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**Adaptations in corticospinal excitability and inhibition are not spatially confined to the agonist muscle following strength training.**

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## ABSTRACT

**Purpose:** We used transcranial magnetic stimulation (TMS) to determine the corticospinal responses from an agonist and synergist muscle following strength training of the right elbow flexors. **Methods:** Motor evoked potentials were recorded from the Biceps Brachii and Flexor Carpi Radialis during a submaximal contraction from 20 individuals (10 women, 10 men, aged 18-35 years; training group; n = 10 and control group; n = 10) before and after three weeks of strength training at 80% of 1-repetition maximum (1-RM). To characterise the input-output properties of the corticospinal tract, stimulus-response curves for corticospinal excitability and inhibition of the right Biceps Brachii and Flexor Carpi Radialis were constructed and assessed by examining the area under the recruitment curve (AURC).

**Results:** Strength training resulted in a 29% ( $P < 0.001$ ) increase in 1-RM Biceps Brachii strength and this was accompanied by a 19% increase in isometric strength of the wrist flexors ( $P = 0.001$ ). TMS revealed an increase in corticospinal excitability AURC and a decrease in silent period duration AURC for the Biceps Brachii and Flexor Carpi Radialis following strength training (all  $P < 0.05$ ). However, the changes in corticospinal function were not associated with increased muscle strength. **Conclusion:** These findings show that the corticospinal responses to strength training of a proximal upper limb muscle is not spatially restricted, but rather, results in a change in connectivity, among an agonist and a synergistic muscle relevant to force production.

**Key Words:** Agonist, corticospinal excitability, corticospinal inhibition, voluntary strength, strength training, synergist.

## **ABBREVIATIONS**

**1RM:** one-repetition maximum

**AURC:** area under the recruitment curve

**AMT:** active motor threshold

**CMEPs:** cervicomedullary motor-evoked potentials

**GABA:**  $\gamma$ -Aminobutyric acid

**LTP:** long-term potentiation

**MEPs:** motor-evoked potentials

**MVIC:** maximal voluntary isometric contraction

**M1:** primary motor cortex

***rms*EMG:** root-mean square electromyography

**sEMG:** surface electromyography

**SICI:** Short-interval cortical inhibition

**TMS:** transcranial magnetic stimulation

## 1.0 INTRODUCTION

During the early stages of strength training, it is axiomatic that the rapid gain in muscle strength occurs too rapidly to be explained solely by muscle-based mechanisms. Therefore, there is a consensus that the central nervous system (CNS) must facilitate the rapid induction of maximal voluntary force that is produced by strength training (Carroll et al. 2002). Potential neural adaptations include an increase in motor unit discharge rate, increased doublet-firing of human motor units and increased “neural-drive” to the agonists and synergists, which represents modulation at the spinal level (Aagaard et al. 2002; Kamen and Knight 2004; Pucci et al. 2006; Sale 1988). In addition, it has been suggested that reduced co-contraction of antagonists may also be an important neural adaptation to strength training (Carolan and Cafarelli 1992; Häkkinen et al. 1998); however, there is also evidence to show that there are no changes in co-activation (Reeves et al. 2005). Previously, it has been suggested that any change in co-activation would indicate that the site of neural adaptation would be confined to the spinal cord (Sale 1988); however, recent evidence has emerged that the control of antagonist muscles may also be controlled at the level of the primary motor cortex (Capaday et al. 2013). Despite this, the involvement of supraspinal structures in these processes remains to be fully explored. Specifically, the potential role of the primary motor cortex (M1) and corticospinal tract underpinning the ‘early’ neural adaptations to strength training remain debated (Carroll et al. 2011; Kidgell et al. 2010; Lee et al. 2009; Jensen et al. 2005; Griffin and Cafarelli 2007).

Emerging evidence has employed transcranial magnetic stimulation (TMS) to reveal the extent that the M1 and corticospinal tract (i.e., corticospinal excitability) contribute to the neural adaptations to strength training (Kidgell et al. 2010). One of the first studies to use TMS and investigate the corticospinal responses following strength training of the first dorsal interosseous (FDI) muscle reported a large increase in muscle strength. However, strength

training did not alter the size of the motor-evoked potential (MEP) at rest, or at higher force levels (i.e. 50% MVC); rather, observing a decrease in MEP amplitude (Carroll et al. 2002). In support of this, Jensen et al. (2005) reported a significant reduction in the size of the maximal MEP and slope of the stimulus-response curve recorded at rest following four weeks strength training of the Biceps Brachii muscle. Further, Lee et al. (2009) observed that four weeks of strength training of the wrist (ulnar deviation) did not modify the size of the TMS evoked recorded at rest MEP. Recently, Coombs et al. (2016) showed that three weeks of wrist extensor strength training had no effect on corticospinal excitability, despite significant increases in muscle strength. In contrast to these findings, Griffin and Cafarelli (2007) observed a 32% increase in MEP amplitude following isometric strength training of the Tibialis Anterior. Based upon the previous TMS strength training studies, it is difficult to draw definitive conclusions as to whether the M1 and corticospinal tract contribute to the neural adaptations that might account for the increase in strength. However, the disparity in the previous studies could simply relate to the type of strength training employed. For example, strength training that is externally paced to an audible metronome has consistently demonstrated increases in M1 and corticospinal excitability following isotonic strength training (Kidgell et al. 2010; Pearce and Kidgell 2011; Weier et al. 2012; Leung et al. 2015). This supports the idea that skill and strength training share a similar neural adaptation within the M1 and corticospinal tract (Carroll et al. 2002), for which evidence has recently been provided (Leung et al. 2015).

Although TMS strength training studies are emerging, many studies have not determined whether corticospinal inhibition contributes to the neural adaptations to strength training. When a supra-threshold single-pulse TMS stimulus is applied over the contralateral M1 whilst maintaining a low-level muscle contraction, there is a pause in the surface electromyographic (sEMG) signal that can last up to a few hundred milliseconds (Wilson et

al. 1993; Di Lazzaro et al. 1998; Kidgell and Pearce 2011) and is referred to as the TMS silent period. This period of sEMG silence is thought to be reflective of inhibitory mechanisms, mediated by  $\gamma$ -Aminobutyric acid (GABA<sub>B</sub>) receptors (Di Lazzaro et al. 1998; Werhahn et al. 1995). To date, only six studies in both young and healthy older adults have reported that the duration of the silent period is reduced following isometric and isotonic strength training (Kidgell and Pearce 2010; Kidgell et al. 2011; Latella et al. 2012; Christie and Kamen 2013; Hendy and Kidgell 2013; Coombs et al. 2016). These data suggest that strength training targets specific populations of intracortical GABA<sub>B</sub> networks that consequently may increase neural drive to the trained muscle.

A significant limitation in the current body of evidence is that corticospinal excitability and inhibition are examined in the agonist muscles only. It is well recognised that changes in the activation of synergistic muscles might also contribute to the net increase in voluntary force (Cannon and Cafarelli 1987), however there have been no TMS strength training studies that have explored this. We chose to examine the synergistic responses of Flexor Carpi Radialis during elbow flexion, as previous strength training interventions have used TMS to examine the M1 and corticospinal responses of this muscle. In addition, it is likely to be substantially active during an isotonic Biceps curl exercise (Kidgell et al. 2015). Therefore, the purpose of the current study was to characterise the input-output properties of the corticospinal tract for the trained agonist and synergist muscle following strength training. It was hypothesised that strength training of the Biceps Brachii muscle would induce changes in corticospinal excitability and inhibition for both the agonist and synergist (Flexor Carpi Radialis), via the activation of an integrated neural network that involves both the M1 and corticospinal tract.

## **2.0 EXPERIMENTAL PROCEDURES**

### ***2.1 Participants***



Twenty participants (10 women, 10 men, and aged 18-35 years) volunteered to participate. All volunteers provided written informed consent prior to participation in the study, which was approved by the Human Research Ethics Committee in accordance with the standards by the Declaration of Helsinki. All participants were right-hand dominant as determined by the Edinburgh Handedness Inventory (Oldfield 1971) with a Laterality Quotient Score greater than 40, had not participated in strength training for at least 12 months, and were free from any known history of neuromuscular impairment. Prior to the experiment, all participants completed the adult safety screening questionnaire to determine their suitability for TMS (Keel et al. 2001).

## ***2.2 Experimental approach***

A schematic representation of the study is presented in Figure 1. After obtaining consent, participants completed a familiarisation session one week prior to the study that involved performing a one-repetition maximum (1-RM) strength test of the right elbow flexors (to establish training load) and were then exposed to single-pulse TMS. Following the familiarisation session, participants were systematically matched for gender and baseline strength, then randomly allocated into either the control (no training) or training group. All participants underwent TMS and maximum strength testing of the Biceps Brachii and Flexor Carpi Radialis before and after a three week supervised strength training program of the right elbow flexors with post-testing occurring within 48 hours of the final training session. Control participants undertook pre- and post-testing only. Previous strength training and TMS studies have shown the efficacy for strength training the Biceps Brachii and Flexor Carpi Radialis in isolation, hence, the elbow flexor was chosen as it involves the agonist Biceps Brachii and one of several synergists, but we chose the Flexor Carpi Radialis as the synergist (Kidgell et al. 2015).

### ***2.3 Voluntary strength testing***

Participants in both groups performed a standard unilateral 1-RM test for the right elbow flexors, specifically targeting the Biceps Brachii. Following previous work (Munn et al. 2005), participants were asked what they believed their 1-RM elbow flexion strength was and this load served as their initial starting weight. Participants performed the 1-RM test standing, holding a weighted dumbbell with one hand, with their elbow in full extension, forearm supinated, and the opposite arm placed behind their back while standing against a wall to prevent extraneous body movement. Participants were then asked to flex their arm and lift the dumbbell as if performing a standard Biceps curl. If the trial was successful, the weight of the dumbbell was increased accordingly (0.5 kg increments) on each trial following a three-minute recovery to minimise the development of muscular fatigue (Munn et al. 2005; Kidgell et al. 2011). This procedure continued until the subject could no longer complete one repetition and their prior successful trial served as their 1-RM isotonic Biceps Brachii strength (Munn et al. 2005; Kidgell et al. 2011). Participants completed on average three trials to achieve their 1-RM strength.

Maximum voluntary isometric contraction force (MVIC) of the right wrist flexors was determined on a custom-made force transducer (Futek Force Transducer LSB302, Melbourne). For the wrist flexor MVIC, participants were seated in a chair, shoulders in a neutral position with their elbow flexed at 110 degrees (Frazer et al. 2016). With the hand supinated and the force transducer positioned over the middle aspect of the palmar surface of the hand and was adjusted to ensure that the external moment arm was individually established for each participant. Once the external moment arm was established, participants were instructed to push up against the transducer as forcefully as possible for three seconds. Three trials were performed, separated by three-minute rest to minimise fatigue. The greatest recorded output was used for data analysis.

## ***2.4 Strength training protocol***

Using the same set-up as in the 1-RM testing, participants completed flexion-extension movements of the right elbow with the forearm supinated (Biceps curl). Participants completed 4 sets of 6-8 repetitions at 80% 1-RM with the right arm only (to contractile failure) with three-minute recovery between sets (Munn et al. 2005; Kidgell et al. 2010). A repetition timing of three seconds concentric and four seconds for the eccentric phase was maintained using an electronic metronome (Kidgell et al. 2010). The use of an automated timing device was selected as previous research has shown that controlled slow velocity strength training facilitates greater changes in TMS evoked MEP responses compared to self-paced training (Leung et al. 2015). Progressive overload was applied once participants could complete 4 sets of 8 repetitions by increasing the training weight by 2.5%.

## ***2.5 Surface electromyography***

The area of electrode placement was shaven to remove fine hair, rubbed with an abrasive skin gel to remove dead skin, and then cleaned with 70% isopropyl alcohol. sEMG was recorded from the right Biceps Brachii and right Flexor Carpi Radialis muscle using bipolar Ag-AgCl electrodes. For the Biceps Brachii, the site of measurement was determined by marking the skin two thirds of the distance between the acromion and the lateral epicondyle, while the participant stood relaxed in the anatomical position (Pearce et al. 2013). This mark was then extended to the most anterior point of the muscle bulk where the electrodes were placed 2 cm apart over the mid-belly of the Biceps Brachii, with a ground electrode secured on the lateral epicondyle of the humerus (Wilson et al. 1993).

sEMG was also recorded from the right Flexor Carpi Radialis muscle using bipolar Ag-AgCl electrodes as described by Selvanayagam et al. 2011. The electrodes for the Flexor Carpi Radialis were positioned 9 cm from the medial epicondyle of the humerus with an

inter-electrode distance of 2 cm (Selvanayagam et al. 2011). A grounding strap was placed around the wrist as the common reference point for all electrodes. sEMG signals were amplified (x1000), band pass filtered (20 Hz - 1 kHz), digitized online at 2 kHz, recorded (1 sec) and analysed using Power Lab 4/35 (AD Instruments, Bella Vista, Australia).

## ***2.6 Transcranial magnetic stimulation***

TMS was delivered using a MagPro Compact (MagVenture A/S, Lucernemarken, Denmark) and a single C-B60 Butterfly Coil (external diameter of each loop 75 mm). The motor hotspots for both the right Biceps Brachii and Flexor Carpi Radialis (with posterior-to-anterior-induced current flow in the cortex) was determined, and active motor threshold (AMT) was established as the stimulus intensity at which at least 5 of 10 stimuli produced motor evoked potential (MEP) amplitudes of greater than 200  $\mu$ V (Rossini et al. 1999). Following the strength training intervention, AMT was retested and adjusted if required. To ensure all stimuli were delivered to the optimal motor hotspots throughout testing, participants wore a tight-fitting cap marked with a latitude-longitude matrix, positioned with reference to the nasion-inion and interaural lines.

All stimuli were delivered during a low-level isometric contraction of the right Biceps Brachii and the Flexor Carpi Radialis. For the MEPs obtained from the Biceps Brachii, participants were required to maintain an elbow joint angle of 90 degrees elbow flexion. Joint angle was measured with an electromagnetic goniometer (ADInstruments, Bella Vista, Australia), with visual feedback provided on a screen visible to both the participant and the researcher (Hendy and Kidgell 2013). Holding the lower arm in this joint position equated to  $5 \pm 1\%$  of the maximal root-mean squared electromyography (*rmsEMG*). Because this position resulted in a low level of muscle activity, and to ensure that background muscle activity was consistent between TMS stimuli, *rmsEMG* were recorded 100-ms before the

delivery of each TMS pulse. During the TMS trials, visual feedback was presented to the volunteer to display an upper limit of 5% *rmsEMG*; participants were instructed to maintain their muscle activation levels below this upper limit. The stimulus delivery software (LabChart 8 software, ADInstruments, Bella Vista, NSW, Australia), was set so that stimuli were not delivered if the *rmsEMG* value, 100 ms immediately prior to the stimulus, exceeded  $5 \pm 1\%$  (Table 1). The MEPs obtained from the Flexor Carpi Radialis were collected during low-level isometric contractions of the wrist flexors. Low-level contractions equated to  $5 \pm 1\%$  of root mean square electromyography (*rmsEMG*) during MVIC and were performed by maintaining the wrist and fingers in a straight position (Hendy and Kidgell 2013). This level of background sEMG has been previously used to produce reliable MEPs amplitudes and SP durations (Sale and Semmler 2005; Kidgell et al. 2015) and represents 2% of MVC force. The order of testing for the construction of corticospinal excitability and inhibition recruitment curves were randomized between the Biceps Brachii and Flexor Carpi Radialis.

### ***2.7 Maximum compound muscle action potential***

Direct muscle responses were obtained from the right Biceps Brachii muscle by supramaximal electrical stimulation (pulse width, 200  $\mu$ s) of the brachial plexus at Erbs point (DS7A; Digitimer, Hertfordshire, United Kingdom). The stimuli were delivered while the participant sat in an upright position, with the elbow at 90 degrees elbow flexion holding  $5 \pm 1\%$  of maximal *rmsEMG*. This low level of muscle activity was used to match the conditions under which TMS was delivered (Frazer et al. 2016). An increase in current strength was applied to Erbs point until there was no further increase observed in the RMS amplitude of the sEMG response ( $M_{MAX}$ ).

Direct muscle responses were also obtained from the right Flexor Carpi Radialis muscle by supramaximal electrical stimulation (pulse width 200  $\mu$ s) of the median nerve under active conditions ( $2 \pm 1\%$  *rmsEMG* [DS7A, Digitimer, Hertfordshire, UK]). The site

of stimulation that produced the largest M-wave was located by positioning the bipolar electrodes in the cubital fossa. An increase in current strength was applied to the median nerve until there was no further increase observed in the amplitude of the sEMG response ( $M_{MAX}$ ) (Kidgell et al. 2015). To ensure maximal responses from both the Biceps Brachii and Flexor Carpi Radialis, the current was increased an additional 20% and the average  $M_{MAX}$  was obtained from five stimuli, with a period of 6–9 seconds separating each stimulus.  $M_{MAX}$  was recorded at baseline and following the strength training intervention to control for possible changes in peripheral muscle excitability that could influence MEP amplitude.

### **2.10 Data analysis**

Pre-stimulus *rms*EMG activity was determined in the right Biceps Brachii and Flexor Carpi Radialis 100 ms prior to each TMS stimulus during pre- and post-testing. The peak-to-peak amplitude of MEPs evoked as a result of stimulation was measured in the right Biceps Brachii and Flexor Carpi Radialis contralateral to the cortex being stimulated in the period 10-50 ms after stimulation. MEP amplitudes were analyzed (LabChart 8 software, ADInstruments, Bella Vista, NSW, Australia) after each stimulus was automatically flagged with a cursor, providing peak-to-peak values in  $\mu$ V, averaged and normalized to the  $M_{MAX}$ , and multiplied by 100, separately for the Biceps Brachii and Flexor Carpi Radialis.

Silent period durations were obtained from single-pulse stimuli delivered at 130-170% AMT during a light elbow flexor contraction ( $5 \pm 1$  % of maximal *rms*EMG), separately from the Biceps Brachii and Flexor Carpi Radialis. The duration between the onset of the MEP and the resolution of background sEMG was visually inspected and manually cursoried, with the experimenter blinded to each condition. The average from 10 stimuli was used for silent period duration (Wilson et al. 1993).

In addition, the total area under the recruitment curve (AURC) was calculated with the method of trapezoidal integration using the data collected during the construction of corticospinal excitability and inhibition recruitment curves for both the Biceps Brachii and Flexor Carpi Radialis separately. In this regard, 10 single-pulse stimuli were delivered at 130-170% AMT for both the Biceps Brachii and Flexor Carpi Radialis. Data from AURC was presented as arbitrary units (AU) (Talelli et al. 2008; Carson et al. 2013).

### ***2.11 Statistical analysis***

All data were screened with the Shapiro-Wilk test and found to be normally distributed (all  $P > 0.05$ ) and thus the assumptions of the ANOVA were not violated. To ensure that there were no significant differences between groups at baseline, a one-way analysis of variance (ANOVA) was used for all dependent variables. A two-way repeated measures ANOVA was used to compare the effects of strength training and no training (GROUP) on multiple dependent variables (1-RM strength, MVIC force, pre-stimulus sEMG, corticospinal excitability, silent period duration and AURC for the agonist and synergist) over 2 TIME points (pre-testing and post-testing). Bonferroni correction for multiple comparisons was applied for each dependent variable where significant multivariate effects were found. In order to determine if any changes in the AURC for corticospinal excitability and inhibition were different between the agonist and the synergist muscle following the strength training program, paired *t-tests* were used. Linear regression analysis was also used to examine any potential association between changes in muscle strength [(post strength/pre strength x 100) - 100], changes in MEP amplitude after training (pooled MEP amplitude post/pre x 100) - 100], and changes in silent period duration after training (pooled silent period duration post/pre x 100) - 100] for both the agonist and synergist muscle. Prism 7.1 for

Windows (Graphpad Software Inc, CA, USA) was used for all statistical analyses with the level of significance set as  $P < 0.05$  for all testing. All data are presented as mean  $\pm$  SE.

### **3.0 RESULTS**

#### ***3.1 Pre-stimulus rmsEMG, Maximal Compound Waves, and Motor Thresholds***

Table 1 presents the mean ( $\pm$  SE) for AMT stimulus intensity,  $M_{MAX}$  and single-pulse TMS pre-stimulus *rmsEMG* amplitude prior to and following strength training for the Biceps Brachii, whilst Table 2 presents the mean ( $\pm$  SE) for AMT stimulus intensity,  $M_{MAX}$  and single-pulse TMS pre-stimulus *rmsEMG* for the Flexor Carpi Radialis. At baseline there were no differences in pre-stimulus *rmsEMG*, AMT stimulus intensity and  $M_{MAX}$  between groups for Biceps Brachii and Flexor Carpi Radialis (all  $P > 0.05$ ). Pre-stimulus *rmsEMG* did not vary for single-pulse TMS trials, and there were no TIME or interactions effects ( $P > 0.05$ ). Similarly, there was no TIME or interactions detected for AMT stimulus intensity or  $M_{MAX}$  (all  $P > 0.05$ ).

#### ***3.2 Maximal voluntary force***

##### ***3.2.1 Biceps Brachii Strength***

At baseline there were no differences in 1-RM Biceps Brachii strength between groups ( $P = 0.938$ ). Following strength training, there was a main effect for TIME ( $P = 0.019$ ) and a GROUP x TIME interaction ( $P = 0.0009$ , Figure 2a). *Post hoc* analysis revealed a 29% increase in 1-RM strength (pre  $11.0 \pm 1.5$  kg compared to post  $14.5 \pm 1.5$  kg) following three-weeks of strength training compared to the control group (pre  $11.0 \pm 1.5$  kg compared to post  $11.0 \pm 1.5$  kg,  $P = 0.0009$ ).



### **3.2.2 Wrist Flexor Strength**

At baseline there was no difference in MVIC force for the wrist flexors between groups ( $P = 0.902$ ). Following strength training, there was a main effect for TIME ( $P < 0.0001$ ) and a GROUP x TIME interaction ( $P < 0.0001$ , Figure 2b). *Post hoc* analysis revealed a 19% increase in strength (pre  $333.5 \pm 32.4$  N compared to post  $397.3 \pm 32.6$  N) following three-weeks of strength training compared to the control group (pre  $338.7 \pm 26.9$  N compared to post  $339.8 \pm 29.2$  N,  $P < 0.001$ ).

### **3.2.3 Change in agonist and synergist strength**

Using linear regression, a significant positive relationship was observed between the change in Biceps Brachii strength and the change in synergistic strength of the Flexor Carpi Radialis ( $r^2 = 0.523$ ,  $P = 0.009$ ), following strength training (Figure 3).

## **3.3 Corticospinal excitability**

### **3.3.1 Biceps Brachii**

Figure 4a-b shows the AURC obtained prior to and following the strength training intervention for the Biceps Brachii and Flexor Carpi Radialis. Total AURC were similar between groups at baseline ( $P = 0.556$ ). Following strength training, there was a main effect for TIME ( $P < 0.001$ ), and a GROUP x TIME interaction ( $P = 0.035$ ). *Post hoc* analysis showed that three-weeks of isotonic strength training of the Biceps Brachii resulted in a 49% increase (pre  $1542 \pm 247$  arb. units; post  $2308 \pm 318$  arb. units) in the total AURC compared to a 2% decrease (pre  $1651 \pm 158$  arb. units; post  $1611 \pm 119$  arb. units,  $P = 0.035$ ) in the control group.

### **3.3.2 Flexor Carpi Radialis**

For the Flexor Carpi Radialis, total AURC were similar between groups at baseline ( $P = 0.839$ ). Following strength training, there was a main effect for TIME ( $P = 0.001$ ) and GROUP x TIME interaction detected ( $P = 0.006$ ). Following strength training, there was a 29% increase (pre  $1756 \pm 165$  arb. units; post  $2274 \pm 150$  arb. units) in the total AURC for Flexor Carpi Radialis. However, *post hoc* analysis revealed that the magnitude of change in total AURC was not statistically significant to the control group (pre  $1841. \pm 147$  arb. units; post  $2009 \pm 179$  arb. units,  $P = 0.441$ , Figure 5a-b).

We also examined if the magnitude of change in the AURC for corticospinal excitability was different between the agonist and synergist muscle following the strength training intervention. Paired-samples *t-test* showed that there was no difference in the magnitude of change in corticospinal excitability between the trained agonist and the synergist muscle ( $t = 0.101$ ,  $P = 0.921$ ).

### **3.3.3 Changes in Corticospinal excitability and muscle strength**

Using linear regression, there was no association between the change in Biceps Brachii MEP amplitude and the change in maximum strength of Biceps Brachii ( $r^2 = 0.017$ ,  $P = 0.351$ ). In a similar manner, there was a poor association between the change in MEP amplitude of the Flexor Carpi Radialis and the change in maximum strength of the synergist wrist flexors ( $r^2 = 0.043$ ,  $P = 0.563$ ).

## **3.4 Corticospinal inhibition**

### **3.4.1 Biceps Brachii**

Figure 6a-b shows the total AURC obtained for corticospinal inhibition prior to and following the strength training intervention for the Biceps Brachii. For the Biceps Brachii,

total AURC were similar between groups at baseline ( $P = 0.462$ ). Following the intervention, there was a main effect for TIME ( $P < 0.001$ ) and a GROUP x TIME interaction detected ( $P = 0.023$ ). *Post hoc* analysis revealed that three-weeks of strength training of the Biceps Brachii, resulted in a 17.5% decrease (pre  $6.20 \pm 0.22$  arb. units; post  $5.11 \pm 0.12$  arb. units) in the total AURC compared to a 1% decrease (pre  $6.11 \pm 0.29$  arb. units; post  $6.04 \pm 0.27$  arb. units,  $P = 0.035$ ) in the control group.

### ***3.4.2 Flexor Carpi Radialis***

Figure 7a-b shows the total AURC obtained for corticospinal inhibition prior to and following the strength training intervention for the Flexor Carpi Radialis. The total AURC for corticospinal inhibition were similar between groups at baseline ( $P = 0.585$ ). Following three-weeks of strength training, there was a main effect for TIME ( $P < 0.0001$ ), and GROUP x TIME interaction detected ( $P = 0.03$ ). Following strength training, there was a 13% decrease (pre  $6.4 \pm 0.3$  arb. units; post  $5.6 \pm 0.2$  arb. units) in the total AURC for the wrist flexors compared to a 1% decrease in the control group (pre  $6.28 \pm 0.3$  arb. units; post  $6.2 \pm 0.2$  arb. Units,  $P < 0.02$ ).

We also examined if the magnitude of change in the AURC for corticospinal inhibition was different following the strength training intervention between the agonist and synergist muscle. Paired-samples *t-test* showed that there was no difference in the magnitude of change in corticospinal inhibition between the trained agonist and the trained synergist muscle ( $t = 0.171$ ,  $P = 0.236$ ).

### ***3.4.3 Changes in Corticospinal inhibition and muscle strength***

Using linear regression, there was no association between change in Biceps Brachii silent period duration and the change in maximum strength of Biceps Brachii ( $r^2 = 0.072$ ,  $P = 0.453$ ). In a similar manner, there was no association between the change in silent period

duration of the Flexor Carpi Radialis and the change in maximum strength of the synergistic wrist flexor ( $r^2 = 0.136$ ,  $P = 0.293$ ).

#### **4.0 DISCUSSION**

In the present study, we examined whether metronome-paced strength training elicited changes in corticospinal excitability and inhibition of the trained agonist and synergist muscle. Our main findings were: corticospinal excitability increased (i.e., AURC) and corticospinal inhibition (i.e., silent period duration) decreased in both the agonist and synergist, however, the changes in corticospinal activity (excitability and inhibition) was not associated with improved muscle strength. Although the relationship between strength improvements and corticospinal excitability and inhibition are not conclusive, these data provide evidence that the corticospinal responses to strength training of a proximal upper limb muscle is not spatially confined, but rather, results in a change in the strength of connectivity, among an agonist and synergist muscle relevant to force production. Collectively, the findings suggest that strength-training manifests in an adaptation that occurs at more than one site on the M1 and along the corticospinal tract to more than one muscle involved in the training task. The finding that metronome-paced strength training induces spatial changes in corticospinal excitability and inhibition, have important clinical implications for movement rehabilitation.

***Corticospinal excitability is not spatially confined to an agonist muscle following metronome-paced strength training:***

Although it is well established that neural mechanisms are to likely mediate the rapid development of strength following strength training (Enoka 1997; Carroll et al. 2002; Gabriel et al. 2006), there is less agreement concerning the sites of adaptation in the CNS (Carroll et

al. 2011; Taube 2011). Studies that have used TMS in either resting and slightly active muscle activity, have reported no changes in corticospinal excitability despite large increases in voluntary strength (Carroll et al. 2002; Jensen et al. 2005; Lee et al. 2009; Kidgell and Pearce 2010; Christie and Kamen 2013; Coombs et al. 2016). In contrast, one study reported a 32% increase in MEP amplitude following isometric strength training of the tibialis anterior (Griffin and Cafarelli 2007), whilst another study reported a 21% increase following ballistic strength training (Beck et al. 2007). Also, both acute and training studies that have used transcranial electrical stimulation (TES) and cervicomedullary stimulation, have shown that strength training alters the functional properties of the spinal cord circuitry, but does not affect the organisation of the M1 (Carroll et al. 2002; Adkins et al. 2006; Nuzzo et al. 2016). More recently, strength training that is paced to an audible metronome (i.e., metronome-paced strength training), have consistently demonstrated, increased MEP amplitudes following isotonic strength training (Kidgell et al. 2010; Kidgell et al. 2011; Pearce et al. 2013; Weier et al. 2012; Leung et al. 2015). Irrespective of this, strength training (at least in part) is a form of motor learning (Carroll et al. 2002), and as such, plastic changes may occur within the CNS at both a cortical level (Butefisch et al. 2000; Weier et al. 2012) and spinal level (Dayan and Cohen 2011) following motor training. However, because the descending volleys elicited by TMS, travel through the corticospinal tract, the change in MEP amplitude and silent period duration following the strength training program suggest that modifications in corticospinal excitability and inhibition are occurring at both a cortical and spinal level, making the site of adaptation within the CNS unclear.

Despite the limitation above, and given that we have reported that the spatial effects of corticospinal excitability are not limited to just the trained agonist muscle (Biceps Brachii), this provides evidence that both the M1 and corticospinal tract work as a dynamic and integrated neural network to execute the required muscle contractions during the strength

training program (Porter and Lemon 1993; De Luca and Erim 2002; Capaday et al. 2013). For example, during the agonist contraction (Biceps Brachii), synergistic muscles (such as wrist flexors) were involved and controlled as a coupled system alongside the agonist, rather than singly and separately activated (Capaday et al. 2013). Consequently, during metronome-paced strength training, the isometric contribution of the synergistic wrist flexors was not a simple, isolated muscle response. Instead, it formed part of the integrated, functional movement synergy, which involved an integrated neural network involving both the M1 and corticospinal tract. On this basis, such a response, is too complex to originate and be co-ordinated/controlled purely at the peripheral muscle level, and is instead executed and controlled by the M1 and corticospinal tract (Smith and Fetz 2009; Capaday et al. 2013).

An important finding from the current study was the overall gain in the stimulus-response curve in the agonist and synergist muscles examined. The increase in the AURC, represents an increase in motor neuron recruitment, over the same stimulus-intensity, showing that metronome-paced strength training increases corticospinal excitability to the same extent for two muscle representations. Taken together, the excitability of the corticospinal tract to the Biceps Brachii and Flexor Carpi Radialis was elevated following strength training, showing enhanced synaptic efficacy within the corticospinal tract. Collectively, the enhanced AURC manifests as an increase in the excitability of corticospinal neurons innervating the agonist and synergist motor neurons. Alternatively, because of the metronome-paced strength training task, there could have been an increase in the activation of a group of corticospinal neurons in a task-specific manner (Porter and Lemon 1993; Capaday et al. 2013). Therefore, we propose that the increase in the AURC following metronome-paced strength training likely results from a decrease in corticospinal inhibition and an increase in persistent excitation between intracortical circuits that control both the Biceps Brachii and Flexor Carpi Radialis. This seems possible, given that, even simple

voluntary isometric contractions (i.e., finger abduction), decreases corticospinal inhibition (Ortu et al. 2008).

***Corticospinal inhibition is reduced following metronome-paced strength training:***

Although previous TMS and strength training literature have reported inconsistencies in corticospinal excitability underpinning the gain in muscle strength, only a few studies have examined the role of intracortical inhibitory mechanisms that may affect muscle strength. In the current study, not only do we report a reduction in the AURC for silent period duration for the trained agonist, but also for a synergistic muscle. Specifically, metronome-paced strength training resulted in an 18% reduction in silent period duration for the Biceps Brachii and a 13% reduction for the synergistic Flexor Carpi Radialis. Importantly, the magnitude of silent period reduction was not different between the agonist and synergist, suggesting that the strength training program led to modified GABA<sub>B</sub>-sensitive neural networks in both cortical representation of the Biceps Brachii and the synergistic Flexor Carpi Radialis.

The reduction in silent period duration of the agonist Biceps Brachii and synergistic Flexor Carpi Radialis is in line with previous research whereby simple, submaximal tasks, including isometric contractions, reduce corticospinal inhibition of the target muscle (Ridding et al. 1995; Ortu et al. 2008; Hortobágyi et al. 2011). However, the reduction in silent period duration, in the current study, is not simply an isolated response due to its submaximal and isometric contribution to the metronome-paced strength training exercise. It seems that corticospinal inhibition mediated at the level of the M1 acts spatially to reduce inhibitory input to muscles, which are involved in a movement synergy (i.e., elbow flexion) and combine in the production of maximal force. This synergy seems to be regulated by a dynamic and integrated neural network between the M1 and corticospinal tract, which is not spatially restricted (Baldissera et al. 1987; De Luca and Erim 2002). The results of this study

support this notion and reductions in inhibition are not confined to the trained agonist muscle, but also to synergistic muscles.

The precise role that corticospinal inhibition plays in motor performance remains unclear, however, there is good evidence to show that the activity of cortico-motoneuronal cells increase linearly with increased force production (Cheney and Fetz 1980; Ashe 1997). For example, in humans it has been shown that the M1 and corticospinal tract are important for the expression of muscle strength (Kidgell and Pearce 2010; Kidgell and Pearce 2011; Latella et al. 2012; Weier et al. 2012; Christie and Kamen 2013; Coombs et al. 2016). Interestingly, following limb immobilization, the silent period duration increases and muscle strength decreases (Clark et al. 2008), whilst motor training seems to attenuate the prolongation of the silent period and maintain strength (Pearce et al. 2013; Clark et al. 2014).

The current findings are in agreement with previous observations that have examined the integrated motor control strategy for an upper-limb, pointing task (Devanne et al. 2002). Because the metronome-paced strength training task involved repeated controlled elbow flexion and extension, this by default requires the co-activation of several muscles. Previous research has shown that muscle co-activation reduces intracortical inhibition, specifically short-interval intracortical inhibition (SICI) and silent period duration is reduced compared to the activation of a single isolated muscle (Devanne et al. 2002). Certainly, this supports recent strength training research, whereby intracortical inhibition is reduced during metronome-paced strength training which engages several sets of muscles (Goodwill et al. 2012; Weier et al. 2012; Leung et al. 2015). Overall, metronome-paced strength training releases intracortical inhibition (i.e., decreased synaptic efficacy between intracortical inhibitory neurons and corticospinal neurons) from two motor cortical areas, which has collectively improved neural transmission along the corticospinal tract, improving the activation of the motor neuron pool for two muscles.



It seems that strength training that involves paced-contractions, have a distinctive capacity to modify the excitability of the corticospinal tract to two distinct muscle representations. Such a finding could be used to enhance functional connectivity and functional capacity in people with neuromuscular deficiencies. Although, we have showed no direct association between the changes in corticospinal activity and muscle strength, this effect is still important because an extensive increase in corticospinal excitability and a reduction in corticospinal inhibition (changes in muscle representations) could feasibly play a critical role in the reacquisition of muscle strength following injury (Clark et al. 2008).

There are several limitations to the present study that should be considered when interpreting the current findings. First, in order to study the pure effect of strength training on corticospinal excitability and inhibition an additional training group without the external pacing would have been helpful (i.e., self-paced training). However, the external pacing does not invalidate the interpretation about the functional connectivity between the two muscles and adds new knowledge regarding the neural adaptations to strength training. Second, some studies report that disinhibition of antagonist muscles is a neural adaptation to strength training (Carolan and Cafarelli, 1992; Häkkinen et al. 1998); however, we did not measure any changes in the Triceps Brachii. In light of this, it should also be noted, there is evidence to show that no changes in co-activation of antagonists occur following strength training (Reeves et al. 2005). In addition, given that strength training increases motor neuron excitability at the level of the spinal cord (Aagaard et al. 2002), measuring cervicomedullary evoked potentials would provide additional information about the site of adaptation in the CNS. Lastly, obtaining TMS voluntary activation (i.e., increase in neural drive to the trained muscles) measures from the agonist and synergist would strengthen the methodological quality, however, such measures are technically difficult.

This is the first TMS metronome-paced strength training study to report changes in corticospinal excitability and inhibition in an agonist and synergist muscle. The main findings suggest that strength training specifically modulates corticospinal excitability and inhibition, via the recurrent excitation of intracortical circuits that control both the agonist and synergetic motor neuron pool. Importantly, corticospinal input to the motor neuron pool of two muscles is balanced, therefore the changes in corticospinal excitability and inhibition are similar between the agonist and synergist. These findings have clinical importance to rehabilitation, whereby an integrated strength training exercise can induce changes in the M1 and corticospinal tract to more than one muscle (i.e., the agonist and synergist), thus demonstrating that metronome-paced strength training has a spatial effect on the activation of the motor neuron pool.

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**Table 1.** Mean ( $\pm$  SE) for AMT stimulus intensity,  $M_{MAX}$  and single-pulse TMS pre-stimulus *rmsEMG* prior to and following three weeks of strength training for the Biceps Brachii.

	Control		Trained		<i>P</i> value
	Pre	Post	Pre	Post	
<b>AMT SI (%)</b>	45.30	46.80	47.80	47.50	0.25
	$\pm 2.35$	$\pm 2.45$	$\pm 2.48$	$\pm 2.26$	
<b><math>M_{MAX}</math> (mV)</b>	7.41	7.68	7.40	7.86	0.55
	$\pm 0.88$	$\pm 0.84$	$\pm 1.38$	$\pm 1.22$	
<b>SP <i>rmsEMG</i></b>	4.27	4.86	3.81	4.65	0.51
<b>(% <i>rmsEMG</i><sub>MAX</sub>)</b>	$\pm 0.88$	$\pm 0.51$	$\pm 0.68$	$\pm 0.84$	

AMT SI: active motor threshold stimulus intensity. Single pulse (SP) *rmsEMG* was pooled across stimulus intensities. *P* values represent the 2 (conditions) x 2 (time) repeated measures ANOVA used to determine any differences between group and time for the dependant variables AMT stimulus intensity,  $M_{MAX}$  and single-pulse TMS pre-stimulus *rmsEMG*.

**Table 2.** Mean ( $\pm$  SE) for AMT stimulus intensity,  $M_{MAX}$  and single-pulse TMS pre-stimulus *rmsEMG* prior to and following three weeks of strength training for the Flexor Carpi Radialis.

	Control		Trained		<i>P</i> value
	Pre	Post	Pre	Post	
<b>AMT SI (%)</b>	50.33	47.80	53.60	52.80	0.47
	$\pm 7.66$	$\pm 7.86$	$\pm 6.59$	$\pm 8.53$	
<b><math>M_{MAX}</math> (mV)</b>	5.13	4.56 $\pm$ 1.88	4.82	4.94	0.17
	$\pm 1.81$		$\pm 2.02$	$\pm 1.91$	
<b>SP <i>rmsEMG</i></b>	4.84	4.79	5.01	4.98	0.87
<b>(% <i>rmsEMG</i><sub>MAX</sub>)</b>	$\pm 1.36$	$\pm 0.98$	$\pm 1.18$	$\pm 1.88$	

AMT SI: active motor threshold stimulus intensity. Single pulse (SP) *rmsEMG* was pooled across stimulus intensities. *P* values represent the 2 (conditions) x 2 (time) repeated measures ANOVA used to determine any differences between group and time for the dependant variables AMT stimulus intensity,  $M_{MAX}$  and single-pulse TMS pre-stimulus *rmsEMG*.

## FIGURE LEGENDS

**Fig. 1** Schematic representation of the experimental design with measures obtained prior to and following three weeks of strength training of the right elbow flexors. Pre- and post-measures included assessment of peripheral muscle excitability ( $M_{MAX}$ ), corticospinal excitability and inhibition recruitment curves and muscle strength of the right Biceps Brachii and wrist flexors.

**Fig. 2a-b:** (a) Mean ( $\pm$  SE) changes in 1-RM strength of the right Biceps Brachii muscle and (b) mean ( $\pm$  SE) changes in MVIC strength of the right wrist flexors following three weeks of strength training of the right elbow flexors. \* indicates significant to control.

**Fig. 3:** Relation between changes in maximum strength of the agonist muscle (Biceps Brachii) and the synergist muscle (Flexor Carpi Radialis). There was a significant positive association between the gain in Biceps Brachii strength and strength of the synergistic wrist flexors ( $r^2 = 0.523$ ,  $P = 0.009$ ).

**Fig. 4a-b:** The AURC was calculated using the method of trapezoidal integration. The AURC obtained prior to the strength training intervention is shaded in grey. The additional area enclosed by the recruitment curve obtained following three weeks of strength training is patterned. (a) depicts the AURC calculated from corticospinal excitability recruitment curves of the Biceps Brachii for the control group whereby MEP amplitude was plotted against stimulus intensity. (b) depicts the AURC calculated from corticospinal excitability recruitment curves of the Biceps Brachii for the strength training group whereby MEP amplitude was plotted against stimulus intensity

**Fig. 5a-b:** The AURC was calculated using the method of trapezoidal integration. The AURC obtained prior to the strength training intervention is shaded in grey. The additional area enclosed by the recruitment curve obtained following three weeks of strength training is

patterned. **(a)** depicts the AURC calculated from corticospinal excitability recruitment curves of the wrist flexors for the control group whereby MEP amplitude was plotted against stimulus intensity. **(b)** depicts the AURC calculated from corticospinal excitability recruitment curves of the wrist flexors for the strength training group whereby MEP amplitude was plotted against stimulus intensity

**Fig. 6a-b:** The AURC was calculated using the method of trapezoidal integration. The AURC obtained prior to the strength training intervention is shaded in grey. The additional area enclosed by the recruitment curve obtained following three weeks of strength training is patterned. **(a)** depicts the AURC calculated from corticospinal inhibition recruitment curves of the Biceps Brachii for the control group whereby silent period duration was plotted against stimulus intensity. **(b)** depicts the AURC calculated from corticospinal inhibition recruitment curves of the Biceps Brachii for the strength training group whereby silent period duration was plotted against stimulus intensity

**Fig. 7a-b:** The AURC was calculated using the method of trapezoidal integration. The AURC obtained prior to the strength training intervention is shaded in grey. The additional area enclosed by the recruitment curve obtained following three weeks of strength training is patterned. **(a)** depicts the AURC calculated from corticospinal inhibition recruitment curves of the wrist flexors for the control group whereby silent period duration was plotted against stimulus intensity. **(b)** depicts the AURC calculated from corticospinal inhibition recruitment curves of the wrist flexors for the strength training group whereby silent period duration was plotted against stimulus intensity

Fig 1

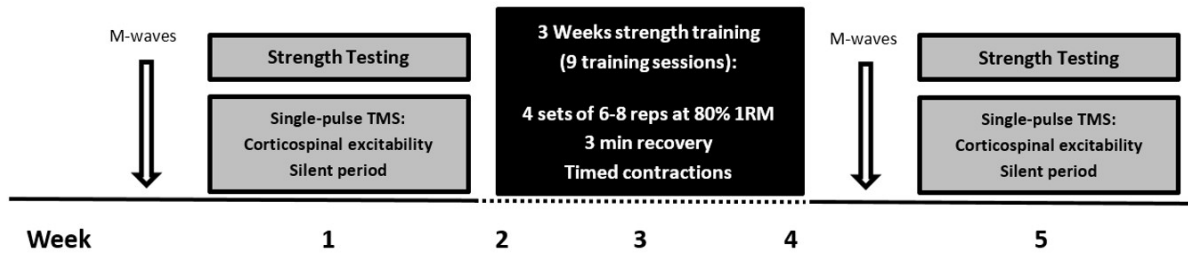


Fig 2

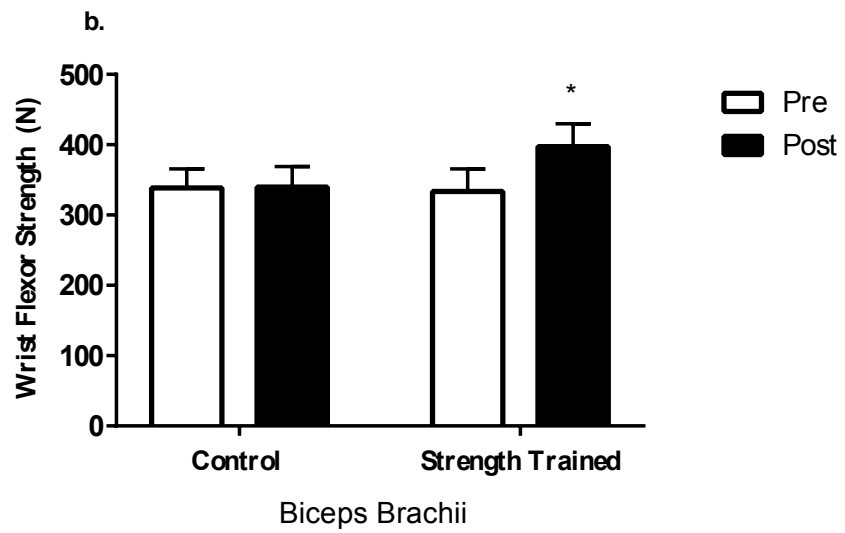
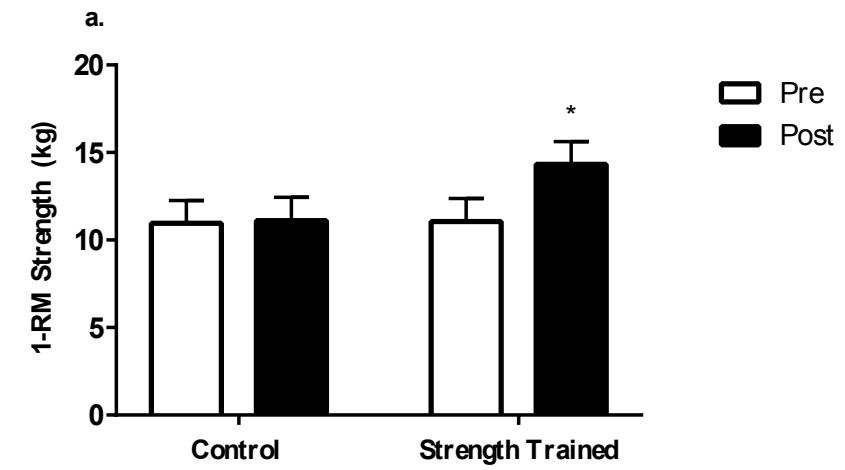


Fig 3

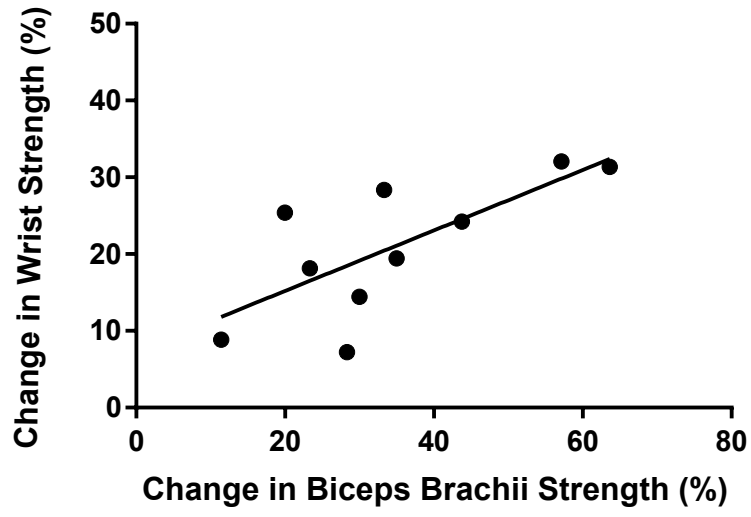




Fig 4

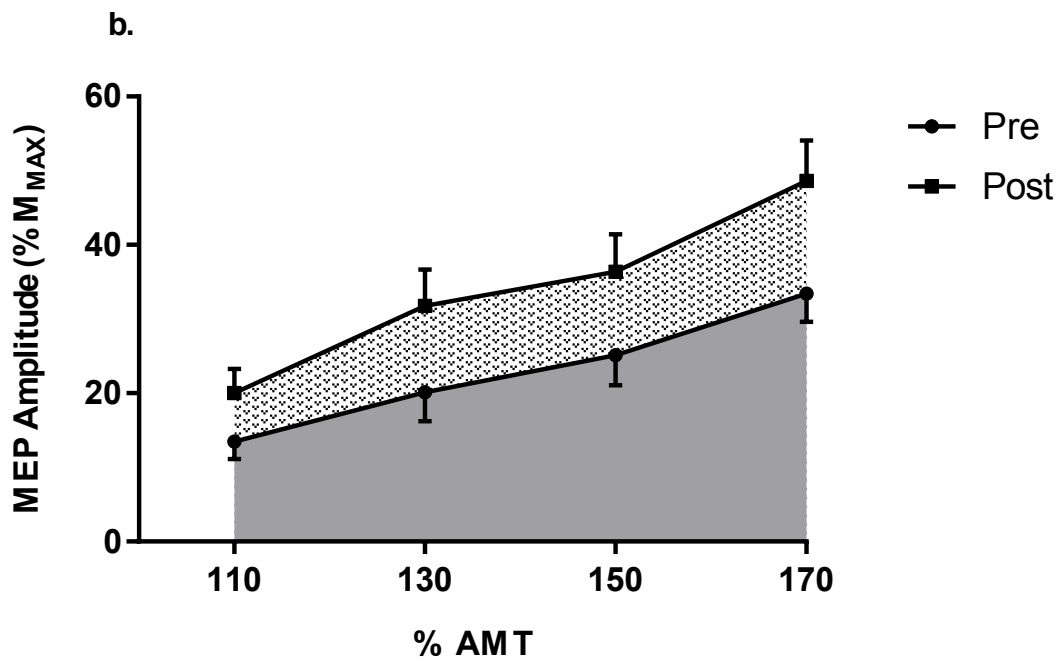
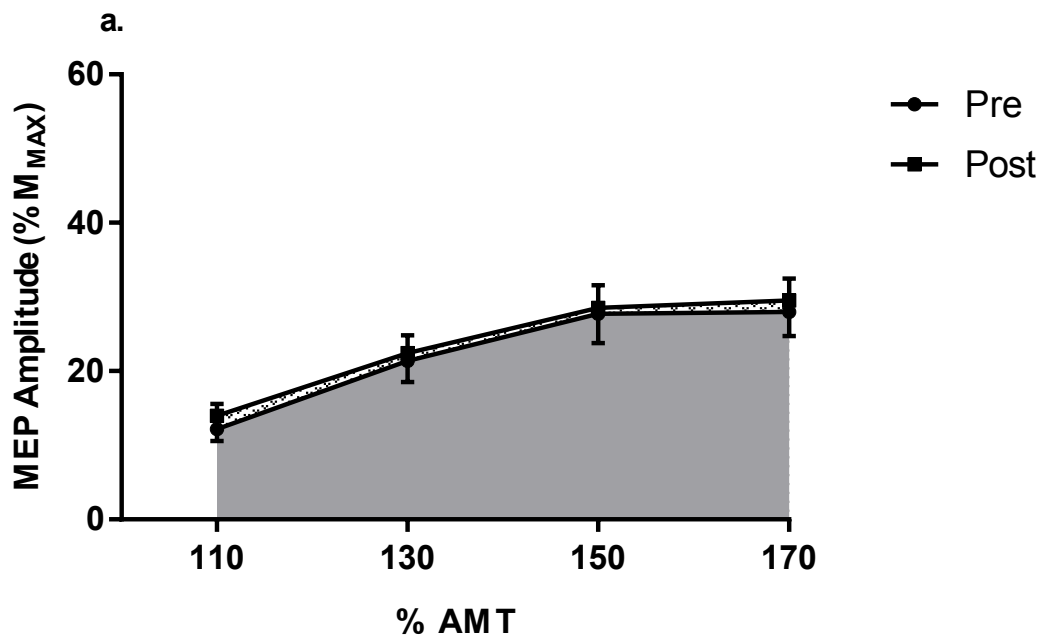


Fig 5

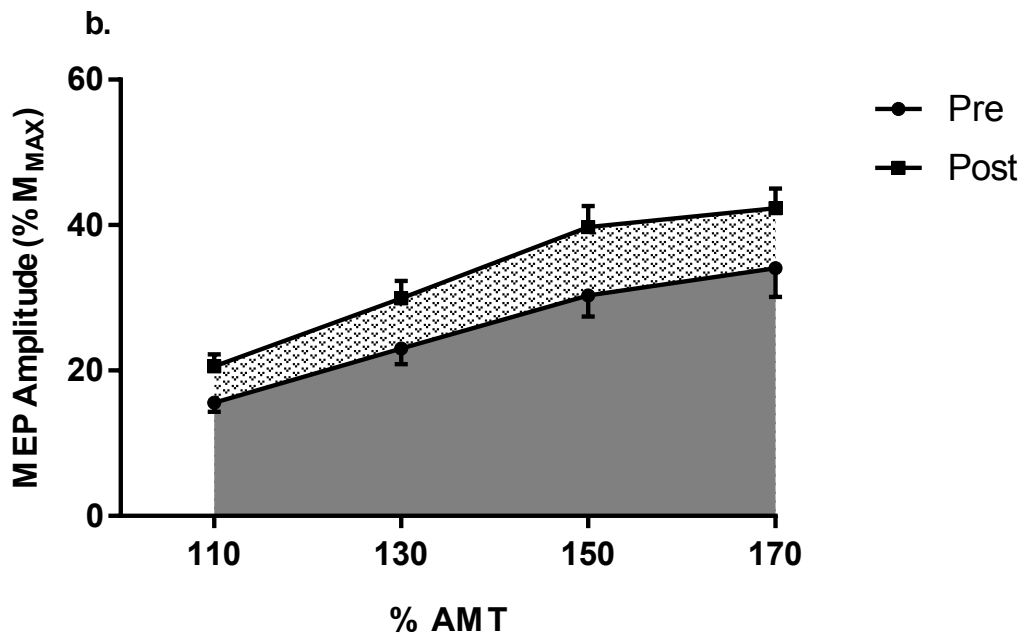
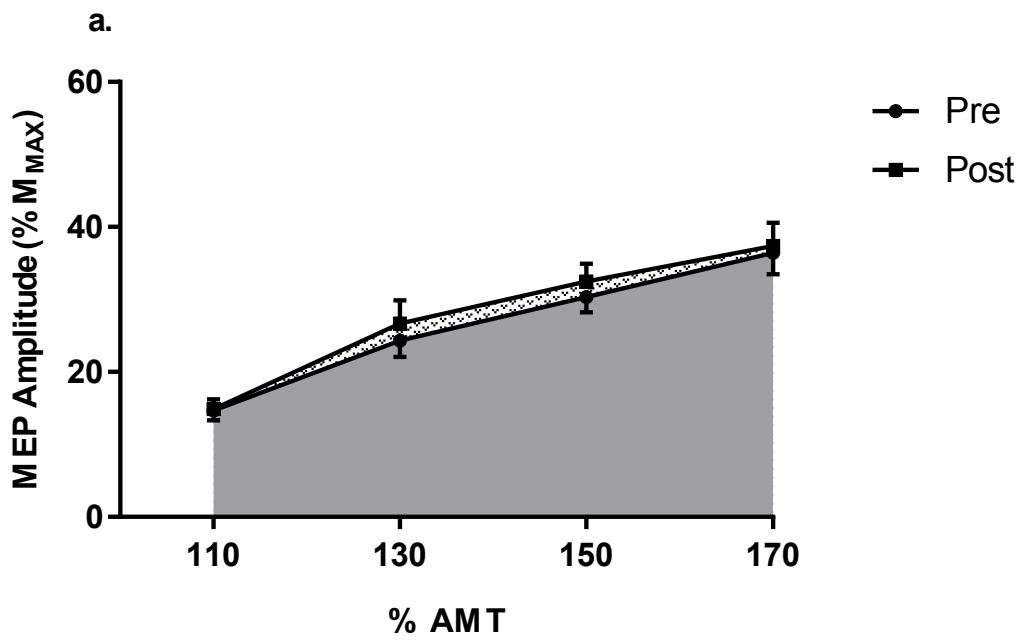


Fig 6

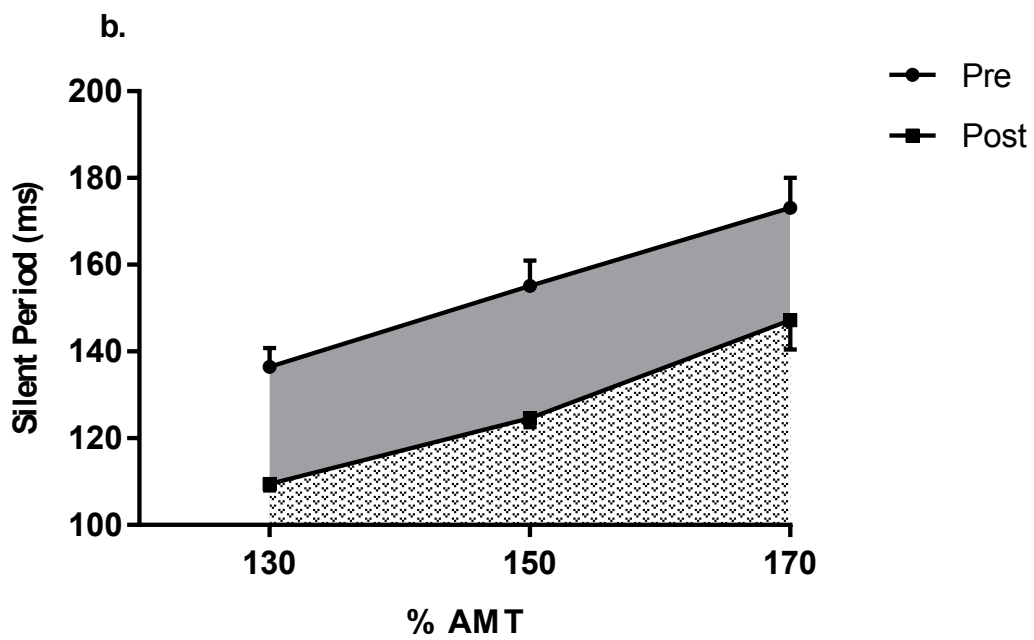
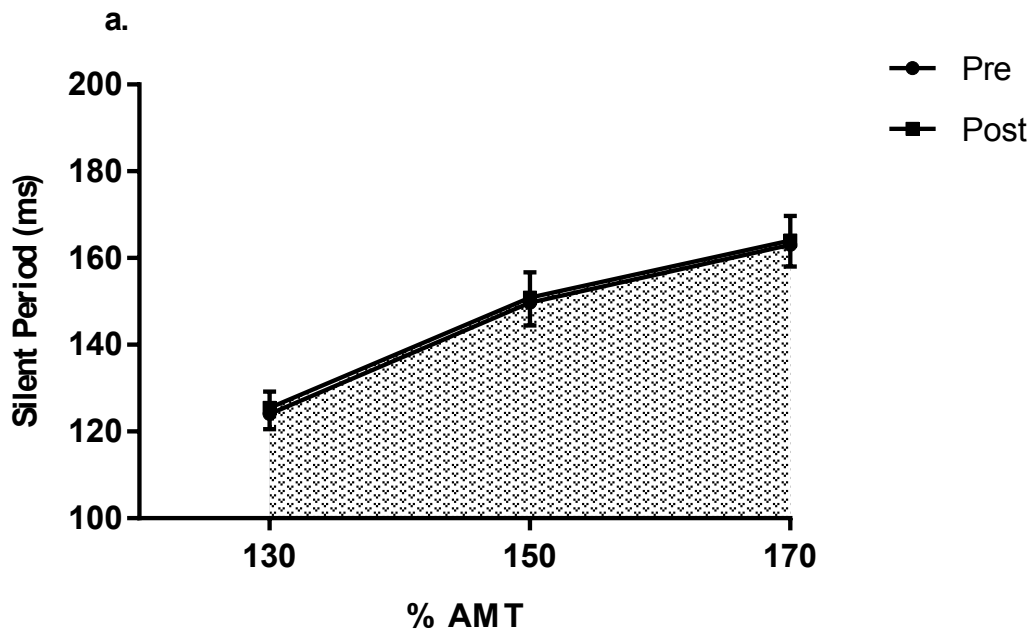


Fig 7

