4-21-2022 10:30 AM

Increased corticospinal inhibition following submaximal and maximal muscle activation in humans

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Kinesiology

Abstract

Following short duration, high intensity muscle activation, there is an enhancement of muscle contractile properties, termed postactivation potentiation (PAP). Corticospinal inhibition, assessed by an increased silent period (SP), was shown previously to increase following voluntary or electrically evoked PAP. Although these changes coexist, the direct effect of PAP on corticospinal inhibition has not been systematically evaluated. In 10 participants, SP duration was measured pre and post 10s maximal and submaximal, voluntary and electrically stimulated contractions. Following maximal contractions, mean twitch torque was enhanced ~180% with no enhancement at submaximal levels (~102%). The SP duration was prolonged following all conditions: ~12% post maximal voluntary and stimulated contractions, and ~5% post submaximal voluntary and involuntary contractions. These findings show that corticospinal inhibition is increased not only when the muscle is enhanced by PAP, but also following submaximal efforts inducing no PAP. Therefore, likely indicating that increases in corticospinal inhibition arise likely from afferent feedback relating to activation of the muscle rather than changes in intrinsic contractile states (PAP) per se.

Key Words

Transcranial magnetic stimulation, silent period, corticospinal tract, postactivation potentiation, posttetanic potentiation, electromyography.

Lay Summary

Muscle function is enhanced following a short duration (<10s) high force (>75% maximal force) contraction for up to 10 minutes. This enhancement is called postactivation potentiation (PAP) and it can be induced after either voluntary, or involuntary contraction. Whether PAP in the muscle has any direct effect on neural drive from the motor cortex is not known. Magnetic brain stimulation of the motor cortex causes a twitch-like response at the muscle known as a motor evoked potential (MEP). After the MEP, neural drive to the muscle is briefly interrupted ~100-300ms, this is known as the silent period (SP). The duration of the SP is used as a measure of inhibition in the motor pathway of the central nervous system. The purpose of this study was to observe changes in inhibition (SP) following high intensity contractions that cause PAP and contrast it with low intensity contractions that do not cause PAP enhancement. In 10 participants (4 females, 6 males) the SP response was measured before and after voluntary and electrically stimulated contraction of the muscle for 10s either inducing PAP, or not. Regardless of PAP, an increase in SP time occurred in all conditions. These results indicate that PAP enhancement does not in itself directly cause increased inhibition and is more likely the activation of the muscle causing this greater inhibition in central nervous system.

Co-Authorship Statement

A.D.P, A.M.Z, and C.L.R. conceived and designed the research study; experimental data were collected and analyzed by A.D.P.; A.D.P and C.L.R interpretated results of experiments. A.D.P prepared figures; A.D.P and C.L.R drafted manuscript. A.D.P, A.M.Z., and C.L.R edited and revised manuscript; A.D.P, A.M.Z, and C.L.R approved the final version of the manuscript.

Acknowledgements

It has been a wonderfully strange and fortuitous trip getting to this point. I think my younger self would be proud of what we have completed thus far and would be excited for the ensuing chapter ahead. Along the way many individuals have provided me with their own unique support, without which I surely wouldn't be where I am sitting today (in my swivel chair with lumbar support pillows). I am lucky to have such brilliant family and friends to learn from and live with.

Firstly, I'd like to thank my lab mates (listed by age because that's what Jacob would want). Mike, it's a shame you won't be joining me in BC, your cool temperament, ability to apply knowledge, and pizza making skills are next to none. Eric, your intellect was intimidating but pushed me to work hard, your tough exterior does not hide your soft and kind nature. Jacob, you never fail to put a smile on my face and make this lab feel like home, your resilience is truly remarkable. Zero, your drive and resolve to make your aspirations become reality never fail to impress, thank you putting up with me and teaching me the ropes. Sohum, you have innate intelligence and don't have guilt from eating animals, thanks for always participating in pilot tests (I know you loved tetanus).

Secondly, I'd like to thank Dr. Charles "Rice-man" Rice. I could have not asked for a better person to introduce me into the world of academics and teach me the skills necessary for future success. To name one example: reading to the end of emails. I consider myself extremely fortunate to have found a mentor who shares similar interests, disposition, and love for "old and gold" music. You manage to take the best in people and let their abilities develop and shine uniquely. You are the G.O.A.T. professor and bow to no mortal.

Last but not least, I'd like to thank my friends and family. Although I know my friends won't read this, I would still like to thank you all for making my life interesting at every turn, even if it leads to trouble #2k14. To my family, Adam, you started me out on this path and for that (and always feeding me) I am forever grateful. I'm thankful I had the opportunity to get closer with you and bridge the 9.5-year age gap, you're an amazing person. Annie, you have been my faithful editor and consigliere in anything that I had to write for the past 10 years, I likely would have failed many classes if it wasn't for you. I believe I may have the best sister on Earth. Andrew, my partner in crime and homie since day one, I can always count on you to either pump up my tires or put me into my place. Your support means the world to me, calling what I do "cool" even though we both know that it's extremely nerdy. Finally, to my parents, words cannot express my thanks to you. Your never-ending support and love shaped me into the man I am today. Thank you for teaching me the importance of hard-work and kindness. I am blessed to have you both.

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List of abbreviations

ADP – activity dependent potentiation

ADP – adenosine diphosphate

ANOVA – analysis of variance

ATP – adenosine triphosphate

[Ca^{2+}] – calcium concentration

CaM – calmodulin

CC – conditioning contraction

FDI – first dorsal interosseus

ITT – interpolated twitch technique

MLCK – myosin light chain kinase

M_{max} – maximal M-wave

MRLC – myosin regulatory light chain

MU – motor unit

MVC – maximal voluntary contraction

N – newtons

PAP – postactivation potentiation

Pi – phosphate

Pt – peak twitch force

PTP – post-tetanic potentiation

RMS – root mean square

ROM – range of motion

RFD – rate of force development

sEMG- surface electromyography

SP –silent period

SR – sarcoplasmic reticulum

TMS – transcranial magnetic stimulation

T-tubules – transverse tubules

VA – voluntary activation

Chapter 1

1 Literature Review

1.1 General Introduction

Without the central nervous system (CNS) providing neural input to muscles, purposeful movement would not be possible. Likewise, without muscle receiving and responding to chemo-electrical signals, we would be an immobile mass of consciousness. It is the interplay of the nervous and skeletomuscular systems which enable humans to interact with our environment and respond accordingly to the demands of a situation. This relationship is of paramount importance to live, and as such the human body acts accordingly to limit suboptimal expenses of the body's energy and resources. An example of this interplay is evident during the state of muscle fatigue in which several mechanisms within the muscle provide feedback to the CNS to inhibit drive to the muscle. Conversely, when the muscle is in an enhanced state, much less in known about whether feedback to the CNS alters neural drive.

1.2 Electromyography

Surface electromyography (sEMG) is a non-invasive technique used to measure the electrical potential generated by a muscle. Recordings are completed by placing electrodes on the skin overlying the muscle belly and grounding the body with an electrode attached to the skin overlying a bony or an electrically neutral structure (tendon). In a monopolar setup an 'active electrode' is placed on the muscle and a second 'reference' electrode is placed on an electrically neutral location. This setup allows for a large area from which to record the electrical activity associated with muscle activation. The myoelectric activity (sEMG) represents the activity from the recruited motor units (MU).

Muscles are composed of numerous MUs, which are defined as the motor neuron originating in the spinal cord and the muscle fibers they innervate (Liddell & Sherrington, 1925). Contractile output by a muscle is controlled by both the recruitment and modulation of firing rates (rate coding) of active MUs (Heckman & Enoka, 2012). Using sEMG, one cannot discriminate

between the relative contribution of recruitment and rate coding; however, the observed electrical signal is representative broadly of the neural drive activating the muscle over time (De Luca, 1997). Although sEMG is a useful tool to assess global muscle activity, it is not without its limitations. This technique is affected by several factors such as subcutaneous tissue thickness, interelectrode distance, skin impedance, and electrode shifts (Farina, 2006; Kamen & Gabriel, 2010). When these limitations are appreciated, sEMG enables a valuable view into the neural control of muscle contraction.

1.3 Transcranial Magnetic Stimulation

Electrical stimulation of the brain began to gain popularity in the scientific community beginning with Fritz and Hitzig in 1874 and it would be over one-hundred years later when the next landmark in brain stimulation occurred. Transcranial magnetic stimulation (TMS) was first described by Barker et al. in 1985. They devised a technique which virtually eliminated sensory pain associated with electrical stimulation of the scalp by bypassing the sensory receptors using electromagnetic induction to excite neurons of the brain (Rothwell, 2018). To stimulate the brain via TMS a magnetic field is produced by small coils of wire that generate an electromagnetic field inducing an influx of positive ions in various areas of the brain, resulting in the generation of action potentials (AP) within the axons of cerebral interneurons (Rossini et al., 2015). When stimulating the motor cortex with a suprathreshold TMS current, a short-latency response occurs at the associated muscle(s) called a motor evoked potential (MEP), which is recorded using sEMG. This motor response is a result of the initial depolarization of cortical interneurons further propagating the input to the descending pathways, and ultimately, preferentially activating corticospinal neurons (Day et al., 1987; Hess et al., 1987). Activation of these neural circuits with a single pulse, is not only determined by the location of the induction, but also the orientation and type of coil used.

Electromagnetic currents can be evoked in primarily two directions: posterior-anterior and anterior-posterior. It has been noted that the recruitment of neurons is different between the two positions, however, evidence as to whys this occurs is currently unknown (Rossini et al.

2015). Depending on the study's aim and required task, certain coil configurations are better suited to stimulate the motor cortex appropriately. Coil types used in human research in the upper limb are of predominately two designs: circular and figure-of-eight. The circular and figure-of-eight coils provide a similar depth of penetration into the cortex (~0.9-3.5 cm), whereas the distribution of the electric field is less focal for the circular coil than the figure-of-eight but minimizing concerns of exact positioning and coil orientation. Historically, circular coils have been the dominant coil used in research, however, with rapidly developing technology in 3-D brain mapping the figure-of-eight coil may become the standard in order to maintain area selectivity within the cortex. When 3-D mapping is unavailable and consistent excitement of the designated cortical area associated with a desired muscle is required, stimulation on the vertex of the skull using a circular coil may be optimal. Nevertheless, TMS is valuable tool for the assessment of corticospinal excitability/inhibition due it the ability to control neural input to the muscle painlessly.

1.4 The Silent Period

Originally acknowledged using peripheral electrical stimulation by Merton and Morton (1980) and later with TMS, an abolishment of the EMG signal occurs immediately after an evoked MEP during a voluntary contraction. This duration of absent EMG activity is called the silent period (SP; Škarabot et al., 2019) and persists for 100-300ms (Groppa et al., 2012; Kennedy et al., 2016; Rossini et al., 2015). An example of this phenomenon can be seen in *Figure 1*. The duration of the SP is directly influenced by the intensity of the incoming stimulus. Therefore, the larger the magnetic output, the longer the SP and is unclear whether a plateau in SP duration is obtainable. Until recently, this period has reflected intracortical inhibition (Säisänen et al., 2008), but recent studies indicate it may be influenced by both intracortical and spinal mechanisms (Yacyshyn et al., 2016); although the extent of their relative contributions under various circumstances is still debatable (Škarabot et al., 2019). The mechanism of this specific measure of CNS inhibition is thought to be mainly mediated by an increased concentration of the neuromodulator γ-aminobutyric acid (GABA; Siebner et al., 1998; Werhahn et al., 1999). This prominence of GABA is seen both at the level of the cortex (Krnjevijc et al., 1966; McDonnell et

al., 2006) and the interneurons within the spinal cord (Inghilleri et al., 1993), acting to reduce net neuronal excitability. Additionally, other supplementary influences from the unloading of muscle spindles (recurrent inhibition) and Ib inhibition from Golgi tendon organs (GTO), discharging from a TMS-induced muscle twitch (Yacyshyn et al., 2016) have been noted. If the SP duration becomes extended under a given condition, compared to resting levels, it can be assumed that the condition elicited greater corticospinal inhibition within the CNS. In past investigations, increases in corticospinal inhibition (i.e., prolonged SP duration) were observed following contractions inducing fatigue (Gandevia et al., 1996; McNeil et al., 2009). Thus, indicating the significant adaptability of the CNS following a contraction of muscle during which peripheral contractile changes also occur. However, due to the multiple neuronal influences, identifying the specific mechanism influencing this change is challenging in a human model (Škarabot et al., 2019). Overall, the SP is a useful measure used to view changes in CNS inhibition following various activation histories of muscle but should be interpreted with caution due to its many influences.

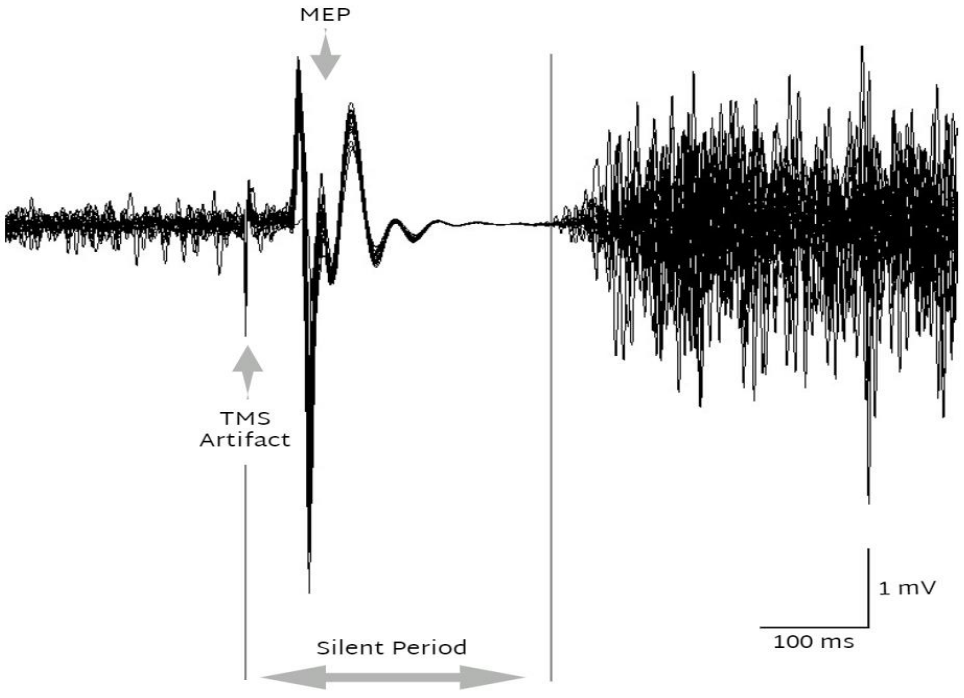

Figure 1. Example of surface electromyography when suprathreshold transcranial magnetic stimulation is evoked during a low-level (~25% MVC) tonic contraction. The silent period being quantified as the time of stimulus onset (TMS artifact) until the return of voluntary EMG.

1.5 The Corticospinal Tract

Motor control systems involve both hierarchical and parallel connections or tracts to provide proper execution of a task. One of these tracts necessary for movement involving both basic and fine motor skills is the corticospinal tract. The corticospinal tract was first observed in the 19th century through the stimulation of the motor cortex and resulting muscle contraction on the contralateral side of the body. Descending fibers within this tract unevenly originate from several cortical loci. The primary motor cortex (M1) accounts for approximately one-half of the corticospinal fibers whereas the remainder arise from adjacent areas of the frontal motor areas and the parietal lobe. Although not directly original to M1, a third of the fibers originate from the premotor cortex and supplementary motor area and project to M1. Meaning that ~80% of the fibers of the corticospinal tract pass through M1 prior to their descent to the spinal cord. Axons of the corticospinal tract fibers pass to the brainstem as a part of large fiber bundles called cerebral peduncles. Travelling further into the medulla the tracts form what is known as the pyramids of the brainstem. Descending further on, ~90% of the corticospinal fibers cross over to the other side of the brainstem at the spinomedullary junction in a nerve bundle called the pyramidal decussation. The decussated axons then descend in the lateral column of the spinal cord, forming the lateral corticospinal tract. The lateral corticospinal tract therefore provides cortical input for movement from the contralateral hemisphere of the brain. The 10% of the tract that does not decussate at the pyramids remains on the ipsilateral side of the spinal cord forming the ventral (or anterior) corticospinal tract (*Figure 2*). These ventral corticospinal axons eventually decussate in the spinal cord when approaching the lower motor neuron of their target muscle (trunk, neck and shoulders). Although the ventral tract is an important component in motor control, when observing limb movements and especially fine control of moment, the lateral corticospinal tract is king/queen (Nolte, 2009).

As the name implies, the corticospinal tract originates in the cortex and terminates in the spinal cord. This is primarily true; however, it is an oversimplification of the connectivity occurring throughout the brain. On its way to the spinal cord the corticospinal tract gives rise to numerous collateral neurons connecting with a wide collection of structures including: the basal ganglia, the thalamus, the reticular formation, and various sensory nuclei. These connections provide

significant evidence for a highly integrative neurological tract which acts and reacts with the cumulative information from several structures to provide an optimal response at the muscle of interest (Nolte, 2009).

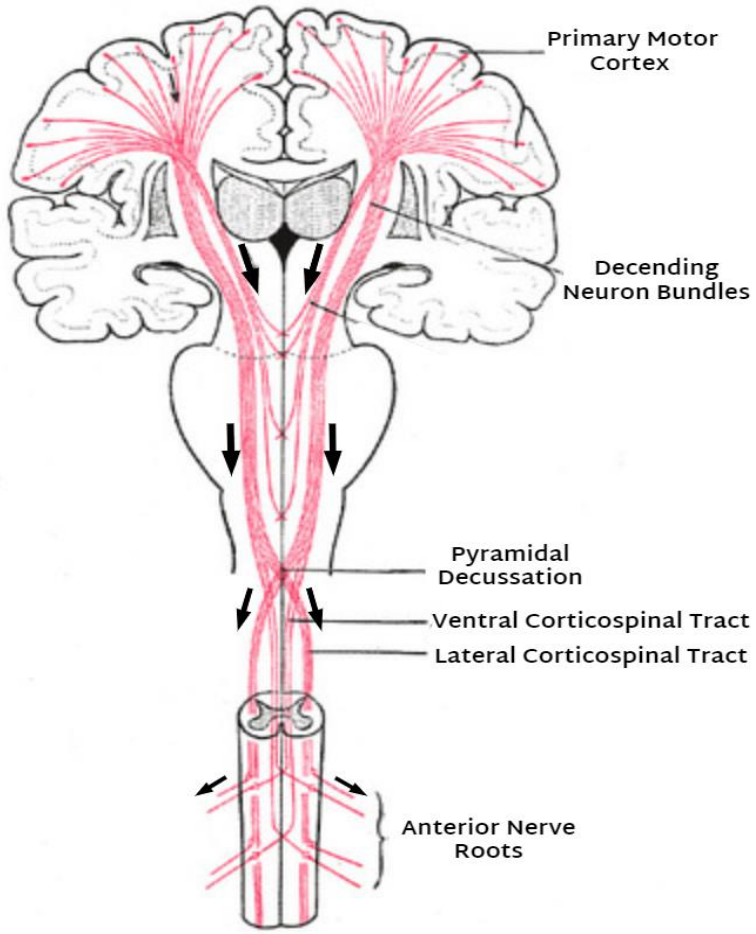

Figure 2. Diagram of the corticospinal pathway from cortex to spinal lower motor neurons in the coronal plane. Originally from Grays anatomy, now out of copyright (Adapted from https://commons.wikimedia.org/wiki/File:Gray764.png).

1.6 Skeletal Muscle Architecture and Function

Skeletal muscle is one of the major tissues that comprise the human body, accounting for 30-40% of the total body mass (Dave et al., 2021). Each individual fiber is multinucleated and comprised of many cells called myofibrils. Within each myofibril are numerous thick and thin myofilaments, which combine to create the smallest anatomical unit of contraction, the

sarcomere. The two most important myofilaments within the sarcomere involved in basic muscle contraction are myosin (thick filament) and actin (thin filament) (Rassier, 2010). These two structures interact and form the basis to cause muscle shortening, which will be covered in a later section. Arranged in series, these sarcomeres are responsible for the histological striated pattern associated with skeletal muscle. Each skeletal muscle is comprised of thousands of muscle fibers wrapped together within connective tissue sheaths. The inner most sheath, called the endomysium, bundles the individual myofibrils together to form the muscle fiber. Multiple muscle fibers are bound in groups by the perimysium, of which there are several which come together in the epimysium which forms the whole muscle and these connective tissue structures all blend eventually to form the tendon (Frontera & Ochala, 2015).

The primary function of skeletal muscle is to provide movement via the excitation-coupling cycle. The sarcomeres in series have an additive effect and result in force transfer to tendon and the bony attachment point which therefore produces movement. However, this is not the only purpose of skeletal muscle, as they also provide numerous necessary roles including: structural support, thermoregulation, amino acid synthesizing, and a last resort energy source in starvation settings (Dave et al., 2021; Frontera & Ochala, 2015; Wolfe, 2006).

1.7 The Motor Unit and E-C Coupling

Known as the smallest functional unit of movement, the motor unit (MU) consists of the motor neuron (referred to as alpha motor neurons) and the muscle fibers that it innervates (Liddell & Sherrington, 1925) which together act in concert to enable functional action and reaction. The group of motor neuron cell bodies (somas) which eventually innervate the fibers of a given muscle reside in the ventral horn of the spinal cord, clustering together to create what is known as a motor neuron pool (*Figure 3*). This motor neuron pool receives synaptic input from supraspinal centers as well as feedback from other sensory fibres and activate in a manner related to the size of the soma, depolarizing smallest to largest; this is called the size principle (Henneman, 1957). Once activated, APs propagate along the alpha motor neuron axon where they reach their designated muscle fibers at what is called the neuromuscular junction (NMJ). At

the NMJ the electrical AP results in the subsequent depolarization the surface membrane of the muscle fiber (sarcolemma). The ensuing sequence of events to produce force generation at the level of the sarcomere is referred to as excitation-contraction coupling or E-C coupling.

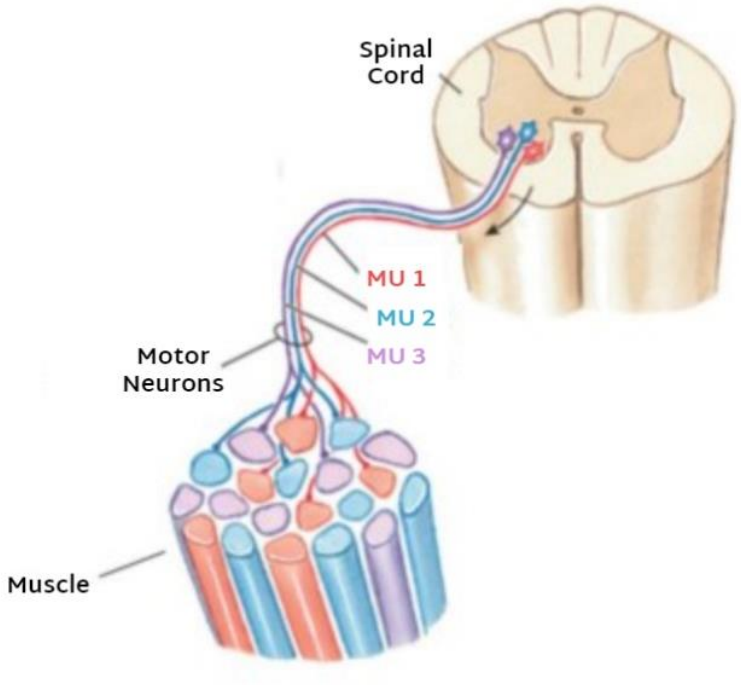

Figure 3. Diagram of three motor units (MU). (Adapted from http://www.saptstrength.com/blog/2014/10/27/rate-of-force-development-what-it-is-and-why-you-should-care)

Depolarization of the sarcolemma, via voluntary or involuntary transmission initiates the E-C coupling process. Once the membrane potential reaches its threshold, voltage gated sensors in the T-tubule of the sarcolemma trigger the release of Ca2+ out of the sarcoplasmic reticulum (SR) where it is stored; ultimately, increasing the [Ca2+] within the muscle myoplasm. Free Ca2+ binds to the regulatory protein Troponin C which causes the exposure of actin binding sites for myosin head attachment (Gordon et al., 1966). Once myosin binding sites are exposed and sufficient ATP is present within the muscle, myosin heads can bind to actin and complete what is known as the 'power stroke'. During this process ATP is hydrolyzed and ADP and inorganic phosphate (Pi) are produced, providing required energy for the contraction. During the power

stoke actin fibres which are anchored to each end of the sarcomere are pulled towards the middle of the sarcomere causing sarcomere shortening. The summation of all shortening sarcomeres results in contraction of the whole muscle where then it can transfer force to tendon and bone for movement. Following the power stroke, the myosin head becomes unbound when a new ATP molecule binds onto it or when an insufficient [Ca2+] within the myoplasm occurs, leaving Troponin C to again cover the once exposed actin binding site. This cycle repeats during an active contraction.

1.8 Muscle Twitch and Tetanus

Recruitment of MUs is one mechanism used to alter force generating capacity and frequency of AP generation of recruited MUs is the second main mechanism. A muscle twitch is a transitory involuntary muscle response evoked by a single electrical stimulus in which force rises and falls rapidly lasting up to 100ms (MacIntosh, 2010). Twitches, which do not occur voluntarily for purposeful movement control, can be electrically evoked by either stimulating through the skin over muscle belly, or with percutaneous nerve stimulation which in both techniques depolarizes peripheral axons or their nerve twigs of peripheral axons, respectively. The depolarization and subsequent muscle twitch encompass the entire E-C coupling cycle. By controlling the input (frequency and intensity) to the muscle, changes in muscle contractile properties can be observed and quantified before and after an intervention. This can be seen with muscle enhancement and decrement in which the amplitude and duration are altered. Thus, the muscle twitch is a useful measure to observe muscle property variations following a given condition.

Tetanic stimulation results when a series of twitches are induced repeatedly at time intervals that are shorter than the duration of the twitch force response causing a summation of force (Buller & Lewis, 1965). The resulting force output is known as a tetanic contraction. At longer intervals between stimulations (measured in pulses per second, or Hertz (Hz)) individual force responses are discernable, known as an unfused tetanus. Conversely, when the muscle is stimulated with shorter intervals (higher frequencies) the muscle is unable to relax and force

becomes fully fused resulting in a maximal tetanus. Being involuntary, twitches and tetanus bypass the spinal alpha motor neurons and supraspinal neurons; thus, allows unique insights into how muscle responds without voluntary central drive. Moreover, tetanic electrical stimulation not only depolarizes axons orthodromically (efferent; towards muscle), but they also generate and propagate APs in the opposite direction (antidromic) towards the motor neuron cell body (Brock et al., 1953; Fatt, 1956). These antidromic APs have been shown to alter spinal motor neuron excitability without the need for voluntary drive (Christensen & Grey, 2013; Kudina & Andreeva, 2022). Therefore, pairing this technique with voluntary contractions, provides an opportunity to assess the level of muscle activation during voluntary drive.

1.9 The First Dorsal Interosseous Muscle

The first dorsal interosseus muscle (FDI) of the hand was first documented in the 2nd century A.D by the Greek physician, Galen. The FDI is the largest of all the dorsal interossei muscles and is comprised of two distinct heads: superficial and deep (Landsmeer, 1949). Both heads are composed of 50% fast twitch (type II) and 50% slow twitch (type I) muscle fibers (Johnson et al., 1973). Although fiber distribution is similar, function between the two heads differs; the superficial head mainly supports abduction of the index finger whereas the deep head causes flexion of the thumb and index finger which forms a pinching movement (Long & Brown, 1964; Masquelet et al., 1968; Nayak et al., 2016). The origin of the superficial head is located at the first metacarpal whereas the deep originates from the second metacarpal (see *Figure 4*). Insertions for the FDI vary among the population and one of three points of insertions are common: the second proximal phalanx, the extensor hood mechanism, and inserting into both the second proximal phalanx and the extensor hood mechanism (Infantolino & Challis, 2010; Valenzuela & Bordoni, 2021). The muscle is innervated by the deep branch of the ulnar nerve which can be easily accessed for electrical stimulation at the wrist where it lies just beneath the skin. Additionally, like other distal muscles that produce fine movements, the FDI is heavily influenced by the corticospinal tract (Nolte, 2009). Thus, due to its neutral fiber typing, ease of

stimulation, and heavy corticospinal influence the FDI is an attractive model to observe both peripheral and central neuromuscular changes during different tasks.

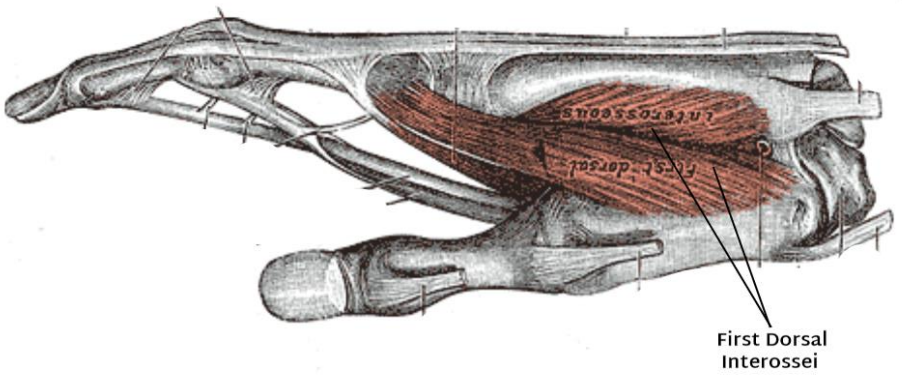

Figure 4. Diagram of the first dorsal interosseous/interossei (FDI) muscle. Originally from Grays anatomy, now out of copyright. Adapted from (https://en.wikipedia.org/wiki/Dorsal_interossei_of_the_hand#/media/File:Gray416.png).

1.10 Activity Dependent Potentiation (PAP & PTP)

First noted by Guttman, Horton, and Wilber in 1936, following brief (5s) activation of skeletal muscle there was an enhancement of successive submaximal contraction amplitudes that occurred with a diminishing effect over time (Guttman et al., 1936; MacIntosh, 2010). There are three subdivisions of this peripheral muscle tissue phenomenon known as activity dependent potentiation (ADP): staircase, posttetanic potentiation (PTP), and postactivation potentiation (PAP). For the sake of this thesis, only PAP and PTP will be discussed, as they are the only subtypes utilized. Evoked responses assessing potentiation are typically done using the muscle's response to supramaximal muscle twitches delivered before and after a high intensity (>75% maximal force) conditioning contraction (CC). Amplitude differences between the two twitches – one pre-CC and one immediately post-CC – represent the degree of muscle enhancement which can be as much as ~200% (Baudry & Duchateau, 2004) (see *Figure 5*).

Following a brief high intensity electrically evoked tetanic contraction (PTP) the magnitude of a twitch is enhanced (G. L. Brown & von Euler, 1938). Although tetanic contractions

evoke synchronous activity from motor units to produce a contraction in a muscle (Heckman & Enoka, 2012), peripheral enhancement is similar to that following natural high intensity voluntary activation. In situations in which voluntary control is not possible, such as in reduced preparations, PTP is commonly utilized to study effects of muscle potentiation. Additionally, PTP can be used to delineate influences of voluntary drive in an intact neuromuscular system by eliminating confounding influences from voluntary control (Smith et al., 2020). However, when studying the human model, postactivation potentiation (PAP) is the more common method (Blazevich & Babault, 2019). When the CC that causes subsequent potentiation is produced by voluntary activation, usually maximal or near maximal voluntary contraction (MVC), it is considered PAP (MacIntosh, 2010). Indeed, if a high intensity contraction is held for a brief time (≤10s) muscle contractility is enhanced, however contractions are held at a high intensity for >10s, twitches can be impaired due to neuromuscular fatigue (Rassier & Macintosh, 2000) Thus, a balance between reduction and enhancement exists following high-intensity activations of skeletal muscle (Vandervoort et al., 1983).

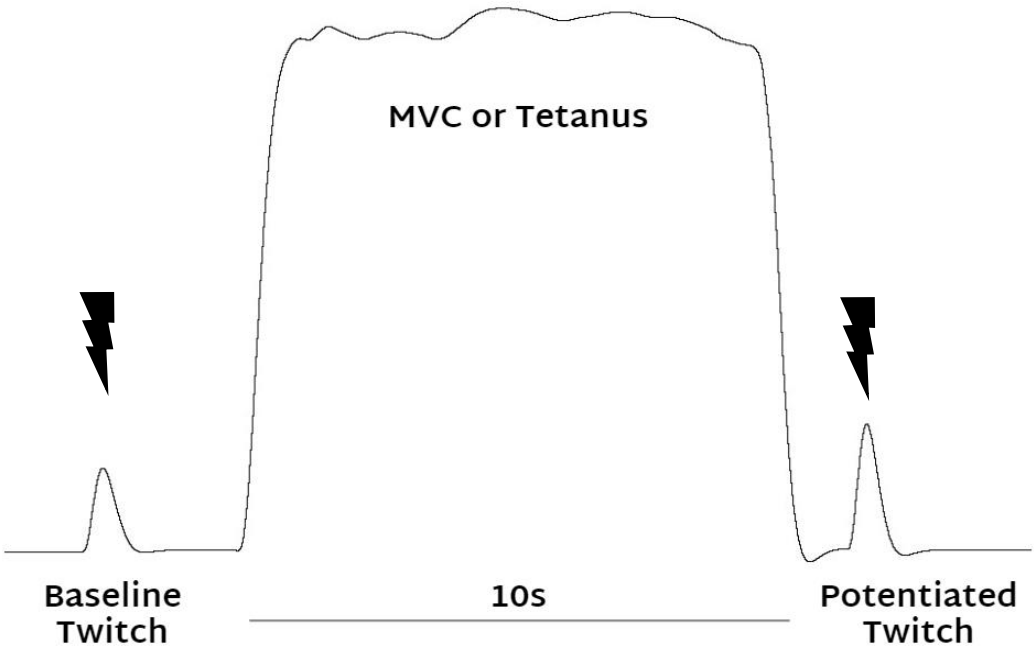

Figure 5. Example of activity dependant potentiation (PAP/PTP). Maximally evoked twitches before and after a brief maximal voluntary or tetanic contraction.

1.11 Mechanisms of Activity Dependent Potentiation

Mechanisms of activity dependent potentiation have been well explored and documented; the primary mechanisms are understood to be the phosphorylation of myosin regulatory light chains (RLC) in relation to increased Ca2+ sensitivity (Grange et al., 1993; Manning & Stull, 1979; Persechini et al., 1985; Sweeney et al., 1993; Vandenboom et al., 1993) During a forceful muscle contraction the sarcoplasmic reticulum releases Ca2+, increasing [Ca2+] and subsequently the concentration of regulatory protein calmodulin (CaM). Released Ca2+ binds to the CaM where it then activates the enzyme myosin light chain kinase (MLCK) (Manning & Stull, 1982). The interaction of CaM and MLCK acts to phosphorylate the regulatory light chain (RLC) of the myosin molecule, resulting in a steepening angle of the myosin away from its thick filament backbone (Levine et al., 1996). Due to this conformational change, a decrease in distance between the myosin head and the actin binding site occurs. Reducing this distance expedites cross bridge attachment rates, however, it does not completely explain observed force enhancement. It was demonstrated by Persechini et al. (1985) that the phosphorylation of RLCs resulted in an increase of Ca2+ sensitivity. Meaning that at a given force level a lower [Ca2+] is needed to produce the outcome. This increased sensitivity has been shown by Sweeney and Stull (1990) to occur as a result of an increased number of cross bridges formed. Thus, submaximal force is enhanced by the overall increase of cross-bridges made at a given [Ca2+], and not increased force per cross bridge. Due to this increase in cross-bridge numbers, more ATP must be utilized to phosphorylate RLC. It has been demonstrated that the CNS reduces overall synaptic input, as reflected by lower overall sEMG (Smith et al., 2011) as well as firing rate frequencies (Hz) required to create muscle contractions (Klein et al., 2001) when the muscle is potentiated. However, whether these changes of descending drive characteristics are coincidental or are directly caused by muscle potentiation is still currently unknown.

1.12 Purpose and Hypothesis

To reiterate, muscular adaptations resulting from activity dependent potentiation in isometric states have been well studied, yet this is only one side of the neuromuscular coin and

any potential central adaptations from acute changes in muscle responsiveness are largely unknown (Zero & Rice, 2021). Recently, a study produced by Smith et al. (2020) reported an increase in corticospinal inhibition while the FDI was maximally potentiated. The study recorded and compared SP changes within the FDI following voluntary and stimulated contractions which induced PAP. Although a coexistence was evident between the two measures, a direct connection could not be concluded. Thus, to elucidate the interaction of potentiation and corticospinal inhibition this thesis characterized central effects during potentiated and non-potentiated states. The aim was to assess SP duration changes following CCs inducing potentiation and CCs of the same duration but that do not result in twitch potentiation. Additionally, this study aimed to determine the influence of voluntary central drive to the muscle via both voluntary and electrically stimulated contractions. It was hypothesized the SP duration would be prolonged following both maximal and submaximal contractions, but to a lesser degree following submaximal contractions when force is lower, and potentiation is absent. This will provide evidence towards the dissociation of corticospinal alteration as a result of muscle potentiation per se.

Chapter 2

2 The effect of brief maximal and submaximal contractions on corticospinal inhibition in humans

2.1 Introduction

Contractile history, such as high intensity repeated or sustained contractions causing fatigue, by definition, results in a loss of force and contractile slowing of the muscle (Gandevia, 2001; Taylor et al., 2016). Although neural control in relation to diminished contractile properties has been well explored, the effects of acute contractile enhancement have received much less attention. Following a short duration (5-10s) high intensity (>75% of maximum) conditioning contraction (CC), skeletal muscle twitch contractile elements will display a transient increase of force and rate of force development (Vandervoort et al., 1983). This feature, termed postactivation potentiation (PAP), can enhance muscle twitch amplitudes immediately, but transiently by as much as 200% and rate of force development by 250% with an exponential decay to baseline from 30s-10min, depending on the muscle (Baudry & Duchateau, 2004; Hamada et al., 2003; Macintosh & Gardiner, 1987; Seitz et al., 2015). This property is primarily due to the phosphorylation of myosin regulatory light chains in relation to enhanced calcium (Ca^{2+}) sensitivity (Grange et al., 1993; Manning & Stull, 1979; Sweeney et al., 1993; Vandenboom et al., 1993). This mechanism acts to change myosin head orientation closer to actin binding sites for subsequent power strokes, thus facilitating expedited cross-bridge formation. However, at higher contraction intensities, [Ca^{2+}] levels increase within the sarcoplasm, eventually saturating. Once saturated, increased Ca^{2+} sensitivity has little effect on contractile enhancement (Blazevich & Babault, 2019; Sweeney et al., 1993). Thus, the effect of PAP is greatest when subsequent measures are observed during low contraction intensities, such as twitches or submaximal contractions.

Muscle potentiation can be induced voluntarily (PAP) via voluntary muscle activation or involuntarily through electrically stimulated contraction (posttetanic potentiation; PTP) (Close, 1972). The difference being that electrical tetanic nerve stimulation essentially bypasses spinal

and supraspinal aspects of voluntary movement; allowing for an assessment of muscle activity that is independent from higher volitional drive influences and subsequent to a known input. However, electrical stimulation of a peripheral nerve has not only orthodromic (efferent) directionality, but also antidromic (afferent) activity (Brock et al., 1953; Fatt, 1956). Antidromic activity conducts action potentials towards the soma of the stimulated motor neurons (Bayliss, 1901; Kudina & Andreeva, 2022) which introduces the potential to influence central measures differently than voluntary contractions.

Corticospinal excitability reflects the net balance between excitatory and inhibitory input to neurons within the corticospinal tract (Weavil & Amann, 2018). To assess this state dependent measure, transcranial magnetic stimulation (TMS) can be used to depolarize cortical interneurons within the primary motor cortex (M1) (Rossini et al., 2015). Ultimately, the stimulation produces a motor response at the muscle termed a motor evoked potential (MEP), which is recorded through surface electromyography (sEMG). Furthermore, if TMS is delivered when an individual is voluntarily contracting, following the MEP, an interruption of the descending drive will occur (Davey et al., 1994; Groppa et al., 2012; Hallett, 2007; Rossini et al., 2015), lasting between 100-300ms (Groppa et al., 2012; Kennedy et al., 2016; Rossini et al., 2015). This interruption or cessation of descending input from the central nervous system (CNS) is referred to as the silent period (SP; Merton & Morton, 1980) and it reflects the level of intracortical and spinal motor neuron inhibition caused by the TMS (Chen et al., 1999; Škarabot et al., 2019; Wilson et al., 1993; Ziemann et al., 1996). Moreover, the SP has been previously shown to increase in duration (reflecting increased inhibition) following fatigue (Benwell et al., 2007; Gandevia et al., 1996; Mckay et al., 1996; McNeil et al., 2009; Taylor et al., 1996). Further demonstrating coexistences of changes in corticospinal excitability and peripheral contractile properties following muscle activation.

Recently, Smith et al. (2020) reported the SP duration to increase ~10% when TMS was delivered during a maximal voluntary contraction (MVC) following a priming maximal CC that caused PAP in the first dorsal interosseus muscle (FDI). Both electrically induced tetanic and voluntary CCs caused both similar increases in potentiation and SP duration. Because the SP duration was not different following the tetanic and voluntary contractions, this indicated an

expectable rise in corticospinal inhibition when the muscle is potentiated, regardless of how it was induced (i.e., voluntarily or electrically). However, evidence of a direct relationship between peripheral enhancement and corticospinal inhibition has not been tested thoroughly. Therefore, this study assessed corticospinal inhibition following voluntary and involuntary potentiating contractions compared with non-potentiating contractions in the FDI. As there is a dearth of evidence towards afferent feedback associated with dynamics of muscle potentiation, it is likely that increases in corticospinal inhibition seen in the SP will occur from the activation of muscle, regardless of the mode of activation. Thus, it was hypothesized that prolonged SP durations will occur following maximal CCs inducing PAP and will also be evident following non-potentiating contractions as a result of muscle activation.

2.2 Methods

Participants

Ten healthy young (four females; 22-31y) individuals free of neurological issues participated in the study (*Table 1*). Individuals with previous serious injury to their right hand, those with histories of concussions and seizures, as well as individuals taking antidepressant, antipsychotic, or anti-seizure medications were excluded from this study. Accepted participants were required to abstain from exercise, alcohol, and caffeine 24 hrs prior to the testing session. This study conformed to the local University's research ethics board for human experimentation. Participants were required to provide oral and written consent prior to any testing.

Experimental Setup

Participants were seated with their right forearm pronated and their hand fixed to a custom-made finger abduction dynamometer. The right distal interphalangeal joint of their index finger was positioned perpendicular to the vector of the transducer. The thumb was fixed in a slightly abducted and extended position, secured by an immovable aluminum divider. Other fingers were secured and isolated from the index finger, avoiding contribution to force generation. The hand was secured into place with inelastic ratchet straps over the dorsum of the metacarpals and a second strap 10cm proximal to the wrist joint (see *Appendix A*).

Electromyography (EMG)

Monopolar sEMG signals were recorded from the FDI with self-adhering Ag/AgCl electrodes (Kendall 5400 Diagnostic Tab Electrodes, Mansfield, MA). Prior to placement, the skin was lightly abraded and cleaned with an alcohol wipe. Electrode placement for the active, reference, and ground were set on the belly of the FDI muscle, on the dorsum of the pollux, and the styloid process of the ulna, respectively. All sEMG signals were preamplified 1000x and sampled at 2500 Hz using a 16-bit A/D converter (model 1401Plus; Cambridge Electronic Design Ltd., Cambridge, U.K).

Ulnar nerve stimulation

Small re-adjustable electrodes and a constant current stimulator (model DS7AH, Digitimer, Welwyn Garden City, Hertfordshire, England) were used to deliver single square-wave electrical stimuli (100μs pulse width; 400V) longitudinally over the ulnar nerve (2cm proximal to the wrist) to evoke maximal M-waves (M_{max}) and muscle twitches. The stimulator current was set to 120% of the current required to produce a maximal twitch response (45-100 mA). Similarly, for maximal 50Hz (10s) tetanic contractions, the current was increased to 120% (30-80 mA) following the plateau of maximal tetanic force output (~95%MVC). The stimulator current for submaximal tetanic CC was determined by stimulating the participant for 10s, evoking twitches pre-and post CC beginning at 50%MVC. If evoked twitch force was enhanced following the submaximal contraction the stimulator current was lowered to evoke force levels 5% lower, this was done until twitch enhancement was absent (i.e., no PTP). The resulting current ranged from 15-50 mA (25-50% MVC).

Transcranial magnetic stimulation (TMS)

TMS was used to assess the level of corticospinal inhibition associated with the FDI. Single TMS pulses were delivered over the vertex of the skull with a Magstim-200 stimulator (The Magstim Company Ltd., Spring Gardens, Whitland, Carmarthenshire, UK), using a 90mm circular coil. The coil induced a magnetic current in a posterior-anterior direction influencing the left primary motor cortex. Stimulator intensity was then set to evoke a maximal MEP response for each participant (~75% of the M_{max} amplitude) during contractions at 25%MVC held for ~3s with 10s breaks between successive contractions. By maximizing MEP amplitude both high and low threshold motor units are likely to be activated. The SP was obtained during tonic contractions of 25% MVC and participants were instructed to contract voluntarily as fast as possible with moderate force (~50%MVC) upon hearing the auditory ‘click’ from the TMS. This “pull-up” action provided definitive ends to the SP for analysis, as a increase in EMG from baseline was evident at higher contraction intensities. Participants were sufficiently familiarized to this protocol within the same session, completing ~12 practice contractions to limit variance due to inconsistent reactions to the TMS click.

Experimental protocol

Once set up, participant maximal resting twitch force and coinciding M_{max} was collected. Participants then completed two or three brief (3s) maximal index finger abductions to establish maximal voluntary contractile (MVC) force. Strong verbal reinforcement and visual feedback of force were provided during each contraction. During MVC attempts, the interpolated twitch technique (ITT; Gandevia, 2001; Merton, 1954) was utilized to measure the level of voluntary activation of the FDI; by which a single supramaximal stimulus was delivered before, during, and ~1s after the MVC. Maximal twitches were recorded before and after a 10s MVC, to obtain individual values of maximal PAP. After five minutes, PTP twitch values were obtained following a 10s maximal tetanic contraction. Following a 5min rest, submaximal CC force levels were determined; beginning with tetanic stimulation (see *ulnar nerve stimulation section* for breakdown), voluntary submaximal CC was then force-matched to the submaximal tetanic absolute force and ensured no PTP and PAP, respectively. Baseline SPs were attained by evoking a single TMS pulse during a brief tonic contraction at 25% MVC. Succeeding the completion of baseline measures, SPs were obtained before and after one of four 10s CCs, obtained in a pseudo-randomized order: maximal and submaximal, voluntary and involuntary contractions. Following the relaxation of each CC, a SP was recorded at 25% MVC. In total, this study consisted of four conditions, which were repeated four times each to account for variability in SP duration. To mitigate fatigue and allow muscle potentiation to return to baseline, a rest period of five minutes was given following each maximal CC and two minutes after each submaximal CC (*Figure 6*).

Data processing and analysis

The sEMG and force recordings were collected in real-time using Spike2 software (version 7.11; Cambridge Electronic Design, Cambridge, UK). Duration of the SP was determined as the time from the TMS pulse to the return of voluntary EMG (McNeil et al., 2011). Peak-to-peak MEP and M_{max} amplitudes were measured between cursors from the initial deflection from baseline and the second crossing of baseline (Martin et al., 2006). All sEMG signals, prior to SP measurement sEMG were filtered using a bandpass Butterworth filter between 25Hz– 450Hz (Smith et al., 2020). Force signals were amplified by x10 (NL 855 preamplifier & NL820A Isolator;

Digitimer, Welwyn Garden City, UK) before being sampled at 500 Hz [CED model power1401, Science Park, Cambridge, UK]. Prior to measurement, force signals were low pass filtered at 50Hz. PAP/PTP was assessed as the difference in twitch amplitude from the baseline twitch at rest and following maximal CCs, assessed in mean percent change across the four trials. Analysis of sEMG was completed using both Spike2 and Signal software (version 5.08; Cambridge Electronic Design, Cambridge, UK).

Statistical analysis

All statistical analysis was conducted using R (version 3.4.3; R Foundation for Statistical Computing, Vienna, Austria). Data normality was confirmed using the Shapiro-Wilk test. A one-way repeated measures ANOVA was used to compare differences in relative SP duration increase across the four conditions: maximal voluntary/tetanic and submaximal voluntary/tetanic. Paired two-sided t-tests were used to compare pre and post CC SP durations for each contraction condition. The level of significance for SP change was modified using the Bonferroni correction factor. The α level was set to 0.05 and 0.005 for the ANOVA and t-test, respectively.

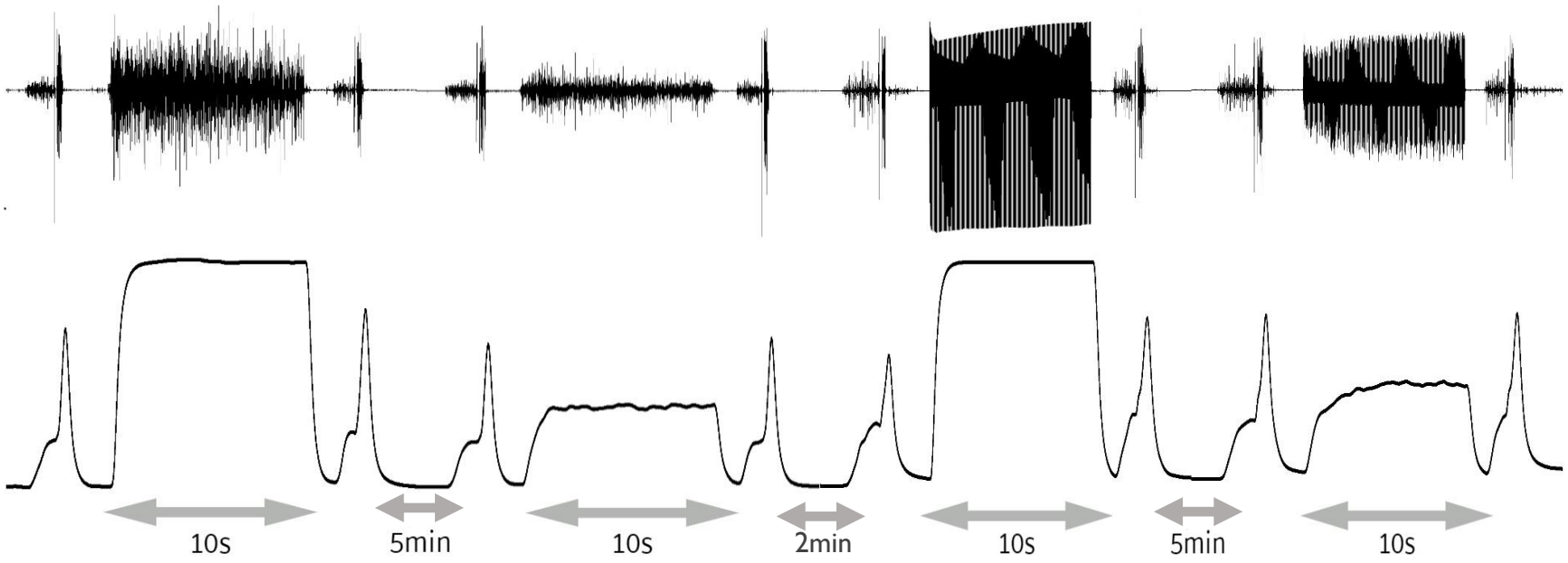

Figure 6. Example of the experimental protocol following the acquisition of baseline testing. Both maximal and submaximal protocols are presented with surface electromyography (sEMG) above the recorded force from the FDI. Before and after the 10s conditioning contraction participants contracted to 25%MVC during which TMS was then evoked, upon the auditory click of the TMS trigger participants were instructed to further contract quickly and moderately forceful in response.

2.3 Results

Baseline measures

Mean participant maximal voluntary force of the FDI was 36.9 ± 1.9N, whereas electrically stimulated maximal tetanic force was 34.8 ± 1.7N. Thus, maximal tetanic contractions reached ~95% of MVC force yet was statistically different ($p < 0.001$). Using the ITT, voluntary activation was measured to be maximal in all participants, ranging from 98-100%. Mean submaximal force level required to eliminate PAP/PTP for voluntary and tetanic contractions was 14.0 ± 2.0N, equating to ~40% of MVC force. Baseline unpotentiated twitch force obtained was 1.9 ± 0.5N. Baseline SP duration measured during the isometric 25% MVC was 180 ± 28ms (*Table 1*).

Potentiated twitches and silent period changes

Following both maximal CCs (voluntary and tetanic), twitch force was significantly potentiated (182.7± 38.9 and 170.2 ± 34.3%, respectively) compared to at rest, with no significant differences between the two types. Moreover, as intended, following submaximal CCs twitch force demonstrated no enhancement (101.5 ± 2.8%; *Figure 7a*). Compared to baseline values, the SP was significantly prolonged following each CC: submaximal voluntary 4.6 ± 3.7% (~9ms; $p < 0.001$), submaximal tetanus 4.8 ± 6.1% (~9ms; $p < 0.001$), maximal voluntary 13.9 ± 5.5% (~22ms; $p < 0.001$), and maximal tetanus 11.3 ± 7.3% (~20ms; $p < 0.001$) (*Figure 7b*). In line with our hypothesis, all CCs produced prolonged silent period following all CCs. The duration of SP following maximal conditions were not different from each other, similarly, submaximal conditions were also not different from one another. However, as hypothesized the SP change post submaximal CCs were significantly shorter than SPs measured after maximal CCs by ~2.5x (~7%; $p<0.001$).

	Characteristics (n = 10)	
Participant characteristics	Age (yrs)	25 ± 3
	Height (cm)	173 ± 9
	Mass (kg)	70.1 ± 10.5
Muscle properties	Maximal CC force (N)	36.9 ± 1.9
	Submaximal CC force (N)	14.1 ± 2.3
	Baseline Tw amplitude (N)	1.9 ± 0.5
	PAP (%)	182.7 ± 38.9
	PTP (%)	170.2 ± 34.3
Electromyographic properties	M_{max} amplitude (mV)	7.6 ± 0.7
	MEP amplitude (mV)	5.2 ± 0.8
	Silent period (ms)	180 ± 28

Table 1. Physical and electromyographic baseline characteristics of 10 participants. Muscle properties include maximal conditioning contraction (CC) force, submaximal CC force, twitch (Tw) amplitude, postactivation potentiation (PAP)%, and posttetanic potentiation (PTP) %. Electromyographic (EMG) properties measured include maximal m-wave (Mmax), motor evoked potential (MEP) amplitude, and the silent period (SP).

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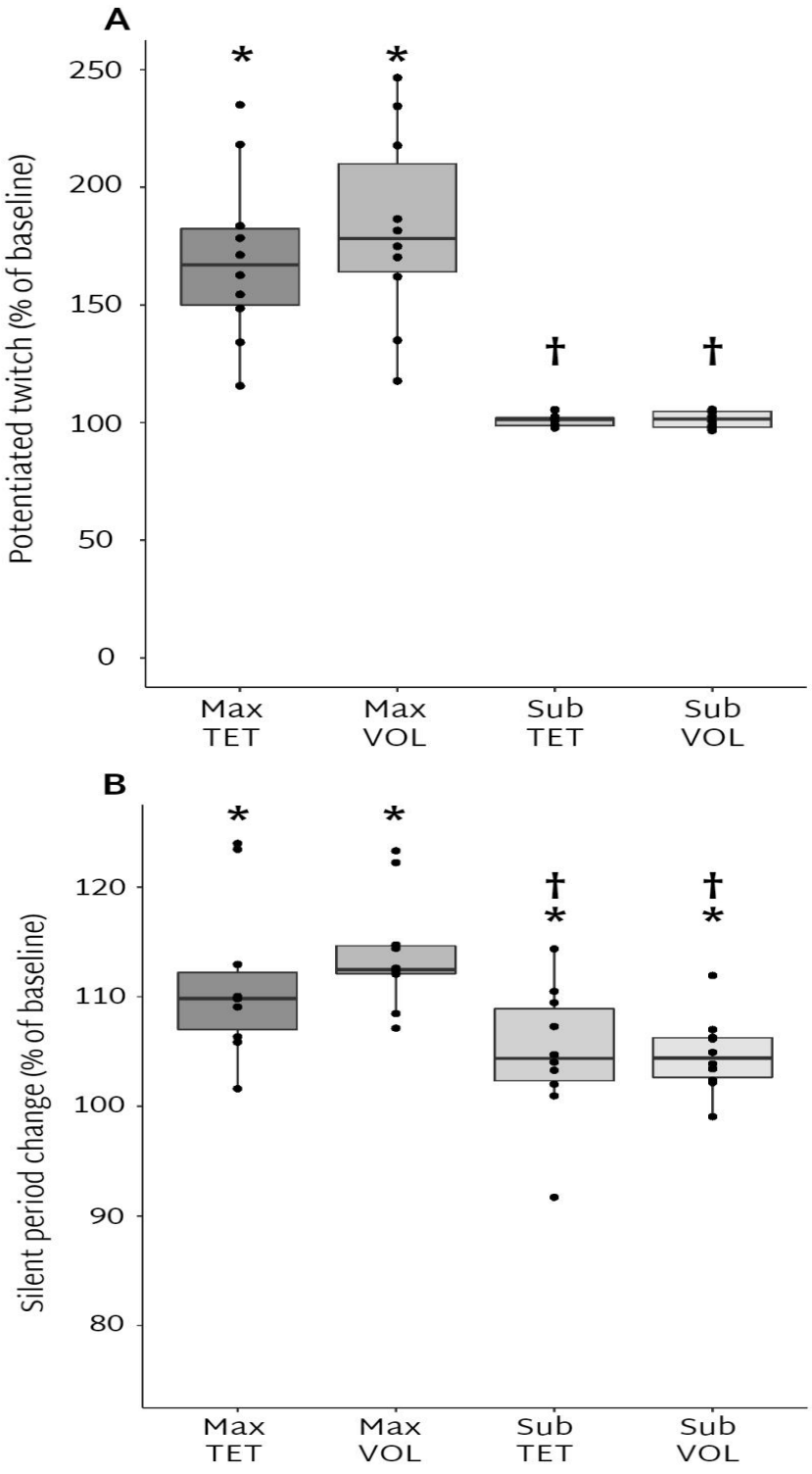

Figure 7. A: Boxplots of twitch force (% of baseline) following maximal tetanic (Max TET) voluntary (Max VOL) and submaximal tetanic (Sub TET) voluntary (Sub VOL) conditioning contractions; B: boxplots of silent period duration (% of baseline) following each of the four conditions. Significance from baseline indicated by (*****), significance from maximal contractions is indicted by (**†**).

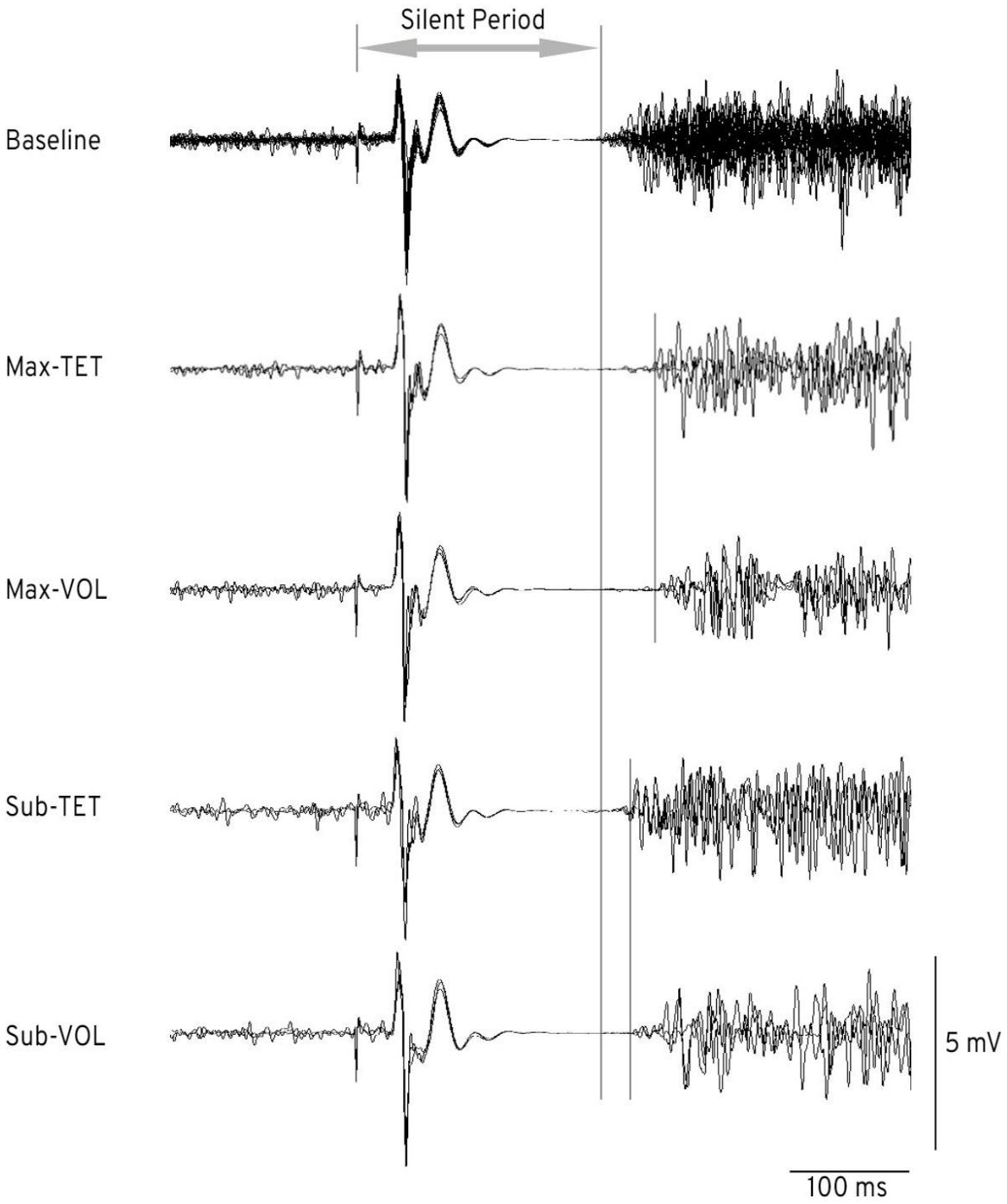

Figure 8. Example of raw surface electromyography (sEMG) signal recording overlays from the first dorsal interosseous muscle (FDI) in a single participant during isometric contractions at a force level of 25%MVC during which a single TMS pulse is evoked to the primary motor cortex. Duration of the SP was measured from stimulus artifact to the return of sEMG. Baseline SP duration is shown first with one line through all other overlays, subsequent lines for conditioned SPs mark EMG return and the difference from baseline.

Chapter 3

3 Discussion and Summary

3.1 Discussion

The current study compared corticospinal inhibition following potentiating and non-potentiating contractions of the same duration under voluntary and involuntary control (electrically evoked). Results, as hypothesized, demonstrated a significant elongation of the SP following both maximal and low intensity (~40%MVC) contractions (~12% and ~5%, respectively). These results agree with a previous study that demonstrated a ~10% increase in corticospinal inhibition when muscle was in a potentiated state (Smith et al., 2020). The prolongation of the SP following a submaximal contraction not inducing potentiation indicates that it is unlikely that muscle potentiation, per se, is affecting the silent period. Moreover, due to voluntary and electrically evoked contractions resulting in similar changes it is likely that the activation of the muscle provides feedback that alters central inhibition rather than centrally controlled feedback mechanisms.

Both postactivation and posttetanic potentiation have been investigated over several decades and are characterized by increased twitch amplitude after a high-intensity contraction compared with at rest (Brown & Tuttle, 1926; R. E. Burke et al., 1976; Guttman et al., 1936; MacIntosh et al., 2012; Ranke, 1865; Sale, 2002). Although this phenomenon occurs within the muscle itself, central adaptations have been noted to occur following this form of activation history similar to muscular decremental states induced by long duration contractions (i.e., neuromuscular fatigue). These relationships indicate that there are potential counterbalancing strategies between the inhibition within the CNS and the contractile state of the muscle, to optimize system output (Grant et al., 2017; Sypkes et al., 2018). However, this is not always the case when conditions eliminate voluntary activation of the muscle; i.e., when electrically evoked contractions have been examined. Investigations of central excitability and fatigue, measured by MEP amplitude (Gandevia et al., 1999), F-waves (Khan et al., 2016), and voluntary activation (D'amico et al., 2020) have demonstrated opposing effects between tetanic and voluntary

contractions. Specifically, MEP amplitude initially (25s) increased then remained depressed for 5min following maximal voluntary contractions sustained for 120s, whereas tetanic contractions of the same duration elicited no change. Similarly, F-wave amplitude, recorded from the FDI, although not altered by electrically evoked contractions was shown to decrease following voluntary contractions sustained for 3min. Lastly, voluntary activation, reflective of voluntary drive at the muscle, has been shown to reduce following a 120s MVC, whereas it remains preserved following involuntary contractions of the same duration.

The main result of this study supports the idea that corticospinal inhibition and contractile enhancement change coincidentally, but there likely is no direct causal relationship. The data presented show not only elongation of the SP (~12%) following both high intensity voluntary and involuntary contractions, but there was also an elongation (~5%) when the muscle was not potentiated. The SP reflects both spinal and supraspinal inhibitory mechanisms, although distinct changes in duration may be influenced more by supraspinal (intracortical) inhibition (Škarabot et al., 2019), however, this is not always the case (McNeil et al., 2009). Unfortunately, the current study did not include segmental assessments of cortical and spinal properties to determine the locus of the change. It has been proposed that a possible mechanism for this corticospinal inhibition includes the reduced excitability of motor neurons within the spinal cord (Smith et al., 2020). Evidence for this was shown originally by Klein et al. (2001) demonstrating a reduced motor unit firing rates during submaximal isometric contractions when the muscle was potentiated. However, in a follow-up study by the same group testing older healthy adults, there was no correlation between potentiation and reduced firing rates following voluntary CC (Klein et al., 2002). That is, the older adults showed half the reduction in firing rate frequency (1Hz) compared to young adults, yet they demonstrated relatively high PAP twitch enhancement (233 ± 29%). Although old adults tend to potentiate less than young adults (Baudry et al., 2005), and such was seen within the aforementioned study, the older adults tested had over a two-fold increase in twitch amplitude following a six second contraction. This value was ~50% higher than that collected within the present study. This discrepancy between evident contractile enhancement from PAP and diminished effects on central inhibition (measured by firing rate) at the motorneuron indicate the potential lack of influence potentiation imparts on the CNS. Yet,

due to the presence of potentiation within the study presented by Klein et al. (2002), dissociation between the two events is impossible. When taken together with findings provided in the current study, evidence may indicate central alterations due to the act of force generation rather than peripheral modification directly due to potentiation.

Throughout a given contraction, it is understood that potentiation and neuromuscular fatigue can exist together, and the effect on the neuromuscular system is ultimately determined by the time a muscle is held under tension (Rassier & Macintosh, 2000). Fatigue is apparent under extended (>30s) high intensity (>75%) bouts of muscle contraction as well as extended (>10min) low level (25%MVC) contractions. Increases in SP duration have been reported following both types of fatiguing tasks (Mckay et al., 1996; McNeil et al., 2009; Taylor et al., 1996). Thus, to investigate alterations in CNS without confounds of neuromuscular fatigue following maximal contractions it is imperative to determine optimal contraction time that does not induce fatigue and maximises PAP. Vandervoort et al. (1983) demonstrated maximal potentiation within the tibialis anterior to be induced with a 10s CC. Moreover, Smith et al. (2020) employed this same duration to induce potentiation and found negligible evidence of fatigue. This duration was also used in the present study and upon investigation there was no apparent fatigue. This was assessed by a lack of decline in MVC amplitudes during the 10s as well as across the protocol. Furthermore, submaximal contractions of the same duration demonstrate no visible fatigue or potentiation, yet they revealed significant increases of corticospinal inhibition seen in longer SP durations. Thus, providing further confidence towards the absent impact of neuromuscular fatigue within the present study.

Not only was the SP prolonged with voluntary CCs, but results also show increased corticospinal inhibition with involuntary tetanic contractions in both maximal and submaximal conditions. This finding is in agreeance with Smith et al. (2020) indicating that voluntary drive was not the key factor inducing corticospinal inhibition and the increase in SP duration is likely due to feedback originating in the muscle. However, because changes were apparent regardless of the state of potentiation, it is unlikely that a feedback mechanism related to the muscle contractile state of potentiation is what causes the increase in SP duration. These results also indicate that it is unlikely that antidromic feedback involved with tetanus was directly inhibiting

corticospinal excitability. These are important findings that together indicate the involvement of some other peripheral afferents providing feedback related to muscle activation.

The effect of small diameter muscle afferents (III/IV) on the SP have been investigated during sustained fatiguing contractions of the biceps brachii in which the SP was elongated yet returned to baseline values despite complete occlusion (Gandevia et al., 1996). This indicated a lack of influence from metabolite sensitivity on SP lengthening. Afferent feedback arising from pain has been reported to prolong the SP (Svensson et al., 2003), however, in the current study, although not objectively assessed, there was no apparent effect of pain associated with any of the conditions or tasks. Large diameter afferents such as type Ia (muscle spindles) and Ib (Golgi tendon organs) have yet to be tested under conditions of PAP/PTP conditions. These may provide feedback that affects corticospinal excitability and indeed may inhibit the corticospinal tract. Golgi tendon organs providing feedback via Ib afferents seem a likely candidate in influencing corticospinal inhibition. Golgi tendon organs, located at the junctions of muscle fibers and their tendons (Houk & Henneman, 1967), act to provide consistent inhibitory afferent feedback with concurrent increases in tension (Edin & Vallbo, 1990). Specifically, exciting internuncial cells within the cord, which ultimately leads to the inhibition of motor neurons of the same muscle (Houk & Henneman, 1967). Therefore, at lower contraction intensities fewer motor units are affected and might act to explain the lesser degree of inhibition within the corticospinal tract that was observed in the present study. Muscle spindles, located within the muscle detect changes in muscle fibre length and are active during bouts of isometric contractions as low as 5% MVC (D. Burke et al., 1978; Edin & Vallbo, 1990). Although the unloading of these receptors has been shown to influence the earlier section of the SP when elicited at 25% MVC (Yacyshyn et al., 2016); it remains questionable whether the impact is great enough to incite overall SP change following brief contraction.

In summary, results of the current study indicate that voluntary and involuntary isometric contractions of 10s at lower (~40% MVC) and higher intensities (~100% MVC) induce significant corticospinal inhibition, albeit to a lesser degree at lower intensities. Furthermore, at this duration, involuntary tetanic contractions provide similar results to force-matched voluntary contractions indicating that the locus of this central change likely originates from peripheral

feedback. Taken together, evidence points towards muscle afferent activity providing inhibitory feedback during muscle contractions which may be mediated by differences in force/tension. Prior work provides evidence against metaboreceptor contribution (III/IV muscle afferents) to changes in the SP; thus, it is likely that other peripheral afferents (Ia and Ib) play an important role in influencing these changes in excitability. Overall, this study proposes that the CNS does not respond directly to the peripheral change of potentiation as was suggested by Smith and colleagues (2021), but arises instead as a result of the activation of the muscle, regardless of how it occurs.

3.2 Conclusions

This study characterized the effect of maximal and submaximal voluntary and involuntary brief contractions on corticospinal excitability. This was completed by measuring SP durations before and after brief conditioning contractions that either caused peripheral force enhancement or did not. The foremost finding was that SP durations were prolonged in both maximal and submaximal conditions, with the latter to a lesser degree. Additionally, it was observed that voluntary and involuntary contractions increased levels of inhibition similarly. Because voluntary and involuntary contractions interact with the CNS differently and a comparable effect between the two occurs, it is reasonable to expect that observed increases in corticospinal inhibition is a result of afferent(s) feedback at the level of the muscle. Furthermore, as a significant yet lesser degree of SP duration increase was observed at sub-maximal intensities, and which produced no visible potentiation, increases in corticospinal inhibition are likely from muscle afferents unrelated to altered states of intrinsic muscle contractility. Due to the differences in SP duration with high and low intensities, muscle afferent feedback relaying changes in muscle tension might be a primary candidate. A possible mechanism responsible for afferent feedback could be Golgi tendon organs which provide inhibitory feedback (based on muscle tension) to alpha motor neurons contributing to the contraction. Further investigation into the locus (cortical or spinal mediated) of corticospinal change is warranted as this would help provide further evidence towards the active mechanism(s) of corticospinal adaptation following brief contractions

3.3. Limitations

Understanding inhibition within the corticospinal tract using techniques such as TMS provides unique and useful views into the active state of the brain and spinal cord, yet it is not without limitations and challenges. Specifically, these are related to mechanical changes in the system and the influence of specific TMS parameters such as coil type and directionality.

The chemo-mechanical alterations of potentiation following the completion of a 10s contraction at a high intensity are readily evident with the assessment of twitch amplitudes. However, when completing a submaximal contraction of the same duration, twitch amplitudes

show no, or minimal change. Although one could argue that potentiation was not a contributing factor to the observed results within the current study, the internal mechanisms associated with potentiation are likely still occurring within the muscle. Regardless, the level of calcium sensitivity and phosphorylation of myosin heads needed to significantly change twitch amplitudes were low enough to virtually eliminate enhancement; and demonstrate the lack of influence this muscular property has on the CNS directly.

The coil used for the present study was a circular coil style which was held in a posterior-anterior direction over the vertex of the participant's skull. By completing the protocol with this approach, the selectivity of stimulation was compromised. This was intentionally completed to reduce the trial to trial and pre to post CC variability of the SP duration for accurate comparison. Because this approach was indeed less selective for the specific cortical site associated with the FDI within the primary motor cortex, a wide array of neural pathways were likely excited. Understandably, this reduction in selectivity could potentially alter acute responses within the CNS. As there are many collateral connections within the human brain, the corticospinal pathway acts likewise, and how non-focal stimulation effects observed results is unknown. However, it should be noted that in a sample of 4 participants the figure-of-eight coil was used and demonstrated similar elongation to the results obtained with the circular coil. The decision to ultimately use the circular coil came down to within trial variability which was far greater with the figure-of-eight coil.

The results indicate that a consistent increase in the SP, and therefore corticospinal inhibition, occurs following contractions of low and high intensities. As nice as that is, we currently do not know the site of this inhibition and what mechanism(s) are involved. Although we cannot determine the primary mechanism(s) of the change we know along the corticospinal pathway a form of afferent feedback is altering the resting excitability, likely by means of increased GABA.

Both males and females participated in the present study. However, due to the limited numbers of female participants differences in SP change and ADP regarding sex differences could not be formally related. However, using the limited sample two tailed t-tests were employed to

observe possible trends. No differences in baseline SP duration were observed between sexes, whereas SP duration increases were statistically lower in females post tetanic but not voluntary contractions. This finding may hold truth, however without more female participants it is impossible to conclude the true nature of this relationship.

3.3 Future Directions

The present study demonstrates consistent adaptation of the CNS following brief bouts of isometric muscle activation, regardless of peripheral enhancement. However, investigation into further CNS measures such as firing rates would be interesting to explore. It has been shown by Klein et al. (2001) that firing rates decrease when the muscle is highly potentiated. Firing rates rely heavily on the excitability of the CNS and if excitability is reduced (increased inhibition) as a result of non-potentiating and potentiating contractions, a lower firing rate may occur without the presence of muscle enhancement, similar to what we have seen in changes in SP duration. Therefore, a future study observing differences in the frequency of MU firing would help elucidate the relationship between peripheral enhancement and central inhibition.

As previously stated, the locus of inhibition cannot be elucidated through the current study. To rectify this challenge, future studies employing both cortical and spinal cord stimulation following maximal and submaximal contractions should be completed. Cortical stimulation using TMS provides an encompassing view of the whole corticospinal tract, whereas spinal cord stimulation (as the name denotes) stimulates the corticospinal tract below the level of the brain per se. Thus, when combined these techniques could elucidate whether the inhibitory effects, seen within the present study, rely primarily on cortical or spinal mechanisms.

The time course of recovery of twitch potentiation is a well-known assessment of the gradual change from enhancement to resting values (Baudry et al., 2008). Moreover, time course of corticospinal inhibition can be assessed with a similar manner, via the SP being evoked during low level contractions at similar intervals (Gandevia et al., 1996). Although we know the SP is prolonged immediately following a given CC, we do not know the time course of this effect. A

comparative view of the potencies of potentiation and SP over time may be useful to further investigate the possible link between muscle activation and corticospinal inhibition.

As an example of using a naturally adapted state, aged adults demonstrate a decrease in potentiation influence (Baudry et al., 2005; Petrella et al., 1989) following a conditioning contraction as well as longer resting baseline SP durations compared with young adults (Petitjean & Ko, 2013). However, it is currently unknown how the CNS of aged adults responds to brief contractions inducing potentiation or not. A more interesting approach to this gap in the literature would be to view twitch enhancement matched young and old adults to observe age related changes to corticospinal inhibition without confounds of potentiation differences. Because of reduced afferent feedback in aged adults (Roos et al., 2011) it would be interesting to see whether increases in SP duration are evident in either condition; if no changes are apparent, it would provide further evidence for the importance of muscle afferents on corticospinal modulation.

Previous work by Pääsuke et al. (2002) indicate the possibility for lower potentiation responses in females but this is not always the case (Simpson et al. 2018). Moreover, evidence for differences in corticospinal excitability is inadequate to conclude sex differences, although sex has been demonstrated to play a minor role in various measures such as MEP amplitude variability (Pitcher et al., 2003). Undeniably, systematic exploration of potential sex differences in corticospinal excitability following brief contractions should be completed to provide further knowledge for potential variances within the neuromuscular system.

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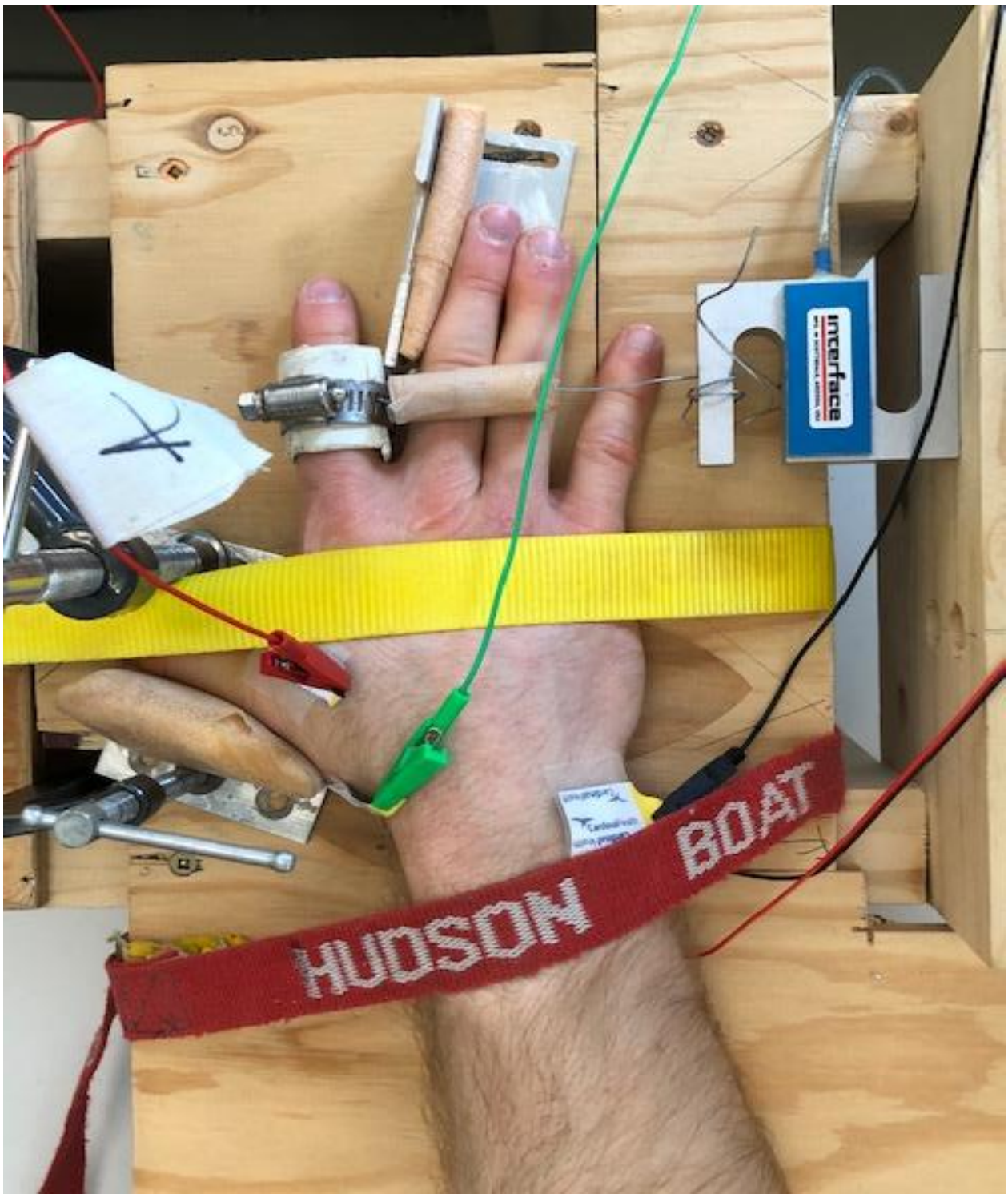
Appendices

Appendix A: Experimental Setup



Appendix B. Ethical Approval

Western Research

Date: 9 March 2022

To: Charles Rice

Project ID: 107505

Study Title: Motor neuron and muscle fiber resilience in humans

Application Type: Continuing Ethics Review (CER) Form

Review Type: Delegated

Date Approval Issued: 09/Mar/2022

REB Approval Expiry Date: 07/Mar/2023

***Ethics Approval Lapse:** March 8 - 9, 2022**

Dear Charles Rice,

The Western University Research Ethics Board has reviewed the application. This study, including all currently approved documents, has been re-approved until the expiry date noted above.

REB members involved in the research project do not participate in the review, discussion or decision.

Western University REB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The REB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

The Office of Human Research Ethics

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Curriculum Vitae

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2016 – 2020 Honours Bachelor of Arts in Kinesiology (Dean's List) University of Western Ontario

2020 – 2022 MSc, School of Kinesiology University of Western Ontario

Honours and awards, and scholarships: Stober Fellowship (PhD) award (2022)

Natural Science and Engineering Research Council

USRA Scholarship (Summer 2020)

Dean's Honour List (2019-2020)

Teaching Assistant

2022/01 – 2022/05 Kinesiology 3495B – Practical Aspects of Strength and Conditioning for High Performance

2021/09 – 2021/12 Kinesiology 4430F – Neuromuscular Physiology

2021/01 – 2021/05 Kinesiology 4457B – Ergonomics and Aging

2020/09 – 2020/12 Kinesiology 4430F – Neuromuscular Physiology

Publications

Paish, A.D (2021) Utilizing creativity in research. Inspiring minds – Showcasing Western's Graduate Research, Scholarship and Creative Activity. 49. https://ir.lib.uwo.ca/inspiringminds/49

Paish A.D, Kirk EA, Rice C.L (2021) Stimulated disruption of cortical or spinal activity during voluntary movement preparation. Abstract in Press *Neuroscience Meeting Planner*.

Paish A.D, Zero A.M, Rice C.L (2022) Effect of maximal and submaximal muscle activation on corticospinal excitability in humans. Abstract in Press *FASEB Journal.*

Conference Presentations

Paish A.D & Rice C.L (2020) Neuromuscular efficiency of old adults following postactivation potentiation. Health and Rehabilitation Science Graduate Research Conference (oral presentation) February 2-3, Virtual, 2020.

Paish A.D, Zero A.M, Rice C.L (2021) Corticospinal excitability following voluntary and stimulated conditioning contractions. Kinesiology Graduate Studies Research Conference (KGSRC) (oral presentation) April 12, Virtual, 2021.

Paish A.D, Kirk E.A, Rice C.L (2021) Stimulated disruption of cortical or spinal activity during voluntary movement preparation. Society for Neuroscience Global Connectome (poster presentation) November 8-12, Virtual, 2021.

Paish A.D, Kirk E.A, Rice C.L (2022) Altered kinematic responses following cortical and spinal stimulation. Health Science Research Conference (oral presentation) February 3, Virtual, 2022.

Paish A.D, Zero A.M, Rice C.L (2022) Effect of maximal and submaximal muscle activation on corticospinal excitability in humans. Federation of American Societies for Experimental Biology (FASEB), Experimental Biology (poster presentation).