Chronic resistance training enhances the spinal excitability of the biceps brachii in the non-dominant arm at moderate contraction intensities.

By

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Abstract

The objective of this thesis was to examine how chronic resistance training influences corticospinal excitability (CE) of the Biceps Brachii in the non-dominant arm. Seven chronic resistance trained (RT) and six non-resistance trained (NRT) completed four sets of five s pseudo-randomized contractions at 100,90,75,50 and 25% of maximal voluntary contraction (MVC). During the contractions, participants received transcranial magnetic stimulation (TMS), transmastoid electrical stimulation (TMES) and peripheral nerve stimulation to elicit motor evoked potentials (MEP), cervicomedullary evoked potentials (CMEP) and maximal muscle compound action potentials (M_{max}) respectively. All MEPs and CMEPs were normalized to M-max. CMEPs were found to be significantly higher at moderate contraction intensities in the RT group. Results indicate that spinal, but not supraspinal excitability is enhanced at moderate contraction intensities in chronic resistance trained individuals.

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List of Symbols, Nomenclature or Abbreviations

RT	Resistance-trained
MVC	Maximum voluntary contraction
MEP	Motor evoked potential
CMEP	Cervicomedullary evoked potential
M_{max}	Maximal muscle compound potential
CE	Corticospinal excitability
CNS	Central nervous system
TMS	Transcranial Magnetic Stimulation
TES	Transcranial Electrical Stimulation
FDI	First Dorsal Interosseous
MG	Medial Gastrocnemius
RD	Radial Deviator
EXT	Wrist Extensors
ECRB	Extensor Carpi Radials Brevis
TA	Tibalis Anterior
VBM	Voxel Based Morphometry
MR	Magnetic resonance
EMG	Electromyography
MSO	Maximal stimulator output

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Chapter 1: Review of Literature

1.1: Introduction

The corticospinal tract is a pathway in the central nervous system (CNS) which connects the cortex of the brain to the spinal cord. This tract is responsible for conveying voluntary movement commands from the motor cortex to the spinal cord which then gets relayed to the muscle through motoneurones. The excitability of this pathway can be altered by such things as voluntary contractions, chronic activity or inactivity and fatigue (Pearcey et al., 2014; Todd, Taylor & Gandevia, 2003). The excitability of the corticospinal tract (CE) can affect how much input from the higher command centers is required to cause a response in the specified muscle. CE may also vary from one side of the body to the other. This could potentially be due to the fact that humans prefer the use of one limb over the other for certain tasks. Furthermore, these potential CE differences could be altered by resistance training (RT) since the limbs are often utilised in a bilateral manner during many RT exercises. The purpose of this review of literature is to 1) provide information on some of the techniques used to assess CE; 2) discuss how voluntary contraction, acute RT and chronic RT influences the CNS; 3) provide information regarding the asymmetries between dominant and non- dominant limbs and how this relates to CE and 4) compare resistance training and motor skill training to determine if they are related.

1.2: Techniques used to assess corticospinal excitability

Several stimulation techniques are employed to assess CE. The main stimulation techniques used to assess CE that will be discussed in this review are transcranial magnetic stimulation (TMS), transcranial electrical stimulation (TES) and transmastoid stimulation. The aforementioned stimulation techniques all activate a specific section of the corticospinal pathway and therefore have different cellular interactions and latencies. TMS uses magnetic impulses that

are applied at the motor cortex, to produce multiple descending volleys. These volleys can be recorded over the spinal cord with epidural electrodes (Burke et al., 1993). The direction of the current from the coil is selected to preferentially activate the left or right side of the body (Martin, Gandevia & Taylor, 2006). This activity is believed to be in corticospinal tract neurons that likely have monosynaptic connections to motoneurones that lead to upper limb muscles, such as the biceps brachii and first dorsal interosseous. The proposed monosynaptic connections that the corticospinal tract has with motoneurones in some of the upper limb muscles are based on the latency and amplitude of muscle responses.These responses can be recorded using muscle electromyography (EMG) (Plamer & Ashby, 1992). TMS activates cortical motoneurones directly and transsynaptically that produce D-waves (direct waves) and I-waves (indirect waves), respectively (Di Lazzaro et al., 1998). D-waves have a shorter latency then I-waves and are produced when the cortical neurones are activated directly, within a few millimetres of the cell body. I-waves on the other hand, have a longer latency (~1-1.4 ms) and are produced when the cortical neurones are stimulated indirectly, via synaptic inputs. These D-waves and I-waves all induce postsynaptic potentials which summate at the motoneurone (Palmer & Ashby, 1992). If the volley summation is excitatory, a response will be induced (or multiple responses) in the muscle, which is called a motor evoked potential (MEP). At active motor threshold, defined as the minimum stimulus intensity that produces a MEP, 50% of the time during isometric contractions of a tested muscle at a pre-determined contraction intensity, TMS has been found to produce I-waves only. As the stimulator level is increased, the magnetic impulse begins to activate the cortical neurones directly (Di Lazzaro et al. 1998). These D-waves and I-waves all induce postsynaptic potentials which summate at the motoneurone (Palmer & Ashby, 1992). Following a MEP evoked during a contraction, there is a period of inactivity in the EMG signal

which is referred to as the silent period. The initial portion of the silent period is thought to be primarily due to spinal inhibitory mechanisms, such as after-hyperpolarization and recurrent inhibition of alpha motor neurons whereas the later component represents intracortical inhibitory mechanisms that are mediated by gamma-aminobutyric acid B ($GABA_B$) Receptors. Shortening of the silent period could mean a reduction in corticospinal inhibition that could improve voluntary motor drive to the muscle (Kidgell & Pearce, 2010). Measuring MEPs allow researchers to examine the performance of the major motor pathway in humans (the corticospinal tract). The issue is that the size of these evoked potentials are not only influenced by cortical excitability, but also by the excitability of the spinal motoneurones so it is not possible to distinguish if changes in motor evoked potentials are occurring at the spinal or supraspinal level using TMS alone (Taylor & Gandevia, 2004).

The motoneurones within the spinal cord vary in responsiveness depending on what type of descending and afferent inputs it is receiving, as well as intrinsic motoneurone properties, such as its firing frequency. The excitability of these spinal motoneurones is very complicated to predict (Taylor & Gandevia, 2004). Another type of electrical stimulation used to assess subcortical excitability is transcranial electrical stimulation (TES). TES uses two electrodes that are placed on the vertex of the skull (anode), and seven cm lateral to the vertex (cathode) (Burke et al. 1992). This method is thought to activate the corticospinal fibers directly, within a few millimeters of the cell body (D-wave) and is therefore unaffected by cortical excitability (Di Lazzaro et al. 1998). This method seems to be reliable at very low stimulator intensities (at threshold) as it produces solely D-waves. As the stimulation is increased, the interneurons of the brain become stimulated and I-waves are produced. The issue with I-waves during a subcortical measure is that they are affected by cortical excitability (Di Lazzaro et al. 1998). This method is

not effective at assessing sub-cortical measures at high stimulator intensities, as it produces both D and I-waves (Di Lazzaro et al. 1998).

Another, more common method used to assess spinal excitability istransmastoid electrical stimulation (TMES) which can evoke responses in a muscle via spinal motoneurons. These responses are called cervicomedullary motor evoked potentials (CMEP) (Taylor & Gandevia, 2004). The applied current activates the corticospinal tract and sends a volley into the spinal cord which excites motoneurones and subsequently causes a motor response in the muscle (Taylor et al. 2002). This paradigm can be used to test the excitability of the motoneurones at a subcortical level (Gandevia et al. 1999). TMES can be combined with TMS to determine whether changes in cortically evoked MEPs predominantly arise from cortical or spinal regions. If CMEPs do not change after an experimental intervention, but MEPs do, the change is said to be of cortical origin. If both the MEP and CMEP change to a similar degree, the change is said to be of subcortical origin (Taylor & Gandevia, 2004). Collision studies have shown TMS, along with TMES activate many of the same axons (Taylor et al., 2002). By applying TMS and TMES at different inter-stimulus intervals, there is a facilitation (when the magnetic cortical stimulus was given 6 ms before the TMES) and reduction (when the magnetic stimulation was given 2ms before, to 5 ms after TMES) of motor outputs measured in the muscle, which indicates that both these stimulation paradigms activate many of the same axons in the corticospinal tract.

There are pros and cons to electrical stimulation at the cervicomedullary junction. Transmastoid electrical stimulation can evoke large CMEPs, even in relaxed muscles. The most prominent issue with using electrical stimulation at this site is that it activates local pain receptors and can cause a high degree of discomfort. It can also stimulate nearby peripheral nerves which can cause a sudden contraction of the muscles in the neck and head. Another issue

with electrical stimulation is the possibility of stimulating nerve roots in addition to spinal tracts, especially at higher stimulator outputs. When the intensity of the stimulator reaches a certain level the latency of the CMEP decreases which reflects the spread of the stimulation to the nerve root. If, with any small increase in intensity there is a change in the latency of 1-2 ms, some peripheral axons have been activated and the response in the muscle reflects activity at both presynaptic and postsynaptic sites. Also, it is important to note that head position can also change the size of CMEPs simply by repositioning the neck. This can cause the electrodes on the skin to move around and activate different portions of the spinal cord (Taylor & Gandevia, 2004).

MEPs and CMEPs are both measures of CE but when measured at the muscle site via EMG, they can be influenced by peripheral excitability. The peripheral nerve, along with the neuromuscular junction and the muscle itself are outside the CNS. Much like the CNS, the properties of these physiological structures can be altered by fatigue (Adam & De Luca, 2005), pain (Button & Behm, 2008), and voluntary contraction (Belanger & McComas, 1981). When assessing MEPs and CMEPs it is important to consider the peripheral aspects of the system to isolate the changes within the CNS. This is made possible by normalizing both measures to a maximal muscle compound action potential (M-max). To elicit an M-max in the muscle of interest, a maximal electrical stimulation is applied to the innervating nerve which causes a maximal response in the muscle as measured by EMG (Rodriguez-Falces, Maffiuletti and Place, 2013). Since EMG is measured at the muscle, MEPs and CMEPs pass through both the central and peripheral systems to evoke a potential at the muscle. The M-max is a measure of excitability of the peripheral nerve, neuromuscular junction and the muscle itself. It can be used to normalize evoked responses from the CNS. By normalizing these central responses, it

eliminates the possible peripheral changes a protocol may induce to isolate the changes to the CNS.

1.3: Evoked response differences between muscles during voluntary contractions

Voluntary muscle contractions provoke an increase in muscle activity that can arise from increases in cortical and/or spinal output to the muscle (Todd et al., 2003). The increased neural output to the muscle can elicit evoked responses at the spinal and supraspinal level to change. Evoked responses in most muscles tend to increase up to a certain intensity of contraction with a subsequent decrease in MEP size (Todd et al., 2003); however, the trend can vary depending on the muscle of interest. Voluntary force is produced differently between muscles, which may account for some of the differences between evoked response patterns. Some muscles are considered rate coding muscles whereas other muscles are considered recruitment muscles. For example, the biceps brachii is considered a recruitment muscle because it recruits new motor units up to ~90% MVC (De Luca et al., 1982) whereas the intrinsic hand muscles fail to recruit more motor units above 50% MVC. These muscles rely heavily on the firing frequency to produce relatively high amounts of force (Milner-Brown et al., 1973). The characterisation of the method of force production within a muscle can affect the evoked responses by whether recruiting more motor units or increasing its firing frequency when an impulse is delivered. It is also important to note that there are inter-muscle differences within individuals regarding their ability to maximally activate (Behm et al., 2002). This could affect evoked responses at high contraction intensities, particularly during MVC.

With the aforementioned inter-muscle differences in mind, it is intuitive that different muscles have different evoked response patterns to spinal and supraspinal stimulation. By evoking MEPs and CMEPs, it is possible to distinguish between cortical and spinal excitability

during muscle contractions at all intensities. For example, the largest MEP evoked in the FDI occurred at 50% MVC and had a subsequent decrease in MEP amplitude at 75% and 100% MVC (Martin, Gandevia & Taylor, 2006). Oya, Hoffman and Cresswell, (2008) elicited MEPs and CMEPs in the soleus and medial gastrocnemius (MG) muscles. They found that six of eight subjects showed an increase in MEP elicited in the soleus and seven of eight subjects showed an increase in CMEPs of the soleus muscle up to 100% MVC. The MG had more variable responses, with five of eight subjects having the largest MEP amplitude elicited at 80% MVC with a further decrease at MVC. CMEP amplitudes of the MG also reached a peak at 80% MVC in five of eight subjects and had a subsequent decrease at MVC. For both muscles, it appeared that CMEPs and MEPs followed the same pattern, indicating that any contraction induced changes probably occurred at the spinal cord level (Oya, Hoffman, & Cresswell, 2008). The inter-muscle differences highlighted above are likely due to the recruitment patterns of the muscles (Martin, Gandevia & Taylor, 2006).

MEPs elicited in the biceps brachii and brachioradialis have been shown to increase up to 50% MVC. Contraction intensities >50% MVC result in a plateau followed by a progressive decrease from 75% MVC up to MVC (Martin, Gandevia & Taylor, 2006). This decrease in MEP amplitude may be due to changes in cortical neuron excitability levels however, it has been suggested that motoneurone responsiveness decreases at a high firing rate (Matthews, 1999). By utilising both MEPs and CMEPs, knowledge could be obtained regarding the origin of the aforementioned excitability changes. The neural adaptions associated with resistance training may alter the established patterns for the studied muscles. Evoking MEPs and CMEPs across a broad range of contraction intensities in a RT and non- RT group could help build and strengthen our knowledge of these neural adaptations associated with RT. The next section will discuss how

motor skill and resistance training can influence the CNS and the accompanying changes in evoked potentials.

1.4: Effect of Motor skill and resistance training on CE

1.4.1: Motor Learning

Strength training is sometimes thought of as a type of skilled learning since resistance training requires individuals to activate specific muscles in the proper patterns in order to optimize performance. It is believed that the early strength gains (3-5 weeks) that occur via resistance training may arise primarily from neural adaptations within the central nervous system, which is followed by primarily hypertrophic changes within the muscle (Hakkinen & Komi, 1983; Mortitani & deVries, 1979). This neural adaptation hypothesis resulting from resistance training is not well documented and is often debated (Seynnes, de Boer & Narici, 2007; Bellamy et al., 2014). For motor skill acquisition, neural adaptations have been well documented; where motor skill training has been shown to change the primary motor cortex by expanding the area used for the skill and increasing the excitability of the neural pathway (Classen et al., 1999; Lotze et al., 2003; Pascual et al., 1995; Remple et al., 2001).

There have been very few studies conducted to compare skilled tasks with and without resistance. Despite the fact that resistance training requires motor coordination, it appears that it is different from motor skill training. In rats, it has been shown that reaching with a resistance elicits similar neural reorganization of the motor cortex compared to reaching without resistance, despite the increase in strength in the resistance trained group (Remple et al., 2001). This indicates it was not the strength training, but the skilled movement that provoked the increase in the proportion of the primary motor cortex that represented the forelimb muscles. Human studies have shown different results. Jensen, Marstrand & Nielsen (2005) used TMS to assess the effect that a fourweek motor skill training and strength training program had on the corticospinal

pathway. It was found that for the skilled learning group, MEP_{max} increased after two weeks and remained relatively the same up to four weeks. They also found that MEP threshold, which is the stimulation intensity required to produce a MEP 50% of the time at rest, decreased after two weeks and remained at that level after four weeks. The strength training group, on the other hand, experienced no change in MEP_{max} after two weeks and a significant decrease after four weeks. The slope of the stimulus response curve decreased after two weeks and continued to decrease up to four weeks, indicating decreased CE (meaning a greater stimulator intensity is required to produce the same response in the muscle after training). This study shows that both visuomotor task training and resistance training alter the CNS, but in opposite ways. The acquisition of a visuomotor skill is associated with increased corticospinal excitability whereas strength training was associated with decreased corticospinal excitability. This study may not be long enough to see the pattern of neurological changes during either skill training or resistance training. A longer study may be more suited to produce a more holistic view of both training types and the effect it has on the central nervous system.

1.4.2: Resistance Training

There have been several acute resistance training studies in which subjects train a specific muscle for 4-6 weeks to assess changes in CE of the specified muscle. Griffin and Cafarelli, 2007 used TMS to determine changes in the CNS after a four week resistance training program of the *tibialis* anterior (TA) muscle. It was found that RT not only caused an increase in force but also an increase in MEP size during the active contraction at both two and four weeks. They also found an increase in surface EMG RMS from day one to day six but it did not increase significantly thereafter. Kidgell and Pearce (2010) also used TMS to try and identify the types of adaptations that occur in the corticospinal tract after four weeks of resistance training of the FDI. They found an increase in abduction strength by 33.8% with no significant changes in the MEP

latency, MEP amplitudes, or active motor threshold from pre to post measure. However, there was a significant reduction in the silent period of the MEP, which is indirect support for a reduction in corticospinal inhibition, thereby improving voluntary motor drive to the muscle (Kidgell & Pearce, 2010). The two outlined studies appear to have different findings that may be due to the differences in neuroplasticity of the cortical areas serving the upper and lower limb. Also the inter-muscle differences outlined in the previous paragraph may play a role (Griffin & Cafarelli, 2007). Although both studies have different outcomes, they indicate that strength training causes changes along the corticospinal tract. The main limitation to these studies is the fact that TMS was the only stimulation techniques used. For this reason, it was impossible for the researchers to determine if the changes were occurring at the spinal, or supraspinal level.

Carroll, Riek and Carson (2002) were the first group to explore the effect of a four week resistance training program of the FDI on the corticospinal tract using cortical and subcortical stimulation paradigms. TMS and TES were utilized to assess changes at the cortical and subcortical levels, respectively. No changes in MEPs at rest were found, but the slope of the relationship between MEP amplitudes and the absolute torque exerted immediately prior to both TMS and TES stimuli was significantly lower following training for the RT group. Thus, the functional properties of the corticospinal pathway were altered in response to RT, such that for a particular absolute level of background contraction, the magnitude of the compound EMG response evoked by TMS and TES were smaller following training. They also found that the ratio of MEP size to absolute torque was significantly reduced in response to RT at 40 and 50% MVC for TES and 40, 50 and 60% for TMS. In order to determine whether RT resulted in a decrease in MEP size at any individual contraction level relative to MVC, the average MEP size was plotted at each target torque (10, 20, 30, 40, 50 and 60% MVC). A plateau in the

relationship between MEP size and target force was apparent at higher target levels because of the rate coding nature of the FDI muscle. This plateau was apparent at lower target forces for the RT group following the training protocol for both TMS and TES. Since these changes were similar in both TMS and TES, it was concluded that these changes were likely of subcortical origin. It was further elaborated that these changes may come from fewer motoneurones being activated by the descending volleys, or that a greater degree of cancellation of motor unit action potentials occurred at the muscle, with the initial being the more likely cause. The limitation to this study is TES was used to assess subcortical changes in the corticospinal tract. As mentioned in an earlier section, this type of stimulation paradigm can activate neurons at the cortical level and can evoke I-waves, which are influenced by cortical excitability (Di Lazzaro et al. 1998).

Carroll et al, (2009) also published a paper on the effects of a four week resistance training program of the radial deviator (RD) muscles of the wrist on the corticospinal tract, using TMS and cervicomedullary stimulation. A significant increase in strength of both the radial deviators and the wrist extensors (EXT) was found. TMS evoked twitches were larger following training at 10% MVC of the RD and EXT. They also found a significant increase in the amplitude of cervicomedullary-induced twitches during EXT contraction at 25% MVC. The MEP sizes followed a different pattern. Significant increase in extensor carpi radials brevis (ECRB) MEP amplitude at 20% above threshold during the 50% MVC EXT task for the control group was found, whereas the training group had significant reductions in ECRB MEP amplitude at the lowest stimulation intensity during 10% MVC and both EXT and RD at 50% MVC. They also found a tendency for reduced CMEP and MEP amplitudes during EXT contractions ranging from 10-75% MVC (the decrease in ECRB MEP amplitude at 75% and the decrease in ECRb CMEP amplitude at 50% MVC were statistically significant). Since the reduction in MEP and

CMEP amplitude followed a similar pattern, it was believed that the induced changes were likely of spinal origin. Both these studies show that resistance training induces changes in the corticospinal tract, and that these adaptations are likely occurring at the spinal level.

Very little is known about the how chronic resistance training alters the neural connections to the skeletal muscle of interest. There have only been three studies conducted on how chronic resistance training (> two years) effects CE. Two of the three studies found no difference in CE. The tibialis anterior (TA) was found to be stronger in a group of RT individuals with no difference found in MEPs or H-reflex between the RT and non- RT groups (Tallent et al., 2013). Del Olmo et al., 2006 assessed the CE to the biceps brachii from 10-90% MVC of the elbow flexors. Although it was found that the chronic RT group produced more force, no difference was seen between the stimulation intensity used to elicit a large MEP (≥200μV) in the RT and non- RT groups. These studies likely did not discover a difference in CE because TA is not a muscle that resistance trainers are likely to train on a weekly bases (Tallent et al., 2013) and also del Olmo et al, 2006 used TMS alone to assess changes in the corticospinal tract and therefore could not distinguish between spinal or supraspinal changes. Pearcey, Power and Button, 2014 assessed corticospinal differences between the dominant arm of chronically trained and untrained indivduals using TMS and cervicomedullary stimulation at varying contraction intensities. CE measures were assessed from 10-100% MVC in both trained and untrained groups. During each contraction intensity, subjects would receive TMS, cervicomedullary electrical stimulation and brachial plexus electrical stimulation. The ratio of MEP and CMEP amplitude (% maximal M-wave) to absolute force recorded from the chronic RT group were found to be reduced, compared to the non-RT group. At relative contraction intensities, MEP amplitudes followed the same pattern in both groups, up to 50% MVC, but beyond 50% MVC,

MEP amplitudes were lower in the chronic RT group. CMEP amplitudes recorded from 10-100% MVC were similar for both groups. An increase in the firing frequency of the spinal motoneurone was said to be the cause of the difference between the trained and untrained group. This increased firing frequency could increase the degree of refractory occurring within the spinal motoneurones, which could blunt the amplitude of the MEP. Decrease co- activation between the biceps brachii and triceps brachii in the trained group was also discovered. This study shows that the effects of an acute resistance training program, such as those listed above, can prevail after several years of continued resistance training. These phenomenon have been found to occur in the dominant arm. However, no study to date have tested the effects of chronic resistance training on CE in the non-dominant arm, despite evidence suggesting that there may be neurological asymmetries in the motor control system between both sides of the body.

1.5: Limb dominance

1.5.1: Neurological asymmetry between limbs

There is a well-known functional asymmetry between dominant and non- dominant limbs in humans. Generally, the dominant hand plays a manipulative role, whereas the non-dominant hand plays more of a stabilizing role that can dictate the movement of the entire upper limb. (Guiard, 1987). Furthermore, muscle torques around both the shoulder and elbow joint are coordinated more efficiently in the dominant as opposed to the non-dominant limb (Sainburg, 2002). This functional asymmetry may be caused by some sort of anatomical differences in either the brain, spinal cord or limb itself. There is a relatively large body of research exploring the different components of the neurological system controlling both the dominant and non-dominant limbs. Although this research has been very inconsistent, which will be discussed in this section, most of the literature suggests there are neurological asymmetries between the limbs.

Brain imagining techniques have been used to assess cortical representations of both limbs. Good et al. (2001) used voxel based morphometry (VBM) to assess human brain asymmetries. Significant asymmetries were discovered in both grey and white matter dispersion. There was extensive grey matter asymmetry common to both left and right handed individuals which entailed larger left occipital, right frontal and right temporal lobes. White matter asymmetry was also common to both groups and they were adjacent to the areas of grey matter asymmetry. Magnetic resonance (MR) has also been used to examine the depth of the central sulcus. Amunts et al. (1996) used In vivo MR morphometry to examine the central sulcus depth in 45 subjects (31 male right handers and 14 male left handers). They found the left central sulcus was deeper in right handed individuals and vice versa for left handers. This may help explain the aforementioned functional asymmetry as more cortical tissue may be devoted to the upper limb in the dominant hemisphere.

Another way to assess cortical differences would be to examine the brain directly. Studies have been done to examine the central sulcus. White, Richards and Purves, (1994) examined the cortical surface of the dorsolateral portion of the central sulcus in 22 deceased adults that did not die of neurological impairment. This part of the central sulcus contains both the primary motor and somatosensory portions in the brain that portray to the upper extremities. The depth of the sulcus of interest was larger in the left hemisphere compared to the right (7.2% difference). These results may suggest that humans have a greater cortical area devoted to the left motor and somatosensory area that portrays to the right upper limb. Despite these findings, this group later reported that measurements taken of the central sulcus depth provided little evidence of structural asymmetry (White et al., 1995).

TMS has also been used as a tool to assess neurological asymmetries along the corticospional pathway. TMS can be used to assess the excitability of the corticospinal tract along with an indirect measure of cortical area devoted to the upper limbs. Triggs, Subramanium and Rossi (1999) used TMS to elicit MEPs in the right and left abductor pollicis brevis (APB) and flexor carpi radialis (FCR) muscles. No difference in MEP threshold or MEP sizes between the dominant and non- dominant limb was found. They did, however, find that there were significantly more stimulation sites for the dominant hemisphere. This, again, could indicate that there is a greater cortical area devoted to the dominant limb.

Stimulus response curves using TMS has found that the non- dominant hemisphere is more excitable than the dominant hemisphere (Daligadu et al., 2013). In accordance with the mapping studies mentioned earlier, if the dominant hemisphere has a greater cortical area, but the non- dominant hemisphere is more excitable, then the cortical neurones are more densely packed in the non- dominant hemisphere. In contrast, the dominant hemisphere may have a greater distribution of neural elements which could cause it to be less excitable following a focal stimulation (Daligadu et al., 2013).

Despite the inconsistencies in the literature, it seems that the organization of the neural elements devoted to the upper limbs is asymmetrical. Past studies using both TMS and TMES have looked at either the dominant limb only, or a predetermined hand (i.e., Right hand only). It would seem logical to use these stimulation paradigms on the non- dominant limb, as the corticospinal projections which relay signals to the muscles of the limb may differ from those in the dominant limb. Cross education, which will be discussed in the next section, is another example of neurological connections between limbs that may be linked to the aforementioned asymmetries.

1.5.2: Cross Education

Cross education is a phenomenon whereby strength training one side of the body leads to strength increases on the opposite side. Even though cross education was discovered over 100 years ago, there are still questions being raised about its existence (Carroll et al., 2006). It has been shown that unilateral training (four-12 weeks, 15-48 training sessions and intensities of 55-100% of MVC) increases contralateral strength by 7.6% of the initial strength (Carroll et al., 2006). This pattern was also shown by Munn et al, 2005. They tested 115 subjects and found that six weeks of intense training (six-eight RM) of the elbow flexors had no effect on the girth or skinfold thickness of the untrained arm, but they did find a significant 7% increase in elbow flexor strength when the subjects completed three sets of eight reps (fast or slow cadence). However, one set of eight reps at a slow cadence was not sufficient in producing an increase in contralateral strength. It has also been suggested that strength training of the non-fractured limb in individuals who suffered a distal radius fracture increases both strength and range of motion of the fractured limb at 12 weeks post fracture (Magnus et al., 2013). Despite all these findings, this phenomenon may be unidirectional. Farthing, Chilibeck & Binsted (2005) found that right handed individuals who train their right hand experience a significant increase in strength of the untrained left arm (39.2%). Conversely, right handed individuals who train their left arm did not experience significant increases in strength of the untrained right arm (9.3%). These studies show that there are connections at the spinal or supraspinal level that connect the two sides of the body which are somehow facilitated by strength training, however this facilitation may be unidirectional, depending on handedness. It is not clear what brings about these improvements in strength of the contralateral limb during ipsilateral training, but changes in cortical areas associated with motor planning and motor command have been suggested (Munn et al., 2005).

Hortobagyi et al (2003) used TMS, transmastoid stimulation and peripheral nerve stimulation to assess changes at the spinal and supraspinal levels of the contralateral arm during unilateral voluntary contraction, tendon vibration and electrical stimulation. They found that weak (25% MVC) contraction of the unilateral wrist flexors slightly decreased the H-reflex, whereas stronger contractions (50 and 75% MVC) caused the H-reflex to be further reduced. MEPs were found to increase substantially at 50 and 75% of MVC (176% and 215% respectively). CMEPs were unchanged during the voluntary contractions, but after a 75% contraction, they were reduced for up to ten seconds. Tendon vibration had no effect on the size of the H-reflex elicited in the contralateral arm. Weak electrical stimulation of the medial cutaneous nerve at the left elbow marginally increased the H-reflex but did not affect the MEP. When the stimulation intensity was increased, there was an increase in H-reflex and MEP in the right FCR. The facilitation of H-reflex was reverted to a depression when voluntary action was added with the electrical stimulation. The aforementioned study suggests that a unilateral voluntary muscle contraction has crossed effects at both cortical and segmental levels and these effects cannot be replicated by electrical or tendon stimulation (muscle spindle input and non-nociceptive cutaneous afferents). The lack of changes in the CMEPs suggest that the excitability of the motoneurone pool didn't change with the contralateral contraction. This information, combined with the increase in the size of the MEP likely shows that these contractions caused an increase in motor cortex excitability. Since there was no change in CMEPs (and likely motoneurone pool excitability) the decrease in the H-reflex is likely due to pre-synaptic inhibition of Ia afferents which are modulated by corticospinal inputs (facilitator or inhibitory, depending on the task and motoneurone pool).

Although the mechanisms behind cross education are somewhat unknown, there has been literature, such as those highlighted above, to suggest that resistance training of the contralateral limb causes changes in neural pathways. This could provide indirect evidence that chronic resistance training alters the corticospinal pathway in such a way that decreases inter-limb differences of the dominant and non-dominant arm.

1.5.3: Bilateral Deficit

Maximal voluntary contraction of both limbs simultaneously has been shown to produce less force than the sum of the unilateral exertions. This is known as the bilateral deficit (Taniguchi, 1998). The mechanisms behind this phenomenon are still unclear but it is thought that there is a neural component mediating it (such as interactions between the cerebral hemisphere or spinal reflexes). The bilateral deficit is not found in everyone, and can be altered by training. Howard and Enoka, 1991 found that the bilateral deficit existed in untrained individuals but was non-existent in cyclists, who tend to do alternating extension of both legs on a regular bases. They also found a bilateral facilitation (more force produced by contralateral contraction than the sum of the unilateral contractions) in weightlifters who do bilateral movements using some type of resistance on a weekly bases. The second experiment they completed measured the MVC of the left leg while the right leg was either at rest, or activated via electrical stimulation. All subjects produced an increase in MVC force of the left leg during right leg electrical stimulation and this increase was greatest among those with a bilateral facilitation. These results suggest that inter- limb interactions during maximal bilateral contractions are mediated by some sort of neural mechanism in the CNS.

Magnus & Farthing (2008) assessed the bilateral deficit in both the upper and lower limb. Leg press and hand grip strength was assessed to see if the bilateral deficit varied between upper and

lower extremities. It was shown that there was a greater degree of deficit during the leg press exercise (-12.08%) compared to the handgrip exercise (-0.677%) with no difference in muscle activation patterns between the unilateral and bilateral contractions. It was suggested that exercises involving postural stability may be more susceptible to the bilateral deficit because unilateral exercises places less ground reaction forces on the body, increasing the ability of the core to maintain postural stability. The increased stability allows the muscles of the lower body to produce more force. Other studies have examined the effect of an acute (4-6 week) resistance training program of both bilateral and unilateral nature on the bilateral deficit. These studies found that the bilateral deficit shifts in a positive direction (closer to 0) when subjects trained in a contralateral manner, whereas the bilateral deficit shift in a negative direction (i.e. increased) when subjects did unilateral training (Tanguchi, 1997; Tanguchi, 1998).

Even though the mechanisms behind the bilateral deficit is not fully understood, it is believed that it is somehow mediated by the CNS. It is possible that changes in CE via chronic resistance training may be, in part, the reason the bilateral deficit is different following resistance training. Most people resistance train in a contralateral manner which may cause the individual limbs ability to produce force converge, despite limb dominance. The bilateral deficit is an example of how both limbs may be different at the neurological levels, which could mean they should be assessed separately.

1.6: Conclusion

Neurological connections to skeletal muscle in the body is very complex. When using the stimulation paradigms outlined in the methods section to assess CE, all the topics discussed in this paper should be considered. The nature of the muscle whether a rate coding or recruitment muscle can influence CE at various contraction intensities, as different muscles produce various

forces differently. The training status of an individual appears to reduce CE, which could have implications on the results of studies unrelated to training. Handedness of an individual is also important to consider when assessing CE, as the track may be different, depending on the limb of interest. Cross education and the bilateral deficit, although not directly related to CE, are important to consider, as they provide evidence for neurological interplay between limbs. By utilizing TMS, TMES and peripheral nerve stimulation, the cortical connection to the muscles can be segmented into spinal, supraspinal and peripheral aspects which allows researchers to determine the level at which resistance training influences the motor system of a given muscle. No study to date has looked at how training status influences CE of the non-dominant arm across various contraction intensities.

1.7: References

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Chapter 2: Co-authorship Statement

My contribution to this thesis is outlined below:

i) I recruited all participants and analyzed all data collected for this thesis.

ii) With the help of fellow masters student, Mr. Davis Foreman, I collected all experimental data for this thesis.

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

iv) Drs. Button and Kevin Power provided constructive feedback on the manuscript and Thesis.

Chapter 3: Chronic resistance training enhances the spinal excitability of the biceps brachii in the non – dominant arm at moderate contraction intensities.

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NOTE: SEE APPENDIX D FOR PUBLISHED MANUSCRIPT IN NEUROSCIENCE LETTERS

3.1: Abstract

The purpose of the study was to assess corticospinal excitability of the biceps brachii in the non-dominant arm of chronic resistance-trained (RT) and non-RT individuals. Seven chronic-RT and six non-RT male participants performed 4 sets of 5s pseudo-randomized contractions of the non-dominant elbow flexors at 25, 50, 75, 90 and 100% of maximum voluntary contraction (MVC). During each contraction, transcranial magnetic stimulation, transmastoid electrical stimulation and Erb's point electrical stimulation were administered to assess the amplitudes of motor evoked potentials (MEPs), cervicomedullary evoked potentials (CMEPs) and maximal muscle compound potentials (M_{max}), respectively, in the biceps brachii. MEP and CMEP amplitudes were normalized to M_{max}. Training did not affect ($p > 0.14$) MEP amplitudes across any contraction intensity. CMEP amplitudes were significantly ($p < 0.05$) higher in the chronic-RT group at 50% and 75% of MVC by 38% and 27%, respectively There was a trend for higher amplitudes at 25%, 90% and 100% MVC by 25% ($p = 0.055$), 36% ($p = 0.077$) and 35% ($p = 0.078$), respectively, compared to the non-RT group. Corticospinal excitability of the non-dominant biceps brachii was increased in chronic-RT individuals mainly due to changes in spinal excitability.

3.2: KEY WORDS:

corticospinal excitability, chronic resistance training, biceps brachii, elbow flexion, motoneuron

3.3: Introduction

Changes in corticospinal excitability (CE) accompany the strength increases with chronic resistance training. Recently, Pearcey et al. (2014) showed that motor evoked potential (MEPs, i.e. supraspinal excitability) amplitudes recorded in the biceps brachii during dominant arm elbow flexion contractions at intensities above 50% MVC were lower in the chronic resistance trained (RT) group than the non-RT, whereas cervicomedullary evoked potentials (CMEPs, i.e. spinal excitability) were similar. They suggested that the decrease in the MEP amplitudes in the chronic-RT group might have been due to an increased firing rate of the spinal motoneurons (i.e. increased spinal and/or spinal motoneuron excitability). Since resistance training increases motor unit maximal firing rates (Cutsem, Duchateau & Hainaut, 1998; Vila-Cha, Falla & Farina, 1985), the increase in strength from chronic resistance training may be due, in part, to enhanced motoneuron firing frequency, especially at the higher force outputs. Two other studies found no effect of chronic resistance training on corticospinal excitability of the biceps brachii ; however, in these studies spinal excitability was not examined (del Olmo et al., 2006; Tallent et al., 2013). Findings from acute resistance training studies have illustrated concomitant changes in CE (utilizing similar stimulation techniques as employed in Pearcey et al., 2014) of the first dorsal interosseous (Carroll, Selvanayagam & Carson, 2002) and extensor carpi radialis (Carroll et al., 2009) and strength. The authors (Carroll, Selvanayagam & Carson, 2002; Carroll et al., 2009) also suggested that the changes in CE following acute resistance training were due to either an increased spinal excitability or increased firing rate of the spinal motoneuron. Thus, the resistance training-induced changes in CE of muscles located in the dominant limb appear to be mainly of spinal origin.

Interestingly, all of the aforementioned studies focused on changes in CE of a muscle in the dominant limb, despite the fact that there is a well-known functional asymmetry between dominant and non- dominant limbs in humans. Generally, the dominant hand plays a manipulative

role, whereas the non-dominant hand plays more of a stabilizing role which can dictate the movement of the entire upper limb (Guiard, 1987). Furthermore, muscle torques around both the shoulder and elbow joint are coordinated more efficiently in the dominant as opposed to the non-dominant limb (Sainburg, 2002). Amunts et al. (1996) used magnetic resonance to show that the left central sulcus was significantly deeper in right handed individuals and vice versa for left handers. To our knowledge, no studies to date have determined how chronic resistance training alters CE of a muscle located in a non-dominant limb. Differences in CE have been shown between dominant and non-dominant fine motor control muscles of the hand (Semmler & Nordstrom, 1998), potentially due to use-dependence; however, an increased usage of the non-dominant limb due to chronic resistance training may alter CE of a given muscle compared to non-RT individuals.

The purpose of the current study was to determine if CE of the biceps brachii in the non-dominant arm was different between chronic-RT and non-RT individuals. In order to compare CE of the biceps brachii in the non-dominant arm to the changes in CE of the biceps brachii in the dominant arm [as shown in Pearcey et al., 2014], we sought to determine how CE of the biceps brachii in the non-dominant arm changes over elbow flexion contractions from low to maximum intensity. Based on work by Pearcey at al. (2014) as described earlier, it was hypothesized that chronic-RT individuals would produce more non-dominant elbow flexor force than non-RT individuals. The increased force would be, in part, due to differences in CE that were mainly of spinal origin. Specifically, the changes in CE may be due to enhanced excitability of spinal motoneurons.

3.4. Material and Methods

3.4.1: Participants

Fourteen participants were recruited for this study. The participants were divided into two groups consisting of 7 chronic-resistance trained (RT) males (height 176.9 ± 4.7 cm, weight

79.2 ± 6.3 kg, age 22.9 ± 3.5 years) and 7 recreationally active, non-RT males (height 182.1 ± 9.3 cm, weight 91.4 ± 18.0 kg, age 22.0 ± 2.2 years). All participants were recruited from the university population. Participants in the chronic-RT group had at least 2 continuous years (≥3 times per week) of resistance training experience. Participants were verbally informed of all procedures, and if willing to participate, they were asked to read and sign a written consent form. Participants also completed a magnetic stimulation safety checklist designed to screen for potential contraindications with magnetic stimulation procedures (Rossi et al., 2011) prior to the start of the experiment and the Edinburg Handedness Inventory: Short Form to determine arm dominance (Veale, 2014). All participants were strongly right-handed or left-handed (laterality quotient (LQ); right-handed LQ = 93 ± 11.5; left-handed LQ = 93 ± 10.0). Subjects were instructed to not smoke, drink alcohol, or exercise at least 6 h prior to testing and to not eat food or caffeinated beverages for at least 2 h prior to testing (CSEP, 2003). The Memorial University of Newfoundland Interdisciplinary Committee on Ethics in Human Research approved this study (ICEHR #20140710-HK) and was in accordance with the Tri-Council guideline in Canada with full disclosure of potential risks to participants.

3.4.2: Experimental Protocol

In a single experimental session (~2 hrs) participants performed isometric contractions for 5s at various low intensities to get accustomed to producing varying contraction intensities in both arms. The participants then performed a MVC of their non- dominant elbow flexors to set the 5% MVC intensity used to determine the Erb's point stimulation, TMS and CES intensities. Once the participant completed the MVC's, they were prepped for EMG and were strapped into the experimental chair. Following the MVC, participants were exposed to the 3 stimulation conditions 1) Erb's point electrical stimulation, 2) TMS and 3) CES while performing a 5% MVC to determine the stimulation intensities to be used throughout the experiment. Once the

stimulation intensities were found the participants began the experimental protocol. The Participants performed a voluntary isometric contraction protocol which included four sets of 5s contractions of the non-dominant elbow flexors at 5 target forces (25, 50, 75, 90, 100% MVC) for a total of 20 contractions (4 contractions at each target force). Once the participant reached the prescribed force they received TMS, TMES and Erb's point stimulation at 1, 2.5, and 4s, respectively. At the start of each set, participants performed a MVC and all subsequent target forces with stimulation protocol (25-90% of MVC) in that set were randomized. During all contraction intensities in one set the MEP, CMEP and muscle compound action potential (M-wave) responses were recorded from the bicep brachii. Due to the high volume of contractions and potential fatigue effects, participants performed a MVC at the beginning of each set and all of the target forces within that set were made relative to it (Pearcey et al., 2014). To further minimize the effect of fatigue, there was 2 minutes of rest following 90% and 100% MVC, 1 minute of rest following 75 and 50% MVCs and 30s of rest following all forces at 25% MVC (Butler, Taylor & Gandevia, 2003; Pearcey et al., 2014; Peterson et al., 2003) (see Figures 1A and B for experimental set-up and stimulation protocol). Verbal encouragement to match the target forces, along with visual feedback of the force being produced was given during all contraction intensities.

3.4.3: Elbow Flexor Force

Participants sat in an upright position with hips, knees and elbows flexed at 90° with forearms in a neutral position and resting on padded support. The upper torso was rested against the backrest and secured with straps around the waist and shoulders. The wrist of the non-dominant arm was inserted into a non-compliant padded strap, attached by a high-tension wire that measured force using a load cell (Omegadyne Inc., Sunbury, OHIO). Forces were detected by the load cell, amplified (x1000) (CED 1902) and displayed on a computer screen for visual feedback.

Electromyography activity was recorded from the biceps brachii muscle. Surface EMG recording electrodes (MediTrace Pellet Ag/AgCl electrodes, disc shape, and 10 mm in diameter, Graphic Controls Ltd., Buffalo, NY) were placed 2 cm apart over the mid-muscle belly of the biceps brachii. A ground electrode was secured on the lateral epicondyle. Thorough skin preparation for all electrodes was completed. This included shaving hair off and removal of dead epithelial cells from the desired area with abrasive sand paper, followed by cleansing with an isopropyl alcohol swab. An inter-electrode impedance of < 5 kOhms was obtained prior to any data collection to ensure an adequate signal-to-noise ratio. EMG signals were analog-digitally converted at a sampling rate of 5 KHz using a CED 1401 interface and Signal 4 software (Cambridge Electronic Design Ltd., Cambridge, UK).

3.4.4: Stimulation Condition

All stimulation conditions and methods utilized in the current study were similar to that previously reported 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 non-dominant biceps brachii were elicited via 1) brachial plexus electrical stimulation at Erb's point, 2) transcranial magnetic stimulation (TMS) and 3) cervicomedullary electrical stimulation (CES). Stimulation intensities were based on maximal M-wave (M_{max}) evoked during 5% MVC.

3.4.4.1: Brachial Plexus (erb's point) Electrical Stimulation

To evoke an M_{max} in the biceps brachii, electrical stimulation was applied to Erb's point during a 5% MVC. Erb's point was electrically stimulated via adhesive Ag-AgCl electrodes (diameter 10 mm) fixed to the skin over the supraclavicular fossa (cathode) and the acromion process (anode). Current pulses (200 μs duration) were delivered via a constant current stimulator (DS7AH, Digitimer Ltd, Welwyn Garden City, UK). The electrical stimulation was

gradually increased until the M-wave of the biceps brachii no longer increased. The stimulator setting used to evoke M_{max} at 5% MVC was then recorded and used for all contractions in the experimental protocol. The average current pulse intensities elicited at the brachial plexus to produce M_{max} in the non-dominant biceps brachii were 207.1 ± 45.0 mA in the chronic-RT group and 187.5 ± 55.0 mA in the non-RT group.

3.4.4.2: Transcranial Magnetic Stimulation

MEP responses of the biceps brachii were elicited via TMS over the motor cortex in the left or right hemisphere (depending on the handedness of the subject being tested) using a circular coil (13.5 cm outside diameter) attached to a Magstim 200 stimulator (Magstim, Dyfed, UK). The coil was placed horizontally over the vertex with the direction of the current flow to specifically activate the left or right cortex. During a 5% MVC, the stimulation intensity was altered until a MEP amplitude of ~15-20% of M_{max} amplitude was elicited. The stimulator setting used to evoke a MEP amplitude that was between ~15-20% of the M_{max} amplitude was then used for all contractions in the experimental protocol. The average TMS intensities applied at the cortex to produce MEPs in the non-dominant biceps brachii were 65.1 ± 18% in the chronic-RT group and 60.1 ± 13.5% of maximal stimulator output in the non-RT group.

3.4.4.3: Transmastoid Electrical Stimulation

CMEP responses of the bicep brachii were elicited via electrical stimulation of the corticospinal tracts at the decussation in the medulla. Stimulation was applied via adhesive Ag-AgCl electrodes fixed to the skin over the mastoid processes and current passed between them (100 μs duration, 150-350 mA; model DS7AH, Digitimer Ltd, Welwyn Garden). During a 5% MVC, the stimulation intensity was altered to elicit a CMEP amplitude that matched the MEP amplitude. This intensity was used to evoke a CMEP for all contractions in the experimental protocol. We paid close attention to the latency of the CMEPs (~8.5 ms) since evoked stimulation

to the mastoid processes can activate axons near the ventral roots which subsequently decreases the latency of the CMEP by ~2 ms. The average current pulse intensities elicited at the cervicomedullary to produce CMEPs in the non-dominant biceps brachii were 198.3 ± 34.0 mA in the chronic-RT group and 183.8 ± 33.5 in the non-RT group.

3.5: Data and Statistical Analysis:

Non-dominant biceps brachii MEP, CMEP and M-wave peak-to-peak amplitudes and onset latencies were measured from all %MVC forces in each set. See Figure 2 for raw EMG with MEPs, CMEPs and M-waves at 75% MVC. Onset latencies for MEP, CMEP and M-waves were defined as the time between the stimulus artifact and the onset of the evoked potential. Force and root mean square (rms) EMG averages were also measured for 50ms prior to each stimulus for each %MVC. All data were analyzed off-line using Signal 4.0 software (CED, UK).

A one-way ANOVA was performed to compare between group differences at 5, 25, 50, 75, 90 and 100% MVC for all dependent variables using SPSS (SPSS 18.0 for Macintosh, IBM Corporation, Armonk, New York, USA). A one-way repeated measures ANOVA was also performed to compare within group differences for rmsEMG and force prior to stimulation at 5, 25, 50, 75, 90 and 100% MVC. If significant main effects were found, a Bonferroni post hoc analysis was used to examine within group differences. Levene's test was performed to assess the equality of variances between groups. Significance was set at $p < 0.05$. Cohen's *d* effect sizes (ES) (Cohen, 1988) were also calculated for maximal elbow flexor force and normalized MEPs and CMEPs at all contraction intensities. Descriptive statistics in text include means ± SD and for clarity purposes figures include means ± SE.

3.6: Results

3.6.1: Maximal Elbow Flexor Force Outputs

Overall, the chronic-RT group produced 24.2 ± 4.4% ($p < 0.001$, ES = 2.3) greater maximal force in the non-dominant elbow flexors compared to the non-RT group. There were no significant differences between each of the four MVC attempts performed by the Chronic-RT (386.9 ± 39.7 to 397.9 ± 44.9 N; p values ranging from $p = 0.57$ to $p = 0.99$) and non-RT (288.7 ± 88.4 to 312.1 ± 74.6 N; p values ranging from $p = 0.98$ to $p = 1.0$) groups.

3.6.2: MEPs and CMEPs Recorded at 5% MVC

In order to compare corticospinal excitability between groups in the non-dominant biceps brachii over various contractions intensities, both MEPs and CEMPs were normalized to M_{max} and matched (i.e. all MEP and CMEP amplitudes were 15-20% of M_{max}) during a 5% MVC contraction. Average MEP amplitudes in the biceps brachii were 17.9 ± 0.03% M_{max} and 17.2 ± 0.02% M_{max} in the chronic-RT and non-RT groups, respectively. Average CMEP amplitudes in the biceps brachii were 18.1 ± 0.02% M_{max} and 16.8 ± 0.03% M_{max} in the chronic-RT and non-RT groups, respectively. There were no significant between group differences for MEP ($p = 0.78$) or CMEP ($p = 0.54$) relative to M_{max} in the biceps brachii.

3.6.3: Control Values During all Contraction Intensities

To ensure that the supraspinal, spinal and nerve sites were being activated, the latencies from the stimulus artefact to the onset of the MEP, CMEP and M_{max} responses in the non-dominant biceps brachii were measured. Overall, MEP, CMEP and M_{max} average latencies were 11.7 ± 1.3 ms, 8.6 ± 0.5 ms and 4.6 ± 0.7 ms, respectively. There were no significant differences between groups for MEP (11.7 ± 2.0 to 12.0 ± 1.3 ms; p values ranging from $p = 0.18$ to $p = 0.93$), CMEP (8.5 ± 0.6 to 8.6 ± 0.4 ms; p values ranging from $p = 0.18$ to $p = 0.99$) or M_{max} (4.5 ± 0.7 to 4.6 ± 0.8 ms; p values ranging from $p = 0.76$ to $p = 0.99$) latencies at each contraction intensity (i.e., 25, 50, 75, 90 and 100% MVC). Average M_{max} amplitudes were 12.7 ± 3.7 mV, 11.8 ± 3.7 mV, 11.6

± 3.9 mV, 10.8 ± 3.5 mV and 10.6 ± 3.2 mV at 25, 50, 75, 90 and 100% MVC, respectively. There were no significant differences for M_{max} amplitudes (*p* values ranging from $p = 0.50$ to $p = 0.99$) between chronic-RT and non-RT groups at each contraction intensity.

During elbow flexion, biceps brachii rmsEMG was measured for 50ms prior to TMS and TMES to ensure similar overall neuromuscular activity occurred within and across similar contraction intensities. Irrespective of group, there were no significant differences (*p*-values ranging from 0.15 to 0.84) in the average biceps brachii rmsEMG values prior to the onset of TMS and TMES at 25%, 50%, 75%, 90% and 100% of MVC. Irrespective of group there were no significant (*p*-values ranging from 0.15 to 0.80) differences in the average elbow flexor forces prior to the onset of TMS and TMES at 25%, 50%, 75%, 90% and 100% of MVC.

3.6.4: Corticospinal Excitability

There were no significant between group differences in MEP amplitudes in the biceps brachii at 25 ($p = 0.89$, ES = 0.10), 50 ($p = 0.19$, ES = 0.76), 75 ($p = 0.21$, ES = 1.18), 90 ($p = 0.40$, ES = 0.45), and 100% ($p = 0.38$, ES = 0.78) MVC (Figure 3A).

3.6.5: Spinal Excitability

Since MEP amplitudes could be affected anywhere along the corticospinal pathway (i.e. from corticoneurons in the brain to the motoneurons in the spinal cord, TMES was utilized in combination with TMS to identify whether or not changes in CE are of supraspinal or spinal origin (Carroll et al., 2009; Martin et al., 2009; McNeil et al., 2011; Pearcey et al., 2014). CMEP amplitudes in the non-dominant biceps brachii were significantly lower in the non-RT group by 38 ± 23.5% ($p = 0.023$, ES = 1.16) and 27 ± 22.3% ($p = 0.049$, ES = 1.07) at 50 and 75% MVC, respectively. There was a trend for CMEP amplitudes to be lower by 25 ± 11.9% ($p = 0.055$, ES = 0.98), 36 ± 13.7% ($p = 0.077$, ES = 0.67) and 35 ± 13.8% ($p = 0.078$, ES = 0.83) at 25, 90 and 100% MVC, respectively (Figure 3B). To illustrate overall CE, MEPs and CMEPs over all the

contraction intensities were plotted together for the chronic-RT (Figure 3C) and non-RT (Figure 3D) groups.

3.7: Discussion

The increased non-dominant arm elbow flexor force output in the chronic-RT group was, in part, due to alterations in the corticospinal pathway. Compared to the non-RT group, the chronic-RT group had significantly higher CMEP amplitudes recorded from the biceps brachiii at moderate contraction intensities (i.e. 50 and 75% MVC). Although not significant, there was a trend and large effect size for CMEPs to be increased at strong contraction intensities (i.e. 90 and 100% MVC) in the chronic-RT group. The current data supports the notion (Carroll et al., 2009; Carroll et al., 2011; Pearcey et al., 2014) that the resistance training-induced alterations in the corticospinal pathway are mainly of spinal origin. More specifically, CMEPs were increased, due to increased spinal excitability.

The changes in CE of the biceps brachii in the non-dominant arm between groups as reported here were different to those reported on the dominant arm by Pearcey et al. (2014). There were no differences in MEP amplitudes of the biceps brachii in the non-dominant arm between the chronic-RT compared to the non-RT group, whereas CMEP amplitudes were significantly greater during various contraction intensities in the chronic-RT group. Although the results of the current study and those of Pearcey et al. (2014) were different, both studies support that chronic-RT individuals have increased spinal excitability of the non-dominant and dominant biceps brachii, respectively. In chronic resistance trained individuals, exposure to years of prolonged training may have affected presynaptic modulation of the spinal motoneuron, modulation of motoneuron intrinsic properties, and changes in motoneuron firing rates. The H-reflex is potentiated by resistance training, illustrating a pre-motoneuronal and/or motoneuronal adaptation (Aagaard et al., 2002). In animals, endurance training enhances motoneuron afterhyperpolarization (AHP)

amplitude (Beaumont & Gardiner, 2002; Carp & Wolpaw, 1994), lowers the action potential voltage threshold and decreases action potential rise time (Beaumont & Gardnier, 2003). Although not known, motoneuron persistent inward currents may be enhanced by resistance training, subsequently amplifying synaptic input (Button et al., 2006; Heckman et al., 2008), which would increase motoneuron firing frequency and enhance force. Persistent inward currents would reduce the amount of synaptic input required to maintain or increase motoneuron-firing frequency (Button et al., 2006; Heckman et al., 2008; Lee & Heckman,1998 A; Lee Heckman, 1998 B). Indeed, in humans, resistance training has been shown to decrease motor unit recruitment thresholds (i.e. earlier activation) (Van Cutsem, Duchateau & Hainaut, 1998) and increase motor unit maximal firing rates (Van Cutsem, Duchateau & Hainaut, 1998; Vila-Cha, Falla & Farina, 2010). Thus, chronic resistance training may modulate the inputs projecting to the spinal motoneuron (i.e. presynaptic mechanisms) or the intrinsic properties of the spinal motoneuron (i.e. postsynaptic mechanisms), ultimately leading to lower recruitment thresholds and increased firing rates and thus increased force production.

Irrespective of group, a shift from supraspinal to spinal control of force output occurred at relative contraction intensities ~50% of MVC. At contraction intensities ≥50% MVC both MEP and CMEP amplitudes plateaued and started to decrease indicating that CE was now predominantly spinally mediated. Other resistance training (Oya, Hoffman & Cresswell, 2008; Pearcey et al., 2014) and non-resistance training (Martin, Gandevia & Taylor, 2006; Taylor et al., 2002; Ugawa et al., 1995) studies have also shown increased CE at the supraspinal level during weak contractions and increased spinal excitability during strong contractions.

Differences in CE between dominant and non-dominant limbs have been shown in non-training studies, which utilized fine motor control muscles of the hand. For example, CE of the

first dorsal interosseous muscle between dominant and non-dominant hands is different during a simplistic finger abduction task involving isometric contractions at varying intensities (Semmler & Nordstrom, 1998). TMS evoked MEPs were significantly larger in the non-dominant hand compared to the dominant hand FDI muscle, while TES evoked MEPs (i.e. spinal excitability) did not differ between dominant and non-dominant hand FDI muscle. Therefore, the differences in CE were due to supraspinal rather than spinal mechanisms. Potentially the cortical neuron involvement is greater in the non-dominant hand because the dominant hand has greater cortical representation for a given muscle (Wassermann et al., 1992) and lower thresholds for activation (Macdonell et al., 1991; Triggs et al., 1994). CE of similar muscles is asymmetrical between hands because of dominant hand use-dependence. However, CE of a gross motor muscle such as the biceps brachii appears to be symmetrical in both trained and untrained individuals (compare findings from here to that of Pearcey et al., 2014). Thus, use-dependency may only alter CE of fine-motor muscles.

3.8: Limitations and future studies

There were several limitations in the study. The paradigms used in this study are very gross measurements of CE, therefore it may be hard to draw specific conclusions from the results. For example, if the CMEP amplitude changes after a protocol, it could be due to changes in corticospinal excitability, spinal motoneuron excitability or changes at the synaptic level. Stimulus response curves (input/output curves) may be a more reliable and robust measure of CE (Cirillo et al., 2010). Furthermore, MEPs are a crude measure of corticospinal excitability of the whole tract. It would be interesting to use paired-pulse stimulation paradigms which could assess changes upstream, at the cortical level such as short latency intracortical inhibition (SICI), long latency intracortical inhibition (LICI) and short interval intracortical facilitation (SICF). These assessments could provide further information regarding resistance training and how it affects the inhibitory and excitatory pathways of the brain.

In the current study, CE of the biceps brachii was assessed in the non-dominant arm. Handedness usually refers to the hand an individual prefers to use during manipulative tasks. The biceps brachii is a gross mover which acts as a flexor and pronator of the forearm. The intrinsic muscles of the hand are very different from the bicep brachii, in that it allows individuals to produce fine motor outputs so they can manipulate objects (Guiard, 1987). Furthermore, biceps brachii produces a large extent of its force via motor unit recruitment (De Luca et al., 1982), whereas the FDI increases its voluntary force via frequency modulation (Milner-Brown et al., 1973). Future studies should assess how resistance training influences CE in fine motor control muscles (e.g. intrinsic muscles of the hand) versus a gross movement muscle (e.g. biceps brachii) using stimulus response curves to obtain a robust measure of CE.

3.9: Conclusion

In conclusion, chronic resistance training enhances the strength of the non-dominant arm elbow flexors concomitantly with altered CE of the biceps brachii. Similar to the dominant arm [22], the predominant site for the altered CE is probably at the spinal motoneuron. This was evidenced by an increased CMEP amplitude in chronic-RT compared to non-RT individuals at relative forces >50% MVC (although not significant at the highest force levels). It appears that within both chronic-RT and non-RT individuals CE of the biceps brachii in the dominant and non-dominant arm are similar during weak and strong muscle contraction forces.

3.10: Acknowledgments

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3.11: References

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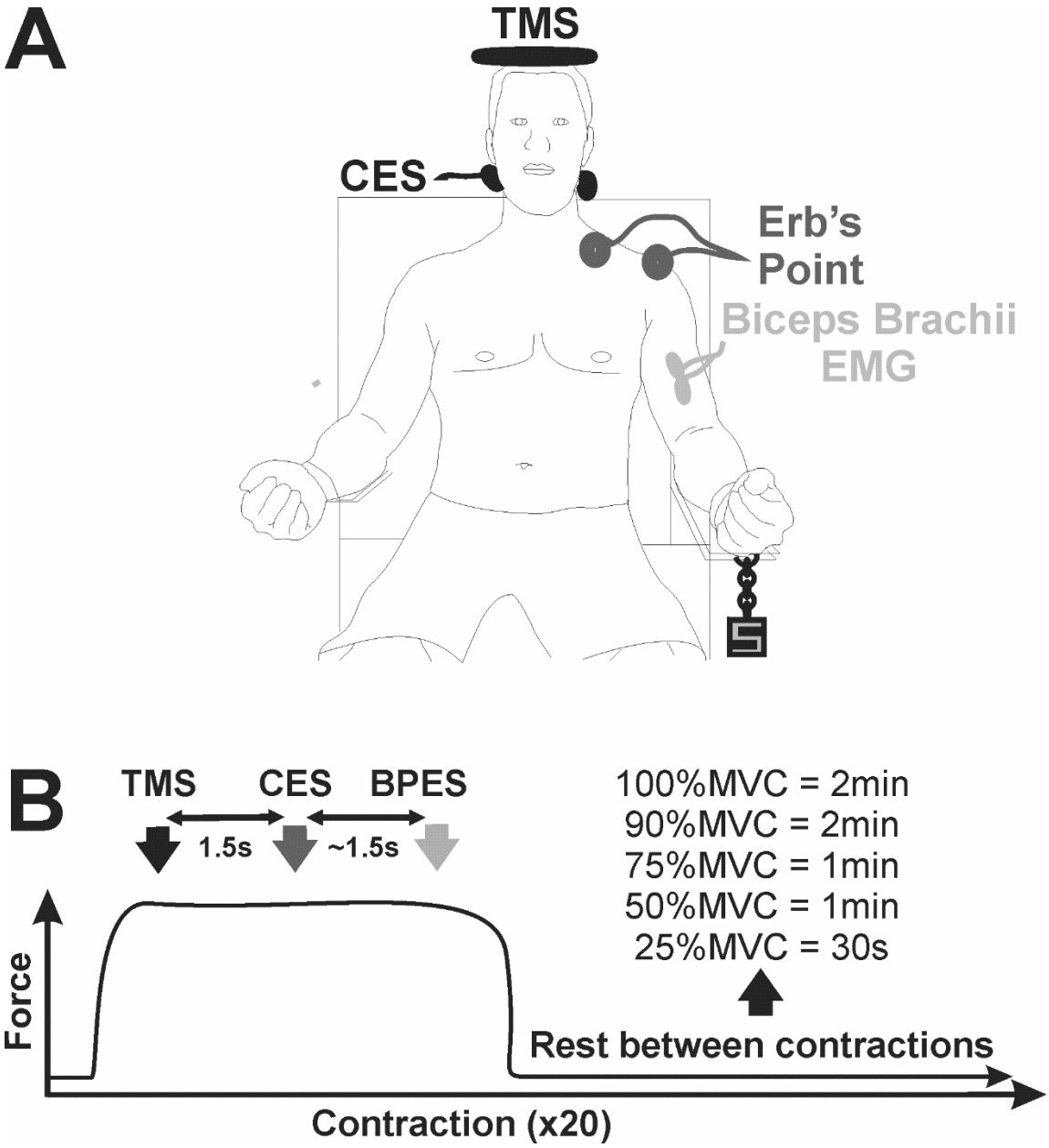
3.12: Figures

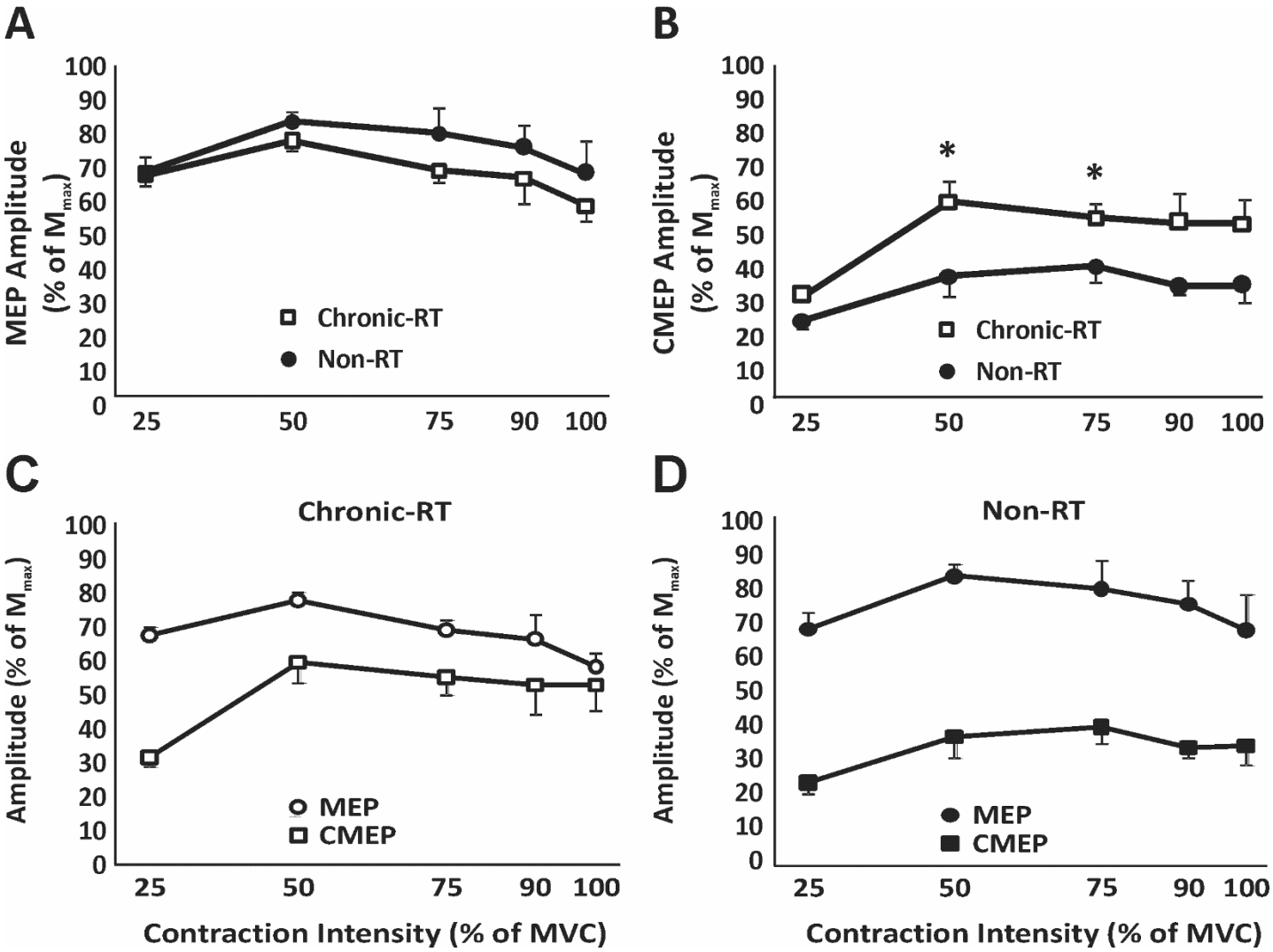
3.12.1: Figure 1 – Experimental Set-up and Protocol

(A) Diagram of experimental apparatus for elbow flexion contractions and time and type of stimulation. (B) Subjects performed 4 sets of 25, 50, 75, 90 and 100% MVCs (20 contractions in total) and received TMS (black arrow, at 1.0s), CES (dark grey arrow, at 2.5s) and Erb's point stimulation (grey arrow, at 4.0s) during each muscle contraction. Rest periods between contractions varied based on the intensity.



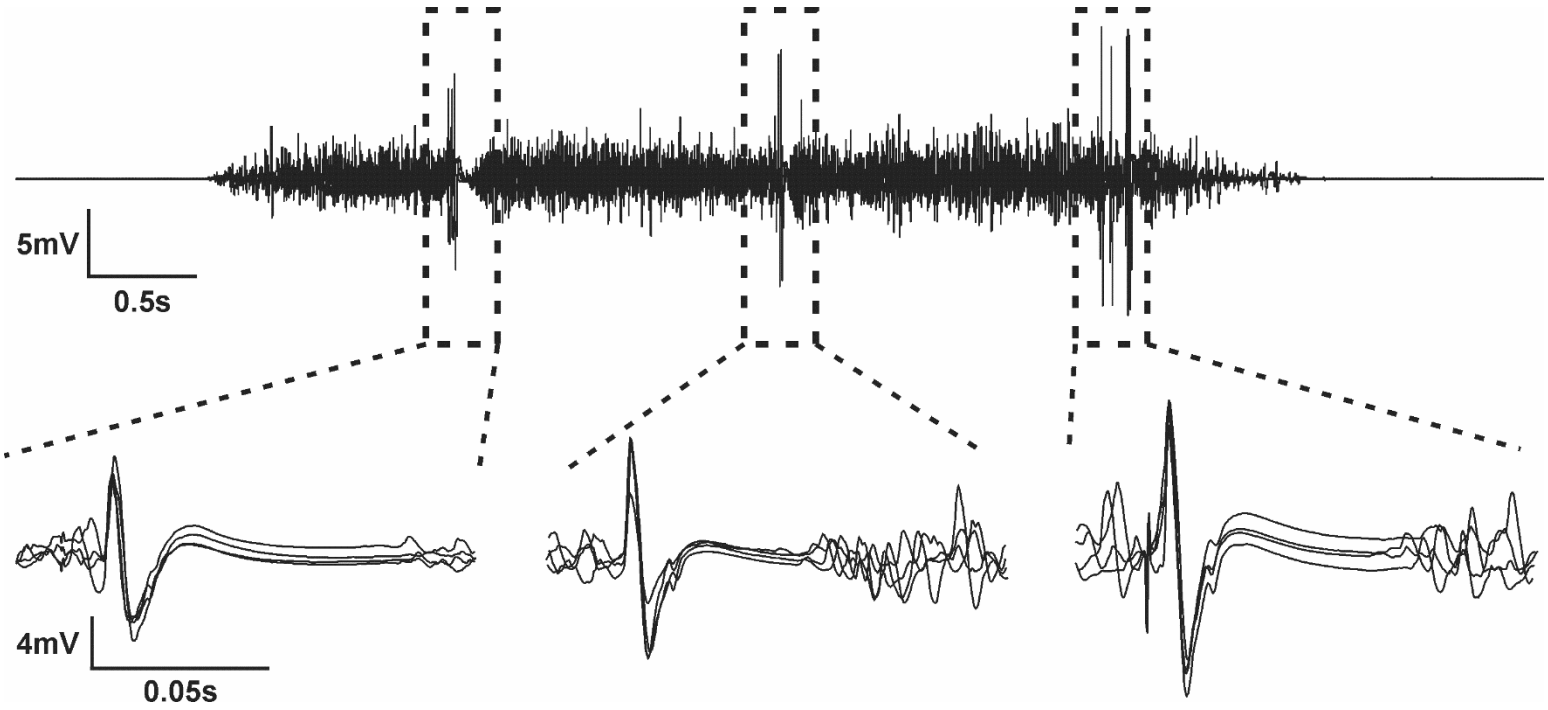
3.12.2: Figure 2 – MEP/ CMEP Results

Corticospinal excitability. Between groups differences for (A) MEPs and (B) CMEPs that were recorded in the biceps brachii during elbow flexion contractions. * Indicates a significant ($p \leq 0.05$) difference between groups. MEPS and CMEPs were plotted together in (C) chronic-RT and (D) non-RT groups. Bars represent standard error.



3.12.3: Figure 3 – Raw Data

Individual raw data traces of EMG and evoked potentials recorded from the non-dominant biceps brachii of a chronic-RT participant during the four elbow flexion contractions at 75% MVC. The traces were overlaid. (top).. Boxes were placed around the MEP, CMEP and M-wave and magnified for clearer illustration (bottom).



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Appendix A: TMS Safety Checklist

The safety of TMS continues to be supported by recent metaanalyses of the published literature (see Machii et al., 2006; Loo et al., 2008; Janicak et al., 2008, Rossi et al. 2009). To ensure safety of the participants they will have to fill out the following questionnaire prior to TMS.

Magnetic Stimulation safety checklist

Please answer the following questions by circling yes or no.

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

Comments:

_____

Date: _____

Medications contraindicated with magnetic stimulation: 1) Tricyclic antidepressants

Name	Brand name
amitriptyline (& butriptyline)	Elavil, Endep, Tryptanol, Trepiline
desipramine	Norpramin, Pertofrane
dothiepin hydrochloride	Prothiaden, Thaden
imipramine (& dibenzepin)	Tofranil
iprindole	-
nortriptyline	Pamelor
opipramol	Opipramol-neuraxpharm, Insidon
protriptyline	Vivactil
trimipramine	Surmontil
amoxapine	Asendin, Asendis, Defanyl, Demolox, Moxadil
doxepin	Adapin, Sinequan
clomipramine	Anafranil

2) Neuroleptic or Antipsychotic drugs

A) Typical antipsychotics

• Phenothiazines: • Thioxanthenes:

- Chlorpromazine (Thorazine) ○ Chlorprothixene
- Fluphenazine (Prolixin) ○ Flupenthixol (Depixol and Fluanxol)
- Perphenazine (Trilafon) ○ Thiothixene (Navane)
- Prochlorperazine (Compazine) ○ Zuclopenthixol (Clopixol and Acuphase)
- Thioridazine (Mellaril) • Butyrophenones:
- Trifluoperazine (Stelazine) ○ Haloperidol (Haldol)
- Mesoridazine ○ Droperidol
- Promazine ○ Pimozide (Orap)
- Triflupromazine (Vesprin) ○ Melperone
- Levomepromazine (Nozinan)

B) Atypical antipsychotics

- Clozapine (Clozaril)
- Olanzapine (Zyprexa)
- Risperidone (Risperdal)
- Quetiapine (Seroquel)
- Ziprasidone (Geodon)
- Amisulpride (Solian)
- Paliperidone (Invega)

C) Dopamine partial agonists:

Aripiprazole (Abilify)

D) Others

Symbyax -A combination of olanzapine and fluoxetine used in the treatment of bipolar depression.
Tetrabenazine (Nitoman in Canada and Xenazine in New Zealand and some parts of Europe
Cannabidiol One of the main psychoactive components of cannabis.

Appendix B: Edinborg Handedness Questionnaire: Short Form

APPENDIX

Edinburgh Handedness Inventory – Short Form

Please indicate your preferences in the use of hands in the following activities or objects:

	Always right	Usually right	Both equally	Usually left	Always left
Writing	☐	☐	☐	☐	☐
Throwing	☐	☐	☐	☐	☐
Toothbrush	☐	☐	☐	☐	☐
Spoon	☐	☐	☐	☐	☐

Appendix C: Free and Informed Consent Form

Informed Consent Form

Title: Methods of determining muscle activation levels using the interpolated twitch technique

Principal Investigators Mr. Devin Philpott

School of Human Kinetics and Recreation, MUN

dtgp84@mun.ca

You are invited to take part in a research project entitled "Methods of determining muscle activation levels using the interpolated twitch technique."

This form is part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. It also describes your right to withdraw from the study at any time. In order to decide whether you wish to participate in this research study, you should understand enough about its risks and benefits to be able to make an informed decision. This is the informed consent process. Take time to read this carefully and to understand the information given to you. Please contact the researchers, Mr. Philpott or Dr.

Duane Button (dbutton@mun.ca) if you have any questions about the study or for more information not included here before you consent.

It is entirely up to you to decide whether to take part in this research. If you choose not to take part in this research or if you decide to withdraw from the research once it has started, there will be no negative consequences for you, now or in the future.

Introduction

This research is being conducted by Mr. Devin Philpott, a master's student in the school of human kinetics and recreation under the supervision of Dr. Duane Button, assistant professors in the School of Human Kinetics and Recreation at Memorial University. This research is aimed at measuring the changes in corticospinal neurone activity during submaximal and maximal muscular contractions. To initiate purposeful movements, corticoneurons in the brain sends signals to the spinal cord to activate cells called motoneurones, which in turn send electrical signals to the muscles for contraction. Previous work has shown that differing intensities of muscle contractions can alter the responsiveness of corticoneurons, spinal motoneurones and muscles. For example, maximal effort muscular contractions cause a reduction in spinal motoneurone excitability; while, very low-level repeated contractions increase the responsiveness of spinal motoneurones which would mean that the amount of effort required initiating and maintaining muscle contraction is reduced, making movement easier. It is currently unknown how the corticospinal excitability/force relationship differs across muscles or if this relationship is affected by being endurance trained.

Purpose of study:

The purpose of this study is to determine the corticospinal excitability/force relationship between muscles, dominant and non- dominant limbs as well as the difference between resistance-trained athletes and sedentary individuals.

What you will do in this study:

This study will consist of two different testing sessions conducted on separate days. The following is a brief description of the techniques being utilized and the protocol for each individual testing session.

TESTING SESSION 1: This session will be used to introduce you to the experimental procedure as well as to gather data that will be needed for the second testing session.

TESTING SESSION 2: The remaining testing session will consist of assessing the effects of repeated muscular contractions on corticospinal excitability in different muscles of the dominant and non-dominate limbs. When you arrive at the lab you will be asked to do a 5 minute warm-up on a stationary bicycle. After completing the warm-up, electrodes will be fixed to your tibialis anterior, gastrocnemieus, soleus, vastus lateralis, biceps femoris, biceps brachii, and triceps brachii muscles as well as over the mastoid processes (on the skull) and supraclavicular space

(just above the collar bone). The vertex on the skull will also be marked. Then you will be seated on a custom-made chair and the force measuring device will be attached to each muscle. Once electrodes and the force measuring device have been attached, you will be asked to perform a maximal voluntary contraction (MVC) for each muscle. You will then perform submaximal and maximal muscle contractions (Starting at 3-10kg and increasing by increments of 2-10 kg until your maximal force is reached) while receiving the stimulation procedures. Each muscle contraction will be separated by 60 seconds to reduce fatigue effects.

General stimulation procedures: Corticoneuron, spinal motoneurone and muscle excitability will be assessed by recording muscle activity in response to stimulation of the brain, spinal cord, nerve and muscle. To do this, it will be necessary to place recording electrodes over the muscle and also to apply magnetic stimulation to the motor cortex and electrical stimulation to, (1) the back of the neck close to the bottom of you skull electrical stimulation of the nerve (2) to nerve, located just above the collar bone and (3) the muscle. Measurements will be taken during each muscle contraction.

Length of time:

Participation in this study will require you to come to a lab located in the School of Human Kinetics and Recreation at Memorial for two testing sessions. The total time commitment will be approximately 3.5 hours (session 1: 1 hour, session 2.5 hours each). You will be asked to not engage in weight training or vigorous exercise prior to all sessions. The following table outlines the testing schedule:

TESTING SESSION	PROCEDURE
1	Familiarization
2	Corticospinal excitability/force relationship measurements

Withdrawal from the study:

You will be free to withdraw from this study at any point. To do so you simply need to inform the researchers and you will be free to leave. Any data collected up to this point will not be used in the study and will be destroyed. If you are a student your participation in and/or withdrawal from this study will not in any way, now or ever, negatively impact either your grade in a course, performance in a lab, reference letter recommendations and/or thesis evaluation.

Possible benefits:

The benefit of participating in his study is that you will learn about the functioning of your nervous system. You will also be aiding our basic understanding of how the nervous system responds to repeated submaximal contractions. This investigation is important because until we understand the basic mechanisms controlling motoneurone and muscle excitability we cannot fully understand mechanisms of impaired motor function. The findings of this research may be used for guiding rehabilitation strategies and exercise interventions for clinical and non-clinical populations.

Possible risks:

There are several minor risks associated with participating in this study:

1) You will have electrodes placed on the front and back of your arm. These electrodes have an adhesive that has a tendency cause redness and minor irritation of the skin. This mark is temporary (usually fades within 1-2 days) and is not generally associated with any discomfort or itching.

2) The electrical stimulations will cause twitching of the muscles and mild discomfort, but is not painful. The sensation has been described as if you flicked your neck and arm muscles firmly with a finger. The sensation will be very brief (less than a second) and will in no way result in any harm to either muscles or skin.

3) Electrical stimulation used to assess spinal excitabliy is applied at the base of the skull between the mastoid processes. This will cause twitching of the neck musculature resulting in head movement and a transient unpleasant sensation (some participants do not experience any discomfort, myself included).

4) Transcranial magnetic stimulation used to assess motor cortex excitability is applied at ~ the apex of the skull. This will cause activation of the motor cortex resulting in small muscle contraction (most individuals do not experience any discomfort).

5) Post experiment muscle soreness, simlilar to that following an acute bout of exercise may also be experienced by some participants.

6) The stimulators used for the experiment are designed for human research, are completely safe and have been used extensively by Dr. Button for many years.

Confidentiality vs. Anonymity

There is a difference between confidentiality and anonymity: Confidentiality is ensuring that identities of participants are accessible only to those authorized to have access. Anonymity is a result of not disclosing participant's identifying characteristics (such as name or description of physical appearance).

Confidentiality and Storage of Data:

a. Your identity will be guarded by maintaining data in a confidential manner and in protecting anonymity in the presentation of results (see below)

b. Results of this study will be reported in written (scientific article) and spoken (local and national conferences and lectures) forms. For both forms of communication only group average data will be presented. In cases where individual data needs to be communicated

it will be done in such a manner that you confidentiality will be protected (i.e. data will be presented as coming from a representative subject).

c. All data collected for this study will be kept in a secured location for 5 years, at which time it will be destroyed. Paper based records will be kept in a locked cabinet in the office of Dr. Button while computer based records will be stored on a password protected computer in the office of Dr. Button. The only individuals who will access to this data are those directly involved in this study.

d. Data will be retained for a minimum of five years, as per Memorial University policy on Integrity in Scholarly Research after which time it will be destroyed.

e. The data collected as a result of your participation can be withdrawn from the study at your request up until the point at which the results of the study have been accepted for publication (~1year post study).

Anonymity:

Your participation in this study will not be made known to anyone except researchers who are directly involved in this study.

Recording of Data:

There will be no video or audio recordings made during testing.

Reporting of Results:

Results of this study will be reported in written (scientific article) and spoken (local and national conferences and lectures). Generally all results will be presented as group averages. In cases where individual data needs to be communicated it will be done in such a manner that your confidentiality will be protected (i.e. data will be presented as coming from a representative subject).

Sharing of Results with Participants:

Following completion of this study please feel free to ask any specific questions you may have about the activities you were just asked to partake in. Also if you wish to receive a brief summary of the results then please indicate this when asked at the end of the form.

Questions:

You are welcome to ask questions at any time during your participation in this research. If you would like more information about this study, please contact: Devin Philpott (dtgp84@mun.ca) or Duane Button (dbutton@mun.ca).

The proposal for this research has been reviewed by the Interdisciplinary Committee on Ethics in Human Research and found to be in compliance with Memorial University's ethics policy. If you have ethical concerns about the research (such as the way you have been treated or your

rights as a participant), you may contact the Chairperson of the ICEHR at icehr@mun.ca or by telephone at 709-864-2861.

Consent:

Your signature on this form means that:

- You have read the information about the research.
- You have been able to ask questions about this study.
- You are satisfied with the answers to all your questions.
- You understand what the study is about and what you will be doing.
- You understand that you are free to withdraw from the study at any time, without having to give a reason, and that doing so will not affect you now or in the future.
- You understand that any data collected from you up to the point of your withdrawal will be destroyed.

If you sign this form, you do not give up your legal rights and do not release the researchers from their professional responsibilities.

Your signature:

I have read and understood what this study is about and appreciate the risks and benefits. I have had adequate time to think about this and had the opportunity to ask questions and my questions have been answered.

☐ I agree to participate in the research project understanding the risks and contributions of my participation, that my participation is voluntary, and that I may end my participation at any time.

☐ I wish to receive a summary of the results of this study Please provide an e-mail address where this summary can be sent: _____

_____ _____

Signature of participant Date

Researcher's Signature:

I have explained this study to the best of my ability. I invited questions and gave answers. I believe that the participant fully understands what is involved in being in the study, any potential risks of the study and that he or she has freely chosen to be in the study.

Signature of Principal Investigator

Date

Appendix D: Neuroscience Letters Published Manuscript

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Short communication

Chronic resistance training enhances the spinal excitability of the biceps brachii in the non-dominant arm at moderate contraction intensities

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HIGHLIGHTS

- Supraspinal excitability of the biceps brachii in the non-dominant arm was not different between chronic resistance trained and non-resistance trained individuals.
- Chronic resistance trained individuals had greater spinal excitability of the biceps brachii in the non-dominant arm.
- Increased strength in the non-dominant limb in chronic resistance-individuals is, in part, spinally mediated.

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ABSTRACT

The purpose of the study was to assess corticospinal excitability of the biceps brachii in the non-dominant arm of chronic resistance-trained (RT) and non-RT individuals. Seven chronic-RT and six non-RT male participants performed 4 sets of 5 s pseudo-randomized contractions of the non-dominant elbow flexors at 25, 50, 75, 90, and 100% of maximum voluntary contraction (MVC). During each contraction, transcranial magnetic stimulation, transmastoid electrical stimulation, and Erb's point electrical stimulation were administered to assess the amplitudes of motor evoked potentials (MEPs), cervicomedullary evoked potentials (CMEPs), and maximal muscle compound potentials (M_{max}), respectively, in the biceps brachii. MEP and CMEP amplitudes were normalized to M_{max}. Training did not affect ($p > 0.14$) MEP amplitudes across any contraction intensity. CMEP amplitudes were significantly ($p < 0.05$) higher in the chronic-RT group at 50% and 75% of MVC by 38% and 27%, respectively, and there was a trend for higher amplitudes at 25%, 90%, and 100% MVC by 25% ($p = 0.055$), 36% ($p = 0.077$), and 35% ($p = 0.078$), respectively, compared to the non-RT group. Corticospinal excitability of the non-dominant biceps brachii was increased in chronic-RT individuals mainly due to changes in spinal excitability.

1. Introduction

Changes in corticospinal excitability (CE) accompany the strength increases with chronic resistance training. Recently, Pearcey et al. [22] showed that motor evoked potential (MEPs, *i.e.*, supraspinal excitability) amplitudes recorded in the biceps brachii during dominant arm elbow flexion contractions at intensities above 50% MVC were lower in the chronic resistance trained (RT) group than the non-RT; whereas, cervicomedullary evoked potentials (CMEPs, *i.e.*, spinal excitability) were similar. They suggested that the decrease in the MEP amplitudes in the chronic-RT group might have been due to an increased firing rate of the spinal motoneurons (*i.e.*, increased spinal and/or spinal motoneuron excitability). Since resistance training increases motor unit maximal firing rates [32,34], the increase in strength from chronic resistance training may be due, in part, to enhanced motoneuron firing frequency, especially at the higher force outputs. Two other studies found no effect of chronic resistance training on corticospinal excitability of the biceps brachii [11] and tibialis anterior [27]. However, in these studies spinal excitability was not

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examined [11,27]. Findings from acute resistance training studies have illustrated concomitant changes in CE (utilizing similar stimulation techniques as employed in [22]) of the first dorsal interosseous [8] and extensor carpi radialis [7] and strength. The authors [7,8] also suggested that the changes in CE following acute resistance training were due to either an increased spinal excitability or increased firing rate of the spinal motoneuron. Thus, the resistance training-induced changes in CE of muscles located in the dominant limb appear to be mainly of spinal origin. Interestingly, all of the aforementioned studies focused on changes in CE of a muscle in the dominant limb. To our knowledge, no studies to date have determined how chronic resistance training alters CE of a muscle located in a non-dominant limb. Differences in CE have been shown between dominant and non-dominant fine motor control muscles of the hand [26], potentially due to use-dependence; however, an increased usage of the non-dominant limb due to chronic resistance training may alter CE of a given muscle compared to non-RT individuals.

The purpose of the current study was to determine if CE of the biceps brachii in the non-dominant arm was different between chronic-RT and non-RT individuals. In order to compare CE of the biceps brachii in the non-dominant arm to the changes in CE of the biceps brachii in the dominant arm [as shown in [22]], we sought to determine how CE of the biceps brachii in the non-dominant arm changes over elbow flexion contractions from low to maximum intensity. Based on work by Pearcey at al. [22] as described earlier, it was hypothesized that chronic-RT individuals would produce more non-dominant elbow flexor force than non-RT individuals. The increased force would be, in part, due to differences in CE that were mainly of spinal origin. Specifically, the changes in CE may be due to enhanced excitability of spinal motoneurons.

2. Material and methods

2.1. Participants

Seven chronic-RT (>2 years at ≥3 times per week of resistance training experience) (height 176.9 ± 4.7 cm, weight 79.2 ± 6.3 kg, age 22.9 ± 3.5 years) and six non-RT (height 182.1 ± 9.3 cm, weight 91.4 ± 18.0 kg, age 22.0 ± 2.2 years) males participated in the study. Participants were verbally informed of all procedures, and read and signed a written consent form. Participants completed the magnetic stimulation safety checklist [25] and Edinburg handedness inventory: short form to determine participants' arm dominance [33] prior to the start of the experiment. All participants were strongly right-handed or left-handed (laterality quotient (LQ); right-handed LQ = 93 ± 11.5; left-handed LQ = 93 ± 10.0). The Memorial University of Newfoundland Interdisciplinary Committee on Ethics in Human Research approved this study (ICEHR #20140710-HK).

2.2. Experimental protocol

Participants performed a voluntary isometric contraction protocol which included four sets of 5 s contractions of the non-dominant elbow flexors at 5 target forces (25, 50, 75, 90, 100% MVC) for a total of 20 contractions (4 contractions at each target force). Once the participant reached the prescribed force they received TMS, TMES, and Erb's point stimulation at 1, 2.5, and 4 s, respectively. At the start of each set, participants performed a MVC and all subsequent target forces with stimulation protocol (25–90% of MVC) in that set were randomized. During all contraction intensities in one set the MEP, CMEP, and muscle compound action potential (M-wave) responses were recorded from the bicep brachii. To minimize the effect of fatigue, there was 2 min of rest following 90% and 100% MVC, 1 min of rest following 75 and 50% MVCs and 30 s of rest following all forces at 25% MVC [4,22,23] (see Fig. 1A and B for experimental set-up and stimulation protocol).

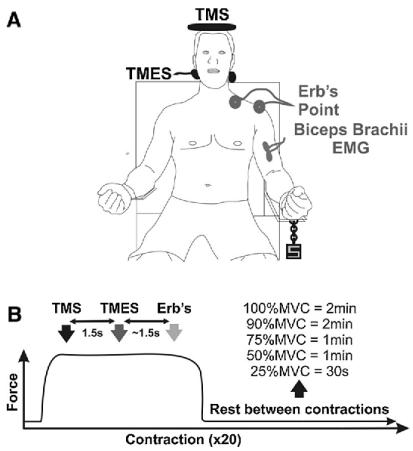

Fig. 1. (A) Diagram of experimental apparatus for elbow flexion contractions and time and type of stimulation. (B) Subjects performed 4 sets of 25, 50, 75, 90, and 100% MVCs (20 contractions in total) and received TMS (black arrow, at 1.0 s), TMES (white arrow, at 2.5 s) and Erb's point stimulation (grey arrow, at 4.0 s) during each muscle contraction. Rest periods between contractions varied based on the intensity.

2.3. Elbow flexor force

Participants sat in an upright position with hips, knees, and elbows flexed at 90° with forearms in a neutral position and resting on padded support. The upper torso was rested against the backrest and secured with straps around the waist and shoulders. The wrist of the non-dominant arm was inserted into a non-compliant padded strap, attached by a high-tension wire that measured force using a load cell (Omegadyne Inc., Sunbury, OHIO). Forces were detected by the load cell, amplified (×1000) (CED 1902) and displayed on a computer screen.

Electromyography activity was recorded from the biceps brachii muscle. Surface EMG recording electrodes (Meditrace Pellet Ag/AgCl electrodes, disc shape, and 10 mm in diameter, Graphic Controls Ltd., Buffalo, NY) were placed 2 cm apart over the mid-muscle belly of the biceps brachii. A ground electrode was secured on the lateral epicondyle. EMG signals were analog-digitally converted at a sampling rate of 5 kHz using a CED 1401 interface and signal 4 software (Cambridge Electronic Design Ltd., Cambridge, UK).

2.4. Stimulation conditions

All stimulation conditions and methods utilized in the current study were similar to that previously reported from our laboratory that compared the corticospinal excitability of the biceps brachii in the dominant arm of chronic-RT and non-RT individuals [22].

2.4.1. Brachial plexus (Erb's point) electrical stimulation

Erb's point was electrically stimulated *via* adhesive Ag–AgCl electrodes (diameter 10 mm) fixed to the skin over the supraclavicular fossa (cathode) and the acromion process (anode). Current pulses (200 μs duration) were delivered *via* a constant current stimulator (DS7AH, Digitimer Ltd., Welwyn Garden City, UK). The stimulator setting (chronic-RT = 207.1 ± 45.0 mA and

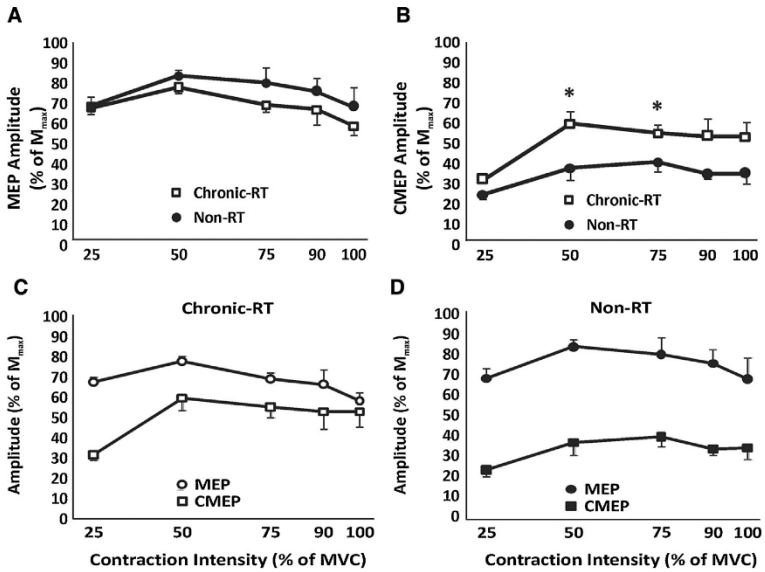

Fig. 2. Individual raw data traces of EMG and evoked potentials recorded from the non-dominant biceps brachii of a chronic-RT participant during the four elbow flexion contractions at 75% MVC (top). Boxes were placed around the MEP, CMEP, and M-wave and magnified for clearer illustration (bottom).

Non-RT = 187.5 ± 55.0 mA) used to evoke M_{max} at 5% MVC was recorded and used for all contractions in the experimental protocol.

2.4.2. Transcranial magnetic stimulation

MEP responses of the biceps brachii were elicited *via* TMS over the motor cortex in the left or right hemisphere (depending on which arm was non-dominant) using a circular coil (13.5 cm outside diameter) attached to a Magstim 200 stimulator (Magstim, Dyfed, UK). The stimulator setting (chronic-RT = 65.1 ± 18% and non-RT = 60.1 ± 13.5% of maximum stimulator output) used to evoke a MEP amplitude that was between ~15–20% of the M_{max} amplitude at 5% MVC was used for all contractions in the experimental protocol.

2.4.3. Transmastoid electrical stimulation

Stimulation was applied *via* adhesive Ag–AgCl electrodes fixed to the skin over the mastoid processes and current passed between them (100 μs duration, 150–350 mA). The stimulation intensity was altered to elicit a CMEP amplitude that matched the MEP amplitude at 5% MVC. This intensity (chronic-RT = 238.3 ± 34.0 mA and non-RT = 183.8 ± 33.5 mA) was used to evoke a CMEP for all contractions in the experimental protocol.

2.5. Data and statistical analysis

Non-dominant biceps brachii MEP, CMEP, and M-wave peak-to-peak amplitudes and onset latencies were measured from all %MVC forces in each set. See Fig. 2 for raw EMG with MEPs, CMEPs, and M-waves at 75% MVC. Onset latencies for MEP, CMEP, and M-waves were defined as the time between the stimulus artifact and the onset of the evoked potential. Force and root mean square (rms) EMG averages were also measured for 50 ms prior to each stimulus for each %MVC. All data were analyzed off-line using signal 4.0 software (CED, UK).

A one-way ANOVA was performed to compare between group differences at 5, 25, 50, 75, 90, and 100% MVC for all dependent variables using SPSS (SPSS 18.0 for Macintosh, IBM Corporation, Armonk, New York, USA). A one-way repeated measures ANOVA was also performed to compare within group differences at for rmsEMG and force prior to stimulation at 5, 25, 50, 75, 90, and 100% MVC. If significant main effects were found, a Bonferroni post hoc analysis was used to examine within group differences. Levene's test was performed to assess the equality of variances between groups. Significance was set at $p < 0.05$. Cohen's d effect sizes (ES) [10] were also calculated for maximal elbow flexor force and normalized MEPs and CMEPs at all contraction intensities. Descriptive statistics in text include means ± SD and for clarity purposes figures include means ± SE.

3. Results

3.1. Maximal elbow flexor force outputs

Overall, the chronic-RT group produced 24.2 ± 4.4% ($p < 0.001$, ES = 2.3) greater maximal force in the non-dominant elbow flexors compared to the non-RT group. There were no significant differences between the four 100% MVC forces performed by the chronic-RT (386.9 ± 39.7–397.9 ± 44.9 *N*; *p* values ranging from $p = 0.57$ to $p = 0.99$) and non-RT (288.7 ± 88.4–312.1 ± 74.6 *N*; *p* values ranging from $p = 0.98$ to $p = 1.0$) groups.

3.2. MEPs and CMEPS recorded at 5% MVC

Average MEP amplitudes in the biceps brachii were 17.9 ± 0.03% M_{max} and 17.2 ± 0.02% M_{max} in the chronic-RT and non-RT groups, respectively. Average CMEP amplitudes in the biceps brachii were 18.1 ± 0.02% M_{max} and 16.8 ± 0.03% M_{max} in the chronic-RT and non-RT groups, respectively. There were no significant between group differences for MEP ($p = 0.78$) or CMEP ($p = 0.54$) relative to M_{max} in the biceps brachii.

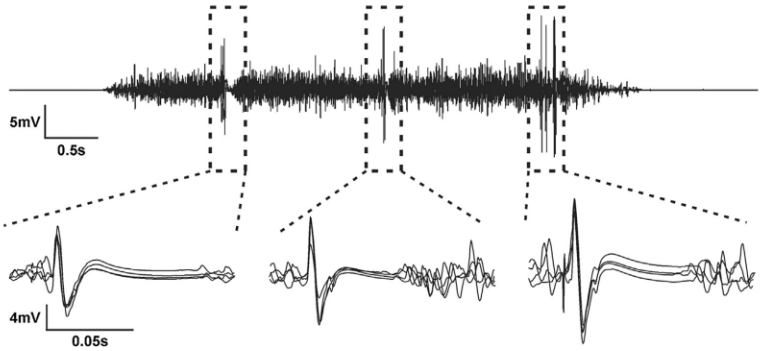

Fig. 3. Corticospinal excitability. Between groups differences for (A) MEPs and (B) CMEPs that were recorded in the biceps brachii during elbow flexion contractions. *Indicates a significant ($p \leq 0.05$) difference between groups. MEPS and CMEPs were plotted together in (C) chronic-RT and (D) non-RT groups.

3.3. Control values during all contraction intensities

Overall, MEP, CMEP, and M_{max} average latencies were 11.7 ± 1.3 ms, 8.6 ± 0.5 ms, and 4.6 ± 0.7 ms, respectively. There were no significant differences for MEP (11.7 ± 2.0–12.0 ± 1.3 ms; p values ranging from $p = 0.18$ to $p = 0.93$), CMEP (8.5 ± 0.6–8.6 ± 0.4 ms; p values ranging from $p = 0.18$ to $p = 0.99$) or M_{max} (4.5 ± 0.7–4.6 ± 0.8 ms; p values ranging from $p = 0.76$ to $p = 0.99$) latencies between chronic-RT and non-RT groups at each contraction intensity (*i.e.*, 25, 50, 75, 90, and 100% MVC). Average M_{max} amplitudes were 12.7 ± 3.7 mV, 11.8 ± 3.7 mV, 11.6 ± 3.9 mV, 10.8 ± 3.5 mV, and 10.6 ± 3.2 mV at 25, 50, 75, 90, and 100% MVC, respectively. There were no significant differences for M_{max} amplitudes (p values ranging from $p = 0.50$ to $p = 0.99$) between chronic-RT and non-RT groups at each contraction intensity.

Irrespective of group, there were no significant differences (p values ranging from 0.15 to 0.84) in the average biceps brachii rmsEMG values prior to the onset of TMS and TMES at 25%, 50%, 75%, 90%, and 100% of MVC. Irrespective of group there were no significant (p values ranging from 0.15 to 0.80) differences in the average elbow flexor forces prior to the onset of TMS and TMES at 25%, 50%, 75%, 90%, and 100% of MVC.

3.4. Corticospinal excitability

There were no significant between group differences in MEP amplitudes in the biceps brachii at 25 ($p = 0.89$, ES = 0.10), 50 ($p = 0.19$, ES = 0.76), 75 ($p = 0.21$, ES = 1.18), 90 ($p = 0.40$, ES = 0.45), and 100% ($p = 0.38$, ES = 0.78) MVC (Fig. 3A).

3.5. Spinal excitability

TMES was utilized to determine if there were changes in spinal excitability [7,18,20,22]. CMEP amplitudes in the non-dominant biceps brachii were significantly lower in the non-RT group by $38 \pm 23.5\%$ ($p = 0.023$, ES = 1.16) and $27 \pm 22.3\%$ ($p = 0.049$, ES = 1.07) at 50 and 75% MVC, respectively. There was a trend for CMEP amplitudes to be lower by $25 \pm 11.9\%$ ($p = 0.055$, ES = 0.98), $36 \pm 13.7\%$ ($p = 0.077$, ES = 0.67) and $35 \pm 13.8\%$ ($p = 0.078$, ES = 0.83) at 25, 90, and 100% MVC, respectively (Fig. 3B). To illustrate overall CE, MEPs, and CMEPs over all the contraction intensities were plotted together for the chronic-RT (Fig. 3C) and non-RT (Fig. 3D) groups.

4. Discussion

The increased non-dominant arm elbow flexor force output in the chronic-RT group was, in part, due to alterations in the corticospinal pathway. The current data supports the notion [7,8,22] that the resistance training-induced alterations in the corticospinal pathway are mainly of spinal origin. More specifically, CMEPs were increased, due to increased spinal excitability.

The changes in CE of the biceps brachii in the non-dominant arm between groups as reported here were different to those reported on the dominant arm by Pearcey et al. [22]. There were no differences in MEP amplitudes of the biceps brachii in the non-dominant arm between the chronic-RT compared to the non-RT group; whereas, CMEP amplitudes were significantly greater during various contraction intensities in the chronic-RT group. Although the results of the current study and those of Pearcey et al. [22] were different, both studies support that chronic-RT individuals have increased spinal excitability of the non-dominant and dominant biceps brachii, respectively. Chronic resistance training in the non-dominant arm may have affected presynaptic modulation of the spinal motoneuron, modulation of motoneuron intrinsic properties, and changes in motoneuron firing rates. The H-reflex is potentiated by resistance training, illustrating a pre-motoneuronal and/or motoneuronal adaptation [1]. In animals, endurance training enhances motoneuron afterhyperpolarization (AHP) amplitude [2,6], lowers the action potential voltage threshold and decreases action potential rise time [3]. Although not known, motoneuron persistent inward currents may be enhanced by resistance training, subsequently amplifying synaptic input [5,12], which would increase motoneuron firing frequency and enhance force. Persistent inward currents would reduce the amount of synaptic input required to maintain or increase motoneuron-firing frequency [5,12,14,15]. Indeed, in humans, resistance training has been shown to decrease motor unit recruitment thresholds (*i.e.*, earlier activation) [32] and increase motor unit maximal firing rates [32,34]. Thus, chronic resistance training may modulate the inputs projecting to the spinal motoneuron (*i.e.*, presynaptic mechanisms) or the intrinsic properties of the spinal motoneuron (*i.e.*, postsynaptic mechanisms), ultimately leading to lower recruitment thresholds and increased firing rates and thus, increased force production.

Irrespective of group, a shift from supraspinal to spinal control of force output occurred at relative contraction intensities ~50% of MVC. At contraction intensities ~ ≥50% MVC both MEP and CMEP amplitudes plateaued and started to decrease indicating that CE was now predominantly spinally mediated. Other resistance training [21,22] and non-resistance training [17,28,31] studies have also

shown increased CE at the supraspinal level during weak contractions and increased spinal excitability during strong contractions.

Differences in CE between dominant and non-dominant limbs have been shown in non-training studies, which utilized fine motor control muscles of the hand. For example, CE of the first dorsal interosseous muscle between dominant and non-dominant hands is different during a simplistic finger abduction task involving isometric contractions at varying intensities [26]. TMS evoked MEPs were significantly larger in the non-dominant hand compared to the dominant hand FDI muscle, while TES evoked MEPs (*i.e.*, spinal excitability) did not differ between dominant and non-dominant hand FDI muscle. Therefore, the differences in CE were due to supraspinal rather than spinal mechanisms. Potentially the cortical neuron involvement is greater in the non-dominant hand because the dominant hand has greater cortical representation for a given muscle [35] and lower thresholds for activation [16,29]. CE of similar muscles is asymmetrical between hands because of dominant hand use-dependence. However, CE of a gross motor muscle such as the biceps brachii appears to be symmetrical in both trained and untrained individuals (compare findings from here to that of Pearcey et al. [22]). Thus, use-dependency may only alter CE of fine-motor muscles.

5. Conclusion

In conclusion, chronic resistance training enhances the strength of the non-dominant arm elbow flexors concomitantly with altered CE of the biceps brachii. Similar to the dominant arm [22], the predominant site for the altered CE is probably at the spinal motoneuron. It appears that within both chronic-RT and non-RT individuals CE of the biceps brachii in the dominant and non-dominant arm are similar during weak and strong muscle contraction forces.

Author contributions

All experimental data collection took place at the Neuromuscular Physiology Laboratory at the School of Human Kinetics and Recreation, Memorial University. Devin Philpott, Gregory Pearcey, Davis Forman, Kevin Power, and Duane Button all contributed to (1) conception and design of the experiments, (2) collections analysis and interpretation of data, and (3) drafting and revising of the article.

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