The influence of shoulder position on corticospinal excitability of the biceps brachii

By

© Brandon Collins

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Abstract

The objective of this thesis was to examine corticospinal excitability (CSE) of the elbow flexors during two shoulder positions (0° shoulder flexion and 90° shoulder flexion) during rest and during an active state (10% maximum voluntary contraction (MVC)). Ten recreationally active males participated in two randomized experimental sessions (Day 1: n=10, Day 2: n=8) with 4 experimental conditions; 1) 0° shoulder flexion with biceps brachii at rest, 2) 0° shoulder flexion with biceps brachii at 10% MVC, 3) 90° shoulder flexion with biceps brachii at rest and 4) 90° shoulder flexion with biceps brachii at 10% MVC. Transcranial magnetic, transmastoid and Erb's point stimulations were used to induce motor evoked potentials (MEPs), cervicomedullary MEP (CMEPs) and maximal muscle action potential (M_{max}). All MEPs and CMEPs were normalized to M_{max}. M_{max} and CMEP amplitudes were position-dependent (0° versus 90°), whereas MEP amplitude was position dependent but differed (higher at rest and lower at 10% MVC) between the state at which it was recorded (rest versus active). At 0° compared to 90°, MEP/M_{max} ratio was higher at rest but lower at 10% MVC. Whereas, CMEP/M_{max} experienced no change at rest but lower at 10% MVC. Finally, MEP/CMEP ratios showed that starting in the 90° position ratios were lower at rest while higher at 10% MVC. On the other hand, starting in the 0° position MEP/CMEP ratios only changed at 10% MVC with the ratio being higher with the change in position. Results showed participants could produce more elbow flexor force in 0° shoulder flexion compared to 90° shoulder flexion. RMS EMG of the biceps brachii was higher and lower at rest and 10% MVC, respectively, at the 90° compared to 0° position. In conclusion, CSE of the biceps brachii is dependent on a change in shoulder position and the state it is recorded. In addition, it seems that there are several factors that play a

role in the change of CSE such as: large changes in M_{max} amplitudes, differences in biceps brachii RMS EMG and changes in cortical excitability.

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List of Symbols, Nomenclature or Abbreviations (in order of appearance)

CMEP	Cervicomedullary-evoked potential
CSE	Corticospinal excitability
EMG	Electromyography
MEP	Motor-evoked potential
Mmax	Maximal muscle compound potential
MVC	Maximum voluntary contraction
TES	Transcranial electrical stimulation
TMES	Transmastoid electrical stimulation
TMS	Transcranial magnetic stimulation
RMS	Root Mean Square

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Chapter 1: Review of Literature

1.1: Introduction

The idea of movements involving common motor cortical circuits has been shown in humans. During pointing movements there is activation of the shoulder, elbow and wrist muscles, which utilize these motor-cortical circuits (Devanne et al. 2002). It is widely recognized that starting posture and geometry of the arm influences the directional preference of cells in the motor cortex and is altered by the spatial direction of hand movement (Kalaska and Drew 1993). The purpose of the thesis was to examine changes in corticospinal excitability (CSE) of the biceps brachii based on shoulder position in active versus resting muscles. This study measured CSE of the biceps with the shoulder positioned at 0˚ (arm parallel to torso) and at 90˚ (arm perpendicular to torso) of shoulder flexion, while the elbow was maintained at 90˚ throughout the full experiment, thus limiting the amount of postural change at the elbow joint. Evoked Potentials in the biceps brachii ~~will~~ were~~be~~ elicited from the cortical, spinal and peripheral levels to determine where changes in CSE occur during rest and a 10% maximal voluntary contraction (MVC). Overall the goal was to determine whether CSE of the biceps brachii is arm posture- and/or state-dependent. Previous literature has shown that arm posture affects CSE of the hand, forearm and upper arm muscles at rest. Currently one study (Forman et al. 2016a) has looked at position changes in active muscles. However, there has yet to be a study that has examined whether shoulder posture affects CSE of the biceps brachii during an active contraction, thus providing rationale for this study.

Throughout this literature review the different types of techniques used to measure CSE of the human motor cortex will be discussed. The review will also discuss how positional

changes of the upper body (i.e. orientations of the wrist, elbow and shoulder joints) affect CSE of the muscles of the upper limb (i.e hand, forearm and upper arm muscles).

1.2: Motor Cortex Output

Human motor output depends on the motor commands from motor areas in the cerebral cortex. Cortical motor commands descend through the corticobulbar and corticospinal tracts. Corticobulbar fibers control the motor nuclei in the facial muscles, whereas the corticospinal fibers control the spinal motoneurones that innervate the trunk and limb muscles. Corticospinal fibers terminate directly onto spinal motoneurones or indirectly via interneurones of the spinal cord, which then project to spinal motoneurones. These connections contribute to the organization of single and multi-jointed movements, such as reaching or walking (Kandel et al. 2000). Thus, the assessment of the corticospinal tract role in voluntary contraction is essential in understanding movement of the human body.

Assessing Corticospinal Tract Excitability

Changes in CSE can occur at a supraspinal and/or spinal level (McNeil et al. 2013). Non-invasive magnetic and electrical stimulation techniques of the brain and spinal cord are used to evaluate corticospinal, spinal and supraspinal excitability in non-healthy and healthy individuals (Rossini and Rossi 1998). This section review will focus on the various central nervous system levels underlying corticospinal excitability and the stimulation techniques used to measure it.

Corticospinal Excitability

The corticospinal tract output can be altered by multiple variables, such as exercise, injury, disuse and disease. The use of transcranial magnetic stimulation (TMS) to investigate corticospinal excitability has increased over the years due to its ease and safety (Petersen et al. 2003). The magnetic field stimulation passes virtually un-attenuated and painless through the scalp and skull making it applicable for most individuals. When the motor cortex is stimulated by TMS, it produces a motor evoked potential (MEP) in a muscle when the stimulus intensity is above the motor threshold (i.e. supra-threshold) required to induce a MEP. By using surface electromyography (EMG) recording electrodes a MEP can be recorded in a desired muscle following a supra-threshold TMS pulse delivered to the motor cortex. Through examining the corticofugal discharge in response to a motor cortical stimulus, Di Lazzaro et al. (1998a) and Amassian et al. (1989) have shown that there are multiple components of the MEP. By using epidural or single motor unit recordings, short latency direct wave (D-waves) followed by several longer latency indirect waves (I-waves) can be found. The D-wave is best activated by using high intensity TMS or transcranial electrical stimulation (TES) and is thought to be caused by direct depolarization of the initial axon segment of the corticospinal neurone. Approximately 1.5ms following the D-wave, I-waves will occur, showing the delay required for the synaptic discharge. The first I-wave is thought to be caused monosynaptically by the depolarization of an axon synapsing directly onto a corticospinal neurone. By using low TMS intensities the I-waves that follow may require local polysynaptic circuits (Reis et al. 2008). The likely cause for preferential recruitment of I-waves using TMS is the current flowing parallel to the surface of the brain. To stimulate the hand muscle for example, in the primary motor cortex the hand area is thought to be in the anterior bank of the central sulcus. However, it is probable that the area continues to some degree along the surface of the precentral gyrus (Jasper and Radmussen 1958).

The pyramidal neurones that are in the area of stimulation will participate in the threshold responses, this is because they are nearest to the surface of the scalp. If the stimulation intensity is increased then deeper-laying pyramidal neurones, which are parallel orientated to the brain, in the anterior bank of the central sulcus may be recruited (Rothwell 1997).

Motor threshold, MEP amplitude, area, latency and silent period, and recruitment curves are the most common measurements to examine changes in corticospinal excitability using TMS.

Motor threshold is defined as the lowest TMS intensity or magnetic stimulator output (MSO) that can evoke a MEP in the muscle of interest at rest or during a contraction. It is usually lower at rest and in distal muscles compared to an active state (i.e. muscle contraction) and in proximal muscles (Rothwell 1997; Rothwell et al. 1999). Motor threshold is determined by increasing the intensity of the stimulator by small increments until a MEP is elicited reliably. In general, motor threshold is defined as the stimulation that elicits a MEP with the peak-to-peak amplitude greater than 50μV in 50% of the stimulation trails (i.e. 4 out of 8 trails). However, this is only applicable in a resting state. In an active state, motor threshold is defined as a MEP that is discernible from the background EMG (Kobayashi and Pascual-Leone 2003) of the muscle of interest. Changes in resting threshold can result from a multitude of reasons such as: the structure and number of excitatory projections onto the primary motor cortex, the neurone membrane, axonal electrical properties, or upregulation of receptors of this region (Maeda and Pascual-Leone 2003). Therefore, motor threshold at rest represents a global assessment of the excitability of inactive pyramidal neurones (Maeda and Pascual-Leone 2003; Ziemann 2004). Whereas, in an active state it is thought that the magnitude of voluntary drive to the corticomuscular pathway results in a significant reduction of motor threshold compared to resting conditions (Tergau et al. 1999) because pyramidal neurones are now active or in a state of subliminal fringe.

Another outcome measure of excitability is MEP amplitude. When TMS is utilized over the motor cortex at an intensity higher than motor threshold I-waves are elicited in the corticospinal tract (Di Lazzaro et al. 2004). These I-waves are modulated by multiple mechanisms such as: activity-dependent changes (i.e. voluntary contraction) (Gandevia et al. 1999), interneurones contacted by corticospinal tract cells, neurotransmitters (i.e., glutamate, GABA), and modulators of neurotransmission (i.e., acetylcholine, norepinephrine, and dopamine) (Ziemann 2004). Evidently, all these factors also potentially influence the MEP amplitude. However, MEP amplitude can be altered at either the cortical or the spinal level making it difficult to locate where within the corticospinal tract change has occurred. A reduction or increase in MEP amplitude can be an indicator of alterations within the neuromuscular system (Kobayashi and Pascual-Leone 2003). In addition, another usage of MEP amplitude to assess CSE is through the development of a recruitment curve. A recruitment curve or an input-output curve illustrates the increase in MEP amplitude with increasing TMS intensity. The recruitment curve enables an assessment of neurones that are intrinsically less excitable or further away from the central activation of the TMS (Hallett et al. 1999). The slope of the input-output curve is a measurement of the excitability of the cortical motor areas (Valls-Sole et al. 1994). A steeper curve is found in muscles with a lower motor threshold, which could be related to the strength of the corticospinal projections (Chen et al. 1998). Plateau levels are the level at which the sigmoidal curve approaches Y*max* (maximal response that may be elicited). Slope and plateau levels show motor unit recruitment efficiency and overall summation of inhibitory and excitatory drive from the corticospinal tract(Devanne et al. 1997).

The silent period is defined as the period of interruption in voluntary activation after TMS has been delivered. The silence in the EMG can last upwards of 200 to 300 msec, but

mainly it depends on the stimulus intensity. The physiological basis behind the silent period is still not fully understood, however it includes inhibition at both the spinal cord and at the motor cortex. The first part of the silent period (50-60ms) is attributed to the spinal cord (activation of Renshaw cells), whereas the later section is attributed to the cortex (y-aminobutyric acid (GABA) type B receptor mediated inhibition) (Chen et al. 1999; Fuhr et al. 1991). Although useful, the silent period is difficult to interpret because if alterations are found it cannot be determined whether the change is due to cortical or spinal components or both.

Variations in the size of the MEP amplitude during different conditions are used to infer changes in the central nervous system. It is important to have a method that activates the corticospinal output at a subcortical level to allowing a better interpretation of responses evoked at the cortex (Furubayashi et al. 2003; Gerloff et al. 1998; Kaelin-Lang et al. 2002; Priori et al. 1999; Stuart et al. 2002). This is because a variation in any of the corticospinal excitability measurements may be caused by changes at the cortex, spinal cord or at the muscle.

Spinal Excitability

Motoneurones are the final common pathway to muscle contraction. Understanding how motoneurones respond to synaptic input and their subsequent output is essential to motor control. However, in humans it is difficult to test motoneurones in a controlled manner (Taylor 2006). Like previously stated TMS directly and/or indirectly activates corticospinal neurones leading to the activation of motoneurones, which results in a response in the muscle. However, the response in the muscle depends on the excitability of both cortical neurones and spinal motoneurones. Thus, TMS alone cannot determine the specific central nervous system site where modulation in excitability has occurred. Stimulation techniques that are used to determine changes in

spinal/motoneurone excitability include: 1) TMES, which activates corticospinal axons of the spinal cord and directly activates motoneurones resulting in a response in the muscle (Taylor et al. 2002), 2) nerve stimulation that activates Ia afferents (which are primary muscle spindle afferents) to induce an H-reflex in the muscle, and 3) nerve stimulation to induce an F-wave, which is the result of antidromic activation of a motoneurone. Each of these stimulation techniques are used to describe motoneurone excitability but all have limitations when testing motoneurone excitability.

In 1991, Ugawa et al. (1991) developed a method to stimulate the descending axons at a subcortical level in order to test the excitability of the spinal excitability (i.e. motoneurones). This method involved passing an electrical stimulus between the mastoid processes, creating a single descending volley. This single volley contrasts with that of TMS because TMS evokes multiple descending volleys that stimulates corticospinal motoneurones multiple times. TMES evokes a muscle response that is termed a cervicomedullary MEP (CMEP), which can be utilized as a measure of motoneurone excitability (Day et al. 1987; Rothwell et al. 1991; Taylor 2006). A fixed latency of the response shows activation of fast descending axons at the level of the pyramidal decussation at the cervicomedullary junction (Amassian et al. 1992; Maccabee et al. 1993). The stimulation is made possible due to the bending of axons at the decussation, however stimulation at this site is found to be unpleasant. What makes TMES the most direct motoneurone measurement is that the descending tracts are not subject to conventional presynaptic inhibition due to primary afferent depolarization (Jackson et al. 2006; Nielsen and Petersen 1994). One major issue with TMES is the possibility of activating ventral roots in addition to stimulating the descending axons in the spinal cord (Ugawa et al. 1995). The ventral root bends along the spinal canal exit, thus enabling it to be a susceptible site for activation. If

the ventral root is stimulated, which may occur with an increase in stimulation intensity, the latency of the recorded response will decrease by ~2ms (Mills and Murray 1986; Rossini et al. 1985; Ugawa et al. 1991). If a decrease in latency occurs, then some peripheral axons have been activated and the final response will reflect a mix of both pre-synaptic activation of the motoneurone (i.e. cortical spinal tract) and postsynaptic motoneurone activation (i.e. antidromic activation of the motoneurone via the ventral root). If stimulation intensity is too high, then the CMEP response will become partially occluded. One possible solution to this limitation is to place the anode on the same side as the muscle in which the CMEP is being recorded from, due to depolarization of the peripheral nerve occurring closer to the cathode (Ugawa et al. 1991).

Another way to stimulate the axons of the spinal cord and subsequently motoneurones is by magnetic stimulation with a double-cone magnetic coil evoking motor responses with the same latencies as TMES (Ugawa et al. 1994). However, magnetic stimulation induced-responses at rest tend to be very small compared to the TMES. The benefit of the magnetic stimulation is that it is far less painful. However, the downfall is that positioning of the coil on the back of the head makes it relatively easy to stimulate the lower threshold nerve roots, thus careful positioning of the coil is needed to avoid their activation (Taylor and Gandevia 2004).

If TMES is to be compared to TMS than it is important to know whether both stimulate the same corticospinal axons. When the two stimulations are delivered at appropriate interstimulus intervals in the biceps brachii, the antidromic volley of the CMEP (from TMES) collides and almost fully (>95%) obstructs the MEP (from TMS) (Taylor et al. 2002). In addition, if a longer interstimulus is used a facilitative effect will occur due to interactions at the motoneurones (Taylor 2006; Taylor et al. 2002; Ugawa et al. 1991). Therefore, it can be said that for the hand and elbow flexors the volley evoked by TMES travels in many of the same

axons that are evoked during TMS. The interaction between the two stimulations, however are complex due to the multiple descending volleys by the TMS. Despite this the two measurements are a novel means to test motoneurone responsiveness during muscle activity or fatigue.

The Hoffman Reflex (H-reflex) can be measured from a muscle when electrical stimulation of large-diameter axons of a primary muscle spindle afferents (located in the peripheral nerve) activates motoneurone(s). Increasing the stimulation intensity during a series of stimulations will create a recruitment curve for the H-reflex and the muscle compound action potential (M_{max}). Once the H-reflex reaches its maximum it is known as the H_{max}. Comparing the size of the H-reflex with the size of M_{max} one can estimate the segmental spinal excitability (including the motoneurone) (Taborikova and Sax 1968). One major mechanism that affects the size of the H-reflex is presynaptic inhibition that acts on the Ia terminals through other afferent and descending pathways (Rudomin 2002). Another mechanism that has been shown to affect the Ia terminal is homosynaptic post-activation. This is caused by the release of transmitter from the terminal resulting in a decrease in efficacy of the action potentials (Hultborn et al. 1996). Finally, the last mechanism is repetitive firing of the Ia afferents, which will diminish the axons excitability to electrical stimulation. Therefore, stimulating with the same intensity will no longer elicit the same response (Burke and Gandevia 1999). The main limitation of H-reflex testing is the difficultly in evoking a response in several muscles, particularly at rest, thus reducing its strength as a technique.

The F-wave is a late response from a stimulation of the peripheral nerve. It reflects the backfiring of a small number of motoneurones that are reactivated by antidromic impulses following supramaximal stimulation (Eccles 1955). F-waves are small and inconsistent in both size and shape, therefore many responses must be recorded and an average calculated in order to

interpret the results (Lin and Floeter 2004). It is believed that the excitability of the axon initial segment is responsible for the production of the F-wave from the motoneurone (Eccles 1955) or possibly the first node of Ranvier (Gogan et al. 1984). The F-wave is a test that activates a small portion of the motoneurone pool and could exclude the smaller, slower motoneurones (Espiritu et al. 2003). However, it is problematic when testing proximal muscles as the larger M-wave's orthodromic response overlaps the small F-wave.

Corticospinal and spinal excitability can be influenced by the periphery. The peripheral nerve, neuromuscular junction and muscle, are all outside of the CNS and can be factors that influence peripheral excitability. These properties can be modulated by a number of factors, such as voluntary contraction (Belanger and McComas 1981), fatigue (Adam and De Luca 2005), and pain (Khan et al. 2011). When understanding where the corticospinal excitability changes are by analyzing MEPs and CMEPs it is important to eliminate the changes occurred at the peripheral level. Thus, MEP and CMEP amplitudes can be normalized to the M_{max} to account for any alterations in the periphery. To elicit a M_{max}, a maximal stimulation is applied to the nerve of the muscle of interest, which creates a response in the muscle (Rodriguez-Falces et al. 2013). By normalizing the MEP and CMEP to the M_{max} it allows the investigator to eliminate any potential differences in peripheral excitability and determine where changes occurred along the corticospinal pathway.

In conclusion, MEPs are based on the excitability of the cortical and spinal levels. With the CMEP not being influenced by the cortical level, it offers a possible way to help detect where the change has occurred. To put this in perspective, if MEP amplitude increases in size after an intervention with no significant increase or decrease in CMEP amplitude, then the change can potentially be located at the cortical level. Although the CMEP travels through many of the same

axons as the MEP to recruit motoneurones it still has some limitations. The fact that the CMEP is a single volley it may lead to a different motoneuronal responses compared to the MEP due to its multiple descending volleys. (Taylor and Gandevia 2004). With an understanding of how the techniques are used to measure CSE in humans, the way variations in upper limb posture affect CSE can be discussed. While H-reflex and F-waves do test the excitability of the motoneurone and gives useful information, the limitations for each measurement must be considered.

Supraspinal Excitability

Paired-pulse techniques of the TMS allow the study of mechanisms of cortical inhibition and facilitation. Kujirai et al. (1993) (1993) created the classic method where evoking a suprathreshold MEP test stimulus is preceded by a variable interstimulus interval (ISI) of a conditioning subthreshold stimulus. The test MEPs size is expressed as the percentage of the MEP elicited by the unconditioned stimulus. If the ISI is 7msec or longer the MEP is facilitated, if the ISI is 2 to 4 ms the MEP is depressed. These interactions originate in the cortex from different neuronal populations and are known as intracortical facilitation (ICF) and short-interval intracortical facilitation (SICI). The difference between the first two techniques and long-interval intracortical inhibition (LICI) is that the conditioning pulse is suprathreshold instead of subthreshold and the ISIs are longer. The test MEPS are facilitated at 20-40ms ISIs and inhibited at ISIs <200ms. This inhibition has also been related with reduced motor cortex excitability (Chen et al. 1999; Wassermann et al. 1996).

A MEP/CMEP ratio has been used by researchers (Gandevia et al. 1999) to show a global assessment of the corticospinal pathway. Since the response from TMS stimulation can be affected by spinal excitability, we can use responses by TMES to explain the spinal

excitability. Therefore, by expressing a ratio one can better understand where the changes in CSE has occurred.

Overall, a combination of the aforementioned stimulation techniques can be used to determine how CSE is altered due to exercise, disease, pain, fatigue or just by simply changing the position of the limb in which the muscle of interest is being stimulated. The following section will discuss the effect of limb position on CSE.

1.3. Upper Limb Posture and CSE

Depending on the position of the upper arm and forearm, MEP amplitude in the hand, forearm and upper arm muscles changes in size (Dominici et al. 2005; Forman et al. 2016a; Ginanneschi et al. 2005; Ginanneschi et al. 2006; Mazzocchio et al. 2008a; b; Mitsuhashi et al. 2007; Mogk et al. 2014; Nuzzo et al. 2016; Perez and Rothwell 2015). A common finding is that CSE is altered in arm muscles after a change in shoulder position. However, there are multiple differences between the studies, such as the state at which CSE is measured and the arm positional variations that are chosen. The following section will be broken down into the specific muscle group that each investigator used within their respective study. The distal muscles of the arm, (i.e. the hand muscles including the abductor digiti minimi (ADM) and first dorsal interosseous (FDI)), will be discussed first. Working proximally up the arm, the forearm muscles (flexor carpi radials (FCR), extensor carpi radials (ECR)) will be reviewed and lastly, the upper arm muscles (biceps brachii, triceps brachii) will be discussed.

The Effect of Arm Posture on CSE of the Hand Muscles

Ginanneschi et al. (2005) were one of the first groups to investigate how arm position affects CSE, specifically in the hand muscles. They examined three shoulder positions; 30˚ adduction, neutral (0˚), and 30˚ abduction to the horizontal. The MEP amplitude input/output curve showed that the ADM relationship changed in relation to shoulder positon. 30˚ abduction produced a right shift in the curve compared to the 30˚ adduction. In other words, a greater stimulation intensity at 30˚ abduction produced a smaller MEP amplitude compared to adduction. A difference in motor threshold cannot be the reason for the MEP amplitude increase in abduction or decrease in adduction because changing shoulder position will have no effect on the motor threshold. The recruitment efficiency (gain) of the evoked potential and the excitatory component, which are indicative of how many motoneurones are recruited, was lower in abduction. Thus, revealing the possibility for differing recruitment strategies for the hand muscles in relation to shoulder position. Coincidently, Dominici et al. (2005) examined the cortico-motoneuronal output of the hand muscles. Their study demonstrated that voluntary drive to ADM either during a MVC or during brief paced finger abductions was reduced with the shoulder in the 30˚ abducted position. This supports the findings for a recruitment deficiency at the 30˚ abducted position in the ADM. Interestingly, Dominici et al. (2005) discovered that the deficit is not applicable to the FDI. They determined that the input-output curve for ADM and the maximal force exertion were unaffected by change in shoulder position. The differences in corticospinal innervation to the FDI and ADM muscles may be due to their different roles in hand movement (Weiss and Flanders 2004; Ziemann et al. 2004). Also, this finding rules out that the diminished MEPs in the ADM at 30˚ abduction are dependent on a vasomotor bias. Since the arm is outside the range of visually guided actions the visuomotor does not affect the excitability of the ADM (Handy et al. 2003).

Perez and Rothwell (2015) studied how different hand positions affect the intrinsic hand muscles CSE. Unlike the first two studies, this group utilized TMS along with TMES and F-waves to look at spinal motoneurone excitability. Nineteen subjects participated in the study, which consisted of grasping a 6mm cylinder with the index finger and thumb while the wrist was held in three differing positions (neutral, pronated and supinated). Their results showed that there was no difference in CMEPs or F-waves across all conditions. However, the MEPs were smaller in FDI but not in the abductor pollicis brevis and ADM during grasping with the hand in pronation or supination compared to the neutral position.

In conclusion, the research shows that the CSE of the hand muscles can be modulated by changing shoulder and wrist position. Since the CSE was modulated by a change in shoulder position in can be inferred that the change in CSE does not need the muscle to cross the joint that is moved.

Possible Mechanisms

It has been previously shown that changes in hip position can modulate motor output of the distal limb muscles such as the soleus in humans. These changes in motor output have been ascribed to neural mechanisms, which originate from a spinal origin (Chapman et al. 1991; Knikou and Rymer 2002a; Knikou and Rymer 2002b). In the Ginanneschi et al. (2005) study, the size of the spinal motoneurone responses, the F-wave and H-reflex, were both significantly lower with the shoulder in the 30˚ abducted position. The reduction in slope of the input-output curve for ADMs H-reflex was highly comparable to the reduction that was shown in the MEP. However, the changes in shoulder position cannot operate exclusively at the spinal level as the supraspinal level is also involved. By using the two paired-pulse TMS techniques, ICF and ICI,

they showed a significant increase in ICF moving from the 30˚ abduction to adduction. The ICF is a long-latency with 15-ms interstimulus intervals of pulses and has been shown to be mainly caused by the activation of cortico-cortical glutamatergic excitatory pathways (Liepert et al. 1997). On the other hand, the ICI, which is a short-latency 5-ms interstimulus interval, showed no differences with shoulder positional change. The ICI is attributed to the activation of intracortical GABAergic inhibitory neurones, which can be ruled out in this case (Ziemann et al. 1996). In the Perez and Rothwell (2015) study, CMEPs and F-waves experienced no significant change in size across all hand tasks. Therefore, it is plausible that the decrease in MEP amplitude size that was found is not related to changes occurring at the spinal motoneurones but at the cortical level. However, it is possible that activity in spinal cord circuits could contribute to the direction of grasping in the hand muscles. It has been previously shown that some spinal interneurones show a preferred direction while generating force (Shalit et al. 2012). In conclusion, it is plausible that variations in tonic excitatory activity in the cortex is responsible for the changes of excitability in the ADM's corticomotor connections as a function of shoulder position. However, it is likely that spinal excitability also plays a role.

In conclusion, the change in CSE of the hand muscles due to shoulder and wrist positional change is predominantly due to the cortical level. Ginanneschi et al. (2005) showed a significant difference in ICF and Perez and Rothwell (2015) showed no significant changes in CMEP amplitudes leading to this conclusion. However, Ginanneschi et al. (2005) also showed that there were significant changes in H-reflex and F-wave, meaning that the spinal level also, in part, contribute to the change in CSE.

The Effect of Arm Posture on CSE of the Forearm Muscles

Changing handgrip position altered forearm muscle activity and depending on the position of the arm it can modulate shoulder muscle activity (Sporrong et al. 1996; 1995). It has been found that based on arm position an individual's preferred grip force will differ (Smets et al. 2009). Ginanneschi et al. (2006) examined the differences of excitability in the forearm muscles during different static shoulder positions. They recorded EMG from two forearm muscles; the flexor carpi radials (FCR) and the extensor carpi radials (ECR). Their results showed MEP input-output curve of the two muscles significantly changed as a function of shoulder posture. Specifically, when the shoulder went from the 30˚ abducted to the 30˚ adducted position the FCRs' MEP input-output curve decreased. Whereas, for the ECR MEP input-output curve increased. Therefore, the same intensity of TMS evoked a larger MEP at 30˚ abduction position in the FCR compared to the ECR muscle.

Currently, all the literature that has been reviewed showed how shoulder position alters excitability of the hand and forearm muscles at rest. Forman et al. (2016a) are the only group to measure CSE while altering arm position in an active state. They looked at six different shoulder positions by adjusting the humeral elevation angle from 45˚ to 90˚, and to 120˚ while the shoulder was either flexed or abducted. They measured from the FCR, ECR, flexor carpi ulnaris (FCU), and extensor carpi ulnaris (ECU) at rest, 5% maximal voluntary excitations (MVE) (derived from normalized EMG as a percentage of the maximum), and 30% MVE from the ECR. During 5% MVE the MEP amplitude for FCR decreased by approximately 15% when going from abduction to flexion. During the 30% MVE only ECR MEP amplitude was modulated by elevation angle, which decreased by ~19% when the angle increased from 45˚ to 120˚. However, no significant changes occurred in the other muscles. Like Ginanneschi et al. (2006) group, Forman et al. (2016a) found corticospinal excitability of all four forearm muscles were

modulated by shoulder position. They also found that the MEP input/output curve for the ECR showed an effect for shoulder plane, with a larger slope in abduction compared to flexion. Thus, TMS during abduction yielded a larger MEP amplitude compared to flexion. The other muscles had no significant changes for slope of the MEP amplitude input/output, however the plateau levels showed a dependency on shoulder position. The input-output relationship for a stimulus response curve is not only influenced by a single motoneurone but the summation of synchronous motor unit potentials. Their work suggests that at rest the recruitment efficiency of the ECR and the descending drive to FCR, ECR, ECU and FCU muscles are affected by shoulder position. Therefore, corticospinal excitability of the forearm muscles can be modulated by shoulder posture at rest and during an active state.

Like the hand, CSE of the forearm muscles is modulated with positional change at the joint it crosses (i.e. the elbow joint) and in a joint that it does not cross (i.e. shoulder joint). However, Forman et al. (2016a) the effect of position change on CSE is not state-dependent because a change in CSE was also shown in the forearm muscles during an active state.

Possible Mechanisms

Utilizing the paired-pulse paradigm, the changes in forearm muscle excitability from altering shoulder position originate, at least in part, from a cortical level. A significantly lower ICF in the FCR was found in Ginanneschi et al. (2006) study with the shoulder in adduction compared to abduction, while no significant change in ICI was found in the FCR. Intra-cortical dis-facilitation may be a depression of the corticomotor projections in the FCR. Alternatively, an increased intracortical facilitation may provide a higher recruitment efficiency, like what was seen in the ECR during the adducted position.

The shoulder joint may be providing somatosensory input to the brain by signaling different spatial configurations of the arm. These inputs could then be influencing the excitability of neurones in the primary cortex, which are responsible for CSE of the forearm muscles. Based upon the findings in a primate's brain, area five neurones of the superior parietal lobe encode both movement of the arm in space and static arm position (Graziano 2001). In addition, it has been found that some area five neurones integrate signals from the elbow and shoulder joints, enabling the brain to know specifically where the position of the arm is with respect to the trunk (Lacquaniti et al. 1995). However, findings in trained monkeys have shown that neurones of the motor cortex are directionally responsive, meaning the neurones are highly reactive in a single directional movement of the upper arm, while not as reactive in any other direction (Georgopoulos et al. 1986). It has been demonstrated that the directionally preference neurones could be modified if the arm was placed in an unusual posture, like when the elbow is elevated (Scott and Kalaska 1997). Ginanneschi et al. (2006) study the participants were required to passively maintain an elevated elbow while the arm was either abducted or adducted. Thus, the changes in CSE may not be from the area five neurones, but from a variation in directional preference of the neurones in the motor cortex itself. It is important to note that in the Forman et al. (2016a) study the arm postures chosen were selected with a workplace setting in mind, and this may have led to the directional preference remaining stable unlike Ginanneschi et al. (2006) study. It is hard to compare the two studies, while CSE of forearm muscles are influenced by shoulder position, the degree of modulation may not be as substantial when shoulder positions are not extreme.

The Effect of Arm Posture on CSE of the Upper Arm Muscles

Unlike the hand and forearm muscles the biceps and triceps brachii cross the shoulder joint complex, thus adding the issue of changing muscle length with a change in shoulder position. Previous research has shown that when a muscle crossing the joint of interest is placed at shorter muscle length, the MEP amplitude tends to increase (Lackner and Hummelsheim 2003; Lewis et al. 2001; Mitsuhashi et al. 2007; Renner et al. 2006). It has been proposed that the target muscle's length influences the excitability of the motor pathway, such as altering the excitability of the muscle in the motor cortex. However, prior to Mogk et al. (2014) this theory has not been tested thoroughly, instead it has only be inferred from experiments of a limited scope (Lackner and Hummelsheim 2003; Lewis et al. 2001; Mitsuhashi et al. 2007; Renner et al. 2006). Specifically, these experiments only looked at a single joint, thus based on joint position they could both alter and measure muscle length consistently. Whereas, the upper arm muscles cross multiple joints, making a consistent muscle length change difficult to measure. Length mediated differences in MEP amplitudes may parallel length-dependent changes in EMG signal amplitude (Frigon et al. 2007; Hashimoto et al. 1994; Lateva et al. 1996). Thus, the relationship between posture-dependent changes in muscle length and differences in MEP amplitudes may be due to electrophysiological changes at the muscle, not the central nervous system. Mogk et al. (2014) examined the effects of corticomotor excitability of the posterior deltoid (PD) and the biceps brachii after changing shoulder and elbow position. The shoulder changes were comprised of thirteen positions; four functional, three different forearm orientations and one reference position. CSE for both muscles were measured in each static multi-joint position and orientation of the upper limb. The biceps brachii MEP amplitude was modulated with changes in shoulder and elbow position. On the other hand, the PD MEP amplitudes were mainly modulated with a change in shoulder position. It is possible that a fixed relationship between the MEP amplitude

and the position of a single joint does not exist in the biceps brachii. This finding shows the potential to shape proximal muscle responses (i.e. PD muscle) by changing distal joint positions (i.e. the elbow joint).

Mogk et al. (2014) compared the TMS-evoked responses to a biomechanical model. It was determined the muscle length alone could not account for the differences that occurred based on the posture-related changes in MEP amplitude. In addition, they determined that the change in CSE was consistent with central modulation of excitability, not at the peripheral level. The PD muscle experienced no change in muscle length when forearm position was altered, yet a significant change in MEP amplitude was found with the forearm in the pressure relief position. Thus, the modulation in MEP amplitude was likely central modulated as no change at the peripheral level (i.e. same muscle length) was observed. On the other hand, biceps brachii did exhibit changes in muscle length when the forearm orientation was altered. It is important to note that changing posture not only affects membrane properties of the muscle, i.e. fiber length and diameter, but can also modulate the spatial orientation of the muscle relative to the electrodes because the skin moves while changing positions. Ultimately, the changes in CSE that occured can be caused by a change in the measured EMG due to skin movement with differing shoulder positions that alter the electrode placement, which is completely unrelated to changes in muscle activation (Mesin et al. 2006; Rainoldi et al. 2000). In the Mogk et al. (2014) experiment, they addressed these peripheral factors by creating a control group. By eliciting both TMS and peripheral nerve stimulation at the same postures they created a ratio of MEP/M_{max}. Using this ratio, they can determine whether the differences in CSE are peripheral in origin. For example, if the changes in posture were caused by an electrode-muscle relationship (orientation of the electrode on the muscle) the MEP/M_{max} ratios would not differ between the control group and the

experiment group. As similar changes in the electrode-muscle relationship would occur in both protocols between forearm orientations. Instead, the MEP/M_{max} ratio significantly changed, meaning that MEP amplitudes increased beyond what would be expected from the peripheral level. Interestingly, the group found that a decrease in muscle length did not always lead to an increase in MEP amplitude. When the shoulder was overhead, the biceps brachii MEP amplitude was smaller compared to the horizontal reach position. This occurred even though the biceps brachii was at a shorter length in the overhead position, further concluding a central modulation of CSE. If muscle membrane properties are the only mechanism responsible for MEP amplitude changes, then a more consistent increase would be expected from all positions when muscle length decreases (Fortune and Lowery 2012). One possible issue with this study is that they passively supported the arm in almost every position. Therefore, there is a possibility that differences in pressure and location of skin contact caused by the support of the investigators may have influenced the responses evoked in each position.

As previously discussed only one study prior to 2016 has looked at the effect of position on spinal excitability (Perez and Rothwell 2015). Their findings showed that during a static finger grasp, MEPS but not CMEPS increased in the first dorsal interosseous when the forearm was supinated compared to pronated. In human biceps and triceps brachii only one recent study by Nuzzo et al. (2016) has determined whether arm position-dependent changes in MEPs are spinal in origin. They measured MEPs and CMEPs in resting biceps and triceps brachii for all the different shoulder and forearm positions. Unlike Perez and Rothwell (2015) their results showed that CMEPs are influenced by shoulder position in the resting biceps brachii. Specifically, the CMEPs were smallest when the arm was hanging to the side or when the forearm was pronated. On the other hand, CMEPs were largest when the shoulder was flexed or

when the forearm was supinated. The triceps brachii experienced the smallest CMEPs when the arm was hanging by the side and was unaffected by forearm orientation. Like the previous study M_{max} was recorded for biceps brachii to account for any peripheral influences on CSE of the muscle. The M_{max} was smallest when the arm was to the side or when the forearm was supinated. Spatial configuration of muscle fibers under the recording electrodes could be a possible reason why these changes occurred, or differences in muscle length (Frigon et al. 2007). Therefore, Nuzzo et al. (2016) normalized the MEPs and CMEPs to M_{max} at a given posture to account for the changes at the peripheral level in the compound muscle fiber action potential. A MEP/M_{max} and CMEP/M_{max} ratio was then calculated with significant changes occurring with alterations in shoulder positon. Therefore, the changes in CSE were deemed to be caused by a central mechanism. A potential methodological issue with their experiment was the fact that the elbow angle was not standardized between the three upper arm orientations. The excitability between the three upper arm orientations therefore reflect postural deviations at both the shoulder and the elbow. In other words, the bicep and triceps brachii cross both the elbow and shoulder joint. By not keeping the elbow angle standardized the length of the two muscles are not consistent because they depend on the position of both joints.

In conclusion, the CSE in the biceps brachii is affected by shoulder and elbow position. The change in muscle length of the bi-articular (crosses both the shoulder and elbow) biceps brachii influences CSE, however it does not account for all the changes.

Possible Mechanisms

The leading hypothesis for the effects of muscle length affecting CSE is that corticomotor excitability increases to compensate the reduced afferent feedback from shorter muscle lengths

(Lewis et al. 2001). The reduction in afferent feedback is thought to be caused by muscle spindles and tendon organ activity. Research has shown that corticomotor excitability will increase with muscle inactivity due to withdrawal of afferent input to the motor cortex (Todd et al. 2006). In subjects who have experienced cortical stoke there is no evidence of cortical involvement when muscle length differs from posture-dependent modulation, whereas there is cortical involvement in both control subjects and those who have suffered a subcortical stroke (Renner et al. 2006). Another possibility is that cutaneous and joint receptors respond predominantly near joint limits of motion. Therefore, in the aforementioned studies, changes in the activity of cutaneous and joint receptors with variations in forearm position may have also impacted CSE of biceps brachii. Another possibility is fluctuations of activity at the level of the motoneurone. Research has shown that small changes in joint angle alters dendritic integration of synaptic input through the effects of Ia reciprocal inhibition (Hyngstrom et al. 2007). As previously discussed, the posture based increases in corticomotor excitability may involve intracortical disinhibition due to the presence of ICF and not ICI (Liepert et al. 1997; Ziemann et al. 1996).

The findings that shoulder position-dependent changes of CSE are from a spinal origin coincide with findings of anesthetized monkeys (Yaguchi et al. 2015). By utilizing cervical spinal cord stimulation, evoked responses in arm muscles were modulated as shoulder and elbow angle were altered even after a spinal transection was above the stimulation site. Even though the Nuzzo et al. (2016) determined that the changes in CSE were potentially spinal in nature, they were unable to determine the specific mechanisms underlying the arm-posture dependent modulation. However, it is possible spinal reflex pathways from the heteronymous muscles are likely responsible for the alteration in biceps brachii activity with forearm positional changes.

Both the brachioradialis (Barry et al. 2008) and the pronator teres (Naito et al. 1998) have been shown to exert an inhibitory effect on the biceps brachii motor units during a voluntary contraction. It has been shown that during forearm pronation (Barry et al. 2008) the brachioradialis exerts the highest inhibitory effect, which is consistent with decreased CMEPs with pronation. It is thought that group I afferents from brachioradialis synapse on inhibitory interneuronal inputs to the biceps brachii motoneurone pool, inhibiting biceps brachii muscle activity. One issue is that previous research (Barry et al. 2008; Naito et al. 1998) has taken measurements in an active state, unlike Nuzzo et al. (2016) who measured CSE at rest. However, the effect these mechanisms have on a resting muscle is still unknown, thus additional research is needed to fully understand the extent these mechanisms have at rest.

The CSE modulation observed from changing shoulder position can be accounted for by multiple potential mechanisms. However, there are certain spinal mechanisms that can be dismissed that influence the biceps brachii. Facilitation from homonymous group Ia muscle afferents are not a possibility as they are the most active at longer muscle lengths (Burke et al. 1978) and the MEPS and CMEPs were reduced at the long lengths and increased at the shortest lengths. Due to the short muscle lengths, reciprocal inhibition can also be excluded as it too is most active at longer muscle lengths. Finally, it has been shown that MEPs at various arm muscle lengths (Lewis et al. 2001; Renner et al. 2006) and H-reflexes of the soleus (Gerilovsky et al. 1989; Hwang 2002) are largest at shorter muscle lengths. Since MEPs and CMEPs access motoneurones through descending paths the changes in H-reflexes with muscle length change cannot account for CSE modulation. This is because H-reflex is caused by homosynaptic post-activation depression of the Ia afferents, thus un-affecting the MEP and CMEP pathway to the motoneurone (Hultborn et al. 1996).

In conclusion, changes in CSE of the biceps brachii with changes in forearm position may originate from a spinal level. Possible influences from heteronymous muscles to the biceps brachii could be the causation. However, the cortical level still likely plays a role in the changes in CSE in cohesion with the spinal level. More research needs to be completed on how an active biceps brachii is affected by positional change as there are many neuromuscular differences between an active and resting muscle (Aboodarda et al. 2015).

Conclusion

This literature review has discussed techniques utilized to measure CSE and how it is affected by arm position. The literature shows that CSE of arm muscles are in fact influenced by arm position, both at the elbow and shoulder. In the hand, forearm and upper-arm muscles, the size of the MEP amplitudes change depending on the position of the arm (Dominici et al. 2005; Forman et al. 2016a; Ginanneschi et al. 2005; Ginanneschi et al. 2006; Mazzocchio et al. 2008a; b; Mitsuhashi et al. 2007; Mogk et al. 2014; Nuzzo et al. 2016; Perez and Rothwell 2015). In the hand muscles during a static finger grasp MEP amplitudes, not CMEP amplitudes, in the FDI increased when the forearm was neutral compared to a pronated or supinated position. The changes in the CSE were within the cortex (Perez and Rothwell 2015). Changes in forearm and upper-arm positions influence bicep brachii CMEP amplitudes, indicating that changes in corticospinal excitability are largely spinal in origin (Nuzzo et al. 2016).

The literature demonstrates that modulation of CSE occurs with positional change at rest, however there is still inadequate information about how CSE is altered during an active state. Another issue that needs to be resolved is that in the literature there are different shoulder and elbow positions being used in research studies that look at changes in CSE of the biceps brachii,

but are then compared to each other. However, it is still unknown that if CSE of the biceps brachii is found in one position if it equals a different position, or if a change in position alters the CSE itself. Also, if the stimulation intensities parameters are determined in one set position, are they equal to another position or do the stimulation parameters must be reset. It has been shown that altering position will alter CSE of the upper body muscles, therefore it is necessary to understand how state- and position effects CSE in the biceps brachii.

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2. Chapter 2: Co-authorship Statement

My contributions to this thesis are outlined below:

1. I recruited all participants and analyzed all data collected for this thesis, with the help of my fellow masters' student Mr. Teddy Cadigan
2. With the assistance of Mr. Teddy Cadigan (masters' student) and Mr. Lucas Stefanelli (masters' student), I collected the experimental data for this thesis.
3. I prepared the manuscript and thesis with the help and guidance of my supervisor, Dr. Duane Button.
4. Dr. Duane Button provided constructive feedback on the manuscript and thesis

Chapter 3: Corticospinal excitability of the biceps brachii is altered by changing shoulder position.

Brandon W. Collins[1], Edward W.J. Cadigan[1], Lucas Stefanelli[1] and Duane C. Button[1,2*]

[1]School of Human Kinetics and Recreation and [2]Faculty of Medicine, Memorial University of Newfoundland, St. John's, NL, A1C 5S7

[*]Corresponding author:

Duane C. Button

School of Human Kinetics and Recreation

Memorial University of Newfoundland

230 Elizabeth Avenue

St. John's, Newfoundland, Canada, A1C 5S7

Phone: 709-864-4886

Fax: 709-864-3979

Email: dbutton@mun.ca

3.1: Abstract

The purpose of this study was to examine the effect of shoulder position on corticospinal excitability of the biceps brachii during rest and a 10% maximal voluntary contraction (MVC). Participants (n=10) completed two experimental sessions with four conditions 1) rest, 0° shoulder flexion, 2) 10% MVC, 0° shoulder flexion 3) rest, 90° shoulder flexion 4) 10% MVC, 90° shoulder flexion. Transcranial magnetic, transmastoid electrical and Erb's point stimulation were used to induce motor-evoked potentials (MEPs), cervicomedullary MEPs (CMEPs) and maximal muscle compound potentials (M_{max}), respectively in the biceps brachii in each condition. At rest, MEP, CMEP and M_{max} amplitudes increased (p<0.01) by 509.7±118.3%, 113.3±28.3% and 155.1±47.9% respectively, at 90° compared to 0°. At 10% MVC, MEP amplitudes did not differ (p=0.08), but CMEP and M_{max} amplitudes increased (p<0.05) by 32.3±10.5% and 127.9±26.1% respectively, at 90° compared to 0°. MEP/M_{max} increased (p<0.01) by 224.0±99.1% at rest and decreased (p<0.05) by 51.3±6.7% at 10% MVC in the 90° compared to 0°. CMEP/M_{max} was not different (p=0.22) at rest, but decreased (p<0.01) at 10% MVC by 33.6±6.1% at 90° compared to 0°. RMS EMG increased (p<0.001) by 8.3±2.0% at rest and decreased (p<0.001) by 21.4±4.4% at 10% MVC in the 90° compared to the 0°. In conclusion, corticospinal excitability of the biceps brachii is dependent on shoulder position and changes within the state it is measured. The position-dependent changes in M_{max} amplitude, RMS EMG and corticospinal excitability itself all contribute to the overall change in corticospinal excitability of the biceps brachii.

3.2: Key Words:

Transcranial magnetic stimulation, transmastoid electrical stimulation, motor evoked potential, cervicomedullary evoked potential, electromyography

3.3: Introduction

Corticospinal neurons that originate in the motor cortex directly and/or indirectly (via interneurons) excite spinal motoneurons of the spinal cord. The excitation of this pathway contributes to single and multi-jointed movements and are affected by positional change (Lemon 2008). One way to quantify the output of this pathway during a positional change is by measuring corticospinal excitability (CSE) via transcranial magnetic stimulation (TMS) and transmastoid electrical stimulation (TMES). TMS and TMES elicits a motor evoked potential (MEP) and a cervicomedullary MEP (CMEP), respectively in a given muscle of interest. The concomitant use of these stimulations indicates whether modulation of CSE is predominantly of supraspinal or spinal origin.

CSE of the hand, forearm and upper arm muscles are altered by a change in limb position or posture (Dominici et al. 2005; Forman et al. 2016a; Forman et al. 2016b; Ginanneschi et al. 2005; Ginanneschi et al. 2006; Mazzocchio et al. 2008a; b; Mitsuhashi et al. 2007; Mogk et al. 2014; Nuzzo et al. 2016; Perez and Rothwell 2015; Renner et al. 2017). For example, as the external rotation angle of the forearm increased, MEP amplitudes of the biceps and triceps brachii, and abductor digiti minimi increased (Mitsuhashi et al. 2007) and an abducted shoulder and/or supinated forearm produced the largest MEPs of the biceps brachii (Mogk et al. 2014). However, these studies could not account for whether the changes in CSE were predominantly of supraspinal and/or spinal origin. Perez and Rothwell (2015) showed that MEPs but not CMEPs

of the first dorsal interosseous increased when the hand was placed in a neutral compared to pronated or supinated position during a hand grasping task, indicating that the increased CSE was potentially of supraspinal origin. However, few studies have determined the effect of shoulder flexion on CSE of the biceps brachii. Nuzzo et al. (2016) showed that MEP and CMEP amplitudes of the biceps brachii in different shoulder (flexion and abduction) and elbow (flexion) positions and forearm orientations were smallest with the arm on the side (hanging neutral) and forearm pronated but largest when the shoulder was flexed and forearm supinated. Their findings indicated that the position-dependent changes in CSE were mainly of spinal origin. A limitation of these studies was that the stimulation intensities were set in one reference position only, thus not controlling for positional-dependent differences in stimulation intensity required to determine CSE.

Research on CSE of an active compared to a resting muscle at different joint positions is rudimentary. Recently, we showed that CSE following a submaximal contraction protocol was state-dependent based on changes in CSE of the biceps brachii at rest being predominantly of surpaspinal origin, whereas during a slight contraction it was of spinal origin (Collins et al. 2017). Although CSE of the biceps was higher during a rhythmic as opposed to a tonic contraction (Copithorne et al. 2015), when the hand was placed in a neutral compared to the pronated grip position, MEP and CMEP amplitudes of the biceps brachii were larger during arm cycling. During tonic contraction, only MEP amplitudes increased indicating increased supraspinal excitability (Forman et al. 2016b). Based on the aforementioned literature, position, muscle type, whether or not the muscle is at rest or in a slight contraction and task all affect CSE. However, to our knowledge no studies have determined whether CSE of the biceps brachii is both state- and shoulder position-dependent.

Two postures that are commonly used for research purposes when determining elbow flexor force output and changes in CSE of the biceps brachii during force outputs are 1) elbow joint flexed to 90° with shoulder at 0° and the forearm partially supinated while being parallel to the ground with the force at the wrist being vertical and 2) elbow and shoulder joints flexed to 90° with the forearm partially supinated and vertical with the force at the wrist being horizontal (Khan et al. 2011; Mizuguchi et al. 2013; Pearcey et al. 2014; Petersen et al. 2002). However, no studies to date have compared CSE of the biceps brachii at rest or during a slight contraction between these positions. The purpose of this study was to: 1) compare CSE of the biceps brachii between 0° and 90° of shoulder flexion with the elbow flexed at 90° and forearm partially supinated, 2) determine whether the potential changes in CSE are state-dependent (i.e. rest versus active) and 3) understand how 0° and 90° of shoulder flexion affect CSE of the biceps brachii in order to determine mechanisms underlying position-dependent changes in CSE and improve future methodologies that measure CSE in these shoulder positions. We hypothesized that 1) CSE would be modulated by changing shoulder position and 2) that the pattern of change in CSE would be different in a resting compared to an active muscle. Since CSE is state-dependent (i.e. different between rest and contraction) (Collins et al. 2017) there was not a direct comparison of CSE of the biceps brachii between rest and 10% MVC in the current study.

3.4: Materials and Methods

3.4.1: Participants

Nine university aged resistance-trained (resistance-trained ≥ 3 times a week for ≥ 1 year) males (181.4 ± 2.4 cm, 86.8 ± 3.1 kg, 24.2 ± 5.3 yrs.) were recruited for the experimental study.

We chose to recruit only resistance-trained males because corticospinal excitability is training dependent (Carroll et al. 2002; Falvo et al. 2010; Pearcey et al. 2014; Philpott et al. 2015). Participants completed a magnetic stimulation safety checklist to screen for potential contraindications with magnetic stimulation procedures prior to participation (Rossi et al. 2009). Participants were told about the procedures being used for the experiment and gave their informed written consent if they accepted. The study was approved by The Memorial University of Newfoundland Interdisciplinary Committee on Ethics in Human Research (#20131456-HK) and was in accordance with the Tri-Council guidelines in Canada with full disclosure of potential risks to participants.

3.4.2: Elbow Flexor Force

Participants were seated in a custom-built chair (Technical Services, Memorial University of Newfoundland) in an upright position, with hips, knees and elbows flexed at 90˚ and chest and head strapped in place to minimize movement. The shoulder was placed at two different positions 1) 0 ˚ and 2) 90 ˚ of flexion. At the 0 ˚ position, both arms were slightly abducted and rested on a padded support. The forearm was held horizontal, positioned midway between neutral and supination, and placed in a custom-made orthosis that was connected to a load cell (Omegadyne Inc., Sunbury, Ohio, USA) (see Figure 1A). At the 90˚position the elbows were rested on a specially designed metal platform. To limit movement, the forearm was held midway between neutral and supination and placed in a wrist restraint that was attached to a chain perpendicular to the forearm and connected to a load cell (Omegadyne Inc., Sunbury, Ohio, USA). The load cell detected force output, which was amplified (x1000) (CED 1902, Cambridge Electronic Design Ltd., Cambridge, UK) and displayed on a computer screen. Data

were sampled at 2000 Hz. Participants were instructed to maintain an upright position with their head in a neutral position during contractions. Verbal encouragement and visual feedback were given to all participants during contractions.

3.4.3: Electromyography

Electromyography (EMG) activity was recorded by using surface EMG recording electrodes (MediTrace Ag-AgCl pellet electrodes, disc shaped and 10 mm in diameter, Graphic Controls Ltd., Buffalo, N.Y., USA) from the dominant arms biceps brachii. Electrodes were placed 2 cm apart (center to center) over the midpoint of the muscle belly of the participant's biceps brachii. A ground electrode was placed over the lateral epicondyle of the dominant knee. Skin preparation for all recording electrodes included shaving to remove excess hair and cleaning with an isopropyl alcohol swab to remove dry epithelial cells. An inter-electrode impedance of <5 kΩ was obtained prior to recording to ensure an adequate signal-to-noise ratio. EMG signals were amplified (×1000) (CED 1902) and filtered using a 3-pole Butterworth filter with cut-off frequencies of 10–1000 Hz. All signals were analog-digitally converted at a sampling rate of 5 kHz using a CED 1401 (Cambridge Electronic Design Ltd., Cambridge, UK) interface.

3.4.4: Stimulation Conditions

Transcranial magnetic stimulation (TMS)

TMS-evoked MEPs were used to measure corticospinal excitability. A TMS (Magstim 200, maximal output 2.0 Tesla) circular coil (13 cm outside diameter) was placed directly over the vertex to induce MEPs in the relaxed and active (10% maximal voluntary contraction (MVC)) biceps brachii muscle (Forman et al. 2014). The vertex was defined by the intersection

of the halfway points between the nasion and inion and tragus to tragus. Electrical currents flowed in an anticlockwise direction through the circular coil. The coil was placed horizontally over the vertex so that the induced current flow in the cortex was anterior to posterior or vice versa to activate the right or left motor cortex (A side up for right side, B side up for left) and subsequently activate the dominant biceps brachii. Stimulation intensity was set to elicit a threshold MEP in either the 0° or the 90° position depending on the experimental session (i.e. the position was randomized for the first session and then in the second experimental session the participant would start at the opposite position), with the size needing to be ≥50μV at rest and discernible from the background EMG at 10% MVC in 50% of the trials (i.e. 4 out of 8 trials) in the biceps brachii. Stimulator output at rest (33-72 %MSO) and 10% MVC (30-53%) was then increased 20% above threshold for the remainder of the experiment (Forman et al. 2014).

Transmastoid electrical stimulation (TMES)

Stimulation was applied via surface electrodes placed over the mastoid processes and current was passed between them (200μs duration, model DS7AH, Digitimer Ltd, Welwyn Garden City, UK). Stimulation intensity was adjusted to prevent ventral root activation by closely monitoring CMEP responses for any decrease in onset latency (~2ms), which shows cervical ventral root activation (Taylor et al. 2006). Stimulation intensity was adjusted to elicit a response that matched the size of MEP amplitude (compared to the position used for TMS) in 50% of the trials (i.e. 4 out of 8 trials), in the biceps brachii during rest (75-167.5 mA) and during 10% MVC (75-200 mA).

Brachial plexus stimulation

Stimulation of the brachial plexus was used to measure maximal compound muscle action potential (M_{max}). Erb's point was electrically stimulated via a cathode on the skin in the supraclavicular fossa and an anode on the acromion process. Current pulses were delivered as a singlet (200 μs duration). The electrical current was gradually increased until M_{max} of the biceps brachii at rest (72-148 mA) and at 10% MVC (76-144 mA) was elicited (in the same starting position as TMS for each session). To ensure maximal stimulation throughout the experiment, a supramaximal stimulation current (120% of maximal current to achieve M_{max}) was then used throughout the rest of the experiment (Aboodarda et al. 2015).

3.4.5: Experimental Set-up

Participants completed a familiarization session (~30 minutes) and two randomized experimental sessions (each ~2 hours) conducted on different days. Each experimental session included four conditions: 1) elbow flexors at rest and shoulder at 0° of flexion, 2) elbow flexors at rest and shoulder at 90° of flexion, 3) 10% MVC of the elbow flexors and shoulder at 0° of flexion and 4) 10% MVC of the elbow flexors and shoulder at 90° of flexion. Each session took place on separate days.

Familiarization session

Participants were asked whether they were right (n=8) or left (n=1) handed in order to determine arm dominance. Then participants performed multiple 5 second MVCs of the dominant elbow flexors, with 2 minutes of rest between contractions until they produced

consistent results (i.e. reached peak force quickly and held it steadily). This was completed for both shoulder positions to ensure that the participant was comfortable completing the MVC in each position. Following completion of the MVCs, participants practiced holding the 10% MVC contraction for 10 seconds at each position. Participants then received the three different types of stimulations at various intensities to ensure that they were comfortable to endure the stimulation paradigm involved in each experimental session.

Experimental session 1

Nine participants performed a semi-randomized protocol where half of the participants started the protocol with the shoulder at the 0˚ position first while the other half started with the shoulder positioned at the 90˚. The participants were prepped for EMG and asked to perform an elbow flexor MVC at the assigned shoulder position. A 10-minute rest period was then issued to ensure no effect of the MVC on the CSE measurements and to reduce fatigue. Thereafter, the experimental procedures began and the stimulation intensities for the M_{max}, MEP, and CMEP of the biceps brachii during rest and 10% MVC were determined. Following a 30-minute break, which was used as a measure to reduce participant fatigue, the shoulder position was changed. The participants were then asked to perform a MVC in the new shoulder position and given a 10-minute rest period. The same stimulation intensities that were used in the previous shoulder position were utilized again to elicit M_{max}, MEP, and CMEP of the biceps brachii during rest and 10% MVC. Immediately following both positions elbow flexor MVCs were performed (see Figure 1B for experimental set-up).

Experimental Session 2

The participants completed experimental session 2 approximately 2 months after experimental session 1. Experimental session 2 was identical to session 1 except the starting shoulder position was opposite to the participant's experimental session 1 starting position (i.e. if the participants started with the shoulder at 0˚of flexion in session 1 they then started with the shoulder position at 90˚of flexion in session 2).

3.5: Data and Statistical Analysis

3.5.1: Data Analysis

To determine if central drive to the biceps brachii was similar within each experimental session, mean biceps brachii root mean square (RMS) EMG was measured for 100ms prior to each stimulus. We measured both areas and amplitudes for all MEP, CMEP and M_{max}. The peak-to-peak amplitudes were measured for MEP, CMEP and M_{max} responses for each shoulder position. Figure 2 shows raw data of one participant during rest and 10% MVC in the 0° (black line) which includes the last M_{max} (left panel), MEP (middle panel) or CMEP (right panel) and M_{max}, MEP or CMEP recorded in the 90° position (hashed line). There were no significant differences (see Results) between pre-stimulus RMS EMG or individual M_{max} (average of 3), MEP (average of 8) and CMEP (average of 8) amplitudes within each experimental condition (see Figure 1B). Therefore, all RMS EMG and individual M_{max}, MEP and CMEP amplitudes were averaged for each state and position combination. All MEPs and CMEPs were normalized to the recorded M_{max} within the same shoulder position and MEP and CMEP data are reported in the results section are expressed as a percentage of M_{max}. To isolate any changes occurring in supraspinal excitability, MEP amplitudes were expressed relative to CMEP amplitudes (MEP/CMEP) (Gandevia et al. 1999). Mean force of the elbow flexor MVC was also measured.

All force, EMG and corticospinal excitability data were measured offline using Signal 4.0 software (Cambridge Electronic Design Ltd., Cambridge, UK).

3.5.2: Statistical Analysis

Statistical analyses were computed using SPSS (SPSS 22.0 IBM Corporation, Armonk, New York, USA). Assumptions of normality (Shapiro-Wilk test) and sphericity (Mauchley test) were tested for all dependent variables. If the assumption of sphericity was violated, the corrected value for non-sphericity with Greenhouse-Geisser epsilon was reported. A two-way ANOVA (position; 0° and 90° X time; pre-and post) with repeated measures was performed on MVC force and EMG. A one-way ANOVA with repeated measures (n=9) was performed on within condition MEP, CMEP, Mmax amplitudes and pre-stimulus EMG for each experimental session and condition to ensure consistency of the data. A paired student t-test (n=18, combination of data from both experimental sessions for 0° and 90° of shoulder flexion at rest and 10% MVC) was performed on the average MEP, CMEP and M_{max} amplitudes to determine the effect of shoulder position on corticospinal excitability during rest and 10% MVC. Since CMEP amplitude was matched to MEP amplitude at 0° or 90° of shoulder flexion in each experimental session, all MEP/CMEP ratio data were not combined for both shoulder positions and therefore the paired t-test was performed within each experimental session (n=9). Corticospinal excitability data during rest and 10% MVC were not compared because of the differences between a resting and active muscle (Collins et al. 2017). The statistical significance was set at $p<0.05$. In the text data were expressed as percentage change and raw data in figures 3-6. All data were reported as means ± SE.

3.6: Results

CSE responses and pre-stimulus RMS EMG values were similar within each condition.

There was no significant main effect (n=9) of shoulder position (0°and 90° of shoulder flexion) for both rest and 10% MVC conditions on individual MEP (range: p=0.094 to p=0.963), CMEP (range: p=0.123 to p=0.956) and M_{max} (range: p=0.094 to p=0.963) amplitudes and pre-stim EMG (range: p=0.085 to p=0.867).

The effect of shoulder position on elbow flexor MVC force and EMG

There was a significant ($F_{(1,9)}$, f=45.7, p<0.001) main effect for position on MVC force (Figure 3) but not ($F_{(1,9)}$, f=4.4, p=0.07) EMG during MVC, respectively. Overall, MVC force was lower by 12.8±1.6% at the 90° position compared to the 0°.

The effect of shoulder position on CSE and EMG of the biceps brachii during rest

MEP (Figure 4A; $t_{(17)}$, t=9.4, p<0.001), CMEP (Figure 4B; $t_{(17)}$, t=3.0, p<0.01) and M_{max} (Figure 4C; $t_{(17)}$, t=5.0, p<0.001) amplitudes were significantly higher by 509.7±118.3%, 113.3±28.3%, and 155.1±47.9%, respectively in the 90° compared to the 0° position. MEP/M_{max} ratios (Figure 5A; $t_{(17)}$, t=3.2, p<0.01) were significantly higher by 224.0±99.1% in the 90° position compared to the 0° position. However, CMEP/M_{max} ratios (Figure 5B; $t_{(17)}$, t=1.4, p=0.22) was not significantly different between the 90° and 0° positions. When starting at the 0° position MEP/CMEP ratios (Figure 6; $t_{(8)}$, t=2.3, p<0.05) were significantly increased by 45.7±19.3% from the 90° and 0° position. However, when starting at the 90° position MEP/CMEP ratios (Figure 6; $t_{(8)}$, t=8.1, p<0.001) were significantly decreased by 69.5±7.8%

from the 90° to the 0° position. EMG (Figure 4D; $t_{(17)}$, t=4.8, p<0.001) was significantly higher by 8.3±2.0% in the 90° compared to the 0° position.

The effect of shoulder position on CSE and EMG of the biceps brachii during 10% elbow flexor MVC.

CMEP (Figure 4B; $t_{(17)}$, t=2.3, p<0.05) and M_{max} (Figure 4C; $t_{(17)}$, t=6.5, p<0.05) amplitudes were significantly higher by 32.3±10.5% and 127.9±26.1%, respectively in the 90° position compared to the 0° position. However, MEP (Figure 4A; $t_{(17)}$, t=1.5, p=0.08) amplitudes were not significantly different between the 90° and 0° positions. MEP/M_{max} (Figure 5A; $t_{(17)}$, t=3.2, p<0.01) and CMEP/M_{max} (Figure 5B; $t_{(17)}$, t=4.2, p<0.001) ratios were significantly lower by 51.3±6.7% and 33.6±2.6%, respectively in the 90° position compared to the 0° position. When starting at the 0° position MEP/CMEP ratios (Figure 6; $t_{(8)}$, t=4.0, p<0.01) were significantly decreased by 32.0±2.6% from the 0° to the 90° position. When starting at the 90° position MEP/CMEP ratios (Figure 6; $t_{(8)}$, t=3.1, p<0.01) were significantly increased by 66.4±9.1% from the 90° to the 0° position. EMG (Figure 4D; $t_{(17)}$, t=4.6, p<0.001) was significantly lower by 21.4±4.4% in the 90° compared to the 0° position. EMG ($t_{(17)}$, t=3.2, p<0.01) during 10% MVC was significantly higher by 30.0±9.0% at the 0° compared to the 90° position.

3.7: Discussion

Overall, our results show that CSE of the biceps brachii was shoulder position-dependent (0° compared to 90° of flexion) and that the pattern of change in CSE differs when MEPs and CMEPs were recorded during rest or during 10% MVC. More specifically, when the shoulder

position was moved from 0° to 90° MEPs (%M_{max}) increased and CMEPs (%M_{max}) did not change at rest indicating increased supraspinal excitability, whereas during a 10% MVC, both MEPs (%M_{max}) and CMEPs (%M_{max}) decreased indicating decreased spinal excitability. We also showed that biceps brachii M_{max} amplitude increased similarly during rest and 10% MVC when the shoulder position was moved from 0° to 90°. Thus, normalizing MEP and CMEP to M_{max} was an adequate method to account for changes in CSE due to the peripheral nervous system when comparing rest versus an active biceps brachii, but this method may not be the suitable for comparing CSE of the biceps brachii between different shoulder positions.

Shoulder position dependent changes in CSE of a resting biceps brachii

In the current study, when the shoulder was placed in the 90° position, the MEPs (%M_{max}) increased by 224% compared to the 0° position and this difference did not depend on the starting shoulder position (0° or 90°). Previous research has shown increases in MEPs of biceps brachii with a change in shoulder and forearm positions. Specifically, Mogk et al. (2014) found the largest MEPs occurred when the shoulder was abducted, or horizontal reach, compared to flexed, hanging by the side, forward reach, overhead reach and pressure relief. A supinated forearm position induced higher MEP responses in all four shoulder positions compared to a neutral or pronated orientation. Nuzzo et al. (2016) reiterated these results showing that MEPs were smaller with the shoulder hanging to the side compared to a flexed position with supinated and neutral forearm orientations producing bigger responses compared to pronation.

There was no difference in CMEPs (%M_{max}) of the biceps brachii during rest when the shoulder position was altered indicating no change in spinal excitability. This contradicts previous research (Nuzzo et al. 2016), that showed CMEPs were larger in the biceps brachii when the upper arm was flexed or when the forearm was pronated compared to when the arm

was by the side or during forearm pronation. The differing results may be due to methodological differences in arm posture. Presently, only shoulder position was manipulated during the experiment whereas, in previous studies (Mogk et al. 2014; Nuzzo et al. 2016) shoulder and forearm positions were manipulated. The biceps brachii is a bi-articular muscle (Langenderfer et al. 2004). When the elbow joint angle was kept consistent (as was done here) and the shoulder position was altered, the biceps brachii muscle length only changed at the shoulder. In the Nuzzo et al. (2016), the biceps brachii muscle length would change at both the shoulder and elbow joints. It is plausible that spinal excitability of a resting biceps brachii may depend on movement of two joints. Other studies have shown that change in forearm orientation or elbow joint angle can affect MEPs in resting biceps brachii (Mitsuhashi et al. 2007; Mogk et al. 2014) and MEPs and CMEPs in an active biceps brachii (Forman et al. 2016b). In our study the forearm and/or elbow orientation remained consistent which, may contribute to a lack of change in spinal excitability.

A ratio of MEP to CMEP provides a way to determine whether a change in CSE was predominantly of supraspinal or spinal origin (Gandevia et al. 1999; Nuzzo et al. 2016; Pearcey et al. 2016). Based on the MEP/CMEP ratios, when the shoulder was moved from 0° to 90° of flexion, the increase in CSE was predominantly due to changes in supraspinal excitability. These results are in agreement with previous research that showed MEPs were modulated in hand (abductor digiti minimi) (Ginanneschi et al. 2005) and forearm (flexor and extensor carpi radialis) (Forman et al. 2016a; Ginanneschi et al. 2006) muscles when the shoulder position was altered from abduction to adduction with no change in H-reflex amplitude in the flexor carpi radialis (Ginanneschi et al. 2006). Therefore, the changes in CSE were mainly of supraspinal origin. Enhanced intracortical facilitation (ICF) but not intracortical inhibition (ICI) was in part,

a contributing mechanism to the change in supraspinal excitability (Ginanneschi et al. 2005; Ginanneschi et al. 2006) which, may also have contributed to the current findings. Because ICF and ICI are not a part of the same mechanism (Ziemann et al. 1996), it was possible that the position-dependent changes we showed, in part, originate from intracortical disinhibition, but there is little research to support this. Furthermore, CSE has been shown to increase in the absence of afferent feedback during motor inactivity (Todd et al. 2006). Potentially supraspinal excitability may increase to compensate for a reduction in afferent feedback when the muscle is placed in shortened lengths (i.e. in our study when the shoulder was placed at 90, the biceps brachii was shortened) (Lewis et al. 2001), which may be due to changes in muscle spindle and/or Golgi tendon organ activity. To further illustrate the influence of the motor cortex on CSE when joint position was changed, CSE of the biceps brachii was altered in healthy and subcortical stroke groups but not in a cortical stroke group at different degrees of elbow flexion (Renner et al. 2006). Based on previous and current findings it appears that supraspinal excitability of the biceps brachii during rest is affected by a change in forearm and shoulder position.

Shoulder position dependent changes in CSE of an active biceps brachii

To our knowledge this was the first study to examine the effect of shoulder position change on CSE of the biceps brachii during an active contraction. Our study showed that both MEPs (%M_{max}) and CMEPs (%M_{max}) decreased by 51 and 34% respectively, at the 90° compared to the 0° position. Previous studies have also measured CSE of active hand (first dorsal interosseous) (Renner et al. 2017), forearm (flexor carpi radialis, extensor carpi radialis, flexor carpi ulnaris and extensor carpi ulnaris) (Forman et al. 2016a) and upper arm muscles

(biceps brachii) (Forman et al. 2016b) during different forearm positions and found changes in CSE. Forman et al. (2016a) showed that during rest, 5% and 30% of maximal voluntary excitations (i.e. expression of EMG as a percentage of MVC), MEPs of the forearm muscles were altered by a change in upper limb position.

The position-dependent change in the MEP/CMEP ratio during 10% MVC was mainly of spinal origin, which was opposite to rest. Di Lazzaro et al. (1998b) showed that compared to rest voluntary contraction enhances the size and number of descending volleys of the MEP which is likely due to an altered threshold for activation of spinal motoneurons. The decrease in spinal excitability may be due to larger inhibition from synergist muscles when the shoulder is placed at 90° compared to 0°. This coincides with previous research (Barry et al. 2008; Naito et al. 1996), which showed reduced motor unit discharge rate of the biceps brachii during elbow flexion due to inhibition from the synergist muscle brachioradialis (Barry et al. 2008) and pronator teres (Naito et al. 1998). In addition, when the forearm was in a neutral position there was greater heteronymous inhibition from the brachioradialis compared to a supinated position (Barry et al. 2008). In our study, when the participants contracted their elbow flexors the forearm was midway between supinated and neutral, therefore it was possible that the brachioradialis and pronator teres partly inhibited the motoneuron pool of the biceps brachii during 10% MVC, thus altering spinal excitability, however little information exists illustrating the effect of these muscles on CSE of the biceps brachii. Forman et al. (2016b) compared a neutral to a pronated handgrip during a tonic contraction and found that supraspinal, but not spinal excitability, was affected by the change in grip. The fact that no change in spinal excitability occurred at a tonic contraction was opposite to the results from the current study. There are two potential reasons for the differences: 1) the position of the elbow and shoulder joints were different from what was

used in our study and 2) the contraction intensity of the elbow flexors was matched to the average peak RMS EMG during mid-elbow flexion during cycling, thus their contraction intensity during their tonic contraction was different to that here. Based on the current findings and others it appears that spinal excitability of the biceps brachii during a contraction is affected by a change in elbow or forearm orientation and in part, shoulder position. Irrespective of shoulder-position, CSE of the biceps brachii is mainly spinally mediated at lower contraction intensities (i.e. 10% MVC) but at higher contraction intensities the cortical involvement increases (Ugawa et al. 1995). It would be interesting to determine if contraction intensity (low and high) would differentially alter CSE of the biceps brachii in different shoulder positions.

Shoulder position dependent changes in normalization procedures

The M_{max} represents the electrical equivalent of recruiting all of the motor units within the motoneuron pool (Maffiuletti et al. 2001). Since the peripheral stimulation that elicits the M_{max} does not travel through the spinal cord it will not be susceptible to changes in excitability that occur centrally (Perez and Rothwell 2015). In the current study M_{max} amplitude substantially increased in the biceps brachii at both rest and 10% MVC when changing the shoulder position from 0° to 90° of flexion. Postural changes in M_{max} amplitude have been shown previously (Frigon et al. 2007; Takahara 2011), which may have been caused by a shortening or lengthening of the muscle. Another factor that may have contributed to an increase in M_{max} was the potential movement of the surface electrodes used to stimulate Erb's point when the shoulder angle was changed. It was possible that the area of nerve being stimulated changed below the stimulating electrodes. The same problem applies with the surface EMG electrodes over the biceps brachii's muscle belly. When muscle length was shortened by flexing the shoulder to 90° different areas of the motor units or the temporal dispersion of the motor unit action potentials may be recorded,

thus potentially changing the size of M_{max} (Frigon et al. 2007; Takahara 2011). Usually, MEP and CMEP amplitudes are normalized to M_{max} to account for potential changes in excitability at the periphery (Barry et al. 2008; Collins et al. 2017; Forman et al. 2016a; Forman et al. 2016b; Gandevia et al. 1999; Nuzzo et al. 2016; Pearcey et al. 2016; Pearcey et al. 2014; Philpott et al. 2015; Taylor 2006; Taylor et al. 2000; Taylor et al. 2002). Comparing changes of CSE at 0° and 90° of shoulder flexion may be problematic because of the large increases in M_{max} amplitude. MEP amplitude increased substantially at rest by over 500% when the shoulder was flexed to 90°, while it experienced no change at 10% MVC. However, when we normalize MEP amplitude with M_{max} amplitude at both rest and 10% MVC, there was an increase and decrease in CSE, respectively. By using this normalization technique, it was possible that we were underestimating CSE at rest and 10% MVC. CMEP amplitude increased at rest and 10% MVC by 113% and 32%, respectively when the shoulder was flexed to 90° indicating a potential increase in spinal excitability. However, by normalizing CMEP amplitudes to M_{max} amplitudes, we show that spinal excitability decreased by 34% at 10% MVC and there was no difference at rest when the shoulder was flexed to 90°. Therefore, it is likely that shoulder position-dependent changes in CSE, both supraspinal and spinal excitability, may be underestimated due to the large increases in M_{max} amplitude.

CSE has also been normalized to pre-stimulus RMS EMG values (Fernandez-del-Olmo et al. 2013; Lemon et al. 1995). Even though biceps brachii EMG was larger during rest with the shoulder flexed at 90° compared to 0°, EMG levels were below 0.05 mV (which is the acceptable cut-off for EMG of resting muscle (Collins et al. 2017; Majid et al. 2015)) in both positions. During 10% MVC the biceps brachii EMG was larger with the shoulder flexed at 0° compared to 90°, which is opposite to rest. The position dependent differences in EMG at rest

and 10% may have in part led to the alterations in CSE. Thus, if we normalized MEP and CMEP amplitude to EMG, like M_{max}, the position-dependent changes in CSE of the biceps brachii EMG may be over- or under-estimated. The position-dependent differences in biceps brachii EMG may have occurred for two reasons: 1) biceps brachii length shortens when the shoulder is flexed, thus causing membrane properties like fiber length and diameter to alter and due to movement of the skin, the spatial orientation of the electrodes may also change leading to differing levels of muscle activation (Mesin et al. 2006; Mesin et al. 2009; Rainoldi et al. 2000) and/or 2) The force-length relationship of the biceps brachii is affected by the change in shoulder position. Moon et al. (2013) demonstrated that when the shoulder was placed at 75° of flexion the greatest amount of force and EMG activity was obtained. During 90° shoulder flexion, the lowest amount of EMG was shown compared to 30°, 45°, 60° and 75° shoulder flexion. They accounted the difference in EMG to the surface-torque relationship, which equates to a non-linear relationship. The biceps brachii is primary an elbow flexor, but it also is a supinator of the forearm, thus the biceps brachii is completing two actions resulting in a non-linear torque-EMG relationship (Dupont et al. 2000; van Zuylen et al. 1988).

Since M_{max} and EMG values were shoulder position-dependent, when CSE was normalized to them there may be an over or underestimation of CSE. Thus, both M_{max} and EMG may be less desirable methods for normalization (Frigon et al. 2007; Takahara 2011) when comparing CSE between 0° and 90° of shoulder flexion. Perhaps a better method would be to use MEP/CMEP ratios when comparing positions as these are a global assessment of the CSE in each position. In general, caution should be taken when examining positional-dependent changes in CSE as the measurements we use to normalize the data could also be affected by the differing positions.

Another factor that has been shown to influence CSE is the amount of force being produced. As force increases so does the CSE responses up to ~40-60% MVC and then it plateaus (Pearcey et al. 2014). This observation held true in our study as 10% MVC consistently produced larger MEP and CMEP responses compared to the rest within the 0° and 90° positions. Although CSE was compared at the same relative intensity of MVC (10% of MVC) at 0° and 90° positions, the absolute MVC force and EMG was higher during the 0° compared to the 90° position. Interestingly, when RMS EMG during 10% MVC was expressed as a percentage of MVC EMG, EMG of the biceps brachii was higher during the 0° compared to 90° of shoulder flexion. The shoulder-position differences in relative EMG at 10% MVC (and rest) is a limitation in the present study and should be addressed in the future. Thus, differences in CSE found here may have been due to participants contracting the elbow flexors at different absolute intensities of MVC and/or different relative percentages of EMG. However, CMEP responses were smaller at the 0° position during 10% MVC compared to the 90° position (i.e. a higher absolute force and EMG with lower CMEPs). Thus, it is possible that the pattern between force, EMG and CSE was different when the shoulder position was altered.

3.8: Conclusion

In conclusion, CSE of the biceps brachii during rest and 10% MVC was shoulder position-dependent. At rest, when the shoulder was flexed from 0° to 90° supraspinal factors play a predominant role for increasing CSE, whereas during the 10% MVC spinal factors likely underlie the decreased CSE. It seems that during rest supraspinal excitability was shoulder position-dependent, whereas spinal excitability was not. During 10% MVC supraspinal and spinal excitability were affected by shoulder position, but also may be due to inhibitory input to

the biceps brachii motoneuron pool via heteronoymous muscles. Finally, normalization techniques frequently used by researchers (i.e. using M_{max} amplitudes and EMG) may under- and over-estimate the excitability of the corticospinal tract when changing shoulder positions. Future research could include TMS and TMES stimulus response curves for CSE of the biceps brachii to determine if the change in CSE is due to a change in motor threshold when changing the shoulder position and how these changes in CSE are affected by fatigue. Furthermore, it would be interesting to determine if the position-dependent changes in CSE of the biceps brachii found here would be similar in elbow flexor synergists or in lower body bi-articular muscles such as the rectus femoris.

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3.10: References

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3.11: Figure Legends

Figure 1. Experimental set-up and experimental protocol. **A)** Participants sat with their arm in 0° or 90° of shoulder flexion at rest and for 10% MVC. TMS (A) was applied over the vertex activating the motor cortex of the contralateral hemisphere. TMES (B) was applied between the mastoid processes and nerve stimulation at Erb's point (C) with all three stimulations responses recorded from the biceps brachii (D). **B)** The protocol consisted of two MVCs, followed by TMS, TMES and nerve stimulation during rest and during 10% MVC and another MVC when the participant had their shoulder at 0° or 90° of shoulder flexion. The dotted line separating the two shoulder positions represents a 30-minute break. The participant then repeated the same protocol as above but with the shoulder position opposite to what they started with (i.e. if the

participant started at 0° of shoulder flexion, after the 30 min break they would start the protocol at 90° of shoulder flexion).

Figure 2. A) MEP and CMEP and **B)** M_{max} raw data of one participant during rest (top) and 10% MVC (bottom) at 0° (black line) and 90° (hashed line) of shoulder flexion. Notice the change in MEP amplitude from 0° to 90° is opposite at 10% MVC compared to rest and that M_{max} increases substantially from 0° to 90° during both rest and 10% MVC. Also, MEP and CMEP amplitude, but not M_{max}, increases substantially during a 10% MVC compared to rest.

Figure 3. Changes in MVC force between pre- and post- experimental protocol and between 0° and 90°. The asterisk (*) represents a significant difference (p<0.05) between 0° and 90°. Bars are group (n=18) mean ± SE.

Figure 4. Biceps brachii **A)** MEPs, **B)** CMEPs, **C)** M_{max} and **D)** RMS EMG responses for rest and 10% MVC at 0° compared to 90° shoulder flexion. The asterisk (*) represents a significant difference (p<0.05) between 0° and 90°. Bars are group (n=18) mean ± SE.

Figure 5. Biceps brachii **A)** MEPs (%M_{max}) and **B)** CMEPs (%M_{max}) for rest and 10% MVC at 0° compared to 90° shoulder flexion. The asterisk (*) represents a significant difference (p<0.05) between 0° and 90°. Bars are group (n=18) mean ± SE.

Figure 6. MEP/CMEP ratios for rest and 10% MVC at 0° compared to 90° shoulder flexion. The arrow in the abscissa indicates the direction of change in shoulder position. The asterisk (*) represents a significant difference (p<0.05) between 0° and 90°. Bars are group (n=9) mean ± SE.

3.12: Figures

Figure 1:

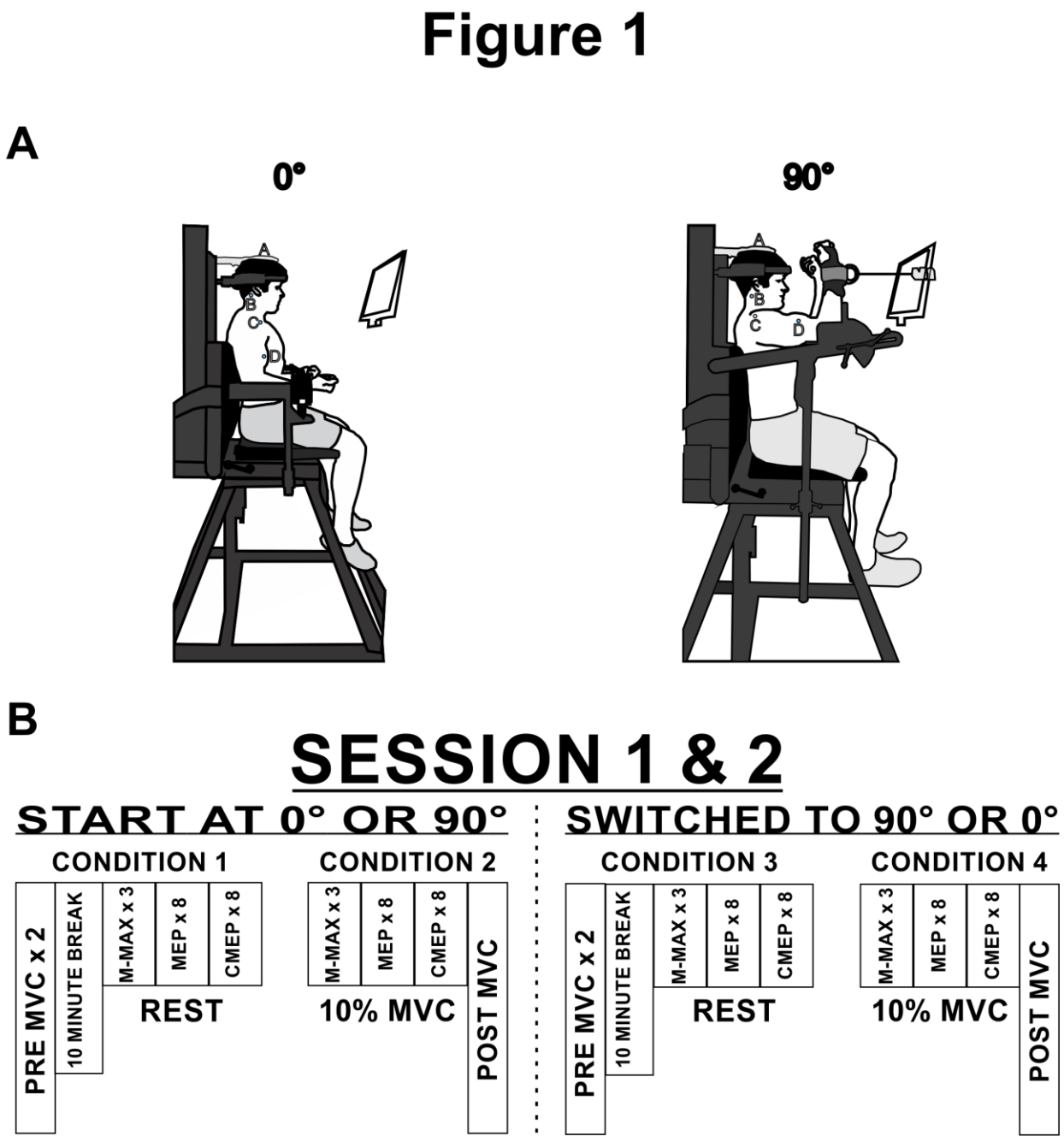

Figure 2:

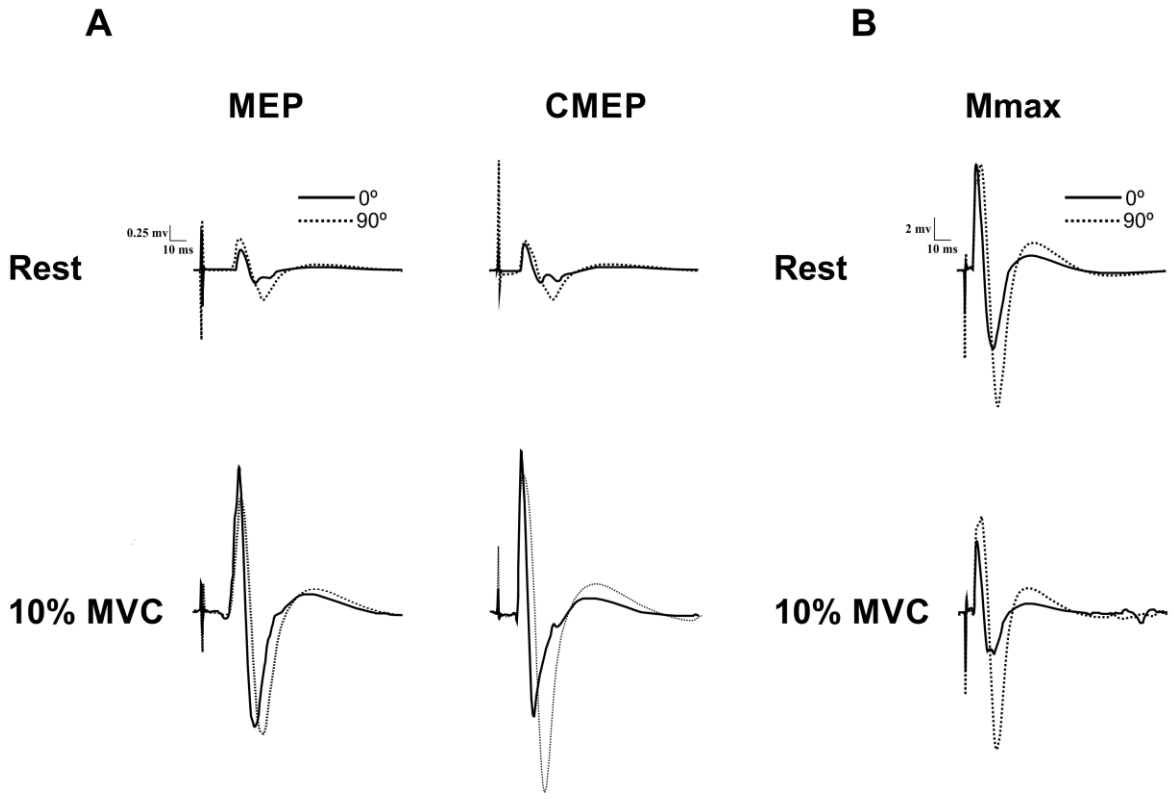
A
B
MEP
CMEP
Mmax
0°
90°
0.25 mv
10 ms
2 mv
10 ms
Rest
Rest
10% MVC
10% MVC

Figure 3:

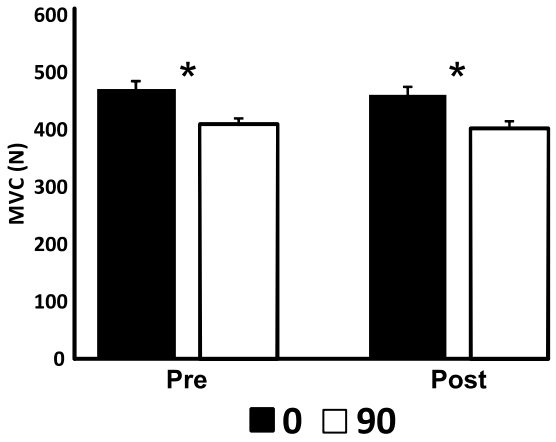

Figure 4:

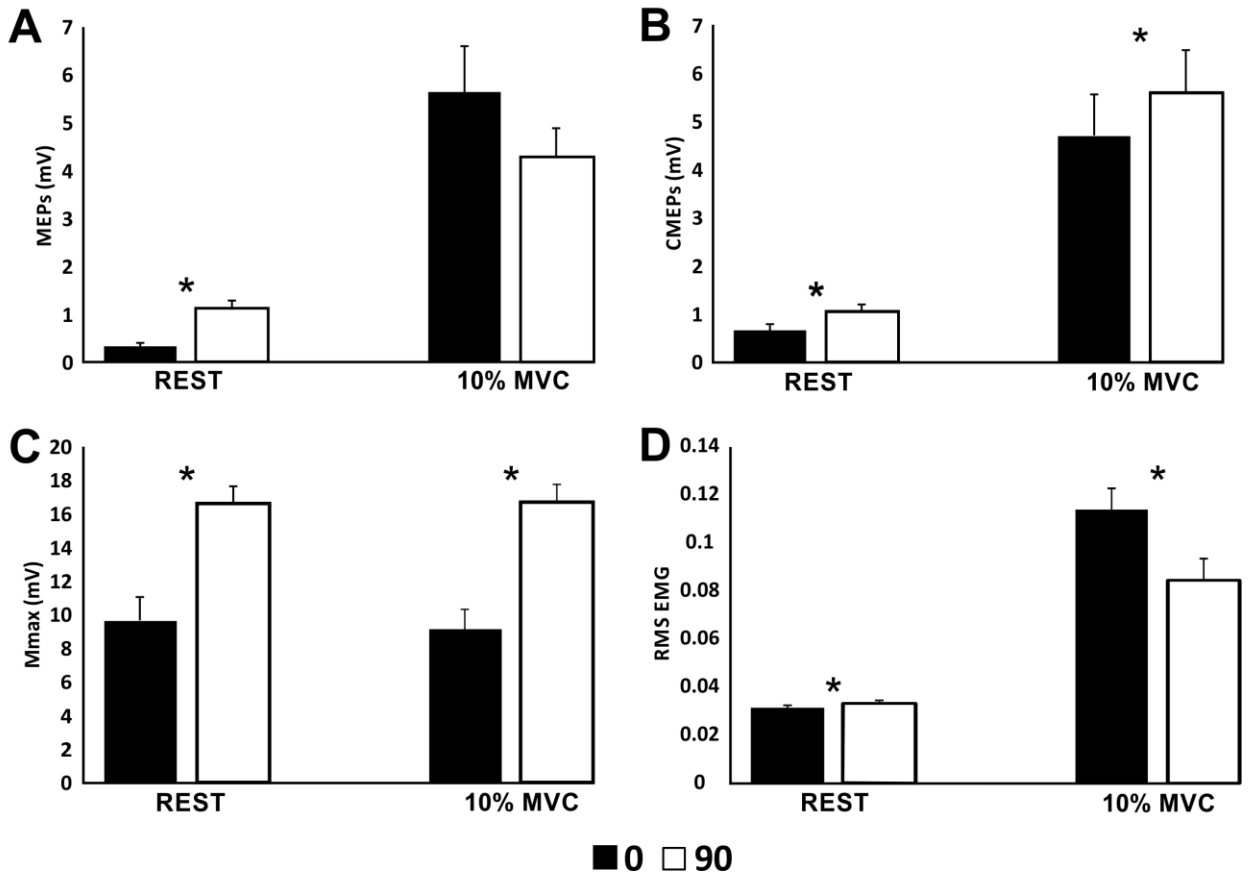
A
MEPs (mV)
0
1
2
3
4
5
6
7
*
REST
10% MVC
B
CMEPs (mV)
0
1
2
3
4
5
6
7
*
*
REST
10% MVC
C
Mmax (mV)
0
2
4
6
8
10
12
14
16
18
20
*
*
REST
10% MVC
D
RMS EMG
0
0.02
0.04
0.06
0.08
0.1
0.12
0.14
*
*
REST
10% MVC
0 90

Figure 5:

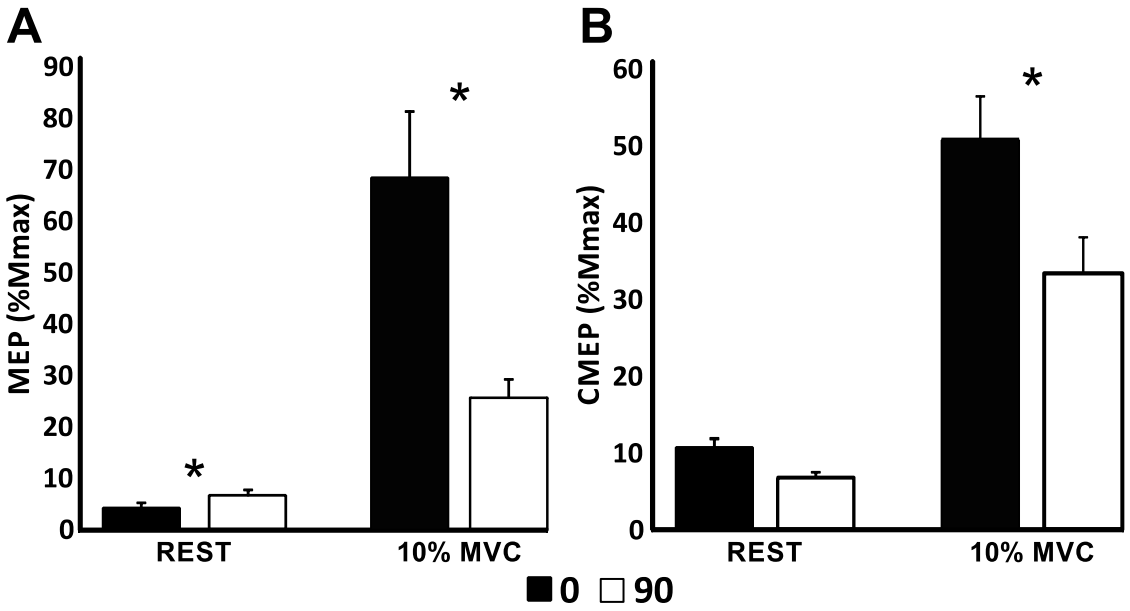
A
B
MEP (%Mmax)
CMEP (%Mmax)
90
80
70
60
50
40
30
20
10
0
60
50
40
30
20
10
0
*
*
*
REST
10% MVC
REST
10% MVC
0
90

Figure 6:

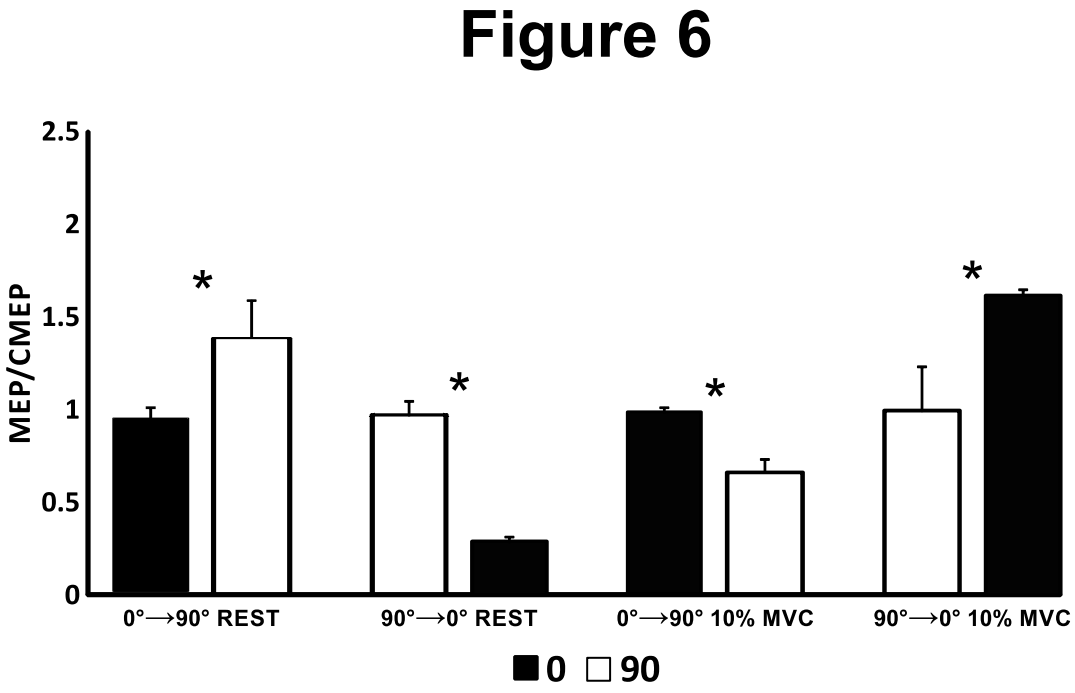
Figure 6
2.5
2
1.5
1
0.5
0
MEP/CMEP
*
*
*
*
0°⟶90° REST
90°⟶0° REST
0°⟶90° 10% MVC
90°⟶0° 10% MVC
0 90

Appendix A: TMS Safety Checklist

The safety of TMS continues to be supported by recent meta-analyses of published research (i.e. Machii et al., 2006; Loo et al., 2008; Janicak et al., 2008; Rossi et al., 2009). To ensure participant's safety, they were required to complete the following questionnaire prior to receiving 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:_____

_____

_____

_____

Name: _____

Signature: _____

Date: _____

Medications contraindicated with magnetic stimulation:

1) Tricyclic antidepressants

2) Neuroleptic or Antipsychotic drugs

A) Typical antipsychotics

• Phenothiazines: • Thioxanthenes:

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

B) Atypical antipsychotics

- Clozapine (Clozaril)
- Olanzapine (Zyprexa)
- Risperidone (Risperdal)

- Quetiapine (Seroquel)

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
[illegible]	[illegible]

- 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: Free and Informed Consent Form

Informed Consent Form

Title:	The effects of shoulder position on corticospinal excitability of the elbow flexors
Principal Investigator	Brandon Collins School of Human Kinetics and Recreation, MUN Bwc568@mun.ca

You are invited to take part in a research project entitled "The effects of shoulder position on corticospinal excitability of the elbow flexors."

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 researcher, Mr. Collins, 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 Brandon Collins, a master student 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 sole purpose of this study is to determine how shoulder position affects the central and peripheral nervous systems of the biceps brachii.

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 procedures and to familiarize with the stimulation protocols. We will also us this time to gather data that will be needed for the second testing session.

TESTING SESSION 2: This session will consist of assessing the effects of shoulder position on corticospinal excitability of the different muscles. When you arrive at the lab electrodes will be fixed to your biceps brachii, triceps brachii, brachioradialis, and anterior deltoid 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 the biceps brachii. The experimental procedures will begin by finding the location and stimulation intensities for the M_{max}, Cmep, and Mep of the biceps brachii during rest. The stimulation intensities will then be re-found while holding a 10% MVC. A 30-minute break will then be allotted to switch the apparatus to the next shoulder position and to prevent muscle fatigue. The stimulation intensities will be found at rest and at 10% MVC in the second position. Immediately following both positions another elbow flexor MVC will be performed to show that no muscle fatigue has occurred.

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 rest and a 10% MVC.

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 three testing sessions. The total time commitment will be approximately 3 hours (session 1: 1 hour, session 2: 2 hours). 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	Shoulder position on corticospinal excitability

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.

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 Drs Power and 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 supervisors Dr. Power or Button while computer based records will be stored on a password protected computer in the office of Dr. Power or 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: Brandon Collins (bwc568@mun.ca) or Ted Cadigan (ewjc63@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