The effect of chronic resistance training on spinal excitability of the biceps brachii

By

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Abstract

One major benefit of resistance training (RT) is increasing strength. However, the neurophysiological changes that chronic RT produces in the nervous system remain unclear. To address this, seventeen participants (9 males and 8 females) were recruited and divided into non-resistance and chronic resistance-trained groups to explore different levels of corticospinal tract excitability using a transcranial magnetic stimulation (TMS) that produces motor evoked potentials (MEP), and transmastoid electrical stimulation (TMES) that produces cervicomedullary evoked potentials (CMEP), and Erb's point stimulation that produces maximal compound muscle action potentials (Mmax). All participants performed a maximum voluntary contraction (MVC) of the biceps brachii, followed by determining the stimulation intensities during a 20% MVC for TMS to achieve a 150-200ms silent period and TMES that produced a CMEP amplitude that was 75% of Mwave. The main task included five isometric elbow contractions at 25%, 50%, and 75% of MVC for eight seconds, with three stimulation techniques applied at 3, 4.5, and 6 seconds in a randomized order. Participants received a Mwave, five TMS, five TMES, and five conditioned TMES (100ms after MEP) at each contraction intensity. Data analysis using t-tests and two-way ANOVAs with contraction intensity and group and contraction intensity and sex as factors revealed that the chronic RT group required less TMS output to achieve the desired silent period ($p=0.003$) and had a lower active motor threshold ($p<0.001$). The chronic RT group exhibited 50% and 90.1% higher amplitude in conditioned and unconditioned CMEP, respectively compared to the non-RT group. Furthermore, males had 50.5% and 112.7% higher amplitudes in conditioned and unconditioned CMEP, respectively compared to females. In conclusion, chronic RT induces neurophysiological adaptations that alter the spinal excitability, showing that it is sex dependent. The alteration in corticospinal tract excitability may occur at the spinal motoneuron.

Keywords: Transmastoid electrical stimulation, transcranial magnetic stimulation, corticospinal tract, motoneuron excitability, electromyography.

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List of abbreviations

- Afterhyperpolarization (AHP)
- Central nervous system (CNS)
- Cervicomedullary Motor evoked potential (CMEP)
- Cambridge Electronic Design (CED)
- Cortical silent period (CSP)
- Electromyography (EMG)
- Fast-twitch fatigable (FF)
- Fast-twitch fatigue-resistance (FFR)
- Gamma-aminobutyric acid (GABA)
- Human Kinetics and Recreation (HKR)
- Interstimulus interval (ISI)
- Neuromuscular fatigue (NMF)
- Nerve conduction velocity (NVC)
- Maximal compound muscle action potential (M-max)
- Motor evoked potential (MEP)
- Maximal voluntary contraction (MVC)
- Persistent inward current (PIC)
- Physical Activity Readiness Questionnaire (PARQ)
- Post exercise facilitation (PEF)
- Resistance trained (RT)
- Slow-twitch fatigue-resistance (SFR)
- Transmastoid electrical stimulation (TMES)
- Transcranial electrical stimulation (TES)
- Transcranial magnetic stimulation (TMS)

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1.0 Review of literature

1.1 Introduction

Resistance training (RT) has been a safe and adequate exercise method for everyone, from sedentary to athletes and neurological patients. RT offers a wide range of possibilities in speed, loads, methods, and instruments used to exercise, leading to muscular adaptations, increasing strength, endurance, and muscular fiber cross-sectional area. These changes depend on different factors like muscles trained, the number of times training occurs in a week and the type of training (Gómez-Feria et al., 2023). Some musculoskeletal adaptations (strength, muscle density, and architecture) will start during acute RT; some of the changes will transfer to chronic RT, and others will come to light only after a year or more of RT. The musculoskeletal system is not the only system in which adaptations occur. There will also be adaptations in the nervous system. All of which will lead to increased force output and overall strength. Studies have shown that RT leads to changes in neural excitability such as changes in motor-evoked potential amplitudes, silent period, and motor unit firing rate (Maeo et al., 2021; Pearcey et al., 2014; Siddique et al., 2020). There are different ways to measure these changes and explore at what level of the corticospinal tract some of these adaptations occur. Evoked potential responses can be recorded in a given muscle of interest from different levels of the corticospinal tract including the cerebral cortex, spinal cord and the peripheral nerves. Studies have shown mixed results when studying acute and chronic RT (Latella et al., 2017; Maeo et al., 2021; Parsowith et al., 2023; Yacyshyn et al., 2020). In a systematic review of neural adaptations produced by RT, there are clear differences in protocols and stimulation paradigms that lead to mixed results, specifically with the motor-evoked potential amplitude (Gómez-Feria et al., 2023). As mentioned above, RT is a form of exercise that leads to muscular and neurological adaptations. Neurophysiological changes related to RT are still

being investigated to further understand the benefits of RT and how these adaptations could increase strength. The benefits and adaptations related to RT will be discussed in depth below.

1.2 Resistance training

RT, also known as strength training, is a modality of repeated short-term and high-intensity exercise against a progressive external load (Khadanga et al., 2019; Kraemer et al., 2002; Kraemer & Ratamess, 2004; Krutki et al., 2017) that leads to increased force output and strength. Numerous researchers have also reported other health benefits of RT including improving functional capacity, performance, metabolic profile, coordination, and psychosocial well-being, as well as reducing the risk of cardiopulmonary, psychological, and neuromuscular disorders (D'Aurea et al., 2019; Khadanga et al., 2019; Kraemer et al., 2002; Taylor et al., 2014; Winett & Carpinelli, 2001).

Previous research has stablished that, resistance exercise can change the morphology of muscles (e.g., muscle architecture and its connective tissue attachments) and the responsiveness of the central nervous system at the cortical and spinal levels (Enoka & Fuglevand, 2001; McNeil et al., 2013). There is ample evidence that supports the effectiveness of RT increased strength due to increased cortical and spinal excitability of cortical and spinal motoneurons (i.e., higher discharge rate (Siddique, Rahman, Frazer, Pearce, et al., 2020), earlier firing and higher firing frequency, and lower interspike intervals (Cutsem et al., 1998), altered expression of myosin heavy chain isoform, and hypertrophy of muscles (Abernethy et al., 1994; Cutsem et al., 1998; del Olmo et al., 2006; Pearcey et al., 2014; Philpott et al., 2015). On the other hand, reduced activity and muscle disuse are associated with reduced strength due to muscle atrophy, changes in contractile properties of muscles, and reduced corticospinal excitability (Button & Kalmar, 2019). The possibility of neuromuscular adaptations to resistance exercise is a fundamental principle for

custom-programming of training besides progressive overload (i.e., gradual increase in force), specificity in the target muscle group, and variation of exercises (i.e., to keep training enjoyable and efficient) (Garber et al., 2011; Kraemer et al., 2002; Kraemer & Ratamess, 2004).

1.2.1 Chronic vs. acute resistance exercise

Exercise is a biological stress that induces body reactions by increasing and altering homeostasis mechanisms like breathing rate, heart rate, blood flow to the muscles, temperature, sweating, oxygen consumption, hormonal secretion, and glycolytic flux (Lambert, 2016). Moreover, the pattern of muscle recruitment could be affected by exercise (Lambert, 2016). Despite debate among scientists, these changes are transient and return to the baseline level after an acute exercise. However, recurrent or chronic exercise leads to long lasting adaptations in the neuromuscular systems (Folland & Williams, 2007b). The type and extent of adaptations depend on the training stimulus (i.e., frequency, load, recovery times), training history, the initial level of strength, individual genetics, the static or dynamic nature of the exercise task, and participating limbs (Abernethy et al., 1994; Khadanga et al., 2019; Kraemer et al., 2002). General outcomes of exercise-induced adaptations make muscles stronger, more fatigue-resistant, and better coordinated (Folland & Williams, 2007b; Lambert, 2016).

Although the exact time course for acute and chronic exercise training has not been determined, early muscular adaptations and hypertrophy are reported after 6 to 7 weeks of regular high-intensity resistance training (Phillips, 2000), the adaptations produced during this time will be related to acute RT and will not have a long-lasting effect if RT stops. It was shown that the MVC and motor unit discharge rate rapidly increased immediately after 1 week of resistance training of the vastus lateralis. Then, by continuing the exercise training, the correlation between

MVC and motoneuron discharge rate decreased for 3 weeks and then increased until six weeks of exercise training (Kamen & Knight, 2004). After six weeks of RT, motoneuron discharge rates were 15% and 49% higher in young and old adults compared to their baseline levels (Kamen & Knight, 2004). In addition, three weeks of exercise training was reported to be enough to increase muscle strength (Siddique, Rahman, Frazer, Pearce, et al., 2020). Del Vecchio et al. (2019) reported that after a few sessions (less than 4 weeks) of resistance training, there is no change in the twitch properties of muscles activated by peripheral nerve stimulation; thus it could be concluded that any increase in muscle strength was due to neural adaptations (Del Vecchio et al., 2019). They attributed neural adaptations to a decrease in recruitment threshold and an increase in the discharge rate of motoneurons, probably due to high excitatory synaptic inputs or adaptations to motoneuron properties(Del Vecchio et al., 2019).

Contrary to abundant studies that reported the effectiveness of short-term resistance training on increasing motoneuron firing rate, limited evidence is available regarding the effects of long-term resistance training on motoneuron firing rate (Sterczala et al., 2018). At high contraction intensities (e.g., 70% MVC), researchers showed that there was no difference in firing rate and motor unit action potential amplitude between chronic (i.e., at least 4 years in this study) and non-resistance trained individuals (Sterczala et al., 2018). However, at lower force intensities (i.e., 40% MVC), chronic resistance trained individuals had a lower range of firing rate and motor unit action potential amplitude compared to non-resistance trained individuals. Probably due to lower motor unit recruitment, which can be inferred that trained individuals contract their muscle with less excitability of the motoneuron pool to match the same force intensity, less voluntary effort, and less fatigue at lower force output (Sterczala et al., 2018). Another study showed that twelve weeks of resistance exercise training of the ankle dorsiflexors improved MVC and

contraction speed (Cutsem et al., 1998). In a systematic review with meta-analysis, Siddique et al. (2019) reported that long-term resistance training increases muscular strength depending on the type of resistance used, isotonic or ballistic training (Siddique, Rahman, Frazer, Pearce, et al., 2020).

Chronic resistance training shifts myosin heavy chain isoforms towards type I and Iia, increases the number of fibers in skeletal muscles (probably by increasing differentiation of satellite cells), and increases endogenous glycogen reserve (Abernethy et al., 1994). Aagaard (2018) reported that prolonged weeks to months of heavy-load resistance training increases H-reflex (i.e., electrically induced spinal reflex with a submaximal stimulation that bypasses muscle spindle, presynaptic inhibition (Weiner, 1948) and V-wave (i.e., electrically induced spinal reflex similar to H-reflex, level of efferent and descending neural drive) with a supramaximal stimulation at the presence of voluntary muscle contraction (McNeil et al., 2013). The changes seen in the h-reflex indicated an enhanced neural drive in the descending CSP, which can be seen as an increase in motoneuron excitability or alterations in presynaptic inhibition. Changes in the V-wave could be caused by an increase in motoneuron recruitment responses, indicating altered excitability of the spinal motoneuron(Aagaard, 2018).

1.3 Motor cortex

The brain has been subject to extensive scientific scrutiny and remains a focal point of ongoing investigation and mapping initiatives. In the late 19th century, mapping of the motor cortex started the journey to identify and relate specific brain areas involved in movement. In 1870, Fritsch and Hitzig applied an electric current to the precentral cortex, inducing movement of a dog's limbs (Hagner, 2012). Later, Sherrington, in 1917, reported the movement of specific body

parts while electrically stimulating the precentral cortex (Sherrington, 2011). Penfield and his group used the same idea of electrical stimulation during surgery, allowing them to identify specific areas within the primary motor cortex, leading to Penfield's homunculus. One of the leading representatives of brain mapping was Korbinian Brodmann (1909), who demonstrated the differences in cytoarchitecture in the brain cortex. Moreover, he presented a map delineating 52 brain regions associated with various functions (Zilles, 2018). This map is invaluable in pinpointing the cortex's primary and secondary motor areas, thereby serving as a crucial tool for activating or inhibiting specific brain regions.

1.3.1 Motor cortex cells

The layers of the cortex are sequentially numbered, ranging from the last formed through neural migration to the initial one, designated as layers I to VI. An insightful examination of the motor cortex's fourth layer was undertaken by Cajal in 1899, characterizing it metaphorically as a "Row of violets flanked by weeds." (Cajal, 1899). This layer serves as a hub for neural processes and interconnections from overlying and underlying layers, thereby establishing connectivity between the superficial and deep regions of the motor cortex. In the primary motor cortex, the fifth layer predominantly comprises gigantopyramidal neurons, colloquially known as Betz cells, with dimensions ranging from 60 to 110µm. These distinctive cells are identifiable by their high-contrast nucleolus, substantial rough endoplasmic reticulum content, and an enlarged circumference in the dendrites (Sasaki & Iwata, 2001; Szocsics et al., 2021). The literature suggests varying perspectives on the projection pathways to layer four, with some proposing inputs from neurons in the ventrolateral thalamus, while others suggest terminations at the soma of Betz cells (Barbas & García-Cabezas, 2015; Lichtman et al., 2000). These neurons, constituting

approximately 79% of all large corticospinal neurons, play a pivotal role in orchestrating gross and refined movements, underscoring their significance in motor function.

1.4 Pyramidal Tract

Also known as the Corticospinal Tract (CST), the pyramidal tract is the principal motor pathway for voluntary movement. This pathway starts at the primary motor cortex and then descends through the internal capsule of the basal nuclei, to the midbrain, and into the brain stem, where the pyramids will cross at the olives. Studies by Ralston 1985 and later by Davidoff 1990 show that 75% of the fibers cross at the pyramid level while approximately 15% decussate at the spinal cord, and the remaining 10% will not cross (Davidoff, 1990; Hong et al., 2009; Ralston & Ralston, 1985). The origin of the CST can differ from person to person; a study showed that around 36.9% would originate from the motor cortex, 31.7% from the somatosensory cortex, 24.7% from the supplementary motor area and 6.7% from the dorsal premotor cortex (Jang, 2014). On one hand, the decussated fibers are located at the dorso-lateral funiculus of the spinal cord contralateral from its origin. On the other hand, the ipsilateral fibers are situated in the ventral and dorso-lateral funiculi of the spinal cord. The tract terminations are in the contralateral intermediate and ventral horns or at Rexe'd laminations V-VIII and IX (Kuypers, 1982). Axons from both lateral and ventral corticospinal tract synapse with lower motor neurons at the ventral horn of the spinal cord in monosynaptic or polysynaptic projections, producing excitability and inhibition.

1.4.1 Excitability and inhibition of the Corticospinal Tract

The cortical areas and neural pathways outlined earlier contribute to modulating neuronal excitability or inhibition, contingent upon their connections and neurotransmitter (NT) involvement. Glutamate and gamma-aminobutyric acid (GABA) emerge as pivotal NT in the

cerebral cortex, functioning as excitatory and inhibitory mediators, respectively. In the Corticospinal Tract (CST) context, the orchestration of movement involves communication between various brain regions and Betz cells. This communication primarily relies on glutamate to depolarize Betz cells, ultimately generating a mass depolarization signal upon reaching the neurons' threshold. This signal traverses the CST, culminating in a voluntary muscle contraction (VMC).

For experimental purposes, depolarization of neurons is induced through methods such as transcranial direct-current stimulation and transcranial magnetic stimulation (TMS) (del Olmo et al., 2006; Ferrucci et al., 2018; Spampinato et al., 2021). Once the CST is activated, a mechanism is required to halt neuronal excitability or maintain a resting potential without intended movement (Walton et al., 2021). The precise mechanisms underlying the inhibitory effects of rTMS are currently under exploration. At the molecular level, each neurotransmitter activates specific ion channels, permitting the influx of Sodium (Na+), Potassium (K+), and Chloride (Cl-). This, in turn, results in either depolarization or hyperpolarization of the neurons, delineating the intricate molecular processes involved in regulating excitability and inhibition within the Corticospinal Tract.

1.5 Spinal cord excitability

The excitability of the spinal cord is intricately influenced by the CST, which exhibits differential termination points in the spinal cord corresponding to specific motoneuron pools. Notably, cortically driven motoneurons governing upper limb musculature cease their projections at the cervical level, whereas those governing lower limb muscles extend to the lumbar region, concluding at the conus medullaris.

The muscles innervated by a particular nerve root are termed myotomes. As previously highlighted, alpha motoneurons (α-MN) in the ventral horn of the spinal cord establish monosynaptic or polysynaptic connections, receiving inputs from descending tracts. These connections are pivotal in innervating skeletal muscles, thereby orchestrating muscle contraction and tone. Crucially, the α-MN functions as integrators, harmonizing cortical and sensory inputs while modulating the excitation and inhibition of spinal interneurons. This dynamic interplay underscores the central role of α-MN in shaping the excitability landscape of the spinal cord, thereby contributing to the regulation of motor activity (Sherrington CS, 1906).

1.5.1 Physiology of motoneuron

Alpha motoneurons innervate extrafusal muscle fibers and, based on the muscle fiber, can be categorized into three groups: slow-twitch fatigue-resistance (SFR) (conduction velocity =85 m/s), fast-twitch fatigue-resistance (FFR), and fast-twitch fatigable (FF) (conduction velocity =100 m/s) motoneurons (Burke et al., 1973). SFR motoneurons have smaller cell bodies and lower stimulation thresholds. Therefore, the SFR is recruited first during muscle contraction. FF motoneurons often have larger cell bodies and are recruited after SFR motoneurons. FF motoneurons contribute to stronger contractions during explosive activities. The characteristics of FFR motoneurons are intermediate between SFR and FF motoneurons (Stifani, 2014). Motoneurons are neuromechanical interfaces that, by modulable latency, convert motor commands of the CNS into mechanical force in muscles (Del Vecchio et al., 2018). In addition, motoneurons are integrative transducers; hence, they receive and integrate voltage responses of dendrites and soma, then convert them to synaptic currents, which induce voltage change at the axon hillock (the most excitable part of the motoneuron) (Gardiner, 2011). Motoneurons have passive and active properties or voltage changes in response to weak resting cell membrane potential changes and

modulated ion-activation channels, respectively (Button & Kalmar, 2019). Rheobase, input resistance, spike threshold, and spike amplitude are some examples of passive properties, while afterhyperpolarization (AHP) duration and amplitude, firing rate, frequency-current relationship (slope of the line), and non-linear firing behavior are some examples of active properties (Button & Kalmar, 2019; Powers & Heckman, 2017). The properties of motoneurons in a pool are not exactly similar. For instance, in a motoneuron pool, the input resistance of each motoneuron may vary considerably from one another (Gardiner, 2011).

When a larger membrane potential change happens due to a small impulse or injected current, the motoneuron is more excitable (Gardiner, 2011). Ohm's law indicates that input resistance is inversely related to current. A motoneuron with higher input resistance requires less current to produce an action potential (Gardiner, 2011). The force output, contraction speed, and fatigue rate of motor units with low current thresholds are less than those with high current thresholds(Heckman, 2003). Rheobase current (the required current to induce action potential) reduction, increased input resistance, higher firing rate, and higher frequency-current slope indicate more excitability of motoneuron (Button & Kalmar, 2019; Gardiner, 2011; Powers & Heckman, 2017). AHP is the temporary and prolonged repolarization of the motoneuron below resting membrane potential immediately after action potential, probably due to activation of the calcium-activated potassium conductance, which disappears gradually (Gardiner, 2011). The most important factor of intrinsic excitability of the motoneuron is input resistance, which is its membrane resistance against the current that flows through it (Gardiner, 2011). Motoneuron recruitment follows a small to large order, the Henneman size principle, while their firing rate is non-linear, intrinsically modulated, and frequency-dependant at their synaptic input (Button & Kalmar, 2019; Powers & Heckman, 2017). In addition, motoneuron, like any other living cell, is

fatigable, and its discharge rate and spike-frequency adaptation are time-dependent (Button & Kalmar, 2019).

The body's simple, rhythmic, and complex movements are primarily mediated by precise and timely releases of neurotransmitters at the synaptic cleft. Based on the type of neurotransmitters, the synaptic drive could be excitatory (e.g., glutamate) or inhibitory (e.g., GABA and glycine) to the motoneurons. A combination of neurotransmitter-induced activation of ionotropic receptors and intrinsic membrane properties of motoneuron leads to action potential generation (Rekling et al., 2000). Modulatory inputs like motivation, exercise, and sleep-wake cycle can affect the excitability of the motoneurons through metabotropic receptors of amines, peptides, and some other transmitters by changing the function of postsynaptic ion channels and presynaptic release processes (Rekling et al., 2000). It was shown that motoneuron has nonlinearity in membrane response, a relationship of input resistance and rheobase current, between resting membrane potential and depolarization threshold. There is calcium-mediated persistent inward current (PIC) at the subthreshold, especially in smaller motoneurons, which results in a higher depolarization threshold (Gardiner, 2011; Heckman, 2003). The synaptic inputs at the motoneuron level induce PICs by ionic channels and ligand-gated receptors, which depolarize motoneuron membrane potential to a level near the voltage threshold (Button & Kalmar, 2019). Therefore, PICs increase the discharge rate of the motoneuron in the presence of a little synaptic input for an extended time.

Furthermore, PICs act as amplifiers for synaptic inputs and increase the gain of motoneuron firing frequency (i.e., a slight increase in input current increases firing frequency greatly) (Button & Kalmar, 2019; Heckman, 2003). Huh et al. (2017) found that PIC has a species-specific level and is larger in smaller animals compared to larger size animals. They concluded that due to this

difference, smaller animals have faster muscle fibers compared to large animals (Huh et al., 2017). Powers and Heckman (2017) found that synaptic input to the motoneuron pool activates PICs, which affects firing frequency nonlinearly. They suggested that motoneuron excitability could be linear by controlling the time-course of excitatory and inhibitory synaptic inputs to the motoneuron pool (Powers & Heckman, 2017). It has been reported that during self-sustained firing, PIC accounts for about 40% of depolarizing drive to the motoneuron (Button & Kalmar, 2019). Although not confirmed, some indirect evidence reported that central pattern generator (CPG), a complex network of spinal neurons that can be activated reflexively or through specialized spinal centers, plays a role in PIC activation and consequently on motoneuron excitability during activities like locomotion (Button & Kalmar, 2019).

1.6 Effects of resistance exercise on muscle

The primary morphological adaptations to resistance exercise involve an increase in the cross-sectional area of the entire muscle and individual muscle fibers, attributed to amplified myofibrillar size and number (Folland & Williams, 2007b). In the earliest stages of training, satellite cells are activated, playing a pivotal role in the hypertrophy response through their proliferation and subsequent fusion with existing fibers (Folland & Williams, 2007b). Beyond this central process, conceivable morphological adaptations encompass hyperplasia, alterations in fiber type, shifts in muscle architecture, variations in myofilament density, and adjustments to the structure of connective tissue and tendons (Folland & Williams, 2007b). The initial adaptation of muscle to exercise training is increased muscle force (Cutsem et al., 1998; Łochyński et al., 2016), which is attributed to changes in myosin heavy chain isoforms (Krutki et al., 2017), increased number of cross-bridge formation per cross-sectional area (Norenberg & Fitts, 2004), and

increased density of muscle fibers (Łochyński et al., 2016). After that, muscle mass increases by the growth of its contractile proteins (Krutki et al., 2017) and by activation and proliferation of the satellite cells, which lead to hypertrophy response following their fusion to the existing fibers (Folland & Williams, 2007a). An article published by Kojic in 2022 reported that the relationship between hypertrophy and strength is related to exercise (i.e., slower eccentric contraction indicates a higher relationship between hypertrophy and strength).

Increased contraction speed of the muscle is another early adaptation that can be attributed to the structural development and functional regulation of the sarcoplasmic reticulum and endoplasmic reticulum, as well as calcium-handling systems (increased rate of calcium uptake by sarcoplasmic reticulum due to higher activity of calcium ATPase, and concentration of calcium binding and transporting proteins) of muscle fibers (Łochyński et al., 2016). However, there are conflicting reports regarding the effectiveness of resistance training on sarcoplasmic reticulum calcium release or uptake and calcium ATPase activity after initial changes (Doss & Karpovich, 1965; Green et al., 1998). Lochynski et al. (2016) believed this conflict could be described based on the timing of structural and functional changes after resistance training. In this way, the increased speed at early stages occurs mainly due to functional mechanisms regulating calcium kinetics. In contrast, at later stages, structural remodeling of the calcium-handling system, calcium binding, and transporting proteins have a major role (Łochyński et al., 2016). The muscle activation latency, which means the delay between neural activity (previously considered from the resting position of muscle) and force generation, is not just a constant muscle property (Del Vecchio et al., 2018). Modulations of motoneurons by CNS and decreasing the stiffness of the musculotendinous junction with training at high forces and speeds could reduce muscle activation delay (Del Vecchio et al., 2018). Research findings demonstrated that increased contraction speed

occurs due to earlier motoneuron activation, decreased AHP time, and enhanced maximal firing rate (Cutsem et al., 1998).

The chosen type of muscle contractions during exercise training (i.e., concentric, isometric, and eccentric) can induce different force output and hypertrophic patterns in muscles. Studies show that the MVC of elbow flexors during eccentric contraction was nearly 14% and 40% higher than that of isometric and concentric contractions, respectively (Doss & Karpovich, 1965). Seger et al. (1998) showed that 10 weeks of maximal intensity eccentric or concentric resistance training causes a 3-4% increase in the cross-sectional area of the quadriceps muscle following eccentric training only (Seger et al., 1998). However, there is a controversy among researchers regarding the hypertrophy of muscle by eccentric and concentric exercise training (Franchi et al., 2017). Franchi et al. (2017) suggested that eccentric and concentric training regimes result in similar increases in muscle size when matched for either maximum load or work. However, different myogenic and molecular responses regulate distinct structural adaptations to eccentric or concentric training (Franchi et al., 2017), probably due to different neural activation patterns (Seger et al., 1998).

It has been shown that even short-term resistance training changes myosin heavy chain isoform content of skeletal muscle fibers and modifies the metabolic profile of fibers toward more oxidative and slower type (Iix to Iia) in humans and animals (Baldwin & Haddad, 2001; Carroll et al., 1998; Łochyński et al., 2016; Norenberg & Fitts, 2004). The structure of myosin molecule has 85% heavy chain and 15% light chain isoforms (Whalen, 1985), and contractile properties of muscle fibers of motor units are coupled with myosin heavy chain isoform protein expression (Łochyński et al., 2016). The majority of skeletal muscle functions are determined by its myosin-heavy chains. For instance, myosin heavy chain protein could determine the speed of cross-bridge

formation, cross-bridge binding strength, speed of fiber contraction, time to peak tension, ATP turnover, and ATPase activity (Abernethy et al., 1994). Indeed, there is genetic machinery in skeletal muscle fibers to simultaneously express the type (i.e., slow type I, fast type Iia, Iix, and Iib) and myosin heavy chain isoform content in response to activity demands (Baldwin & Haddad, 2001). However, changes in muscle strength are not strongly related to changes in myosin heavy chain isoform profile (Carroll et al., 1998). The level of physical activity/inactivity, along with endocrine activity, impacts cardiac and skeletal muscles. For instance, it has been shown that in skeletal muscles, hyperthyroidism, and unloading or reduced weight-bearing changes the content profile of myosin heavy chain isoform from slow to fast (Baldwin & Haddad, 2001). The reverse conversion of myosin heavy chain isoform content happens during hypothyroidism and resistance or endurance training.

It has been shown that short-term heavy resistance training by increasing the activity of some enzymes, such as those that participate in glucose phosphorylation and glycolysis, influences energy consumption and restoration in the body (Abernethy et al., 1994; Costill et al., 1979). Evidence shows that resistance training reduces lipid volume density in weight lifters when their lipid volume is lower than inactivity and endurance-trained individuals (Abernethy et al., 1994; Staron et al., 1984). On the other hand, seven months of withdrawing from resistance training has been shown to cause an increase in lipid volume density just in slow-twitch fibers, while both slow-twitch and fast-twitch fibers atrophied (Staron et al., 1981). Therefore, the structure and modalities of exercise affect the cytosolic and mitochondrial oxidative enzyme adaptation. Likewise, lipid metabolism has a greater role in resistance training. Furthermore, hypertrophy training weakens endogenous lipid density (Abernethy et al., 1994).

1.7.1 Effects of resistance exercise on the central nervous system

Using a SEMG in the agonist and antagonist muscle offers a visual and quantitative representation of activation, showing that both muscles will be active differently during resistance exercise. Specifically, the agonist muscle will have a greater EMG signal representing an increased central dive, while the antagonist will have a smaller signal output. The most acceptable explanation for increased strength after resistance training is related to the changes in the recruitment pattern of muscles and their coordination concerning the antagonist and synergist muscles (del Olmo et al., 2006).

At the cortex level, it has been shown that chronic resistance training decreases the process in which GABA inhibits interneurons that lead to intracortical inhibition, thus increases supraspinal descending drive that consequently improves muscle strength and voluntary activation (Lahouti et al., 2019). Lahouti et al. (2019) suggested that chronic resistance training (> 2 years) could induce neural adaptation, which cancels out intracortical inhibition and allows increased corticomotor drive to exercised muscles (Lahouti et al., 2019). However, this mechanism is not solely cortical; some spinal mechanisms probably play a role in this process (Nuzzo et al., 2017).

Voluntary exercise increases the excitability of the corticospinal pathway through a process referred to as post-exercise facilitation (PEF) (Aboodarda et al., 2015). PEF is transient and dissipates after 1-16 seconds post contraction. It was reported that during high contraction intensities of the biceps brachii, which last 10 seconds to 2 minutes, PEF occurs concurrently with decreased amplitude of the CMEP, which indicates increased supraspinal excitability and decreased spinal motoneuron excitability (Aboodarda et al., 2015; Gandevia et al., 1999). It was found that nearly 2 minutes of recovery is required until CMEP returns to its baseline level (Gandevia et al., 1999). They believed that one session of high-force isometric resistance training

improved CMEP responses not due to improved excitability of the motoneurons but higher facilitation and increased efficacy of the corticospinal motoneuronal synapses (Nuzzo et al., 2017). In a study conducted by del Olmo et al. (2006), the corticospinal excitability of motoneuron was tested in two groups of chronic (> 2 years) and non-resistance trained individuals. They showed that the output force of the biceps brachii significantly decreased after exercise training between 30-70% MVC, while there was no significant change in MEP amplitude and response latency (del Olmo et al., 2006). In a similar study, Philpott et al. (2015) reported a higher CMEP amplitude in the chronic-resistant training group in 50 and 75% of MVC with no significant difference in 90 and 100% of MVC. These findings support the idea that resistance training induces alterations in spinal origin. Therefore, based on significant differences in the CMEP amplitude, they attributed higher corticospinal excitability in the chronic resistance trained group due to changes in spinal excitability (Philpott et al., 2015). Pearcey et al. (2014) studied the corticospinal excitability of the motoneuron at ten different intensities of 10-100% MVC of the biceps brachii in chronic and non-resistance trained individuals. They reported that MEP amplitudes were similar between the two groups, up to 50% MVC; after that, MEP amplitudes lowered in the chronic resistance trained individuals after 50% MVC. However, the CMEP amplitudes were similar for both groups without significant differences. Therefore, they reported that at higher contraction intensities (i.e.,> 50% MVC), supraspinal excitability of the motoneuron was lower in chronic resistance trained individuals compared to non-resistance trained individuals, while the spinal excitability of both groups was similar (Pearcey et al., 2014). It is suggested that the decreased MEP could be related to an increase in firing rate or modulation of neural intrinsic properties related to the after-hyperpolarization potential, both related to chronic resistance training. Chronic resistance training was reported to decrease muscle co-activation during isometric elbow flexion, which could be

attributed to increased sensitivity of the descending drive at the spinal level or decreased reciprocal inhibition. Therefore, muscle activation is more efficient with lower required excitation and probably energy consumption (Pearcey et al., 2014). In contrast, a systematic review by Gomez-Feria 2023, showed that despite the RT modality, muscle strength increases are accompanied by a significant MEP amplitude increase and decrease in the corticospinal silent period in acute studies. Concluding that hypertrophy is not the only reason for increased force, but the neural adaptations RT produces (Gómez-Feria et al., 2023).

In a recent systematic review with meta-analysis, resistance training was reported to increase MEP amplitude as a measure of corticospinal excitability (Siddique, Rahman, Frazer, Pearce, et al., 2020). Moreover, it was reported that resistance training reduces the cortical silent period as a measure of corticospinal inhibition (Siddique, Rahman, Frazer, Pearce, et al., 2020). Interestingly, these authors reported that resistance training did not affect the amplitude of the CMEP twitch forces. Chronic resistance training increases motoneuron firing and discharge rates, consequently providing higher contraction strength, especially at higher target force intensities (Siddique, Rahman, Frazer, Pearce, et al., 2020) and voluntary contraction speed (Christie & Kamen, 2010; Cutsem et al., 1998).

Resistance training could increase the excitability of motoneurons by activating PICs and inducing adaptive changes in motoneurons such as shorter spike duration, earlier recruitment, higher input resistance, lower rheobase current, increase in maximal firing rate, higher discharge frequencies, and increase in slopes of frequency-current relationships (Button & Kalmar, 2019; Christie & Kamen, 2010; Cutsem et al., 1998; Krutki et al., 2017). PICs have dendritic origins and are intrinsic mechanisms of the motoneuron, which affect discharge rates, firing frequencies, and the gain of the motoneuron, regardless of the descending and ascending drive to recruit the

motoneuron (Button & Kalmar, 2019; Heckman, 2003). PICs are responsible for bistable behavior, self-sustained firing, and plateau potentials in motoneurons. The amplitude of dendritic PIC is larger during exercise and activities that need further force (e.g., fight or flight or activities that need more than 50% to 80% MVC) due to an increase in the synaptic input by excitatory brainstem-released monoamines (e.g., serotonin by caudal raphe nucleus and norepinephrine by locus coeruleus), as well as an increase in inhibitory serotonergic activity on peripheral sensory inputs, which could potentially be the response to changes in blood PH during exercise (Heckman, 2003). Moreover, the noradrenergic system plays a significant role during exercise by providing higher consciousness for participants (Heckman, 2003). A study showed that two weeks of isometric resistance training of the ankle dorsiflexors reduces the duration of the motoneuron AHP (Christie & Kamen, 2010). Despite these findings, there are conflicting reports regarding the impact of resistance training on intrinsic characteristics of motoneurons. It was shown that the slope of the correlation line between muscle force and motoneuron discharge rate was not different at different target force intensities. However, by increasing the intensity of the target force, the discharge rate of the motoneuron goes up (Del Vecchio et al., 2019), which could be inferred that resistance training does not affect the intrinsic characteristics of the motoneuron. On the other hand, it potentially meant that an increase in motoneuron adaptation to excitability, presynaptic inhibition, changes in motoneuron ionic conductance, or cortical neuromodulation of motoneurons all play a role (Del Vecchio et al., 2019).

Contrary to the aforementioned reports, resistance training has no effect on the firing rate of motoneuron at submaximal contractions. Sterczala et al. (2018), by investigating the impact of chronic resistance training on isometric contraction in the first dorsal interosseous muscle at 40% and 70% of maximum voluntary contraction (MVC), showed a lower mean firing rate and

recruitment of motoneurons between groups. They reported the leftward shift of the force-frequency correlation line during 40% MVC as an indication of less excitability of the motoneuron pool to provide the same relative force. Notably, the firing rate will not increase exponentially nor linearly with increasing excitation but with a sudden increase with a plateau, minimizing other possible increases. Furthermore, they suggested that providing the same relative force with fewer active motoneurons and lower firing rates could be a fatigue-protecting and energy-reserving mechanism during moderate-intensity submaximal contractions (Sterczala et al., 2018).

1.7 Techniques to test motoneuron excitability

The examination of motoneuron excitability in humans relies on non-invasive and indirect measures for safety reasons. Testing the excitability of the motoneuron can be done for a single motoneuron or a group of motoneurons (i.e., motoneuron pool) (Cutsem et al., 1998; McNeil et al., 2013). The most common techniques used to test human motoneuron pool excitability are non-invasive nerve stimulations (i.e., H-reflex, F-wave, tendon jerk, and V-wave), transmastoid electrical stimulation (TMES), transcranial magnetic stimulation (TMS), and transcranial electrical stimulation (TES) (McNeil et al., 2013; Pearcey et al., 2014).

Applying H-reflex to interpret motoneuron excitability could be problematic since the magnitude of H-reflex response is sensitive to presynaptic inhibition (McNeil et al., 2013). In addition, the V-wave shows the overall motor output of the motoneuron pool due to the activation of descending central pathways (Aagaard et al., 2002). Several factors can affect the V-wave amplitude, including motoneurons' number and firing rate, their responsiveness, and synaptic transmission of the motoneurons and Ia afferents involved in the voluntary contraction (Siddique, Rahman, Frazer, Pearce, et al., 2020). Therefore, the popularity of reflex techniques has decreased.

However, combining reflex techniques with more recently introduced technologies is still prevalent. For instance, peripheral nerve stimulation during maximal voluntary contraction is a technique to assess the excitability of the cortical motoneuronal pathway by producing superimposed twitch (added torque). However, this technique cannot show the site of the neural adaptation (Nuzzo et al., 2017). Likewise, motor evoked potentials (MEP) can be used during MVC to induce superimposed twitch to test voluntary contraction (Nuzzo et al., 2017), and this technique can give details on whether or not motor cortex activation has been altered by training or fatigue or whatever the intervention may have been.

TMS is a non-invasive and safe technique of placing a magnetic coil over the motor cortex to induceelectrical currents in underlying intracortical and corticospinal neurons by fast-changing magnetic fields (Kobayashi & Pascual-Leone, 2003; Siddique, Rahman, Frazer, Pearce, et al., 2020). Barker et al. (1985) applied TMS for the first time on the human motor cortex (Barker et al., 1985). Under Faraday's law, TMS produces a magnetic field leading to an electric field, that can stimulate neural activity. TMS induces two waves, a direct wave (D-wave) and an indirect wave (I-wave). On the one hand, D-waves are the direct response of the TMS pulse, showing the immediate activation of the motor cortex. On the other hand, I-waves represent the intermediary motoneuron pathways that can be seen at a later component of the MEP. Once the cortical motoneurons activate there are descending volleys of action potentials through the CST, which produce MEP in muscles (Siddique, Rahman, Frazer, Pearce, et al., 2020).

The silent period is a short time interval that can be observed immediately after eliciting a MEP using TMS or TMES to activate a target muscle. It was first introduced in 1919 by Hoffmann (Suyama et al., 1996). During the silent period, the contracting target muscle's background electromyography (EMG) activity is missing. Therefore, the silent period can be measured as the

time interval from the start of the MEP and the reappearance of the EMG activity of the target muscle (Suyama et al., 1996). It was reported by Suyama et al. (1996) that the silent period is sensitive to the intensity of stimulation and will increase with increasing intensity of the stimulation. However, the increment of the target muscle's contraction force does not influence the silent period. They found that the silent period differs for the upper and lower limb muscles but does not correlate with the participant's contraction force (Suyama et al., 1996).

The silent period was primarily considered a cortical-based process or cortical silent period (CSP). However, it's considered a spinal-based process lasting 50-150ms (Fuhr et al., 1991; Yacyshyn et al., 2016). The spinal mechanisms thought to contribute to the first 50-80ms of the silent period are motoneuron AHP and recurrent inhibition by Renshaw cells (i.e., inhibitory interneurons found in the gray matter of the spinal cord) or Ia interneurons while the remaining time of the silent period is mediated by GABAb neurotransmitter due to inhibitory activity of GABAergic interneurons (i.e., cortical inhibitory mechanisms) (Damron et al., 2008; Inghillerj et al., 1992; Kim et al., 2005; Siddique, Rahman, Frazer, Pearce, et al., 2020; Yacyshyn et al., 2016). Moreover, muscle spindle unloading and Golgi tendon organ inhibition in response to large muscle twitch following conditioning TMS and axon conduction perturbation may also play a role in the latter time frame of the silent period (Cantello et al., 1992; Suyama et al., 1996; Yacyshyn et al., 2016).

The use of the silent period has scientific and clinical applications, such as evaluating neurophysiology and plasticity, investigating the pathophysiology of various neurological disorders like Parkinson's disease, stroke, epilepsy, and multiple sclerosis, as well as a diagnostic tool for some neurological diseases like amyotrophic lateral sclerosis (Damron et al., 2008). Suyama et al. (1996) reported that a silent period could be used as an indicator to detect spasticity

and its severity, and in their study, patients with cervical myelopathy had shorter silent periods than healthy individuals. Furthermore, higher spasticity was associated with a shorter silent period (Suyama et al., 1996).

No consensus exists on the best method to assess and quantify the silent period. The effective intensity of the TMS to elicit a silent period was different in previous studies, ranging from 10% to 100% above the resting or active motor thresholds (Damron et al., 2008; Jaberzadeh et al., 2008; Kang et al., 2007). Visual analysis and mathematical threshold approaches are common methods of quantifying the silent period. Both of these methods are affected by the determination of the onset (i.e., at the start of the MEP, at the end of the MEP, or the TMS stimulus delivery) and offset points of the silent period; the visual method is slightly more reliable than the mathematical method (Damron et al., 2008). Higher stimulation intensity results in a more reliable silent period, while differences in muscle contraction intensity have no significant effect on the duration of the silent period (Damron et al., 2008). However, the relationship between the motor-evoked potential and the duration of the silent period needs further investigation (Kim et al., 2005).

TMES is a technique of passing an electrical or magnetic stimulation using electrodes or coils to the mastoid processes at the cervicomedullary junction to induce subcortical volleys of action potentials in muscles (Nuzzo et al., 2017; Siddique, Rahman, Frazer, Pearce, et al., 2020). The CMEP response due to electrical stimulation is preferable for short-term applications. Electrical-induced CMEP can be problematic in long-term applications due to the reliability of electrode attachment sites and the existence of skin and tissue resistance against passing electrical currents. Therefore, using a cone of magnetic coils at the back of the scalp could be a better choice for long-term evaluations (Martin et al., 2009; Nuzzo et al., 2017).

The pitfall of using TMES to elicit CMEP to assess the excitability of the spinal motoneuron pool is uncontrollable supraspinal interference due to the participant instinctively "tensing up" in anticipation of the stimulus (McNeil et al., 2013). However, pairing TMS and TMES is a promising way to overcome this issue. In this way, TMES delivered immediately after a TMS stimulation (i.e., during the silent period) with a short inter-stimulus interval (i.e., ~ 50-200ms). The conditioned CMEP elicited by this relatively new technique can be the most accurate representation of only spinal excitability of the motoneuron pool (McNeil et al., 2013) since there is no supraspinal interference.

Moreover, the underestimation of the motoneuron activity due to signal cancellation is high (Siddique, Rahman, Frazer, Pearce, et al., 2020). For assessing spinal excitability during biceps brachii contractions, many researchers normalize CMEP amplitudes based on maximal muscle compound potentials (M-max) (i.e., the largest electrical response of a muscle when it is stimulated maximally, as an assessment of the muscle's maximal response to nerve stimulation) derived by Erb's point electrical stimulation (Philpott et al., 2015). M-max serves as a reference point for the maximum electrical response that can be obtained from the target muscle. Normalizing MEPs and CMEPs to Mwave serves as a way to standardize data for a more accurate and reliable comparison. After normalizing CMEPs it is a more acceptable method to investigate the motoneuron firing rate is exploring the recruitment pattern by observing the increase in the potential amplitude of motoneuron action from a lower to higher contraction intensity (Sterczala et al., 2018).

It is worth noting that the elicited evoked potentials of M-max, MEP, and CMEP by themselves, neither directly measure the excitability of the motoneuron nor are they related to the intrinsic passive properties of the motoneuron. These evoked potentials reflect the excitability of a variable quantity of motoneuron pool and depend on the characteristics of the stimulus, intrinsic

excitability of motoneurons, synaptic inputs, synaptic facilitation and inhibition, and descending drive (Button & Kalmar, 2019). In addition to techniques to elicit evoked motor potentials, technique and technology advances in EMG recording could affect the quality of motoneuron excitability studies. For instance, surface EMG electrodes and decomposition algorithms are developing, and their application in motoneuron excitability studies is increasing (Farina et al., 2010).

1.8 The effect of sex on CSE

Studies examining CSE aim to understand the differences between untrained and acute or chronic resistance-trained individuals, considering factors such as age, muscle mass, physical activity, and type of exercise. In most studies, there are male and female participants; in some cases, only males are recruited. In a meta-analysis by Gomez-Feria et al. (2023), 20 articles were selected to see the corticospinal adaptations following resistance training, and 18 studies showed the number of males and females recruited. No sex differences were reported in the meta-analysis, and no mention of any sex differences within any of the studies was reported (Gómez-Feria et al., 2023). The same can be seen in a study by Siddique et al. (2020), where 42 participants were recruited, 22 male and 20 female, and no sex differences in CSE were reported in any of the groups or muscle strength (Siddique, Rahman, Frazer, Leung, et al., 2020). Lastly, in a meta-analysis by Siddique et al. (2020) with 31 articles with male and female participants, no sex differences for any of the findings were reported (Siddique, Rahman, Frazer, Pearce, et al., 2020).

Olalekan et al. (2022) reported sex differences in muscle thickness and CSE in males and females. Results showed a positive correlation between %MSO and AMT with fat thickness and muscle size. There was also a negative correlation between MEP amplitude and skinfold thickness

in female participants. This is the first study examining sex-dependent differences in muscle size, subcutaneous fat thickness, and CSE. More studies are needed to better understand the sex differences in resistance training and CSE.

1.9 Conclusion.

This literature review has established how the neurological and musculoskeletal systems work and adapt together during RT exercise. Acute RT has been heavily studied for muscular and neurological adaptations, showing that an increase in strength is related to an increase in motoneuron firing rate. The transition from acute to chronic RT is still not established; it is known that some adaptations, such as increased strength and fatigue resistance, will carry on to chronic RT. While specific adaptations will occur due to chronic RT, such as the shift of myosin-heavy isoforms, other muscular adaptations can occur during this time. The adaptations produced in the nervous system are harder to understand due to the system's complexity. Using different stimulation techniques widens the researcher's possibilities to study different levels of the corticospinal tract. The literature review revealed controversial results regarding the effect of resistance training on motoneuron discharge rate at maximal versus submaximal MVC intensities, which could be attributed to the nature of exercises, design of studies, and selected group of motoneurons pool (Del Vecchio et al., 2019; Gómez-Feria et al., 2023; Herda et al., 2015). To lower the mixed results, adequate techniques, and paradigms must be used when looking at neural adaptations and excitability; measuring the responses in muscles that are typically resistance trained is crucial. Based on some of the submaximal contractions and stimulations (TMS, TMES, and Mwave) used in the articles reviewed, the paradigm for the study was created to determine how chronic RT affects spinal excitability. This work would help support two previous study from

our lab one by Pearcey et al. 2014 who showed changes in corticospinal excitability in chronic-RT and hypothesized that these changes were spinally driven and the second one by Olarogba et.al 2022 who showed correlations with CSE and muscle mas and subcutaneous fat between males and females.

1.10 Purpose of the study

Main objective

- Assess the influence of chronic resistance training background and sex on spinal motoneuron excitability of the biceps brachii at submaximal contraction intensities.

Specific objectives

- Examine active motor threshold, evoked potential amplitude and area, and response latency of the motoneuron pool by comparing Unconditioned CMEPs to Conditioned CMEPs (MEP-CMEP), and M-max at different submaximal force intensities between chronic- and non-resistance trained and male and female participants.

1.11 Research hypothesis

- The excitability of the spinal motoneuron pool of the biceps brachii will be higher in chronic- versus non-resistance trained participants during submaximal force intensities.
- The excitability of the spinal motoneuron pool of the biceps brachii will differ between male and females during submaximal force intensities.

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Co-authorship Statement

My, Wilhelm Moreno Roman, contributions to this thesis are outlined below:

-I recruited all participants and analyzed all data collected for this thesis with the assistance of my peers, Mr. Benjamin Nazaroff (master's student).

-I prepared the manuscript and thesis with the help and guidance of my supervisor, Dr. Duane Button.

- Dr. Duane Button provided constructive feedback on the manuscript and thesis.

Chapter 2

The effect of chronic resistance training and sex on spinal excitability of the biceps brachii

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2.0 Abstract

One major benefit of resistance training (RT) is increasing strength. However, the neurophysiological changes that chronic RT produces in the nervous system remain unclear. To address this, Seventeen participants (9 males and 8 females) were recruited and divided into non-resistance and chronic resistance-trained groups to explore different levels of corticospinal tract excitability using a transcranial magnetic stimulation (TMS) that produces a motor evoked potential (MEP), and transmastoid electrical stimulation (TMES) to measure the cervicomedullary evoked potentials (CMEP), and maximal compound muscle action potential (Mmax) amplitudes. All participants performed a maximum voluntary contraction (MVC) of the biceps brachii, followed by determining the stimulation intensities during a 20% MVC for TMS to achieve a 150-200ms silent period and TMES that produced a CMEP amplitude that was 75% of Mwave. The main task included five isometric elbow contractions at 25%, 50%, and 75% of MVC for eight seconds, with three stimulation techniques applied at 3, 4.5, and 6 seconds in a randomized order. Participants received a Mwave, five TMS, five TMES, and five conditioned TMES(100ms after MEP) at each contraction intensity. Data analysis using t-tests and two-way ANOVAs with contraction intensity and group and contraction intensity and sex as factors revealed that the chronic RT group required less TMS output to achieve the desired silent period ($p=0.003$) and had a lower active motor threshold ($p<0.001$). The chronic RT group exhibited 50% and 90.1% higher amplitude in conditioned and unconditioned CMEP, respectively compared to the non-RT group. Furthermore, males had 50.5% and 112.7% higher amplitudes in conditioned and unconditioned CMEP, respectively compared to females. In conclusion, chronic RT induces neurophysiological adaptations that alter the spinal excitability showing that it is sex dependent. The alteration in corticospinal tract excitability may occur at the spinal motoneuron.

Keywords: Transmastoid electrical stimulation, transcranial magnetic stimulation, corticospinal tract, motoneuron excitability, electromyography.

2.1 Introduction

The corticospinal tract and its excitation are very important for volitional muscle contraction. The examination of CSE in humans relies on non-invasive and indirect measures. The most common techniques used to test human motoneuron pool excitability are non-invasive nerve stimulations (H-reflex), transmastoid electrical stimulation (TMES), transcranial magnetic stimulation (TMS), and transcranial electrical stimulation (TES) (McNeil et al., 2013; Pearcey et al., 2014). TMS has been used to evoke the electrical currents that activate intracortical and corticospinal neurons by producing descending action potentials that can be recorded in the target muscle as a motor-evoked potential (MEP) using surface electromyography (sEMG) (Siddique et al., 2020). Following the MEP there is a short interval where no electrical activity is registered in the sEMG, known as the silent period (SP). The SP was primarily considered a cortical-based process or cortical silent period (CSP). Research shows that the SP has a cortical and spinal component. In a 50-150ms SP, the spinal mechanisms (i.e.,motoneuron afterhyperpolarization and recurrent inhibition by Renshaw cells or Ia interneurons) contribute to the first 50-80ms of the SP. The remaining time of the silent period is mediated by GABAb neurotransmitter due to inhibitory activity of GABAergic interneurons (cortical inhibitory mechanisms) (Damron et al., 2008; Inghillerj et al., 1992; Kim et al., 2005; Siddique et al., 2020; Yacyshyn et al., 2016). Moreover, muscle spindle unloading and Golgi tendon organ inhibition in response to large muscle twitch following conditioning TMS and axon conduction perturbation may also play a role in the latter time frame of the silent period (Cantello et al., 1992; Suyama et al., 1996; Yacyshyn et al., 2016). TMES is used as a measure of spinal excitability and the stimulation can be either electrical or magnetic at the cervicomedullary junction to induce subcortical volleys of action potentials, producing a cervicomedullary motor evoked potential (CMEP) (Nuzzo et al., 2017; Siddique et

al., 2020). A limitation of using TMES to measure spinal excitability is the constant signaling of the cortical motoneurons during volitional muscle contraction, which does not have an isolated measurement of spinal excitability. When TMES is delivered during the 150-200ms SP produced by the MEP (interrupting the descending drive), no cortical interference is present in the recorded CMEP amplitude making a more accurate representation of the spinal excitability of the spinal motoneuron pool (McNeil et al., 2013).

One way to enhance force output during volitional muscle contraction is through long-term resistance training (RT) (i.e. chronic RT). The effect of chronic RT on corticospinal excitability (CSE) along the corticospinal tract has been shown to be contradictory. These contrasting results may be due to studying CSE of muscles not typically resistance trained, such as the tibialis anterior (Tallent et al., 2013). At the cortex level, it has been shown that chronic RT decreases the process in which GABA inhibits interneurons that lead to the attenuation of the motor cortex, also referred to as intracortical inhibition, thus increasing supraspinal descending drive that consequently improves muscle strength and voluntary activation (Lahouti et al., 2019). This way, the intracortical inhibition decreases further and increases the output force. Lahouti et al. (2019) suggested that chronic resistance training (> 2 years) could induce neural adaptation, which cancels out intracortical inhibition and allows increased corticomotor drive to exercised muscles. However, this mechanism is not solely cortical; some spinal mechanisms probably play a role in this process (Nuzzo et al., 2017). In a study by del Olmo et al. (2006), the corticospinal excitability of motoneuron was tested in chronic and non-resistance-trained individuals. The output force of the biceps brachii significantly decreased after exercise training between 30-70% maximum voluntary contraction (MVC), while there was no significant change in MEP amplitude and

response latency. In a similar study, Philpott et al. (2015) reported a higher CMEP amplitude in the chronic RT group in 50 and 75% of MVC with no significant difference in 90 and 100% of MVC. These findings support the idea that RT induces alterations in spinal origin. Therefore, based on significant differences in the CMEP amplitude, they attributed higher corticospinal excitability in the chronic RT group to changes in spinal excitability (Philpott et al., 2015). Pearcey et al. (2014) reported that MEP amplitudes were lower in the chronic RT individuals from 50-100% MVC while there were no differences in CMEP amplitudes. However, they hypothesized that the reduced supraspinal excitability was due to an increase in motoneuron excitability (i.e. the high firing rates of the motoneurons masked the size of the MEP amplitude) in the chronic resistance trained individuals. One way to potentially alleviate this masking effect would be to evoke a CMEP during the CSP. During the CSP, an evoked CMEP would occur when volitional muscle contraction is momentarily silenced and does not impact the excitability of the motoneuron pool.

No sex differences were reported in the aforementioned studies and there is very little research focusing on understanding the adaptations in CSE between trained and untrained males and females. In a study by Olarogba et.al 2022, there is a positive correlation between %MSO at AMT and MVC, and MEP amplitude with muscle mass in males and a negative correlation between MEP amplitude and skinfold thickness in females. Another article by Leung et al. (2023) looked at differences between CSE between males and females in the quadriceps after ligament reconstruction, showing that male participants presented higher CSE after surgery in comparison with female participants (Leung et al., 2024). However, to our knowledge, no other articles have determined whether or not CSE is sex-dependent.

The current study aimed to investigate the changes in spinal excitability of the biceps brachii in chronically RT compared to non-trained individuals and whether spinal excitability is

sex dependent. Spinal excitability was quantified by comparing an unconditioned CMEP to a conditioned CMEP (evoked during a MEP silent period) of the biceps brachii during elbow flexor contractions at differing submaximal MVC intensities to measure changes at different force outputs. We hypothesized that spinal excitability of the biceps brachii would be higher in chronic resistance trained individuals during varying submaximal elbow flexor contraction intensities and that spinal excitability would be sex dependent.

2.2 Material and Methods

2.2.1 Participants

Seventeen apparently healthy participants with no known neurological or musculoskeletal impairments were recruited for this study. Using G*Power software (Faul et al., 2007) it was determined that a sample of fourteen participants was needed based on Pearcey et al, 2014. The seventeen subjects were divided into two groups: 9 chronic RT (5 males and 4 females) and 8 non-RT (4 males and 4 females). The chronic RT group participants had at least 1 year (≥3 times per week) of resistance training experience (why a year and not two). The resistance exercises should include high-intensity multi-joint movements such as squats, deadlifts, presses, and rows. The non-RT participants were not resistance trained in the past year or were entirely sedentary. Participants completed Physical Activity Readiness Questionnaire, Edinburg Handedness Inventory (15 and 2 participants were right and left-handed, respectively), TMS safety checklist, and consent forms. Participants were instructed to refrain from strenuous exercise (24 h), caffeine (12 h), alcohol (24 h), and any other substance (24 h) before participation (Walton et al., 2002; Weber, 1993). Before data collection, all participants were informed of all potential risks of the study via verbal and written explanation and were allowed to ask questions. All participants then gave written informed consent. The study was approved by The Memorial University of Newfoundland Interdisciplinary

Committee on Ethics in Human Research (ICEHR No. 20201414-HK) and was in accordance with the Tri-Council guidelines in Canada with full disclosure of potential risk.

2.2.2 Experimental setup

2.2.2.1 Elbow flexor force

Participants were seated in a custom-built chair (Technical Services, Memorial University of Newfoundland, St. John's, NL, Canada) in an upright position, with hips and knees flexed at 90º. The elbow was flexed at 90º. Both arms were slightly abducted and rested on a padded support. The forearm was held horizontal and positioned in a supinated position, and placed in a custom-made orthosis that was connected to a load cell (Omegadyne Inc., Sunbury, OH, USA). All forces were detected by the load cell and amplified (x1000) with a sampled rate of 2000 Hz, low-pass filtered (10 Hz cut off, four-order Butterworth filter) using a CED 1902 (Cambridge Electronic Design Ltd., Cambridge, UK). Participants were instructed to pull up on the orthosis by performing isometric contractions of the elbow flexors. A computer monitor was placed for visual feedback on their muscle activation and force production (see Figure 1 for details).

2.2.2.2Electromyography recording

Based on SENIAM recommendations (Hermens et al., 1999), EMG activity of the biceps brachii muscle was recorded using 10 mm diameter MediTrace Pellet Ag/AgCl electrodes (disc shape, Graphic Controls Ltd., Buffalo, NY). The electrodes were placed 2 cm apart (center to center) over the mid-muscle belly of the participant's biceps brachii. A ground electrode was placed on the lateral epicondyle of the same limb. Before the EMG acquisition, the skin overlying the biceps brachii was prepared by shaving hair, rubbing an abrasive gel to remove topical products or dead epithelial cells, and cleaning with a 70% isopropyl alcohol swab. An inter-electrode impedance of <5 KΩ was obtained during the noise test to ensure an adequate signal-noise ratio

seen in the background EMG before and after a submaximal contraction. The EMG signals were amplified (x 1000) using a CED 1902 amplifier and sampled at 5kHz using a Power 1401-3A data acquisition interface (16 Bits). All signals were band-pass filtered (10 - 1000 Hz, third order, Butterworth) and recorded using Signal data collection software (Cambridge Electronic Design Ltd., Cambridge, UK).

2.2.3 Stimulation conditions

All stimulation conditions and methods utilized in the current study were done in accordance with what has been reported previously from our laboratory that compared the corticospinal excitability of the biceps brachii in the dominant arm of chronic-RT and non-RT individuals (Pearcey et al., 2014). Motor responses from the dominant biceps brachii were elicited via brachial plexus electrical stimulation at Erb's point, transcranial magnetic stimulation (TMS), and transmastoid electrical stimulation (TMES). All stimulation intensities were set during an isometric elbow flexor contraction at 20% MVC.

Electrical stimulation was applied to Erb's point during a 20% MVC to evoke an M-max in the biceps brachii. Erb's point was electrically stimulated via adhesive electrodes fixed to the skin over the supraclavicular fossa (cathode) and the acromion process (anode). Current pulses (200 μs duration) were delivered via a current stimulator (DS7AH, Digitimer Ltd, Welwyn Garden City, UK). The electrical stimulation was gradually increased until the M-wave amplitude of the biceps brachii no longer increased. The stimulator setting used to evoke M-max at 20% MVC was recorded and used during the experimental protocol.

2.2.3.1Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation was delivered by a (Magstim 2002, Whitland, UK) 13.5 cm outside diameter circular coil over the motor cortex with stimulation going to the left or right

hemisphere, depending on the participant's handedness. The coil was placed horizontally over the vertex (the intersection of two imaginary lines from nasion to inion and from the tragus to contralateral tragus) (Lahouti et al., 2019) to produce a motor evoked potential (MEP) in the dominant biceps brachii. TMS was delivered during a 20%MVC, to identify the participant's active motor threshold (lowest stimulus intensity to elicit a MEP ≥200μV in 5 out of 10 consecutive trials during an isometric contraction) (AMT) using the Rossini-Rothwell method. Followed by an increase in stimulation intensity to produce a MEP with a silent period of 150 to 200 milliseconds. This TMS intensity was used for the remainder of the experiment.

2.2.3.2Transmastoid electrical stimulation (TMES)

Transmastoid electrical stimulation was delivered by a DS7AH constant current stimulator (Digitimer Ltd., UK) with rectangular pulses (200μs duration) to the cervicomedullary junction to excite axons of the corticospinal tract and evoke a CMEP in the biceps brachii of the dominant arm. Electrodes were placed over the mastoid processes. The anode electrode was placed ipsilateral to the dominant side, and the cathode electrode was placed on the contralateral side. During a 20% MVC contraction, TMES was delivered starting at a low intensity (e.g., 25mA) and gradually increasing the output until the CMEP amplitude reached ~75% M-max amplitude. This stimulation intensity elicited both unconditioned and conditioned CMEPs during all contractions. As per previous studies, the unconditioned CMEPs were defined when a TMES pulse was delivered by itself, while the conditioned CMEP occurs at 100ms in the silent period of a TMS-evoked MEP (McNeil et al., 2013). Close attention to the electrode placement and CMEPs latency was monitored at the pretest to ensure no ventral root axons were activated. It can be identify by an abrupt decrease of ~ 2ms in the response latency. CMEP latencies were always ~8.5 ms (Lockyer et al., 2019).

2.2.4 Experimental Protocol

The experiment was completed in a single session (~2 hrs). Prior to the start of the experimental protocol participants were prepped for EMG and stimulation conditions. The participants then performed isometric contractions of the dominant elbow flexors at different intensities of MVC to get accustomed to producing isometric force outputs. Participants then completed two elbow flexors MVCs. If the force measurements (N) were not within 5% of one another, a third MVC was performed, and the average force of the 3 trials was used as the participant MVC. Following the MVCs, participants rested for 3 minutes. Following the rest period, the intensities for each stimulation type were set. Participants received an Erb's point stimulation during a 20% MVC to evoke a M-wave of the biceps brachii. The intensity of the Erb's Point stimulation was gradually increased until the M-wave amplitude reached a plateau, and this plateau was considered M_{max} (~10 stimulations to reach the plateau). TMES intensity was gradually increased to evoke a CMEP amplitude of the biceps brachii that was ~75% of the M_{max}. TMS intensity was increased to determine AMT and then further increased to evoke a MEP with a cortical SP that was 150-200 ms in duration. Once the stimulation intensities were set, participants performed a voluntary isometric contraction protocol, which included 5 sets of 8s of biceps brachii contractions at 3 sequential target forces (25, 50, 75% MVC) for 15 contractions in total. Once the participants contracted to the set MVC percentage, they received a M-wave, TMS with conditioned CMEP, and unconditioned CMEP at 3, 4.5, and 6 seconds in a randomized order. M-wave was delivered once at 25, 50, and 75% MVC that were delivered at the first or last contraction for a total of 3 M-waves in total. To minimize participant fatigue, 30, 45, and 60 s rest was provided after each contraction at 25, 50, and 75% MVC, respectively. All participants received verbal encouragement to match the target forces, as well as visual feedback on the target

force and force production during all contraction intensities, by a monitor placed in front of the participants showing the force output with a red line in the target force during all trials (see Figure 1 for details).

2.2.5 Data and Statistical Analysis:

All data analyses were performed offline using Jamovi (The Jamovi project (2024), Version 2.3.28, [Computer Software]) and SPSS software (SPSS 25, IBM Corporation, Armonk, New York, USA). MVC, MEP, CMEP, and M-wave peak-to-peak amplitudes and onset latencies and MEP and CMEP SPs were measured during all contractions. Analysis was performed on a total of 1 M-waves, 5 MEPs, and 10 CMEPs (5 conditioned and 5 unconditioned) at each %MVC. MEPs and CMEPs were normalized to M-wave amplitude for each %MVC. At each %MVC, the amplitude of unconditioned CMEP was divided by the amplitude of the conditioned CMEP to quantify the effect of the cortical SP on the CMEP (i.e. spinal excitability). Onset latencies for M-waves, MEP, and CMEP were defined as the time between the stimulus artifact and the onset of the evoked potential. The MEP SP was measured from the start of the MEP to the start of the stimulus artifact of the CMEP. While the CMEP SP was measured from the start of the CMEP to the renewal of the sEMG.

A series of T-tests were used to assess the differences in stimulation intensities, AMT, MSO, and cortical SP between the Chronic and non-RT groups and between SEX. A two-way analysis of variance (ANOVA) (GROUP: Chronic and NON-RT and CONTRACTION INTENSITY: 25, 50, and 75% MVC) was performed to compare the conditioned and unconditioned CMEP amplitudes and SP, MEP amplitudes, and SP, and M-wave amplitude. Another two-way analysis of variance (ANOVA) (SEX: males and female and CONTRACTION INTENSITY: 25, 50, and 75% MVC) was performed to compare the conditioned and

unconditioned CMEP amplitudes and SP, MEP amplitudes, and SP, and M-wave amplitude. Normality of the data was calculated with Levene's test, and for the two-way ANOVA sphericity with Mauchly's test, Greenhouse-Geisser correction was also performed. If significant interactions occurred, a post-hoc Tukey Test was used to identify statistical differences with the factors used between and within groups. T and F ratios were considered statistically significant at $p < 0.05$. Data in text and table are reported as means ± SD and ranges and data in figures are reported as box and wiskers plots. For T-tests, Cohen's D qualitative descriptors of standardized effects were assessed using these criteria: trivial < 0.2, small 0.2-0.5, moderate 0.5-0.8, and large> 0.8 (Cohen, 1988). For F ratios, partial eta-squared ($p\eta 2$) measures indicating the magnitude of changes associated with significant main effects were provided and reported as small (< 0.01), medium (≥ 0.06), or large (≥ 0.14) (Cohen, 1992). Last, simple bivariate correlations (Pearson's r) were calculated between force and measures of spinal excitability. The strength of the correlation coefficients (r) was interpreted as <0.3 (negligible), 0.3–0.5 (weak), 0.5–0.7 (moderate), and 0.7–0.9 (strong) (Mukaka, 2012).

2.3 Results

Table's 1 and 2 report the raw data mean±SD, ranges, and significance for each dependent variable at each contraction intensity for chronic and non-RT groups and males and females, respectively. Table 3 reports the normalized (MEP and CMEP amplitudes normalized to M_{max} amplitude) for chronic and non-RT groups and males and females.

2.3.1 Force (N)

The chronic RT group produced 44.8% more (t_{14} =3.8, p <0.001, d =0.88) force than the non-RT group (Table 1). Males produced 98.1% more (t_{13} =9.09, p <0.001, d =2.05) force than females (Check variability at all contration intensities).

2.3.2 Stimulation intensities

The chronic RT group required 20% less (t_{14} =3.568, p =0.003, d= 1.798) MSO (figure 2A) and 36% less (t_{14} =11.372, p <0.001, d =5.731) AMT (figure 2C) to elicit the required MEP SP and MEP response in the biceps brachii, respectively. There were no differences between groups for the stimulation intensity to elicit a Mwave (t_{14} =-0.32, p =0.71, d =0.19) (figure E) response in the biceps brachii.

There were no differences between sex (t_{13} =1.3, p =0.2, d =0.67; t_{13} =0.4, p =0.67, d =0.22; and t_{13} =0.08, p =0.99, d =0.004) for MSO (figure 2B), AMT (figure 2D) or Mwave (figure 2F) to elicit the required MEP SP, MEP and Mwave response in the biceps brachii, respectively.

2.3.3 Compound muscle action potential

There was a significant main effect for GROUP ($F_{1, 41}$ =11.43; p <0.01, η^2p =0.218) on M_{max} amplitude. The chronic RT group had an 83.9% (10.3±5.8 mV vs. 5.6±1.8 mV) higher amplitude compared to the non-RT group.

There was a significant main effect for SEX ($F_{1, 41}$ =15.99; p <0.001, η^2p =0.281) on M_{max} amplitude. Males had a 103.8% (10.6±5.5 mV vs. 5.2±2.0 mV) higher amplitude compared to females.

2.3.4 Motor evoked potential

There was a significant main effect for GROUP ($F_{1, 229}$ =58.2; p <0.001, η^2p =0.203) on MEP amplitude. The chronic RT group had a 95.1% (8.0±4.8 mV vs. 4.1±1.9 mV) higher amplitude compared to the non-RT group. There was a significant main effect for GROUP ($F_{1, 234}$ =7.2; p <0.01, η^2p =0.03) and an interaction of GROUP X INTENSITY ($F_{2, 234}$ =5.6; p <0.01, η^2p =0.05) on the normalized MEP amplitude. Overall, the chronic RT group had a 10.1% (0.76±0.18 $\%M_{max}$ vs. 0.69±0.21 $\%M_{max}$) higher normalized MEP amplitude compared to non-RT group. Post

hoc comparisons showed that the chronic RT group had a 24 and 13.7% higher normalized MEP amplitude (%M_{max}) at 25 and 50% MVC, respectively, compared to non-RT group. There was no difference between groups at 75% MVC.

There was a significant main effect for SEX ($F_{1, 229}$ =66.6; p <0.001, η^2p =0.225) on MEP amplitude. Males had a 107% (8.1±4.7 mV vs. 3.9±2.3 mV) higher amplitude compared to females.

2.3.5 Spinal excitability

2.3.5.1 Conditioned and unconditioned CMEP

There was a significant main effect for GROUP ($F_{1, 229}$ =10.3; p <0.01, η^2p =0.043) and INTENSITY ($F_{2, 229}$ =3.5; p =0.031, η^2p =0.03) on conditioned CMEP amplitude. The chronic RT group had a 50% (3.9±3.65 mV vs. 2.6±1.8 mV) higher amplitude compared to the non-RT group. The intensity Post hoc comparisons showed that at 75% MVC, there was a 32.8% (2.7±2.9 mV vs. 3.9±3.1 mV) lower CMEP amplitude compared to 25% MVC. There were no other differences for intensity (Table 1). There was also a significant main effect for INTENSITY ($F_{2, 229}$ =3.5; p =0.032, η^2p =0.03) on the normalized conditioned CMEP amplitude. Post hoc comparisons showed that at 75% MVC, there was a 20% (0.4±0.3 %M_{max} vs. 0.5±0.2 %M_{max}) lower CMEP amplitude compared to 25% MVC.

There was a significant main effect for SEX ($F_{1, 229}$ =11.5; p <0.01, η^2p =0.048) on conditioned CMEP amplitude. Males had a 50.5% (3.9±3.8 mV vs. 2.6±1.3 mV) higher amplitude compared to females. There was also a significant main effect for SEX ($F_{2, 229}$ =16.3; p <0.001, η^2p =0.07) on the normalized conditioned CMEP amplitude. Males had a 27% (0.38±0.3 %M_{max} vs. 0.52±0.26 %M_{max}) lower normalized amplitude compared to females.

There was a significant main effect for GROUP ($F_{1, 229}$ =46.3; p <0.001, η^2p =0.17) on unconditioned CMEP amplitude. The chronic RT group had a 90.1% (7.3±4.7 mV vs. 3.8±1.8 mV) higher amplitude compared to the non-RT group. There was a significant main effect for INTENSITY ($F_{2, 229}$ =12.8; p <0.001, η^2p =0.1) and an interaction of GROUP X INTENSITY ($F_{2, 229}$ =10.7; p <0.001, η^2p =0.09) on the normalized unconditioned CMEP amplitude. Post hoc comparisons showed that at 75% MVC, there was a 11.6% (0.7±0.2 mV vs. 0.64±.2 mV) and a 9.9% (0.7±0.2 mV vs. 0.66±.2 mV) higher normalized unconditioned CMEP amplitude compared to 25% and 50% MVC, respectively. Post hoc comparisons showed that the chronic RT group had a 22.8% higher normalized unconditioned CMEP amplitude (%Mmax) at 25 (0.7±0.19 mV vs. 0.57±0.21 mV) MVC, respectively, There was no difference between groups at 50 and 75% MVC (Table 3).

There was a significant main effect for SEX ($F_{1, 229}$ =66.0; p <0.001, η^2p =0.224) on unconditioned CMEP amplitude. Males had a 112.7% (7.5±4.6 mV vs. 3.5±1.7 mV) higher amplitude compared to females.

2.3.5.2 Conditioned and unconditioned CMEP ratio

There was a significant main effect for INTENSITY ($F_{1, 229}$ =11.0; p <0.001, η^2p =0.09) on the conditioned and unconditioned CMEP ratio. Post hoc comparisons showed that at 75% MVC, there was a 45% (0.5±0.4 mV vs. 0.9±0.5 mV) and 28.6% (0.5±0.4 mV vs. 0.7±0.4 mV) lower conditioned to unconditioned CMEP ratio compared to 25 and 50% MVC, respectively. There were no other differences for intensity.

There was a significant main effect for SEX ($F_{1, 229}$ =12.5; p <0.001, η^2p =0.052) on the conditioned to unconditioned CMEP ratio. Males had a 25% (0.6±0.4 mV vs. 0.8±0.5 mV) lower normalized amplitude ratio compared to females.

2.3.5.3 Conditioned and unconditioned CMEP SP

There was a significant main effect for GROUP ($F_{1, 229} = 10.7$; $p < 0.01$, $\eta^2p = 0.045$), INTENSITY ($F_{2, 229} = 25.9$; $p < 0.001$, $\eta^2p = 0.184$) and interaction of GROUP X INTENSITY ($F_{2, 229} = 5.1$; $p < 0.01$, $\eta^2p = 0.043$) on unconditioned CMEP SP. The non-RT group had an 20% (0.06±0.01 ms vs. 0.05±0.02 ms) longer SP time compared to the chronic RT group. Post hoc comparisons showed that at 75% MVC, there was a 33% (0.06±0.02 ms vs. 0.04±0.01 ms) and a 20% (0.05±0.01 ms vs. 0.04±0.01 ms) shorter duration of the unconditioned CMEP SP compared to 25 and 50% MVC, respectively. Also, at 50% MVC, there was a 20% (0.06±0.02 ms vs. 0.05±0.01 mV) shorter duration of the unconditioned CMEP SP compared to 25% MVC. Post hoc comparisons showed that at 50% and 75% MVC, there was a 28.5% (0.05±0.01 ms and 0.05±0.01 ms vs. 0.07±0.01 ms) shorter duration of the unconditioned CMEP SP compared to 25% MVC within the non-RT group. Also, the chronic RT group showed that at 75% MVC, there was a 33% (0.04±0.01 ms vs. 0.06±0.01 ms) and a 20% (0.04±0.01 ms vs. 0.05±0.01 ms) shorter duration of the unconditioned CMEP SP compared to 25% and 50% MVC, respectively. The chronic RT group showed that at 75% MVC, there was a 20% (0.04±0.01 ms vs. 0.05±0.01 ms) shorter duration of the unconditioned CMEP SP compared to 75% MVC of the non-RT group.

2.3.5.4 Correlation of MVC and spinal excitability

There were negative, positive, and negative correlations between force output at all intensities and normalized conditioned CMEP amplitudes, CMEP amplitudes, and conditioned to unconditioned CMEP ratios, respectively, for all participants and the chronic RT group (Table 4). Not all these correlations held for the non-RT- group or males and females. Lastly, females had a moderate to strong negative correlation in conditioned CMEP SP.

2.4 Discussion

To our knowledge, this is the first study to use conditioned and unconditioned CMEPs during different intensities of isometric submaximal voluntary contractions of the biceps brachii to examine the effects of chronic RT and non-RT and sex on spinal excitability. The chronic RT group showed higher amplitudes of raw conditioned and unconditioned CMEPs compared to the non-RT group. When the CMEPs were normalized to M_{max}, the chronic RT showed higher and lower CMEP amplitude at 25% and 75% MVC, respectively, compared to the non-RT group, suggesting higher spinal excitability at lower forces. Furthermore, the conditioned to unconditioned CMEP ratio decreased as force increased. For the CMEP SP, the non-RT group showed a 20% longer SP than the chronic RT group. Lastly, males showed higher amplitudes of raw conditioned and unconditioned CMEPs, lower amplitudes in conditioned to unconditioned CMEP ratio, and a lower conditioned CMEP amplitude normalized to M_{max}. Based on the current findings, chronic resistance training and sex influence the spinal excitability of the biceps brachii during isometric contractions. In the present study, it is possible that the increase in normalized CMEP amplitude at 25% in the chronic RT group is related to an increase in spinal excitability due to a lower spinal motor unit recruitment threshold or by an increase in the firing frequency of the spinal motoneurons.

2.4.1 Effect of chronic RT on outcome measures of spinal and corticospinal excitability

A study by Pearcy et al. (2014) used TMS and TMES to elicit MEP and CMEP amplitudes that were 10% to 20% of M_{max} amplitude and showed that MEP (but not CMEP) amplitudes were decreased in the chronic RT group compared to the non-RT group at contraction intensities >50% MVC. They hypothesized that CSE (i.e. the decreased MEP amplitude) was decreased in the biceps brachii of the chronic RT individuals during higher percentages of MVC due to increased spinal excitability (i.e. the decreased MEP amplitude was due to increased motoneuron firing

frequencies). One way to test this hypothesis was to elicit a CMEP during the silent period of a MEP. During this silent period, the corticospinal pathway is quiescent and the motoneurons will not be firing. An interaction between group and intensity showed that the chronic RT group had a higher normalized unconditioned CMEP amplitude at 25% MVC, showing differences in spinal than the non-RT group. Thus, the Chronic RT spinal excitability is different than the non-RT group, at low contraction intensities .

In the work by Pearcey et al. (2014), they did not find differences in CMEP amplitudes between chronic-RT and Non-RT groups. Their study used TMS and TMES to elicit a MEP and CMEP amplitude of around 10% to 20% of M_{max} during a 5% MVC. In the current study, we evoked CMEP amplitudes ~75% of M_{max} during a 20% MVC. Thus, the stimulation paradigms used in each study were quite different. Thus, the stimulation paradigm probably has a strong effect on CSE outcome responses of the biceps brachii.

Regardless of training status, our results showed differences due to contraction intensity with normalized unconditioned CMEPs, where 75% MVC had a higher amplitude than 25% and 50% MVC, indicating increased spinal excitability as contraction intensity increases. These findings were similar to the results reported by Yacyshyn et al. (2020), where 50% MVC had higher normalized unconditioned CMEPs amplitude than 25% and 10% MVC with the arm in a supine position (Yacyshyn et al., 2020). However, for the normalized conditioned CMEP, the higher the force produced, the lower the amplitude, which may have been affected by the inhibition of cortical motoneurons. These results were not reported by (Yacyshyn et al., 2020).

Chronic RT individuals required less MSO to obtain the MEP SP duration to evoke a conditioned CMEP. It is essential to mention that TMS output in the study was increased as needed to achieve the SP duration required for the experiment. Previous studies limited the amount of

MSO by delivering a percentage of M_{max}. Additionally, the chronic RT group had a lower AMT during a 20% MVC compared to the non-RT group. This finding is supported by Lahouti et al. (2019), who found that the chronic RT group also exhibited a reduction of AMT compared to the non-RT group. In addition, Lahouti et al. looked for a correlation between AMT and short-interval intracortical inhibition (SICI), resulting in a strong negative correlation between moderate force output (25 and 40% of MVC), proposing that intracortical interactions can modulate AMT in strong contractions. This difference in SICI also suggests intracortical adaptations occur in chronic RT. Thus, some of the changes in CSE may occur due to inherited properties in the pyramidal tract, intracortical inhibition, and facilitation, or changes in the spinal motoneurons having augmented transmembrane potentials.

In addition, our study showed that chronic RT participants had a higher M_{max} amplitude than non-RT participants. In comparison, Lahouti et al. (2019) reported no differences between groups or intensities in M_{max}. The paradigm in each study could explain these differences; our study elicited Mmax at 20% MVC, while in the Lahouti study, 5% MVC was used, and the targeted contraction intensities having 25%, 50%, and 75% MVC compared to 15%, 25%, and 40% MVC, respectively. Considering that our study did not find any differences in the stimulation intensity to reach the ceiling amplitude for the Mwave, having a higher M_{max} in the chronic RT group could be considered a possible adaptation related to chronic RT. Furthermore, changes in body composition and hydration may also influence the results of the studies. No other study reviewed reported the stimulation intensity and comparison between groups. To our knowledge, the other studies reported differences in M_{max} between arm positions (neutral, pronated, and supine) during the task (Nuzzo et al., 2016; Yacyshyn et al., 2020).

We are unaware of any other studies that assessed adaptations in CSE produced by resistance training using the same paradigm as here. Similar to the results for unconditioned CMEP, there are group differences in conditioned CMEP amplitudes; the chronic RT group had higher conditioned CMEP amplitudes than the non-RT group. This difference between conditioned and unconditioned CMEP could be explained by the silencing of the descending drive caused by the TMS pulse,. Moreover, when examining the corticospinal tract, it is essential to understand that the areas of the motor cortex (M1) that are silenced have the primary motor neurons (i.e. pyramidal and Betz cells) that project to the spinal cord, producing around 31% of the corticospinal fibers. The fiber bundle produced by M1 is in charge of voluntary contraction. Silencing these neurons decreases the overall response of the tract. The second main piece of the study was to assess the differences between conditioned and unconditioned CMEP amplitudes. The differences between the two can lead to a better understanding of the recruitment of the spinal motoneuron pool. Our findings suggest that with high contraction intensities (75% MVC), there is a decrease in spinal excitability. While no differences were observed between groups, further research with a larger sample size could reveal statistical differences between chronic RT and non-RT groups, as hypothesized.

Two systematic reviews by Siddique et al. (2020) and Gomez-Feria et al. (2023) reported that RT produces changes in CSE, measured by increased MEP amplitude (Gómez-Feria et al., 2023; Siddique et al., 2020). Our findings showed that the chronic RT group had higher MEP amplitudes in raw and normalized data. Additionally, it is reported that RT shortens the MEP SP mediated by GABAb (Siddique et al., 2020).. The current study includes measurements of the silent period (SP) produced by the unconditioned CMEP. The results show that the non-RT group had a higher overall SP duration than the chronic RT group. Moreover, the chronic RT group

showed differences within contraction intensities, 75% of MVC had shorter SP duration than 25% and 50% of MVC. Thus, we propose that the chronic RT group had a faster inhibition recovery to sustain muscle activation (i.e., at higher MVC %, the inhibition of motoneuron activity is reduced, allowing for quicker reactivation of the motor neurons). In contrast with Lahouti et al. (2019), as stated above, a strong negative correlation between force output and SICI (i.e., higher force lower SICI) and resistance trained (lower SICI compared to non-RT) was seen, similar to our conditioned MEP SP where SP duration is lower in chronic RT and as force output increases SP duration decreases. The results above suggest that chronic RT lowers the refractory period of the motoneuron pool, especially at higher contraction intensities. The reduction of the SP duration in the chronic RT group could be attributed to an improvement in movement control, reducing the SP duration needed to avoid unwanted neural firing.

2.4.2 Effect of sex on outcome measures of spinal and corticospinal excitability

There have not been many studies regarding sex differences and spinal excitability, but some proposed mechanisms that can modify CMEPs between sexes are muscle mass and subcutaneous fat thickness, muscle fiber composition and metabolic responses that might be sex specific (Olarogba et al. 2024).

In our study, males had lower normalized conditioned CMEPs and no difference in unconditioned CMEPs than females. These findings suggest a higher spinal excitability in females. Supporting this, Jenz et al. (2023) reported that females had higher estimated PIC magnitudes in motor units, indicating that biological sex predicts PIC magnitude. The observed higher spinal excitability in females can be attributed to motor unit recruitment and differences in spinal cord mechanisms that could be sex-specific, especially as cortical neurons were silenced during conditioned CMEPs in our study. Conversely, males had a higher raw conditioned and

unconditioned CMEP amplitudes, suggesting higher overall spinal excitability when the entire corticospinal tract was analyzed. Notably, Jenz et al. (2023) found no sex differences in motor unit discharge rates despite the tendency of higher discharge rates in females. The lack of differences between males and females reported in the Jenz et al. (2023) article should be considered further since methodological limitations could have diminished statistical differences. In both cases, the following factors should be considered when looking at sex differences as referred by Jenz et al. in the methodological considerations. First, the menstrual cycle was not accounted for. While males have minor changes in testosterone and no drastic or significant changes in their levels of estrogens and progesterone, females present fluctuations that may affect the motor system and excitability. Secondly, muscle size and subcutaneous fat tissue were not considered. Sex differences in CSE should be studied further for a better understanding.

Furthermore, our study found a moderate to strong negative correlation between MVC and conditioned CMEP SP duration in females (i.e., as force increases, spinal SP duration decreases). These findings suggest a complex relationship between neurophysiological factors such as GABAergic inhibitions, intracortical connectivity, and intrinsic factors that could be sex-specific, such as hormones like allopregnanolone that has been shown to increase the neuroinhibitory effect of GABA receptors (Soedirdjo et al., 2023).

To our knowledge, this is the first study to report sex differences in CSE using conditioned and unconditioned CMEPs. Our study found no differences between the sexes in MSO, AMT, and Mwave. In contrast, Chaves et al. (2021), using TMS comparing both brain hemispheres in the upper limbs, showed that female multiple sclerosis patients had lower AMT and higher MEP amplitudes. Pagan et al. (2023) showed that females had a lower AMT measured from the rectus femoris during a 10% MVC in apparently healthy individuals. The results obtained in our study

could have been influenced by the fact that both males and females had chronic RT and non-RT individuals. A higher sample size would be needed to examine sex and group differences. There were sex differences in M_{max} amplitudes in that males had double the M_{max} amplitude than females, suggesting higher peripheral excitability during muscle activity. Differences in overall muscle size and muscle fiber type can explain the difference. Nuzzo (2023) reported that men exhibited greater cross-sectional areas for all fiber types with a higher distribution of Type II or fast-twitch fibers, while females exhibited a greater type I or slow twitch.

Males had a higher MEP amplitude than females, indicating greater overall CSE. Our results differ from those of the previously mentioned studies, in which females had higher CSE than males. Another study by Jenz et al. (2023) found that females had a greater PIC contribution to the lower limb motor unit discharge, which could translate to higher CSE in apparently healthy individuals. However, none of the studies mentioned reported whether participants exercised regularly. For our study, the differences seen could align with the findings of Olarogba et al. (2024), where muscle size had a positive relationship with measures of CSE in males. Thus, males may have a higher CSE during the biceps brachii activation than females.

2.4.3 Methodological considerations

There are several methodological considerations for the current study. First, our data analysis included a sample of 17 participants (9 males and 8 females) and is underpowered to compare a GROUP X SEX interaction. A sample size of n=40 (10 participants of each sex in the chronic and non-RT group each) would be required to have adequate statistical power to make this comparison. Second, our study did not use TMS stimulation as a percentage of M_{max} as used in other paradigms. Higher TMS stimulation could lead to the activation of secondary pathways or areas, facilitating either activation or inhibition. Furthermore, a stimulation intensity to induce a

MEP amplitude that was 75% of M_{max} amplitude was used to produce a SP duration long enough to elicit a conditioned and unconditioned CMEP. This intensity may have created a ceiling effect on CSE outcome measures and reduced the sensitivity of the measurements to allow for true group and sex differences. For sex differences, a primary consideration should be the effect of the menstrual cycle (including hormone anti-contraceptive medication, implants, and intrauterine devices) on the outcome measures, which was not done in the current study. Furthermore, when assessing differences in sex and resistance training, further consideration should be given in this regard. Dasa et al. (2021) reported no differences in performance based on hormonal contraceptives in high-level female athletes but no references on how untrained female participants could be influenced by menstrual cycle or hormonal anti-contraceptives. Lastly, considering muscle mass, hydration, and subcutaneous fat thickness should be considered for both variables (resistance training and sex) for a better understanding of changes in CSE outcomes.

2.4.4 Conclusion

This study showed that chronic RT alters spinal excitability, which some authors consider that it can partially be translated to enhanced strength. The spinal motoneuron recruitment threshold could be one of the adaptations related to chronic resistance training. This was evidenced by the increase in raw and normalized unconditioned CMEP amplitudes in the chronic RT compared to the non-RT group. Normalized conditioned CMEP was lower in the chronic RT group; one possible reason is that within the SP, there is an interruption of the cortical descending drive to the spinal motoneurons that can decrease or alter the full spinal excitability. Moreover, the sex related differences in spinal excitability outcome measures may be due to an evolutive background or other adaptations related to hormone levels, motor unit recruitment, muscle fiber

type differences, and muscle and fat thickness. Further studies are required to determine mechanisms of training and sex dependent differences in CSE and spinal excitability.

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Tables

Table 1. Raw data of non-RT and chronic RT values. Mean ± SD, data range, and p value.

Resistance training (RT), maximal voluntary contraction (MVC), muscle compound action potential (Mmax), motor evoked potential (MEP), cervicomedullary motor evoked potential (CMEP), conditioned cervicomedullary motor evoked potential (C-CMEP), silence period (SP)

	NRT	CRT	p value
MVC (N)	234.457 ± 97.785 (105.2- 373)	339.244 ± 142.237 (190- 577)	**<.001**
25% MVC			
M-WAVE (mV)	5.46 ± 2.02 (2.31 - 8.57)	10.9 ± 6.32 (3.72 - 18)	**0.048**
MEP AMPLITUDE (mV)	3.91 ± 2.08 (0.418 - 7.92)	8.85 ± 4.97 (1.92 - 17.6)	**<.001**
C-CMEP AMPLITUDE (mV)	3.07 ± 1.98 (0.012 - 8.56)	4.75 ± 3.55 (1.03 - 14.5)	**0.014**
CMEP AMPLITUDE (mV)	3.35 ± 1.79 (0.396 - 7.813)	7.56 ± 4.89 (1.82 - 15.68)	**0.002**
CMEP SP (ms)	0.07 ± 0.015 (.046- 0.104)	0.06 ± 0.016 (.022- 0.099)	0.01
C-CMEP SP (ms)	0.12 ± 0.042 (.073- 0.226)	0.11 ± 0.037 (.047- 0.211)	0.39
C-CMEP/CMEP (mV)	1.01 ± 0.632 (0.02 - 2.733)	0.74 ± 0.35 (0.09 - 1.342)	0.184
50% MVC			
M-WAVE (mV)	5.29 ± 1.96 (2.26 - 7.79)	10.53 ± 5.61 (3.95 - 18.47)	**0.034**
MEP AMPLITUDE (mV)	3.9 ± 2.15 (0.349 - 7.49)	8.55 ± 5.18 (1.92 - 17.8)	**0.001**
C-CMEP AMPLITUDE (mV)	2.512 ± 1.74 (0.525 - 7.54)	3.89 ± 3.65 (0.078 - 14.43)	0.043
CMEP AMPLITUDE (mV)	3.67 ± 1.97 (0.581 - 7.72)	7.51 ± 5.02 (0.86 - 18.23)	**0.009**
CMEP SP (ms)	0.05 ± 0.01 (.03- 0.071)	0.05 ± 0.011 (.019- 0.084)	0.13
C-CMEP SP (ms)	0.11 ± 0.041 (.058- 0.2)	0.11 ± 0.036 (.058- 0.192)	0.326
C-CMEP/CMEP (mV)	0.76 ± 0.403 (0.214 - 2.124)	0.665 ± 0.489 (0.01 - 2.303)	0.37
75% MVC			
M-WAVE (mV)	6.01 ± 1.60 (3.8 - 8.76)	9.58 ± 6.07 (2.77 - 20.15)	0.187
MEP AMPLITUDE (mV)	4.53 ± 1.63 (1.29 - 7.54)	6.47 ± 4.41 (1.43 - 17.4)	**0.01**
C-CMEP AMPLITUDE (mV)	2.28 ± 1.41 (0.688 - 5.68)	2.98 ± 3.62 (0.179 - 14.936)	0.316
CMEP AMPLITUDE (mV)	4.54 ± 1.575 (1.929 - 8.535)	6.69 ± 4.29 (1.196 - 17.68)	0.01
CMEP SP (ms)	0.05 ± 0.01 (.03- 0.084)	0.04 ± 0.014 (.011- 0.066)	**0.001**
C-CMEP SP (ms)	0.136 ± 0.071 (.028- 0.311)	0.12 ± 0.042 (.049- 0.207)	**0.16**
C-CMEP/CMEP (mV)	0.53 ± 0.295 (0.09 - 1.202)	0.53 ± 0.450 (0.039 - 1.609)	0.94

Table 2. Raw data of male and female participants values.Mean ± SD, data range, and p value.

Muscle compound action potential (Mwave), motor evoked potential (MEP), conditioned cervicomedullary motor evoked potential C-CMEP, cervicomedullary motor evoked potential (CMEP), silence period (SP)

	Male	Female	p value
MVC (N)	436 ± 116 (265 - 577)	220 ± 32.2 (190 - 266)	**< .001**
25% MVC			
M-WAVE (mV)	11.3 ± 6 (3.76 - 18)	4.97 ± 1.63 (2.31 - 6.65)	**0.009**
MEP AMPLITUDE (mV)	8.74 ±4.86 (1.37 - 17.6)	3.99 ± 2.4 (0.418 - 9.21)	**< .001**
C-CMEP AMPLITUDE (mV)	4.82 ±3.76 (0.87 - 14.5)	2.98 ±1.28 (0.01 - 4.53)	**0.007**
CMEP AMPLITUDE (mV)	7.53 ± 5 (1.25 - 15.7)	3.38 ± 1.47 (0.4 - 5.23)	**0.012**
CMEP SP (ms)	0.07 ± 0.02 (0.022 - 0.1)	0.06 ± 0.01 (0.034 - 0.096)	**0.006**
C-CMEP SP (ms)	0.12 ± 0.04 (0.022 - 0.21)	0.11 ± 0.04 (0.05 - 0.23)	0.2
C-CMEP/CMEP (mV)	0.81 ± 0.63 (0.09, 2.73)	0.92 ± 0.29 (0.02, 1.6)	0.34
50% MVC			
M-WAVE (mV)	10.4 ± 5.61 (3.35 - 18.5)	5.49 ± 2.48 (3.35 - 18.5)	**0.025**
MEP AMPLITUDE (mV)	8.57 ± 5.01 (1.13 -17.8)	3.86 ± 2.56 (0.35 - 9.97)	**< .001**
C-CMEP AMPLITUDE (mV)	3.91 ± 3.78 (0.08 - 14.4)	2.48 ± 1.29 (0.525 - 4.65)	**0.035**
CMEP AMPLITUDE (mV)	7.7 ± 4.91 (1.45 - 18.2)	3.43 ± 1.81 (0.581 - 8.12)	**0.008**
CMEP SP (ms)	0.06 ± 0.01 (0.02 - 0.08)	0.05 ± 0.01 (0.034 - 0.06)	**0.05**
C-CMEP SP (ms)	0.11 ± 0.03 (0.06 - 0.2)	0.12 ± 0.04 (0.06 - 0.2)	0.034
C-CMEP/CMEP (mV)	0.6 ± 0.44 (0.01 - 2.12)	0.84 ± 0.44 (0.2 - 2.3)	**0.02**
75% MVC			
M-WAVE (mV)	10.2 ± 5.43 (3.8 - 20.1)	5.12 ± 2.26 (2.8 - 8.9)	**0.026**
MEP AMPLITUDE (mV)	7.04 ± 3.98 (1.29 - 17.4)	4.04 ± 2.04 (1.43 - 8.43)	**< .001**
C-CMEP AMPLITUDE (mV)	2.98 ± 3.68 (0.18 - 14.9)	2.28 ± 1.13 (0.76 - 5.15)	0.32
CMEP AMPLITUDE (mV)	7.2 ± 3.9 (1.93 - 17.7)	3.77 ± 1.72 (1.2 - 7.89)	**0.002**
CMEP SP (ms)	0.05 ± 0.02 (0.013 - 0.084)	0.04 ± 0.01 (0.011 - 0.068)	0.66
C-CMEP SP (ms)	0.12 ± 0.06 (0.028 - 0.311)	0.13 ± 0.05 (0.057 - 0.229)	0.47
C-CMEP/CMEP (mV)	0.42 ± 0.37 (0.039 - 1.39)	0.69 ± 0.37 (0.143 - 1.61)	**0.003**

Table 3. Normalized data to M_{max} of Groups and Sex values. Mean ± SD, data range, and p value.

Normalized (N), Muscle compound action potential (Mwave), motor evoked potential (MEP), conditioned cervicomedullary motor evoked potential C-CMEP, cervicomedullary motor evoked potential (CMEP), silence period (SP)

	NRT	CRT	p
25% MVC			
M-WAVE (mV)	5.46 ± 2.02 (2.31 - 8.57)	10.9 ± 6.32 (3.72 - 18)	**0.048**
N MEP AMPLITUDE (mV)	0.66 ± 0.24 (0.181 - 0.972)	0.81 ± 0.21 (0.406 - 1.386)	**0.002**
N C-CMEP AMPLITUDE (mV)	0.52 ± 0.23 (0.005 - 0.99)	0.52 ± 0.28 (0.062 - 0.99)	0.99
N CMEP AMPLITUDE (mV)	0.57 ± 0.21 (0.172 - 0.912)	0.70 ± 0.19 (0.320 - 0.974)	<0.01
50% MVC			
M-WAVE (mV)	5.29 ± 1.96 (2.26 - 7.79)	10.53 ± 5.61 (3.95 - 18.47)	**0.034**
N MEP AMPLITUDE (mV)	0.67 ± 0.24 (0.154 - 0.961)	0.76 ± 0.18 (0.380 - 1.055)	**0.05**
N C-CMEP AMPLITUDE (mV)	0.44 ± 0.23 (0.134 - 0.968)	0.41 ± 0.29 (0.008 - 0.970)	0.63
N CMEP AMPLITUDE (mV)	0.63 ± 0.21 (0.257 - 0.991)	0.68 ± 0.21 (0.160 - 1)	0.25
75% MVC			
M-WAVE (mV)	6.01 ± 1.60 (3.8 - 8.76)	9.58 ± 6.07 (2.77 - 20.15)	0.187
N MEP AMPLITUDE (mV)	0.75 ± 0.15 (0.340 - 0.915)	0.71 ± 0.14 (0.371 - 0.951)	0.4
N C-CMEP AMPLITUDE (mV)	0.43 ± 0.23 (0.078 - 0.987)	0.38 ± 0.35 (0.021 - 1.133)	0.99
N CMEP AMPLITUDE (mV)	0.96 ± 0.53 (0.457 - 1.429)	0.71 ± 0.18 (0.331 - 0.988)	0.28
	Male	Female	
25% MVC			
N MEP AMPLITUDE (mV)	0.75 ± 0.16 (0.36 - 0.98)	0.74 ± 0.31 (0.18 - 1.39)	0.784
N C-CMEP AMPLITUDE (mV)	0.46 ± 0.27 (0.06 - 0.99)	0.59 ± 0.24 (0.005 - 0.998)	**0.35**
N CMEP AMPLITUDE (mV)	0.64 ± 0.20 (0.230 - 0.946)	0.65 ± 0.21 (0.172 - 0.974)	0.94
50% MVC			
N MEP AMPLITUDE (mV)	0.79 ± 0.18 (0.34 - 1.05)	0.64 ± 0.21 (0.15 - 0.99)	<**0.001**
N C-CMEP AMPLITUDE (mV)	0.39 ± 0.2 (0.008 - 0.968)	0.47 ± 0.25 (0.134 - 0.970)	0.17
N CMEP AMPLITUDE (mV)	0.70 ± 0.20 (0.160 - 1.00)	0.60 ± 0.21 (0.217 - 0.978)	**0.04**
75% MVC			
N MEP AMPLITUDE (mV)	0.68 ± 0.14 (0.34 - 0.915)	0.77 ± 0.14 (0.37 - 0.95)	<0.01
N C-CMEP AMPLITUDE (mV)	0.29 ± 0.27 (0.022 - 0.987)	0.52 ± 0.3 (0.110 - 1.13)	**<0.01**
N CMEP AMPLITUDE (mV)	0.72 ± 0.17 (0.331 - 0.988)	0.74 ± 0.21 (0.404 - 1.43)	0.57

Table 4. Correlation between force and spinal excitability.

(*) represents statistical differences. (-) represents a negative correlation. Normalized (N), Muscle compound action potential (Mwave), motor evoked potential (MEP), conditioned cervicomedullary motor evoked potential C-CMEP, cervicomedullary motor evoked potential (CMEP), silence period (SP)

		All Force output N= 17		Chronic RT Force N=9		non-RT Force N=8		Males Force N=9		Female Force N=8	
		r	p-value	r	p-value	r	p-value	r	p-value	r	p-value
25%	N C-CMEP	-0.3 *	=0.01	-0.4*	<.01	-0.07	=0.7	-0.4*	=0.01	0.5*	<0.01
	CMEP	.4*	<0.001	0.4*	=0.01	-0.3	=0.09	.1	=0.4	-0.2	=0.3
	C-CMEP/ CMEP	-0.3*	=0.03	-0.4*	=0.01	0	=1	-0.3*	=0.03	0.3*	=0.04
	C-CMEP SP	0.09	=0.4	0.45	<0.01	-0.35	=0.04	0.2	=0.2	-0.7	<0.001
	CMEP SP	0.04	=.7	0.3	=0.1	0.3	=0.8	-0.4	<0.01	-0.2	0.2
50%	N C-CMEP	-0.24 *	=0.03	-0.3	=0.07	-0.1	=0.4	-0.4*	=0.01	0.4*	=0.01
	CMEP	.4*	<0.001	0.3*	=0.02	-0.25	=0.1	.05	=0.7	-0.2	=0.3
	C-CMEP/ CMEP	-0.3*	=0.01	-0.3*	=.04	-0.13	=0.5	-0.3*	=0.04	0.4*	=0.02
	C-CMEP SP	0.1	=0.3	0.3	=0.08	-0.2	=0.2	0.6	<0.001	-0.6	<0.001
	CMEP SP	01	=0.3	.1	=0.4	-0.1	=0.5	-0.08	=0.6	0.1	=0.3
75%	N C-CMEP	-0.4*	<0.01	-0.4*	=0.01	-0.4*	=0.01	-0.3 *	=0.02	0.4*	=0.03
	CMEP	0.3*	<0.01	0.3*	=0.03	-0.3	=0.1	0.02	=0.913	-0.4*	=0.02
	C-CMEP/ CMEP	-0.4*	<0.01	-0.4*	=0.01	-0.4*6	=0.01	-.4*	=0.02	0.03	=0.07
	C-CMEP SP	-0.2	=0.05	0.2	=0.1	0.03	=0.9	0.4	=0.01	-0.6	<0.001
	CMEP SP	0.06	=0.6	-0.2	=0.1	0.2	=0.2	-0.6	<0.001	-0.3	=0.2

Figure legend

Figure 1. (A) Schematic diagram of the experimental set-up and stimulation location and protocol. (B). Participants were asked to complete 5, 8s duration elbow flexor contractions at 25, 50, and 75% MVC represented in the lower trace (total of 15 contractions). Conditioned and tested stimulus TMS, TMES, and M-wave delivered at 3, 4.5, and 6 seconds during each contraction as seen in the sEMG trace (top trace). The sEMG trace is actual raw data from one participant. Maximal voluntary contraction (MVC), transcranial magnetic stimulation (TMS), transmastoid electrical stimulation (TMES), maximal muscle compound action potential (Mmax), and electromyography (EMG). Group means ±SE. * Indicates a significant ($p \leq 0.05$) difference between groups.

Figure 2. Differences between the chronic resistance trained and untrained groups on A) MSO, C) AMT, and E) Mwave and sex on B) MSO, D) AMT and F) Mwave. * Represents a statistical significance of $p < 0.05$. Maximal stimulator output (MSO), active motor threshold (AMT), muscle compound action potential (Mwave). Group means ±SE. * Indicates a significant ($p \leq 0.05$) difference between groups.

Figure 3. Differences between groups and sex on**A)** C-CMEP, **C)** N C-CMEP, **E)** CMEP, and **G)** N CMEP and sex on **B)** C-CMEP, **D)** N C-CMEP, **F)** CMEP, **H)** N CMEP. * Represents a statistical significance of $p < 0.05$. Conditioned cervicomedullary motor evoked potential (C-CMEP), normalized (% Mmax) conditioned cervicomedullary motor evoked potential (N C-CMEP), cervicomedullary motor evoked potential (CMEP), normalized (% Mmax) cervicomedullary motor evoked potential. Group means ±SE. * Indicates a significant ($p \leq 0.05$) difference between groups.

Figures

Figure 1.

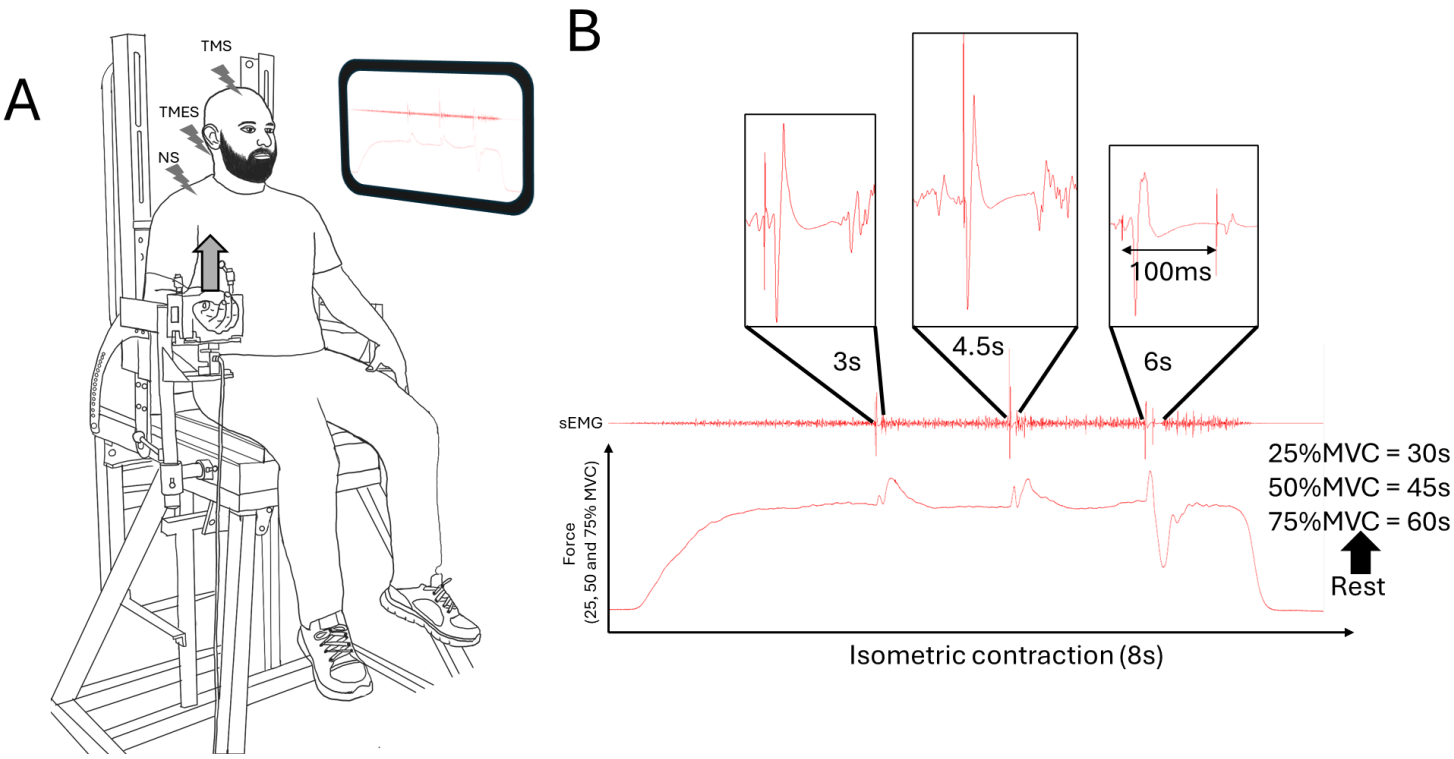
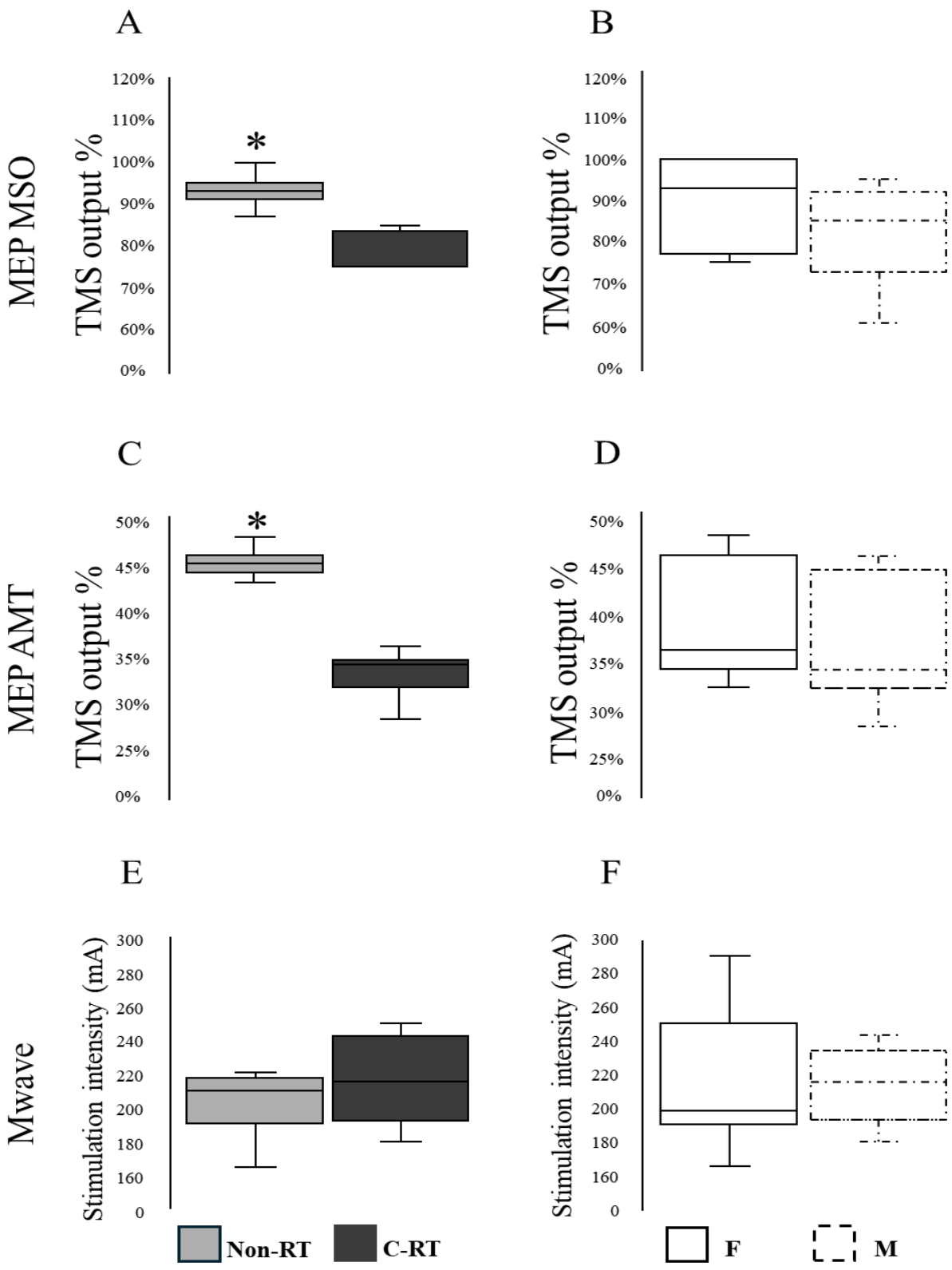


Figure 2.


A
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MEP MSO
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TMS output %
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110%
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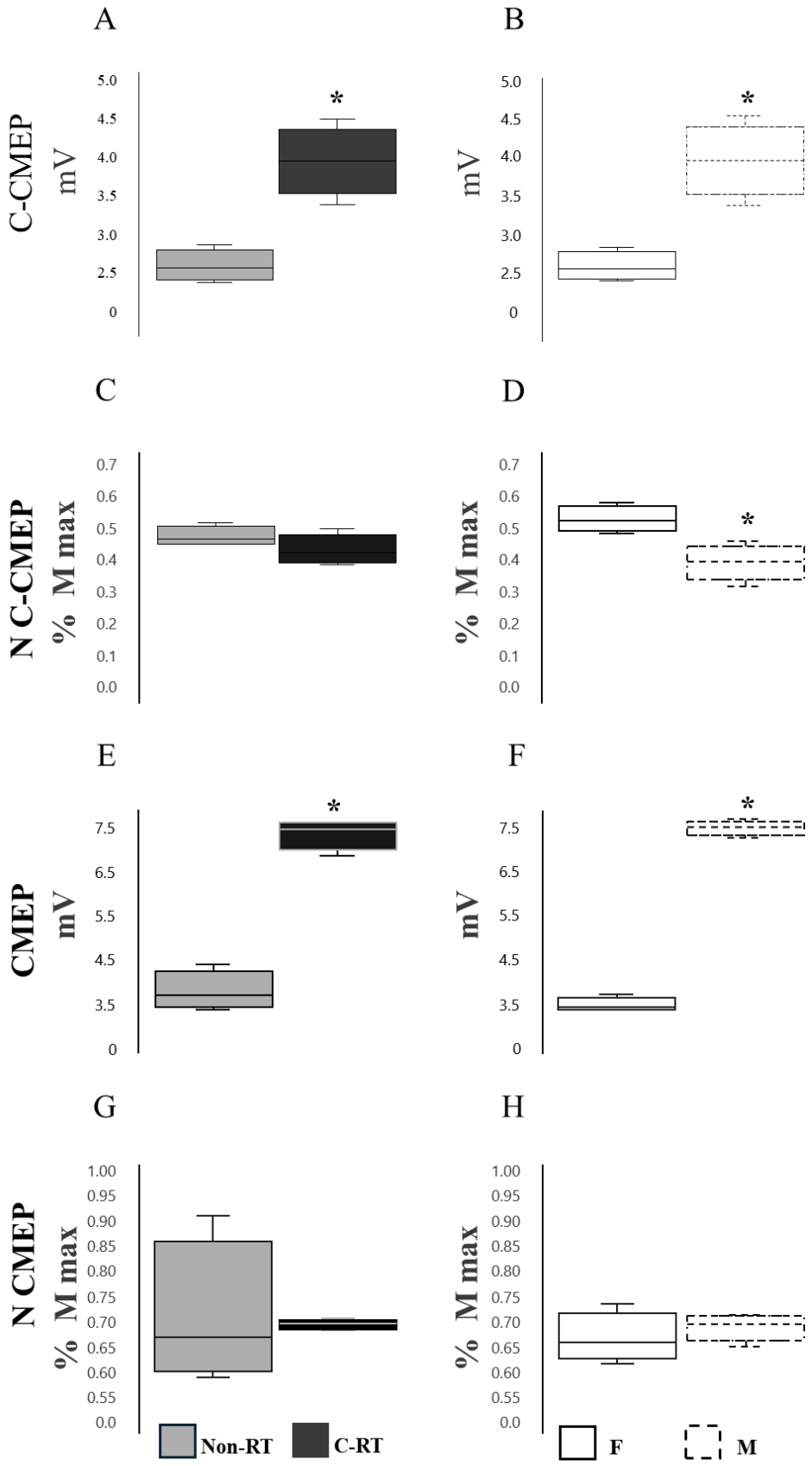
Figure 3.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Appendix A: Ethical Approval

MEMORIAL UNIVERSITY

Interdisciplinary Committee on
Ethics in Human Research (ICEHR)

St. John's, NL Canada A1C 5S7
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www.mun.ca/research/ethics/humans/icehr

ICEHR Number:	**20201414-HK**
Approval Period:	January 28, 2020 – January 31, 2021
Funding Source:	NSERC [RGCS# 20181886; Button]
Responsible Faculty:	Dr. Duane Button School of Human Kinetics and Recreation
Title of Project:	*The effect of chronic resistance training on spinal excitability of the biceps brachii*

January 28, 2020

Mr. Kamiar Ghoseiri
School of Human Kinetics and Recreation
Memorial University of Newfoundland

Dear Mr. Ghoseiri:

Thank you for your correspondence of January 17, 2020 addressing the issues raised by the Interdisciplinary Committee on Ethics in Human Research (ICEHR) concerning the above-named research project. ICEHR has re-examined the proposal with the clarification and revisions submitted, and is satisfied that the concerns raised by the Committee have been adequately addressed. In accordance with the *Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans (TCPS2)*, the project has been granted *full ethics clearance* to January 31, 2021. ICEHR approval applies to the ethical acceptability of the research, as per Article 6.3 of the *TCPS2*. Researchers are responsible for adherence to any other relevant University policies and/or funded or non-funded agreements that may be associated with the project.

The *TCPS2* **requires** that you submit an Annual Update to ICEHR before January 31, 2021. If you plan to continue the project, you need to request renewal of your ethics clearance and include a brief summary on the progress of your research. When the project no longer involves contact with human participants, is completed and/or terminated, you are required to provide an annual update with a brief final summary and your file will be closed. If you need to make changes during the project which may raise ethical concerns, you must submit an Amendment Request with a description of these changes for the Committee's consideration prior to implementation. If funding is obtained subsequent to approval, you must submit a Funding and/or Partner Change Request to ICEHR before this clearance can be linked to your award.

All post-approval event forms noted above can be submitted from your Researcher Portal account by clicking the *Applications: Post-Review* link on your Portal homepage. We wish you success with your research.

Yours sincerely,

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

KB/bc

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