Premovement excitability changes of the corticospinal tract are not dependent on the forthcoming task but due to a general excitation of the motor system

by

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Thesis Abstract

Premovement excitability changes of the human corticospinal tract have focused mainly on isometric contractions. Little is known about the corticospinal changes prior to a rhythmic and alternating contraction, such as cycling, and whether the modulation of excitability is different from an isometric contraction. Studies using a decerebrate cat model have shown that excitability of the spinal motoneurone is modulated very differently prior to a rhythmic and alternating movement when compared to an isometric contraction. The current study was designed to assess corticospinal excitability using transcranial magnetic stimulation and spinal motoneurone excitability using transmastoid electrical stimulation, prior to arm cycling and an intensity-matched isometric contraction. Using these techniques we sought to determine whether a difference in corticospinal excitability occurred prior to cycling and an intensity-matched isometric contraction, as well as determine whether the changes were spinal or supraspinal in nature.

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List of Abbreviations

Vth – voltage threshold

CMEPs – cervicomedullary motor evoked potentials

ms - millisecond

TMS – transcranial magnetic stimulation

MEPs – motor evoked potentials

TMES – transmastoid electrical stimulation

FCR – flexor carpi radialis

EPSPs – excitatory post-synaptic potentials

RPM – revolutions per minute

Mmax – M-wave max stimulation

MVC – maximal voluntary contraction

EMG - electromyography

FDI - first dorsal interosseous muscle

mV - millivolt

CPG – central pattern generator

Hz - hertz

s – seconds

kHz – kilohertz

µV – microvolt

mA – milliamp

µs – microsecond

cm – centimeter

SE – standard error

SD – standard deviation

1. Introduction

1.1 Background of study

Premovement changes in spinal motoneurone excitability have been shown in the adult decerebrate cat to be characterized dependent on the forthcoming motor output. Power et al. (2010) used a decerebrate cat model to examine premovement modulation of the motoneurone during fictive movement (efferent axons cut to prevent movement). The study found that prior to a rhythmic and alternating motor output (fictive scratch of the ear) motoneurone excitability was modulated very differently than the contralateral side which performed an isometric contraction (fictive stance). Prior to fictive scratch the excitability of the spinal motoneurone was enhanced while the opposite occurred prior to the stance phase (decreased excitability). The study indicated that prior to fictive scratch the voltage threshold (Vth) of the motoneurone pool was hyperpolarized, thus requiring less excitation to produce an action potential. Prior to the stance phase the Vth was depolarized, thus requiring a larger amount of excitation to produce an action potential. The findings of this study led to the design of a study involving humans that used transcranial magnetic stimulation to measure supraspinal excitability changes and transmastoid stimulation to measure spinal motoneurone excitability (Power and Copithorne, 2013). Power and Copithorne (2013) hypothesized that prior to arm cycling in humans; corticospinal excitability would be enhanced partly due to an increase in spinal motoneurone excitability as a result of the rhythmic and alternating nature of the movement, similar to the results found in the cat model. The results of the study showed that spinal motoneurone excitability remained unchanged prior to arm cycling when compared to rest with no intention of movement, while supraspinal excitability was enhanced. Supraspinal excitability refers to the excitation of the motor cortex or the secondary structures that are involved in movement execution and planning,

such as the premotor area. The study concluded that corticospinal excitability prior to arm cycling was enhanced due to supraspinal but not spinal motoneurone excitability changes. The study however did not characterize any changes prior to a tonic contraction that may be different from the modulation of the corticospinal tract prior to arm cycling. A study by Geertsen et al. (2010) did find changes in spinal motoneurone excitability (measured by cervicomedullary motor evoked potentials (CMEPs) in the antagonist soleus muscle prior to dorsiflexion, when the stimulation was placed approximately 25ms prior to motor output. The study by Power and Copithorne (2013) placed transcranial magnetic stimulation and transmastoid stimulation approximately 50ms prior to motor output. It was therefore hypothesized that the absence of change in spinal motoneurone excitability was perhaps due to placing the stimulation too far away from the motor output to detect a measureable difference from rest.

1.2 Purpose of the study

A growing number of studies are looking at premovement excitability that focus on goal orientation (Marangon et al., 2013) or motor output complexity (Hiraoka et al., 2010). Power and Copithorne (2013) assessed corticospinal excitability prior to arm cycling and found that supraspinal excitability was increased while spinal motoneurone excitability remained unchanged. However, this study did not characterize excitability modulation prior to intensity-matched cycling and isometric motor outputs, to determine if the changes in excitability are dependent on the forthcoming movement. The matching of motor output intensity will remove any confounding variables affecting the corticospinal excitability. Therefore, the purpose of this experiment was to assess corticospinal excitability prior to arm cycling and intensity-matched tonic contraction, with stimulation placed ~25ms prior to motor output to assess spinal motoneurone excitability.

1.3 Significance of the study

The information obtained from this study will shed light on how corticospinal excitability is modulated prior to forthcoming outputs. This may lead to rehabilitation sessions focusing on the integration of select movement patterns or aspects leading to movement initiation (i.e. prior to movement) to attain goals for patients suffering from nervous system disorders such as Parkinson's disease, where patients have difficulty initiating movement.

1.4 References

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2. Literature Review

2.1 Premovement excitability changes of the central nervous system

The human central nervous system has been shown to make preparatory changes before movement. Changes in neural activity of supraspinal motor structures such as the primary motor cortex (Tanji and Evarts, 1976) and supplementary motor area (Tanji et al., 1980) occur up to several hundred milliseconds prior to the onset of a response (Riehle & Requin, 1995). There is evidence that corticospinal excitability is modulated in anticipation of a forthcoming motor output (Power and Copithorne, 2013; Hiraoka et al., 2010; Sharples and Kalmar, 2012), that is affected by the type of motor output and its complexity (Hiraoka et al., 2010), and goal-directed tasks (Marangon et al., 2013). To observe corticospinal modulation in humans, transcranial magnetic stimulation (TMS) is a commonly used technique. TMS is not considered selective, however, it is generally agreed that TMS over the motor cortex, transynaptically activates cortical motoneurones discharging a descending volley to the spinal motoneurone and out to the muscle for contraction. Motor evoked potentials (MEPs) from TMS, are analysed for amplitude and latency changes which are indicative of corticospinal excitability. Premovement changes of spinal excitability have been shown in the adult decerebrate cat through motoneurone Vth hyperpolarization (Power et al., 2010) and in humans through changes in cervicomedullary motor evoked potentials (Geertsen et al., 2010) and H-reflex modulation (Nielson and Peterson,1995). The changes in the adult decerebrate raised a question that was examined by Power and Copithorne (2013). Power et al. (2010) using an adult cat preparation showed that spinal motoneurone excitability was enhanced prior to a rhythmic and alternating movement (fictive stretch) and decreased prior to the isometric stance phase in the contralateral limb. They

concluded that prior to a rhythmic and alternating movement the firing threshold of the motoneurone pool was hyperpolarized, requiring less excitatory input to activate an action potential. If these physiological changes occurred in humans, a non-invasive technique would have to be used to assess motoneurone excitability. Power and Copithorne (2013) elicited cervicomedullary motor evoked potentials (CMEPs) to assess this spinal motoneurone excitability prior to motor output in humans. Unlike MEPs produced by TMS, CMEPs are not influenced by changes in cortical excitability (Taylor, 2006). Therefore, CMEPs provide information about motoneurone excitability without cortical input, similar to the decerebrate cat due to the removal of the cortical tissue. The experiment by Power and Copithorne (2013) sought to determine if corticospinal excitability modulation prior to a rhythmic and alternating motor output (cycling) was produced by supraspinal and/or spinal excitability changes. They showed that supraspinal excitability was increased prior (~50ms) to movement onset, while spinal motoneurone excitability remained unchanged. However, this experiment did not assess whether these changes were task-dependent (cycling vs. isometric contraction) or simply due to a general excitation of the motor system prior to motor output regardless of the motor task. Also, would supraspinal and/or spinal excitability be modulated differently closer to the motor output (~25ms) as was demonstrated by Geertsen et al. (2010) prior to an isometric contraction?

2.2 Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a commonly used technique to assess corticospinal excitability. This technique uses a magnetic stimulator which generates a magnetic field that is passed into the motor cortex. TMS activates the cortical motoneurones transynaptically to elicit a MEP. According to Martin et al. (2008) the magnetic field that is

generated will activate interneurons within the cortex which synapse to the large pyramidal cells and descend along the corticospinal tract. It is likely that the initial response in some neurones will result from direct stimulation of the axon or axon hillock of the corticospinal neurone called the D response, and others from indirect, transsynaptic activation, called the I response (see review Taylor et al., 2002). The indirect stimulation of the cortical motoneurone produces a descending volley (multiple signals) of I waves that are separated by ~1.5ms intervals. The descending volleys temporally summate upon the motoneurone which will either elicit an action potential or increase its excitability by slightly depolarizing the cell. The motor pathway from the motor cortex to the spinal motoneurone is thought to be primarily monosynaptic especially in the biceps (Palmer et al., 1992; Rothwell, 1991). Therefore, the activation of the descending motor pathway provides a measure of corticospinal excitability. The excitability is referred to as supraspinal rather than motor cortex excitability since the MEP can be affected by intracortical facilitation and interhemispheric inhibition. TMS on its own can only assess corticospinal excitability as a whole, thus it cannot distinguish between changes that are spinal in nature. Therefore transmastoid electrical stimulation (TMES) must be used along with TMS to indicate the location of the changes.

2.3 Transmastoid stimulation

Electrodes are placed just below the mastoid processes at the back of the skull through which an electrical current is passed to activate the descending corticospinal tract. Taylor (2006) suggested TMES to be the most direct means available to examine motoneurone response to synaptic input in humans. Through collision experiments involving both TMS and TMES it is suggested that many of the same axons sub serve the two responses (Taylor et al., 2002). The single volley evoked by transmastoid stimulation can largely ‘occlude’ the response to cortical

stimulation when the interstimulus interval is appropriate (Taylor et al., 2002), through the collision of the antidromic volley interacting with the descending action potential. This stimulation elicits a cervicomedullary motor evoked potential (CMEP). The resulting CMEP is a measure of the spinal excitability void of supraspinal input. The application of this technique can be used to measure motoneurone excitability prior to cycling and tonic contractions of the upper limbs. Changes seen in the CMEPs are indicative of the excitability changes within the motoneurone. Since motor pathway from the motor cortex especially in the biceps brachii is thought to be primarily monosynaptic (Palmer et al., 1992; Rothwell, 1991), any changes seen in CMEP amplitude can be assumed to be changes at the motoneurone void of supraspinal excitability changes as well as through sensory feedback loops.

2.4 Contraction intensity and corticospinal excitability

Contraction intensity has also been shown to affect MEP and CMEP amplitudes during contraction, thus, motor outputs should be intensity-matched since the preparation of the motor system may be affected by the intensity of the forthcoming motor output. A study by Oya et al. (2008) looked at the interaction between contraction intensity and MEP and CMEP amplitudes in the soleus and medial gastrocnemius muscle. The study found an increase in MEPs and CMEPs in both muscles as the voluntary contraction intensity increased from 0-100%. The amplitudes for MEPs and CMEPs increased significantly along the lower end of the contraction intensity range (~0-60%) then began to plateau as the intensity was increased further. It was hypothesized by the researchers that the plateau or decrease with increasing intensity was likely muscle dependent (Oya et al., 2008). Martin et al. (2006) found a decrease in MEP amplitude as the contraction intensity of the biceps brachii increased >50%, with similar results for the brachioradialis. MEP amplitudes also decrease in the flexor carpi radialis (FCR) with contraction

intensities >50%. CMEP amplitudes began to decline in the biceps brachii with voluntary efforts >75% (Martin et al., 2006). The results of these studies suggest the contraction intensity variations can result in significantly different MEP and CMEP amplitudes during contraction. Therefore if the intensity of the contractions is not matched it is possible that the preparation of the motor system prior to a more intense motor output would result in an increase in corticospinal excitability compared to a less intense motor output.

2.5 Motor output complexity and corticospinal excitability

The cortical preparatory process for executing sequential movement is likely different from that for executing simple movements (Hiraoka et al., 2010). This difference is supported through findings in human studies (Duclos et al., 2008; Geertsen et al., 2010) involving isometric motor outputs which likely involve a larger supraspinal drive than a rhythmic and alternating motor output. It has been shown that there is a larger Bereitschaftspotential ("readiness potential") prior to sequential movement which begins earlier than prior to a simple movement (Simonetta et al., 1991). Positron emission tomography is an indirect measure of localized blood flow and increased neural metabolism which would suggest an increase in functional activation of discrete neuron populations. This technique has shown an increase in regional blood flow in the ipsilateral premotor area, bilateral posterior parietal areas, and precuneus, which is positively related to the length of the sequential movement (Catalan et al., 1998). Therefore a sequential or more "complex" movement may require an increased degree of planning and activation of more pre frontal cortex regions. Hiraoka et al. (2010) used seven healthy adults and looked at MEP amplitude changes prior to a simple and sequential hand movement. Each participant placed their hand pronated on a flat table with their fingers held in place using flat metal bars. Underneath the thumb, index and little finger were force transducers that were pressed upon when performing

the tasks. The simple task was to press on the force transducer underneath the index finger, while the sequential tasks was to press down with the index finger, little finger, thumb, little finger, and index finger in that order. The study found that premovement facilitation of corticospinal excitability was increased during the sequential task (MEP = 3,883%) and simple movement (MEP = 2,908%) when compared to the resting condition, also the sequential task had an earlier onset when compared to the simple movement. The findings by Hiraoka et al. (2010) suggest that corticospinal excitability is modulated task-dependently because of the complexity of sequential tasks compared to simple movements.

2.6 Mental imagery and corticospinal excitability

It has been shown that the observation of someone's actions will increase corticospinal excitability (Fadiga et al., 1995; Loporto et al., 2013). The Loporto et al. (2013) study used video observation that showed separate abduction videos of the index and little-fingers. MEP amplitudes recorded from the abductor digiti minimi (ADM) were increased following observation of the little-finger abductions but not following the index finger abduction videos. These results indicate that action observation has a muscle specific effect on corticospinal excitability (Loporto et al., 2013). It is also likely that there is some shared neural substrate between motor execution, action observation and movement imagery (Holmes et al., 2010). A study by Fadiga et al. (1999) observed significant increases in MEP amplitudes following imagery of forearm extension; however, there was no observed increase in MEP amplitudes from the opponens pollicis (OP) muscle following forearm movement imagery. This suggests a similar effect to that occurring during action observation in the corticomuscular excitability was only found when the muscles involved in the physical task were imaged to perform as force-generating agonists (Loporto et al., 2013).Therefore instructions to imagine an upcoming

movement or contraction can greatly affect corticospinal excitability prior to the forthcoming motor output. .

2.7 Inhibitory and facilitation mechanisms prior to motor outputs

MEP amplitude changes can be measured to assess corticospinal excitability prior to and during motor outputs. For example and increase in MEP amplitude could be the result of a hyperpolarization of the cortical motoneurone pools firing threshold. A hyperpolarization of the firing threshold requires less temporal or graded summation of excitatory post-synaptic potentials (EPSP's) to activate the already excitable cortical motoneurone. It is also suggested that intracortical facilitation can be enhanced in the motor cortex by other areas involved in motor planning (Nikolova et al., 2006). If MEP amplitudes decreased it could be due to a depolarization of the firing threshold requiring a greater temporal or graded summation of EPSP's to activate the less excitable cortical motoneurone. Decreases in cortical motoneurone excitability may be due to an increase in interhemispheric inhibition of the motor cortex described by Duque et al. (2007). Therefore MEP amplitude changes can be used to characterize changes in supraspinal excitability *prior to* and *during* motor output.

Mechanisms of inhibition or facilitation affecting corticospinal excitability would result in the decrease or increase in MEP amplitude as the motor cortex and secondary cortical structures change excitability. Duque et al. (2010) tested 13 participants using TMS in a choice reaction time test of the bilateral index fingers. Participants were cued to abduct their left or right index finger when a visual representation of a soccer ball appeared, the ball was to be kicked (finger abduction) into a goal in the middle of the screen. Participants were informed before trials if the left index finger was to be used (relevant) or the right index finger was to be used (irrelevant). TMS was applied over the right motor cortex and MEPs were measured from the left

FDI muscle. The study found MEP suppression (decrease of 36% from baseline measures) of the right motor cortex preceding (100ms) abduction of the left index finger (relevant), but found no suppression of the MEP when the participants were informed to use the right index finger (irrelevant). Duque et al. (2010) described the MEP suppression preceding the finger abduction as “impulse-control”, a control mechanism that prevents early execution of a planned movement before being cued to do so. If “impulse-control” was present preceding a bilateral cycling or unimanual isometric contraction, it would manifest as a decrease in MEP amplitude immediately prior to the selected motor output.

Nikolova et al. (2006) assessed motor cortex excitability changes prior to a simple reaction time task. Seven participants were instructed to perform a ballistic isometric contraction of the right FDI muscle. The study used single-pulse TMS, paired-pulse TMS (interstimulus interval = 3ms), and paired-pulse TMS (interstimulus interval = 13ms). TMS was placed 160-20ms prior to EMG onset of the FDI. The study found that as the TMS pulse (single or paired) approached the onset of movement (100ms and less), the ICI (intracortical inhibition) decreased or was completed abolished ~50ms prior to movement compared to control. The study also noted a higher ICI at longer time intervals (120ms+ from EMG onset) for the movement trials compared to the control (no movement) trials. The results of this study and the study by Duque et al. (2010) suggest that as the motor output approaches ICI will decrease MEP amplitude, However, ICI of the corticospinal tract begins to decrease closer to the movement onset (100ms or less). This would manifest as an increase in MEP amplitude as the corticospinal tract becomes more excitable.

2.8 Corticospinal excitability changes prior to and during motor outputs

A study completed by Carroll et al. (2006) examined corticospinal excitability changes during a rhythmic and alternating arm movement (cycling) as well as during a tonic contraction. The study looked at nine healthy individuals with no known neurological deficits. Participants were seated in front of a custom built, arm cycle ergometer and asked to cycle at 60 rpm. The study found a depressed corticospinal pathway during the flexion phase of the rhythmic arm movement (27% of Mmax, smaller) when compared to the tonic contraction when the arm was in mid-flexion (6 o'clock position), this data would suggest a reduction in the excitability of corticospinal cells during rhythmic arm movement compared to tonic contraction. Power and Copithorne (2013) assessed corticospinal excitability prior to cycling and found an increase in MEP amplitudes along with no change in CMEP amplitudes. The study looked at 10 male volunteers with no known neurological deficits, and asked them to cycle at a "comfortable pace" upon hearing a response tone. MEP amplitudes were significantly higher prior to cycling (14.3 ± 7.3% of Mmax) when compared to the rest position (4.5 ± 2.3% of Mmax). These findings suggest that prior to movement the excitability changes are very different then the excitability assessed during movement. For example the Carroll et al. (2006) study found a decrease in corticospinal excitability with an increase in spinal motoneurone excitability *during* arm cycling, while Power and Copithorne (2013) found an increase in corticospinal excitability with no change in motoneurone excitability *prior* to arm cycling. Hiraoka et al. (2010) found MEP amplitude increases prior to a simple and sequential task compared to control, as the stimulation onset approached a motor output (EMG onset). These finding suggest that as a motor output approaches the excitability of supraspinal structures is increased in order to perform the forthcoming task. A study by Geertsen et al. (2010) showed corticospinal excitability increased

in the tibialis anterior prior to dorsiflexion and in the soleus muscle prior to dorsiflexion and plantar flexion. The MEP amplitudes did not reach significance until the stimuli were set closer to the motor output. Stimuli were elicited after an auditory tone to contract but prior to the onset of motor output. Subjects rested comfortable in an arm chair with the ankle in a slightly plantar flexed position (140 degrees). Subjects were asked to either dorsi flex or plantar flex their ankle at 30% of MVC as fast as possible. TA MEP amplitude gradually increased around 100ms prior to onset of dorsi flexion and reached significance at 50ms prior. At ~25ms prior to dorsi flexion, TA MEPs were significantly increased (327 ± 77%) compared to the MEP size at the auditory cue to contract. Soleus MEP size gradually increased around 75-100ms prior to both plantar flexion and dorsi flexion, but did not reach significance until 50ms prior to onset of contraction. Soleus MEPs increased significantly at 25ms prior to onset of plantar flexion (810 ± 105%) compared to MEP size at the auditory tone to contract. At 25ms prior to dorsi flexion, soleus MEPs increased (233 ± 34%) compared to MEP size at the auditory tone to contract. A study by Hiraoka et al. (2010) looked at MEP amplitude increases as the stimulation onset approached a motor output (EMG onset). MEPs were stimulated after a start cue but prior to motor output, stimulation timing ranged from 160-0ms prior to EMG onset. MEP amplitudes increased to a larger extent as the motor output (EMG) approached, with the largest MEP amplitude in the 20-40ms prior to EMG range. These findings suggest that as a motor output approaches the excitability of supraspinal structures are increased in order to perform the forthcoming task. An increase in corticospinal excitability has been shown ~75ms prior to EMG onset prior to both voluntary activation (i.e. during a heel raise) and an anticipatory postural reaction (Peterson et al, 2009). These findings along with the Hiraoka et al. (2010) and Geertsen et al. (2010) studies suggest that the onset of stimulation is an important factor when looking at corticospinal

excitability changes prior to motor output. Another study by Sharples and Kalmar (2012) found that cortical excitability of the contralateral (active) motor cortex was enhanced at rest prior to contraction and during a contraction. The study looked at ten healthy individuals with no known neurological deficits, and asked them to contract their right index finger while measuring MEP amplitudes from the first dorsal interosseous muscle (FDI). Measurements were taken at rest and during contraction (5% of MVC). Testing MEPs of 1mV were used during the rest, pre-contraction, and contraction trials, however, the intensity required to elicit the 1mV test MEP was significantly less for the pre-contraction and during contraction compared to rest. This decrease in intensity required to elicit the 1mV test MEP suggests an increase in corticospinal excitability possible due to a hyperpolarization of the Vth of cortical motor cells.

2.9 MEP onset latency changes prior to motor outputs

Power and Copithorne (2013) found increases in MEP amplitude along with a decrease in MEP onset latency, which is indicative of an increase in corticospinal excitability. The study defined the onset latency as the time between the stimulation artifact and the point at which the voltage trace become tangent to a straight line along the horizontal voltage trace baseline. The study found a significantly shorter mean onset latency (-1.5ms; $P < 0.05$) prior to cycling when compared to rest. Hiraoka et al. (2010) found a similar result in MEP latency decreases prior to simple and sequential motor outputs, with a larger onset decrease prior to a sequential motor output. The Bereitschaftspotential (readiness potential) describes larger MEP amplitudes and decreased MEP onset latencies prior to sequential movements in comparison to simple movements. TMS activates cortical motoneurones transynaptically, producing a descending volley of I waves separated by 1.5ms intervals. Power and Copithorne (2013) showed an average decrease prior to cycling in MEP onset latency of 1.5ms. This finding would suggest that the

required summation of EPSP's produced by the descending I waves, was less prior to cycling when compared to the resting condition. Therefore it is plausible that prior to cycling the firing threshold of the cortical motoneurones was reduced sufficiently that the need for the temporal or graded summation of the EPSP's caused by the I waves was less.

2.10 Spinal excitability changes

Rhythmic motor outputs such as the patterns seen in locomotion or upper body cycling, are generated via commands traveling from supraspinal structures down the pyramidal tract to spinal motoneurones in order to excite and contract the muscle. It is suggested that locomotion is characterized by a functional reorganization of intrinsic spinal cord excitability creating a new functional locomotor state within the spinal cord when compared to rest (Power et al. 2010). The spinal motoneurone has been referred to as the "final common pathway". It is therefore the action of the spinal motoneurone that transfers all descending commands into muscular contractions. Motoneurone modulation has been explored during fictive locomotion and scratch in the decerebrate cat, and found such characteristic changes as: decreased rheobase current (Krawitz et al., 2001; Power et al., 2010), reduced afterhyperpolarization amplitude (Brownstone et al., 1992; Power et al., 2010), the emergence of intrinsic voltage-dependent depolarizations (Brownstone et al., 1994; Power et al., 2010), and hyperpolarization of the voltage threshold (Vth) for action potential initiation (Krawitz et al., 2001; Power et al., 2010). Fictive scratch and weight bearing refers to motoneurone firing in the absent of actual muscular contractions, during these preparations the motoneurones are severed from the connecting muscle so that firing of the motoneurone does not result in movement of the efferent muscle. The results of these preparations show clear differences in motoneurone characteristics. During ipsilateral scratch in

both spinal-intact and spinal transected preparations there is a hyperpolarization of Vth for the action potential initiation (Power et al., 2010).

Studies supporting the involvement of spinal processes have been looked at using data obtained from monkeys. The firing rates of spinal interneurons have shown modulation associated with prior information about the movement parameters (Prut & Fetz., 1999). The findings of the animal models have led to studies now looking at how humans modulate spinal motoneurone excitability prior to and during motor outputs. A study by Duclos et al. (2008) showed that prior to submaximal ballistic isometric wrist extension, motoneurone interspike intervals increased and discharge variability decreased. The lengthening of the mean interspike interval observed prior to the response demonstrates that inhibitory mechanisms are activated during the preparation for movement (Duclos et al., 2008). The results obtained from the Duclos et al. (2008) study suggest that spinal inhibitory mechanisms are involved in motor preparation. CMEP amplitude increases or decreases describe the changes in the excitability of the spinal motoneurone. Increase in CMEP amplitude can be a result of hyperpolarization in the Vth of the motoneurone pool resulting in activation of a greater number of spinal motoneurones. An increase in H-reflex is also observed ~25-50ms prior to EMG activity (Peterson et al., 2009); this increase in H-reflex is likely due to modulation of the motoneurones excitability properties due to descending corticospinal volleys (Peterson et al., 2009).

The H-reflex is considered to be an analogue of the stretch reflex, but bypasses the effects of the gamma motoneurones and muscle spindle discharge (Brooke et al., 1997a; Schieppati, 1897). Stimulation to evoke the H-reflex activates both afferent sensory axons and efferent axons resulting in both an M-wave which represents efferent excitability as well as the H-reflex representing the sensory feedback loop to the motoneurone. Therefore the H-reflex is not a direct

measure of alpha-motoneurone excitability due to the effect of presynaptic inhibition on reflex amplitude (Zehr, 2002). For these reasons the H-reflex cannot be used as a measure of spinal motoneurone excitability but rather a measure of spinal excitability. The H-reflex should therefore not be selected as a measure of motoneurone excitability; instead CMEPs are the optimal measure for assessing spinal motoneurone excitability in the human subjects, primarily based upon findings from Taylor (2006) which suggested TMES to be the most direct means available to examine motoneurone response to synaptic input in humans.

Previous findings by Power and Copithorne (2013) showed that stimulation proximity of ~50ms prior to motor output (cycling) had no change on the excitability of the spinal motoneurone (no increase or decrease in CMEP amplitude). However, Geertsen et al. (2010) showed an increase in MEP and CMEP amplitude closer to the onset of motor output (~25ms) in the antagonist soleus muscle during dorsiflexion. The findings by Geertsen et al. (2010) has the current study hypothesizing that if the stimulation was placed closer to the motor output then perhaps a change in spinal motoneurone excitably (CMEP amplitude) can be observed.

2.11 Conclusion

In conclusion, the literature indicates that supraspinal excitability prior to cycling will be increased due to the more complex nature and/or spinal motoneurone excitability will increased prior to the rhythmic and alternating nature of the cycling task. Whereas, supraspinal excitability will be smaller prior to a tonic contraction because of its simplicity and/or spinal motoneurone excitability will be decreased similar to the findings by Power et al. (2010) using the adult decerebrate cat. Another factor that will affect the excitability of the corticospinal tract is the placement of the stimulation closer to the motor output (~25ms) then the one used in the Power

and Copithorne (2013) study (~50ms), this may produce changes in the spinal motoneurone excitability similar to those found in the Geertsen et al. (2010) study.

2.12 References

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3. Thesis Manuscript

Premovement excitability changes of the corticospinal tract are not dependent on forthcoming task but due to a general excitation of the motor system

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Running Head: Premovement changes in corticospinal excitability

3.1 Abstract

Current studies have not compared corticospinal excitability modulation prior to a rhythmic and alternating motor output and an intensity-matched isometric contraction. The purpose of this study was to determine if supraspinal and/or spinal excitability were modulated differently prior to arm cycling and tonic contraction when compared to rest with no intention to move. Supraspinal and spinal motoneurone excitability were assessed using transcranial magnetic stimulation (TMS) over the motor cortex and transmastoid stimulation over the mastoid processes, respectively. Surface EMG recordings of motor evoked potentials (MEPs) and cervicomedullary motor evoked potentials (CMEPs) were made in the relaxed biceps brachii prior to arm cycling, tonic contraction and at rest with no intent of movement. The MEP amplitudes were larger prior to arm cycling (4.37 ± 0.58% of Mmax; P = .022) and tonic contraction (4.32 ± 0.91% of Mmax; P = .022) compared to control (2.32 ± 0.78% of Mmax), but showed no difference between contraction types. MEP onset latencies were also shorter prior to cycling (14.05 ±0 .24ms; P = .026) and tonic contraction (14.24 ± 0.14ms; P = .029) compared to control (15.61 ± 0.55ms). The CMEP amplitudes remained unchanged prior to cycling and tonic contraction compared to rest. We conclude that premovement enhancement of corticospinal excitability is due to an increase in supraspinal but not spinal motoneurone excitability, independent of the forthcoming motor output.

Key Words: transmastoid stimulation, transcranial magnetic stimulation, cycling, isometric, intensity-matched

3.2 Introduction

The excitability of many central nervous system structures is altered in preparation for movement in humans and primates. Premovement changes have been observed in supraspinal structures including the primary motor cortex (Tanji and Evarts, 1976) and supplementary motor area (Tanji et al., 1980), presumably in an attempt to improve the efficiency of the upcoming motor output. The degree to which corticospinal excitability is modulated prior to movement has been assessed using transcranial magnetic stimulation (TMS) applied to the motor cortex. The results have inconsistently demonstrated both increases (van Elswijk et al., 2007) and decreases (Davranche et al., 2007; Duque et al., 2010; Hasbroucq et al., 1997) in corticospinal excitability. Spinal excitability changes prior to movement also occur. Interneuronal firing patterns are modulated in both excitatory and inhibitory processes prior to motor output in primates (Prut and Fetz 1999). The H-reflex, a measure of spinal excitability is usually depressed during the preparatory period (Hasbroucq et al., 1999) but is facilitated immediately prior (~50ms) to movement onset (Nielson and Peterson, 1995). It is thus evident that nervous system excitability is modulated prior to motor output and that this modulation is dependent on factors such as the experimental design, preparatory period duration, timing of nervous system assessment and/or the number of movement choices. Importantly, these studies (Hiraoka et al., 2010; Marangon et al., 2013) typically assess corticospinal excitability prior to motor output using isometric (Hiraoka et al., 2010), goal-directed (Marangon et al., 2013), simple or sequential tasks (Hiraoka et al., 2010) as the forthcoming movement. The neural strategies used to control motor output in animals (Perreault, 2002; Power et al., 2010) and humans (Tax et al., 1990; Thomas et al., 1987), however, are task-dependent. It thus reasons that the manner in which the nervous system prepares for a given motor output may also be task-dependent.

The examination of changes in corticospinal excitability prior to a rhythmic and alternating motor output, is thought to be partially generated by spinally located circuits referred to as central pattern generators (i.e. CPGs; Carroll et al., 2006), is limited (Power and Copithorne, 2013). Findings from the adult decerebrate cat preparation (Power et al., 2010), illustrated spinal motoneurone excitability enhancment prior to fictive scratch, a rhythmic and alternating motor output. Based on these findings, Power and Copithorne (2013) assessed supraspinal and spinal motoneurone excitability in the quiescent state prior to arm cycling in humans. They used TMS to assess the excitability of the motor cortex and transmastoid electrical stimulation (TMES) to assess spinal motoneurone excitability (Taylor, 2006). Supraspinal excitability (i.e. increased motor evoked potential (MEP) amplitude and reduced onset latency) was enhanced, whereas, spinal motoneurone excitability (i.e. cervicomedullary motor evoked potentials (CMEPs) was not prior to arm cycling. However whether or not the increased corticospinal excitability was cycling-dependent or a general response of the motor system in preparation for motor output remains unknown.

The timing of TMES prior to arm cycling is important to observe changes in spinal motoneurone excitability. One reason why Power and Copithorne (2013) may not have found changes in spinal motoneurone excitability is because they measured the CMEPs approximately 50ms prior to the onset of electromyography in the target muscle (biceps brachii). However, Geertsen et al. (2010) demonstrated that soleus CMEPs were enhanced prior (~25ms) to dorsiflexion indicating that subcortical, possibly spinal motoneurone, excitability was increased in the soleus muscle prior to the activation of the antagonist tibialis anterior. Thus, it is possible that spinal motoneurone excitability was modulated closer to the onset of EMG for cycling, a time period that was not assessed by Power and Copithorne (2013).

The purpose of this study was to determine whether: 1) differences existed between the modulation of supraspinal and/or spinal motoneurone excitability of the biceps brachii prior to arm cycling and an intensity-matched tonic contraction 2) Specifically, we sought to determine whether the enhanced supraspinal excitability we previously reported (Power and Copithorne, 2013) was cycling-dependent and also to determine if spinal motoneurone excitability was modulated closer to movement (i.e. EMG) onset. We hypothesized that: 1) corticospinal excitability would be enhanced prior to both arm cycling and an intensity-matched tonic contraction when compared to rest and 2) there would be a larger increase in corticospinal excitability prior to arm cycling than the tonic contraction due, in part, to increased spinal motoneurone excitability.

3.3 Methods

Participants

The study was performed on 10 male volunteers from a university population, without any known neurological dysfunctions. Participants were verbally informed of experimental procedures prior to testing, and gave informed, written consent prior to participation. Prior to the experiment all participants completed a magnetic stimulation safety checklist to screen for contraindications to stimulation procedures (Rossi et al., 2009). The experiment was approved by the Interdisciplinary Committee on Ethics in Human Research (ICEHR# 20140534-HK) committee in accordance with the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans with full disclosure of any potential risks to the participants.

Experimental Set-Up

Stimulation of the corticospinal tract at the supraspinal and spinal level, were performed prior to arm cycling and an intensity-matched isometric contraction. Participants were seated in an upright position facing an upper-body cycle ergometer (Rehab Trainer 881E, Monark), secured to an adjustable stand (UBE Rehab Table, HealthCare International, Inc. Langley, WA). The ergometers arm cranks were offset 180 degrees with the arm crank shaft aligned approximately to the shoulder height of each participant. Participants were instructed to grip the ergometer handles loosely with their forearms pronated. See Fig.1 for illustration of set-up.

General Procedures

A time-preparation protocol was utilized consisting of an auditory warning signal (frequency, 200Hz; duration, 100ms) which started a 1s preparatory period, followed by a response signal (frequency, 100Hz; duration, 100ms), and finally by a stop signal (frequency, 300Hz; duration, 100ms) 3s after the response signal. Participants were informed ahead of time whether they would perform the cycling or the isometric contraction and were instructed to continue each of the conditions until hearing the stop signal (see Fig.2). Upon hearing the stop signal participants were instructed to return the right arm crank to the 6 o'clock position and left arm crank to the 12 o'clock, resetting for the next trial. Each stimulation response was evoked during separate trials for the cycling and isometric conditions. For the cycling condition, participants were instructed to prepare for cycling during the preparatory period and to begin cycling at a "comfortable pace" upon hearing the response tone. The cycle ergometer was then fixed with the right handle in the 6 o'clock position to prevent any movement for the next condition. For the isometric condition, participants were instructed to prepare for the upcoming

isometric contraction during the preparatory period and to match a contraction intensity displayed on a computer monitor in front of the subject as a horizontal line. The horizontal contraction line was intensity matched to the average first EMG burst during the cycling condition of the bicep brachii. Reponses to transcranial and transmastoid stimulation were evoked following the response signal and prior to the movement onset (see Fig.2b and Fig.2c) defined by an increase in EMG activity (point at which the rectified signal was ≥ 2 times the standard deviation of a 50ms window of EMG measured at rest (Power and Copithorne, 2013) of any of the recorded muscles (anterior deltoid, flexor carpi radialis, bicep and triceps brachii). To establish the placement of the stimulation following the response tone, participants completed eight trials without stimulation to determine the average reaction time of the target muscle, indicated by the time between the response signal and a visual increase in EMG activity. To ensure the participants did not anticipate the response tone and therefore decrease their reaction time, the response tone was removed in three trials in which participants were instructed to remain at rest. Transcranial and transmastoid stimulations have differing latency periods (transcranial: ~14ms, transmastoid: ~9ms) which would vary the placements of the stimulation potentials prior to the EMG activity. Therefore transcranial stimulation was set at ~25ms while transmastoid stimulation was set at ~20ms prior to EMG activity, to ensure each stimulation potential occurred at approximately the same time prior to EMG activity. When using a constant-duration preparatory period, which was used in the current study (1s), participants can respond essentially simultaneously with the response signal following practice (Henry et al., 1960). Since MEP and CMEP amplitudes can be increased by voluntary contraction, it was important to prevent muscle contraction before stimulation, due to signal anticipation. To prevent response signal anticipation, the response tone was removed in 15% of the trials (i.e. 5 of 34) and

subjects were instructed to remain at rest if the response tone was absent. To ensure reaction times remained similar to pre-test values, the stimulations following the response tone were removed in 15% of the trials (i.e. 5 of 34); therefore reaction time could be monitored throughout the experiment. A 20s inter-trials interval with a 10% variance was used to allow sufficient time for participants to reposition between trials and prevent response signal anticipation. Trials in which EMG activity was recorded prior to or in conjunction with stimulations in any of the recorded muscles were considered non-valid and were excluded from analysis (control at rest mean: MEP = 2; CMEP = 2, cycling mean: MEP = 2; CMEP = 3, tonic mean: MEP = 1; CMEP = 2). The absence of voluntary contraction was analyzed using a 50ms mean rectified EMG activity recorded immediately prior to stimuli in all recorded muscles and compared between trials.

Electromyography

EMG activity was recorded in the flexor carpi radialis, anterior deltoid, triceps brachii and biceps brachii using pairs of Ag-AgCl surface electrodes (Kendall 130 foam electrodes conductive adhesive hydrogel) placed 2cm apart (centre-centre). A ground electrode was placed over the lateral epicondyle at the elbow. Skin preparation protocols for all recording electrodes included abrasive paper for dead epithelial cell removal and cleansing using isopropyl alcohol swabs. Impedance levels were kept < 5kOhms to obtain adequate signal-to-noise ratio. Data was collected on-line at 2kHz for off-line analysis using a CED 1401 interface and the Signal 5 (Cambridge Electronic Design Ltd., Cambridge, UK) software program. Signals were amplified (CED 1902) and filtered using a 3-pole Butterworth with cut off frequencies of 10-1000Hz.

Brachial Plexus Stimulation

Nerve stimulation was elicited in the resting biceps brachii using electrical stimulation of the brachial plexus over the supraclavicular fossa (Erb's point) with simulation parameters of a 200μs pulse duration at 100-250mA (DS7AH, Digitimer Ltd, Welwyn Garden City, Hertfordshire, UK). The cathode was placed in the supraclavicular fossa and anode over the acromion process. The electrical stimulation was gradually increased until the M-wave of the biceps brachii reached a plateau. The stimulation intensity was then increased by 10% to ensure maximal M-waves (Mmax) for the duration of the experiment. MEP and CMEP amplitudes were normalized to Mmax to account for potential changes in the peripheral excitability (Taylor, 2006). The onset latency of M-wave was also used to ensure the validity of the CMEP response, ensuring no activation of the ventral roots.

Transcranial Magnetic Stimulation

Stimulation of the motor cortex was delivered at the vertex of the skull using a circular coil (13.5cm diameter) attached to a Magstim 200 stimulator (Magstim, Dyfed, UK). Vertex was measured using the halfway distances from nasion to inion and from tragus to tragus and marked directly on the scalp for both measurements. The coil was held parallel to the floor with the current flow directed to preferentially active the left motor cortex. The coil was held by the researcher and coil positioning was realigned on the vertex and parallel to the ground to ensure reliability during each trial. Stimulation intensity was adjusted to elicit a resting threshold response of ≥50μV, in 50% of the trials (i.e. 4 out of 8 trials) in the biceps brachii. Stimulator intensity was then be increased by 20%. This stimulation intensity (mean = 66 ± 15% MSO) was then used for the remainder of the experiment. The CMEP amplitude was matched to the MEP

amplitude as closely as possible therefore the average amplitude of 8 MEPs elicited with this stimulation intensity was used to set the intensity for transmastoid stimulation. Transcranial magnetic stimulation was repeated for 12 trials, and then averaged.

Transmastoid Electrical Stimulation

Stimulation was applied via surface electrodes placed over the mastoid processes and current was passed between them (100μs duration, 100-350 mA; model DS7AH, Digitimer Ltd, Welwyn Garden City, UK). Stimulation intensity was adjusted to match CMEP amplitude to MEP amplitude as closely as possible. Stimulation was also adjusted to prevent ventral root activation. To ensure the ventral roots were not activated during the experiment, CMEP responses were monitored for a decrease in onset latency of ~2ms which would be indicative of ventral root activation (Taylor, 2006) (transmastoid stimulation was repeated for 12 trials, and then averaged).

Measurements

Data was analyzed off-line using Signal 5 software (CED, UK). Measurements of transcranial, transmastoid, and nerve stimulation included peak-to-peak amplitude and onset latency for MEPs, CMEPs and M-waves. MEPs and CMEPs were normalized to Mmax taken at the end of each condition (mean control at rest: 14.66 ± 3.27mV, mean cycling: 14.76 ± 3.29mV, mean tonic: 14.44 ± 3.35mV). The latency of MEP and CMEP onset was defined as the time between stimulation artifact and the point the voltage trace deviates from the horizontal baseline. The onset of EMG was defined as the point at which the rectified signal was ≥ 2 times the standard deviation of a 50ms window of EMG measured at rest (Power and Copithorne, 2013). Trials that contained EMG activity prior to or simultaneously with the stimulation, were deemed

invalid and removed from the analysis (a minimum of 8 MEPs/CMEPs per condition were required for statistical analysis).

Statistical Analysis

Tests of normality were performed. Conditions that were normally distributed according to the Kolmogorov-Smirnov normality test were then examined for statistical significance using repeated measures Anova. Conditions that were not normally distributed according to the normality test were then examined for significance using a non-parametric Friedman's analysis and a Wilcoxon matched-pair signed-rank test (i.e. MEP/Mmax amp and CMEP/Mmax amp). The independent variables were the testing conditions (i.e. control at rest, cycling and isometric contraction that was intensity matched to cycling). Analysis was completed off-line using SPSS 19.0 (IBM SPSS Statistics), to search for within-group and within-subject differences. For all comparisons a significance level of $P < 0.05$ was used. Group data are reported as means ± SD and shown as ± SE in the figures.

3.4 Results

Corticospinal excitability

Amplitude: MEP amplitudes were significantly greater immediately preceding both the cycling and tonic conditions in comparison to control (control at rest: 2.32 ± 0.78% of Mmax, cycling: 4.37 ± 0.58% of Mmax; $P = .022$, tonic: 4.32 ± 0.91% of Mmax; $P = .022$). TMS stimulation remained constant throughout the conditions for each subject. M-wave remained unchanged following each of the conditions ($P > 0.05$). Although MEPs were normalized to M-wave taken immediately following each condition experiment for statistical comparison, Fig.3a is an illustration using raw data to show the increases in MEP amplitude prior to the cycling and

isometric conditions in comparison to control (control at rest: 196μV, cycling: 778μV, tonic: 781μV). Fig.4a shows representation of the group data for the MEP amplitude increases prior to cycling and isometric contractions. MEP amplitude changes are increased during voluntary contraction (Martin et al., 2006), therefore the background mean rectified muscle EMG was measured 50ms prior to stimulus onset (EMG was measured in the flexor carpi radialis, anterior deltoid, triceps brachii and biceps brachii to ensure the testing arm was at rest, and trials with voluntary contraction were removed). Pre-stimulus EMG was not different between conditions ($P > 0.05$), results are visible in Fig.4c. Contraction intensity was analyzed using the mean rectified EMG between first cycling bursts and tonic contractions with no significant differences ($P > 0.05$). Group data for contraction intensity is visible in Fig.4d.

Latency: Fig.3b is an expanded view of the area outlined in Fig3a. This shows the MEP latency changes prior to the cycling and tonic conditions. The MEP latency is defined as the point the MEP begins to deviate from horizontal, and is measured from the beginning of the stimulation artifact (not shown in Fig3b). Arrows point to the area that this deviation occurs for the control, and cycling/tonic conditions. MEP latency of the group data for cycling and tonic conditions were significantly shorter than control (control at rest: 15.61ms ± 0.55, cycling: 14.05ms ± .24; $P = .026$, tonic: 14.24ms ± 0.14; $P = .029$), illustrated in Fig.4b. Fig.3b shows the control MEP latency at 15.2ms and the cycling and tonic MEP latency at 13.8ms for one subject.

Spinal motoneurone excitability was not altered prior to cycling or tonic conditions

Since corticospinal excitability was shown to be altered prior to the cycling and tonic conditions, spinal motoneurone excitability was also measured using transmastoid stimulation (see above methods) to determine if altered excitability was due to changes in the motoneurone.

Fig.5a illustrates group data that shows the CMEP amplitude was not statistically different between conditions ($P > 0.05$). CMEP latencies were also not affected by any of the conditions, seen in Fig.5b. CMEP amplitude can also be affected by increases in voluntary contractions, therefore the background mean rectified muscle EMG was measured 50ms prior to stimulus onset. EMG was measured in the flexor carpi radialis, anterior deltoid, triceps brachii and biceps brachii, and trials with above average activity in any of the muscles were removed. Pre-stimulus EMG was not different between conditions ($P > 0.05$), results are visible in Fig.5c. Contraction intensity was analyzed using the mean rectified EMG between the first cycling burst and tonic contraction with no significant differences ($P > 0.05$). Group data for contraction intensity is visible in Fig.5d.

3.5 Discussion

The purpose of this study was to assess supraspinal and spinal excitability prior to cycling and a tonic contraction. This study sought to determine if supraspinal and spinal excitability were modulated differently due to task-dependence (cycling vs. tonic contraction), and if stimulation placement closer to the onset of a motor output would affect spinal motoneurone excitability. The results demonstrate that corticospinal excitability is increased prior to motor output but was not task dependent. This was evident via an increase in the amplitude of the MEP and a decrease in the onset latency during both cycling and tonic contraction compared to control at rest. Spinal motoneurone excitability was not altered prior to motor output (i.e. no change in CMEP amplitude or onset latency). Therefore the observed changes in corticospinal excitability were due to an increase in supraspinal excitability.

Premovement increases in supraspinal excitability

Previously Power and Copithorne (2013) were unable to conclude with certainty that the pre-cycling increase in supraspinal excitability was due the cycling task or if it was simply due to a general premovement increase in corticospinal excitability. The current study assessed corticospinal excitability prior to a cycling and tonic contraction to determine if the modulation was task-dependent, but found no observable difference in excitability between the tasks. However, previous studies have found corticospinal excitability changes prior to different forthcoming tasks (Hiraoka et al., 2010; Marangon et al., 2013; Tax et al., 1990) . Hiraoka et al. (2010) showed that MEP amplitude was higher a sequential task when compared to a simple task. They concluded from the results that prior to a more complex motor output increased corticospinal excitability was required. The current study used bilateral arm cycling seen as a more complex task (i.e. number of muscles, joints and limbs involved) versus an isometric contraction viewed as more simple. If the excitability was modulated according to the forthcoming task, it would be expected to see a greater increase in excitability prior to arm cycling, which was not observed. The results of the current study found a general increase in corticospinal excitability prior to motor output that was not modulated differently between tasks.

The increase in MEP amplitude could be a result of increased intracortical facilitation (Nikolova et al., 2006) leading to enhanced input to the primary motor cortex from pre motor areas known to be involved in motor planning. There is also evidence of decreased interhemispheric inhibition of the motor cortex as the motor output approaches (Duque et al., 2007) which would result in an increase in excitability due to the decrease in inhibition. These mechanisms could result in an increase in the number of corticospinal neurones activated prior to the motor output, therefore increasing the MEP amplitude.

Premovement decreases in MEP latency

MEP latency has been previously shown to decrease prior to motor output (Power and Copithorne 2013, Hiraoka et al. 2010), which is indicative of a supraspinal excitability increase. Power and Copithorne (2013) showed an average decrease of 1.5ms in MEP onset latency prior to cycling compared to control at rest. When compared to control at rest with no intent to move, the MEP onset latencies were significantly shorter for each condition (cycling: 1.56 ± 0.75ms, P = .026; tonic: 1.37 ± 0.44ms, P = .029, see Fig.3). However, there was no difference between the cycling and tonic conditions, indicating that supraspinal excitability is increased prior to motor output regardless of the forthcoming task. TMS activates cortical motoneurones transynaptically, producing I waves that are separated by ~1.5ms intervals, thus less I waves were required during cycling and tonic contraction to activate the corticospinal motoneurones compared to control at rest according to the decrease of 1.5ms in MEP onset latency. This suggests a modulation of the firing threshold required to activate the cortical motoneurones, requiring a smaller summation of excitatory post-synaptic potentials (EPSPs) produced by the volley of descending I waves or that the descending I wave was larger causing a great excitation of the post-synaptic cell. Hiraoka et al. (2010) demonstrated a decrease in MEP onset that was larger prior to a sequential task compared to a simple task. The study (Hiraoka et al. 2010) referenced the Bereishaftspotential (Simonetta et al., 1991) (readiness potential) which has shown earlier onsets prior to more complex tasks, but the current study did not find differences between MEP onset latencies prior to the cycling or tonic contraction.

Spinal motoneurone excitability remained unchanged prior to movement

Since changes in MEP amplitude do not distinguish between supraspinal and spinal excitability, CMEPs were used to measure spinal excitability. Unlike MEPs produced by transcranial magnetic stimulation, CMEPs are not influenced by changes in cortical excitability (Taylor, 2006). Previous results by Power and Copithorne (2013) showed that spinal excitability remains unchanged prior to arm cycling. The same results were found in the current study along with the assessment of the task-dependent differences in cycling and tonic contraction. No changes in spinal excitability were found prior to either the cycling or tonic contraction, suggesting spinal motoneurone excitability remains unchanged prior to motor output regardless of the forthcoming task in humans. Power et al. (2010) using animal models, showed that spinal motoneurone excitability is modulated in a task-dependent manner, with an increase in excitability prior to rhythmic and alternating motor outputs (fictive scratch) and a decrease in excitability prior to an isometric motor output (stance phase). These excitability changes were the result of voltage threshold depolarization (fictive scratch) and hyperpolarization (stance phase), along with a suppression of the after-hyperpolarization phase of the action potential (fictive scratch). It was therefore hypothesized that if these changes occurred in humans they would manifest as an increase in CMEP amplitude prior to cycling and a decrease in CMEP amplitude prior to tonic contraction. Since no changes in spinal excitability were found prior to either motor output, it suggests that humans do not modulate spinal motoneurone excitability in the same way that an adult decerebrate cat does. In humans, premovement changes in spinal motoneurone excitability have been reported. Geertsen et al. (2010) found an increase in spinal motoneurone excitability (increase CMEP amplitude) in the antagonist soleus muscle when performing dorsiflexion. This study placed the stimulation closer to the motor output (~25ms)

than the previous Power and Copithorne (2013) study (~50ms). Therefore, it was hypothesized that the placement of the stimulation closer to motor output would produce spinal motoneurone excitability increases that were previously unchanged at ~50ms prior to motor output. However, the current study showed no spinal motoneurone excitability increases prior to motor output even as the stimulation was placed closer to movement onset (~25ms). The difference between the current study and the Geertsen et al. (2010) study was the use of the biceps brachii compared to the soleus, perhaps the biceps brachii requires a different stimulation timing. This increase in spinal excitability found by Geertsen et al. (2010) that was found in the antagonist muscles (soleus) during dorsiflexion, although inconsistent with the current study is perhaps the result of intramuscular differences between the upper and lower limb and/or differences in the antagonist and agonist muscles. The composition of biceps brachii and soleus muscle are very different with a larger portion of type 1 fibers making up the soleus (~85%), whereas the biceps brachii is ~50% type 1 fiber. Duclos et al. (2008) found a decrease in interspike intervals of the motoneurone firing rate which is indicative of an increase in motoneurone excitability through a decrease in after-hyperpolarization of motoneurone action potential. The Duclos et al. (2008) study look at isometric ballistic wrist extension (weak contraction prior to strong ballistic contraction of the wrist extensors), whereas the current study assessed spinal motoneurone excitability prior to cycling and tonic contraction during the quiescent period and found no changes in spinal motoneurone excitability.

3.6 Conclusion

The conclusion of the present study is that supraspinal excitability is increased but not spinal excitability prior to both cycling and tonic motor outputs. These findings suggest that supraspinal strategies prime the motor system in anticipation of motor output regardless of the

forthcoming movement. There is perhaps a point after the onset of motor output that supraspinal excitability will decrease and spinal motoneurone excitability will be increased during cycling. This has been suggested prior to a rhythmic and alternating motor output, thought to be partially generated by spinally located circuits referred to as central pattern generators (i.e. CPGs; Carroll et al., 2006). While supraspinal excitability will increase and spinal motoneurone excitability will decreased during tonic contraction that has yet to be observed. The current study measured corticospinal and spinal motoneurone excitability prior to movement at the 6 o'clock position; however, changes in excitability may be present with a different resting position (i.e. 3 o'clock position). These possibilities remain to be determined.

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3.8 Figure Legends

Fig.1. Experimental set-up. Participants were seated in front of the upper-body cycle ergometer and grasped the handle of the ergometer at the 6 o'clock position using the right hand. The left hand grasped the handle of the ergometer with the arm at the 12 o'clock position. The same position was used for all participants.

Fig.2. EMG recording from the right biceps brachii and experimental timing. The control shows a warning tone at 2s followed by a response tone 1s later (at 3s). Movement onset was determined by a visual deviation of the EMG from a horizontal baseline. Cycling and tonic show a stimulation potential evoked during the premovement period. The arrows represent stimulation onset and EMG onset, respectively. The stimulation was placed as closely to 25ms prior to EMG as possible, determined by the average onset of EMG in all muscles recorded.

Fig.3. Corticospinal excitability is increased prior to movement onset. A shows MEPs from one subject (rest = black, dotted; cycling = black, solid; tonic = grey, solid). The area outline in dotted lines represents the expanded timescale shown in b. B shows MEP onsets indicated by arrows (rest = black, dotted; cycling = black, solid; tonic = grey, solid). Onset latencies were 15.2ms for control and 13.8 for cycling and tonic.

Fig.4. Group data for MEP amplitude in A (mean ± SE; n = 10) for control, cycling and tonic conditions. Values are normalized to Mmax. The asterisk indicates a significant difference from control to cycling/tonic conditions. B shows MEP latency (mean ± SE, n = 10) with the asterisks indicating significant difference between control to cycling/tonic conditions. C represents pre-stimulus EMG values (mean ± SE, n = 10) for cycling and tonic using the mean rectified EMG

50ms prior to stimulus onset. D shows the contraction intensity measured using the mean rectified EMG of the first burst during cycling, and the same epoc during the tonic condition.

Fig.5. Group data for CMEP amplitude in A (mean ± SE; n = 8) for control, cycling and tonic conditions. Values are normalized to Mmax. No significant differences were found between conditions. B shows CMEP latency (mean ± SE, n = 10) with no significant difference between conditions. C represents pre-stimulus EMG values (mean ± SE, n = 10) for cycling and tonic using the mean rectified EMG 50ms prior to stimulus onset. D shows the contraction intensity measured using the mean rectified EMG of the first burst during cycling and the same epoc during the tonic condition.

3.9 Figures

Fig.1

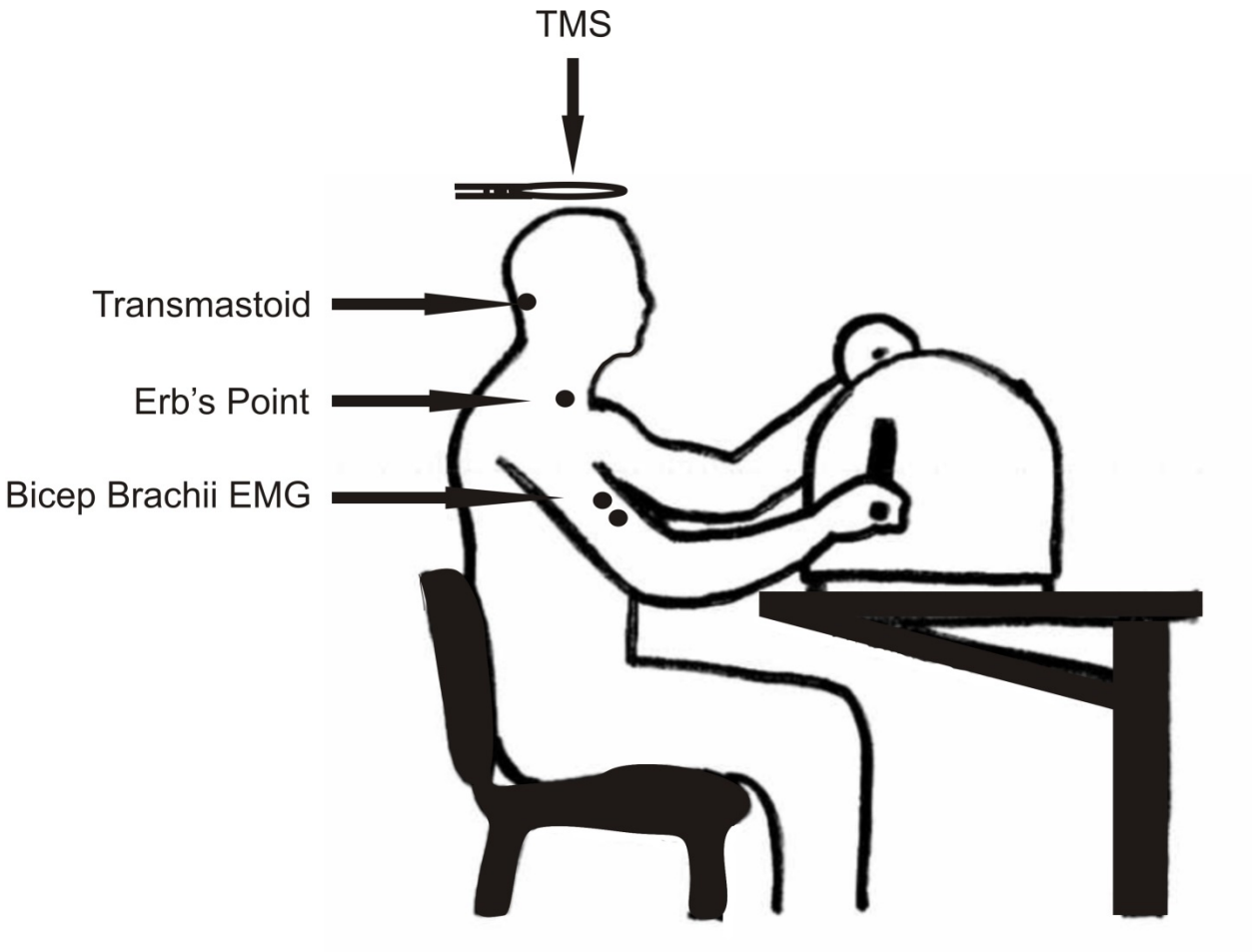


Fig.2

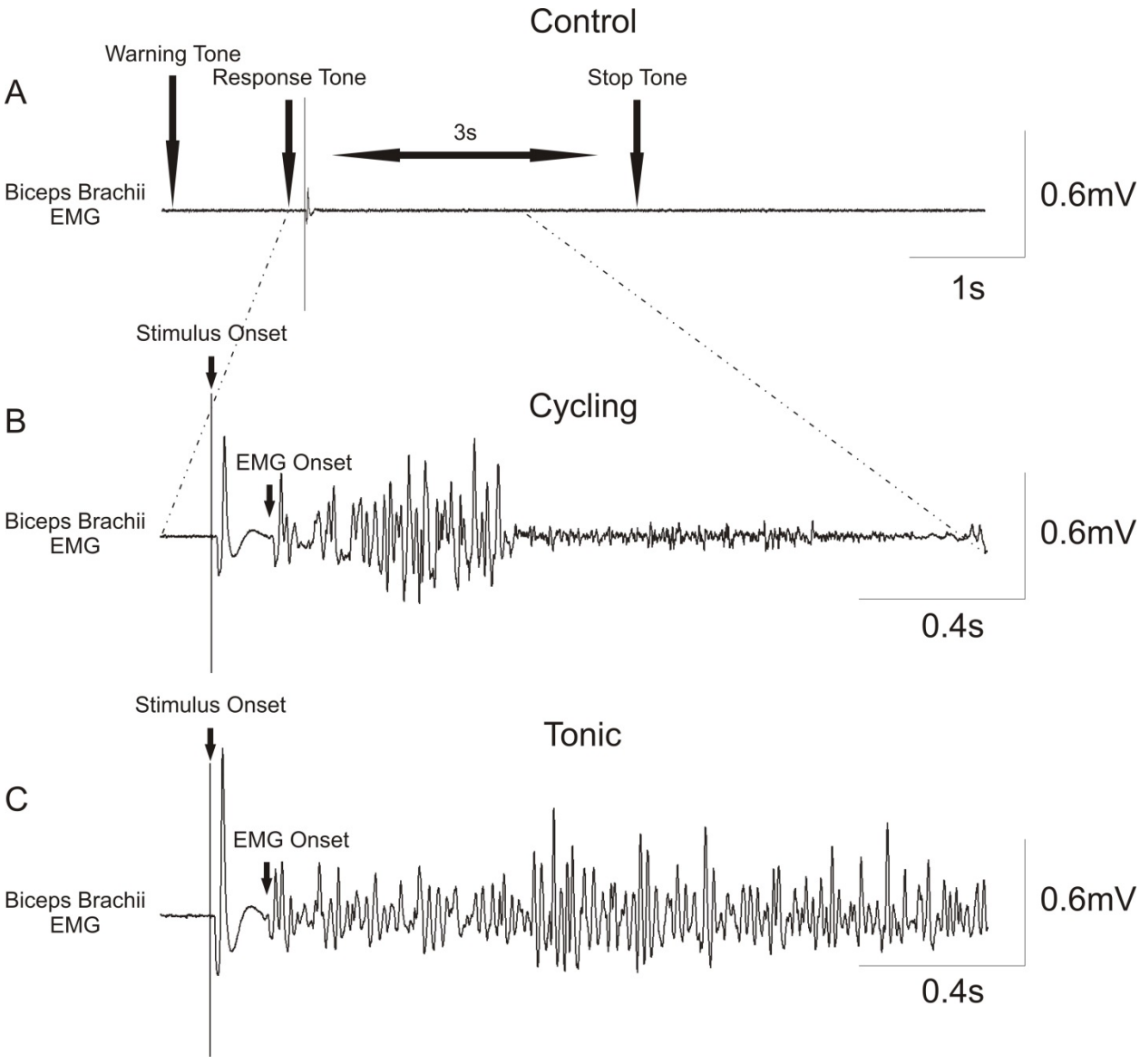

Control
Warning Tone
Response Tone
Stop Tone
A
3s
Biceps Brachii
EMG
0.6mV
1s
Stimulus Onset
B
Cycling
EMG Onset
Biceps Brachii
EMG
0.6mV
0.4s
Stimulus Onset
Tonic
C
EMG Onset
Biceps Brachii
EMG
0.6mV
0.4s

Fig.3

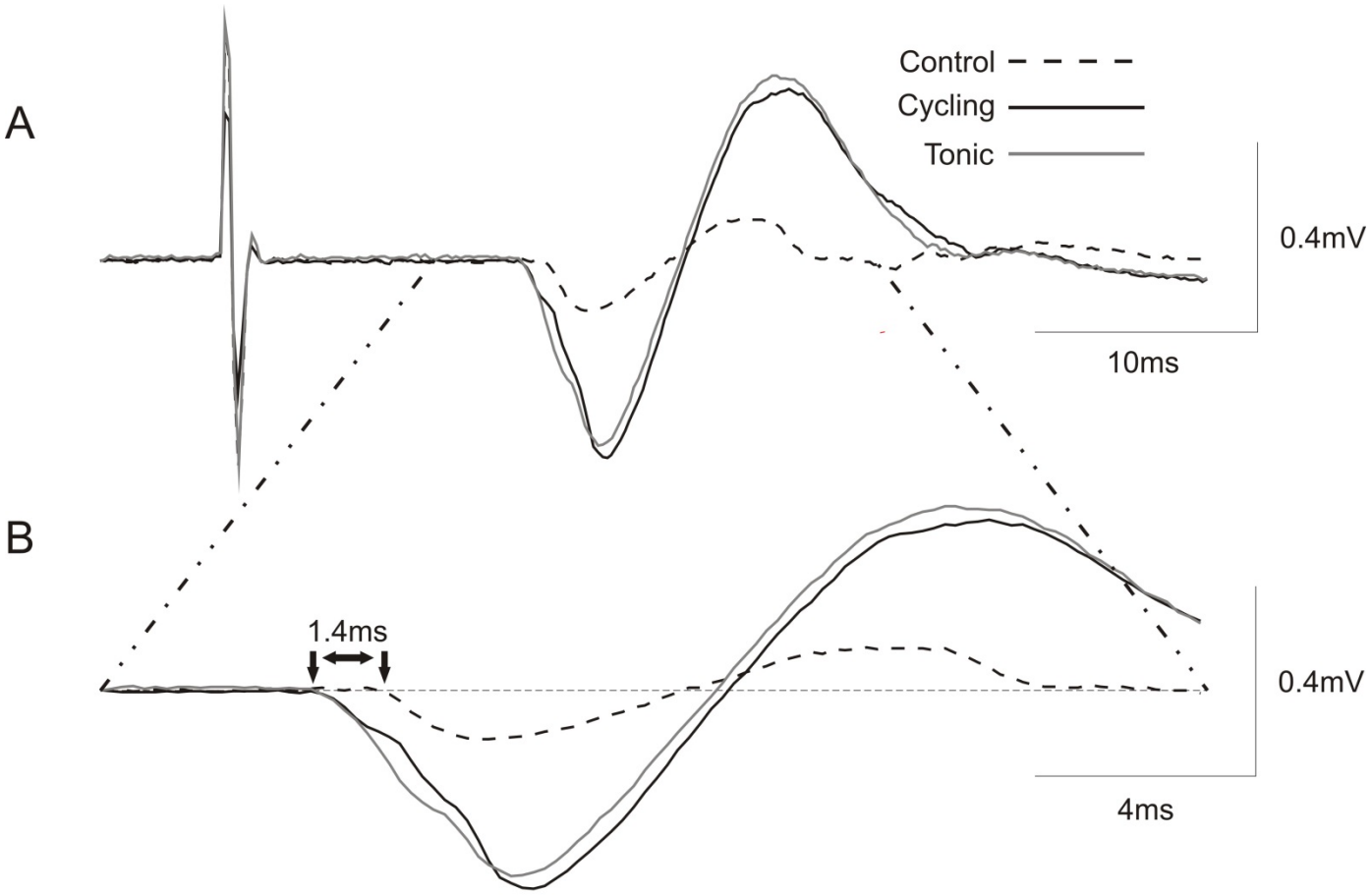


Fig.4

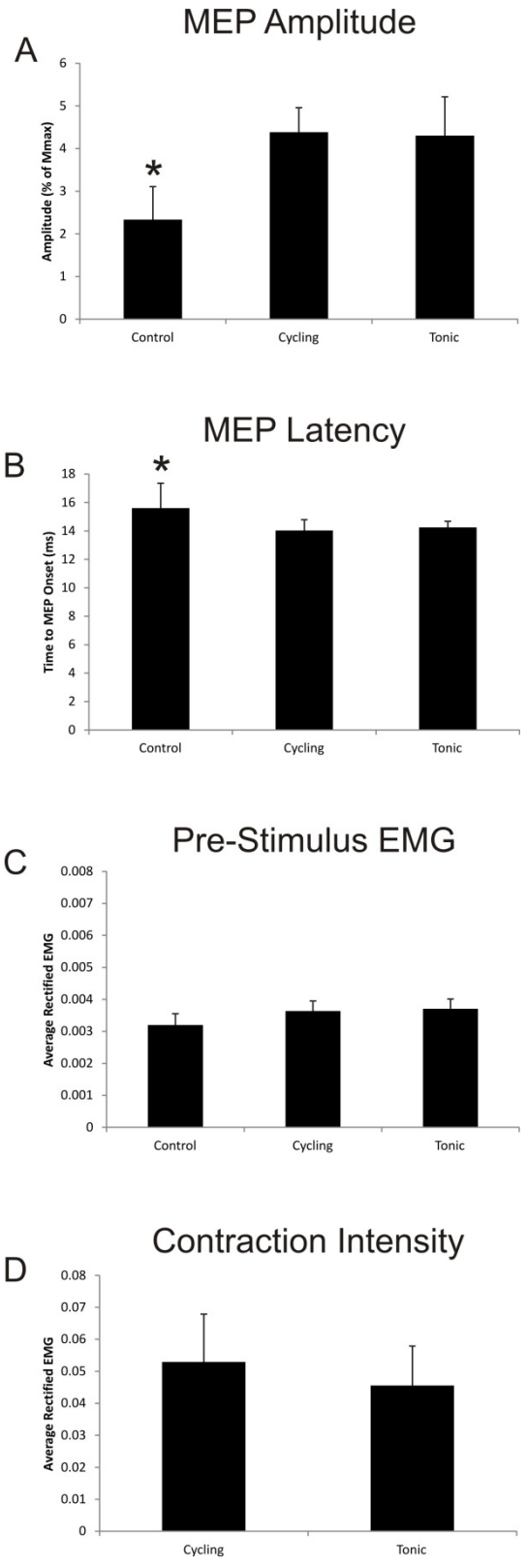
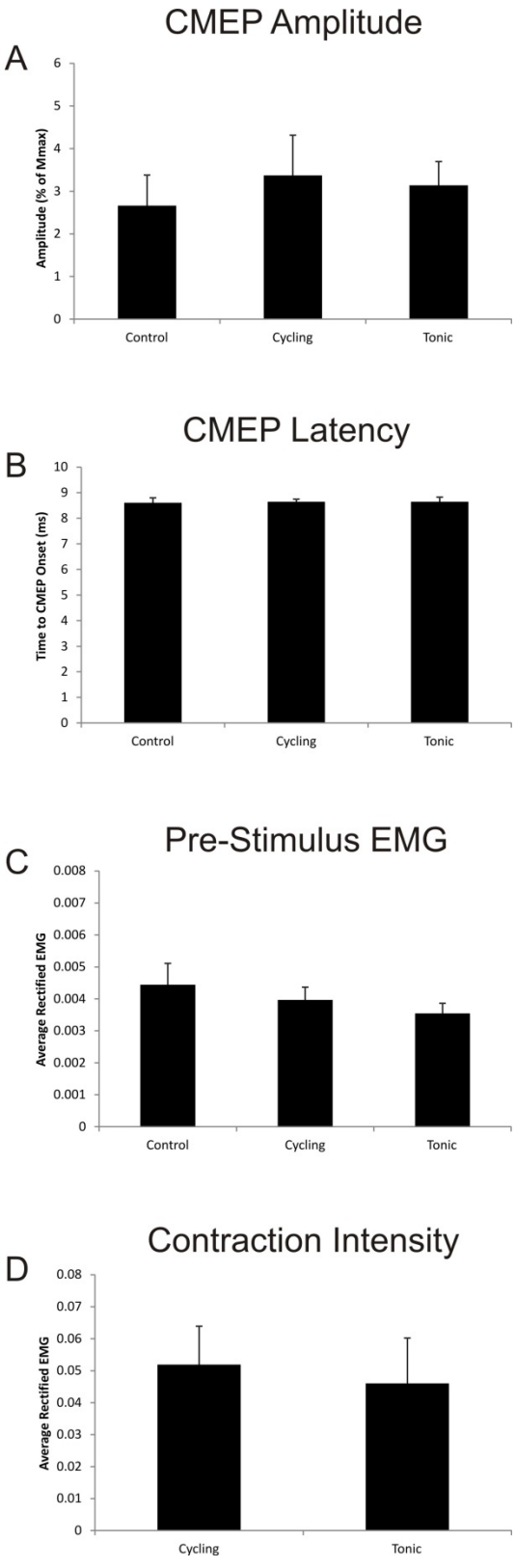

A
MEP Amplitude
Amplitude (% of Mmax)
0
1
2
3
4
5
6
*
Control
Cycling
Tonic
B
MEP Latency
Time to MEP Onset (ms)
0
2
4
6
8
10
12
14
16
18
*
Control
Cycling
Tonic
C
Pre-Stimulus EMG
Average Rectified EMG
0
0.001
0.002
0.003
0.004
0.005
0.006
0.007
0.008
Control
Cycling
Tonic
D
Contraction Intensity
Average Rectified EMG
0
0.01
0.02
0.03
0.04
0.05
0.06
0.07
0.08
Cycling
Tonic

Fig.5


CMEP Amplitude
A
Amplitude (% of Mmax)
0
1
2
3
4
5
6
Control
Cycling
Tonic
CMEP Latency
B
Time to CMEP Onset (ms)
0
1
2
3
4
5
6
7
8
9
10
Control
Cycling
Tonic
Pre-Stimulus EMG
C
Average Rectified EMG
0
0.001
0.002
0.003
0.004
0.005
0.006
0.007
0.008
Control
Cycling
Tonic
Contraction Intensity
D
Average Rectified EMG
0
0.01
0.02
0.03
0.04
0.05
0.06
0.07
0.08
Cycling
Tonic

4. Concluding Thoughts

The experiment has shown that premovement excitability is modulated regardless of the forthcoming task due to a general increase in corticospinal excitability. This general increase in excitation prior to intensity-matched cycling and isometric motor outputs is a novel addition to the understanding of how motor outputs are planned and executed. These findings may lead to the integration of select movement patterns or aspects of movement, into a rehabilitation intervention in order to initiate movements in patients suffering from neurological disease. Although this study has found that the excitability of the corticospinal tract appears to be modulated in a general sense prior to differing forthcoming tasks, this does not mean that the modulation of the corticospinal tract is by any means simple or predictable. Perhaps excitability modulation would manifest differently for tasks involving more fine motor control, such as a movement involving precision use of the hand muscle to touch or grasp objects. The addition of a goal-oriented task in which the subjects are given a choice between an incorrect or correct execution of the movement, may result in excitability modulation different from the examined motor tasks. This may lead to future projects in which these ideas would be examined.

4.1 Future Goals

In the future, the researchers involved in this project could focus on other task-oriented motor outputs, the addition of a final goal for the tasks instead of just gross movement, and/or the addition of other muscles involved within the task to examine corticospinal excitability thoroughly. The addition of a goal to the pre-planned movement, such as the selection of different objects to grasp, may require additional or different activation of the supraspinal centres to ensure correct object and/or movement selection. This additional excitation and planning may

result in differing modulation of corticospinal excitability when compared to gross movements such as cycling or an isometric contraction. Perhaps prior to the forthcoming task, synergistic musculature involved would be excited in a different fashion then the biceps brachii. The brachioradialis or flexor carpi radialis (involved in grasping the handle) may be modulated differently according the forthcoming movement pattern. Although these ideas could be implemented into future projects involving premovement, some limitations will arise.

4.2 Limitations

The limitations of the current study included the placement of stimulation at 25ms prior to movement onset and the variability of MEP and CMEP signals. To place the stimulation 25ms prior to movement was dependent of the pattern of muscle onset involved in the movement. For example, if the hand were to grip the handle before the biceps brachii began to contract (as evident via an increase in FCR activity), then the placement of stimulation would have to be adjusted according to the timing of the FCR. Since contraction of the FCR would affect the excitability of the biceps brachii, stimulations may be placed closer to movement onset or farther away in relation to the muscle of interest (biceps brachii). This resulted in a range of stimulation around 25ms but not exclusively at 25ms. If this study were to be repeated then perhaps the stimulation placement could be measured as separate variable, placed into accurate timing epochs (i.e stimulation 0-20ms prior to onset, 20-40ms, 40-60ms, etc.). This would allow the researcher to examine exactly how the timing of the stimulation can affect corticospinal excitability. Also the variability of the MEP and CMEP signals results in the addition of more stimulation to provide an accurate average. For example, if too few signals are collected, a single large or small MEP/CMEP can greatly affect the average amplitude change (excitability) prior to a forthcoming task. Therefore, additional stimuli could provide more accurate insight into the

excitability changes, however, this increases the time involved in data collection and the amount of time the subject remains stationary which can become uncomfortable. Although there is no other solution to decreasing the variability of a MEP or CMEP, this study has provided insight to the researchers as to how many stimuli may be too many or too little.