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Modulation of corticomotor excitability during passive and active wrist flexion and extension

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MODULATION OF CORTICOMOTOR EXCITABILITY DURING PASSIVE AND ACTIVE WRIST FLEXION AND EXTENSION

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This thesis is presented in fulfilment of the requirements for the degree of
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ABSTRACT

Various mechanisms may alter corticomotor excitability to agonist and antagonist muscles during passive and active limb movement depending on parameters of movement and their functional role. A better understanding of these relationships is important for understanding basic motor control mechanisms, and may be relevant to motor rehabilitation programs after brain injury. The purpose of the present study was to compare changes in corticomotor excitability to wrist flexor and extensor muscles during different phases of movement (flexion/extension), and at rest and during actively or passively-mediated length changes.

Motor evoked potentials (MEP) of the flexor carpi radialis (FCR) and extensor carpi radialis (ECR) were recorded from 17 participants during resting and four movement conditions (passive wrist flexion and extension, active wrist flexion and extension) with their palm inserted into a hand piece. Passive and active movements were carried out by moving the hand piece for 22.5° wrist flexion and 22.5° wrist extension from the neutral wrist position of 0° at a cycle rate of 1 Hz. Transcranial magnetic stimulation (TMS) was delivered at the neutral position (0°) every ten cycles to obtain 12 MEPs. The mean MEP amplitude was compared across the resting, lengthening and shortening phases for passive and active movements for the FCR and ECR separately by a paired t-test. Comparison was also made between FCR and ECR, and between passive and active movements by a two-way repeated measures ANOVA.

The MEP amplitude was significantly ($P<0.05$) reduced during passive lengthening for the FCR and ECR; but increased significantly during shortening only for the FCR compared with the resting state. In contrast, the MEP amplitude of the FCR and ECR increased in both active lengthening and shortening compared with the resting state, but the increase was significantly ($P<0.05$) greater for shortening than lengthening phase.

These results suggest that changes in corticomotor excitability are similar between the FCR and ECR, and between passive and active movements, and suggest that common underlying mechanisms exist in the modulation of corticomotor excitability during passive and active wrist movements.

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ABBREVIATIONS

APB: Abductor pollicus brevis

ECR: Extensor carpi radialis

EMG: Electromyography

FCR: Flexor carpi radialis

FDI: First dorsal interosseous

MEP: Motor evoked potential

ms: milliseconds

mV: millivolts

SEM: Standard error of mean

TMS: Transcranial magnetic stimulation

CHAPTER 1

INTRODUCTION

Transcranial magnetic stimulation (TMS) is widely used as a tool to evaluate cortical and corticospinal excitability by non-invasive stimulation of motor cortex and measurement of the amplitude of motor evoked potential (MEP) via electromyographic activity of the corresponding muscles (Barker, Jalinous, & Freeston, 1985; Butler & Wolf, 2007; Kobayashi & Pascual-Leone, 2003). The MEP amplitude reflects the number and firing rate of recruited corticospinal axons in response to the TMS, and the level of spinal excitability (Talelli, Greenwood, & Rothwell, 2006). The MEP response can be used as a prognostic indicator of motor and functional recovery in stroke patients such that the existence of MEP in response to TMS in patients with acute stroke indicates a favourable recovery, while the absence of MEP suggests a poor outcome (Escudero, Sancho, Bautista, Escudero, & Lopez-Trigo, 1998; Pennisi et al., 1999). However, it should be noted that the amplitude of MEP in response to TMS varies even among healthy individuals and the interpretation of the amplitude of MEP is qualitative rather than quantitative (Kobayashi & Pascual-Leone, 2003).

There has been interest in the use of TMS to investigate the response of MEP amplitude during movement. It is found that the amplitude of the MEP is affected by several factors such as muscle length, frequency of limb movement, range of movement, and TMS testing intensity (Coxon, Stinear, & Byblow, 2005; Lewis & Byblow, 2002; Lewis, Byblow, & Carson, 2001). For example, Lewis et al. (2001) investigated changes in corticomotor excitability for the flexor carpi radialis (FCR) and abductor pollicus brevis (APB) using single-pulse TMS during rhythmic passive wrist movements generated by a custom-made motorised device. They showed a decrease in MEP amplitude during muscle lengthening and an increase during muscle shortening for the FCR, but not for the APB which did not undergo length changes. They also found that the MEP amplitude for the FCR was more suppressed during muscle lengthening and more facilitated during muscle shortening at movement frequency of 1 Hz in comparison to the movement frequency of 0.2 Hz.

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Lewis & Byblow (2002) compared corticomotor excitability between the FCR and extensor carpi radialis (ECR) using single-pulse TMS during rhythmic passive wrist movements. They found that the MEP amplitude for the FCR and ECR decreased during muscle lengthening and increased during muscle shortening, and that this was more conspicuous at movement frequency of 0.2 Hz compared with 0.05 Hz. They also reported that the inhibition and facilitation of the MEP amplitude for the ECR were not as great as that for the FCR. They quoted a study by Cheney, Fetz, & Mewes (1991) which demonstrated that the extensor muscle has a lesser distribution of direct corticomotoneuronal pathways than the flexor muscle, and speculated that this might contribute to the reduced sensitivity of the ECR to length changes. They also explained the differences might also be due to a reduction of subject numbers as some were unable to maintain quiescence in the ECR during rhythmic passive wrist movements, and the determination of stimulus location and intensity for the ECR was based on the responses recorded in the FCR. Thus, the difference between the FCR and ECR found in the study needs further investigation.

Coxon et al. (2005) compared the changes in corticomotor excitability for the FCR and ECR using single-pulse TMS during rhythmic passive wrist movements at different TMS intensities, ranging from 30% to 90% of maximum stimulator output in 10% increments. They found that the MEP amplitude of the FCR and ECR were more suppressed during muscle lengthening and more facilitated during muscle shortening at higher TMS intensity. They also compared changes in corticomotor excitability for the FCR and ECR between two ranges of movements, 22.5° and 90° of wrist flexion-extension. They found that MEP amplitudes from the FCR and ECR were more facilitated during muscle shortening with 90° compared with 22.5° wrist flexion-extension movement; however, there was no significant difference in MEP amplitude during muscle lengthening between 22.5° and 90° wrist flexion-extension. Thus, it is important to standardise the factors influencing the MEP responses.

It is well known that there is a large cortical involvement during active or voluntary rhythmic muscle movements in healthy subjects. It has been shown that the MEP amplitude decreases during active muscle lengthening and increases during active muscle shortening of the elbow flexors (Abbruzzese, Morena, Spadavecchia, & Schieppati, 1994; Sekiguchi, Kimura, Yamanaka, &

Nakazawa, 2001) and soleus muscle (Sekiguchi, Nakazawa, & Suzuki, 2003) when compared with isometric contractions and between the lengthening and shortening phases. However, Sekiguchi et al. (2007) found that the MEP amplitude of the first dorsal interosseous (FDI) muscle increased during active muscle lengthening and decreased during muscle shortening when compared between muscle phases, and this contrasts with the findings based on the elbow flexors and soleus. Previous studies have not compared between FCR and ECR for the changes in MEP amplitude during active wrist movements. The FCR and ECR are an important muscle combinations involved in many activities closely related to daily living and dexterity, for example feeding and drinking. It is of interest to examine whether the MEP responses for the FCR and ECR during active muscle lengthening and shortening are similar to the FDI or elbow flexors and soleus.

Moreover, previous studies have also not systematically compared the MEP responses from the FCR and ECR during lengthening and shortening phases with passive and active wrist movements in one study. Various mechanisms may alter excitability to agonists and antagonists during movement, for example, reciprocal inhibition at the spinal level occurs in the antagonist muscle when the agonist muscle is voluntarily contracted (Nielsen, Petersen, Crone, & Sinkjaer, 2005). Thus, corticomotor excitability for the FCR (agonist) may increase and ECR (antagonist) may decrease during wrist flexion with the reverse during extension. However, whether this might differ with active and passive movements is not certain. The factors contributing to a change in corticospinal excitability may vary with active and passive movement and with parameters of movement, and will also depend on the functional role of the muscles during different movements. In this study, wrist flexor and extensor muscles (FCR and ECR) were chosen for their well-defined agonist-antagonist relationship during wrist movement, and the pattern of excitability changes was compared when these muscles were involved in different phases of movement (flexion/extension), or underwent actively or passively-mediated length changes.

More specifically, this study has investigated corticomotor excitability by measuring MEP amplitude from the FCR and ECR muscles in response to a change in muscle length during passive and active wrist movements (flexion

and extension) by standardising the frequency of movement (1 Hz), range of movement (45°) and testing intensity for individual muscle and participant.

Significance of the study

Passive and active movements are common approaches that therapists employ to rehabilitate individuals with motor deficits, for instance after a stroke. The present study will provide a better understanding of corticomotor excitability in the agonist and antagonist muscles during passive and active movements of wrist flexion and extension, and also help to understand the basic motor control mechanisms. Various mechanisms may alter corticomotor excitability to agonist and antagonist muscles during movement, and these mechanisms in turn will vary with active and passive movement and with parameters of movement, and will depend on the functional role of the muscles during different movements. A better understanding of these relationships is important for understanding basic motor control mechanisms, and may be relevant to motor rehabilitation programs after brain injury. One possible application might be that the use of active movements of the affected limbs may increase excitability of the affected hemisphere, whilst the use of passive movement of the unaffected limbs may decrease excitability of the unaffected hemisphere. This approach may help to stabilise the excitability between the two hemispheres after stroke.

CHAPTER 2

LITERATURE REVIEW

2.1 Sensory and motor pathways

Sensory information received from our limbs ascends from the spinal cord to the central nervous system for processing via the anterolateral and dorsal column system. The anterolateral system transmits pain and temperature information while the dorsal column carries information about the perception of touch and proprioception of the body (Cohen, 1999; Kandel, Schwartz, & Jessell, 2000). Therefore, the sensory input arising from limb movements in this study ascends to the central nervous system via the dorsal column pathway. The dorsal column pathway travels to the dorsal column nuclei in the medulla where it synapses and decussates, forming the medial lemniscus and continuing to the thalamus. The recipient nuclei in the thalamus project to somatosensory regions of the cerebral cortex. Sensory input from the limb provides important feedback to the motor pathways, assisting the guidance and production of smooth and coordinated fine movement, as well as aiding our perception and awareness of limbs (Cohen, 1999).

The primary motor cortex provides the final output for voluntary movement via the corticospinal tract. Motor commands are sent via pyramidal neurons in layer five of the primary motor cortex decussating at the medulla oblongata and descending the spinal cord to synapse on the cell body of alpha (α) or gamma (γ) motor neurons innervating the skeletal muscle (Canedo, 1997; Kandel et al., 2000). The α motor neurons innervate the extrafusal muscle fibres, which are responsible for producing force while the γ motor neurons innervate the intrafusal muscle fibres, which adjust the sensitivity of the muscle spindles (Kandel et al., 2000). Each α motor neuron axon divides into several terminals as it enters the muscle. Each axon terminal ending forms a neuromuscular junction with only one muscle fiber. Hence when the motor neuron fires an action potential, the muscle fibers that are innervated by this motor neuron would contract (Marieb & Hoehn, 2007).

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2.2 Sensory receptors

The ability to sense the position of limbs comes from the proprioceptive receptors in the muscles and joints (Naito, 2004). Generally, there are three types of mechanoreceptors in the muscles and joints (Cohen, 1999). They are stretch receptors in the muscle spindles, Golgi tendon organs and the joint receptors. The muscle spindle is located within a muscle and is sensitive to the rate of change in the muscle length. The muscle spindle is innervated by both sensory (afferent) and motor (efferent) axons. The velocity of the action potential conduction depends on the diameter of nerve axons and myelination; the larger the axon, the faster it can conduct (Kandel et al., 2000). Each muscle spindle is innervated by primary (or Type Ia afferent) and secondary (or Type II afferent) spindle afferent fibers. The primary spindle afferent fiber is considered more sensitive to dynamic changes in muscle length during lengthening while the secondary spindle afferent fiber provides information about static muscle length (Cohen, 1999).

While muscle spindles are sensitive to changes in muscle length during lengthening, Golgi tendon organs are sensitive to changes in muscle tension during muscle shortening (Castro, Merchut, Neafsey, & Wurster, 2002). Golgi tendon organs are found at the junction between the muscle tendon and a small group of extrafusal muscle fibers. These receptors send information along Type Ib afferent fibers to spinal cord. Golgi tendon organs are normally activated by muscle contraction and the activation of the Type Ib afferent fibers leads to the inhibition of motor neurons in the muscle that these fibers supplied (Cohen, 1999).

The joint receptors are only primarily activated towards the limits of joint movement and they serve as a limit detectors that prevent damage to the joint (Burke, Gandevia, & Macefield, 1988). They are innervated by separate nerve branches which includes nerve branches supplying the adjacent muscles and overlying skin. In addition, the cutaneous receptors, for example Ruffini endings, and Merkel cells, also provide proprioceptive information. These stretch-sensitive receptors have no directional specificity and they are activated in response to both flexion and extension movements (Castro et al., 2002). Collins, Refshauge, Todd, & Gandevia (2005) reported that there was an increase perception of flexion in finger, elbow and knee when strong skin stretch was

delivered during vibration of the muscle spindles around these joints. They concluded that inputs from the cutaneous receptors, muscle receptors or both were likely contributed to the kinesthesia at joints throughout the body.

2.3 Brain representation during passive and active movements

Passive and active movements are common methods used by therapists in rehabilitating individuals with motor deficits after a brain injury. Hence, there has been an interest in examining how the brain is activated during these movements. Modern neuroimaging techniques, for example functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) scanning allows the examination of brain activation during passive and active movements. Passive movement is defined as imposed movement of a joint without deliberate muscle contraction, hence it does not primarily involve the motor cortex, the limbic system, basal ganglia and other related subcortical nuclei (Cohen, 1999). The primary sensory cortex, located at postcentral gyrus, is the major source of somatosensory input to the primary motor cortex as it has direct connections to the primary motor cortex (Rossini, Calautti, Pauri, & Baron, 2003).

Carel et al. (2000) and Weiller et al. (1996) found that during passive wrist and elbow flexion-extension movements, the contralateral sensorimotor cortex, supplementary motor cortex and bilaterally inferior parietal lobe had an increased regional cerebral blood flow. Mima et al. (1999) reported only contralateral primary somatosensory area and inferior parietal lobe were activated during passive finger flexion-extension. They explained that it may due to the sensory afferents were too small to be detected in their study. Nevertheless, these studies (Carel et al., 2000; Mima et al., 1999; Weiller et al., 1996) demonstrated that there is a tight coupling between afferent somatosensory input and sensorimotor activation in the brain. Therefore, passive movements may serve as a useful rehabilitation method to aid in the brain reorganisation of individuals who are unable to move their extremities after a brain injury (Weiller, 1995). It is known that by helping a weakened patient to complete a movement through a normal range of motion may help to enhance somatosensory input involve in cortical plasticity, drive neural reorganisation and enhance movement planning (Carel et al., 2000; Mima et al., 1999; Nudo, Wise, SiFuentes, & Milliken, 1996; Weiller et al., 1996).

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During active elbow movement, the contralateral sensorimotor cortex, supplementary motor area, cingulated gyrus, bilaterally inferior parietal lobe and basal ganglia are activated with significant increased regional cerebral blood flow to these areas (Weiller et al., 1996). Similarly Mima et al. (1999) showed comparable brain activities during active finger movement. Although the locations of the brain activation in the primary sensorimotor cortex is almost identical during active and passive movements, the volume of regional cerebral blood flow is greater during active movements compared to passive movements (Weiller et al., 1996).

2.4 Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is one of the emerging investigative tools for motor cortex function and output, and is a promising development for neurorehabilitation (Young & Kong, 2007). Transcranial magnetic stimulation was introduced by Anthony Barker in 1985 (Barker et al., 1985). Preceding this, researchers had made unsuccessful attempts to stimulate the human brain through the scalp using trains of stimuli similar to those conventionally used to stimulate the exposed cortex during neurosurgery in the 1950s (Gualtierotti & Paterson, 1954). It was not until the early 1980s that the first clinical transcranial electrical stimulation (TES) method was devised to study the central motor pathways in healthy individuals and patients with particular condition such as multiple sclerosis, stroke and movement disorders (Merton & Morton, 1980). However, TES is not suitable for routine clinical purpose as only a small portion of the current flows into the brain to depolarise the neurons while most of the current flows between the electrodes on the scalp and causes local discomfort (Curra et al., 2002; Rothwell, 1997).

Transcranial magnetic stimulation has become the most popular method used by researchers because it is a non-invasive, safe and painless method of activating the motor cortex and assessing the connectivity of the central motor pathways (Hallett, 2000; Kobayashi & Pascual-Leone, 2003). This non-invasive method operates on the principle of electromagnetic induction (Kobayashi & Pascual-Leone, 2003). A powerful and rapid changing current is applied to a coil held over the scalp (Barker, 1999; Wassermann, 1998). A magnetic field is generated perpendicularly to the plane of the coil, inducing an eddy current that depolarises the neurons beneath (Barker et al., 1985; Hallett, 2000; Rothwell,

1997; Rothwell et al., 1999; Siebner & Rothwell, 2002). Figure-of-right shaped coils are commonly used to produce a more focal stimulation as the induced current at the intersection of two round coils is twice greater. The neurons are primarily activated indirectly through synaptic inputs from horizontally-aligned interneurons (Hallett, 2000; Ziemann, 2000). The depolarisation of the neurons will result in either facilitation or inhibition of brain activity depending on the frequency and intensity of the stimulation as well as the location where the magnetic coil is placed (Butler & Wolf, 2007). The corticomotor excitability is quantified by measuring the amplitude of motor evoked potential (MEP) via electromyographic activity of the corresponding muscles (Barker et al., 1985; Butler & Wolf, 2007; Kobayashi & Pascual-Leone, 2003). The MEP amplitude reflects the number and firing rate of recruited corticospinal axons in response to the TMS, and the level of spinal excitability (Talelli et al., 2006). The MEP response can be used as a prognostic indicator of motor and functional recovery in stroke patients such that the existence of MEP in response to TMS in patients with acute stroke indicates a favourable recovery, while the absence of MEP suggests a poor outcome (Escudero et al., 1998; Pennisi et al., 1999). However, it should be noted that the amplitude of MEP in response to TMS varies even among healthy individuals and the interpretation of the amplitude of MEP is qualitative rather than quantitative (Kobayashi & Pascual-Leone, 2003).

2.5 Corticomotor excitability during passive and voluntary movements

Studies using TMS have shown that constant stimulation of afferent input enhanced the excitability in the motor cortex (Carel et al., 2000; Lewis & Byblow, 2004). The single-pulse TMS technique has been used to assess the excitability of the motor cortex during movement. It is found that corticomotor excitability during movement is affected by several factors such as muscle length, frequency of limb movement, range of movement, and TMS testing intensity (Coxon et al., 2005; Lewis & Byblow, 2002; Lewis et al., 2001). For example, Lewis et al. (2001) investigated changes in corticomotor excitability for the flexor carpi radialis (FCR) and abductor pollicus brevis (APB) using the single-pulse TMS technique during rhythmic passive wrist movements generated by a custom-made motorised device. The authors reported a decrease in MEP amplitude during muscle lengthening and an increase during muscle shortening for the FCR, but not for the APB which did not undergo any significant muscle lengthening. They also found that the MEP amplitude for the FCR was more

suppressed during muscle lengthening and more facilitated during muscle shortening at movement frequency of 1 Hz in comparison to the movement frequency of 0.2 Hz.

Lewis & Byblow (2002) compared corticomotor excitability between the FCR and extensor carpi radialis (ECR) using single-pulse TMS during rhythmic passive wrist movements. They found that the MEP amplitude for FCR and ECR decreased during muscle lengthening and increased during muscle shortening, and this was more conspicuous at movement frequency of 0.2 Hz compared with 0.05 Hz. They also reported that the inhibition and facilitation of MEP amplitude recorded from the ECR were not as great as those from the FCR. They cited a study by Cheney, Fetz, & Mewes (1991) which indicated that the extensor muscle has a lesser distribution of direct corticomotoneuronal pathways than the flexor muscle, and speculated that this might contribute to the reduced sensitivity of the ECR to length changes. They also explained the differences might be due to a reduction of subject numbers as some were unable to maintain quiescence in the ECR during rhythmic passive wrist movements, and the TMS stimulating location and intensity for the ECR were based on the responses recorded in the FCR. Thus, the difference in MEP amplitude between the FCR and ECR found in the study was uncertain and requires further investigation.

Coxon et al. (2005) compared the changes in corticomotor excitability for the FCR and ECR using single-pulse TMS during rhythmic passive wrist movements at different TMS intensities, ranging from 30% to 90% of the TMS stimulator output in 10% increments. They found that the MEP amplitude of the FCR and ECR were more suppressed during muscle lengthening and more facilitated during muscle shortening at a higher TMS intensity. They also compared changes in corticomotor excitability for the FCR and ECR between two ranges of movements, 22.5° and 90° of wrist flexion-extension. They found that the MEP amplitudes from the FCR and ECR were more facilitated during muscle shortening with 90° compared to 22.5° wrist flexion-extension movement, however, there was no significant difference in MEP amplitude during muscle lengthening between 22.5° and 90° wrist flexion-extension. Thus, in order to better understand the changes in corticomotor excitability, it is important to standardise the various factors that influencing the MEP responses.

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It is well known that a large cortical involvement is observed during active or voluntary rhythmic muscle movements in healthy subjects. It has been shown that MEP amplitude decreases during active muscle lengthening and increases during active muscle shortening of the elbow flexors (Abbruzzese et al., 1994; Sekiguchi et al., 2001) and soleus muscle (Sekiguchi et al., 2003) when compared with isometric contractions and between lengthening and shortening phases. However, Sekiguchi et al. (2007) found that the MEP amplitude for the first dorsal interosseous (FDI) muscle increased during active muscle lengthening and decreased during muscle shortening when compared between muscle phases, which was in contrast to the findings based on the elbow flexors and soleus. Previous studies have not compared between FCR and ECR for the changes in MEP amplitude during active wrist movements. The FCR and ECR are an important muscle combinations involved in many activities closely related to daily living, for instance, feeding and drinking. It is of interest to examine whether the MEP responses for the FCR and ECR during active muscle lengthening and shortening are similar to the FDI or elbow flexors and soleus muscles.

Previous studies indicate that Ia afferent input from muscle spindles is one of the factors that mediates corticomotor excitability during passive and active movements (Abbruzzese et al., 1994; Coxon et al., 2005; Edwards, Thickbroom, Byrnes, Ghosh, & Mastaglia, 2002, 2004; Lewis & Byblow, 2002; Lewis et al., 2001; Sekiguchi et al., 2001). Increased corticomotor excitability during muscle shortening was associated with a reduction in muscle spindle activity, while decreased corticomotor excitability was associated with an increase in muscle spindle actvities during muscle lengthening. The contribution of the joint and cutaneous receptors is considered relatively small in comparison to that from the muscle spindles. This is because the limits of the joint were not reached and great skin stretch was not made. It is known that afferent inputs project to the motor cortex and this could potentially alter the excitability of descending corticomotor pathways. In addition, reciprocal Ia inhibition and Ib inhibition via interneurons are also likely to be involved in the agonist and antagonist muscles during passive and active movements (Nielsen et al., 2005). In order to maintain smooth coordination of agonist and antagonist muscle during wrist movements, reciprocal inhibition via the Ia inhibitory interneurons

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occurs in the antagonist muscle while Ib inhibition occurs in the agonist muscle. It seems likely that corticomotor excitability for the FCR (agonist) would increase and ECR (antagonist) would decrease during wrist flexion while corticomotor excitability for the ECR (agonist) would increase and FCR (antagonist) would decrease during wrist extension. The purpose of the present study was to investigate whether this phenomenon existed.

Although passive and active movements are common rehabilitation approaches employed by therapists, previous studies have not systematically compared the changes of corticomotor excitability for the FCR and ECR in different muscle phases during both passive and active wrist movements. It is well known that various mechanisms may alter corticomotor excitability to agonist/antagonist muscle pairs during movement. Thus, a better understanding of the changes in corticomotor excitability during passive and active movements is important for enhancing our understanding of the basic mechanisms governing motor control. Furthermore, this may potentially improve the design of motor rehabilitation programs after brain injury which is particularly relevant to therapists involved in neurorehabilitation.

CHAPTER 3
METHODS

3.1 Participants

Seventeen (11 male and 6 female) healthy participants, aged between 21 and 38 years old, volunteered for this study. All participants completed a brief medical history questionnaire indicating that they had neither neuromuscular and neurological disorders nor any musculoskeletal problems of the right wrist joint. The experimental procedures were explained clearly to the participants, and an informed consent was obtained from each participant. Ethical approval for the study was obtained from the Edith Cowan University Human Research Ethics Committee and the Ethics Boards at Sir Charles Gairdner Hospital, Western Australia. All participants were advised not to exercise before the experiment. Testing was commenced after participants had remained seated on a chair for at least 15 min.

3.2 Experimental setup

All participants were asked to report to the laboratory once and the testing session lasted approximately 90 – 120 min, including preparation time. The preparation time before the actual testing included the completion of the inform consent form, medical history questionnaire, skin preparation for electromyographic electrode placement and setting up of the custom-made wrist device. The testing was conducted in a quiet room, which was air-conditioned (20-25ºC). All participants were comfortably seated on a chair throughout the study with their right shoulder in a slight abduction (10°-20°), elbow joint angle at 90°-110°, with the forearm supported in a cradle of a custom-made wrist device (Figure 1). The height of the chair was adjusted to ensure that the forearm was comfortably rested in the cradle. Four 8-mm diameter Ag-AgCl electromyographic (EMG) electrodes were placed on the flexor carpi radialis (FCR) and extensor carpi radialis (ECR) muscles and a grounding cable was placed proximal to the elbow joint (Figure 2). The right palm was inserted in a hand piece that allowed flexion and extension of the wrist joint, and a goniometer (MLTS720, ADI Instruments, NSW) was attached to the wrist joint. The purpose of the hand piece was to minimise the afferent

input from participants' cutaneous skin receptors while it was moved by the investigator. Each participant was asked to rest their left hand comfortably on the table throughout the study.
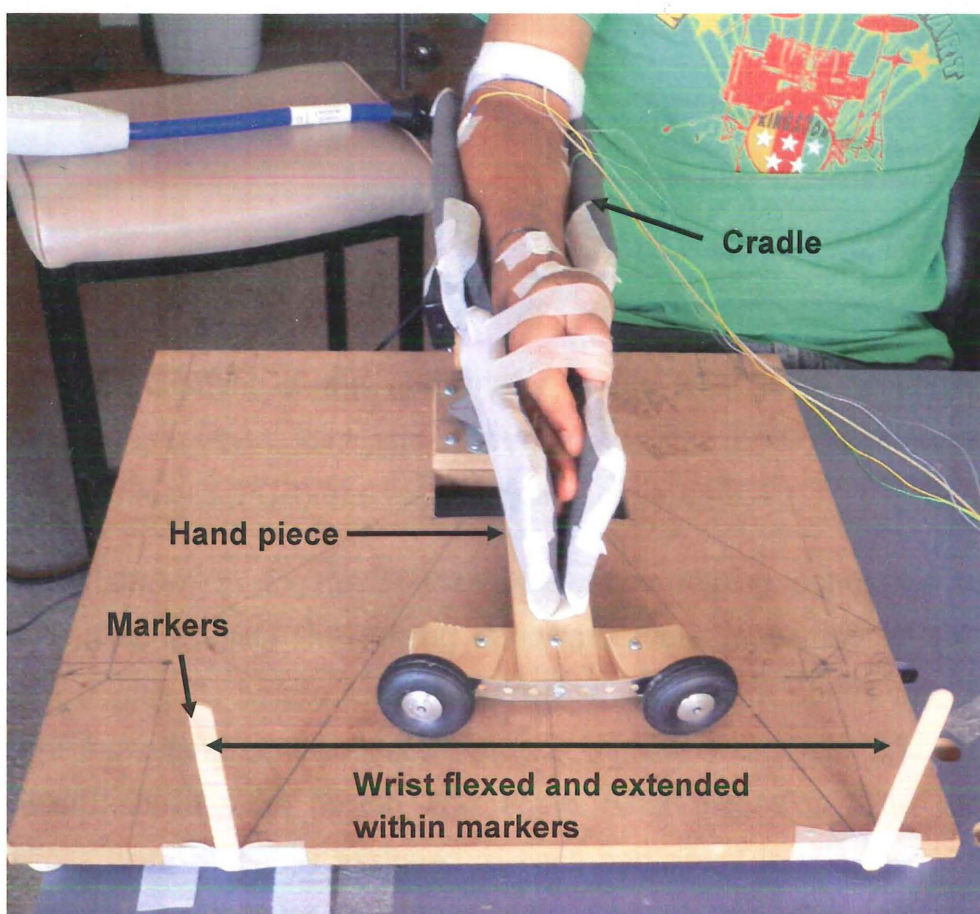
Figure 1. Custom-made wrist device. Participant's forearm is resting in the cradle with the palm inserted in the hand piece with wheels that allowed wrist flexion and extension movements. The markers specify the 45° range of wrist movement in the study (±22.5° wrist flexion, ±22.5° wrist extension about a neutral wrist angle of 0°). The participant's forearm is pictured in the 'neutral' position.
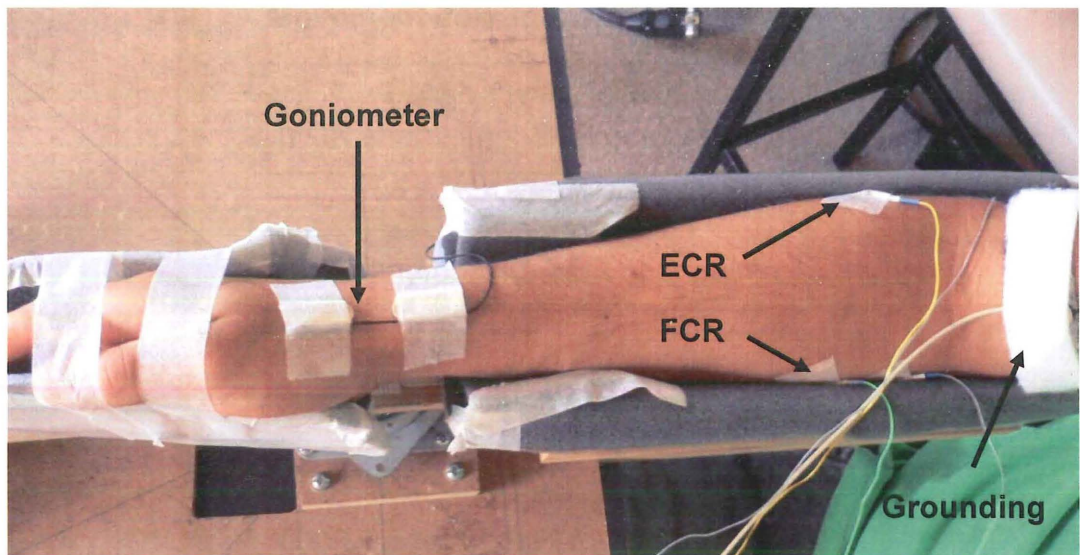
Figure 2. Placement of the goniometer at the wrist joint, grounding cable proximal to the elbow joint and electromyographic (EMG) electrodes at the flexor carpi radialis (FCR) and extensor carpi radialis (ECR).

As shown in Figure 3, there were two resting conditions and four movement conditions. The resting conditions were measured at the neutral position (Figure 1) before and after the four movement conditions. The four different movement conditions consisted of passive wrist flexion, passive wrist extension, active wrist flexion and active wrist extension. The movement conditions were randomly assigned to each participant to minimise a possible order effect. Five minutes of rest were given before and after each movement condition. Although changes in actual muscle length during the movements could not be measured, the muscle condition during the phase of wrist extension or flexion movement is referred to as 'lengthening' or 'shortening', depending on the muscle under consideration.

Movement conditions randomized

| Passive wrist flexion (FCR shortening, ECR lengthening) |
| Passive wrist extension (FCR lengthening, ECR shortening) |
| Active wrist flexion (FCR shortening, ECR lengthening) |
| Active wrist extension (FCR lengthening, ECR shortening) |

Resting ⟹ [four conditions] ⟹ Resting
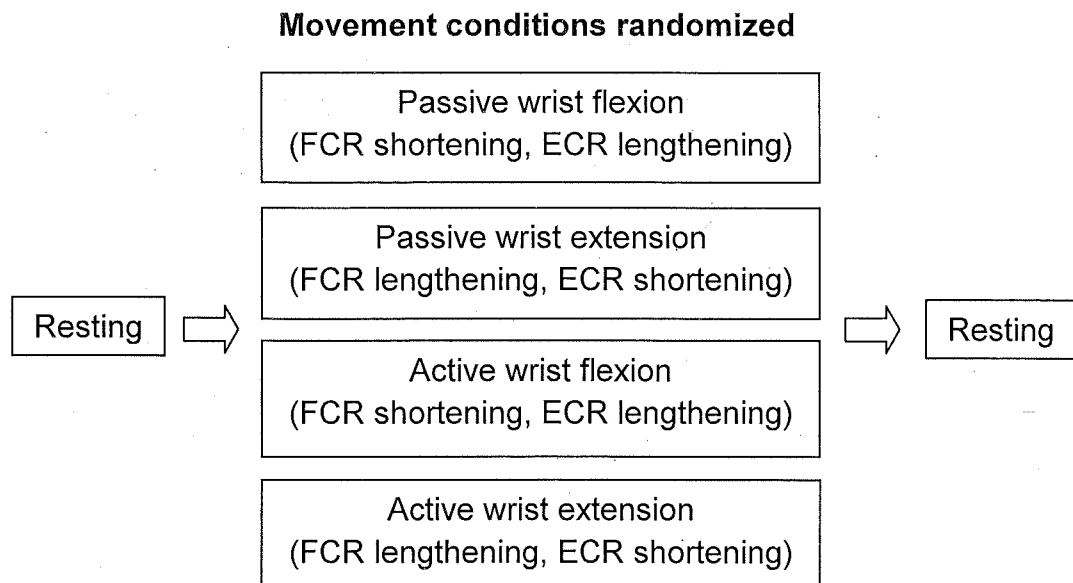
Figure 3. Experimental protocol. After the resting measures, four conditions (passive wrist flexion, passive wrist extension, active wrist flexion and active wrist extension) that were randomly assigned, followed by another resting measures. For the wrist flexion, when the flexor carpi radialis (FCR) was shortened, the extensor carpi radialis (ECR) was lengthened. Likewise during the wrist extension, when the FCR was lengthened, the ECR was shortened. A 5-min rest interval was given before and after every movement condition.

3.3. Resting condition

The resting MEP amplitudes were recorded with the right palm positioned at neutral position (0°) and participants were asked to remain relaxed and still while looking directly ahead. Participants were also advised not to look at their palm during stimulation to avoid any anxiety or anticipation which might affect the MEP amplitudes.

3.4. Passive movements

The investigator moved the participant's wrist passively through a movement of 45° (±22.5° wrist flexion, ±22.5° wrist extension) about a neutral wrist angle of 0° at a cycle rate of 1 Hz with the assistance of a metronome (Figure 4). One cycle movement was defined as the movement of the wrist from 22.5° flexed or extended position neutral position (0°) to 22.5° wrist extended or flexed position and back to the starting position. The passive movement of the wrist was carried out by the investigator holding the hand piece of the device. There was no contact with the hand of any participant throughout the study. The

goniometer was programmed to send a trigger signal to the TMS stimulator at the neutral position (0°).

Figure 4. Typical passive movement condition. An investigator is carrying out passive wrist movement for one participant in the study.

For the wrist flexion, the stimulus was delivered at the neutral position when the wrist moved from the 22.5° wrist extended position to the 22.5° wrist flexed position (Figure 5). For the wrist extension, the stimulus was also delivered at the neutral position when the wrist moved from the 22.5° wrist flexed position to the 22.5° wrist extended position. The wrist was passively moved for ten cycles to ensure the constant movement frequency before the stimulus was delivered. The stimulus was delivered every ten cycles and at least 120 cycles were required to obtain 12 MEPs.

(A)   (B)
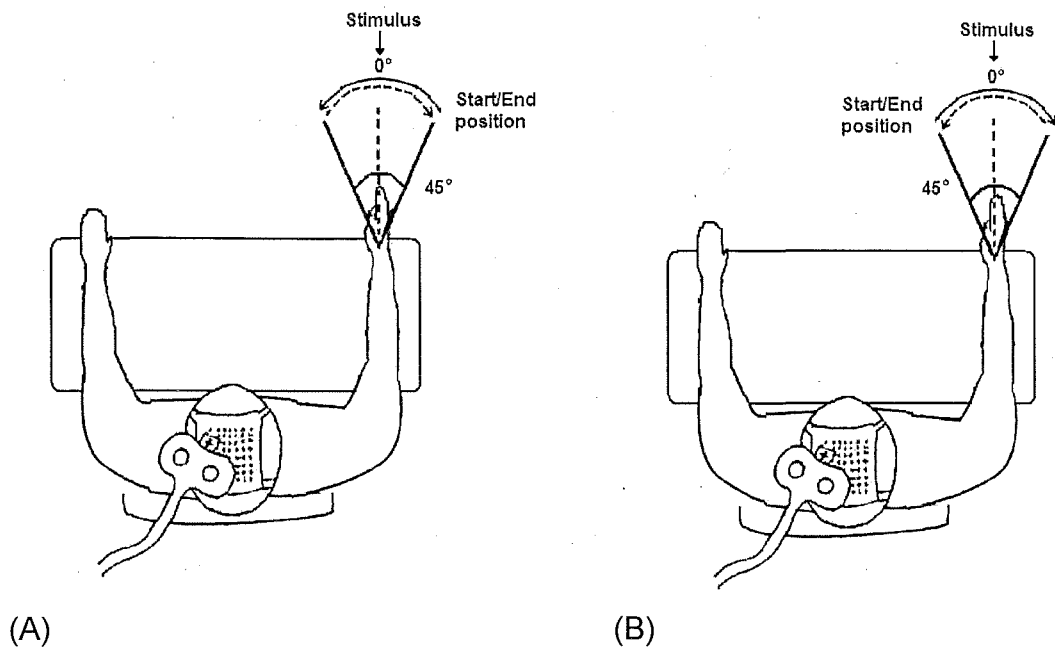
Figure 5. Range of movement. One movement cycle is defined as one complete movement of wrist from either 22.5° flexion/extension via the neutral position (0°) to extension/flexion and back to the starting position. (A) Stimulation at wrist flexion phase. The stimulus is delivered at the neutral position (0°) when the wrist initially moves from 22.5° wrist extension through (0°) to 22.5° wrist flexion and then back to the starting position. (B) Stimulation at wrist extension phase. The stimulus is delivered at the neutral position (0°) when the wrist initially moves from 22.5° wrist flexion through (0°) to 22.5° wrist extension and then back to the starting position. (Adapted from Coxon et al., 2005)

3.5 Active movements

The participants were asked to actively move their wrist through a 45° flexion-extension about a neutral wrist angle of 0° at a cycle rate of 1 Hz, timed by a metronome. Two markers were fixed to the device to show the outer limits range of movement (Figure 1). The participants practiced the movement rhythm until they felt comfortable performing it correctly. The TMS stimulator was triggered by a goniometer and stimulus was delivered at the neutral position for the wrist flexion and extension tasks respectively as explained in the passive movements (Figure 5). Similarly, the stimulus was delivered every ten cycles and at least 120 cycles were required to obtain 12 MEPs.

3.6. Transcranial magnetic stimulation

Single-pulse TMS was delivered through a Magstim 200 magnetic stimulator (Magstim Company, Dyfed, UK) connected to a 70mm figure-of-eight coil (Magstim Company, Dyfed, UK). The participant wore a tight fitting latex cap with pre-marked grid locations (1 cm apart), which was securely fastened to the head by velcro straps (Figure 6).
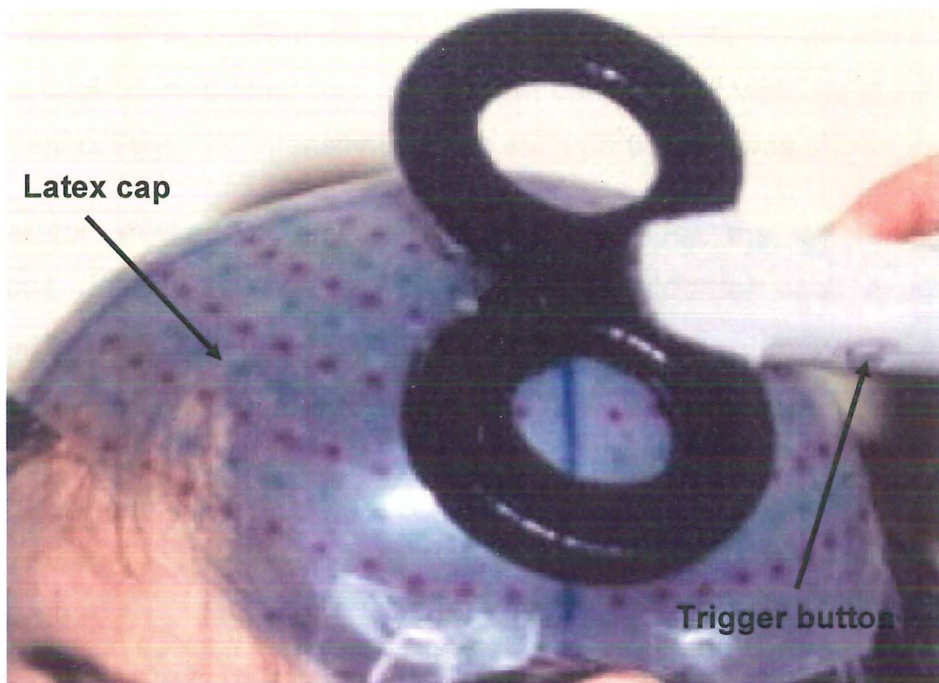
Figure 6. Placement of the transcranial magnetic stimulation (TMS) coil. A participant is wearing a tight latex cap with pre-marked grid locations. The TMS coil is positioned over the motor strip of left cortex at approximately 45° to the midline and tangential to the scalp. The trigger button is pressed to deliver a stimulus during resting and movement conditions.

The centre of the cap (0,0) was aligned to the vertex of the scalp (intersection of the inter-aural and nasion-inion lines). The TMS coil was positioned over the participant's left motor cortex oriented at an angle of approximately 45° to the midline and tangential to the scalp, such that the induced current flow was in a posterior-anterior direction across the motor strip of the cortex (Figure 6). This setup was shown to be optimal for activating the corticospinal pathways transynaptically (Kaneko, Kawai, Fuchigami, Morita, & Ofuji, 1996). The TMS coil was systematically moved around the pre-marked grid locations to locate the optimum stimulating position for the FCR and ECR by delivering four stimuli at each pre-marked grid location, until a clear MEP

amplitude was elicited. The optimum stimulating positions for the FCR and ECR were determined separately. The optimum stimulating position for each muscle was defined as a 'hot spot' and further stimuli were delivered at that position (Table 1). The placement of the TMS coil at the optimum position was checked repeatedly throughout the study to ensure that the stimulus was delivered at the desired position. The testing intensity for the FCR and ECR was also determined separately for each participant by altering the TMS stimulator output in 5% increment or decrement until a stable MEP amplitude between 0.5 to 1 mV was evoked in at least four out of eight consecutive trials for the FCR and ECR, respectively. The intensity used for each participant was shown in Table 1.

Motor evoked potentials were recorded for the six experimental conditions (Figure 3). Twelve MEPs were recorded for each experimental condition for analysis. In some participants, more stimuli were required to collect the required number of MEP responses. Resting MEPs were recorded before any of the movement conditions were carried out and then again recorded after all the movement conditions were completed.

Table 1. Optimum position (medial-lateral grid, anterior-posterior grid) and testing intensity used for the flexor carpi radialis (FCR) and extensor carpi radialis (ECR) of each participant.

Participant	FCR		ECR	
	Optimum position (cm)	Testing intensity (%)	Optimum position (cm)	Testing intensity (%)
1	5, 0	75	5, 0	75
2	5, 0	80	5, 0	80
3	5, 0	70	6, 0	65
4	4, 0	80	5, 0	80
5	6, 0	70	5, 0	50
6	5, -1	89	5, -1	80
7	6, 0	80	6, 0	65
8	5, 0	87	5, 0	73
9	6, 0	88	6, -1	75
10	5, -1	87	6, -1	75
11	6, 0	87	6, 0	70
12	6, -1	88	5, -1	55
13	6, -1	87	6, -1	67
14	6, -1	80	6, -1	50
15	5, 0	75	5, 0	56
16	6, 0	67	6, 0	56
17	6, 0	87	6, 0	66
Mean		81		67
SEM		2		2

3.7. Electromyography

For the FCR and ECR, Ag-AgCl electromyographic electrodes were placed 2 cm apart in a bipolar configuration over each muscle belly. Each participant was asked to perform a light concentric wrist flexion and extension to ensure the location of the muscle belly of the FCR and ECR. Electromyographic (EMG) activities of the FCR and ECR were recorded separately. For each stimulus applied, 200 ms of post-stimulus EMG data was collected, and pre-stimulus data was also acquired to check if any unwanted muscle contraction occurred prior to the stimulus during resting and passive movement conditions, and muscle activities during active movement conditions. The EMG signals were amplified (x1000) using an in-house made amplifier and band-pass filtered between 30 and 3000 Hz. A miniature goniometer, connected to a PowerLab

4/30 System (ML866, ADI Instruments, NSW), was attached to the wrist joint (Figure 2) to trigger the TMS stimulator during passive and active wrist movements via a Chart 5.5 program (ADI Instruments, Bella Vista, NSW). The MEP amplitudes elicited were displayed and recorded using LabView software (National Instruments, Chatswood, NSW) and were then stored for off-line analysis.

3.8 Data processing

If any pre-stimulus EMG activities were recorded in the FCR or ECR during the resting and passive movement conditions then the recording was rejected. The root mean square (RMS) EMG activities during 200 ms prior to the stimulus of each response during resting, active muscle lengthening or shortening was analysed for noise signal during resting, and muscle activities during active movements (Figure 8). The peak-to-peak MEP amplitude (mV) was digitised using a Java Analyzer for Waveform Signals (JAWS) program developed in-house (Figure 7).

Mean MEP amplitudes and RMS EMG values were compared between resting, lengthening or shortening and passive or active movements for each muscle. For the comparison between the FCR and ECR, during active and passive movements, the MEP amplitude of each muscle was normalised to the resting MEP amplitude for that muscle.
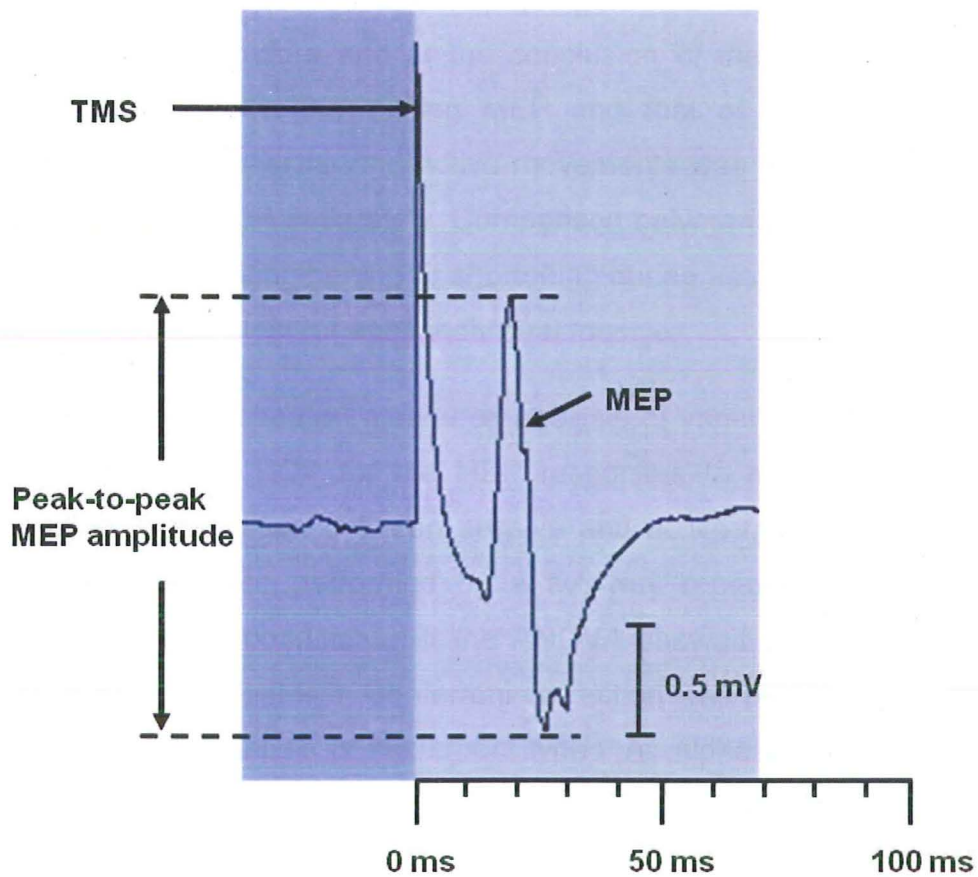
Figure 7. A waveform showing the stimulus and the peak-to-peak motor evoked potential (MEP) amplitude.
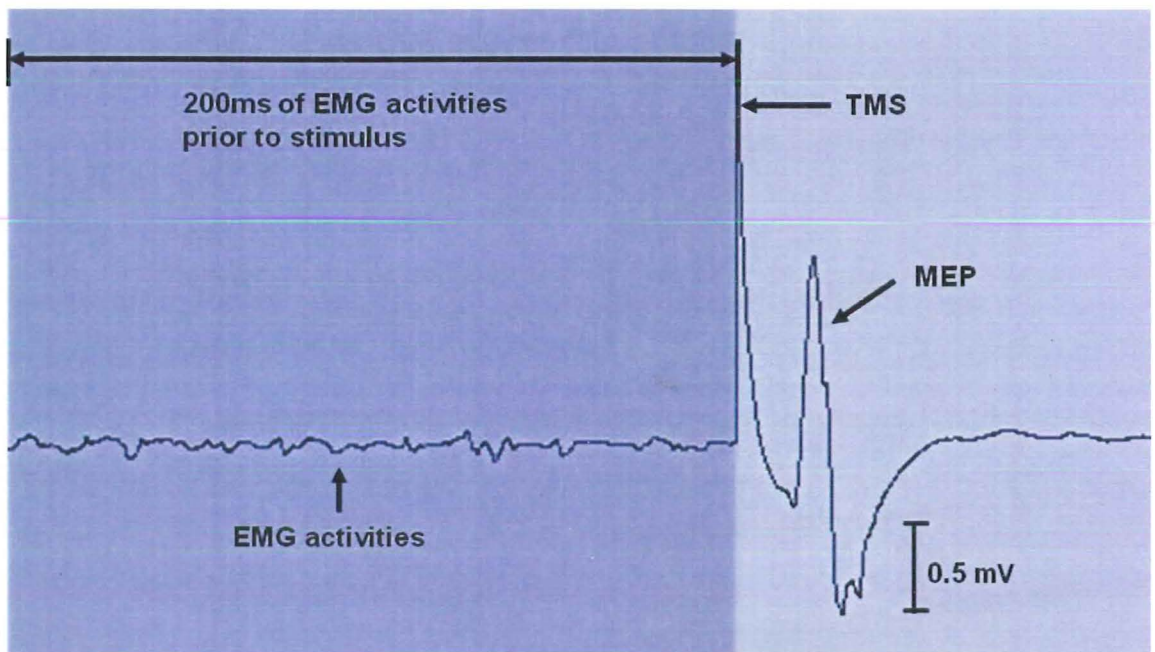
Figure 8. A waveform showing the pre-stimulus electromyographic (EMG) activities prior to stimulus during active movements.

3.9 Statistical analysis

A paired t-test was used to compare the two sets of resting MEP amplitudes taken before and at the conclusion of the movement recordings. Comparison between the resting MEP and that of muscle lengthening or shortening during passive and active movements was made by a paired t-test for the FCR and ECR separately. Comparison between the resting EMG values and that of muscle lengthening or shortening during active movements was also made by a paired t-test for each individual muscle.

A two-way repeated measures analysis of variance (ANOVA) compared between FCR and ECR for the MEP responses to muscle lengthening and shortening. Comparison between passive and active movements for the MEP amplitudes was also performed by a two-way repeated measures ANOVA (movement type x conditions). If the ANOVA showed a significant interaction effect, a Student t-test with Bonferroni correction was performed as a post-hoc test to compare muscles or movement types. An alpha value of 0.05 was used as the criterion for statistical significance. All data was presented as mean ± SEM.

CHAPTER 4

RESULTS

4.1 Resting

4.1.1 MEP amplitude of the FCR and ECR

The resting MEP amplitude measured before and after the movement conditions were not significantly different for the FCR (0.64 ± 0.06 mV vs 0.59 ± 0.07 mV, $P=0.169$) and ECR (1.08 ± 0.09 mV vs 1.16 ± 0.11 mV, $P=0.34$). Therefore, the average of 24 MEP amplitudes (12 before and 12 after the movement conditions) was used as the resting MEP amplitude, which was 0.62 ± 0.06 mV for the FCR and 1.12 ± 0.09 mV for the ECR. The resting MEP amplitude for the FCR and ECR were significantly different ($P<0.001$).

4.1.2 RMS EMG values of the FCR and ECR

The resting RMS EMG values represent the signal noise level. No significant difference in the RMS EMG values was evident for resting recordings taken before and after the movement conditions ($P>0.05$ for the FCR and ECR). Therefore, the pooled (before and after) RMS EMG data was used as a measure of signal noise level, and the value was 15.64 ± 0.95 μV for the FCR and 15.4 ± 1.1 μV for the ECR.

4.2 Passive movements

4.2.1 MEP amplitude of the FCR

The MEP amplitude during lengthening was significantly smaller (0.40 ± 0.04 mV; P=0.002; 65%), and the MEP amplitude during shortening was significantly greater (1.19 ± 0.23 mV; P=0.014; 192%) than that of the resting MEP amplitude (0.62 ± 0.06 mV) (Figure 9). A significant difference between lengthening and shortening (P=0.004) was also found.

Figure 9. Mean motor evoked potential (MEP) of the flexor carpi radialis (FCR) during resting, passive muscle lengthening and shortening.
* denotes significant difference between conditions.

4.2.2 MEP amplitude of the ECR

As shown in Figure 10, the MEP amplitude during lengthening was significantly smaller than at rest (0.76 ± 0.12 mV vs. 1.12 ± 0.09 mV; P=0.02; 68%). However, while the MEP amplitude during shortening was greater than at rest (162%), this did not quite reach statistical significance (1.8 ± 0.4 mV; P=0.067). A significant difference between lengthening and shortening was also found (P=0.012).

Figure 10. Mean motor evoked potential (MEP) of the extensor carpi radialis (ECR) during resting, passive muscle lengthening and shortening.

* denotes significant difference between conditions.

There was no significant difference between resting and shortening conditions.

4.2.3 Comparison between FCR and ECR

Figure 11 shows normalised FCR and ECR MEP responses to lengthening and shortening movements relative to the resting MEP amplitude. No significant difference between the normalised FCR and ECR was found during either lengthening or during shortening movement phases ($F_{2,32}=1.086$, $P=0.35$)
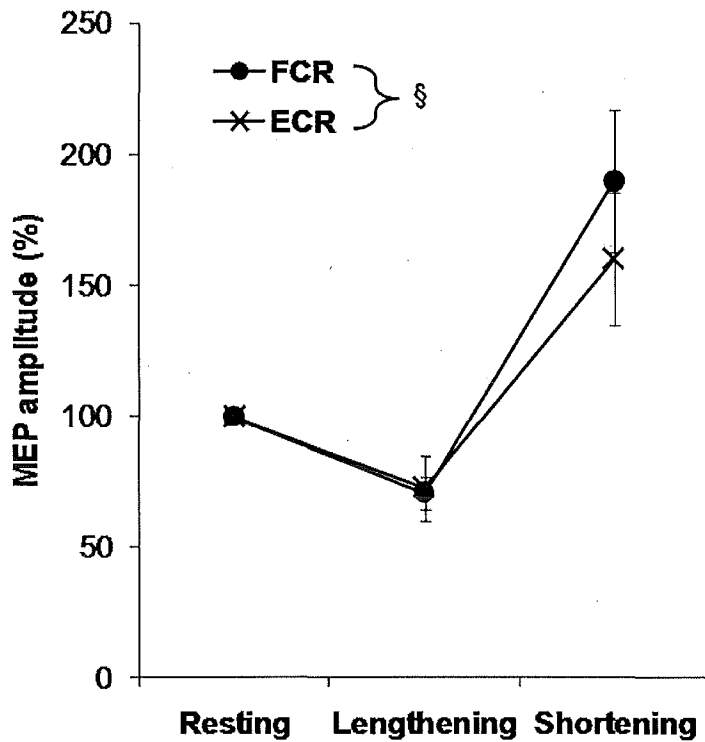
Figure 11. Comparison between the normalised mean motor evoked potiental (MEP) values of the flexor carpi radialis (FCR) and extensor carpi radialis (ECR) during passive movements.

§ denotes no significant difference between FCR and ECR.

However, when comparing the FCR and ECR MEP amplitude during wrist flexion and wrist extension phases as shown in Figure 12, significant differences were observed. During wrist flexion, the MEP amplitude of the FCR (190%) was significantly increased ($P<0.001$) compared to the ECR (73%). Correspondingly during the wrist extension, the MEP amplitude of the ECR (160%) was significantly increased ($P=0.002$) compared to the FCR (70%).

Figure 12. Comparison between the normalised mean motor evoked potential (MEP) of the flexor carpi radialis (FCR) and extensor carpi radialis (ECR) by resting value during passive wrist flexion and extension movements.

* denotes significant difference between conditions, S denotes muscle shortening, L denotes muscle lengthening.

4.3 Active movements

4.3.1 RMS EMG values of the FCR

The RMS EMG values during lengthening (18.9 ± 1.5 μV) and shortening (25.5 ± 1.9 μV) were significantly greater ($P<0.05$ for both) than that of the resting baseline (15.64 ± 0.95 μV). A significant difference was also found between lengthening and shortening ($P<0.001$).

4.3.2 MEP amplitude of the FCR

The MEP amplitude was significantly greater (1.53 ± 0.14 mV; $P<0.001$; 247%) during shortening than at rest (0.62 ± 0.06 mV), but was not significantly greater (0.91 ± 0.18 mV; $P=0.138$; 147%) during lengthening than at rest (Figure 13). There was a significant difference between lengthening and shortening ($P=0.01$).
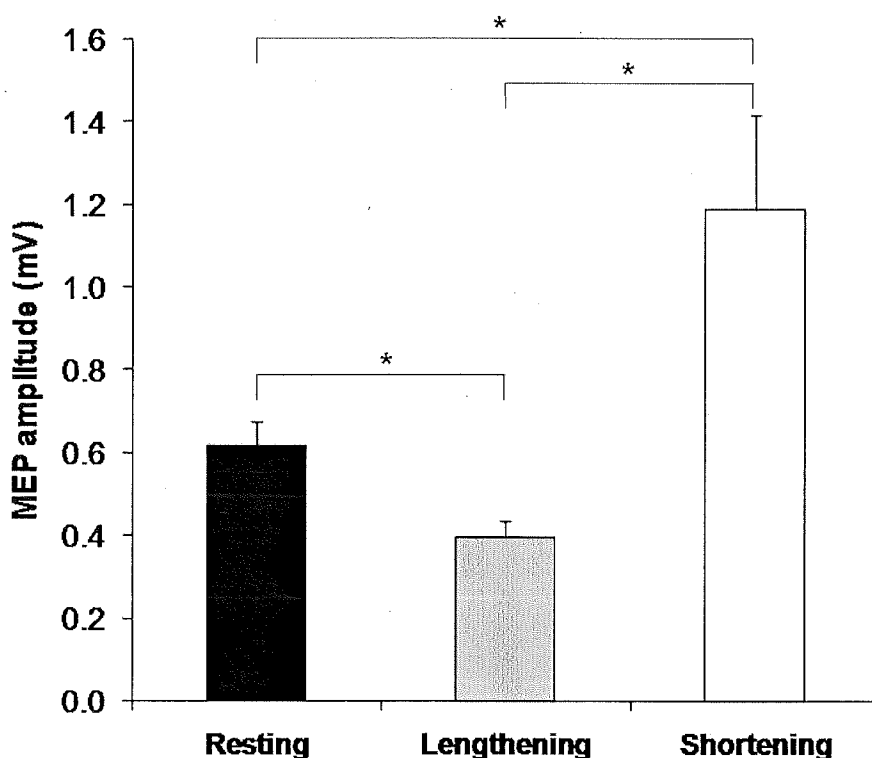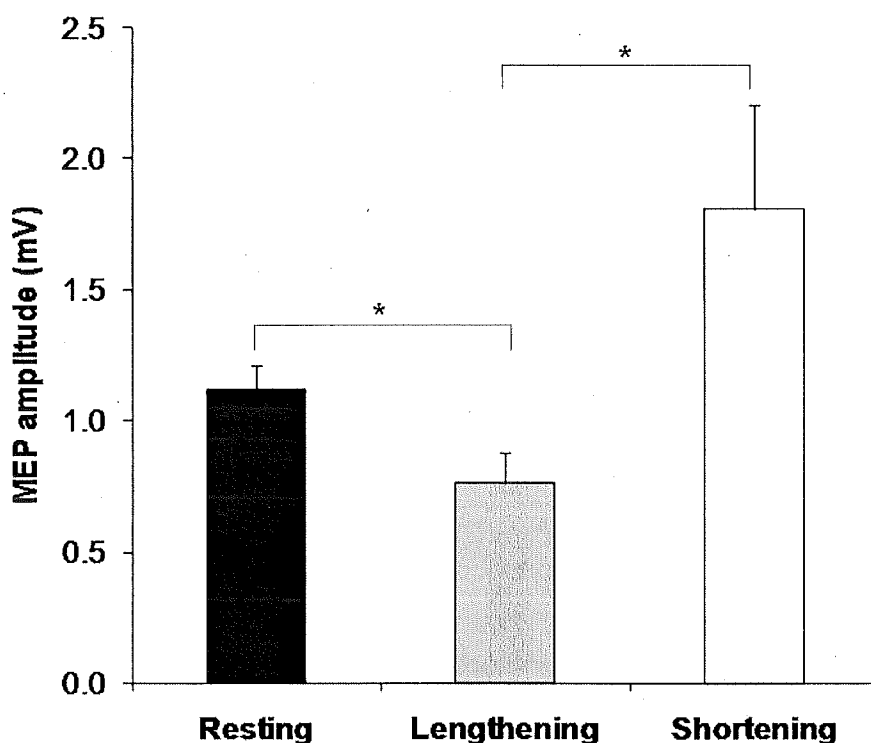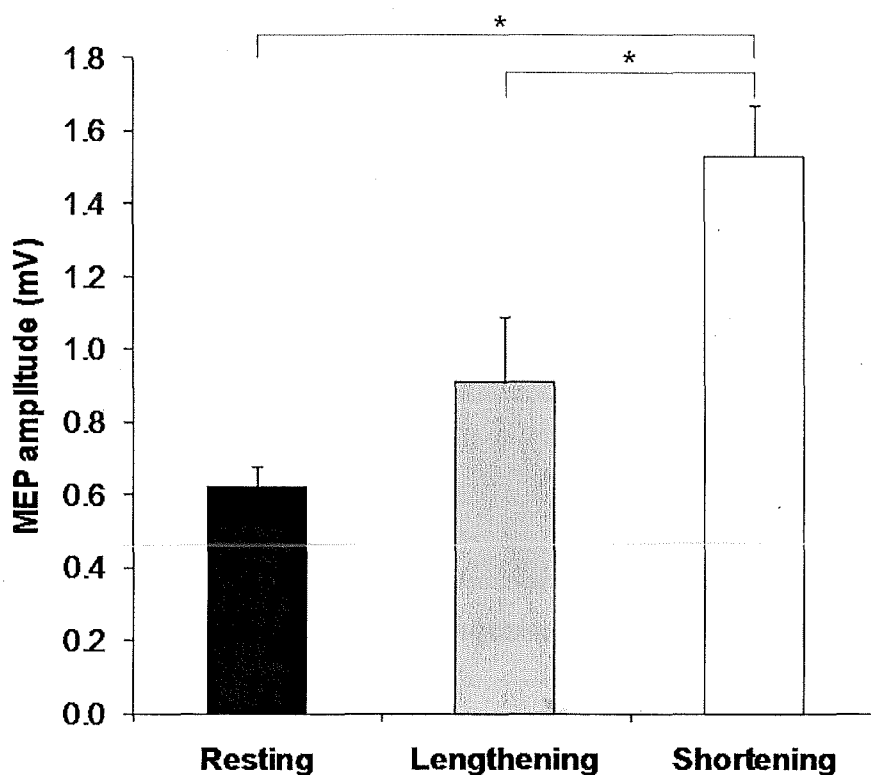

Figure 13. Mean motor evoked potential (MEP) amplitudes for the flexor carpi radialis (FCR) during resting active muscle lengthening and shortening.

* denotes significant difference between conditions.

There was no significant difference between resting and lengthening conditions.

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4.3.3 RMS EMG values of the ECR

The RMS EMG values during lengthening (38.2 ± 4.2 µV) and shortening (101.2 ± 8.6 µV) was significantly greater ($P<0.001$ for both) than that at rest (15.4 ± 1.1 µV). A significant difference was found between lengthening and shortening ($P<0.001$).

4.3.4 MEP amplitude of the ECR

As shown in Figure 14, the MEP amplitude was significantly greater during lengthening (2.93 ± 0.29 mV; $P<0.001$; 262%) and during shortening (4.82 ± 0.44 mV; $P<0.001$; 430%) compared with rest (1.12 ± 0.09 mV). The difference between lengthening and shortening was also significant ($P<0.001$).
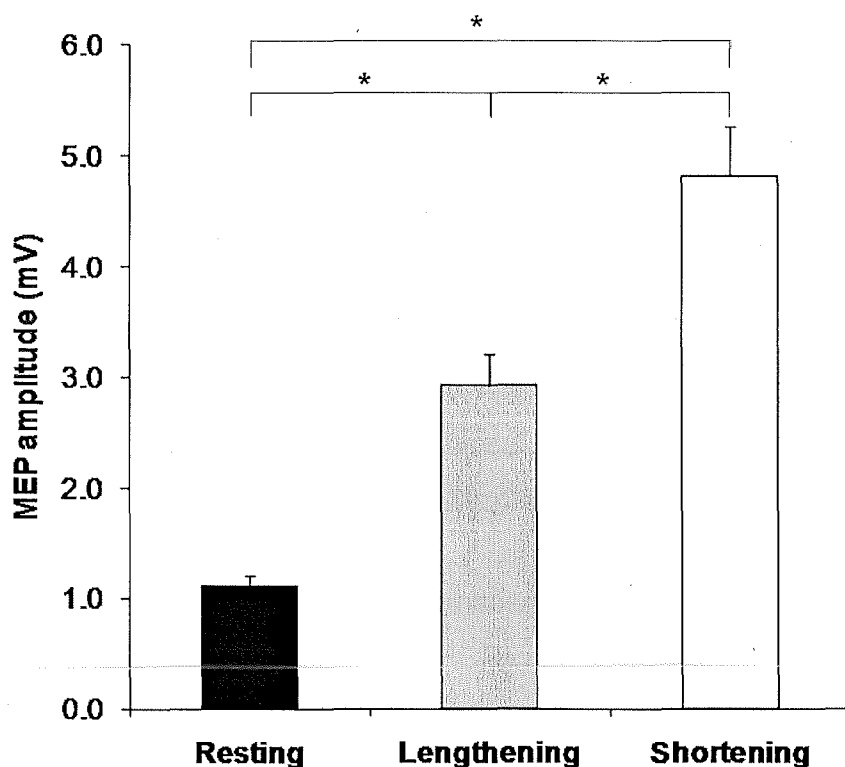
Figure 14. Mean motor evoked potential (MEP) for the extensor carpi radialis (ECR) during resting, active muscle lengthening and shortening.

* denotes significant difference between conditions.

4.3.5 Comparison between FCR and ECR

Figure 15 compares FCR and ECR MEP responses to lengthening and shortening phases relative to the resting MEP amplitude. A significant interaction effect was evident between the FCR and ECR ($F_{2,32}=12.199$, $P=0.001$). Post-hoc tests revealed that there was a significant difference in the lengthening ($P=0.007$) and shortening conditions ($P<0.001$).
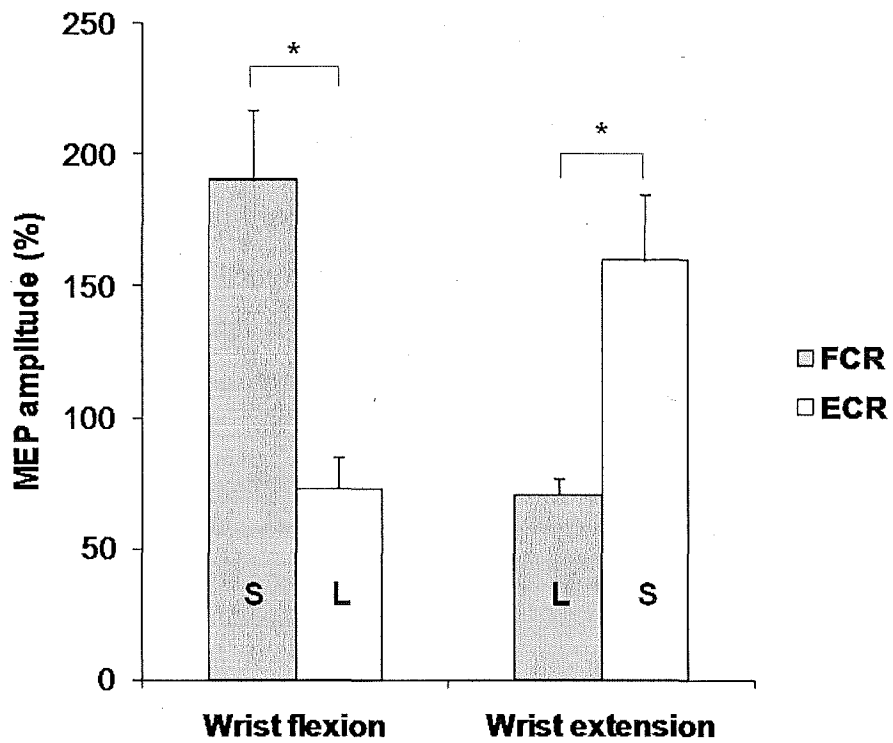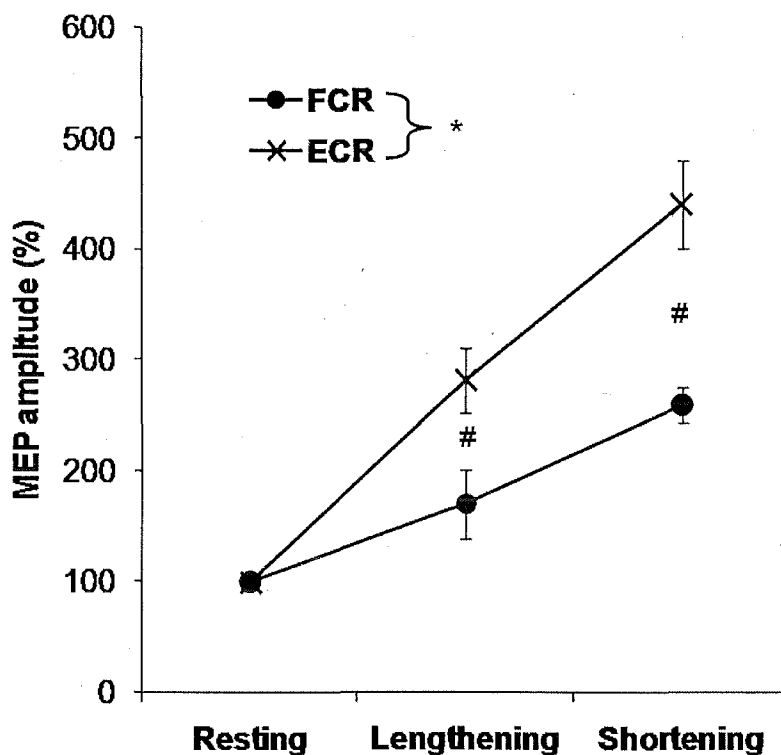

Figure 15. Comparison between the normalised mean motor evoked potential (MEP) values of the flexor carpi radialis (FCR) and extensor carpi radialis (ECR) during active movements.

* denotes significant difference between FCR and ECR, # denotes significant difference between lengthening and shortening conditions.

Figure 16 compares FCR and ECR during wrist flexion and wrist extension phases. During wrist flexion, the MEP amplitude of the FCR (259%) had no significant difference (P=0.258) compared to the ECR (282%). However during the wrist extension, significant difference was found between FCR and ECR, with the ECR (441%) significantly increased (P<0.001) compared to the FCR (170%).
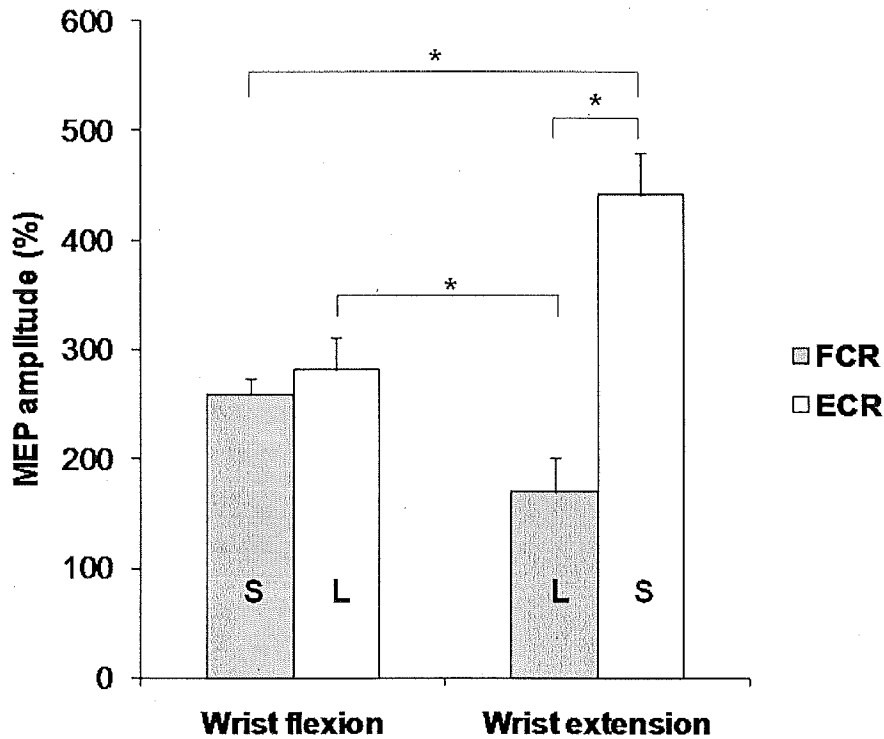
Figure 16. Comparison between the normalised mean motor evoked potential (MEP) of the flexor carpi radialis (FCR) and extensor carpi radialis (ECR) by resting value during active wrist flexion and extension movements.
* denotes significant difference between conditions, S denotes muscle shortening, L denotes muscle lengthening.
There was no significant difference between shortening and lengthening conditions for the wrist flexion phase.

4.4 Comparison between passive and active movements for the FCR

Figure 17 compares passive and active movements during lengthening and shortening for the FCR. A significant interaction effect was found ($F_{2,32}$=4.801, P=0.015). The post-hoc tests revealed that the MEP amplitude during lengthening was significantly smaller (P=0.005) for passive compared with active movements, but no significant difference between movements was evident during shortening (P=0.112).
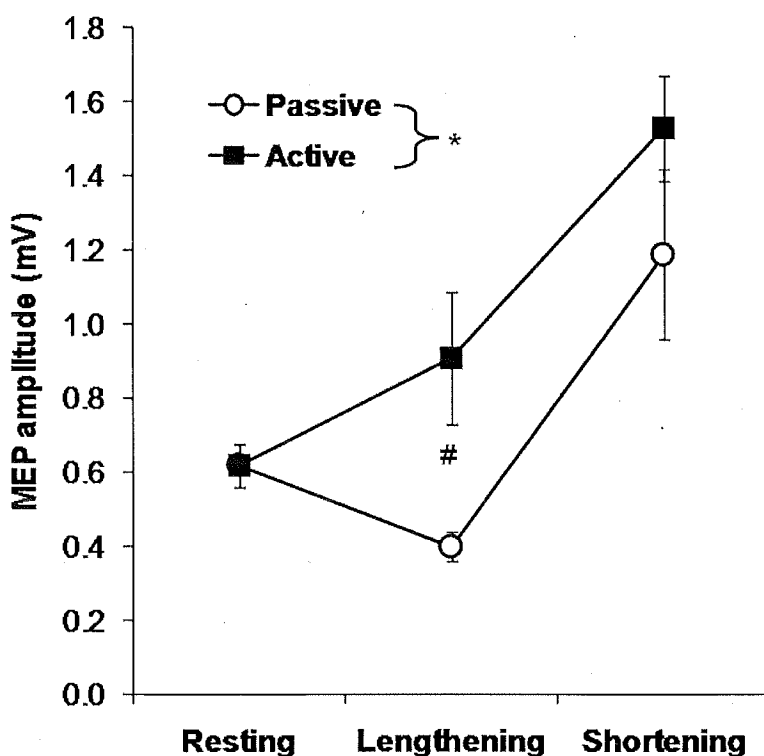
Figure 17. Comparison between passive and active movements for the motor evoked potential (MEP) responses of the flexor carpi radialis (FCR).

* denotes significant difference between passive and active movements, # denotes significant difference between passive lengthening and active lengthening conditions.

There was no significant difference between active shortening and passive shortening conditions.

4.5 Comparison between passive and active movements for the ECR

Figure 18 compares passive and active movements during lengthening and shortening for the ECR. A significant interaction effect was found ($F_{2,32}=32.996$, $P<0.001$), and the post-hoc tests revealed that the MEP amplitude was significantly smaller for passive compared with active movements for both lengthening and shortening phases ($P<0.001$ for both).
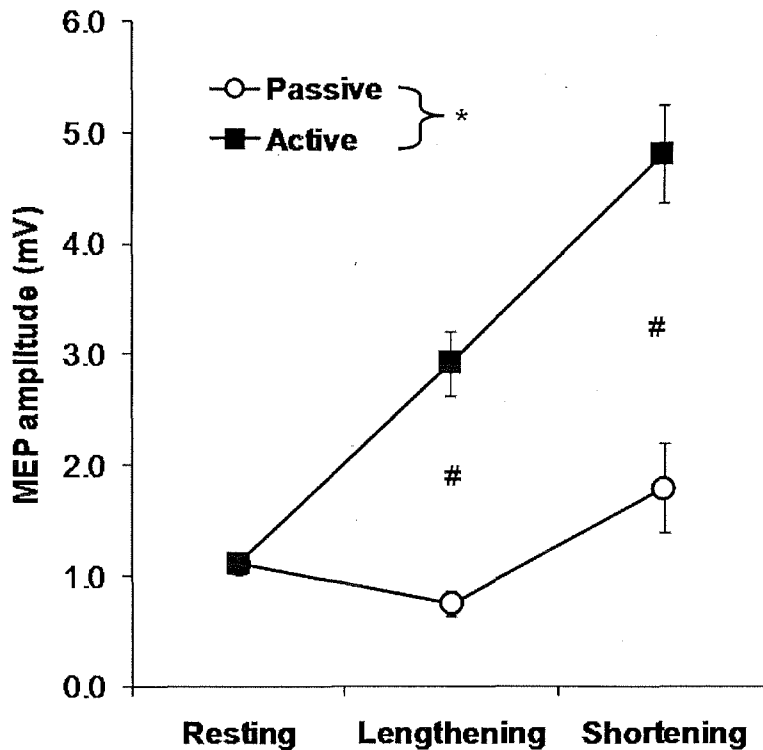
Figure 18. Comparison between passive and active movements for the motor evoked potential (MEP) responses of the extensor carpi radialis (ECR).
* denotes significant difference between passive and active movements, # denotes significant difference between lengthening and shortening conditions.

CHAPTER 5

DISCUSSION

The present results demonstrate that corticomotor excitability is modulated during lengthening and shortening of the FCR and ECR with passive and active movements. During passive movements, the MEP amplitude for both muscles has been shown to decrease during lengthening and increase during shortening compared with the resting state. In contrast, the MEP amplitude during active movements has been shown to increase for lengthening and shortening compared with the resting state for both muscles, but the increase was greater during the shortening than the lengthening phase. These results have revealed that corticomotor excitability decreases during muscle lengthening compared with muscle shortening in both passive and active movements.

Passive movements

The findings of the present study for corticomotor excitability during passive lengthening and shortening are in line with those reported in the previous studies (Coxon et al., 2005; Lewis & Byblow, 2002; Lewis et al., 2001). As shown in Figure 9, the MEP amplitude of the FCR was reduced during lengthening and increased during shortening compared with the resting state; however, the change in MEP amplitude of the ECR was only significant for lengthening (Figure 10). This may be due to the large variation of the MEP responses among participants. Lewis & Byblow (2002) showed no significant effect of lengthening or shortening on the MEP amplitude of the ECR. It should be also noted that Lewis & Byblow (2002) recorded the MEP responses from the same stimulation site for both FCR and ECR. However, the present study determined the optimum stimulating position and intensity for each muscle separately in each participant and this may have contributed to the differences between the findings of the present study and the previous study.

The change in MEP amplitude during passive lengthening and shortening were similar for FCR and ECR when normalised to their corresponding resting MEP amplitude (Figure 11). This suggests that muscle lengthening has an inhibitory effect and muscle shortening has an excitatory

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effect on the excitability of the corticomotor pathways regardless of muscles. The results also indicate that the changes in corticomotor excitability between FCR and ECR are comparable when they are lengthened or shortened within the range of ± 22.5° from the neutral position. However in the present study, the actual muscle length change for both muscles was not measured. It is possible that the FCR and ECR did not undergo the same amount of muscle length change. Further investigation is required to determine the muscle length change during the passive lengthening and shortening movements.

The FCR and ECR act as agonist and antagonist muscles during wrist flexion and extension. As shown in Figure 12, the agonist muscle has greater increase of corticomotor excitability compared with the antagonist muscle. The MEP amplitude of the agonist was more than two times greater than that elicited in the antagonist during passive wrist flexion and extension. Munson (2004) documented that when one muscle shortened, reciprocal muscle relaxed with minimal resistance to permit movement. Nielsen (2004) reported that reciprocal inhibition via Ia inhibitory interneuron occurred at the spinal level during movement when there was a decrease in the Ia afferent input from the agonist muscle and allowed the antagonist muscle to be lengthened without evoking a stretch reflex. It is possible that this also occurred during the passive wrist flexion and extension in the present study. The results also showed that corticomotor excitability for the FCR and ECR during passive wrist flexion and extension was comparable and there was no indication of directional preference towards flexor or extensor muscles. However, it is known that when the brain has an injury, for example a stroke, the upper limbs tend to regress into flexion position, although it is still unclear whether there is a stronger corticomotor projection to flexor muscles. Palmer & Ashby (1992) reported that the FCR had more direct corticospinal neuron projections than the ECR. Nielsen, Petersen, Crone, & Sinkjaer (2005) stated that spasticity of limbs was due to the failure of the spinal inhibitory mechanism after a brain injury. These reports may offer explanation as to why the flexor muscles are more likely to be affected than the extensor muscles after a brain injury.

Active movements

During active movements, the MEP amplitude of the FCR and ECR increased during lengthening and shortening compared with the resting state. However the increase was greater for shortening than the lengthening phase, although the change in MEP amplitude for FCR during lengthening was not significant (Figures 13 and 14). This may imply that there is a greater inhibition of corticomotor excitability during lengthening for the FCR. The greater MEP amplitude during the movements compared to at rest is likely to be explained by an overall increase in central motor drive to the wrist muscles during active movements. The EMG activities recorded prior to TMS showed that the FCR and ECR were both activated. Lestienne (1979) reported that during voluntary limb movements, an initial burst of activity from agonist muscle was required to set the limb moving, and the antagonist muscle was activated as a braking mechanism for the movement. However, in the present study there was ongoing EMG in both agonist and antagonist muscles, suggesting that during this relatively slow and controlled movement there is coactivation of both muscles. Ni et al. (2006) and Di Lazzaro et al. (1998) reported that an increase in muscle contraction during voluntary movement led to an increase in the MEP amplitude. In the present study, maximal muscle activation level of the FCR and ECR was not assessed, thus the muscle activation level during active movement was uncertain. It is possible that the participants had different level of muscle activation for the FCR and ECR which contributed to the differences in MEP amplitude. Further investigation is required to determine the level of muscle activation during active lengthening and shortening movements, and whether this has an effect on corticomotor excitability.

The findings of the present study for corticomotor excitability during active lengthening and shortening of the FCR and ECR were in line with those found in elbow flexors (Abbruzzese et al., 1994; Sekiguchi et al., 2001) and soleus muscles (Sekiguchi et al., 2003). In contrast, Sekiguchi et al. (2007) reported that the MEP amplitude of the first dorsal interosseous (FDI) was greater during active lengthening compared with the shortening phase, and they speculated that this may due to FDI is anatomically and functionally different from the elbow flexors and soleus muscles. Further investigation may be

required to determine muscles with different anatomical and functional roles on the changes in corticomotor excitability.

The MEP responses of the FCR and ECR are the same during active lengthening and shortening after they were normalised to the resting MEP amplitude, however, the ECR showed greater MEP amplitude in lengthening and shortening phase compared with the FCR (Figure 15). As mentioned previously, the FCR is reported to have more direct corticospinal neuron projections than the ECR (Palmer & Ashby, 1992). It seems that greater corticomotor excitability is required to activate the ECR than FCR. Figure 15 also shows that the MEP amplitude during the lengthening phase for both muscles is smaller compared with the shortening phase. This suggests that muscle lengthening has an inhibitory effect and muscle shortening has a facilitatory effect on the excitability of the corticomotor pathways to both muscles during active movements, which is similar to that seen in passive movements. Figure 16 shows the pattern of modulation of corticomotor excitability in the FCR and ECR during wrist flexion and extension movements. Despite the similar MEP amplitude between the FCR and ECR during wrist flexion, which is quite different to that during passive movement (Figure 12), it seems likely that reciprocal inhibition may still have occurred. Nielsen et al. (2005) reported that during voluntary movement the descending motor commands were not only sent via monosynaptic connections to motor neurons but also via collateral connections with interneurons which to trigger reciprocal inhibition allowing movement to occur. It is possible that this also occurred during active wrist flexion and extension in the present study.

As shown in Figures 17 and 18, the MEP amplitude of the FCR and ECR was greater during active compared with passive movements. The MEP responses from the FCR exhibited the same pattern of modulation between passive and active movements, with the MEP amplitude being smaller during lengthening compared with the shortening phase. The MEP amplitude of the ECR exhibited same pattern of modulation between passive and active movements as the FCR. This suggests that there are common motor strategies or underlying mechanisms that the brain employs during passive and active movements. As mentioned earlier, muscle lengthening has an inhibitory effect and muscle shortening has excitatory effect on corticomotor excitability. In the

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present study, the excitability of the corticomotor pathway to the FCR was only significantly decreased in lengthening phase during passive and active movements. In contrast, the excitability of the corticomotor pathway to the ECR was significantly decreased and increased in both lengthening and shortening during passive and active movements. This may imply that corticomotor excitability for the ECR is more sensitive to the change of muscle length than the FCR.

The findings of the present study may have positive implications for therapists who tailor rehabilitation programs. Liepert, Restemeyer, Kucinski, Zittel, & Weiller (2005) reported that the affected hemisphere of the brain after a stroke had a decrease in corticomotor excitability while the unaffected hemisphere had an increase in corticomotor excitability. One possible application of the present results could be the use of active movements with the affected limbs to increase excitability of the affected hemisphere while the use of passive movements with the unaffected limbs could be used to decrease excitability of the unaffected hemisphere. This approach may help to stabilise the excitability between two hemispheres.

Mechanisms

The possible mechanisms influencing corticomotor excitability during passive and active wrist movements include the effect of afferent inputs from the proprioceptive receptors such as joint and cutaneous receptors, Golgi tendon organs and muscle spindles (Cohen, 1999; Kandel et al., 2000). The range of wrist movement in present study was ±22.5° about the neutral position (0°) when the TMS was delivered. The normal range of movement for wrist flexion is 90° from the neutral position and 70° from the neutral position for wrist extension (Marieb & Hoehn, 2007). Burke, Gandevia, & Macefield (1988) reported that joint receptors are only activated at the limits of the range of movement. Therefore, the joint receptors were unlikely to be involved in the present study. The contribution of cutaneous receptor activation from excessive skin stretch was minimised as the palm of the participants in the present study was inserted in a customised hand piece and passive movements were carried out by moving the hand piece. In addition, the cutaneous receptors are known to contribute more to the perception of distal joints such as fingers than to proximal joints, such as the wrist (Collins et al., 2005). Therefore, the

contribution from cutaneous receptors to corticomotor excitability measured in the present study would have been minimal.

Burg, Szumski, Struppler, & Velho (1973) reported that Ib afferents were less influential during passively induced movements compared with active movements. Cohen (1999) also documented that muscle contraction activates the Golgi tendon organs more effectively than passive stretch. In the present study, there was no EMG activity evident from the muscles during passive movements. Although the level of EMG activities in relation to maximum voluntary contraction of each muscle was not recorded during active movement, the absolute level of muscle contraction was low. Therefore, the contribution from the Golgi tendon organs to the changes in corticomotor excitability during passive and active movement was likely to be minimal.

The sensory contribution from muscle spindles is a likely candidate mechanism for mediating changes in corticomotor excitability during passive and active movements. The firing rate from the muscle spindles increases during muscle lengthening, but decreases during muscle shortening in passive and active movements (Kandel et al., 2000; Stuart, Butler, Collins, Taylor, & Gandevia, 2002). Previous studies (Abbruzzese et al., 1994; Coxon et al., 2005; Lewis & Byblow, 2002; Lewis et al., 2001; Sekiguchi et al., 2001; Sekiguchi et al., 2003) have reported that the afferent input from muscle spindles were the main contributor to the change in corticomotor excitability. Kandel et al. (2000) documented that the gamma (γ) motoneurons were involved in maintaining the sensitivity of the afferent input from the muscle spindles during active movements. The involvement of the γ motoneurons during active movements may contribute to the difference in the afferent input from muscle spindles which in turns affecting the MEP amplitude between passive and active movements in the present study. Since the actual muscle length changes in the FCR and ECR are not known during the passive and active movements, the actual contribution from the afferent input from muscle spindles is therefore uncertain. Further investigation should be conducted to examine the muscle length changes during movements in relation to corticomotor excitability. As well as differences in afferent inputs during active and passive movement, a difference in central motor drive during active movement may also contribute to the changes observed in corticomotor excitability.

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Conclusion

The present study has confirmed that corticomotor excitability for the FCR and ECR changes in response to the change in muscle length during passive and active movements, with the excitability decreased during muscle lengthening and increased during muscle shortening. These results suggest that there is a reciprocal modulation in corticomotor excitability to wrist flexor and extensor muscles during passive and active movements. The degree of change in excitability to these muscles is comparable when normalised to resting levels, indicating that there is no preferential targeting of excitability changes to flexors or extensors of the wrist. While there is an overall increase in excitability to both muscles during relatively slow and controlled active wrist movements, the pattern of excitability changes still resembles those during passive movement. It seems that there are some common mechanisms underlying excitability changes during both passive and active movements, and that these may be mediated by afferent inputs in both situations.

Future direction

Further investigations are necessary to better understand the influence of muscle length and afferent inputs from proprioceptive receptors on corticomotor excitability. The changes in muscle length during passive and active lengthening and shortening movements should be determined, and the level of muscle activation in agonist and antagonist (in relation to maximal activation) should be explored. Further investigation is necessary to investigate the mechanisms underlying the effect of movements on corticomotor excitability in relation to the contribution from the muscle spindles, Golgi tendon organs, joint and cutaneous receptors. Furthermore, it is important to investigate how passive movements should be introduced in a rehabilitation program to maximise its effect on corticomotor excitability for injured brain after a stroke together with active movements.

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APPENDIX A

Ethics approval

EDITH COWAN UNIVERSITY   MEMO

FACULTY OF COMPUTING, HEALTH AND SCIENCE

Human Ethics Subcommittee

TO: Tamara Harold, Admin. Officer, Higher Degrees

FROM: Angus Stewart, Chair, Faculty Human Ethics Subcommittee

SUBJECT: Human Ethics Clearance Application/s

DATE: 9th January, 2008

Dear Tammie,

The following ethics application by

Chye Min Yen Lilian	Manual limb movements alter corticomotor excitability in phase dependent manner

is approved (category 2), subject to the following:

1. The information letter should be prepared according to the university template and include the clear statement that participation is voluntary and the subjects may withdraw at any time without penalty.
2. It should indicate that there is no connection with any ECU course of study
3. (Suggestion) Soften the tone of the letter, it is too authoritative.
4. Is Dr Edwards going to be available all year as a contact person? If not, a second name must be included in the information letter.

Best wishes,

Angus.

Informed consent form

INFORMATION FOR PARTICIPANT

STUDY TITLE: Manual Limb Movements Alter Cortiocomotor Excitability In A Phase Dependant Manner

INVESTIGATORS: Lilian Chye / Dr Dylan Edwards / A/P Ken Nosaka

AIM OF STUDY: To assess the corticomotor excitability using transcranial magnetic stimulation as a result of active and passive movement.

PROCEDURE:

You will only be requested to present at the Brain Research laboratory of Sir Charles Gairdner (Level 4 Block A) or the laboratory in ECU (Joondalup campus, Building 17.101a) on **one** occasion for the study. The duration of the study will take about 2 hours. This study includes active and passive movements of your right wrist.

You will be comfortably seated in a chair and remain relax throughout the study. Your right forearm will be placed on a device on a table throughout the study. Two muscles in your forearm (flexor carpi radialis (FCR) and extensor carpi radialis (ECR)) muscles will be examined in this study. Four electrode discs will be taped on these muscles. Electromyographic (EMG) activity of these muscles will be recorded via these electrodes and the information will be fed to a computer.

Transcranial magnetic stimulation (TMS) will be used in this study. The procedure is non-invasive. Each stimulus will be very short, much less than 1 second. It is not painful; you will feel a slight tap on your head where stimulation is applied. You may also notice some small movements in your arm. For example, when we stimulate the part of the brain responsible for hand movements, the muscles in the hand will contract and a small movement of the hand will be felt.

A snugly fitting cap with pre-marked spacings will be fitted on your head and a magnetic coil will be positioned on the left side of your head according to the pre-marked spacings. Stimulus will then be applied to that part of the brain (Figure 1). An optimal site ('hot spot') will be located on your head for the best

location where it best represents your forearm muscles (FCR and ECR muscles). After which, a testing stimulus intensity will be determined at the 'hot spot' location by slowing increasing the stimulus intensity till a satisfactory motor evoked potential is achieved. This testing intensity will be used throughout the study. Single-pulse TMS will only be used in this study.

Stimulus will be applied during rest (pre and post movement), active wrist movement (flexion phase and extension phase) and passive wrist movement (flexion phase and extension phase) as shown below. Flexor carpi radialis and extensor carpi radialis muscles will be measured separately.

Wrist movement (randomized)

FCR	→	REST	⇒	Active Extension	
				Active Flexion	⇒ REST
				Passive Extension	
				Passive Flexion	

Wrist movement (randomized)

ECR	→	REST	⇒	Active Extension	
				Active Flexion	⇒ REST
				Passive Extension	
				Passive Flexion	
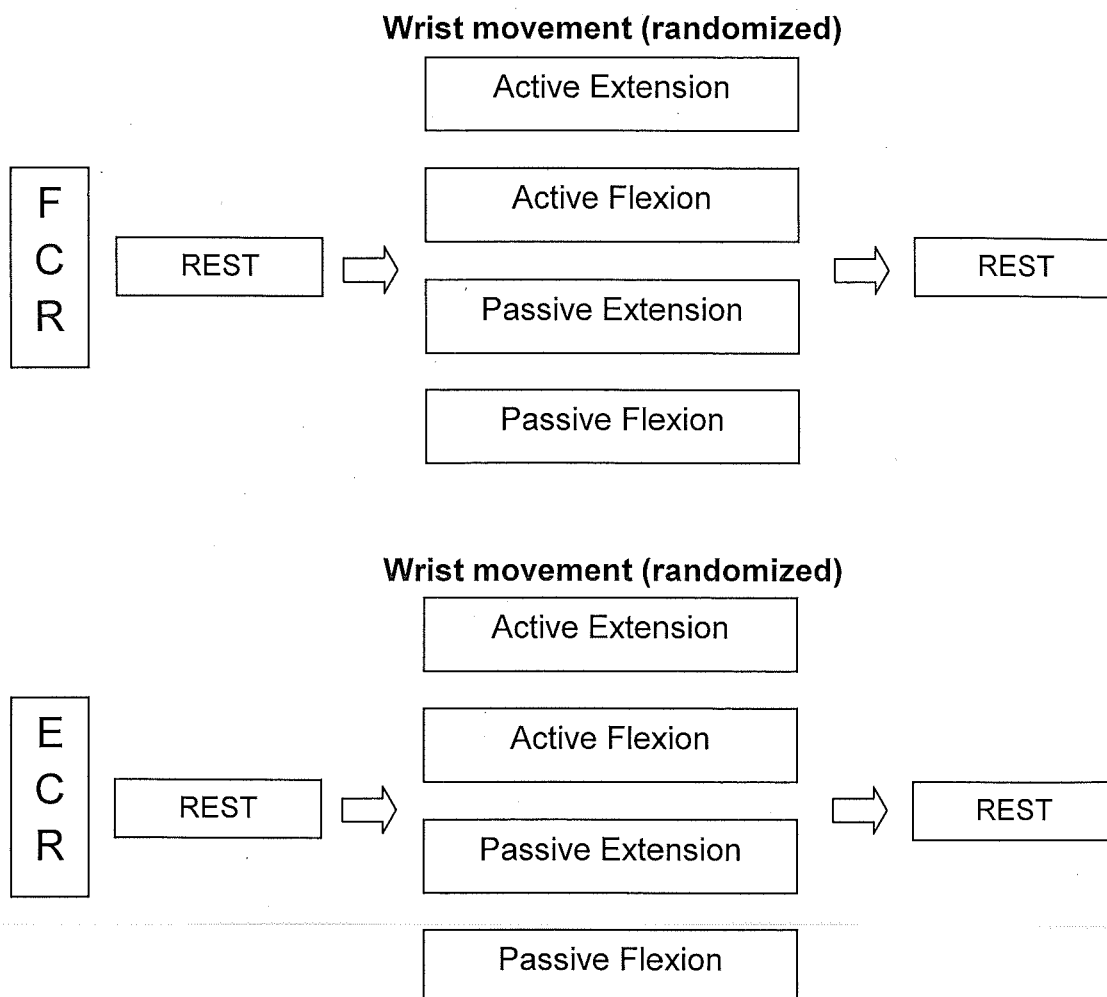
For resting condition, your right hand will be positioned at neutral position (0°). You will be requested to remain relax throughout so to avoid any arm movement hence maintaining EMG silence in your right forearm muscles. The investigator will position the TMS coil on the left side of your head and stimulus will be delivered every 10 seconds.

For active wrist movement, you will be requested to flex and extend your right wrist within the 2 markers placed in front of you at a frequency of 1 Hz (Figure 1) with the help of a metronome. You will be given some time to

familiarize with the movement rhythm before the start of the stimulation. Stimulus will be delivered every time your wrist passes through the neutral position (0°) at every 10 seconds.

For passive wrist movement, the process is similar to the active wrist movement except that the wrist movement will be carried out by another investigator in front of you.

(A)   (B)

Figure 1. Movement design. (A) Stimulation for wrist flexion phase. (B) Stimulation for wrist extension phase. (Adapted from Coxon et al., 2005, pg 110)
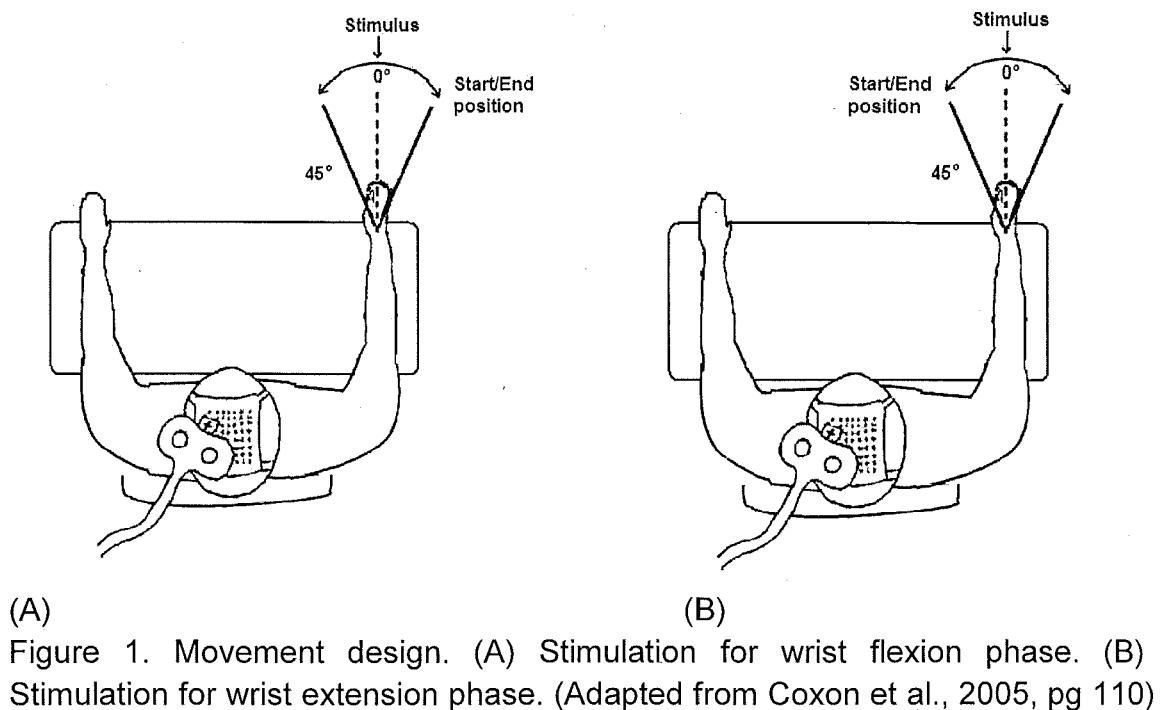
POSSIBLE RISKS/ ADVERSE EFFECTS:

There are no long-lasting adverse effects associated with TMS and the intensity used in this study is of low intensity. There are very few possible discomforts associated with these procedures. On rare occasions magnetic stimulation may cause a headache. If this occurs and you wish to stop the session, we will stop the session. You may withdraw from the study at any time without prejudice or penalty.

EXCLUSION:

Transcranial magnetic stimulation uses magnetism and as such, there are various factors which may exclude you from participating in this study. These include having a pacemaker or metal objects like cerebral aneurysm clips inside your body. You will be asked a series of questions to determine if there are any factors which may stop you from participating in this study.

CONFIDENTIALITY:

All information obtained will remain confidential and no names will be used in any publications.

CONSENT:

The study will be carried out in a manner conforming to the principles set out by the National Health and Medical Research Council. You are free to withdraw your consent and discontinue with your participation at any time for any reason without penalty. Please take note that your participation in this study does not prejudice any right to compensation, which you may have under statute or common law. This study has no connection with any course of study you might be taking at ECU.

FURTHER INFORMATION:

If you have any questions regarding this study you can contact A/P Ken Nosaka at 6304 5655.

You will be given a copy of this information sheet and consent form to read and keep prior to indicating your consent to participate by signing the consent form.

CONSENT FORM

STUDY TITLE: Manual Limb Movements Alter Corticomotor Excitability In A Phase Dependant Manner

INVESTIGATORS: Lilian Chye / Dr Dylan Edwards / A/P Ken Nosaka

I have been given clear information (verbal and written) about this study and have been given time to consider whether I want to take part.

I have been told about the possible risks of taking part in the study and I understand what I am being asked to do.

I have been able to ask questions and all questions have been answered satisfactorily.

I know that I do not have to take part in the study and that I can withdraw at any time during the study without affecting my future medical care. I understand that participation in this study does not affect any right to compensation, which I may have under statute or common law. I know that this study has no connection with any course of study I might be taking at ECU.

I agree to take part in this research study and for the data obtained to be published provided my name or other identifying information is not used.

....

Name of Subject   *Signature of Subject*   *Date*

....

Name of Investigator   *Signature of Investigator*   *Date*

All study participants may obtain a copy of the Information Sheet and Consent Form for their personal records upon request.

MEDICAL HISTORY – Date:_____

SURNAME:_____ GIVEN NAMES:_____

DATE OF BIRTH:_____

HANDEDNESS: **LEFT / RIGHT / AMBIDEXTROUS** (Please circle)

QUESTION	YES	NO	COMMENTS
Brain Surgery			
Shunt			
Craniotomy			
Cranioplasty / Metal Plates in Skull			
Aneurysm Clip			
Deep Brain Electrodes			
Other Devices			
Pacemaker			
Valve Replacement			
Hearing Aid			
Cochlear Implant			
Metal Foreign Bodies			
e.g. shrapnel			
Intracranial			
Orbit / Eyeball			
Other region			
Epilepsy			
Migraine			
Medication			
Braces			
Other			

Resting motor evoked potential amplitude before and after all movement conditions

Resting motor evoked potential amplitude of the flexor carpi radialis (FCR) before and after all movement conditions for all participants and mean (±SEM) of the participants.

Participants	FCR resting amplitude (mV)	
	Before	After
1	0.33	0.29
2	0.34	0.26
3	0.73	0.54
4	1.08	0.75
5	0.97	1.24
6	0.38	0.22
7	1.05	0.92
8	0.62	0.57
9	0.38	0.33
10	0.59	0.29
11	0.44	0.44
12	0.66	0.65
13	0.45	0.54
14	0.60	0.56
15	0.92	0.76
16	0.89	0.82
17	0.53	0.81
Mean	0.64	0.59
SEM	0.06	0.07

Resting motor evoked potential amplitude of the extensor carpi radialis (ECR) before and after all movement conditions for all participants and mean (±SEM) value of the participants.

Participants	ECR resting amplitude (mV)	
	Before	After
1	0.83	0.44
2	0.37	1.03
3	1.21	1.11
4	1.90	2.35
5	0.93	1.14
6	0.66	0.90
7	1.14	0.97
8	1.15	0.96
9	1.06	1.08
10	0.61	0.81
11	0.96	0.81
12	1.08	1.49
13	1.11	0.78
14	1.52	1.16
15	1.50	1.54
16	1.23	1.46
17	1.10	1.64
Mean	1.08	1.16
SEM	0.09	0.11

Resting root mean square electromyographic values before and after all movement conditions

Resting root mean square electromyographic values of the flexor carpi radialis (FCR) before and after movement conditions for all participants and mean (±SEM) of the participants.

Participants	FCR resting EMG (μV)	
	Before	After
1	16.02	15.89
2	13.17	13.19
3	14.34	12.33
4	20.63	22.58
5	11.99	12.11
6	14.44	14.80
7	14.06	14.31
8	14.98	14.12
9	11.09	11.00
10	27.21	24.59
11	20.40	20.82
12	18.10	14.67
13	14.08	14.49
14	15.11	15.06
15	7.05	28.22
16	10.46	11.69
17	13.51	15.26
Mean	15.10	16.18
SEM	1.11	1.19

Resting root mean square electromyographic values of the extensor carpi radialis (ECR) before and after movement conditions for all participants and mean (±SEM) of the participants.

Participants	ECR resting EMG (µV)	
	Before	After
1	23.38	22.90
2	12.36	14.68
3	12.19	11.92
4	20.00	19.13
5	28.69	12.54
6	13.45	13.53
7	19.18	18.80
8	15.21	16.96
9	13.08	12.63
10	15.40	15.28
11	15.34	16.59
12	14.19	14.48
13	22.50	22.14
14	19.04	18.89
15	8.07	9.12
16	8.23	7.87
17	8.91	9.09
Mean	15.84	15.09
SEM	1.37	1.47

Motor Evoked Potentials during passive and active movements

Motor evoked potential amplitude for all participants and mean (±SEM) of the participants during resting, passive lengthening and shortening of the flexor carpi radialis.

*: significantly different from the resting value, ^: significantly different from the muscle lengthening value.

Participants	Resting (mV)	Passive (mV)	
		Lengthening	Shortening
1	0.31	0.34	0.32
2	0.30	0.21	0.19
3	0.64	0.52	1.26
4	0.91	0.44	4.40
5	1.10	0.40	1.64
6	0.30	0.20	1.02
7	0.99	0.29	1.60
8	0.59	0.37	0.91
9	0.36	0.36	0.82
10	0.44	0.26	1.46
11	0.44	0.43	0.77
12	0.66	0.44	1.76
13	0.49	0.61	0.64
14	0.58	0.38	0.51
15	0.84	0.79	0.65
16	0.86	0.44	1.70
17	0.67	0.26	0.58
Mean	0.62	0.40*^	1.19*^
SEM	0.06	0.04	0.23

Motor evoked potential amplitude for all participants and mean (±SEM) of the participants during resting, active lengthening and shortening of the flexor carpi radialis.

*: significantly different from the resting value, ^: significantly different from the muscle lengthening value.

Participants	Resting (mV)	Active (mV)	
		Lengthening	Shortening
1	0.31	0.43	0.74
2	0.30	1.05	0.98
3	0.64	2.99	1.77
4	0.91	0.38	3.07
5	1.10	0.48	1.58
6	0.30	0.51	0.61
7	0.99	0.34	1.67
8	0.59	0.97	1.09
9	0.36	0.57	1.19
10	0.44	0.35	1.54
11	0.44	0.63	1.10
12	0.66	1.24	1.57
13	0.49	1.36	1.55
14	0.58	2.16	1.93
15	0.84	1.23	2.21
16	0.86	0.41	2.01
17	0.67	0.45	1.44
Mean	0.62	0.91	1.53*^
SEM	0.06	0.18	0.14

Motor evoked potential amplitude for all participants and mean (±SEM) of the participants during resting, passive lengthening and shortening of the extensor carpi radialis.

*: significantly different from the resting value, ^: significantly different from the muscle lengthening value.

Participants	Resting (mV)	Passive (mV)	
		Lengthening	Shortening
1	0.64	0.40	1.41
2	0.70	0.53	0.55
3	1.16	0.41	2.62
4	2.13	0.88	7.08
5	1.03	0.44	0.79
6	0.78	1.00	2.09
7	1.06	0.51	2.96
8	1.05	0.91	0.87
9	1.07	1.14	1.88
10	0.71	0.29	0.81
11	0.89	0.44	0.99
12	1.28	0.53	0.56
13	0.95	2.30	3.52
14	1.34	1.22	1.10
15	1.52	0.81	0.66
16	1.35	0.54	0.81
17	1.37	0.49	2.13
Mean	1.12	0.76*	1.81^
SEM	0.09	0.12	0.40

Motor evoked potential amplitude for all participants and mean (±SEM) of the participants during resting, active lengthening and shortening of the extensor carpi radialis.

*: significantly different from the resting value, ^: significantly different from the muscle lengthening value.

Participants	Resting (mV)	Active (mV)	
		Lengthening	Shortening
1	0.64	1.31	2.18
2	0.70	1.67	1.67
3	1.16	2.99	3.02
4	2.13	1.26	6.62
5	1.03	3.69	6.23
6	0.78	4.18	6.11
7	1.06	4.14	5.45
8	1.05	2.34	2.21
9	1.07	3.56	5.73
10	0.71	2.18	3.53
11	0.89	2.20	3.01
12	1.28	5.16	7.43
13	0.95	4.45	6.52
14	1.34	3.22	5.50
15	1.52	2.90	5.71
16	1.35	3.23	6.11
17	1.37	1.28	4.96
Mean	1.12	2.93*	4.82*^
SEM	0.09	0.29	0.44

Root mean square electromyographic values during active movements

Root mean square electromyographic values for all participants and mean (±SEM) of the participants during resting, active lengthening and shortening for the flexor carpi radialis (FCR).

*: significantly different from the resting value, ^: significantly different from the muscle lengthening value.

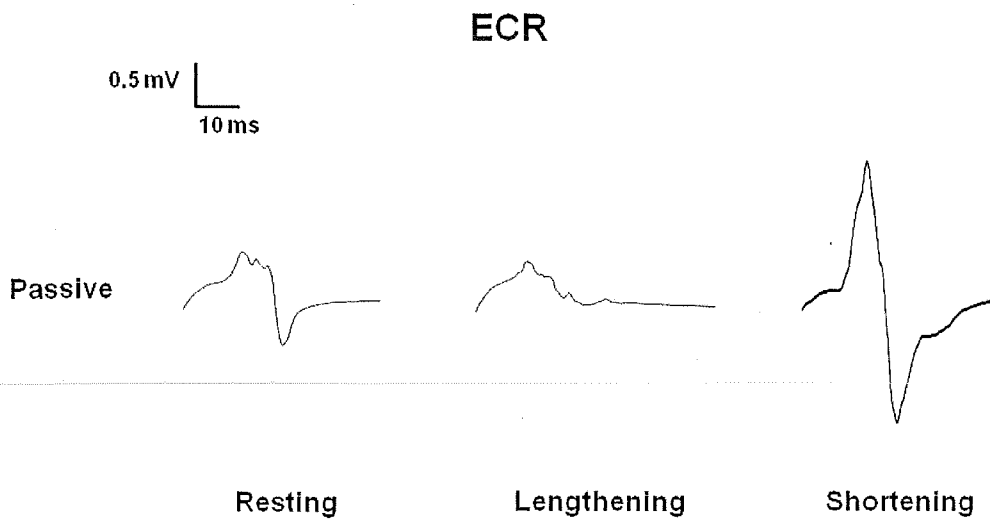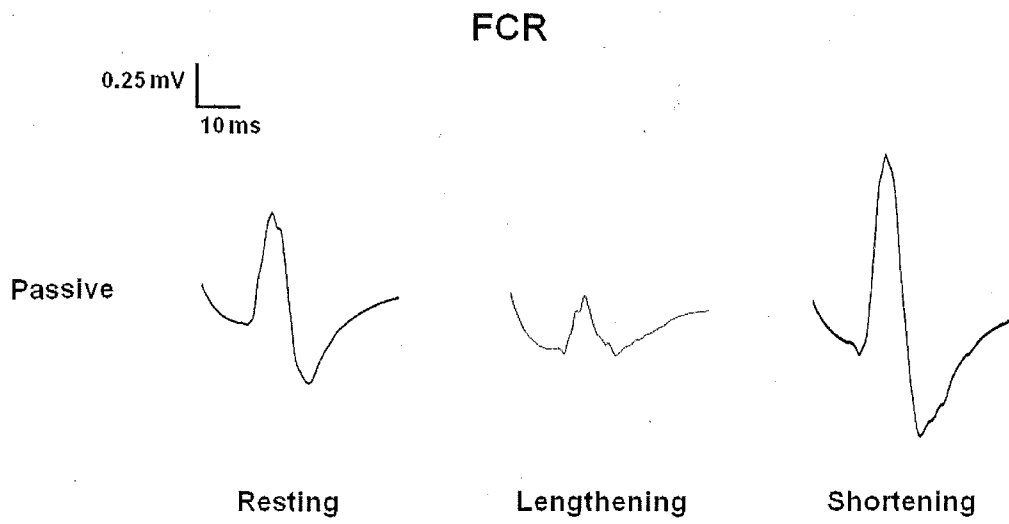| Participants	FCR (μV)		
	Resting	Lengthening	Shortening
1	15.96	15.89	24.99
2	13.18	24.44	31.87
3	13.33	33.19	36.39
4	21.61	27.00	43.17
5	12.05	15.75	30.99
6	14.62	15.27	16.77
7	14.19	18.32	24.10
8	14.56	15.51	25.31
9	11.04	13.59	21.91
10	25.90	28.44	27.01
11	20.61	23.36	22.94
12	16.38	18.21	18.36
13	14.28	18.24	19.45
14	15.08	16.55	33.62
15	17.63	10.14	18.58
16	11.08	13.07	13.96
17	14.39	14.43	23.19
Mean	15.64	18.91*	25.45*^
SEM	0.95	1.51	1.86

Root mean square electromyographic values for all participants and mean (±SEM) of the participants during resting, active lengthening and shortening for the extensor carpi radialis (ECR).

*: significantly different from the resting value, ^: significantly different from the muscle lengthening value.

Participants	ECR (μV)		
	Resting	Lengthening	Shortening
1	23.14	37.05	76.79
2	13.52	15.31	43.18
3	12.06	45.95	79.98
4	19.57	83.35	98.70
5	20.62	27.65	73.06
6	13.49	48.90	139.96
7	18.99	61.15	112.30
8	16.08	47.39	66.02
9	12.50	31.86	77.34
10	15.34	30.57	101.29
11	15.97	31.34	90.28
12	14.33	48.62	173.23
13	22.32	46.57	155.42
14	18.96	29.92	86.59
15	8.60	17.09	109.58
16	8.05	15.97	83.43
17	9.00	29.99	152.48
Mean	15.44	38.16*	101.15*^
SEM	1.13	4.23	8.60

Typical waveform during passive and active movements

FCR

A typical MEP waveform of the flexor carpi radialis (FCR) and extensor carpi radialis (ECR) from one participant during passive muscle lengthening and shortening.
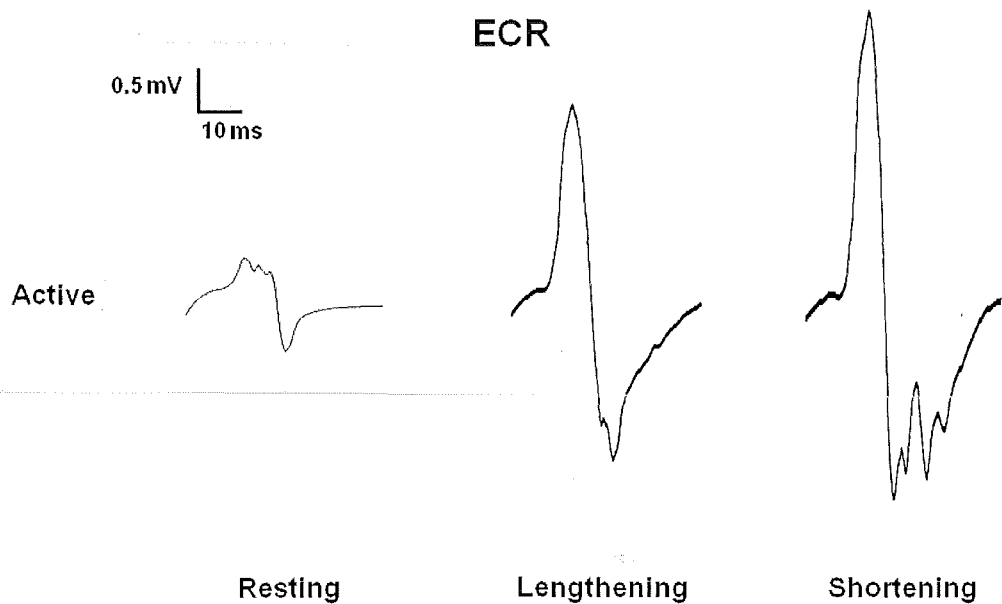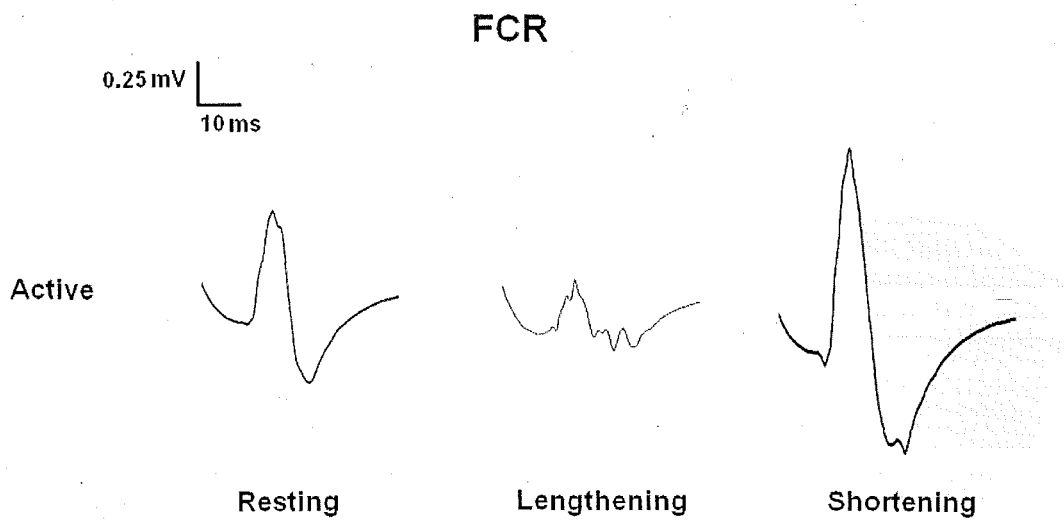
FCR

A typical MEP waveform of the flexor carpi radialis (FCR) and extensor carpi radialis (ECR) from one participant during active muscle lengthening and shortening.