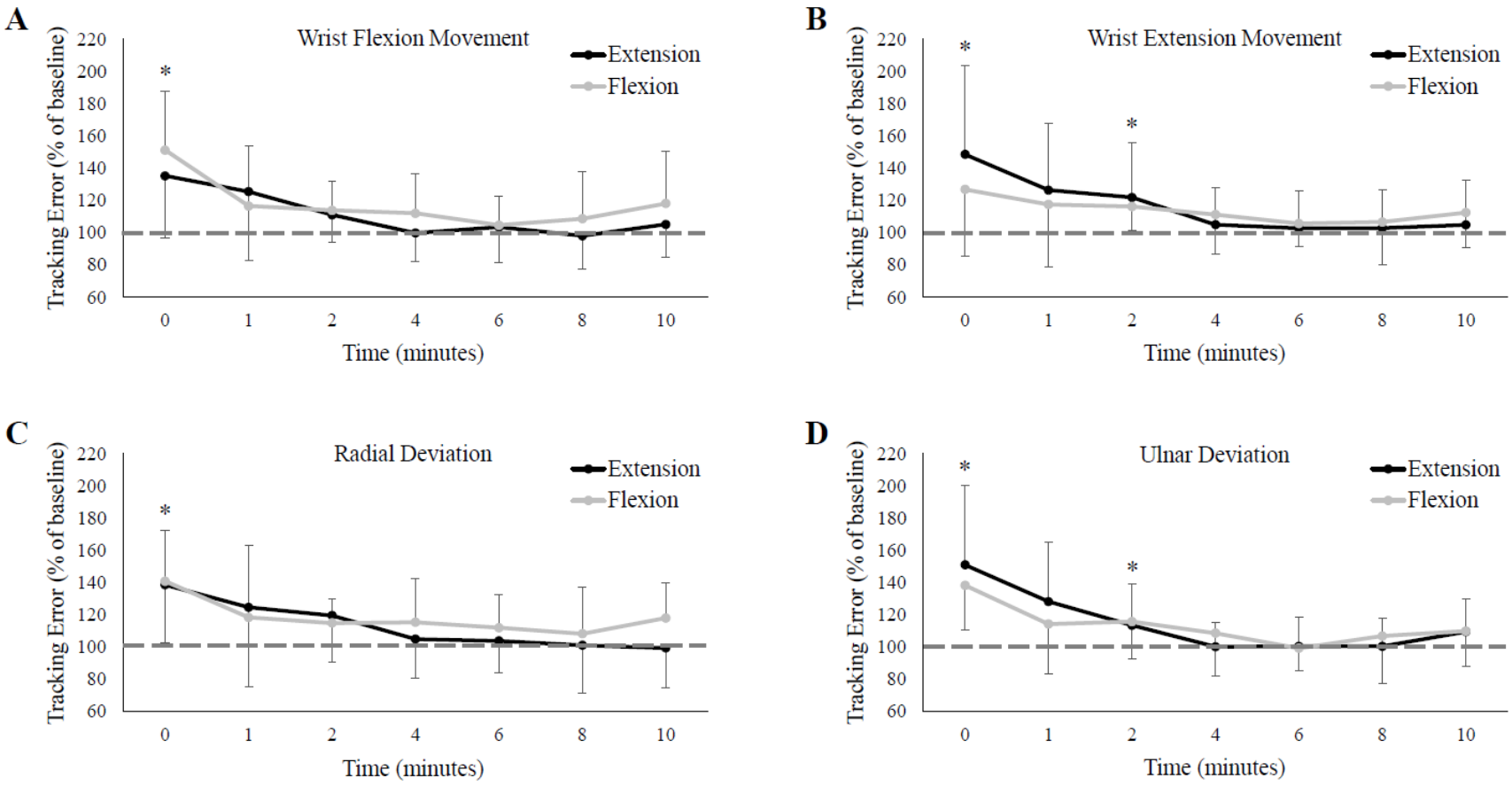


Figure 5.4. *Group averages of mean tracking error calculated over the entire Lissajous curve (excluding the dotted-line portion). Tracking error is normalized to baseline (shown by the dashed horizontal line), and data points are shown in minutes after fatigue (0-10). Black lines represent tracking error from the wrist extension fatigue session, while grey lines represent tracking error from the wrist flexion fatigue session. * denotes a significant difference of both extension and flexion compared to baseline.*

Although group means never returned to (or fell below) baseline error (even up to 10 minutes post-fatigue), tracking error recovered rapidly and was not significantly different from baseline at, or following, 1 minute post-fatigue. To examine if there were any movement-specific trends, tracking error was separated into the four primary movement directions (Figure 5.5). However, results were mostly similar to data calculated over the full curve. There was no difference in tracking error between the extension and flexion sessions for any movement direction, although all four directions showed a main effect of time (Flexion movement: $F_{(7,77)}$ = 6.32, P < 0.05, ES = 0.37; Extension movement: $F_{(7,77)}$

= 4.04, $P < 0.05$, ES = 0.27; Radial deviation: $F_{(7,77)} = 4.42$, $P < 0.05$, ES = 0.29; Ulnar deviation: $F_{(7,77)} = 8.99$, $P < 0.05$, ES = 0.45). Error significantly increased immediately post-fatigue in both the flexion (Baseline: 1.40 ± 0.71°, 0: 2.02 ± 0.65°, $P < 0.05$) and radial (Baseline: 1.39 ± 0.57°, 0: 1.90 ± 0.56°, $P < 0.05$) directions, but was not significantly different from baseline at, or following, 1-minute post-fatigue. Error was also significantly greater immediately post-fatigue during extension (Baseline: 1.36 ± 0.48°, 0: 1.80 ± 0.56°, $P < 0.05$) and ulnar (Baseline: 1.40 ± 0.56°, 0: 2.00 ± 0.63°, $P < 0.05$) movement, however, error was also greater at 2-minutes post-fatigue (Extension: Baseline: 1.36 ± 0.48°, 0: 1.60 ± 0.48°, $P < 0.05$; Ulnar: Baseline: 1.40 ± 0.56°, 0: 1.59 ± 0.43°, $P < 0.05$).

Figure 5.5. *Group averages of mean tracking error* ***A)*** *only when the wrist was flexing,* ***B)*** *only when the wrist was extending,* ***C)*** *only when the wrist was moving in radial deviation, and* ***D)*** *only when the wrist was moving in ulnar deviation. Tracking error is normalized to baseline (shown by the dashed horizontal lines in each graph), and data points are shown in minutes after fatigue (0-10). Black lines represent tracking error from the wrist extension fatigue session, while grey lines represent tracking error from the wrist flexion fatigue session. * denotes a significant difference of both extension and flexion compared to baseline.*


A
Wrist Flexion Movement
Extension
Flexion
Tracking Error (% of baseline)
220
200
180
160
140
120
100
80
60
*
0
1
2
4
6
8
10
Time (minutes)
B
Wrist Extension Movement
Extension
Flexion
Tracking Error (% of baseline)
*
*
Time (minutes)
C
Radial Deviation
Extension
Flexion
Tracking Error (% of baseline)
*
Time (minutes)
D
Ulnar Deviation
Extension
Flexion
Tracking Error (% of baseline)
*
*
Time (minutes)

5.4.4 Longitudinal and normal error components

Figures 5.6 A and B depict group data of the longitudinal (ahead or behind) and normal (right or left) components, respectively, of the tracking error. As a group, participants tended to rush ahead of the target as it moved around the Lissajous curve. Even at baseline, the longitudinal component averaged 0.24 ± 0.61° between the two testing sessions. This tendency increased immediately post-fatigue, with participants significantly farther ahead than at baseline (Baseline: 0.24 ± 0.61°, 0: 0.85 ± 0.70°, $P < 0.05$). However, there was no difference in the longitudinal component between testing sessions, and the error across both sessions was not significantly different from baseline at, or following, 1-minute post-fatigue. Regarding the normal component of error, data seemed to hover around 0 for all conditions, meaning that as a group, participants missed the target to the right and to left to a nearly equal extent. The normal component of error was not significantly different between the two testing sessions ($F_{(7,77)} = 0.52$, $P = 0.50$, ES = 0.05), nor did it significantly change over time ($F_{(7,77)} = 1.61$, $P = 0.21$, ES = 0.13).

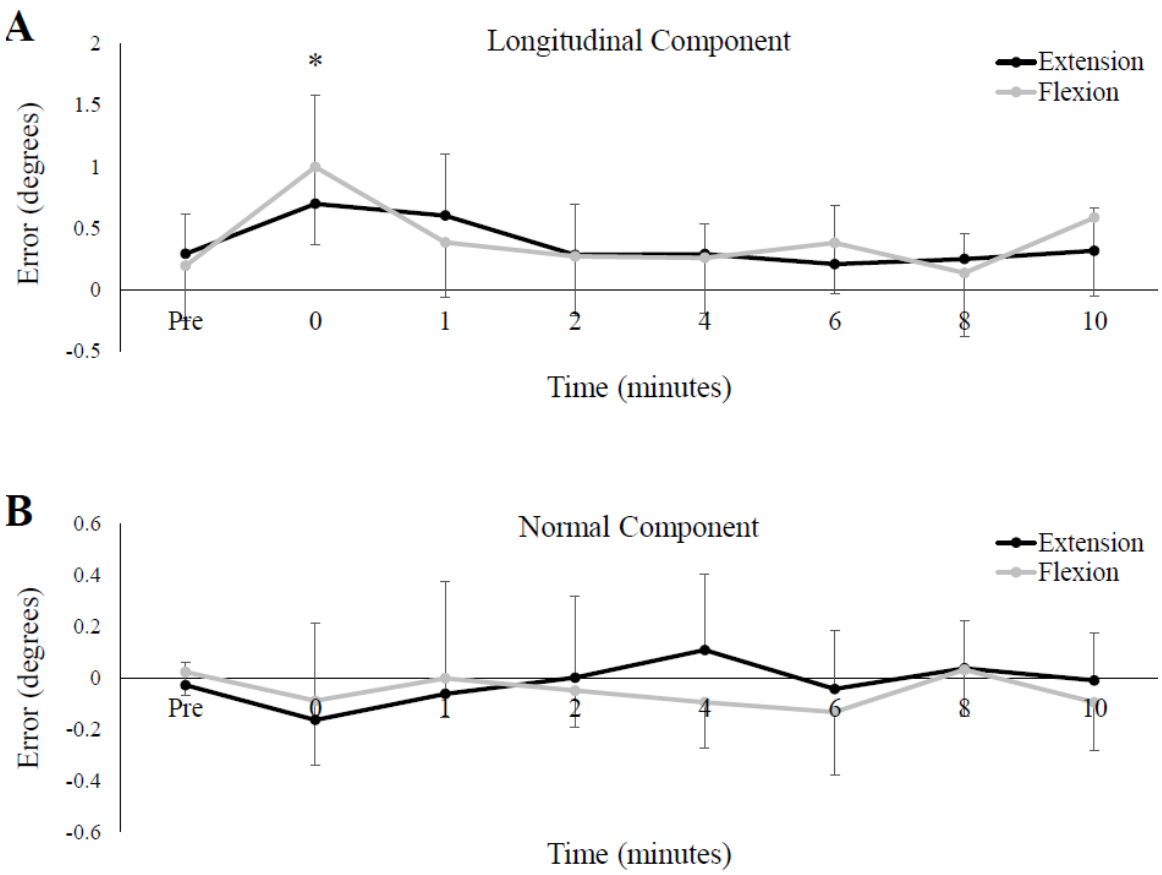


Figure 5.6. *Group averages of the mean* ***A)*** *longitudinal component of the tracking error, and* ***B)*** *the normal component of the tracking error. For both metrics, error is shown in degrees (°) and data points are shown from pre-fatigue to 10 minutes-post. Black lines represent tracking error from the wrist extension fatigue session, while grey lines represent tracking error from the wrist flexion fatigue session. * denotes a significant difference of both extension and flexion compared to baseline.*

5.4.5 Figural error and jerk ratio

Group data on figural error is shown in Figure 5.7 A, and much like tracking error, demonstrated a main effect of time ($F_{(7,77)} = 7.10$, $P < 0.05$, ES = 0.392), with no difference between the flexion and extension sessions ($F_{(7,77)} = 1.55$, $P = 0.24$, ES = 0.12). Figural error significantly increased immediately post-fatigue (Baseline: 0.74 ± 0.19°, 0: 0.94 ± 0.22°, $P < 0.05$), but was not significantly different from baseline at, or following, 1-

minute. Jerk ratios (representing movement smoothness) also demonstrated a main effect of time ($F_{(7,77)} = 3.37$, $P < 0.05$, ES = 0.23), although interestingly, pairwise comparisons revealed no differences between any two time points. There was also no difference between the flexion and extension test sessions on jerk ratios ($F_{(7,77)} = 0.07$, $P = 0.79$, ES = 0.01).

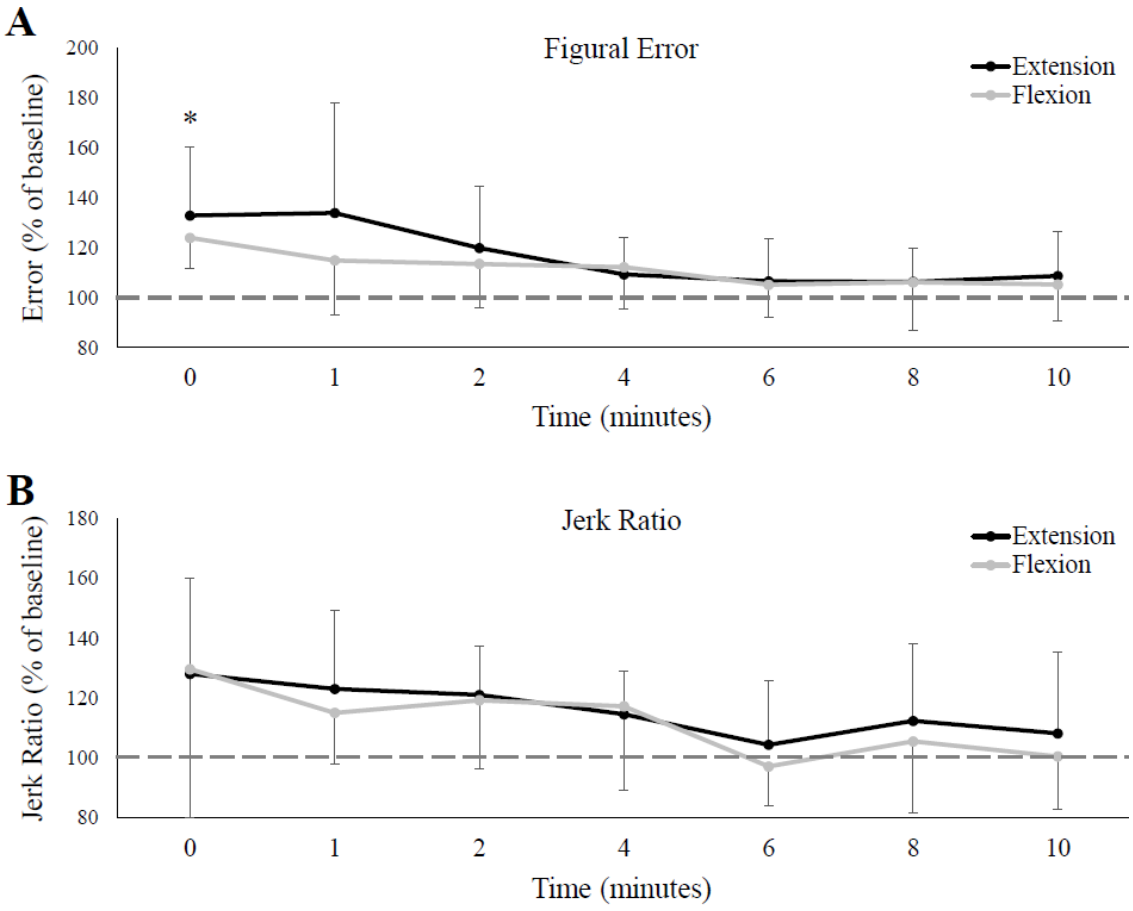


Figure 5.7. A) *Group averages of figural error, and* ***B)*** *group averages of the jerk ratio. Error is relative to baseline (shown by the dashed horizontal lines in each graph), and data points are shown in minutes after fatigue (0-10). Black lines represent tracking error from the wrist extension fatigue session, while grey lines represent tracking error from the wrist flexion fatigue session. * denotes a significant difference of both extension and flexion compared to baseline.*

Discussion

To the best of our knowledge, this is the first study to have examined sustained isometric MVCs in opposing forearm muscle groups and their subsequent influence on precision movements of the hand and wrist. Results demonstrated that hand-tracking accuracy was impaired across nearly all analysis metrics, although most of these measures recovered within 1-minute. Increased tracking error seemed to be mostly consistent throughout the full trace; minimal differences were seen when examined in the four primary directions. A tendency to rush (longitudinal component) while tracking may explain part of the increased tracking error; left/right error tendencies averaged out to be the same following fatigue. However, the most interesting finding of this study may be the lack of differences between the flexion and extension fatigue sessions. Across all metrics, there were no differences in tracking proficiency whether the wrist flexors or the wrist extensors were fatigued. This raises new questions regarding the functional roles of the wrist flexors and extensors in both sustained contractions and in the execution of fine motor skills.

5.5.1 Flexors versus extensors

Prior to the fatigue-inducing trial, participants produced significantly more absolute wrist flexion MVC force than wrist extension, although when normalized (Figure 5.3 A), there were no differences in MVC force recovery. For every other metric, there were also no differences between the two sessions. Participants produced equal tracking error between the wrist flexion and extension sessions and even demonstrated similar error tendencies (Figures 5.6 and 5.7). This finding was surprising, given the differences in

anatomy and physiological roles of the two muscle groups. The wrist flexors possess a physiological cross-section area (PCSA) that is approximately twice as large as the wrist extensors (Flexors: ~24.8 cm^2, Extensors: ~11.8 cm^2; Jacobson et al., 1992; Lieber et al., 1992, 1990). The wrist flexors also cumulatively possess larger moment arms than the wrist extensors (Gonzalez et al., 1997). Since PCSA is a strong predictor of a muscle's strength, these two factors indicate that the wrist flexors are capable of generating a peak moment in excess of 2:1 of the extensors (Gonzalez et al., 1997). Muscle lines of action, at least in the most superficial forearm muscles, only compound this force-generating disparity. Both the flexor carpi radialis (FCR) and ulnaris (FCU) possess a mostly direct line of action towards wrist flexion (Bawa et al., 2000). In contrast, the extensor carpi radialis (ECR) and ulnaris (ECU) are more closely aligned with radial and ulnar deviation, respectively (Bawa et al., 2000). Consequently, the wrist extensors must function at a higher percentage of maximal activation in order to counterbalance the activity of the stronger flexors, particularly in movements that are closer to the flexors' more direct line of action. This has been repeatedly shown experimentally, whereby the wrist extensors exhibit significantly higher levels of muscle activity than the flexors across a multitude of handgrip and wrist forces (Forman et al., 2019b; Mogk and Keir, 2003; Chris J Snijders et al., 1987). These recruitment characteristics have contributed to the notion that the wrist extensors make a greater contribution to wrist joint stability (Holmes et al., 2015). They are also the primary reason why the wrist extensors exhibit an earlier onset of fatigue than the wrist flexors (Hägg and Milerad, 1997). Considering all of the above, it was well within reason to hypothesize that separately inducing fatigue through wrist flexion and wrist extension would result in unique performance impairments.

The most plausible explanation for this lack of difference may arise from the recruitment characteristics of the wrist extensors. In a recent study (Forman et al., 2019b), we demonstrated that during isolated wrist extension trials, the wrist flexors averaged just 2.8% of maximal activity (versus 23.2% for the extensors). However, in the pure wrist flexion trials, the wrist extensors averaged 9.8% of maximal activity (compared to 28.1% in the flexors). To summarize, the wrist extensors were highly active even in pure wrist flexion exertions, while the opposite was not true. Thus, in the present study, it is entirely possible that prolonged wrist extension successfully isolated the wrist extensor muscles (i.e. the wrist flexor muscles were not fatigued). However, during prolonged wrist flexor fatigue, literature would suggest that both wrist flexors and extensors may have fatigued simultaneously (Forman et al., 2019b). If so, then the wrist flexors were only fatigued in a single session of the present study, while the wrist extensors were fatigued in both (although likely not to the same extent). The two sessions would therefore be more similar than previously assumed. However, this also further complicates the comparison between the two muscle groups in regards to fatigue; it would be very difficult to isolate the two using any form of exercise. Future investigations examining antagonist fatigue metrics following agonist fatigue (i.e. is wrist extension MVC impaired following prolonged wrist flexion, and vice versa?), or using alternative fatigue measures (such as surface electromyography), would help address these questions.

Finally, it is possible that during both the flexion and extension fatigue-inducing sessions, compensation from synergistic muscles diminished the influence of fatigue on tracking accuracy measures. For instance, in studies that have induced isolated fatigue in single muscles (i.e. vastus lateralis via localized electrical stimulation), the muscle activity

of adjacent/synergistic muscles (i.e. rectus femoris and vastus medialis) increases during synchronous muscle actions (i.e. knee extension) (Akima et al., 2002; Stutzig et al., 2012; Stutzig and Siebert, 2015a, 2015b). Thus, while fatigue of the wrist flexors or extensors might be uniquely detrimental to tracking accuracy of the hand/wrist in isolation, compensation from synergistic muscles (such as the forearm muscles devoted more to phalangeal actions) may diminish these differences during the execution of complex motor tasks. It is unclear if this was the case in the present study, given that the fatigue-inducing task likely fatigued forearm muscles on a "global" scale (the prime movers and synergists might have fatigued simultaneously). Regardless, this suggestion requires further investigation.

5.5.2 Time to exhaustion

To fairly compare tracking error between fatigue-inducing contractions of the wrist flexors and extensors, a relative cut-off criterion (25% of MVC for each session) was established. Interestingly, although there was large variability between participants, the duration of the fatigue-inducing trial averaged across our sample was ultimately not different between days; the wrist flexors took just as long to reach the 25% cut-off as the extensors. This is surprising given the differences in function and muscle architecture of the two muscle groups. Direct assessments of joint stiffness (Holmes et al., 2015) and investigations using muscle activity and co-contraction as surrogate measures for joint stiffness (Forman et al., 2019b; Hägg and Milerad, 1997; Mogk and Keir, 2003) suggest that the wrist extensors contribute more to wrist stability than the flexors. Since stabilizing muscles elsewhere in the body (for example, the trunk) are composed primarily of type 1

muscle fibers (Arbanas et al., 2009; Boyd-Clark et al., 2001; Mannion et al., 1997), it is possible that the wrist extensors also possess a higher percentage of type 1 muscle fibers than the wrist flexors. The only study we are aware of that has directly compared muscle fiber typing in the forearm muscles comes from Johnson et al., (1973). In this study, muscle fibers representing thirty-six unique muscles from six male specimen were extracted during an autopsy. Of the primary digitorum musles (FDS, FDP, and EDC), the flexors were composed of ~45.9% type 1 muscle fibers, compared to ~46.3% for the wrist extensors. While these values are nearly identical, it is important to point out that no other wrist flexors or extensors were examined. There was also enormous variability across the individuals. For the FDS, one individual exhibited type 1 fiber distribution as low as 23.8%, while another individual demonstrated 72.0%. It is therefore difficult to state from this data whether there are differences in wrist flexor versus wrist extensor fiber typing. However, if the wrist extensors do possess an overall greater percentage of type 1 fibers than the wrist flexors, it would be intuitive to hypothesize that the wrist extension session should have taken longer for participants to reach exhaustion. Given our experimental setup (forearm supinated for flexion fatigue; pronated for extension), it is possible that forearm posture contributed to this lack of difference (La Delfa et al., 2015; Yoshii et al., 2015). However, while the average time to exhaustion was not different between sessions, there was large variability between participants; 6 participants took longer to fatigue during flexion; 6 took longer to fatigue during extension. It is possible that certain anthropometric characteristics, such as hand size, hand length, or forearm muscle moment arms predisposed some individuals to fatiguing earlier in one session over the other. Additionally, the participants recruited in the present study were highly active (varsity athletes and strength athletes).

Differences in training status, or differences in inter-flexor/extensor strength, may have also contributed to a certain fatigue predisposition.

5.5.3 Performance fatigability and hand tracking

In the present study, isometric fatigue significantly impaired hand-tracking performance immediately after the cessation of the fatigue trial. Tracking deficits mostly recovered within 1-minute post-fatigue, although tracking in certain directions (wrist extension and ulnar deviation) remained impaired for up to two minutes. A shift in error tendencies was also observed; participants were more inclined to be ahead of the target immediately following fatigue as compared to baseline. While there was no ***net change*** in left/right error tendencies throughout the study, Figure 5.7 A suggests that participants were tracking with greater ***absolute*** left/right error following fatigue. The equation used to calculate figural error is insensitive to time, and thus, any increase in figural error must be due to greater deviations to the left/right of the target pathway.

This is not the first study to report fatigue-induced accuracy impairments. Indeed, these findings are well supported by literature (Huysmans et al., 2008; Jaric et al., 1999; Missenard et al., 2008a). Although separate laboratory groups have attributed fatigue-induced accuracy deficits to isolated mechanisms, the underlying cause is almost certainly multi-factorial. Literature has reported numerous factors, including decreased force availability (Jones et al., 2002), greater signal-dependent noise (Missenard et al., 2008b), slower contractile speed (de Haan et al., 1989), decreased co-contraction during precision movements (Gribble et al., 2003; Missenard et al., 2008a), and impaired proprioception (Mugnosso et al., 2019; Pedersen et al., 1999). Force availability is likely linked with

signal-dependent noise (SDN), where "signal" is the optimal force output to execute a given task, and "noise" is any force deviation from that ideal. Should a fatigue-inducing task decrease available force (i.e. decrease MVC), a larger relative portion of available force is then required to complete tasks with absolute force requirements (although very low, the force required to move the handle in the present study). This is noteworthy as SDN (force variability) increases linearly with higher force outputs (Jones et al., 2002) and is greater still following fatigue (Missenard et al., 2008b). Greater fatigue-induced force variability would have assuredly contributed to tracking error in the present study where accurate tracking required precise movements and speed. Speed itself may help explain why participants tended to rush the target (Figure 5.6 A). Both maximal velocity and maximal torque decrease following fatigue (Buttelli et al., 1996); muscle relaxation-time is similarly prolonged (de Haan et al., 1989). In precision tasks, this has manifested experimentally as a reduction in peak velocity when rapidly moving to a known target (Jaric et al., 1997). In the present study, it is possible that participants altered their tracking strategy following fatigue. To compensate for a potential loss of available speed, participants may have opted to remain ahead of the target (even at the expense of error) so as to avoid the poorer alternative of falling behind and struggling to catch-up.

While neither co-contraction nor proprioception were assessed in this study, both factors have been reported as significant contributors to movement accuracy. Greater co-contraction increases limb impedance (Osu and Gomi, 1999), reduces kinematic variability (Selen et al., 2005), and subsequently leads to improved accuracy (Gribble et al., 2003). This is all relevant given that performance fatigability impairs co-contraction to a similar extent as tracking error, even when force availability is controlled for (Missenard et al.,

2008a). Finally, extensive evidence has demonstrated that fatigue results in significant joint position sense impairment (Björklund et al., 2003; Carpenter et al., 1998; Pedersen et al., 1999; Roberts et al., 2003). This impairment arises from numerous factors, including, but not limited to, decreased discharge rate of muscle spindles (Macefield et al., 1991), decreased activity of golgi tendon organs (Hutton and Nelson, 1986), and alterations in central pathways (Sharpe and Miles, 1993; Zabihhosseinian et al., 2015). The extent to which co-contraction and proprioception may have influenced the findings of the present study is unclear, and future investigations quantifying these measures at the forearm would add valuable insight.

5.5.4 Central and peripheral mechanisms

In the presence of performance fatigability, changes occur at all levels of the neuromuscular pathway, from the central nervous system (CNS), the neuromuscular junction (NMJ), and the muscle fibers themselves. Research utilizing isometric fatigue-inducing tasks would suggest that these mechanisms likely had some influence over our study's findings. At the level of the motor unit, ample literature has shown that performance fatigability decreases motor unit firing rates (Bigland-Ritchie et al., 1983a; Gandevia, 2001; Grimby and Hannerz, 1977; Peters and Fuglevand, 1999; Petrofsky, 1980; Petrofsky and Lind, 1980; Woods et al., 1987). A similar decrease in spinal excitability (Butler et al., 2003; Taylor et al., 2000b, 1996; Taylor and Gandevia, 2008) suggests that alpha motoneurones are inhibited, either through intrinsic motoneuron adaptations or peripheral inhibitory pathways (Heckman and Enoka, 2012), in the presence of fatigue. These changes can all occur without a subsequent reduction in force (in non-maximal contractions), which

is made possible by a simultaneous increase in motor unit recruitment (DeVries, 1968; Eason, 1960; Edwards and Lippold, 1956; Hendrix et al., 2009; Johnson et al., 2004; Lynn et al., 1978; Scherrer and Bourguignon, 1959). Greater recruitment may result from an increase in descending neural drive, as studies utilizing transcranial magnetic stimulation (TMS) have shown motor evoked potentials (MEPs) to increase following fatigue (Klass et al., 2008; Lévénez et al., 2008; Søgaard et al., 2006), although MEP amplitudes are generally a poor indicator of voluntary activation. Increased neural drive (or cortical excitability) is thought to act as a compensatory mechanism to ensure adequate recruitment in the presence of decreased spinal excitability. Interestingly, in these studies, both corticospinal and spinal excitability change rapidly following the cessation of a fatigue-inducing task, either returning to baseline or overcorrecting in approximately 1-minute post-fatigue. This is remarkably similar to the patterns observed in the present study, whereby metrics of tracking error significantly worsened immediately post-fatigue but mostly recovered following 1-minute of recovery. It is therefore possible that fatigue-induced changes in central pathways altered voluntary activation in the present study, which may have driven patterns of tracking accuracy post-fatigue.

In terms of peripheral mechanisms, resting twitch force evoked by electrical stimulation of motor point decreases following a sustained MVC (Gandevia et al., 1996). Since some studies have found that the compound muscle action potential (M_{wave}) is unchanged following either sustained (B. Bigland-Ritchie et al., 1986b) or intermittent (Neyroud et al., 2014) MVCs, this decrease in force is at least partially explained by changes at the intramuscular level. This may be the result of reduced sarcoplasmic reticulum release/impaired renewal of intracellular calcium and a reduced myofibrillar

calcium sensitivity (Allen et al., 2008; Fitts, 1994; Glaister, 2005; Westerblad et al., 1991). Importantly, as voluntary activation typically recovers to near pre-fatigue levels within 30 seconds of recovery from sustained MVCs (Gandevia et al., 1996; Hunter et al., 2008, 2006; Kennedy et al., 2015, 2013), any lasting impairment in voluntary force production is likely due to intramuscular mechanisms. Thus, in the present study, fatigue-induced changes to intramuscular systems are likely the primary reason why MVC force remained lower from baseline all the way up to 10-minutes post-fatigue. However, this reduction in available MVC force was insufficient to impair tracking accuracy, at least beyond 1-2 minutes post-fatigue.

5.5.5 Practical implications

Given the results of the present study, one could be mistaken for concluding that the effects of fatigue dissipated after 1-2 minutes, given that most tracking metrics recovered by 1-minute. However, it should be reiterated that MVC force was still significantly reduced from baseline up to 10-minutes post-fatigue (Figure 5.3A). Thus, participants *were not* tracking better because they were no longer fatigued; they were tracking better *despite* still being fatigued. Similar work has shown that fatigue may not change kinematic measures, despite fatigue manifesting in surface electromyography (Mugnosso et al., 2019). This is particularly relevant for industries that may rely on performance as an indicator of fatigue, from athletic training and health to occupational settings. If fatigue is only identified once movement accuracy has noticeably worsened, then fatigue was likely present well beforehand. Delayed identification of workplace fatigue could have the potential to exacerbate the development of chronic overuse injuries.

This, however, should be considered in relation to the sample population examined in this study. Collected from young, active adults, the findings of this study may not be ideally suited for generalization to some workplace settings. In one sense, certain workers performing repetitive tasks could be classified as "industrial athletes," which might lead to a number of similarities to the present sample. In another sense, since such large performance detriments were observed in a young and active sample, these findings might be more pronounced in an older or more vulnerable working population.

Understanding how performance fatigability manifests in the wrist flexors/extensors is an important first step in addressing the earlier fatigue onset (Hägg and Milerad, 1997) and the higher incidence of injury that has characterized the wrist extensors (Shiri et al., 2006). The findings of the present study seem to indicate that fatigue of either muscle group results in similar accuracy losses, as performance metrics were equally impaired between sessions. However, this may have occurred due to difficulties in isolating the muscles of the forearm, given that the wrist extensors exhibit high muscle activity even as the antagonists (Forman et al., 2019b; Mogk and Keir, 2003).

5.5.6 Study limitations

In the present study, fatigue was induced via a sustained isometric MVC. Given the known differences of how maximal versus submaximal contractions influence central (Taylor and Gandevia, 2008) and peripheral (Smith et al., 2007; Søgaard et al., 2006) pathways, the results of the present study should not be generalized to lower intensity fatiguing tasks. Likewise, as this study induced fatigue through an isometric contraction, these findings should not be generalized to fatigue induced by dynamic contractions. The

present study also induced fatigue using controlled postures. Not only was the wrist flexion day performed in forearm supination and the wrist extension day performed in forearm pronation (forearm posture may have influenced the development of fatigue), but the wrist angle was also maintained at neutral (0° of flexion/extension). Had the wrist been held at a different angle throughout the sustained MVC, there might have been differences in tracking accuracy (Behrens et al., 2019; Place et al., 2005).

Finally, while the objective of the present study was purely to examine the consequences of performance fatigability on precision hand/wrist movements, our discussion has proposed a number of underlying mechanisms to explain our findings. It should be clarified that none of these mechanisms were quantified, and their contribution to the present results are speculative. Future investigations utilizing techniques such as electromyography (EMG) or TMS following a similar fatigue-inducing task would add valuable insight to this work.

Conclusion

This report was the first investigation to examine performance fatigability of wrist flexion/extension and its influence on hand tracking accuracy. Contrary to our hypothesis, there were no differences in hand tracking errors between the two testing sessions, which raises questions as to how precisely forearm muscles can be isolated in fatigue-inducing studies. Tracking error was impaired similarly for the two muscle groups immediately following a sustained MVC, but mostly recovered at 1-minute post-fatigue. However, MVC force remained lower from baseline for all post-fatigue measures, indicating that participants were capable of accurate tracking in the presence of force deficits.

Chapter 6. Sustained isometric wrist flexion and extension maximal voluntary contractions on corticospinal excitability to forearm muscles during low-intensity hand-gripping

A study in preparation for submission to Brain Sciences

Reference:

Forman, D.A., Forman, G.N., Murphy, B., Holmes, M.W.R., 2020. Sustained isometric wrist flexion and extension maximal voluntary contractions on corticospinal excitability to forearm muscles during low-intensity hand-gripping. Brain Sciences. Submitted May 2020

Preface

Chapter 5 demonstrated that sustained isometric wrist flexion and wrist extension MVCs impaired hand-tracking accuracy, although only for a short duration. Following one minute of recovery, nearly every tracking metric returned to baseline levels, despite MVC forces remaining significantly lower from baseline up to 10 minutes post-fatigue. However, there were no differences in hand-tracking accuracy between the two sessions (wrist flexion/extension MVCs). This finding may have been due to the fact that the wrist extensors are active to a high degree even during pure wrist flexion contractions. Thus, the wrist extensors may have fatigued during both test sessions, which likely would have contributed to the lack of differences in tracking impairment between the two sessions.

Two ways to test this possibility are by using surface EMG and TMS-induced motor evoked potentials (MEPs). Following fatigue, and in submaximal contractions, the EMG signal tends to grow in magnitude as more motor units are recruited to sustain force production. The MEP amplitude also increases as fatigue develops, and remains elevated for a short period of time after the cessation of the fatigue-inducing protocol, which may be to compensate for reduced motoneuron excitability. If the wrist extensors were indeed fatigued equally following either sustained isometric wrist flexion MVCs or sustained isometric wrist extension MVCs, then their EMG signals and MEP amplitudes should increase equally following both sessions. This, however, has never been investigated before, nor is there an abundance of research that has examined changes in corticospinal excitability following fatigue in an antagonist muscle. Thus, the purpose of Chapter 6 was to examined forearm muscle activity and corticospinal excitability of forearm muscles

during a low-intensity handgrip task following sustained isometric wrist flexion and extension MVCs.

Abstract

The wrist extensors demonstrate an earlier onset of performance fatigability than the wrist flexors. However, it is not currently understood whether fatigue induces unique changes in muscle activity or corticospinal excitability between these muscle groups. Thus, the purpose of this study was to examine how sustained isometric wrist extension/flexion maximal voluntary contractions (MVCs) influence muscle activity and corticospinal excitability of the forearm. In 14 male participants, corticospinal excitability to the flexor carpi radialis, flexor carpi ulnaris, flexor digitorum superficialis, extensor carpi radialis, extensor digitorum, and extensor carpi ulnaris were measured using motor evoked potentials (MEPs) elicited via transcranial magnetic stimulation. Responses were elicited while participants exerted 10% of their baseline maximal handgrip force, both before and after a single bout of sustained wrist flexion or extension MVC (performed on separate sessions). The sustained MVCs were terminated when participants could no longer maintain 25% of their baseline MVC force, and post-fatigue measures were collected up to 10-minutes post-fatigue. Immediately post-fatigue, extensor muscle activity was significantly greater following the wrist flexion than wrist extension fatigue session, although corticospinal excitability (normalized to muscle activity) was greater on the wrist extension day. Responses were largely unchanged in the wrist flexors. However, for the flexor carpi ulnaris, normalized MEP amplitudes were significantly larger following wrist extension fatigue. These findings demonstrate that sustained isometric flexion/extension MVCs result in a complex reorganization of forearm muscle activity during hand-gripping. Based on these findings, previously observed corticospinal behaviour following fatigue may not apply when the fatiguing task and measurement task are different**.**

Introduction

Although traditionally defined as a reduced capacity to generate muscle force, fatigue is understood to be a symptom in which both physical and cognitive functions may be limited (Enoka and Duchateau, 2016; Kluger et al., 2013). These limitations arise through interactions of perceived fatigability and performance fatigability; perceived fatigability refers to the subjective state of the individual (and thus, involves subjective measures), while performance fatigability is measured through objective laboratory-based assessments characterizing the functional decline of performance (Marrelli et al., 2018). Performance fatigability can manifest experimentally as decreased voluntary activation (Löscher et al., 1996a, 1996b; Zijdewind et al., 1998), decreased contractile speed (de Haan et al., 1989), and changes in cortical and spinal excitability (Gandevia, 2001). However, most studies examine the consequences of performance fatigability either at rest or within the same motor task that induced fatigue. In certain aspects, the findings of these studies apply well to sports and workplaces, where the same motor task is often performed long after it has induced performance impairments. However, it is less clear how the effects of performance fatigability induced in one motor task can manifest in another which shares similar muscle actions.

Recently, we explored this topic by examining how sustained wrist flexion and extension MVCs influenced dynamic hand-tracking accuracy (D. A. Forman et al., 2020). In this study, hand-tracking was performed on a three-degrees-of-freedom wrist manipulandum before and after a sustained MVC which ceased when participants could no longer maintain 25% of their baseline MVC force. It was hypothesized that wrist extensor fatigue would impair wrist joint stability, and subsequently hand-tracking accuracy, more

than fatigue of the flexors, given that the wrist extensors contribute more to total wrist joint stability (Holmes et al., 2015). However, while nearly every accuracy metric worsened following the sustained MVCs, there was surprisingly no difference between the wrist flexion and extension sessions. The absence of differences was attributed to the unique muscle recruitment patterns between the two muscle groups. During isometric wrist flexion, the wrist extensor muscles exhibit high levels of muscle activity (Forman et al., 2019b). In contrast, the wrist flexors are largely inactive during wrist extension. These patterns are likely the consequence of several factors: 1) the wrist extensors are smaller and mechanically disadvantaged compared to the flexors (Gonzalez et al., 1997; Jacobson et al., 1992; Lieber et al., 1992, 1990), 2) the wrist extensors possess muscle lines of action that are closer to radial-ulnar deviation than flexion-extension (Bawa et al., 2000), and 3) the extensors provide greater joint stability to the wrist (Holmes et al., 2015). Consequently, the wrist extensors must function at a higher percentage of maximal activation (Forman et al., 2019b; Mogk and Keir, 2003), and this is the primary reason why the extensors fatigue more rapidly than the flexors (Hägg and Milerad, 1997). It was therefore suggested that sustained wrist flexion may have induced fatigue in *both* muscle groups (D. A. Forman et al., 2020). Thus, if wrist extensor fatigue does impair wrist joint stability, and subsequently tracking accuracy, that instability would have been present following each fatigue session. Additional measures of performance fatigability were recommended to explore this possibility.

Of the many ways to quantify performance fatigability, two include measures of muscle activity and corticospinal excitability. Following fatiguing contractions, motor unit discharge rates progressively decrease (Bellemare et al., 1983; Marsden et al., 1971), which

manifests in electromyography (EMG) as reduced median power frequency. To maintain force output in spite of lower frequencies, motor units will typically be recruited in greater numbers (assuming the contraction was not already maximal) (B. Bigland-Ritchie et al., 1986a; Person and Kudina, 1972). The amplitude of the EMG signal will consequently increase (Bigland-Ritchie et al., 1981; Edwards and Lippold, 1956). Similarly, resting motor evoked potentials (MEPs), elicited via transcranial magnetic stimulation (TMS), increase in amplitude *immediately* following sustained contractions before falling below baseline for up to 30 minutes (Samii et al., 1996; Zanette et al., 1995). This initial increase in corticospinal excitability is thought to originate from supraspinal sources, given that spinal excitability decreases during and immediately after sustained contractions (Taylor et al., 1996). Functionally speaking, elevated supraspinal excitability is thought to act as a compensatory mechanism to ensure adequate voluntary activation of less excitable motoneurons and is likely driven by intracortical pathways (Hunter et al., 2016; Maruyama et al., 2006). Thus, following a sustained contraction, an increase in EMG and/or MEP amplitudes tends to indicate the development of performance fatigability. However, as stated earlier, these findings typically occur during the same motor task that was used to induce fatigue. It is presently unclear how performance fatigability induced in one task (example: isometric wrist exertions) might manifest in a second motor task (example: hand-gripping).

Thus, the purpose of the present study was to examine the influence of sustained isometric wrist flexion and extension MVCs on forearm muscle activity and corticospinal excitability during a low-intensity handgrip task. Our hypotheses were twofold. 1) Given that the wrist extensors provide significant co-contraction during wrist flexion, it was

hypothesized that muscle activity and corticospinal excitability of the extensors would increase following both fatigue sessions. 2) It was hypothesized that the wrist flexors, which are highly task-dependent and produce little co-contraction during wrist extension, would exhibit increased muscle activity and corticospinal excitability *only* following the wrist flexion fatigue session.

Methods

6.3.1 Participants

Experimental procedures were approved by the research ethics boards (REB) of Brock University (REB# 18-154) and Ontario Tech University (REB# 15855). Written consent was obtained from all participants prior to the experiment. 14 right-handed males (Height: 182.9 ± 9.0 cm; Weight: 83.9 ± 12.5 kg; Age: 24.9 ± 2.5 years) were recruited for this study. Participants were excluded from participation if they had any known neurological impairments or were unfit for vigorous physical activity, screened via a magnetic stimulation safety checklist (Rossi et al., 2009) and a Physical Activity Readiness Questionnaire for Everyone (PAR-Q+; Canadian Society for Exercise Physiology (CSEP)), respectively.

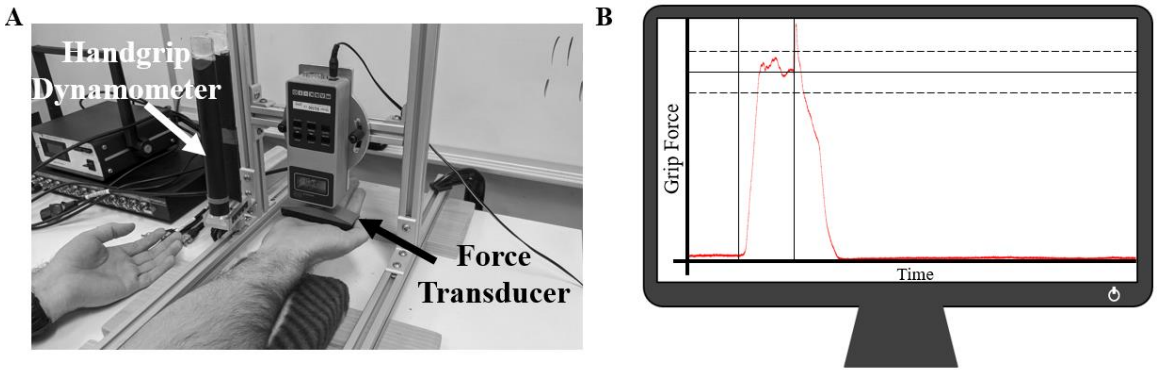


Figure 6.1. A) *Experimental setup for wrist flexion MVCs. In this photo, the force transducer is positioned above the palm and aligned along the distal portion of the metacarpal bones. The forearm could be pronated to perform wrist extension MVCs. The left (non-dominant arm) was rested upon the table, palm up, to prevent any assistance during MVC trials. The same setup was utilized for the fatigue-inducing trial where participants exerted a sustained MVC until they reached the 25% cut-off. The handgrip dynamometer is also shown attached to the aluminum framing in close proximity to the force transducer.* ***B)*** *Example of handgrip force displayed to participants. The solid horizontal line represented 10% of the individual's maximal handgrip force, while the top and lower dashed lines represented 11 and 9%, respectively. Participants were instructed to begin gripping when the trace reached the first vertical line and would be stimulated 1.5 seconds later at the second vertical line.*

6.3.2 Experimental setup

Participants were seated at a table in front of a handgrip dynamometer (MIE Medical Research Ltd, Leeds, UK) suspended above the table top by a custom-built aluminum frame (Figure 6.1 A). With their right elbow supported by a foam pad, participants gripped the handgrip dynamometer with their right hand. Hand placement was established via a band of red tape wrapped around the back prong of the dynamometer. Participants either aligned their index or middle finger (depending on hand size) to the red tape, and this position was maintained throughout the entirety of both collection sessions. The chair was also positioned at a comfortable distance from the table so that participants were neither leaning forward nor overcrowding the table while gripping the handgrip dynamometer. While upper-limb position was not controlled between participants, upper-limb joint angles *were* manually assessed using a goniometer and matched between the two experimental sessions (elbow extension: 136.0 ± 5.6°; shoulder flexion: 70.1 ± 6.1°; shoulder internal rotation: 2.5 ± 2.2°). In this posture, muscle activity and corticospinal excitability were assessed while participants exerted 10% of their maximal grip force upon the handgrip dynamometer. Hand-gripping was chosen as the measurement motor task over isolated wrist flexion or extension, as hand-gripping is known to elicit muscle activity in *all* forearm muscles (both flexors and extensors) (Forman et al., 2019b; Mogk and Keir, 2003). A 10% grip force target was chosen as it is likely comparable to the intensities of many workplaces for continuous work. Grip force was digitally displayed in real-time to participants on a computer monitor (placed directly in front of participants so that they did not have to turn their heads) as a horizontal line representing 10% of their maximal grip force (Figure 6.1 B) (Signal 6, Cambridge Electronic Design, UK). Two additional

horizontal lines (representing 9 and 11% of maximal grip force) were also displayed as an acceptable force margin. During experimental trials, participants were instructed to match the 10% force target as close as possible by squeezing the handgrip dynamometer, but at minimum, to keep their force within the 9 and 11% margins.

All wrist flexion or extension MVCs were performed against a force transducer (Model: BG 500, Mark-10 Corporation, New York, USA) attached to the same aluminum frame as the handgrip dynamometer (Figure 6.1 A). The transducer was raised above the table to allow participants to place their right hand underneath. Two separate foam pads provided support to the forearm during all MVCs; the proximal pad supported the olecranon, while the distal pad supported the distal radio-ulnar joint just proximal to the carpal bones (wrist joint). Two separate pads were utilized over one larger pad in order to allow the forearm surface electrodes (see *Electromyography*) to be suspended above the table rather than being compressed into the skin during MVCs. For the wrist flexion session, the transducer made contact with the distal anterior surface of the metacarpal bones (top of the palm), while for the wrist extension session, the transducer made contact with the distal posterior surface of the metacarpal bones (back of the most proximal knuckles). This placement for both sessions was marked on the hand with a black marker to match alignment throughout the experiment. For both sessions, the angle of the wrist was maintained at neutral (neither flexed nor extended). While performing MVCs, participants were instructed to 1) rest their left forearm upon the table, supinated, and palm open to limit any assistance from the non-tested limb, 2) keep their right forearm fully in contact with the foam pads at all times (should their forearm come off the pad(s), they were likely using elbow/shoulder flexion to assist in the MVC), 3) maintain an open hand throughout

the MVC and to avoid closing their fingers, and 4) to exert maximal force against the transducer by either flexing or extending their wrist (for the wrist flexion or extension sessions, respectively). Participants were provided with ample verbal encouragement from the researchers for all MVCs as well as visual feedback of their force at all times.

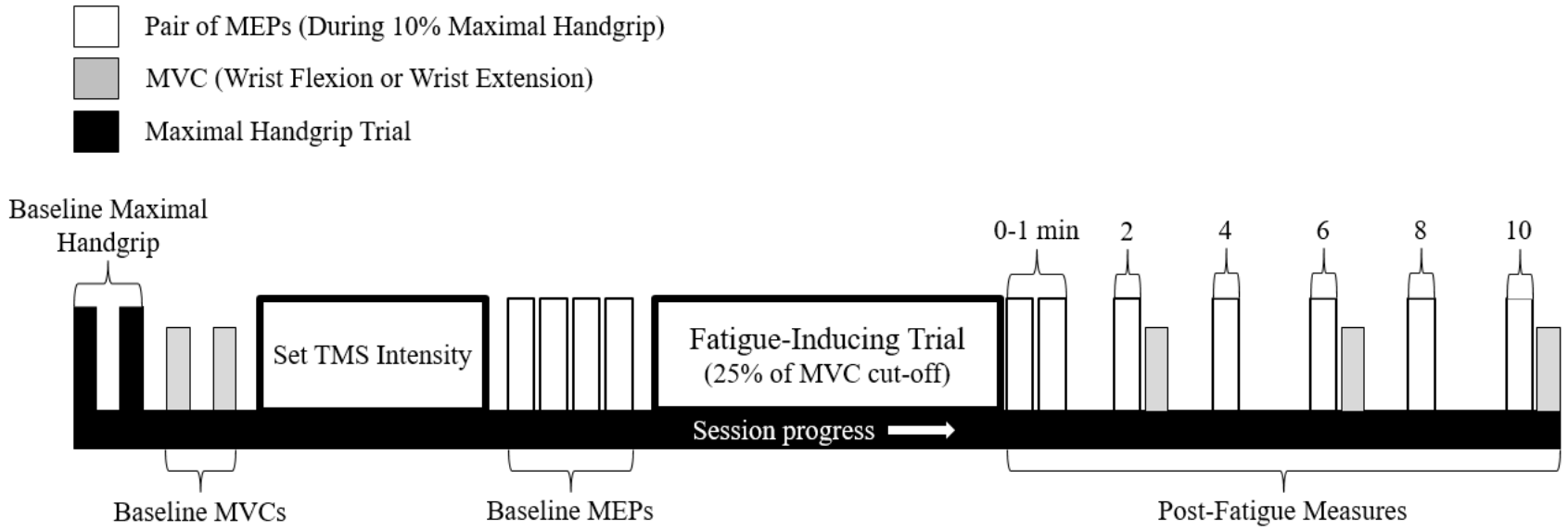
6.3.3 Electromyography

Muscle activity was recorded using pairs of surface electrodes (Blue Sensor, Ambu A/S, Denmark) from six muscles of the right arm: flexor carpi radialis (FCR), flexor carpi ulnaris (FCU), flexor digitorum superficialis (FDS), extensor carpi radialis (ECR), extensor carpi ulnaris (ECU), and extensor digitorum communis (EDC). Electrodes were placed over the muscle belly, in-line with fiber orientation, and procedures followed previous placement guidelines (Forman et al., 2019b, 2016; Holmes et al., 2015; Mogk and Keir, 2003; Perotto and Delagi, 2011). A ground electrode was placed on the lateral epicondyle of the right arm. Prior to electrode placement, all recording sites were shaved of hair using a disposable razor and were sanitized with an isopropyl alcohol swab. EMG was band-pass filtered (10-1000 Hz) and differentially amplified (gain of 500; CMRR > 100dB at 60 Hz; input impedance ~ 10 GΩ; AMT-8, Bortec Biomedical Ltd, Calgary, AB, Canada). EMG and grip force data was sampled at 5000 Hz (Power 1401-3A, Cambridge Electronic Design Ltd., Cambridge, UK).

6.3.4 TMS

MEPs were elicited in the six forearm muscles via TMS using a Magstim 200 (Magstim, Dyfed, UK). Stimulations were delivered over the participant's vertex with a circular coil (13.5cm outside diameter). Vertex was determined by measuring the mid-point between the participant's nasion and inion and the mid-point between the participant's tragi. The intersection of these two points was marked and defined as the anatomical vertex of the skull (Power and Copithorne, 2013). The coil was held tangentially to the participant's skull with the direction of the current flow preferentially activating the left motor cortex (thus, activating the individual's right upper-limb). The coil was held firmly against the participant's head by one of the investigators to ensure careful and consistent alignment over vertex for each trial. For uniformity, the same experimenter was responsible for holding the coil for all participants and between both collection sessions. Active motor threshold was determined while participants produced 10% of their maximal handgrip force. Active motor threshold was defined as the lowest % of maximum stimulator output (%MSO) that produced a recognizable MEP from the background FDS muscle activity in approximately 4 out of 8 trials (Forman et al., 2019c). Active motor threshold was determined separately on each collection day and was ultimately not different between the two sessions (Flexion: 41.6 ± 7.1 %MSO, Extension: 40.9 ± 5.6 %MSO, $P = 0.44$). This stimulation intensity was then increased by 20% and used to elicit MEPs for the remainder of the experimental protocol.

Figure 6.2. *Schematic of the experimental protocol. This protocol was repeated for both the wrist flexion fatigue session and the wrist extension fatigue session (separated by 96 hours minimum). The black bars represent the two maximal grip trials performed at the start of the collection. Grey bars represent wrist flexion/extension MVCs (performed on separate days), while white bars represent two MEPs (elicited during 10% of maximal handgrip force).*


Pair of MEPs (During 10% Maximal Handgrip)
MVC (Wrist Flexion or Wrist Extension)
Maximal Handgrip Trial
Baseline Maximal Handgrip
Set TMS Intensity
Fatigue-Inducing Trial
(25% of MVC cut-off)
0-1 min
2
4
6
8
10
Session progress
Baseline MVCs
Baseline MEPs
Post-Fatigue Measures

6.3.5 Experimental protocol

This experiment consisted of two separate testing sessions. Each session was separated by a minimum of 96 hours and consisted of either 1) maximal sustained isometric wrist flexion, or 2) maximal sustained isometric wrist extension (order was pseudorandomized across sample; 8 participants started with flexion, 6 started with extension). A visual overview of the experimental protocol can be seen in Figure 6.2.

Upon obtaining informed consent, participants had electrodes placed over the six forearm muscles of interest (see *Electromyography* for details) of their right arm. While seated, muscle-specific, isometric maximal voluntary contractions (MVCs) were then performed to determine maximal voluntary excitation (MVE) of all six forearm muscles. MVCs were performed against the manual resistance of one of the researchers and included specific grip and wrist actions to target individual muscle actions (Forman et al., 2019b). Participants then rotated in their seat to face the custom-built aluminum frame and grasped the attached handgrip-dynamometer. Relevant joint angles of the upper-limb (see *Experimental setup* above) were assessed at this time. Participants performed two maximal handgrip trials by squeezing the handgrip dynamometer as hard as possible for 3-5 seconds. The two trials were separated by one minute of rest, and the higher force value of these two trials was deemed the true maximal handgrip force. Participants then rested their forearm upon the two foam supports and had their right hand aligned to the force transducer, which was raised above the table. Two wrist flexion or extension MVC trials (flexion MVC on the flexion collection session, extension MVC on the extension collection session) were then performed for 3-5 seconds with one minute of rest provided between trials. The greater of the two trials was deemed their true wrist flexion or extension MVC.

Participants then returned their right hand to the handgrip dynamometer and had their scalp marked for TMS coil placement (see *TMS* for details). Once marked, participants were familiarized with the computer display and the handgrip force targets (10 ± 1% of maximal handgrip force). Participants were instructed to begin gripping up to and hold the 10% target 1.5 seconds prior to being stimulated (this time period was marked with two vertical lines; see Figure 6.1B) and to relax once they had been stimulated. To ensure that participants were sufficiently matching the 10% handgrip force, a number of practice trials were provided prior to any stimulations. The number of trials varied between people (typically 5-10 trials) depending on how quickly they learned to produce 10% of their maximal handgrip. Following sufficient practice, TMS was then delivered over vertex while participants matched the force target. The stimulation intensity began at 30 %MSO for all participants and was steadily increased until active motor threshold was established (see *TMS* for details). This stimulation intensity was then increased by 20% and used throughout the remainder of the protocol. Following the establishment of TMS intensity, 8 baseline MEPs were collected while participants matched the handgrip force target. Each MEP was separated by 15 seconds (in separate contractions) to allow for sufficient MEP amplitude recovery (Vaseghi et al., 2015) and is in following with previous research methods (Aboodarda et al., 2017, 2015a).

For the fatigue-inducing trial, participants placed their right hand back underneath the table-mounted force transducer. Fatigue was then induced by a maximal sustained isometric wrist flexion/extension (on separate days) MVC. The MVC was performed following the same guidelines as mentioned in *Experimental Setup* (hand open on both days). The cut-off criteria for the sustained MVC was when participants could no longer

maintain 25% of their pre-fatigue MVC force. This cut-off criteria was not disclosed to participants, who were instead told that they would be exerting maximal force for approximately 1-2 minutes. They were to relax only once the researchers (who were actively monitoring the force readings) told them to stop. Ample verbal encouragement was provided to participants throughout the fatigue-inducing trial.

Following the 25% cut-off, participants immediately returned their right hand to the handgrip dynamometer to perform their first post-fatigue MEP trial. While the time between the end of the fatigue-inducing trial and the start of the first post-fatigue MEP was not measured, it is estimated that the time period was approximately 5 seconds; since the force transducer and grip dynamometer were attached to the same frame, transition time was minimal. The first MEP trial was labeled as "0" minutes post-fatigue. All MEPs post-fatigue were grouped into pairs and occurred at 0, 0.5, 2, 4, 6, 8, and 10 minutes (or 0, 30, 120, 240, 360, 480, and 600 seconds) post-fatigue; the first MEP occurred at the specified time-point, while the second occurred 15 seconds later. An MVC was performed immediately after the MEP trials at 2, 6, and 10 minutes post-fatigue to track wrist flexion/extension force recovery (flexion MVCs on flexion fatigue day/extension MVCs on extension fatigue day). These MVCs were not sustained and only lasted approximately 3-5 seconds.

6.3.6 Data analysis

Data was analyzed off-line using Signal 6 software (CED, UK). The peak-to-peak amplitudes of MEPs evoked in all six forearm muscles were individually measured from the initial deflection of the voltage trace from the background muscle activity to the return

of the trace to background levels. The amplitudes of the 8 MEPs elicited at baseline were averaged into a single "baseline" value. All MEP amplitudes were then normalized to baseline within each collection session and are shown in figures as "% of baseline." Mean pre-stimulus handgrip force was measured individually for all MEP trials as a 50 ms window prior to the delivery of stimulation (50 ms prior to the TMS stimulus artifact). Mean Pre-stimulus muscle activity was also assessed in all individual trials for all six forearm muscles. DC offsets were removed, EMG signals were rectified, and the average EMG of a 50 ms window was measured immediately prior to stimulation. The pre-stimulus muscle activity of the 8 baseline handgrip trials were averaged into a single "baseline" value. All pre-stimulus measures of muscle activity were then normalized to baseline within each collection session and are shown in figures as "% of baseline." Finally, to examine if changes in MEP amplitudes were dictated purely by changes in muscle activity, MEP amplitudes (as a % of baseline) were normalized to muscle activity (as a % of baseline) to make MEP/EMG ratios.

6.3.7 Statistics

Statistical analyses were performed using SPSS software (SPSS, IBM Corporation, Armonk, NY, USA). Assumptions of sphericity were tested with Mauchley's test of sphericity, and in cases where violated, degrees of freedom were corrected with Greenhouse-Geisser. The assumption of normality was assessed with the Shapiro-Wilk test. A two-way repeated measures ANOVA (fatigue day x measurement time) was conducted for pre-stimulus handgrip force (2x15) (% of pre-fatigue maximal grip force) and wrist flexion/extension MVCs (2x4/2x3; absolute and % change from baseline). To

test our main study hypotheses, two separate statistical tests were performed on MEP amplitudes and pre-stimulus EMG: 1) Separate one-way repeated measures ANOVAs (measurement time) were conducted for each collection session on raw data to examine if MEP amplitudes and/or pre-stimulus EMG changed throughout the session (from baseline to post-fatigue measures); 2) A 2x14 two-way repeated measures ANOVA (fatigue day x measurement time) was conducted for MEP amplitudes and pre-stimulus EMG normalized to baseline measures (or % change from baseline), as well as MEP/EMG ratios to examine if there were any differences in the post-fatigue period between the two sessions, between any of the post-fatigue measurement times, or an interaction of the two factors. In cases where interactions were observed, separate paired t-tests were performed between the two collection sessions at each individual measurement time. In cases where a main effect of measurement time was found, post-hoc pairwise comparisons were conducted with a Bonferroni correction. Effect sizes (ES) were evaluated using partial Eta squared calculated as the division of the sum of squares of the effects (SS_{Effect}) by both the SS_{Effect} and the sum of squares of the error (SS_{Error}). Significance level was set at $P < .05$. Although certain statistical tests were performed on raw MEP and EMG data, all figures are shown normalized to baseline. Group data is reported as mean ± standard deviation (SD) in text and illustrated in figures as standard error (SE).

Results

6.4.1 Pre-stimulus handgrip force

To compare muscle activity and corticospinal excitability measures throughout this study, it was important that pre-stimulus handgrip force was consistent between the two collection sessions and between pre- and post-fatigue measures (Figure 6.3). A 2-way repeated measures ANOVA demonstrated that there was no main effect of collection

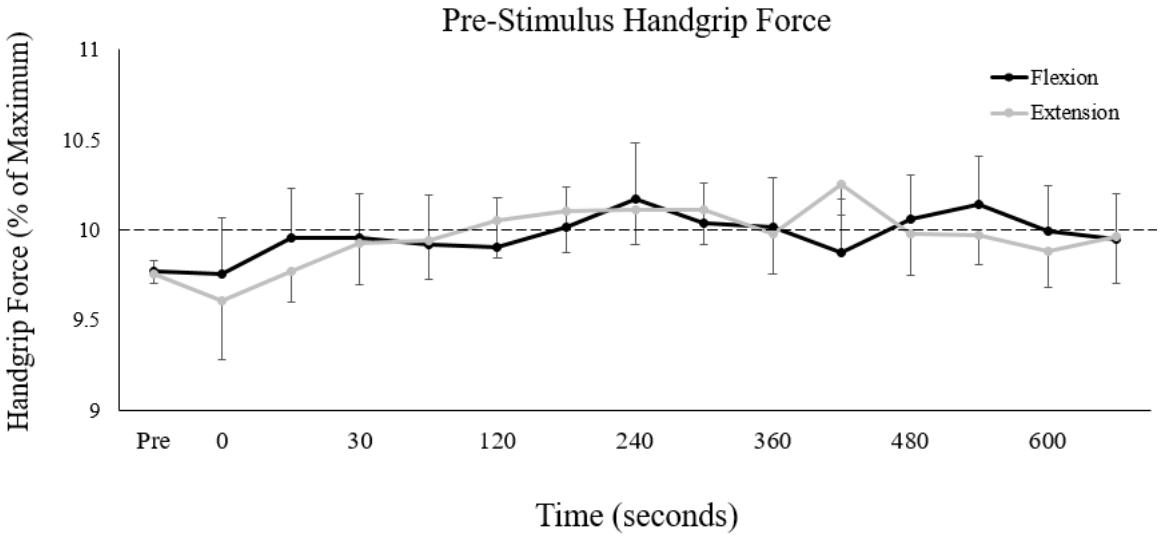


Figure 6.3. *Group averages of pre-stimulus (50 ms) handgrip force immediately prior to TMS. Black/grey lines represent pre-stimulus handgrip force during the flexion/extension fatigue sessions, respectively. The y-axis is scaled to the total target range allotted to participants (10 ± 1% of maximal handgrip force). The dashed horizontal line represents the 10% target participants were instructed to match. The x-axis displays time of measurement, with "pre" representing the non-fatigued baseline measures and "0" representing the first measurement immediately after the cessation of the fatigue-inducing trial. All unlabeled points occurred 15 seconds after the preceding time point.*

session ($F_{(1,13)} < 0.01$, $P = 0.98$, ES < 0.01) or interaction of session and time ($F_{(14,182)} = 0.79$, $P = 0.68$, ES = 0.06) on pre-stimulus handgrip force. There was, however, a main effect of measurement time on pre-stimulus handgrip force ($F_{(14,182)} = 2.04$, $P < 0.05$, ES = 0.14), although there were no differences in post-hoc pairwise comparisons between any two measurement times. For group averages, the magnitude of difference was small, and

ranged from 9.3 – 10.3% of maximal handgrip force (a difference of only 1% between the lowest and highest group average values).

6.4.2 Fatigue-inducing trial

As a group, participants took significantly longer to reach the 25% of pre-fatigue MVC cut-off during wrist extension than they did during wrist flexion (Figure 6.4 A) (Wrist flexion: 77.5 ± 16.0 seconds, Wrist extension: 92.8 ± 22.8 seconds, $P < 0.05$). However, there was some variability in this finding; not all participants took longer to reach exhaustion during extension. In total, 10 participants took longer to reach exhaustion during wrist extension, while 4 participants took longer during wrist flexion (Figure 6.4 B).

Prior to fatigue, participants produced significantly more force during wrist flexion than wrist extension (Figure 6.5 A) (Wrist flexion: 166 ± 27.2 N, Wrist extension: 137.2 ± 28.7 N, $P < 0.05$). There were no significant differences between wrist flexion/extension force throughout the first 6 minutes following the fatigue-inducing trial, but wrist flexion force was again greater at 10 minutes post-fatigue (Wrist flexion: 143.8 ± 24.7 N, Wrist extension: 123.2 ± 29.1 N, $P < 0.05$). Absolute MVC force significantly decreased following the fatigue-inducing trial and remained significantly reduced from baseline all the way to 10-minutes post-fatigue ($P < 0.05$ for all three time points). Normalized to baseline MVC force, Figure 6.5 B shows relative MVC force in the post-fatigue recovery period. In this recovery period, there were no significant differences between the flexion or extension sessions ($F_{(1,12)} = 0.90$, $P = 0.36$, ES = 0.07), nor was there an interaction effect of session and time ($F_{(2,24)} = 0.59$, $P = 0.56$, ES = 0.05). However, there was a main effect of time ($F_{(2,24)} = 28.81$, $P < 0.05$, ES = 0.71) with relative MVC forces different from each

other at all time points ($P < 0.05$ for all comparisons). This indicates that at each subsequent time point, MVC force was significantly recovering from the previous time point.

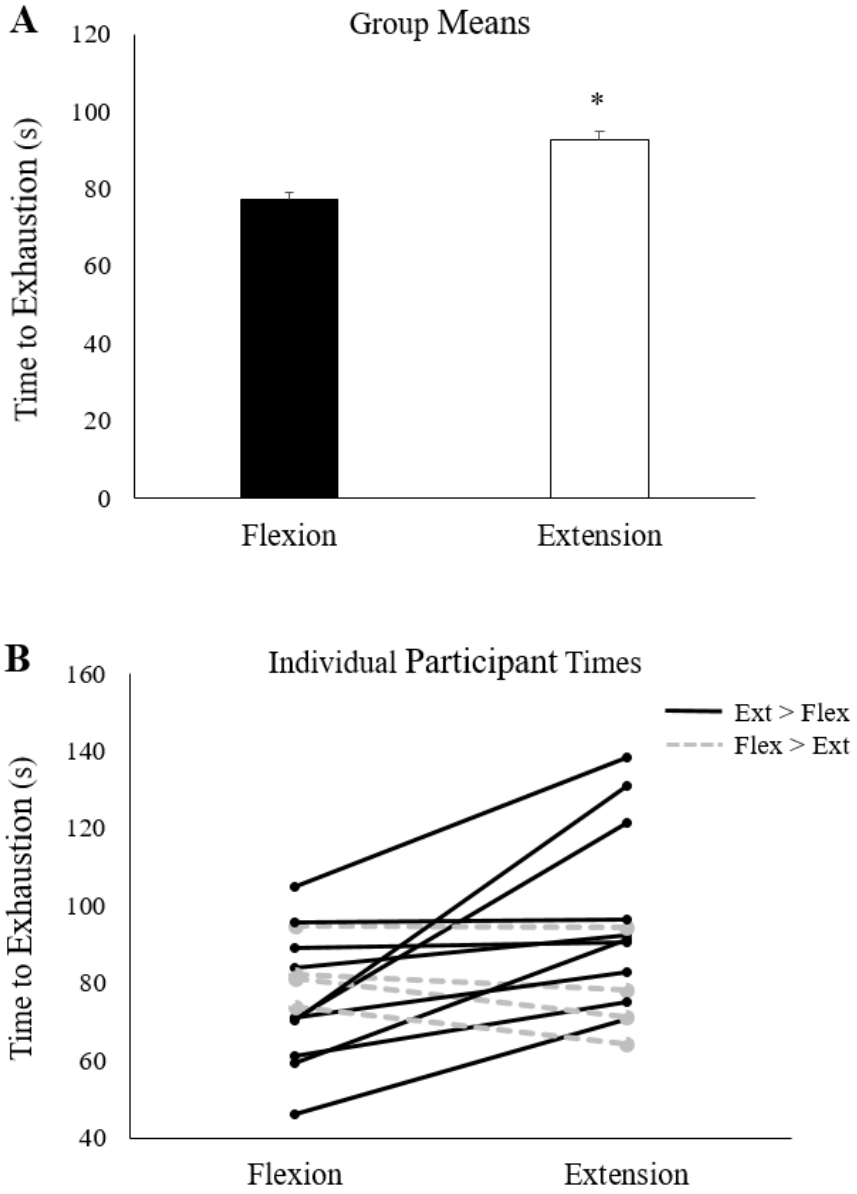


Figure 6.4. A) *Group averages of time to exhaustion. * denotes a significant difference between collection sessions.* ***B)*** *Time to exhaustion for all 14 participants on both testing sessions. Black lines represent the 10 participants who took longer to reach the 25% cut-off on the extension day; grey dashed lines denote the 4 participants who took longer on the flexion day.*

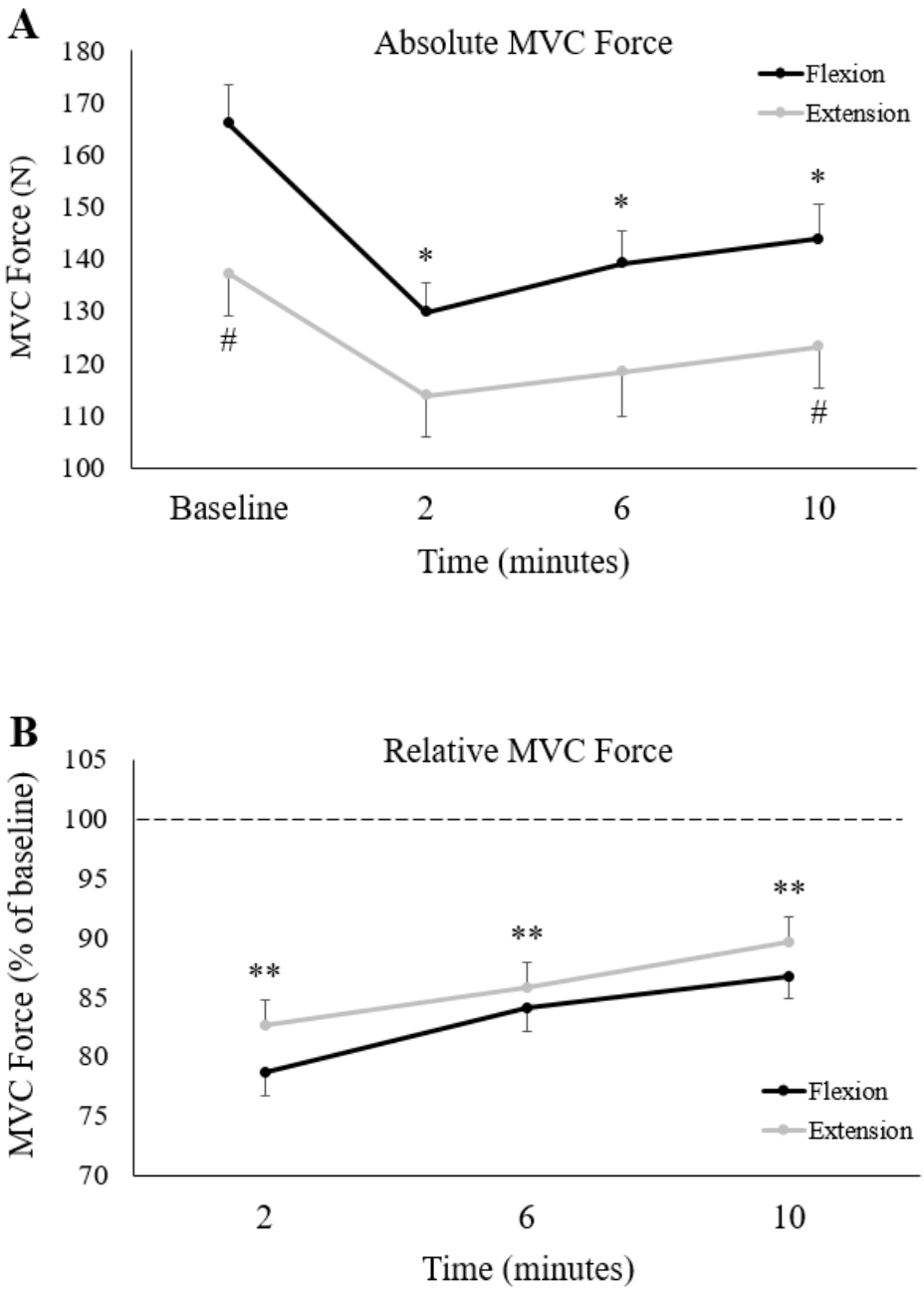


Figure 6.5. *Group averages of* ***A)*** *absolute and* ***B)*** *relative MVC forces between the wrist flexion and extension sessions. Black lines depict wrist flexion MVC force collected on the wrist flexion fatigue day, while grey lines represent wrist extension MVC force collected on the wrist extension fatigue day. The x-axis denotes the time of collection; the numbers refer to time of collection after fatigue. The dotted-line in* ***B)*** *represents pre-fatigue (or baseline) MVC force. #denotes a significant difference between sessions at a single measurement point. *denotes a significant difference of a single measurement point (across both sessions) to baseline. **denotes a significant difference of a single measurement point (across both sessions) to all other measurement points.*

6.4.3 Muscle activity

FCR, FDS, ECR and EDC all demonstrated a main effect of measurement time on raw (one way ANOVA) pre-stimulus muscle activity (Table 6.1), although, not necessarily for both testing sessions. FCR and FDS had a main effect of measurement time only during the extension fatigue sessions, while ECR only demonstrated this effect during the flexion fatigue session. EDC demonstrated a main effect of measurement time for both sessions. Despite these main effects, only ECR showed differences in post-hoc pairwise comparisons. During the flexion fatigue session, ECR pre-stimulus muscle activity significantly increased immediately post-fatigue (time of zero) compared to baseline measures (Baseline: 10.0 ± 3.5 μV, 0: 14.7 ± 5.6 μV, $P < 0.05$). Measurement time had no influence on pre-stimulus muscle activity for FCU or ECU for either fatigue session.

Table 6.1. *Results from one-way (measurement time) repeated measures ANOVAs performed separately for each collection session on raw pre-stimulus muscle activity. Outputs are listed as P-Values, F-statistics, and effect sizes (represented by Partial Eta Squared (η_p^2)).*

		FCR	FDS	FCU	ECR	EDC	ECU
Flex	*P*-value	0.54	0.60	0.14	**0.02***	**0.01***	0.07
	F-Statistic	$F_{(14,182)} = 0.92$	$F_{(14,182)} = 0.86$	$F_{(14,182)} = 1.43$	$F_{(14,182)} = 2.03$	$F_{(14,182)} = 2.12$	$F_{(14,182)} = 1.69$
	Effect Size	0.07	0.06	0.12	0.16	0.15	0.16
Ext	*P*-value	**< 0.001***	**0.02***	0.32	0.29	**< 0.001***	0.19
	F-Statistic	$F_{(14,182)} = 3.84$	$F_{(14,182)} = 1.98$	$F_{(14,182)} = 1.14$	$F_{(14,182)} = 1.19$	$F_{(14,182)} = 3.94$	$F_{(14,182)} = 1.35$
	Effect Size	0.23	0.13	0.09	0.10	0.25	0.13

Table 6.2. *Results from two-way repeated measures ANOVAs performed on pre-stimulus muscle activity normalized to baseline.*

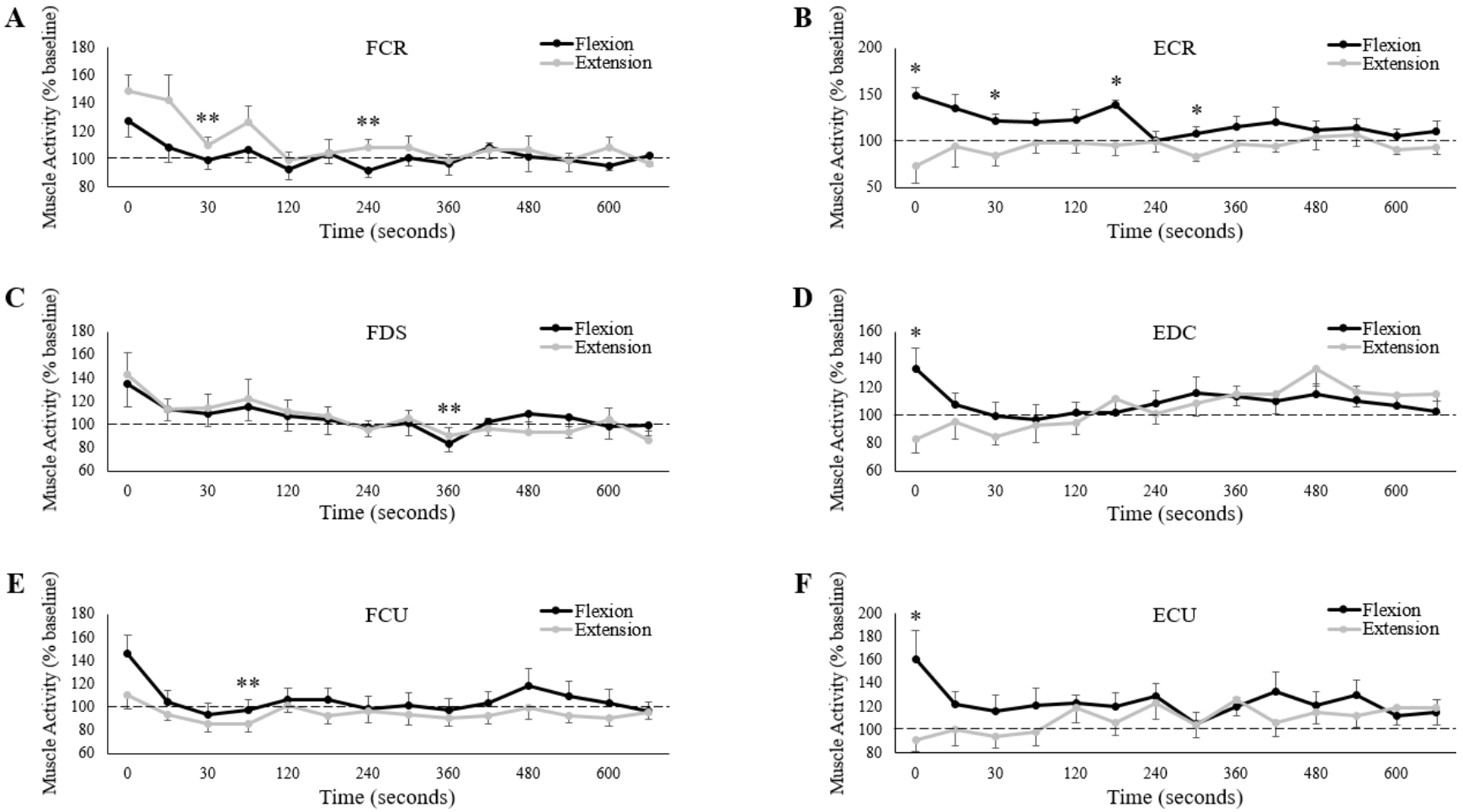
		FCR	FDS	FCU	ECR	EDC	ECU
Session	*P*-value	0.11	0.97	0.24	**0.004***	0.78	0.10
	F-Statistic	$F_{(1,13)} = 3.03$	$F_{(1,13)} = 0.002$	$F_{(1,11)} = 1.52$	$F_{(1,11)} = 13.0$	$F_{(1,12)} = 0.08$	$F_{(1,9)} = 3.34$
	Effect Size	0.19	< 0.001	0.12	0.54	0.01	0.27
Time	*P*-value	**< 0.001***	**< 0.001***	**< 0.001***	0.75	**0.001***	0.40
	F-Statistic	$F_{(13,169)} = 4.91$	$F_{(13,169)} = 4.04$	$F_{(13,143)} = 3.22$	$F_{(13,143)} = 0.71$	$F_{(13,156)} = 2.76$	$F_{(13,117)} = 1.06$
	Effect Size	0.27	0.24	0.23	0.06	0.19	0.11
Interact	*P*-value	0.51	0.94	0.68	**0.014***	**0.003***	**0.02***
	F-Statistic	$F_{(13,169)} = 0.95$	$F_{(13,169)} = 0.47$	$F_{(13,143)} = 0.78$	$F_{(13,143)} = 2.20$	$F_{(13,156)} = 2.55$	$F_{(13,117)} = 2.11$
	Effect Size	0.07	0.04	0.07	0.16	0.18	0.19

Normalized to baseline, all three wrist extensors demonstrated an interaction effect of session and measurement time on muscle activity (Table 6.2). Pre-stimulus muscle activity immediately post-fatigue (time point "0") was significantly greater during the flexion session than the extension session for ECR (Flexion: 149.0 ± 29.5% of baseline, Extension: 73.0 ± 60.9% of baseline, $P < 0.05$), EDC (Flexion: 133.2 ± 53.4% of baseline, Extension: 82.7 ± 36.4% of baseline, $P < 0.05$), and ECU (Flexion: 161.1 ± 78.9% of baseline, Extension: 91.8 ± 31.7% of baseline, $P < 0.05$). For ECR, muscle activity was also greater during the flexion session than extension at 30, 135, and 255 seconds post-fatigue ($P < 0.05$) (Figure 6.6 B). Separate one-way repeated measures ANOVAs revealed a main effect of measurement time (normalized muscle activity) for ECR during the flexion session and EDC during both sessions. However, only ECR showed any differences in pairwise comparisons from immediately post-fatigue; muscle activity was significantly lower at 600 seconds post-flexion fatigue (0: 149.0 ± 29.5% of baseline, 600: 106.2 ± 24.0% of baseline, $P < 0.05$).

Although there were no differences in normalized muscle activity between sessions for the three flexors (FCR, FDS, and FCU), all three muscles demonstrated a main effect of measurement time (Table 6.2). Post-hoc pairwise comparisons also revealed differences from the first measurement point (immediately post-fatigue) for all three muscles. For the FCR, normalized muscle activity was significantly lower at 30 (0: 138.4 ± 42.9% of baseline, 0.5: 105.0 ± 24.6% of baseline, $P < 0.05$) and 240 seconds (0: 138.4 ± 42.9% of baseline, 240: 100.2 ± 22.4% of baseline, $P < 0.05$) post-fatigue. For the FDS, normalized muscle activity was significantly lower at 360 seconds post-fatigue (0: 139.4 ± 70.4% of baseline, 360: 86.9 ± 25.6% of baseline, $P < 0.05$), while for the FCU, normalized muscle

activity was lower at 45 seconds post-fatigue (0: 128.2 ± 50.6% of baseline, 45: 100.2 ± 22.4% of baseline, $P < 0.05$).

Figure 6.6. *Group averages of normalized (% of baseline) pre-stimulus muscle activity for all six forearm muscles during a 10% handgrip force. Black/grey lines are muscle activity collected on the wrist flexion/extension fatigue sessions, respectively. Horizontal dashed lines represent baseline (pre-fatigue) values. The x-axes denote time, with "0" representing the first measurement immediately after the cessation of the fatigue-inducing trial. All unlabeled points occurred 15 seconds after the preceding time point. *denotes a significant difference between sessions at a single measurement point. **denotes a significant difference of a single measurement point (across both sessions) to "0".*


A
FCR
Flexion
Extension
Muscle Activity (% baseline)
Time (seconds)
B
ECR
C
FDS
D
EDC
E
FCU
F
ECU

6.4.4 Corticospinal excitability

All three wrist flexors, as well as EDC, demonstrated a main effect of measurement time on raw (one way ANOVA) MEP amplitudes (Table 6.3), although, only FCU was for both testing sessions. FCR and FDS demonstrated a main effect only during the extension fatigue session, while the main effect for EDC only occurred in the flexion session. Despite these main effects, there were no differences in pairwise comparisons between baseline raw MEP amplitudes and any post-fatigue measures.

Table 6.3. *Results from one-way (measurement time) repeated measures ANOVAs performed separately for each collection session on raw MEP amplitudes. Outputs are listed as P-Values, F-statistics, and effect sizes (represented by Partial Eta Squared (η_p^2)).*

		FCR	FDS	FCU	ECR	EDC	ECU
Flex	*P*-value	0.12	0.06	**< 0.001***	0.20	**< 0.001***	0.12
	F-Statistic	$F_{(14,182)} = 1.49$	$F_{(14,182)} = 1.68$	$F_{(14,154)} = 3.30$	$F_{(14,154)} = 1.33$	$F_{(14,168)} = 3.93$	$F_{(14,140)} = 1.49$
	Effect Size	0.10	0.11	0.23	0.11	0.25	0.13
Ext	*P*-value	**< 0.001***	**< 0.001***	**0.01***	0.08	0.10	0.14
	F-Statistic	$F_{(14,182)} = 3.87$	$F_{(14,182)} = 3.45$	$F_{(14,154)} = 2.15$	$F_{(14,154)} = 1.61$	$F_{(14,168)} = 1.54$	$F_{(14,140)} = 1.44$
	Effect Size	0.23	0.21	0.16	0.13	0.11	0.13

Table 6.4. *Results from two-way repeated measures ANOVAs performed on MEP amplitudes normalized to baseline.*

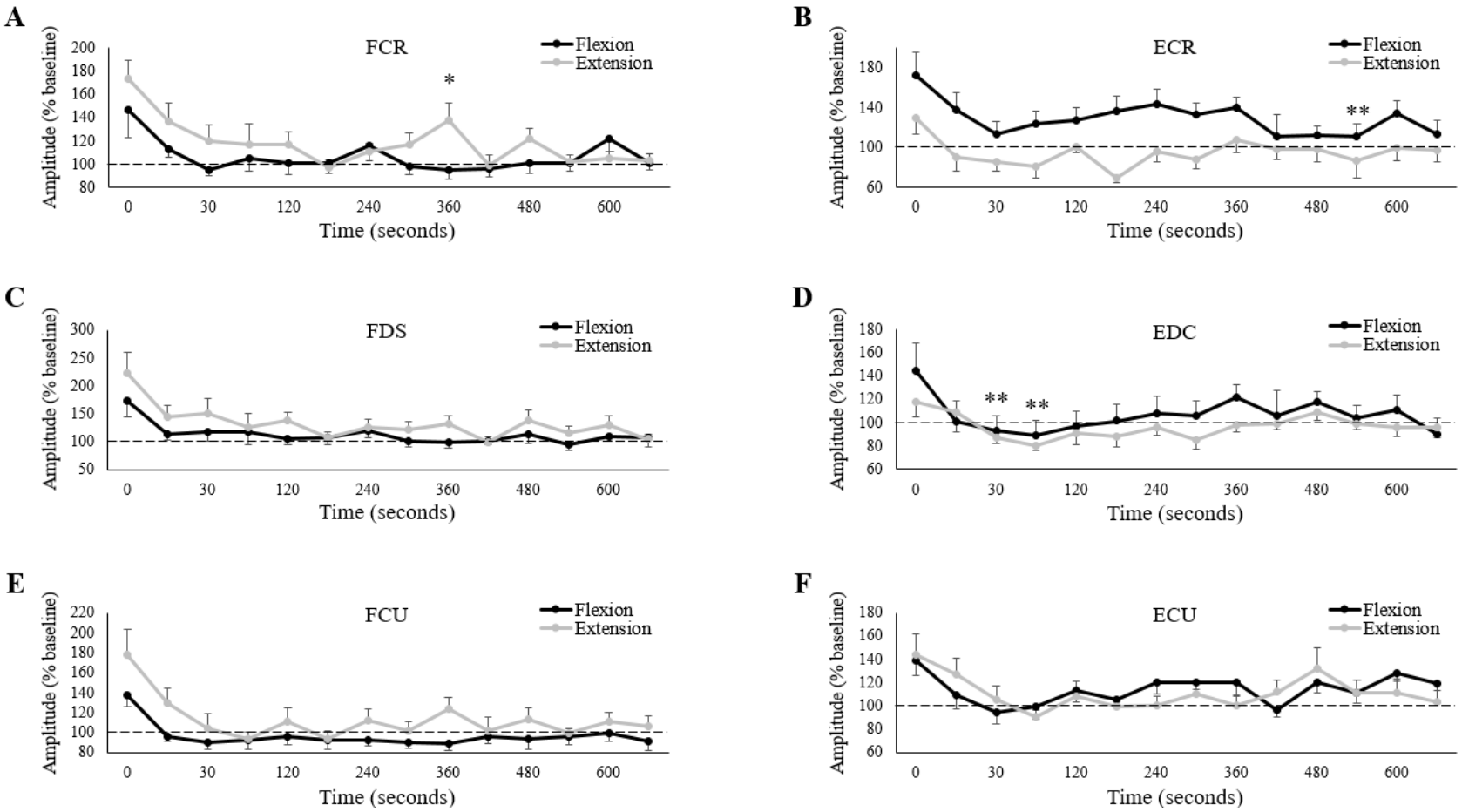
		FCR	FDS	FCU	ECR	EDC	ECU
Session	*P*-value	0.25	0.21	0.12	**0.006***	0.22	0.68
	F-Statistic	$F_{(1,13)} = 1.44$	$F_{(1,13)} = 1.73$	$F_{(1,11)} = 2.91$	$F_{(1,11)} = 11.46$	$F_{(1,12)} = 1.70$	$F_{(1,10)} = 0.19$
	Effect Size	0.10	0.12	0.21	0.51	0.12	0.02
Time	*P*-value	**< 0.001***	**< 0.001***	**< 0.001***	**0.001***	**< 0.001***	**0.002***
	F-Statistic	$F_{(13,169)} = 5.16$	$F_{(13,169)} = 5.38$	$F_{(13,143)} = 5.52$	$F_{(13,143)} = 2.95$	$F_{(13,156)} = 4.82$	$F_{(13,130)} = 2.67$
	Effect Size	0.28	0.29	0.33	0.21	0.29	0.21
Interact	*P*-value	**0.04***	0.41	0.19	0.43	0.58	0.33
	F-Statistic	$F_{(13,169)} = 1.84$	$F_{(13,169)} = 1.05$	$F_{(13,143)} = 1.35$	$F_{(13,143)} = 1.03$	$F_{(13,156)} = 0.88$	$F_{(13,130)} = 1.14$
	Effect Size	0.12	0.07	0.11	0.09	0.07	0.10

Normalized to baseline, only FCR demonstrated an interaction effect of session and measurement time on MEP amplitude (Table 6.4). Separate paired t-tests revealed that normalized MEP amplitudes were larger during the extension session than the flexion session 360 seconds post-fatigue (Figure 6.7 A). Separate one-way repeated measures

ANOVAs revealed a main effect of measurement time for both testing sessions, although there were differences in pairwise comparisons only during the extension fatigue session. Compared to immediately post-fatigue, normalized MEP amplitudes were significantly lower at 120 (0: 173.3 ± 58.8% of baseline, 120: 117.4 ± 40.8% of baseline, $P < 0.05$), 135 (0: 173.3 ± 58.8% of baseline, 135: 97.6 ± 23.5% of baseline, $P < 0.05$), and 495 (0: 173.3 ± 58.8% of baseline, 495: 102.3 ± 20.3% of baseline, $P < 0.05$) seconds post-fatigue.

All five remaining muscles demonstrated a main effect of measurement time on normalized MEP amplitudes (Table 6.4), however, only ECR and EDC showed differences in pair-wise comparisons. Compared to immediately post-fatigue, normalized MEP amplitudes were significantly lower 495 seconds post-fatigue for ECR (0: 150.9 ± 72.6% of baseline, 495: 99.1 ± 51.3% of baseline, $P < 0.05$) (Figure 6.7 B), and at 30 (0: 131.0 ± 46.8% of baseline, 30: 90.1 ± 20.5% of baseline, $P < 0.05$) and 45 (0: 131.0 ± 46.8% of baseline, 45: 84.8.1 ± 18.4% of baseline, $P < 0.05$) seconds post-fatigue for EDC (Figure 6.7 D). Lastly, ECR was the only forearm muscle that showed a main effect of session (Table 6.4), with normalized MEP amplitudes significantly larger during the wrist flexion session.

Figure 6.7. *Group averages of normalized (% of baseline) MEP amplitudes for all six forearm muscles. Black/grey lines are muscle activity collected on the wrist flexion/extension fatigue sessions, respectively. Horizontal dashed lines represent baseline (pre-fatigue) values. The x-axes denote time, with "0" representing the first measurement immediately after the cessation of the fatigue-inducing trial. All unlabeled points occurred 15 seconds after the preceding time point. *denotes a significant difference between sessions at a single measurement point. **denotes a significant difference of a single measurement point (across both sessions) to "0".*


A
FCR
Flexion
Extension
Amplitude (% baseline)
Time (seconds)
*
B
ECR
**
C
FDS
D
EDC
**
**
E
FCU
F
ECU

6.4.5 MEP/EMG ratios

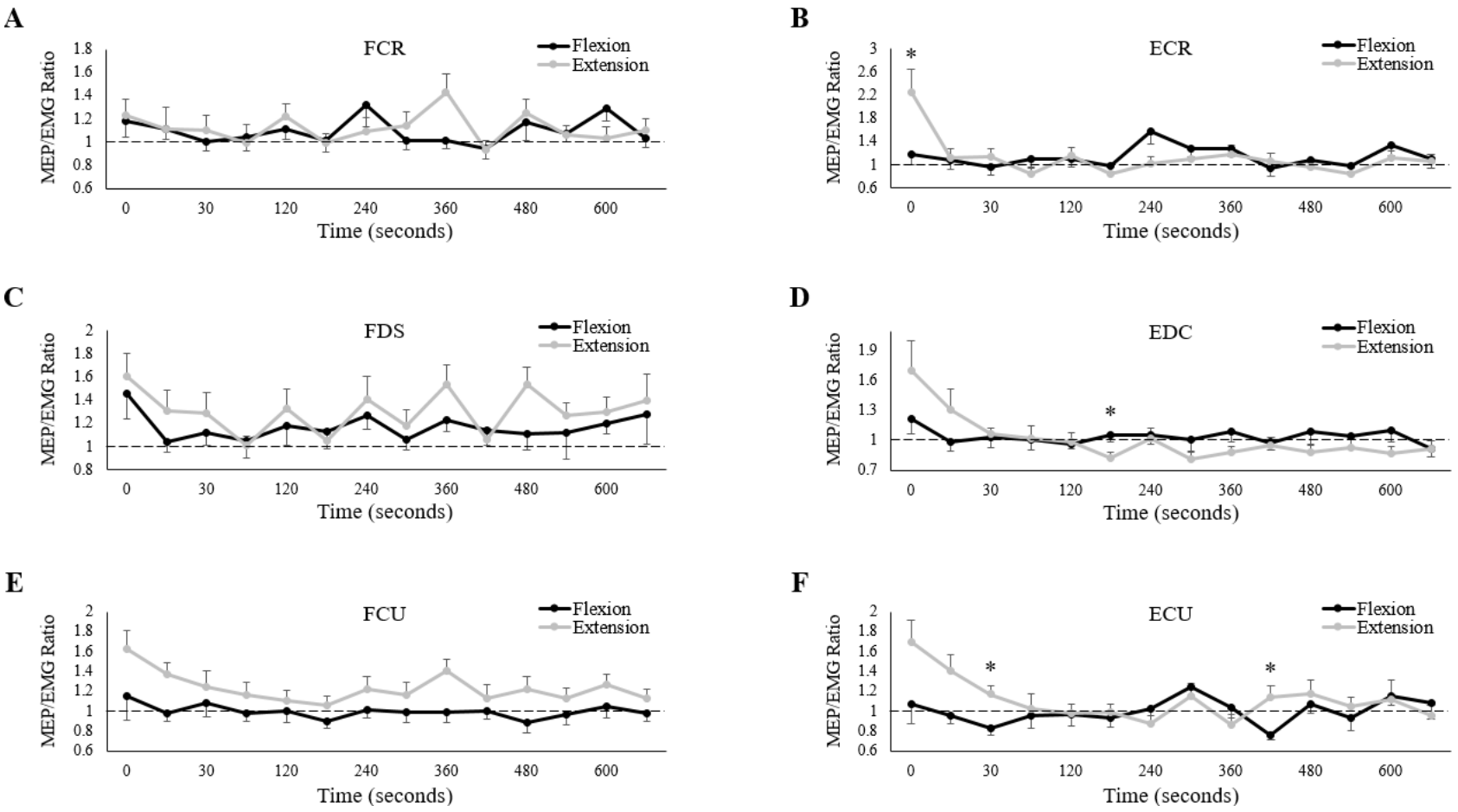
Of the three wrist flexors, only FCU demonstrated a main effect of session on MEP/EMG ratio (Table 6.5), with ratios significantly larger during the extension fatigue session. Measurement time had no influence on any of the three wrist flexors.

All three wrist extensors exhibited interaction effects of session and measurement time on MEP/EMG ratios (Table 6.5). Separate paired t-tests revealed larger ratios during the extension fatigue session for ECR immediately post-fatigue (Flexion: 1.17 ± 0.60, Extension: 2.26 ± 1.36, $P < 0.05$) and for ECU at 30 (Flexion: 0.83 ± 0.22, Extension: 1.17 ± 0.29, $P < 0.05$) and 375 seconds (Flexion: 0.76 ± 0.18, Extension: 1.14 ± 0.35, $P < 0.05$) post-fatigue (Figure 6.8). For EDC, ratios were larger during the flexion fatigue session at 135 seconds post-fatigue (Flexion: 1.05 ± 0.25, Extension: 0.83 ± 0.22, $P < 0.05$). Separate one-way repeated measures ANOVAs revealed a main effect of measurement time on MEP/EMG ratios for ECR (both sessions), EDC (only extension), and ECU (only extension), although there were no differences in pairwise comparisons for any muscle.

Table 6.5. *Results from two-way repeated measures ANOVAs performed on ratios of MEP amplitudes (% of baseline) and pre-stimulus muscle activity (% of baseline). Outputs are listed as P-Values, F-statistics, and effect sizes (represented by Partial Eta Squared (η_p^2)).*

		FCR	FDS	FCU	ECR	EDC	ECU
Session	*P*-value	0.81	0.26	**0.02***	0.90	0.75	0.16
	F-Statistic	$F_{(1,13)} = 0.06$	$F_{(1,13)} = 1.41$	$F_{(1,11)} = 6.85$	$F_{(1,11)} = 0.02$	$F_{(1,12)} = 0.11$	$F_{(1,10)} = 2.38$
	Effect Size	0.01	0.10	0.38	0.002	0.01	0.21
Time	*P*-value	0.18	0.08	0.18	**< 0.001***	**< 0.001***	**0.002***
	F-Statistic	$F_{(13,169)} = 1.55$	$F_{(13,169)} = 1.95$	$F_{(13,143)} = 1.70$	$F_{(13,143)} = 4.12$	$F_{(13,156)} = 3.43$	$F_{(13,130)} = 2.71$
	Effect Size	0.11	0.13	0.13	0.27	0.22	0.23
Interact	*P*-value	0.21	0.94	0.80	**< 0.001***	**0.012***	**0.004***
	F-Statistic	$F_{(13,169)} = 1.47$	$F_{(13,169)} = 0.46$	$F_{(13,143)} = 0.66$	$F_{(13,143)} = 3.95$	$F_{(13,156)} = 2.20$	$F_{(13,130)} = 2.56$
	Effect Size	0.10	0.03	0.06	0.26	0.16	0.22

Figure 6.8. *Group averages of MEP/EMG (both values normalized to baseline) ratios for all six forearm muscles. Black/grey lines are muscle activity collected on the wrist flexion/extension fatigue sessions, respectively. Horizontal dashed lines represent baseline (pre-fatigue) values. The x-axes denote time, with "0" representing the first measurement immediately after the cessation of the fatigue-inducing trial. All unlabeled points occurred 15 seconds after the preceding time point. *denotes a significant difference between sessions at a single measurement point.*


A
FCR
Flexion
Extension
MEP/EMG Ratio
1.8
1.6
1.4
1.2
1
0.8
0.6
0
30
120
240
360
480
600
Time (seconds)
B
ECR
Flexion
Extension
MEP/EMG Ratio
3
2.6
2.2
1.8
1.4
1
0.6
*
0
30
120
240
360
480
600
Time (seconds)
C
FDS
Flexion
Extension
MEP/EMG Ratio
2
1.8
1.6
1.4
1.2
1
0.8
0
30
120
240
360
480
600
Time (seconds)
D
EDC
Flexion
Extension
MEP/EMG Ratio
1.9
1.6
1.3
1
0.7
*
0
30
120
240
360
480
600
Time (seconds)
E
FCU
Flexion
Extension
MEP/EMG Ratio
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0
30
120
240
360
480
600
Time (seconds)
F
ECU
Flexion
Extension
MEP/EMG Ratio
2
1.8
1.6
1.4
1.2
1
0.8
0.6
*
*
0
30
120
240
360
480
600
Time (seconds)

Discussion

This is one of the first studies to have examined sustained MVCs performed by opposing muscle groups (wrist flexors/extensors) and their influence on muscle activity and corticospinal excitability. Additionally, this is perhaps the most robust investigation of performance fatigability assessed in a separate motor task (hand-gripping) than what was used to induce fatigue (wrist exertions). While results demonstrated that performance fatigability changed muscle activity in all forearm muscles to some extent, these adaptations were more complex in the wrist extensors. Motor pathway excitability was also influenced by sustained MVCs, although only FCR and ECR showed differences in normalized MEP amplitudes between sessions. When the changes in MEPs were normalized to the changes in muscle activity, there were notable differences between fatigue sessions. For the wrist extensors in particular, MEP/EMG ratios were significantly larger following wrist extension fatigue, suggesting that supraspinal excitability may have been elevated. These collective results suggest that the effects of performance fatigability may be motor-task specific.

6.5.1 Muscle activity

As performance fatigability develops, the discharge rate of motor units decreases (Bellemare et al., 1983; Bigland-Ritchie et al., 1983a; Marsden et al., 1971). If the sustained contraction is maximal, this reduced firing frequency will result in gradual force and muscle activity loss (B. Bigland-Ritchie et al., 1986b; Enoka, 1995). However, in sustained submaximal contractions, muscle activity can increase if force output remains constant (Bigland-Ritchie et al., 1981; Edwards and Lippold, 1956). This is made possible by an

increase in motor unit recruitment (B. Bigland-Ritchie et al., 1986a; Person and Kudina, 1972) that ensures sufficient force production in the presence of slower motoneurons. Considering these findings, it was hypothesized that **1)** wrist extensor muscle activity would increase *equally* between testing sessions, but also **2)** that wrist flexor activity would only increase following sustained wrist flexion. To recap, the wrist extensors contribute more to wrist joint stiffness than the flexors (Holmes et al., 2015). Consequently, the wrist extensors are more active during isolated wrist flexion than the wrist flexors are during isolated wrist extension (Forman et al., 2019b). It was therefore anticipated that the wrist extensors would fatigue equally regardless of session. In contrast, the wrist flexors would be mostly inactive during sustained wrist extension.

However, the present findings dispute these hypotheses. There was no difference in muscle activity during hand-gripping between sessions for any of the wrist flexors, while for the wrist extensors, muscle activity was actually greater following sustained wrist flexion than extension. Perhaps most interesting, ECR, EDC, and ECU produced 27.0, 17.3, and 8.2% less muscle activity than baseline, respectively, immediately following sustained wrist extension, although these decreases were not statistically significant (Figures 6.6 B, D, and F). This final point begs the question, why did extensor muscle activity not increase following sustained wrist extension? Unfortunately, drawing comparisons to previous literature is challenging, given that studies typically examine performance fatigability in the same motor task that was used to induce fatigue (Gandevia, 2001; Sidhu et al., 2013). What can be said is that, during low-intensity hand-gripping, the central nervous system seemingly employs unique control strategies for the wrist flexors and extensors following fatigue of the forearm. Included in this strategy, the activity of the

wrist extensors does not increase following sustained wrist extension. Our explanations for this finding are proposed below.

Fatigue specificity: Fatigue was induced by sustained wrist flexion or extension MVCs, but muscle activity was assessed while participants exerted 10% of their maximal handgrip force. While research has demonstrated that muscle activity and certain neurological measures can be state, intensity, and muscle dependent following fatigue (Gandevia, 2001; Søgaard et al., 2006; Taylor and Gandevia, 2008), it is intuitive to suggest that they might be task-dependent as well. Not just in terms of the task used to induce performance fatigability but also in terms of the task in which measurements are conducted. For instance, it is possible that handgrip force as low as 10% of maximum can be produced mostly with intrinsic finger muscles–muscles that may not have been fully recruited during maximal wrist exertions. Thus, the muscles that were active during the handgrip task may not have been effectively fatigued during isolated wrist extension. Alternatively, to compensate for this post-fatigue decrease in extensor activity, contributions from other muscles (such as the extensor pollicis longus, which lies deep to the ECR and was not assessed) may have increased. Subsequent investigations utilizing indwelling EMG would add valuable insight to this possibility.

Metabolic optimization: Motor outputs are optimally executed when there is an appropriate balance of joint stability (greatest contribution to joint stability produced by muscle contraction) and metabolic expenditure (Burdet et al., 2001; Hogan, 1984). Prior to fatigue, the level of wrist extensor activity in the present study was theoretically optimal in magnitude and energy expenditure to counter the forces produced by the flexors. However, following wrist extension fatigue, not only would greater motor unit recruitment of the

extensors have been needed to exert the same level of co-contraction (since motoneuron discharge rates were likely reduced), but available energy reserves would have also been reduced. Thus, exerting similar baseline forces would cost more energy in a moment of reduced availability. It is therefore possible that wrist joint stability, provided by the wrist extensors, decreased in favour of energy expenditure. While support for this possibility is scarce, some studies have shown that co-contraction (Missenard et al., 2008a), limb impedance (Selen et al., 2007), and joint stiffness (Dutto and Smith, 2002) all decrease following fatigue. It should be noted that these studies were all conducted during dynamic reaching, not isometric conditions. However, antagonist muscle activity also increases less post-fatigue than agonist activity during isometric actions of the torso (Potvin and O'Brien, 1998).

Forearm co-contraction: The suggestions raised above were likely present following the wrist flexion session as well. Thus, it is unclear why extensor muscle activity only increased following the wrist flexion session. Since the wrist flexor muscles demonstrate little activity during isolated wrist extension (Forman et al., 2019b), sustained wrist extension may have only induced fatigue in the wrist extensor muscles. Thus, a feasible reduction in extensor co-contraction (for metabolic purposes) may have been compensated for by other, non-fatigued muscles. In contrast, the wrist extensors are highly active during isolated wrist flexion (Forman et al., 2019b), meaning that performance fatigability was likely induced in the entire forearm following sustained wrist flexion. If so, any reduction in wrist extensor co-contraction might have adversely decreased wrist joint stability. As other forearm muscles (predominantly the wrist flexors) were also likely fatigued, and unable to compensate, wrist extensor co-contraction may have increased out

of necessity. Thus, muscle activity in all three extensors was higher following sustained wrist flexion than sustained wrist extension.

6.5.2 Corticospinal excitability

Compared to baseline, resting MEP amplitudes elicited in hand and forearm muscles increase *immediately* post-fatigue (Liepert et al., 1996; Samii et al., 1996). These measures decrease at approximately 15 seconds and can remain reduced for as long as 30 minutes (Samii et al., 1996; Zanette et al., 1995). It is suspected that the initial increase in corticospinal excitability is due to an increase in supraspinal excitability, given that spinal excitability, measured through motoneuron current injection (Kernell and Monster, 1982b; Sawczuk et al., 1995a) and cervicomedullary evoked potentials (CMEPs) (Taylor et al., 1996), decreases immediately post-fatigue (although this finding is muscle-dependent (Giesebrecht et al., 2010)). These findings suggest that spinal excitability is reduced following a sustained contraction but is compensated for by increased supraspinal excitability to ensure adequate motor unit recruitment and volitional drive (Gandevia, 2001). The latter half of this statement needs further investigation, given that voluntary activation decreases (Löscher et al., 1996a, 1996b; Zijdewind et al., 1998) and that some measures of cortical inhibition increase following fatigue (*see below*).

Our hypotheses regarding MEP amplitudes matched our hypotheses for muscle activity, in that post-fatigue MEPs would increase similarly after each session for the wrist extensors, while MEPs would increase to a greater extent for the wrist flexors following wrist flexion fatigue. However, our findings did not support these hypotheses. There was a tendency (only FCR and ECR were significant) for post-fatigue MEP amplitudes to be

larger in the wrist flexors following wrist extension (grey dots larger than black; Figures 6.7 A, C, and E), while for the wrist extensors (excluding ECU), MEP amplitudes tended to be larger following wrist flexion (black dots larger than grey; Figures 6.7 B and D). Collectively, these results might indicate that corticospinal excitability increases more when forearm muscles are fatigued as the antagonists. However, corticospinal excitability tends to increase with muscle activity (Di Lazzaro et al., 1998c; Ugawa et al., 1995b). In the present study, where the "measurement task" was different than the "fatigue task", there were complex changes in muscle activity post-fatigue (Figure 6.6). It was therefore important to consider changes in MEP amplitudes in relation to changes in muscle activity (Figure 6.8).

When normalized to muscle activity, MEP amplitudes in the extensors tended to be greater immediately following wrist extension fatigue. This suggests that corticospinal excitability was relatively greater on the wrist extension day, and thus, the extensors may have been fatigued to a greater extent than on the wrist flexion day. Counter to our hypothesis, this would indicate that the stabilizing function of the wrist extensors (as antagonists) does not result in equivalent fatigue development compared to agonistic muscle actions. Increased supraspinal excitability almost certainly explains this increase, as spinal/motoneuron excitability decreases following fatigue (at least, for the agonist muscle) (Butler et al., 2003; Martin et al., 2006; McNeil et al., 2011, 2009). The basis for an increase in supraspinal excitability is currently unclear. Given that voluntary activation is reduced following fatigue, it stands to reason that volitional drive, and therefore cortical excitability, must be impaired (Gandevia, 2001; Sidhu et al., 2013). Literature of underlying mechanisms both supports and opposes this notion. Several studies have shown

that cortical inhibition may increase following fatigue. Corticospinal silent periods (CSPs), thought to be indicative of cortical inhibition (via $GABA_B$ receptors and inhibitory interneurons (Inghilleri et al., 1993; Siebner et al., 1998)), increase following fatigue (Hunter et al., 2008; McNeil et al., 2009; Taylor et al., 1996). EMG suppression, elicited via subthreshold TMS, similarly increases post-fatigue (Seifert and Petersen, 2010), while resting intracortical facilitation (ICF) decreases (Hunter et al., 2016; Tergau et al., 2000). Additionally, more direct evidence has shown that I waves (repetitive, descending volleys of active pyramidal tract neurons) are reduced in size immediately post-exercise, although it cannot be confirmed to which muscle the I waves are travelling to (Di Lazzaro et al., 2003). However, there is also evidence that cortical excitation increases following fatigue. Separate investigations have found no change in ICF following fatigue, while short-interval intracortical inhibition (SICI) decreases following fatigue (Hunter et al., 2016; Maruyama et al., 2006; Vucic et al., 2011). Thus, interpretations of increased supraspinal excitability remain difficult to decipher. It is mostly accepted, however, that said increases indicate the development of fatigue, which occurred in the wrist extensor muscles of the present study.

Interestingly, there were no differences in normalized MEP amplitudes between sessions for either the FCR or FDS; our hypothesis that the wrist flexors would exhibit greater fatigue during the wrist flexion session was therefore not supported. However, in the case of FCU, MEP amplitudes were relatively larger following the wrist extension session (Table 6.5 and Figure 6.8 E). This finding was surprising, and given known forearm muscle recruitment patterns, it is challenging to explain. One possibility that deserves discussion is the notion of "cross-over" effects of fatigue. While wrist flexion and extension fatigue sessions were performed on separate days to "isolate" the wrist flexors and

extensors, respectively, it is difficult to truly isolate a single muscle group while performing a normal human motor task. Not only will the antagonist muscle(s) provide co-contraction during the "isolated" agonist actions, but strong evidence also indicates that performance fatigability can manifest globally (Halperin et al., 2014; Rattey et al., 2006; Zijdewind et al., 1998). For instance, fatigue induced in the elbow flexors modulates corticospinal excitability in the contralateral upper-limb (Aboodarda et al., 2016) and the knee extensors (Aboodarda et al., 2015b). Similarly, fatigue induced in the knee extensors modulates corticospinal excitability in the elbow flexors (Aboodarda et al., 2017; Behm, 2016). These changes are frequently attributed to central mechanisms (possibly increased activity of group III/IV afferents (Amann et al., 2013)), given a lack of peripheral changes in the non-exercised muscles. Thus, in the present study, it is highly likely that fatigue-inducing wrist flexion modulated the wrist extensors through this cross-over effect, and vice-versa. The surprising responses of the wrist flexors may therefore be the result of not only their functional roles during wrist exertions, but also a cross-over effect of the contracting extensors.

6.5.3 Additional mechanisms

Since no independent measures of spinal or peripheral excitability were utilized in this study, attributing modulations in motor pathway excitability to specific sources is limited. That said, alterations in spinal pathways likely occurred to some extent. There is abundant support that muscle spindle discharge rates (which facilitate motoneurons) decrease during sustained efforts (Macefield et al., 1991; Vallbo, 1974). This disfacilitation is thought to partially contribute to reduced motoneuron excitability. The behaviour of

golgi tendon organs (GTOs) following fatigue is less clear, although some research has shown a reduced sensitivity to passive muscle stretch (Hutton and Nelson, 1986; Smith et al., 1974). Intrinsically, motoneuron discharge rates decrease with sustained current injection (Kernell and Monster, 1982b, 1982a), while the motoneuron itself becomes less responsive to afferent and descending excitation (Brownstone et al., 1992; Sawczuk et al., 1995b). These mechanisms contribute to a collective decrease in spinal excitability, and, in studies utilizing stimulation techniques (such as the H-reflex and CMEPs), spinal excitability decreases post-fatigue (Butler et al., 2003; Garland and McComas, 1990; McNeil et al., 2011). These changes almost certainly influence MEP amplitudes and might exert unique influences between agonist or antagonist fatigue-inducing contractions. Such differences could explain some of the behaviour of forearm muscles in the present study. Future investigations assessing spinal excitability would represent a meaningful improvement on this work.

Lastly, it is mostly accepted that the propriospinal system in humans influences motor outputs by relaying (and subsequently altering) descending and afferent signals to spinal motoneurons (Pierrot-Deseilligny, 2002). The activity within this system is measurable via stimulation of cutaneous afferents and recording the ensuing suppression of voluntary muscle activity (Burke et al., 1994). In the ECR, this suppression increases following sustained wrist extension MVCs but decreases in the coactive triceps brachii (Martin et al., 2007). Greater suppression of muscle activity is thought to indicate an increase in inhibition acting upon propriospinal neurons. Thus, propriospinal contributions to descending drive may be impaired following fatigue, at least to the agonist muscle. In the present study, changes to propriospinal activity may have contributed to both

corticospinal excitability and muscle activity measures, although further research is needed to confirm this.

6.5.4 Methodological considerations

TMS intensity was established based solely on the FDS motor threshold. This follows publications in the field that report on multiple sites despite setting stimulation intensities to just one (Forman et al., 2019a; Nuzzo et al., 2016; Perez and Rothwell, 2015; Spence et al., 2016). This is noteworthy for the following reason: while +20% of motor threshold was sufficient to elicit MEPs in all six forearm muscles, motor threshold was found only in FDS. Thus, it is unclear if TMS intensity was 20% greater than the motor thresholds for the remaining five muscles. Small variations in motor thresholds likely exist between muscles, and if so, TMS would have activated slightly different portions of the available motor pool for each muscle. While it is unlikely that this effect fundamentally altered the findings of the present study, it nevertheless deserves mentioning.

Secondly, given the known differences of how maximal versus submaximal contractions influence central (Taylor and Gandevia, 2008) and peripheral (Smith et al., 2007; Søgaard et al., 2006) pathways, the results of the present study should not be generalized to lower intensity fatiguing tasks. Likewise, as this study induced fatigue through an isometric contraction, these findings should not be generalized to fatiguing dynamic contractions.

Finally, fatigue was induced while participants maintained an open hand/extended fingers. This was done in the hopes of isolating wrist flexor and extensor muscle contractions. For instance, had a closed hand been used, participants may have squeezed

their fist during the wrist extension session. At the very minimum, FDS activity would likely have been high throughout the fatigue-inducing trial, and thus, any differences between sessions might have been difficult to decipher. However, a closed hand is likely more applicable to actions of the workplace. Typically, fatigue of the distal upper-extremity develops while the hand is gripping or manipulating some sort of object. Had a closed hand been used (or should it be used in the future), results might have differed.

Conclusion

Sustained wrist flexion and extension did not result in similar increases of wrist extensor muscle activity during hand-gripping. Rather, a complex adaptation in forearm muscle recruitment was observed, with extensor activity higher as the antagonists. In contrast, fatigue session had no influence on the wrist flexors. It is possible that a combination of fatigue-specificity and co-contraction optimization contributed to these results. When MEPs were normalized to muscle activity, corticospinal excitability of the wrist extensors was higher following the wrist extension session, while for FCU, responses were surprisingly higher following wrist extension. These increases likely indicate elevated supraspinal excitability, which may be the result of intracortical processes. While possible cross-over effects of fatigue may have contributed to experimental findings, the surprising behaviour of certain forearm muscles remains difficult to explain. The complexity of these results suggest that previous conclusions regarding corticospinal behaviour following fatigue may not apply when the fatiguing task and the measurement task are different. This highlights the need for further research on the specificity of performance fatigability.

Chapter 7. Final comments

Summary of thesis findings

In Chapter 3, the muscle activity of the wrist flexors and wrist extensors exhibited similar characteristics to what has been reported in literature. This occurred despite the added experimental complexity of this protocol, whereby handgrip forces and wrist exertions were performed simultaneously. Across all experimental conditions, the wrist extensors demonstrated static behaviours, whereby changes in task parameters resulted in relatively small changes to extensor muscle activity. In contrast, wrist flexor muscle activity was highly task-dependent and changed to a much larger extent with changes in task parameters than the extensors (as noted by larger effect sizes). Co-contraction was significantly greater during palmar forces than dorsal forces for nearly all experimental conditions, which was driven by the more active extensors. These findings were nearly identical to those found in Chapter 4, where muscle activity was examined during dynamic wrist flexions and extensions. Although nearly every muscle demonstrated an interaction effect between force direction (flexion and extension) and movement phase (concentric and eccentric), the effect sizes of these factors were generally larger for the flexors than the extensors. Co-contraction was also significantly greater during dynamic wrist flexion than dynamic wrist extension, which was driven by the more active wrist extensors. Although this was not an original hypothesis, and so no statistical test was conducted, the wrist extensors (even as the antagonists) were sometimes more active than the wrist flexors during dynamic wrist flexion. Contrary to our hypothesis, posture had almost no influence

on muscle activity in the forearm muscles, with only ECU demonstrating a three-way interaction.

In Chapter 5, nearly every hand-tracking performance metric worsened immediately following fatigue. These reductions in hand-tracking accuracy recovered quickly, with most metrics not significantly different from baseline following just one minute of recovery. However, there were surprisingly no differences in post-fatigue metrics between the sustained wrist flexion and sustained wrist extension sessions. This may have occurred as a result of the unique wrist flexor/extensor functions, whereby the wrist extensors are typically active to a high degree regardless of the hand/wrist task. It was therefore possible that the wrist extensors fatigued as the prime movers during the wrist extension session, but also fatigued as the co-contracting antagonists during the wrist flexion session (although, to a lesser extent). This possibility was explored in Chapter 6, where muscle activity and corticospinal excitability were assessed in the forearm muscles following sustained wrist flexion and sustained wrist extension MVCs. Interestingly, the results of this study failed to support a single hypothesis. While wrist extensor activity was expected to increase equally following both fatigue sessions, it instead increased only following the flexion session. It even decreased following the wrist extension session, although this decrease was not significant. When corticospinal excitability was normalized to muscle activity, there were still differences between sessions for the three wrist extensors. However, in this measure, signs of fatigue were more pronounced following the wrist extension fatigue sessions. The behaviour of the wrist flexors was also unexpected. With the exception of MEP/EMG ratios for the FCU, there were almost no differences in

either muscle activity or corticospinal excitability between sessions for the three wrist flexors.

Implications

Chapter 3 and Chapter 4 assessed forearm muscle activity in perhaps the most extensive protocols to date, including one of the first investigations into forearm muscle recruitment during dynamic contractions. However, the main study outcomes largely supported previous research. The most important finding was that the wrist extensors were always active to at least a moderate degree, regardless of handgrip forces, wrist torques, torque directions, postures, movement phases, or whether the extensors were contracting as the agonists or the antagonists. This is concerning from an occupational ergonomics and overuse injury perspective. One of the primary methods for mitigating overuse injury risks is to reduce duty cycles, which both reduces the duration of mechanical loading and increases rest time. With less loading and more rest, stressed tissues are given adequate time to recover. For muscles that demonstrate task-dependent characteristics, such as the wrist flexors, this can be accomplished by simply varying the motor tasks performed throughout the work day. In some tasks, the muscles will be highly active, but in others, there will be breaks in activity. This doesn't seem to be the case for the wrist extensors, which will be active during any task of the distal upper limb. Thus, adequate rest periods can only be accomplished by complete cessation of work, which is particularly challenging in today's workforce that is increasingly reliant on technology. A "break" from regular work may include interactions on a cell phone that would likely recruit the wrist extensors to at least a low level of activity. If work-related tasks are already hand/wrist dominant,

then individuals in these scenarios are never truly resting. Of all the implications derived from this thesis, this issue is perhaps the most complex to address.

However, from a performance perspective, Chapter 5 demonstrated that fatigue induced through sustained wrist flexion or sustained wrist extension results in similar accuracy impairments. This remains surprising, given the unique recruitment patterns found in Chapters 3 and 4 between these two muscle groups. The most probable implication is that it may be challenging, if not outright impossible, to isolate fatigue to the wrist flexors, since the wrist extensors will remain highly active through co-contraction even during pure wrist flexion tasks. If this was the case, it was expected that signs of fatigue in the wrist extensors would manifest equally between sessions in measures of muscle activity and corticospinal excitability. However, in Chapter 6, the complete opposite outcome was observed. Muscle activity and corticospinal excitability to the wrist extensors were influenced differently by fatigue session but were mostly similar in the wrist flexors. It is entirely possible that the unique experimental protocol drove this finding, in that fatigue was induced by isolated wrist exertions, but signs of fatigue were measured during low handgrip forces. The vast majority of fatigue literature tends to use a more specific approach, where signs of fatigue are measured either at rest or within the same motor task that induced fatigue. The implication presented here is that previous research using this approach may not be applicable to motor tasks which are different than the fatigue task. In other words, signs of fatigue may be task-dependent.

Future directions

With the findings of Chapter 3 and Chapter 4, there is now a substantial body of evidence that the wrist extensors function chiefly as wrist stabilizers. As stated in the previous *Implications* section, this is concerning from an injury-risk perspective. If the wrist extensors never exhibit breaks in activity during tasks of the hand and/or wrist, then they are at a far greater risk of developing chronic overuse injuries. It is recommended that future research regarding forearm muscle recruitment addresses this issue. In particular, methods for reducing wrist extensor activity in occupational settings should become a primary focus. Alternatively, explorations into preventative training strategies may also yield important findings. If the wrist extensors are chronically active, then strengthening these muscles may reduce how active they are during normal tasks of the distal upper-limb. For instance, in the 2003 paper by Mogk and Keir, it was reported that participants with stronger handgrip forces tended to exhibit less forearm muscle activity during an absolute gripping task of 50 N. While this statement is intuitive, it highlights the fact that stronger individuals can recruit fewer motor units to accomplish the same absolute task as weaker individuals. Thus, strength may provide a protective barrier to the vulnerable wrist extensors. This possibility should be extensively explored.

Chapter 5 and Chapter 6 represent an essential first step into understanding the consequences of forearm fatigue on performance and the underlying mechanisms that drive them. However, it is important to note that the fatigue-inducing tasks of these studies are hardly applicable to tasks of the workplace or of daily living. Individuals simply don't reach exhaustion by exerting a maximal sustained isometric contraction for up to two minutes at a time. Fatigue in occupational settings typically develops during the repetitive

completion of lower-intensity tasks over a much longer period of time. Additionally, while fatigue can develop from sustained isometric contractions, particularly in postural muscles, there are many workplace settings where fatigue develops as a result of repetitive dynamic contractions. Future research should seek to explore these fatiguing paradigms which more closely mimic real-world tasks.

Finally, as stated in the *Implications* section, the unexpected findings of Chapter 6 almost certainly arise from a task-dependency of fatigue, where the signs of fatigue developed in one task may not translate to another. This possibility currently lacks empirical support, given that literature has not examined the transferability of fatigue to other motor tasks that share similar muscle actions. If research is to fully understand the mechanisms behind fatigue development, then this notion should be directly explored by future investigations.

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