THE ROLE OF CENTRAL DRIVE AND AFFERENT FEEDBACK ON CORTICOSPINAL EXCITABILITY DURING ARM CYCLING

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ABSTRACT

Corticospinal excitability to the biceps brachii muscle is modulated in a phase-dependent manner during arm cycling, being high during the elbow flexion phase and low during the elbow extension phase. As the intensity of cycling is increased by increasing the cadence, however, corticospinal excitability to the biceps brachii is enhanced during the elbow extension while spinal excitability is decreased. This led to the conclusion that the increase in corticospinal excitability during elbow extension was likely mediated via supraspinal mechanisms, though the potential mechanisms were not examined. This gave rise to the current study, the primary objective of which was determine whether the previous demonstration of a cadence-dependent increase in supraspinal excitability to the biceps brachii during the elbow extension phase of arm cycling was due to central drive and/or afferent feedback.

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Lists of Symbols, Nomenclature or Abbreviations

BL – bilateral arm cycling

bEMG – background electromyography

CMEP – cervicomedullary evoked potential

CPG – central patter generator

CSE – corticospinal excitability

EMG – electromyography

fMRI – functional magnetic resonance imaging

GABA – gamma-aminobutyric acid

IHI – interhemispheric inhibition

MEP – motor evoked potential

PET – positron emission tomography

RPM – revolution per minute

SICI – short latency intracortical inhibition

TMS – transcranial magnetic stimulation

TMES – transmastoid electrical stimulation

ULR – unilateral arm cycling with dominant arm rest

ULP - unilateral arm cycling with dominant arm passively cycling

1 INTRODUCTION

1.1 Overview

Arm cycling is regarded as a rhythmic and alternating motor output, partially mediated by spinally located central pattern generators (CPG; Grillner 1981; Zehr and Duysens 2004). Supraspinal and sensory inputs, however, also contribute towards the ultimate generation of action potentials by the spinal motoneurons producing CPG-mediated motor outputs, such as arm cycling, in humans (Forman et al. 2014; Peterson et al. 2001; Sidhu et al. 2012). Both supraspinal input and afferent feedback are important for the regulation and timing of rhythmic and alternating motor outputs, both of which can be altered as the cadence/velocity of the motor output changes (Forssberg et al. 1977; Pearson et al. 1998; Forman 2015).

Corticospinal excitability (CSE) refers to the overall excitability (cortical and spinal) of the corticospinal pathway and has previously been investigated during arm cycling, mainly by work arising from our lab. The results of different studies have shown that CSE to the biceps brachii muscle is phase-dependent, being highest during the elbow flexion phase or arm cycling and task-dependent in that CSE to the biceps brachii is higher during arm cycling when compared to a tonic contraction (Forman et al. 2014). Tonic contraction of the biceps brachii represents a similar activation level of the motoneuron pool but exhibiting reduced or null activation of the network of spinal interneurons (the CPG) presumed to contribute in rhythmic and alternating of arm cycling.

Certainly, increased CSE to the biceps brachii during the elbow flexion phase of arm cycling is expected as it is an elbow flexor. A similar increase during the elbow extension phase is less likely as the muscle is relatively inactive given that the triceps brachii is used to extend the elbow. Forman et al. (2015), however, showed that CSE to the biceps brachii *increased* during the extension phase of arm cycling as the cadence (intensity) of arm cycling increased. This increase in CSE to biceps brachii was assumed to be of supraspinal origin as spinal excitability decreased during the extension phase (Forman et al. 2015). The decrease in spinal excitability was likely mediated by changes in afferent feedback and/or reciprocal inhibition. What was less clear was why, or how, CSE to the biceps brachii increased during the extension phase of arm cycling without an increase in biceps brachii activity (i.e. no increase in EMG)? The purpose of this thesis/study was an attempt to determine whether differences in central drive and/or sensory feedback were responsible for this finding.

Three experimental tasks were formulated to examine the hypotheses of this study. The first experimental task involved bilateral arm cycling (BL) which provided a mode where both supraspinal drive and afferent feedback were present. The second task was unilateral, non-dominant arm cycling with the dominant arm moving passively (ULP). In this task supraspinal drive to the resting arm was absent (or substantially reduced) while afferent feedback was still present. The third and final task was unilateral, non-dominant arm cycling with the dominant arm at rest (ULR). During this task both supraspinal drive and afferent feedback were absent (or substantially reduced) from the resting arm. Each of the three tasks were done at two different cadences as a measure of intensity (60 and 90 rpm). By combining these tasks we sought to tease out whether central drive or afferent

feedback was responsible for the previously observed increase in CSE to the biceps brachii during the elbow extension phase of arm cycling as cadence increased.

1.2 Purpose of Study

The purpose of this study was to determine if the increase in CSE to the biceps brachii muscle during the elbow extension phase of arm cycling was due to the modulation of supraspinal drive and/or afferent feedback.

1.3 Research Hypotheses

Experiment 1:

(1) CSE to the biceps brachii (of the dominant arm) will be higher during bilateral arm cycling (BL) at a higher cadence than during non-dominant unilateral arm cycling.

(2) CSE to the biceps brachii will be higher during unilateral non-dominant arm cycling with the dominant arm passively moving (ULP) at a higher cadence than during unilateral non-dominant arm cycling when dominant arm will be at rest (ULR).

Experiment 2:

(1) Spinal excitability to the biceps brachii will be higher when the dominant arm is at rest while non-dominant arm is cycling compared to bilateral arm cycling at 60 and 90 RPM.

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2 REVIEW OF LITERATURE

2.1 Introduction

Co-ordinated and cyclical flexion and extension of the elbow and shoulder joints are commonly used in movement tasks of daily human life. The neural control of these types of movements, however, can be very different. Arm cycling, for example, has been shown that its production is mediated by an interaction of spinally located central pattern generators (CPGs), as well as cortical and subcortical centres, the majority of which can be modified via sensory feedback (Duysens and Van De Crommert 1998; Dietz 2003). Corticospinal excitability (CSE), comprised of cortical and spinal regions, during cycling of upper- and lower-limbs has been assessed in previous studies to determine the motor excitability during different phases of these complex motor outputs and also to determine at what level (i.e. supraspinal or spinal) overall changes in the excitability of the corticospinal tract occur.

Relatively little information is currently available regarding CSE during arm cycling, thus it is important to consider work done using isometric contractions. This is particularly important when considering the fact that arm cycling is bilateral and most studies using isometric contractions as a model are unilateral. With this in mind, an important observation to consider arises from knowledge regarding strong voluntary contractions where activity is not restricted to the target muscles during isometric contractions. Additional ipsilateral (heterologous and homologous) and contralateral muscles have been shown to also be active during contraction of an ipsilateral muscle (Curschmann 1906; Cernacek 1961; Todor and Lazarus 1986; Gandevia et al. 1993;

Armatas et al. 1994; Zijdewind and Kernell 2001; Shinohara 2003). These observations lead to interest in interactions between the two cerebral hemispheres as a possible means to explain the inadvertent activation of ipsilateral and/or contralateral muscles as opposed to just the muscle of interest. In humans for example, several lines of experiments show the existence of both facilitatory and inhibitory effects from one hemisphere to the other (Hess et al. 1986; Zwarts 1992; Meyer et al. 1995; Tinazzi and Zanette 1998; Stedman et al. 1998; Muellbacher et al. 2000; Lipert et al 2001; Carson et al. 2004). Studies have reported that if the force of a contraction is low and/or dynamic it will suppress the excitability of the ipsilateral (supposedly non-active) motor cortex (Leocani et al. 2000; Sohn et al. 2003), but if the force of contractions are high, there will be enhanced excitability of the ipsilateral motor cortex (Hess et al. 1986; Zwarts 1992; Meyer et al. 1995; Tinazzi and Zanette 1998; Stedman et al. 1998). Hortobagyi et al (2003) stated that increased excitability in the ipsilateral motor cortex is observed with strong voluntary contractions without any change in spinal excitability, suggesting that CSE facilitation occurred at the supraspinal level.

The objective of this Chapter is to review the literature which discusses CSE to the biceps brachii muscle during arm cycling, the tools used to assess it, interhemispheric connections between the motor cortices and their role in modulating CSE, as well as how sensory feedback and the cadence/speed of a motor output influence CSE.

2.2 The corticospinal tract

The corticospinal tract is one of the pyramidal tracts originating from several parts of the cortex but most of the neurons originating from the primary motor cortex and

terminating on motoneurons in the spinal cord (Kolb & Whishaw 2009). It is a white matter motor pathway which controls movements of the limbs and trunk. The pyramidal neurons originating from the primary motor cortex travel through the posterior limb of the internal capsule in the forebrain and eventually enter the base of the midbrain at the cerebral peduncle (Purves 2012). The tract then courses through the brain stem via the pons and the medulla. The corticospinal tract forms two pyramids along with the corticobulbar tract on the sides of the medulla. The corticospinal tract divides into two parts, lateral and anterior corticospinal tracts. The limbs and digits are controlled by the lateral corticospinal tract as the neurons of this tract cross the midline at the medulla and synapse on the spinal motoneurons both directly and indirectly.

2.3 Central pattern generators

CPGs are neuronal circuits present in the spinal cord that are capable of producing rhythmic motor patterns such as breathing, walking and swimming in the absence of descending and sensory inputs. Brown (1914) was the first to explain that the alternate flexion and extension of the muscles of leg could be produced by the circuits present in the spinal cord where the antagonistic muscles can be activated by neurons that inhibit each other. The generation of patterned rhythmicity basically requires two or more processes that interact in a manner that each process increases and decreases sequentially and as they interact the whole sequence returns to starting point to repeat itself again. Similarly, cycling requires sequential activation and relaxation of biceps brachii and triceps brachii muscles.

This study incorporates arm cycling to examine corticospinal excitability to biceps brachii muscle during the extension phase of arm cycling.

2.4 Corticospinal excitability during locomotor outputs

Studies in animals have shown that locomotor activities are largely mediated by spinally located CPGs (Grillner 1981), though supraspinal centres and sensory feedback are important for the voluntary and well-coordinated production of locomotion. The neural processes leading to muscle activation during locomotor output are complex and involve extensive rearrangements of intraspinal excitability, comprised of 'state-dependent' changes in the central nervous system (e.g. spinal reflexes). The process of transformation of one state (rest) into another (locomotion) occurs following information processing within the central nervous system. This processing includes inputs from supraspinal centres, sensory feedback, descending tracts and spinal circuitry. Essentially, spinal motoneurons are responsible for transforming all of these inputs into action potential which results in movement.

Although there is a lot of information available regarding the control of CPG-mediated motor behaviours of various animals, there is a lack of understanding of the role played by the different parts of central nervous system (i.e. cortical, subcortical and spinal) to rhythmic and alternating motor outputs in humans thought to also be mediated, in part, via spinal CPGs (Capaday et al. 1999; Caroll et al. 2006; Pyndt and Nielson 2003; Zehr et al. 2009; Zehr and Stein 1999). An accumulating body of evidence suggests that motor outputs arising from the supraspinal centres are relayed to the spinal motoneurons via

multiple descending tracts, with the corticospinal tract being perhaps the most important for the control of voluntary movements in humans. This includes locomotor outputs which are initiated by descending commands to activate the CPG causing it to oscillate (similar to quadrupeds), which then activates spinal motoneurons to produce muscle contraction and movement (Jordan 1998; Grillner 1981; Capaday et al. 1999; Carroll et al. 2006; Zehr et al. 2009; Sidhu et al. 2012). It is likely that supraspinal inputs are more important for the production of locomotor outputs in humans than in our quadruped counterparts (Peterson et al. 2001; Sidhu et al. 2012).

Little is known, however, regarding the precise role of the motor cortex in human locomotor movements. TMS has been used to assess the soleus and tibialis anterior muscles during treadmill locomotion, the results of which suggest that supraspinal centres are indeed involved in human locomotion (Capaday et al. 1999; Petersen et al. 1998). Sidhu et al. (2012) documented the active role of motor cortex in driving the motoneurons of the leg muscles during leg cycling and isometric contraction following subthreshold TMS stimulation. TMS that is subthreshold for MEP production activates low threshold intracortical inhibitory neurons which in turn project to descending corticospinal cells. These intracortical inhibitory neurons have the ability to inhibit corticospinal cells in the absence of activation of descending commands to motoneurons (Butler et al 2007). This inhibition of descending corticospinal cells results in the depression of ongoing electromyography (EMG) activity in the active muscle, indicating that corticospinal cells play an active role in motoneuron activation. They found a greater suppression of EMG activity during static contraction than cycling, suggesting that supraspinal centres are involved in the production of muscle activity for both motor outputs, even though leg

cycling is partially mediated via spinal CPGs. Similar observations have been reported during human locomotion (Petersen et al., 2001).

In addition to changes at the supraspinal level, changes in overall CSE can also be mediated by changes at the spinal level. Thus, to ascertain whether changes in CSE are of supraspinal or spinal origin, spinal excitability must be assessed. Ugawa et al. (1991) were the first to examine spinal excitability by passing electrical current across the spinal cord at the level of the mastoid processes to elicit a motor response recorded from the muscle, similar to that evoked via TMS. This technique is commonly referred to as implementing transmastoid electrical stimulation (TMES), which directly activates the corticospinal axons at the level of the pyramidal decussation eliciting cervicomedullary motor evoked potentials or CMEPs, which are independent of supraspinal activation (Taylor et al 2002; Gandevia et al. 1999). A series of collision experiments were performed to determine which descending motor tracts were activated via TMES.. Responses were recorded from the right hand first dorsal interosseous muscle following TMES along with left motor cortex stimulation delivered simultaneously during voluntary muscle contraction. A suppression in the cortical response was observed as a result of collision of descending cortical volley with an antidromic volley from the TMES. This collision indicates that the observed response travelled in the same axons (Taylor et al. 2002). Thus, assessing TMS-evoked MEPs and TMES-evoked CMEPs during the same experiment allows one to compare supraspinal and spinal excitability of the corticospinal tract during various motor outputs. It is also important, however, to have a measure of peripheral excitability to ensure that changes observed in MEPs are of central, and not peripheral (i.e. muscle) origin. Peripheral excitability can be recorded from nerve to muscle as a motor response known as the M-

wave. The M-wave represents the electrical activity of the muscle fiber starting from the neuromuscular junction and the propagation of action potential along the sarcolemma and t-tubules. MEPs and CMEPs are thus made relative to the M-wave to account for changes in peripheral excitability.

2.5 Corticospinal excitability to the upper limb during arm cycling

Forman et al., (2014) assessed whether there was a difference in supraspinal and/or spinal excitability between arm cycling and an intensity-matched tonic contraction in the biceps brachii. TMS and TMES were used to assess supraspinal and spinal excitability, respectively. Motor-evoked potential (MEPs) and cervicomedullary-evoked potential (CMEPs) were measured at three different positions during cycling (3, 6 and 12 o'clock). The results showed that at 3 and 6 o'clock positions, MEP amplitudes were higher during arm cycling in comparison to tonic contraction whereas at 12 o'clock (elbow extension) there was no difference in the MEP amplitudes between the tasks. In contrast, the CMEP amplitudes recorded were higher for cycling in comparison to tonic contraction only at the onset of elbow flexion (3 o'clock). Hence, they concluded that corticospinal excitability was enhanced during the flexion phase of the arm cycling, whereas spinal excitability was high at the onset of elbow flexion. Another striking finding was that at the 6 o'clock position, there was no difference in the spinal excitability between the two tasks. This suggests that larger MEP amplitudes during cycling were mediated via supraspinal regions. At the 3 o'clock position, however, the larger MEP was partially due to increased spinal excitability during cycling relative to tonic contraction. One possibility could be that the

elbow joint at 3 o' clock position puts the muscle at a lengthened state, activating the stretch reflex which would enhance sensory feedback to the muscle, which in turn could increase spinal excitability.

In contrast to this study, Carroll and colleagues (2006) showed that CSE was *lower* during rhythmic arm movement compared to an intensity-matched tonic contraction. In this study, EMG was recorded from the flexor carpi radialis muscle during arm cycling while MEPs and H-reflexes were elicited by TMS and nerve stimulation, respectively. The MEPs and H-reflexes were found to be significantly smaller during arm cycling than during tonic contraction with responses measured at four different positions (3, 6, 9 and 12 o'clock). The muscle activity levels were kept the same during cycling and tonic contraction. Four positions were recorded for which the H-reflexes were depressed during rhythmic arm movement relative to tonic contraction, with significant findings at 3 and 6 o'clock. The MEPs were similar for 3 positions (12, 3 and 9 o'clock) between rhythmic and tonic contractions but were significantly less for rhythmic than tonic at mid-flexion (6 o'clock). The small size of the MEP and H-reflex at the 6 o'clock position shows that neural transmission via corticospinal pathway was depressed at the same position as the H-reflex during rhythmic cycling. This coinciding phenomenon of depression of MEP and H-reflex implies that excitatory drive from periphery and descending tracts to the wrist flexors during flexion phase of arm cycling is suppressed by the central nervous system. Hence, these results suggest a *reduction* in cortical contribution to the production of rhythmic arm cycling when compared to tonic contraction due to the operation of a spinal CPG. The difference between the Forman (2014) and Carroll (2006) studies may be related to muscle function during arm cycling. The decrease in excitatory drive from descending and

peripheral pathways to induce excitation to the wrist flexor during cycling could be attributed to the muscle function during arm cycling which is stabilisation of the wrist for a firm grip on the arm crank handle which keeps the muscle active throughout arm cycling with little phase-dependent changes in activation alterations (Carroll et al 2006). In comparison, the biceps brachii assessed via Forman et al., (2014) shows strong phase-dependent activation, being very active during elbow flexion (from 3 to 9 o'clock) and inactive during elbow extension (from 9 to 3 o'clock).

2.6 Transcallosal connections during bilateral and unilateral contractions

Movement coordination depends on both the activation of two independent hemispheres and the communication between them. This communication between the two hemispheres is mediated via axons that connect the hemispheres, the corpus callosum. The motor excitability, or command from the primary motor cortex, is predominantly transmitted to the contralateral spinal motoneurons by a bundle of fast-conducting corticospinal axons crossing to the opposite side of the body at the pyramidal decussation (Carson 2005). For the execution of unimannual motor tasks, a neural network is required which is capable of limiting the majority of neuronal motor output activity to the primary motor cortex contralateral to the voluntary movement. The transcallosal connections appear to primarily exhibit mutual inhibition although they can be facilitatory as well (Gennaro 2004). The mutual inhibition is typically modulated depending on the task. Increases in inhibitory drive from the active hemisphere to the inactive hemisphere during unilateral

movement have been previously shown, whereas a more balanced inhibitory action exists between the hemispheres for coordinated bilateral movements (Fling 2012; Shim 2005).

Evidence of transcallosal facilitation or inhibition has been demonstrated in the human motor cortex by assessing TMS-evoked MEPs (Bäumer et al. 2006; Ferbert et al. 1992). Interhemsipheric inhibitions (IHI) can be assessed either by paired- or single-pulse TMS paradigms. In the paired-pulse paradigm, TMS is applied bilaterally with a test MEP elicited following a conditioning stimulus delivered to other hemisphere after a short (10ms) or long (40ms) interstimulus interval. The resulting MEP amplitude is suppressed due to the effect of the conditioning stimulus due to interhemispheric inhibition (Ferbert et al. 1992). Using a single-pulse paradigm the ipsilateral silent period (iSP) can be assessed by application of focal TMS to the motor cortex which is ipsilateral to the extremity being tested during the voluntary activation of the muscle. The TMS pulse results in a brief interruption of ongoing muscle activity, thus referred to as the iSP. The iSP is thus thought to reflect transcallosal inhibition assumed to be mediated by the contralateral primary motor cortex (Meyer 1995).

Perez et al. (2014) demonstrated changes in interhemispheric inhibition with bilateral activation of antagonists and agonists, the biceps and triceps brachii muscles. TMS-evoked iSPs were measured using during unilateral and bilateral isometric voluntary contractions of the proximal arm muscles. The voluntary contractions were performed by one arm at 10% of maximal isometric voluntary effort of elbow flexion or extension (this was the arm from which recordings were made) while the contralateral arm was held either at rest or performed 30% of maximal isometric voluntary elbow flexion or extension. During the bilateral activation of homologus muscles (extension-extension) the depth and

area of iSP was increased whereas it decreased during bilateral activation of heterologous muscles (extension-flexion). To determine whether spinal excitability changes could account for the iSP differences, CMEPs were evoked during the silent period which was found to be unchanged. This suggests that the changes in iSP were of supraspinal origin. These observations portray a distinct pattern of reciprocal inhibitions between the motor cortex regions controlling bilateral arm flexor and extensor muscles. This study shows interesting results which can help us to understand the mechanism behind the accomplishment of motor tasks in humans by using both of the arms together. The combination of movements required to carry out certain activities might require a partial decoupling between the arms for asymmetric bilateral muscle contraction which can be aided by the combination of interhemispheric inhibitions or facilitations.

Bilateral innervation of axial and proximal limb muscles has been shown in primates. Stronger crossed cortical connections (contralateral connections) are found between motor cortices for the muscles of the upper limb, however ipsilateral innervations, if present are not as strong as contralateral innervations (Bawa et al. 2004). The presence of ipsilateral connections from the motor cortex has been seen in humans and higher primates (Kuypers 1985). Bawa and associates (2004) examined distal and proximal upper limb muscles in humans to find if they are controlled contralaterally or bilaterally. Stimulations were delivered to the right motor cortical area representing the upper limb and surface EMG was recorded from various upper limb muscles bilaterally (ipsilateral and contralateral) during rest and phasic voluntary contractions. This study showed that high-intensity TMS applied over the ipsilateral motor cortex elicits ipsilateral MEPs frequently in the biceps brachii and deltoid only during a biphasic contraction while only small

background contraction was required to elicit ipsilateral MEPs from trapezius and pectoralis muscle. This observation points towards the presence of ipsilateral connections in the motor cortex for upper limb muscles, biceps brachii being the important one for our study. This has been shown by others as well. Ziemann and colleagues (1999) used focal TMS to examine the ipsilateral corticospinal connections of hand and arm muscles in humans. They recorded ipsilateral MEPs from 10 healthy adult individuals. MEPs were only present in the fingers, wrist extensor muscles and biceps brachii muscle but not in opponens pollicis, wrist flexors or the triceps brachii. In the study production of ipsilateral MEPs required contraction of the target muscle. The TMS threshold intensity for ipsilateral MEPs was on average 1.8 times higher and the onset was 5.7 ms later when compared to contralateral MEPs which were size-matched.

2.7 Effect of sensory feedback on corticospinal excitability

The sensory feedback from the skin and muscle play important roles in the regulation of locomotor outputs. Data from animals have shown that sensory feedback is integrated with the activity of the spinal network for the generation of the locomotion. For example, Graham Brown (1914) demonstrated that locomotion can be adjusted for speed and slope of the treadmill in decerebrate cats. Grillner and Rossignol (1978) experimented on spinalised cats and documented that changes in the hip position have a significant effect on the regulation of timing and the amplitude of the locomotor bursts. Another interesting way of addressing the sensory feedback was documented in a study by Conway et al. (1987). This study showed resetting of locomotion movement of the cat by the stimulation of the

different afferents like Ib afferents and also for flexor reflex afferents (Schomburg et al. 1998). This implies that sensory feedback has a strong influence on the locomotion generating spinal networks. A study by Sinkjær et al. (2000) investigated in humans if sensory feedback is involved during walking. They showed that unloading of the ankle extensors during the stance phase of walking resulted in reduction in soleus muscle activity by 50% in the early and mid-stance phase. This indicates that muscle afferent feedback via spinal interneurons affect the soleus motoneuron activation during the walking stance phase.

Many studies have examined the influence of different speeds/cadences changes in locomotion or cycling on sensory information processing. Studies have compared running and walking and have found soleus H-reflex gain suppression during running (Capaday and Stein 1987; Simonsen and Dyhre-Poulsen 1999; Ferris et al. 2001). This implies that as the speed of the movement changes, sensory inputs from muscles and skin also changes. Pyndt and Nielson (2003) investigated transmission in the corticospinal and Ia pathways to soleus motoneurons during bicycling. The results of the study showed that H-reflexes and MEPs from the soleus muscle were larger during downstroke and smaller during upstroke, which was the opposite of what occurred in tibialis anterior MEPs. In the later study by Pyndt and colleagues (2003) they investigated the role of reciprocal inhibition during bicycling in the regulation of antagonist ankle muscles. Reciprocal inhibition is important in ensuring that antagonistic muscles are not active when prime mover is contracting. In the pathway, both descending and peripheral sensory afferents activate the inhibitory interneurons in parallel with the antagonist motoneurons (Edgley 2001). In the aforementioned study by Pyndt et al. (2003), 20 participants were tested and reciprocal inhibition was induced by stimulation

of the peroneal nerve. In the first part of the study, reciprocal inhibition was recorded during tonic contraction and bicycling, whereas in second part reciprocal inhibition was recorded during bicycling at different cadence (30-90 RPM). A positive linear relation was observed between the external load (0.5-2.5 kg) as well as a pedaling rate (30-90 RPM) with the level of soleus muscle bEMG (the amount of inhibition) in the early downstroke. Therefore, during leg cycling, a reduction in reciprocal inhibition between antagonistic muscles was observed following an increase in cadence. Other studies also report similar H-reflex modulation in the soleus muscle along with background EMG activity. (Brooke et al. 1992; Boorman et al. 1992).

Corticospinal excitability to the biceps brachii has been examined during arm cycling in several experiments, however only one assessed the influence of cadence (Forman et al., 2015). Forman et al., (2015) examined cadence-dependent modulations in CSE to the biceps brachii during arm cycling. TMS and TMES stimulations were used to record MEPs and CMEPs, respectively, from the biceps brachii at two different positions during arm cycling, elbow flexion and extension (i.e. 6 and 12 o'clock, respectively) at 30, 60 and 90 rpm. During elbow flexion, MEPs and CMEPs were increased significantly as the cadence increased. The MEPs followed the same trend during the extension phase exhibiting increases in amplitude with increasing cycling cadence while CMEPs followed a reverse trend by decreasing in amplitude with increases in cadence. The authors concluded that by increasing the cadence, the supraspinal excitability increases throughout the cycling whereas spinal excitability is phase-dependent, demonstrating decreased excitability during the extension phase. This finding laid the foundation of the present study. The increase in MEP amplitude during the extension phase of arm cycling when the biceps brachii is

supposed to be relaxing might be due to cortical spread from both homologous and/or heterologous cortical connections (Innocenti 1986). The authors also acknowledged that there were likely cadence-dependent differences in afferent feedback at both the supraspinal and spinal level that may have influenced the results. Neither cortical nor afferent feedback were assessed.

2.8 Inter-limb coupling coordination and cross talk mechanism

Tasks done at variable frequencies have been used to exhibit patterns of bilateral interactions during bimanual activities. The arms can work in various combinations of patterns, for example, coordination in alternating movement (when walking), synchronous movement of both arms (rowing), and tasks which may require different contribution from each arm (playing guitar). Vasudevan and colleagues (2011) examined inter-arm coupling by using multi frequency arm cycling. They hypothesized that when temporal coordination was altered changes in background EMG and cutaneous reflexes would reveal bilateral coupling. In this study they tested 12 subjects as they performed arm cycling with one arm at a frequency of 1 and 2 Hz while the contralateral arm was either at rest, cycling at the same frequency or cycling at a different frequency. The results showed that at a higher cycling frequency of the contralateral arm, the ipsilateral arm will show a significant increase in EMG as compared to other low frequency trials. This finding demonstrates that inter-arm coupling is enhanced during multi-frequency arm cycling. Background EMG amplitude showed significant effects of contralateral activity on ipsilateral (crossed-effects) which could be important in equalizing muscle activity between the arms from high

frequency arm to low frequency arm and hence increasing the movement symmetry. The observation that the equalization of the EMG occurred in the low frequency arm may have happened because 2 Hz cycling requires greater muscle activity than 1 Hz cycling. As the muscle activation can't be decreased without a concomitant decrease in the cycling frequency, it may be possible for EMG to decrease instead. Another possibility could be that the more active arm influences the less active arm. According to Peper et al. (2008) when one arm had larger amplitude movement than the other arm during an asymmetrical rhythmic bimanual task, the arm with smaller amplitude movements was affected strongly by the contralateral arm than vice-versa. It has also been documented in the study that there is a lack of crossed effects in reflexes, which shows that they are influenced by ipsilateral circuits while influences from the contralateral arm is little (Carroll et al 2005).

Kennerley and associates (2002) worked on a hypothesis that temporal coupling depends on communication across the corpus callosum during continuous movements and found that this interhemispheric transmission across the corpus callosum is present during synchronisation between the hands as they move continuously. They compared two modes of coordination, symmetric (hands cycle in same direction) and asymmetric (hands cycle in opposite direction). The asymmetric mode was a more unstable state, which accredited to the ipsilateral descending corticospinal pathways activation of homologues muscles (Cattaert et al, 1999). As each effector gets signals from contralateral as well as ipsilateral descending pathways and it requires activation of homologous muscles in symmetric condition therefore signals are congruent, while the asymmetric condition requires non homologous muscle activation and hence crossed and uncrossed corticospinal pathways may give rise to conflicts. Alternatively interhemispheric interaction is responsible for this

instability in asymmetric condition. Mirror-symmetrical patterns are the result of callosal connections between parietal, premotor, and motor cortex corresponding to direction of movement of the contralateral hand (Kennerley et al, 2002).

Projection of signals arising from unilateral strong contraction to the contralateral hemisphere results in activity of the contralateral homologus muscles and has been described as associated activity (Zijdewind et al., 2006; Zijdewind and Kernell, 2001; Curschmann, 1906). Zijdewind and colleagues (2006) investigated the source of ipsilateral biceps brachii muscle activity due to voluntary muscle contraction of the contralateral biceps brachii. In their experiment they recorded responses at the same intensity of muscle activation during voluntary activation and during the activation with strong contraction of the other arm and then they compared the TMS-evoked MEP. The unintended associated contraction during the contraction of the other arm was measured and was used later as a target to be achieved during voluntary contraction. They assumed that by matching the contraction levels the excitability of the ipsilateral motor cortex as an effect of strong voluntary contraction of the other arm could be measured without possible effect of inhibition generated to ensure relaxation of the muscle. The hypothesis, whether contralateral or ipsilateral cortex was the source of associated activity, was tested by 3 protocols. The first protocol was comprised of a maximal contraction of the elbow flexors of the right arm followed by another (after 30 seconds) submaximal elbow flexor contraction of the left arm. The EMG of the biceps brachii from the left arm was kept as a target to be achieved during submaximal contraction of left arm. Therefore, the aim was to have similar EMG during two contractions of the left biceps. TMS was delivered to the right motor cortex for an initial excitatory response followed by a silent period (in the left

biceps). It was assumed that if the contralateral cortex generated associated activity then the silent period in the left biceps brachii following stimulation of the right hemisphere should be same as of during the associated and voluntary contraction. The third protocol was a combination of TMS, CMS and electrical stimulation of the brachial plexus to rule out spinal contribution. The results of the study showed that the duration of silent period was the same for associated and voluntary contraction following right motor cortex stimulation while no similar findings were present during left motor cortex stimulation. These findings support that the origin of unintended contraction of biceps brachii is from contralateral cortex. On the basis of silent period results drawn in this study were in sync with previous studies by Mayson et al (1999) and Carson et al (2006) as both studies concluded that the associated activity in muscle (contralateral to the muscle of stimulation) were relayed from the contralateral side. Associated activity in the contralateral muscle varies in amount majorly depending upon the strength and duration of the contraction of ipsilateral target muscle (Shinohara et al., 2003; Zijdewind and Kernell, 2001.)

2.9 Effects of passive and unilateral movements on corticospinal excitability

In order to establish the contribution from sensory feedback to the neural activation of corticospinal regions, it is important to compare active and passive movements. Passive movements alone yield sensory feedback when compared to active which has sensory as well as motor components. Studies involving active and passive movements during pedaling (Christensen et al. 2000; Mehta et al. 2009, 2012), pseudo-gait (Martinez et al.2014), and gait imagination (Malouin et al. 2003) using functional MRI (fMRI) have

shown activity in the primary motor and sensory cortices as well as the secondary somatosensory cortex. Along with fMRI, positron emission tomography (PET) studies evaluated the contribution of active and passive movements and consistently demonstrated similar activation of primary sensory and motor areas (Yetkin et al. 1995; Weiller et al. 1996; Mima et al. 1999). Mounting evidences from the literature shows that enhanced sensory experience can improve cortical organisation after somatosensory deafferentation (Feldman and Brecht, 2005). This has been implemented to improve residual function of affected extremities by exercising (Hutchinson et al. 2004). Passive movements provide an effective alternative mode for improving the power of weaker muscle and maintaining the muscle integrity.

Supraspinal structures monitor sensory information from the periphery during the movement of the limbs and eventually utilize this information to prepare a response. Mehta and collogues (2012) investigated human brain activity using fMRI during slow (30rpm), fast (60 rpm), passive (30rpm) and at variable pedalling rate. The results of this study showed that brain activity in primary sensory motor cortices (S1, M1) and supplementary the motor area (SMA) did not vary significantly between active and passive pedalling. Similar results were found in a study by Christensen et al 2000, in which cerebral activation was investigated by PET in seven healthy subjects. Active and passive cycling when compared to rest showed almost equal activation in the S1, M1 and SMA. During active and passive movements of lower limbs (unilateral ankle movements, bilateral multi-joint tasks) significant overlap of neural activation in cortical and subcortical bilateral sensorimotor areas (Christensen et al. 2000; Mehta et al. 2012; Francis et al. 2009; Dobkin et al, 2004). In conclusion of the study by Mehta et al (2012) the neural activation in M1

and S1was not significantly different between active and passive pedaling, while the volume of activity was lower during passive movement as compared to active in the cerebellum. The intensity of the activity in these areas increased with the increase in the pedalling rate and complexity. Also similar changes in M1, S1 and SMA were observed as a response to changing task. The most important finding in this study was that during active and passive pedalling similar levels of cortical activity were present which implies that sensory signals play crucial role in producing brain activity during pedalling. Another viewpoint which cannot be ignored is the possibility of some of the brain activity during passive pedalling occured as a result of unintended muscle contraction. Nonetheless, this result is not surprising in the light of support from previous studies which documented similar results. Studies by (Christensen et al. 2000; Radovanoic et al, 2002; Weiller et al. 1996) documented that there was a significant increase in regional cerebral blood flow in the contralateral S1, M1 and SMA during active as well as passive pedalling.

A study was done in spinal cord injury population to compare passive and active pedalling exercise effects on leg motor cortical area excitability (Nordone et al. 2016). The study consisted of two-exercising conditions during which TMS was employed at the time of pedalling tasks. They found a significant effect of pedalling during active and passive movements on short-interval intracortical inhibition (SICI). SICI in ipsilateral arm represents activity in intracortical GABAergic inhibitory interneurons (Ziemann et al.,1 996; Kujirai et al.,1993) which can alter the output from corticospinal neurons of contralateral side (Reynolds and Ashby, 1999; Ziemann et al.,1996; Buccolieri et al.,2004). In the aforementioned study (Nordone et al. 2016) SICI was found to be reduced along with no significant effect of pedalling on intracortical facilitation. Hence, they concluded that

the passive exercise could produce cortical neuroplasticity reorganisation. Following passive bike exercise in transected animals, it was observed that neurons in the deafferented hindlimb cortex were found to have higher responsiveness to tactile stimuli delivered to the forelimb (Graziano et al, 2013). Based on additional researches, passive exercise can also produce systemic effects (increase in cardiovascular fitness, improved circulation and neuroendocrine change) which in turn influence brain function by stimulating neurogenesis and to increase the levels of growth factors such as BDNF, thereby promoting brain plasticity (Van Praag et al, 1999 a,b).

2.10 Conclusion

Rhythmic and alternating motor outputs are partially mediated by spinally located CPGs, including arm cycling. Studies on corticospinal excitability during arm cycling have led to interesting findings which gave rise to the present research. Increased corticospinal excitability to the biceps brachii during the elbow extension phase or arm cycling raises the question as to what was causing this increase as the muscle was relatively inactive. Heterologous and homologous muscles have shown to be active during contraction of an ipsilateral muscle which depicts interactions between the two cerebral hemispheres. Movement coordination largely depends on the activation of the two motor cortices and their interactions. Sensory feedback from skin and muscle plays an important role in regulation of motor output and hence changes in sensory feedback as a result of changes in the cycling cadence (or any movement) may also have a strong influence on the generation of locomotion, which makes it an important factor to be considered.

Several studies have recorded neural activity from the brain during active and passive arm cycling and walking and shown bilateral cortical activity of the motor cortex. Results have shown task, load and cadence dependent modulations in the motor output. Based on the literature available, this study looked into possible mechanisms behind excitability in the biceps brachii muscle during extension phase of arm cycling.

2.11 References

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3 The role of central drive and afferent feedback on corticospinal excitability during arm cycling

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3.1 Abstract

It was recently demonstrated that supraspinal excitability to the biceps brachii, an elbow flexor, was enhanced during the extension phase of arm cycling as cadence increased from 60 to 90 rpm. The purpose of the present study was to determine if the increase in supraspinal excitability was due to the modulation of supraspinal drive and/or afferent feedback. Corticospinal excitability was measured using motor evoked potentials (MEPs) and cervicomedullary evoked potentials (CMEPs) elicited via transcranial magnetic stimulation (TMS) and transmastoid electrical stimulation (TMES) respectively. Recordings were made from the biceps brachii of the dominant arm during mid-elbow extension (12 o'clock relative to a clock face) while arm cycling using three experimental tasks and two cadences (i.e. 60 and 90 rpm). The three tasks were: 1) bilateral arm cycling (BL; supraspinal drive and afferent feedback present); 2) unilateral, non-dominant arm cycling with the dominant arm moving passively (ULP; no supraspinal drive with afferent feedback present); and 3) unilateral, non-dominant arm cycling with the dominant arm at rest (ULR; no supraspinal drive or afferent feedback present). MEPs were normalised to M_{max} and were expressed as a percentage. Statistical data analysis demonstrates significant main effects for cadence ($p = 0.010$) and tasks ($p = 0.012$). As expected, the peak-to-peak amplitudes were significantly larger during cycling at 90 vs 60 rpm (60 rpm: 8.2 ± 1.8 % M_{max} 90 rpm: 14.8 ± 3.01, $p = 0.010$). During arm cycling at three different tasks at 60 and 90 rpm, corticospinal excitability (MEP amplitudes) to the biceps brachii of the dominant arm was highest when at rest followed by passive arm cycling and finally during bilateral arm cycling. MEP amplitudes were $8 \pm 0.7\%$ M_{max} larger during ULR than BL (15.1 ± 2.8

% M_{max} vs 7.1 ± 2.1% M_{max}; p = 0.028) arm cycling. MEPs were 5.2 ± 0.9 % M_{max} larger during ULP than BL (12.3 ± 3% M_{max} vs 7.1 ± 2.1% M_{max}; p = 0.062) arm cycling, the difference was not significant, though there was a trend. There were no significant main effects for task (p = 0.542) or cadence (p = 0.568) for spinal excitability. Changes in interhemispheric inhibition (IHI) may partially explain the current findings. Enhanced corticospinal excitability in the higher cadence may result from cross facilitation and/or reduced IHI between motor cortices as the limbs attempt to cycle synchronously. Reduced IHI may also contribute to the increase in corticospinal excitability with the higher cadence in dominant arm as it becomes less active as the need to inhibit an inactive hemisphere may not be required.

3.2 INTRODUCTION

Rhythmic and alternating locomotor outputs are complex but well-coordinated activities controlled, in part, by a spinally located network of neurones referred to as the central pattern generators (CPG) (Grillner 1981). Motor outputs such as locomotion are initiated by descending commands, which in turn increase the excitability of the spinal interneurons thereby activating the CPG (Jordan et al., 2008). These descending commands and spinal networks are heavily influenced by sensory feedback, which although not required to produce locomotor output is nonetheless important for the proper control of locomotion. Similar to locomotion, additional rhythmic and alternating motor outputs, such as cycling (legs and arms) are also thought to be generated by spinally located CPGs, though supraspinal input is required (Capaday et al. 1999; Carroll et al 2006; Forman 2014; Peterson et al 200; Sidhu et al 2012).

Corticospinal excitability can be assessed by measuring the amplitude of motor evoked potentials (MEPs) elicited by transcranial magnetic stimulation (TMS) over the motor cortex. MEP amplitudes represent the excitability of the entire corticospinal tract and thus do not provide information as to where along the corticospinal tract (supraspinal or spinal) changes in excitability may have occurred. To do so requires a separate assessment of spinal excitability. Transmastoid electrical stimulation (TMES) elicits cervicomedullary evoked potential (CMEPs) by directly activating corticospinal axons (Gandevia et al 1999) which are independent of changes in supraspinal excitability (Taylor et al 2002). CMEPs are considered to have a large monosynaptic component to the spinal motoneurone pool of the biceps brachii (Petersen et al. 2002), indicating that CMEPs represent the excitability of the spinal motoneurone. Using these techniques, a previously published study from our lab was

the first to demonstrate the influence of different cadences of arm cycling in modulating supraspinal and spinal excitability to the biceps brachii. The study reported a significant increase in MEP amplitudes during both the elbow flexion and extension phases of arm cycling as the cadence increased. CMEP amplitudes, however, increased during elbow flexion but decreased during elbow extension (Forman et al 2015). These findings suggest that the enhanced corticospinal excitability observed during the extension phase of arm cycling as cadence increased was likely mediated by changes at supraspinal level, given the decrease in spinal excitability (i.e. CMEPs). We hypothesized that the enhanced supraspinal excitability may have been due to cortical spread from both homologous and/or heterologous cortical connections (Innocenti 1986). For example, activity-dependent alterations in the primary motor cortex ipsilateral to the limb in action have been previously reported, indicating that heterologous motor cortices may influence each other (Cohen 1971). Similarly, during contralateral rhythmical isotonic and static isometric wrist contractions (flexion and extension), excitability of resting wrist muscle was shown to be increased as load demands increased to contralateral wrist (Ibey and Staines 2013).

In addition to changes in central command at the supraspinal level, we could not rule out the influence of afferent feedback (Dubner and Sessle 1971) in our findings given its importance in the control of locomotor outputs (Zehr et al., 2004). Sensory information processing can be altered by changes in cadence or velocity of the movement (walking and running). For example, running has been reported to be accompanied by suppression of soleus H-reflex gain when compared with walking suggesting increased levels of presynaptic inhibition of incoming afferent feedback (at the spinal level) as speed increases (Capaday and Stein, 1987; Ferris 2001). Another experiment studied locomotor output

using cycling concluded that somatosensory evoked potentials and the H-reflex gets reduced with increase in cadence (Staines et al 1997). As the cadence increases during leg cycling, reciprocal inhibition was decreased between antagonistic muscles (Pyndt et al). In the present study different cadences are used during arm cycling.

The purpose of the present study was to determine if the increase in supraspinal excitability of the biceps brachii muscle during the elbow extension phase of arm cycling was due to the modulation of supraspinal drive and/or afferent feedback. To address this question, we tested corticospinal excitability to the *dominant* biceps brachii during the extension phase of arm cycling under three different conditions: (1) during bilateral arm cycling, (2) during unilateral arm cycling when the dominant arm was passively cycled by the torque produced by the non-dominant arm and (3) during unilateral arm cycling of the non-dominant arm while the dominant arm was at rest. We hypothesized that corticospinal excitability to the biceps brachii would be higher during bilateral arm cycling when both central and afferent commands were present than during arm cycling with the non-dominant arm while the dominant arm was resting (no afferent or central drive present) or passively cycling (afferent feedback present and no central command). Though we expected changes in overall corticospinal excitability to be at the supraspinal level based on our previously described work (Forman et al., 2015), we assessed both supraspinal and spinal excitability to confirm that this was in fact the case.

3.3 METHODOLOGY

3.3.1 Ethical Approval

Each participant was provided with all the necessary information about the experiment protocol prior to the session. A signed consent form was obtained from the participants once any concerns were clarified. The Interdisciplinary Committee on Ethics in Human Research at Memorial University of Newfoundland (ICEHR no 20162257-HK) approved the study. Tri-council guidelines were followed and all the potential risks were disclosed to the participants beforehand.

3.3.2 Participants

Ten (8 males and 2 females; eight right-hand dominant, two left-hand dominant) volunteers were recruited to participate in the first part of the study (TMS) and four participants (all male) for the second part (TMES). Absence of neurological disorder or injury was the main inclusion criteria. In addition, a magnetic stimulation safety checklist was administered before the experiments for each participant as a screening measure for contraindications to magnetic stimulation (Rossi et al. 2009). Screening for any contraindication to exercise was also done by asking participants to complete a Physical Activity Readiness Questionnaire (PAR-Q+). The Edinburg Handedness Inventory was used to determine hand dominance (Oldfield, 1971).

3.3.3 Experimental Set up

Each participant was taken through a familiarization session prior to the actual experiment to make sure they understood the procedure and were comfortable with the different forms of cycling and stimulations techniques (described below). The familiarization session was crucial to avoid use of the dominant arm which was designated as the resting or passive arm during unilateral arm non-dominant arm cycling. Participants were instructed to sit comfortably in an upright position on the cycle ergometer maintaining a comfortable distance from the hand pedals such as to avoid undue reaching and changes in trunk posture during cycling. An arm cycle ergometer (SCIFIT ergometer, model PRO2 Total Body) was used for all cycling trials and the height of the seat was adjusted to have the shoulder joint horizontally aligned with the axis of rotation of the arm crank axis of rotation. The hand pedals were fixed 180 degrees out of phase. Participants wore wrist braces during cycling to limit undesirable wrist movement due to the presence of heteronymous reflex connection between the biceps brachii and wrist flexors and extensors (Manning and Bawa, 2011).

As with our previous work we defined positions during arm cycling relative to the face of a clock with reference to the dominant arm. During arm cycling, the positions from

3 to 9 o'clock are considered the elbow flexion phase while from 9 to 3 o'clock is the extension phase. All measurements (see below) were taken from the dominant arm while it was at the 12 o'clock position relative to a clock face, also referred to as "top dead centre." During arm cycling this position coincides with mid-elbow extension and as such is associated with minimal activity in the biceps brachii, an elbow flexor. The position of the non-dominant arm (always actively cycling) was used to trigger external stimulations at the 6 o'clock position also referred to as mid-elbow flexion, or "bottom dead centre," when activity in the biceps brachii is high. Given that the pedals were 180 degrees out of phase, this meant that the dominant arm, from which recordings were made, was simultaneously at the 12 o'clock position as noted above.

Corticospinal excitability was assessed during three randomized experimental conditions, all of which involved measurements being taken from the dominant arm while at the 12 o'clock position: (1) bilateral arm cycling (BL), (2) non-dominant unilateral arm cycling used to passively cycle the dominant arm (ULP) and (3) non-dominant unilateral arm cycling with the dominant arm at rest (ULR) (Fig. 1A and 1B). Each condition was assessed during arm cycling at both 60 and 90 rpm, denoted by subscripts for each condition. For the BL condition, participants used both arms to cycle (i.e. BL_{60} and BL_{90}). In the ULP condition, participants performed active cycling with the non-dominant arm

while the dominant arm was passively cycled (i.e. ULP_{60} and ULP_{90}). Finally, in the ULR condition the non-dominant arm cycled while the dominant arm was at rest (i.e. ULR_{60} and ULR_{90}). For all three conditions the hands were strapped to the pedals. For the ULR condition, the dominant arm was held at the 12 o'clock position by strapping the hand to a separate, stable structure (not the SCIFIT ergometer) of equal height and elbow joint angle to that during the BL and ULP conditions. During the BL condition the power output was set to 30 Watts while 15 Watts was used during each of the UL cycling conditions. This was done with the assumption that each arm contributed equally to the production of the 30 Watt cycling task (i.e. 15 Watts per arm), though we could not measure the wattage independently with our current set-up. Each of the three conditions was performed while receiving TMS (*Experiment 1*; see below) and TMES (*Experiment 2*; see below).

3.3.4 Electromyography Recordings

Biceps brachii EMG activity of the dominant arm was recorded using surface electrodes (Medi-Trace 130 ECG conductive adhesive electrodes). Surface recording electrodes were positioned on the midline of the biceps brachii muscle and a ground electrode was placed on the lateral epicondyle. Skin preparation was done before placing the electrodes and included removal of dead epithelial cells with an abrasive paper followed by sanitization with an isopropyl alcohol swab. EMG was collected on-line at 5 KHz using

CED 1401 interface and Signal 5 [Cambridge Electronic Design (CED) Ltd., Cambridge, United Kingdom] software program. Signals were amplified (gain of 300) and filtered using a 3-pole Butterworth with cutoff frequencies of 10-1000 Hz.

3.3.5 Stimulation techniques

Responses were elicited in the biceps brachii using each of the following techniques:

1) transcranial magnetic stimulation (TMS)
2) Erb's point electrical stimulation
3) transmastoid electrical stimulation (TMES)

Transcranial magnetic stimulation (TMS)

A Magstim 200 (Magstim, Dyfed, United Kingdom) was used for TMS to elicit MEPs. A circular coil (13.5cm outside diameter) delivered stimulation over vertex, defined as the intersection of the midpoints between nasion and inion and the midpoint between the tragi (Power & Copithorne, 2013; Copithorne *et al.*, 2014; Forman *et al.*, 2014; Pearcey *et al.*, 2014; Philpott, 2014). The position of the coil was held tangent to the skull of the participant and parallel to the floor. As per the hand dominance this alignment made sure that the direction of the current flow was preferentially activating the left or right motor cortex. The intensity of the stimulation was started at 25% of magnetic stimulator output (MSO) and was gradually increased until motor threshold was reached. Motor threshold

was defined as the lowest %MSO resulting in a MEP amplitude of 50 ≥ μV in 50% of the trials (4 out of 8). The intensity used for the remainder of the experiment was % MSO recorded at motor threshold plus an additional 20% to ensure MEPs were visible at mid-elbow extension (12 o'clock) as per Forman et al., (2015).

Electrical stimulation at Erb's point (brachial plexus stimulation)

Maximum M-wave (i.e. M_{max}) was elicited through electrical stimulation of the brachial plexus at Erb's point (stimulator model DS7AH, Digitimer Ltd., Welwyn Garden City, Hertfordshire, United Kingdom). The stimulation intensities ranged from 100-300 mA using a pulse duration of 200 μs. The cathode and anode electrodes were placed in the supraclavicular fossa and over the acromion process, respectively. Stimulation intensity began at 25 mA and was gradually increased until the M_{max} of the biceps brachii was obtained. To ensure M_{max} the stimulus intensity was increased by 10% given that M_{max} is muscle length dependent and can change over time during an experiment (Simonsen and Dyhre-Poulsen 1999). M_{max} was used to normalize MEP and CMEP amplitudes to account for peripheral neuromuscular propagation changes (Taylor, 2006).

Transmastoid electrical stimulation (TMES)

TMES was delivered using adhesive Ag-AgCl surface electrodes placed over the mastoid processes. Stimulation intensities with a range of 125 to 350 mA with a pulse

duration fixed at 200 μs were used (DS7AH, Digitimer Ltd., Welwyn Garden City, Hertfordshire, United Kingdom). CMEP stimulation intensity was determined by identifying the minimum and maximum CMEP amplitudes obtainable. Criteria for maximum CMEP amplitudes were either a shift in the onset latency which is associated with ventral root activation and/or a stimulation intensity that induced undue discomfort in the participant. The midway point between those two amplitudes was then determined and the stimulation intensity that elicited a CMEP equal to that value was used. By using this CMEP amplitude we ensured that the CMEPs amplitudes were capable of increasing or decreasing, thus avoiding a 'ceiling' or 'floor' effect.

Experimental protocol

Experiment 1: Following stimulation intensity determination, the protocol began. The order of the six experimental trials (i.e. BL, ULP and ULR; each at 60 and 90 rpm) was randomized. During each cycling trial a total of 12 MEPs and 3 M-waves were delivered with each stimulation separated by approximated 5-6 s. An additional 3 frames without stimulation were added to prevent anticipation of the stimulation. The total duration of each cycling condition was approximately two minutes and 30 seconds of rest was provided between trials (Fig. 1A and 1B).

Experiment 2: In second part of the study we aimed to assess the spinal excitability during all three tasks. This experiment was conducted on a different day and followed the same procedures as described for *Experiment 1*.

Measurements

The Signal 4.08 software (CED, UK) was used for the off-line data analysis after data collection. The MEPs, CMEPs and M_{max} amplitudes were measured from peak-to-peak which was defined as the initial deflection of the voltage trace from the baseline EMG to the point where it returns back to the baseline. Changes at peripheral level can account for changes in MEP and/or CMEP amplitude therefore, MEP and CMEP amplitudes were normalized to the M_{max} which were evoked during the same trial. An average of rectified, prestimulus EMG (50ms) was done for each trial.

Statistics

Statistical analysis was done using IBM's SPSS statistics version 23. Two-way (task x cadence) repeated-measures ANOVAs were used to test whether there were statistically significant differences in MEP or CMEP amplitudes (normalised to M_{max}) and pre-stimulus EMG. If a significant main effect was identified post-hoc tests were performed using planned comparisons. Group data was used for analysis and a significance level of $P < 0.05$ was used for all comparisons. Data is reported in the text as mean ± SD and shown in figures as means ± SE.

3.4 RESULTS

Task- and cadence-dependent changes in corticospinal excitability to the biceps brachii

MEPs. Fig 2. shows data from one representative subject. In this example, 12 MEPs were averaged for each condition and overlaid. Average of 12 MEPs, expressed as a percentage of $M_{max,}$ and portraying difference in MEP amplitudes between different tasks at 60 and 90 RPM. In this example MEPs expressed as a percentage of M_{max} were 5.08, 8.87, and 29.71% (60 RPM) and 5.25, 5.89, 30.42 % (90 RPM) during BL, ULP and ULR conditions, respectively. Fig. 3A. There were significant main effects for task ($p = 0.012$) and cadence ($p = 0.010$; Fig 3B) with no significant interaction effect ($p = 0.067$). Posthoc analysis indicated that MEP amplitudes were $8 \pm 0.7\%$ M_{max} larger during ULR than BL (15.1 ± 2.8 % M_{max} vs $7.1 \pm 2.1\%$ M_{max}; $p = 0.028$) arm cycling. MEPs were 5.2 ± 0.9 % M_{max} larger during ULP than BL ($12.3 \pm 3\%$ M_{max} vs $7.1 \pm 2.1\%$ M_{max}; $p = 0.062$) arm cycling, the difference was not significant, though there was a trend (Fig. 3A). There was no significant difference in MEP amplitudes between ULP and ULR ($12.3 \pm 3\%$ M_{max} vs $15.1 \pm 2.8\%$ M_{max}; $p = 0.714$). Corticospinal excitability was higher during 90 RPM than 60 RPM (14.8 ± 3.01vs 8.2 ± 1.8 % M_{max}; Fig. 3B).

bEMG for MEP. Fig. 3C and 3D No significant main effects for task ($p = 0.205$) or cadence (0.137) with no interaction ($p = 0.271$) were observed for bEMG for biceps brachii muscle.

Task and cadence dependent changes in spinal excitability of biceps brachii during elbow extension phase of arm cycling

CMEPs. Changes in MEP amplitude are attributed to changes in supraspinal and /or spinal excitability. To examine spinal excitability separately, we employed TMES. Fig. 4 shows the data from one representative subject, as an average of 12 CMEPs, expressed as a percentage of $M_{max,}$ and portraying difference in CMEP amplitudes between different tasks at 60 and 90 RPM. In this example CMEPs expressed as a percentage of M_{max} were 13.98, 35.53, and 42.22% M_{max} (at 60 RPM) and 8.98, 22.1, 45.2 % (at 90 RPM) during BL, ULP and ULR tasks, respectively.

Fig. 5A and 5B. There were no significant main effects for task (p = 0.542) or cadence (p = 0.568) with no interaction effect (0.910). Though there were no significant effects for task or cadence, a clear pattern emerges once the data is heavily scrutinized. This was not surprising given the low sample size, indicated that CMEP amplitudes were 8.8 ± 7.96 % M_{max} larger during ULR than BL (33.25 ± 9.21 % M_{max} vs 24.38 ± 17.18 % M_{max}; p = 0.866) arm cycling. CMEPs were 6.92 ± 3.82 % M_{max} larger during ULP than during BL (31.3 ± 13.36 % M_{max} vs 24.38 ± 17.18 % M_{max}; p = 0.569) arm cycling. There was no significant difference in CMEP amplitudes between ULP and ULR (31.3 ± 13.36 % M_{max} vs 33.25 ± 9.21 % M_{max}; p = 0.714; Fig 5A).

There was no significant effect of cadence observed for CMEPs (p = .568) but an opposite pattern was revealed as the CMEP amplitudes were smaller for 90 RPM cadence in comparison to 60 RPM (Fig. 5B).

Fig. 5C and 5D bEMG forCMEP. No significant main effects for task ($p = 0.244$) or cadence ($p = 0.926$) with no interaction ($p = 0.891$) were observed for b EMG for the biceps brachii muscle.

3.5 DISCUSSION

The purpose of this study was to determine if increased corticospinal excitability to the biceps brachii as seen in our previous work during the elbow extension phase of arm cycling as cadence increase was due to modulation in central and/or afferent feedback. Corticospinal excitability (MEP amplitudes) as recorded from the biceps brachii of the dominant limb, was highest when the dominant limb was at rest (ULR), followed by when the limb was passively cycled (ULP) and finally during bilateral arm cycling (BL). Surprisingly, a similar trend was seen in spinal excitability (CMEP amplitudes). Our results suggest that there is a complex interplay between supraspinal and spinal regions that alters corticospinal excitability during arm cycling as cadence increases. Putative mechanisms are discussed.

Corticospinal Excitability

In the present study, corticospinal excitability was highest during ULR, followed by ULP and finally the BL condition (Fig. 2). In the ULR task neither supraspinal command nor movement-related afferent feedback were present, or was substantially reduced to the resting biceps brachii. The enhancement in corticospinal excitability could have arisen in part due to changes in cortical excitability which could be derived from a combination of

either ipsilateral and/or contralateral homologous and/or heterologous connections. For example, the motor cortex ipsilateral with the dominant arm was active in producing the arm cycling motion for the non-dominant limb. Activity in the ipsilateral motor cortex could have induced a 'cortical spread' of excitation, or reduced inhibition, through interhemispheric connections to the motor cortex projecting to dominant arm biceps brachii (contralateral motor cortex). This notion is supported by research that has shown the presence of extensive callosal connections that exists between the axial and proximal muscle representations in the motor cortex (Carson, 2005). It is thought that excitatory callosal inputs are suppressed during bimanual tasks by local inhibitory interneuron activation. These interneurons work differently during unilateral tasks as it is assumed that they are in a subthreshold, inactive state (Rokni, 2003). The relative strength of excitatory and inhibitory activities decides the degree of activation or suppression of the ipsilateral arm. This implies that there is greater suppression of excitatory inputs during bimanual tasks due to activation of local inhibitory interneurons as compared to unilateral tasks. Higher corticospinal excitability during the ULR condition could be because less inhibitory interneurons are active in order to partially suppress contralateral cortical excitability compared to the BL condition, when cortical inhibitory inteneurons would be active.

An additional finding of this study was that corticospinal excitability was higher during ULP cycling when compared to BL cycling. BL arm cycling involves voluntary activation of the motor cortex in addition to a somatosensory component as a result of proprioceptive feedback along with exteroreceptive sensory afferents due to bilateral limb movements (Fox et al., 1985; Colebatch et al., 1991; Passingham, 1993; Seitz et al., 1991). ULP cycling, however, consists only of the passive activation of the somatosensory system and does not

involve a central command, and thus motor cortex activation, of the passively moving limb (Weiller et al., 1996). Supraspinal structures ipsilateral to the moving limb are instead responsible for monitoring sensory information. Mehta et. al., (2012) showed that the activity in motor cortex was not significantly different between passive and active movements during slow (30 RPM), fast (60 RPM), passive (30 RPM) and variable pedaling rate. This result was consistent with other studies (Christensen et al., 2000; Weiller et al., 1996). Weiller et al., 1996 that showed an increase in regional cerebral blood flow during active and passive elbow movement, suggesting that neurones in the same regions were active. Altogether, these results suggest that sensory input likely accounts for a portion of the cerebral activation observed during motor output.

Spinal Excitability

We did not find any statistically significant difference in spinal excitability between three tasks as the sample size was small for second experiment, but the spinal excitability also increased in similar fashion as corticospinal excitability as dominant arm became less active, however it followed an opposite trend with higher cadence as CMEPs decreased as cadence increased. Similar results were obtained in previous work from our lab with arm cycling which demonstrated increase in MEPs, representing corticospinal excitability and decrease in CMEPs, representing spinal excitability during extension as cadence increased from 30 to 90 RPM. Another study done in our lab showed higher CMEPs during rest as compared to 60 and further lowered at 90 RPM during extension which is in agreement with this study.

Intensity

Previous work has shown that as the intensity of a motor output increases so too does the activity in the primary sensory and motor cortices as assessed via functional magnetic resonance imaging (fMRI) (Mehta JP et al., 2012; Jancke et al.,1999; Rao et al.,1996.) Lutz et al. (2005) have stated that for increasing movement velocity and generating higher muscle force, increased neuronal firing is required, which is recorded as increased signals on fMRI (Lutz et al., 2005). This notion is supported by early work in primates that showed a positive correlation between firing rates in the primary motor cortex neurones and increased force and velocity required for faster movement (Humphrey, 1972).

A number of previous findings have shown that there is an increase in corticospinal excitability in the resting arm when contralateral arm performed high level force activities (Hortobagyi et al., 2003; Hess et al., 1986; Stedman et al., 1998; Meyer et al., 1995; Muellbacher et al.,2000). The level of muscle force production as a measure of motoneuron excitability can be crudely measured by background EMG. In the present study workload was kept same for unilateral tasks however, similar results were found at higher cadence. In an attempt to describe the underlying mechanism, a study was carried out to measure short-interval intracortical inhibition (SICI) and interhemispheric inhibition (IHI) associated with high force unimanual tasks (Perez and Cohen, 2008). SICI in ipsilateral arm represents activity in intracortical GABAergic inhibitory interneurons (Ziemann et al.,1996; Kujirai et al.,1993) which control the output from corticospinal neurons of contralateral side (Reynolds and Ashby, 1999; Ziemann et al.,1996; Buccolieri et al.,2004). The IHI from primary motor cortex contralateral to ipsilateral are basically mediated by transcallosal glutamatergic projections acting via local GABAergic interneurons (Ferbert

et al.,1992; Gerloff et al.,1998; Chen, 2004; Meyer et al.,1995; Berlucchi, 1990). Perez and Cohen showed decrease in the magnitude of SICI in the resting wrist as the magnitude of force performed by contralateral wrist increased. This study also documented changes in IHI. IHI decreased with increasing magnitude of force at matched condition MEP amplitudes. Many similar results support the finding that, there is activity-dependent changes in SICI which might play role in facilitation of corticospinal excitability in ipsilateral motor cortex (Reynolds and Ashby, 1999; Ziemann et al.,1996; Buccolieri et al.,2004).

3.6 Conclusion

In conclusion, the hypotheses of the study did not stand true as we found CSE was higher during ULR followed by ULP and BL at higher cadence. The results of this study suggest that corticospinal excitability to the biceps brachii during the elbow extension phase of arm cycling as cadence increase is a result of intricate interplay and interaction between supraspinal and spinal regions. Further investigations to test putative mechanisms stated in the study will be helpful in filling in the gap.

3.7 Figure legends

Figure 1 (A). (right side view) Experimental setup: participants were comfortably seated. Right arm positions were made relative to a clock face. In the picture shown, the participant was positioned (ULR) with the dominant arm held in the 12 o' clock position and strapped securely. The non-dominate arm (visible in left side view) was free to cycle. Transcranial magnetic stimulation (TMS) was applied over the vertex to preferentially activate the left motor cortex. Transmastoid magnetic stimulation (TMES) was applied between the mastoid process and nerve stimulation at the erb's point. Evoked potentials were recorded from the dominant (mostly right - as shown in the picture) biceps brachii using EMG.

Figure 1 (B). (left side view) Experimental setup as viewed from the left side. In this view non-dominant arm can be seen in the cycling position.

Figure 1 (C). Rectified EMG from a single subject showing values of the biceps brachii and triceps brachii throughout one full revolution of arm cycling. The burst of EMG shows biceps brachii activation followed by relaxation (no activity), simultaneously triceps gets activated when biceps brachii is relaxing.

Figure 2. Average motor evoked potentials (MEP) traces following 12 stimulations during arm cycling at 60 (A) and 90 (B) RPM. Showing three different task 1) BL (Black), 2) ULP (grey), 3) ULR (red). Amplitudes are expressed as a percentage of M_{max}.

Figure 3. Group data (means ± SE, n = 10) during extension phase (12 o'clock position) for MEP amplitude at three different tasks (A), and cadence (B) Biceps brachii bEMG prior to TMS for task (C) and cadence (D). MEP amplitudes are expressed relative to the M_{max} taken during cycling at the same cadence *Indicates significant difference ($p < 0.05$); ($p = 0.028$). #indicates differences that approached significance ($p = 0.062$).

Figure 4. Average motor evoked potentials (CMEP) traces following 12 stimulations during arm cycling at 60 (A) and 90 (B) RPM. Showing three different task 1) BL (Black), 2) ULP (grey), 3) ULR (red). Amplitudes are expressed as a percentage of M_{max}.

Fig. 5. Group data (means ± SE, n = 10) during extension phase at the 12 o'clock position for CMEP amplitude at three different tasks (A), and cadence (B). Biceps brachii bEMG prior to TMS for task (C) and cadence (D). CMEP amplitudes are expressed relative to the M_{max} taken during cycling at the same cadence.

Figure 1(A)

Figure 1(B)

Figure 1(C)

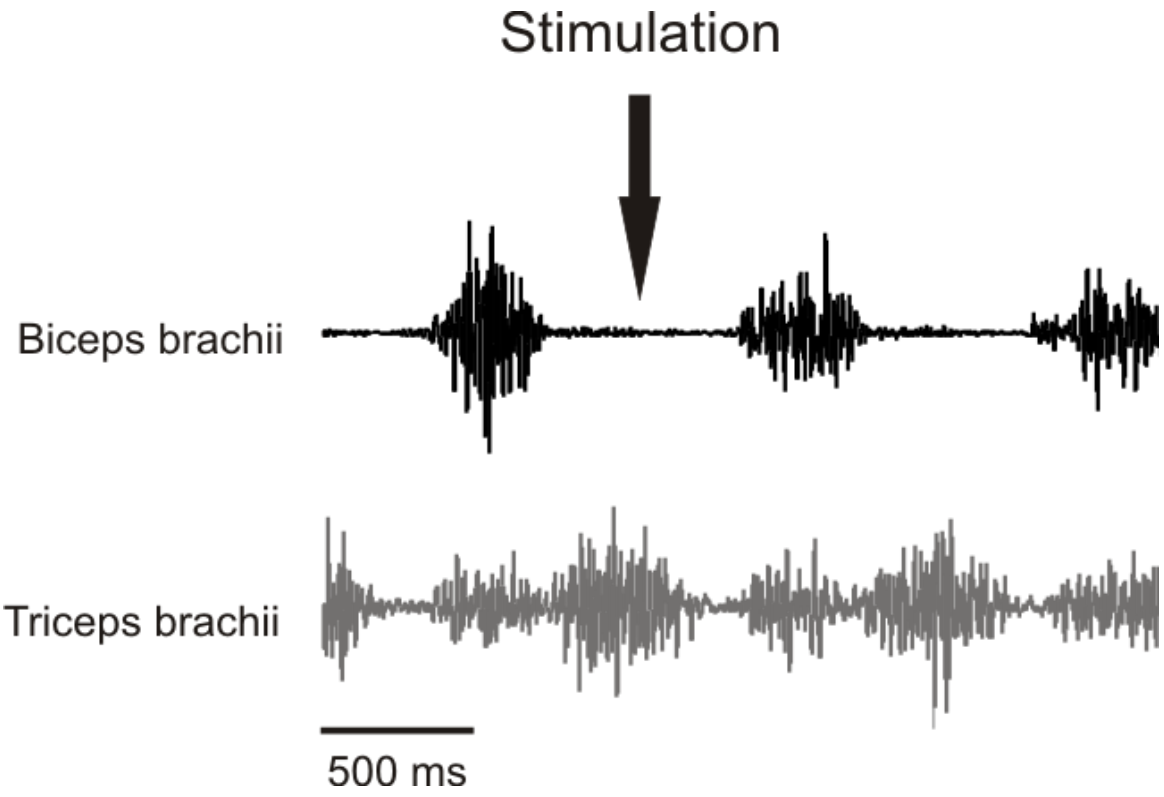


Figure 2

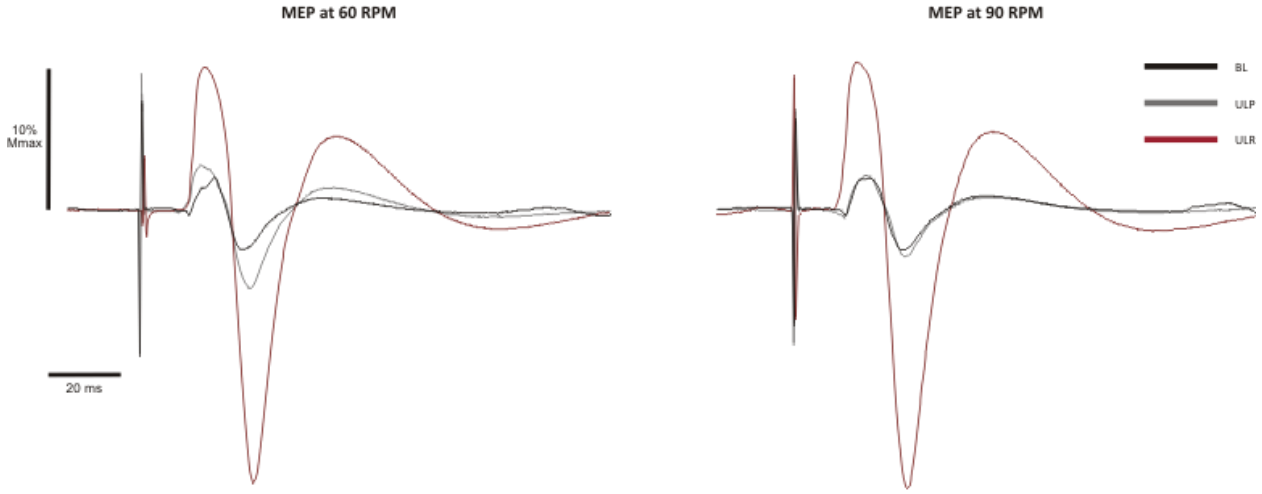


Figure 3

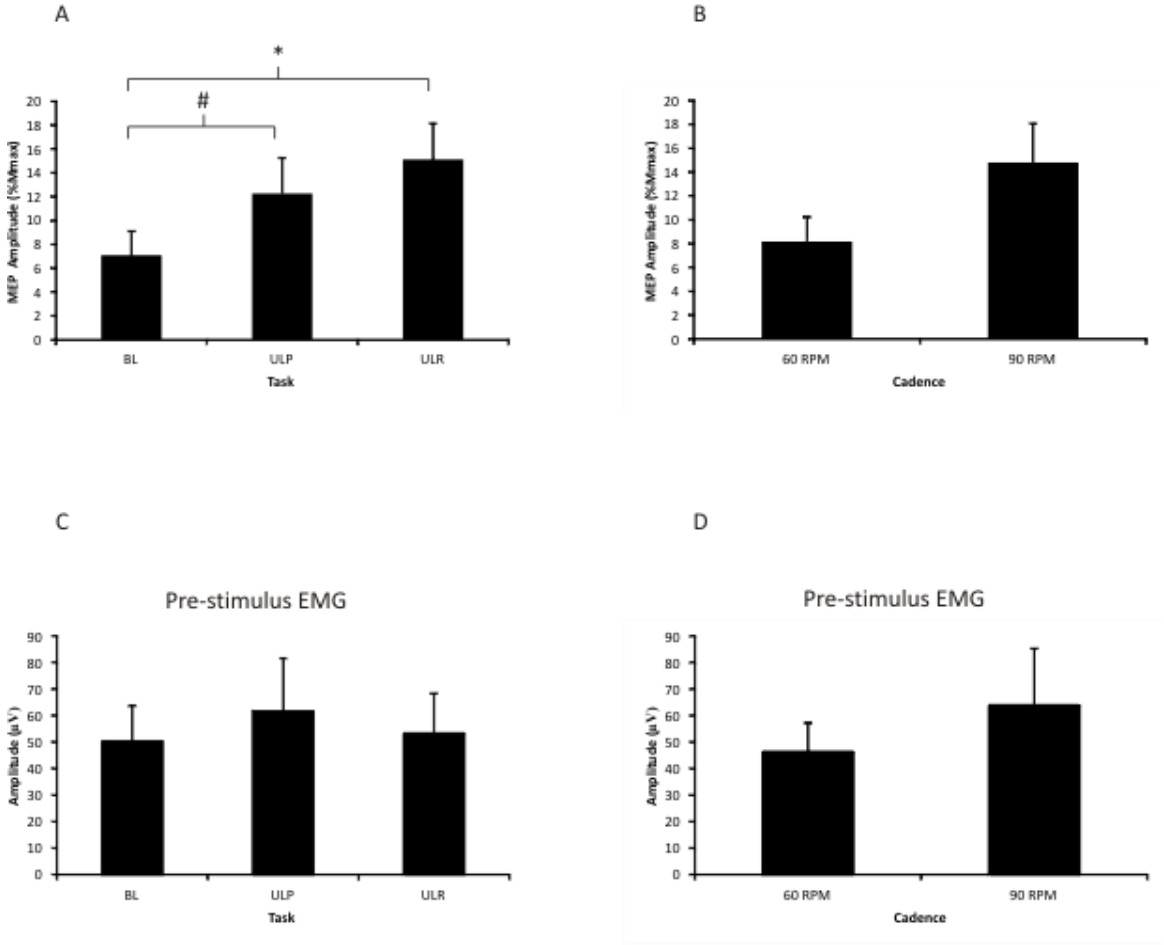

MEPs
A
*
#
MEP Amplitude (%Mmax)
BL
ULP
ULR
Task
B
MEP Amplitude (%Mmax)
60 RPM
90 RPM
Cadence
C
Pre-stimulus EMG
Amplitude (μV)
BL
ULP
ULR
Task
D
Pre-stimulus EMG
Amplitude (μV)
60 RPM
90 RPM
Cadence

Figure 4

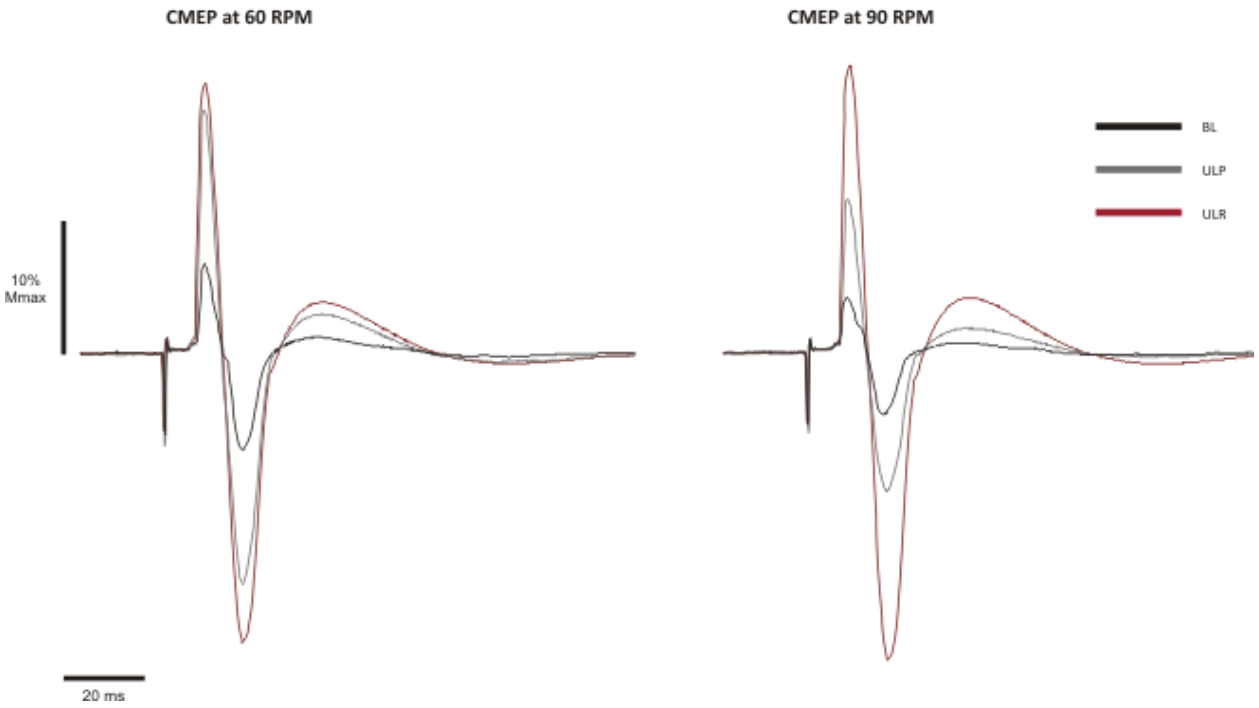
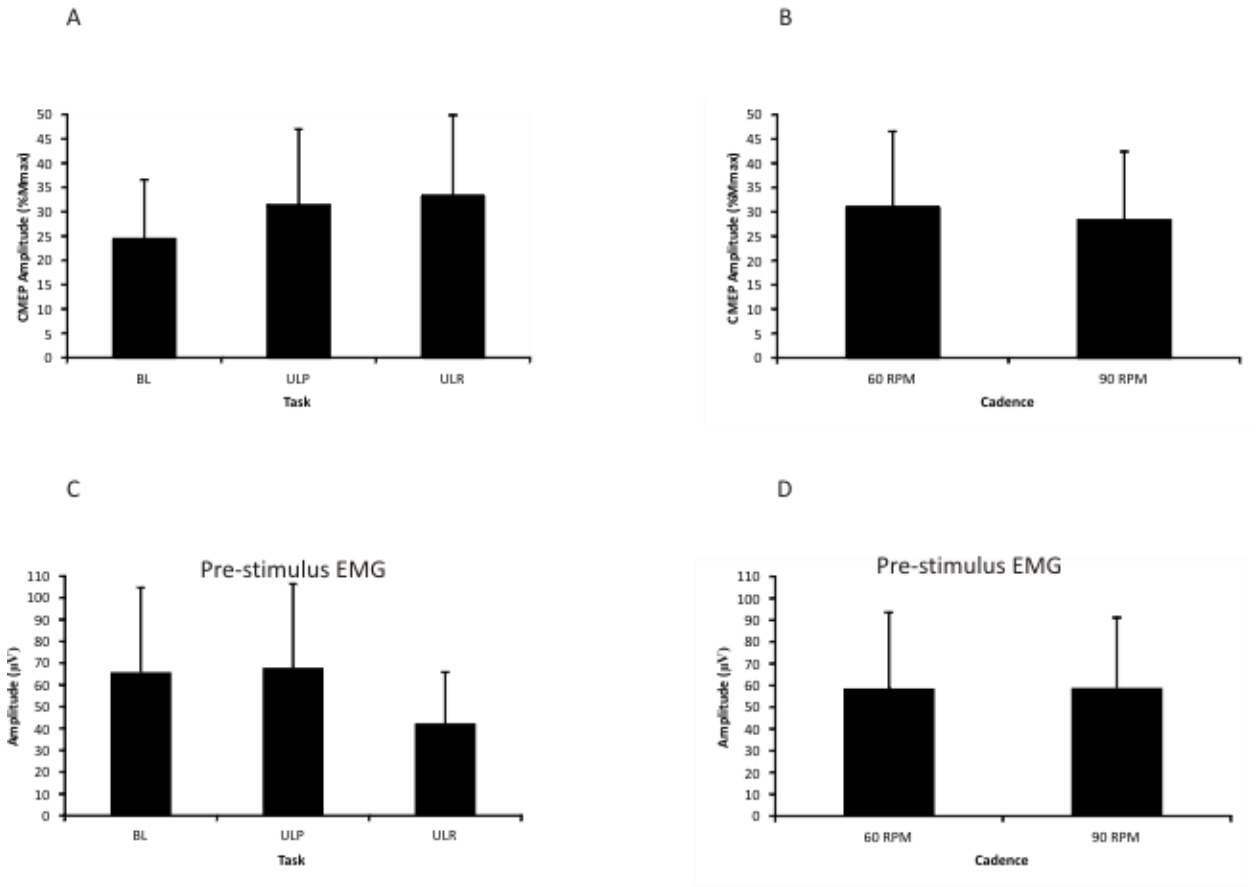


Figure 5

CMEPs



3.8 Future directions

The present study attempted to explore the reason behind excitability to the biceps brachii during the extension phase of arm cycling as cadence increased, using a very creative methodology which rendered interesting results. Yet there is a need of further research to reach a final and potential mechanism to describe this observation.

One of the very next step could be testing of spinal excitability using same methodology with more subjects to be enough to yield statistically significant result for better interpretation of spinal mechanism involved. Another way to add more precise explanation could be to investigate interhemispheric connections by testing SICI and IHI. Corpus callosum is the structure between two cerebral hemisphere connecting homologous cortical areas for transmition of sensory, motor and cognitive information. The technique of estimating interhemispheric inhibitions and facilitations could provide strong backgrounds to explain the real mechanism behind the principle observation. Paired-pulse TMS stimulation provides fantastic tool to evaluate physiological strength of transcallosal interaction (inhibition and facilitation) millisecond by millisecond.

H-reflex is another valuable tool available to evaluate modulation of monosynaptic reflex activity in the spinal cord which can help in estimating alpha motoneuron excitability provided presynaptic inhibition and intrinsic excitability of the motoneuron remain constant. This technique could be helpful in elucidation of spinal mechanisms involved in the three tasks assessed in the study. At last, there is always scope for new inventions and discoveries to add to the present knowledge pool and is always appreciated and welcomed.

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