Modulation of intracortical inhibition and excitation in agonist and antagonist muscles following acute strength training.

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Abstract

Purpose: Transcranial magnetic stimulation (TMS) usually investigates the corticospinal responses of the agonist muscle to strength training, despite the role of the antagonist muscle in strength development. We examined the intracortical responses from an agonist and antagonist muscle following a single session of heavy-loaded strength training (dominant-arm only) to identify the early antagonistic responses to a single session that may accompany improvements in strength.

Methods: Corticospinal and motor-cortical excitability and inhibition was collected from agonist and antagonist muscles prior to and following a single session of heavy-loaded wrist flexor training in 18 individuals. Training consisted of 4 sets 6-8 repetitions at 80% of 1-repetition maximum (1-RM). Recruitment curves for corticospinal excitability and inhibition of the right wrist flexor and wrist extensor muscles were constructed and assessed by examining the area under the recruitment curve (AURC). Intracortical measures were obtained using paired-pulse TMS.

Results: Following a single training session, increases in corticospinal excitability (CSE) were observed in both the agonist and antagonist muscles. This was accompanied by decreases in corticospinal inhibition (CSP) in both muscles. Intracortical inhibition was reduced and intracortical facilitation was increased for the agonist muscle only. Intracortical measures in the antagonist muscle remained unchanged after training.

Conclusions: These findings indicate that the corticospinal responses to a single session of strength training are similar between agonist and antagonist muscles, but the intrinsic cortico-cortical circuitry of the antagonist remains unchanged. The corticospinal responses are likely due to increased involvement/co-activation of the antagonist muscle during training as the agonist muscle fatigues.

Key words: Agonist; antagonist; corticospinal excitability; corticospinal silent period; intracortical facilitation; short-interval cortical inhibition; strength training

ABBREVIATIONS

1-RM: One-repetition maximum
AURC: Area under the recruitment curve
CSE: Corticospinal excitability
CSP: Corticospinal silent period
ECR: Extensor carpi radialis
EMG: Electromyography
FCR: Flexor carpi radialis
GABA: γ-Aminobutyric acid
ICF: Intracortical facilitation
LICI: Long-interval cortical inhibition
MEP: Motor-evoked potential
M_{MAX}: maximal compound wave
MVIC: Maximal voluntary isometric contraction
M1: Primary motor cortex
rmsEMG: Root-mean-square electromyography
sEMG: Surface electromyography
SICI: Short-interval cortical inhibition
TMS: Transcranial magnetic stimulation

Introduction

Following multi-week training programs, evidence indicates that factors such as increases in motor unit firing rates, increased neural drive to agonist muscles, as measured using voluntary activation, volitional waves, and reduced motor unit recruitment thresholds, accompany improvements in force production (Keen et al. 1994; van Cutse et al. 1998; Aagaard et al. 2002; Kamen & Knight 2004; Sale 1988). Some of the most profound insights regarding these early adaptations have been generated through the use of transcranial magnetic stimulation (TMS). TMS stimulates the primary motor cortex (M1) and corticospinal tract, allowing assessment of the excitatory and inhibitory pathways that provide understanding regarding voluntary movement and contribution of the nervous system to the expression of muscular strength. A single TMS pulse over the M1 generates a response in the corresponding muscle, which is captured via electromyography (EMG). This response is considered a reliable measure of corticospinal excitability ([CSE]; Christie et al. 2007; Hallett 2000) and is referred to as a motor evoked potential (MEP). During voluntary muscle activity and immediately following the MEP, a period of non-activity on the EMG trace reflects GABA-$_B$ mediated inhibition (Yacyshyn et al. 2016; Škarabot et al. 2019), which is referred to as the corticospinal silent period (CSP).

Paired-pulse TMS techniques can also be used to detect changes that are confined to neural networks of M1, through measures such as intracortical facilitation (ICF), and inhibitory measures such as short- and long-interval intracortical inhibition (SICI and LICI). Importantly, alterations in inhibitory responses are regarded as indices of improved motor performance, with reductions in inhibition consistently accompanying increases in muscular strength (Kidgell et al. 2018; Kidgell & Pearce 2010; Frazer et al. 2019; Leung et al. 2015; Latella, Kidgell & Pearce 2011; Manca et al. 2016). Accumulating evidence indicates that following a single session of strength training, the agonist muscle experiences an immediate increase in corticospinal and spinal excitability, as well as reductions in inhibitory measures (Mason et al. 2018; Nuzzo et al. 2016; Leung et al. 2015; Latella et al. 2016; Latella et al. 2017).

Notwithstanding, an inherent limitation of the TMS-strength-training literature is that responses are typically only assessed from the agonist muscle. This provides a narrow assessment of the corticospinal responses to training that does not account for the intermuscular co-ordination required for the development and expression of strength. This is particularly important given that a shift in the agonist-antagonist relationship appears to play a key role in driving strength increases (Tillin, Pain & Folland 2011). For example, Carolan & Cafarelli (1992) reported a 20% decrease in co-activation as early as 1-week in to an 8-week isometric strength training program of the quadriceps, which produced a 32.8% increase in muscular strength. These findings are supported by other research that showed decreases in co-activation that accompanied improvements in strength following training programs of up to six months in duration (Hakkinen 1998; 2000). The behaviour of the antagonist muscle in strength

performance is further validated by cross-sectional evidence that strength and power-trained athletes show lower levels of co-activation than untrained participants (Baratta et al. 1988; Osternig et al. 1986), and regular tennis players display less elbow flexion co-activation than non-players (Bazzucchi, Riccio & Felici 2008). Decreased levels of strength because of age or disease are also accompanied by substantial increases in co-activation (Macaluso et al. 2002; Busse, Wiles & van Deursen 2005; Morita et al. 2001). Therefore, gaining a greater understanding of the corticospinal responses of antagonist muscles following strength training can provide insight into the neural mechanism that regulate strength development.

The evidence that the antagonist muscle is important in the development and expression of strength is clear, but the locus and control of these changes remains less well established. It is purported that antagonist activity is modulated by a complex interaction between spinal and cortical mechanisms (Hortobagyi & Devita 2006). Spinal cord circuitry is well evidenced to be a mediator of intermuscular co-ordination (Nielsen 2004), including reciprocal inhibition, which ensures that motoneurones innervating antagonist muscles are synchronously inhibited with the activation of motoneurones innervating agonist muscles (Crone & Nielsen 1989; Baldissera, Hultborn & Illert 2011; Gorassini et al. 2002). Similar inhibitory connections also exist in the M1, which ultimately project to the antagonist muscles (Capaday et al. 1998, 2013; Bertolasi et al. 1998). This reinforces evidence that central mechanisms are responsible for the control of antagonist muscles (Dal Maso et al. 2017; De Luca & Mambrito 1987; Mullany et al. 2002; Levenez et al. 2008).

Given reductions in co-activation are a primary determinant of strength improvements, and that these changes may be observable as early as the second session of training (High et al. 2017), it is hypothesised that the antagonist muscle experiences immediate modulation of both corticospinal and intracortical circuitry, as is the case with the agonist muscle. However, this remains unexamined. Therefore, the aim of the current study was to identify the motor cortical and corticospinal responses of antagonist muscle in relation to the corresponding changes of the agonist muscles following a single bout of heavy-loaded strength training, in order to determine the early neural responses of the antagonist muscle that may ultimately generate improvements in strength.

Method

Study Design and Participants

This was a randomised, counterbalanced, cross-over design whereby participants completed a control condition and an experimental condition that involved heavy-loaded strength training of the wrist flexors. All participants provided written informed consent prior to participation. Eighteen healthy individuals (8 female, age 23.38 ± 3.29; 10 male, age 26.80 ± 9.60) were selected on a voluntary basis

and all experiments were conducted according to the standards established by the Declaration of Helsinki, and the project was approved by the University Human Research Ethics Committee (MUHREC 11882). All participants were right handed according to the Edinburgh Handiness Inventory (Oldfield 1971) with a laterality quotient >85, were free from peripheral and neurological impairment, and had not participated in strength training for a period of twelve months prior to the commencement of the study. Further, participants had little or no history of strength training, but were recreationally active. All participants were recruited from the University population and were required to complete an adult safety-screening questionnaire to determine their suitability for TMS (Keel et al. 2011).

Experimental approach

Once recruited, participants attended a familiarisation session to introduce testing procedures, minimise the effects of learning and balance baseline levels. Each participant completed a control condition that involved pre and post measures of strength (one-repetition maximum [1-RM]) and motor cortical and corticospinal responses using TMS. The control condition also required participants to sit quietly for 15-min in the laboratory after pre testing. The experimental condition involved a single session of heavy-loaded dynamic strength training of the dominant right wrist flexors. Prior to and following the strength training session, measures of muscle strength (1-RM), motor cortical and corticospinal responses using TMS were obtained. The order of these conditions were counterbalanced and randomized across participants, with a one-week rest between each condition (Figure 1). All post testing TMS measures occurred following a 5-min rest period after the single session of strength training. A purpose made Excel macro was used to randomize each experimental condition. This was a single-blinded trial as all data was analysed by an independent researcher that was blinded to the conditions.

Voluntary strength testing

Participants performed a standard unilateral 1-RM strength test for the right wrist flexor (agonist) and right wrist extensor (antagonist) through a range of motion that equated to 20° of wrist flexion and extension. If the trial was successful, the weight of the dumbbell was increased accordingly (0.5 kg increments) on each trial following a 3-min recovery to minimise the development of muscular fatigue (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 wrist flexor or wrist extensor strength (Kidgell et al. 2011). Participants completed on average three trials to achieve their 1-RM strength. The maximum weight lifted, was then used to calculate the training intensity for the single session of strength training.

Strength training protocol

Participants performed supervised, loaded unilateral wrist flexion/extension exercise monitored by a metronome (2 s concentric; 4 s eccentric; Kidgell et al. 2011). Participants completed 4 sets of 6-8 repetitions using their dominant limb at 80% of their 1-RM, with 2.5 min rest between sets.

Surface electromyography (sEMG)

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. Surface electromyography (sEMG) was recorded from the right flexor carpi radialis (FCR) and right extensor carpi radialis (ECR) muscles using bipolar Ag-AgCl electrodes. As described by Selvanayagam et al. (2011) the electrodes for the FCR were positioned 9 cm from the medial epicondyle of the humerus with an inter-electrode distance (center to center) of 2 cm. The ECR electrodes were positioned at 45% of the distance from the medial epicondyle of the humerus to the radial styloid process with an interelectrode distance of 2 cm. A grounding strap was placed around the wrist as the common reference point for all electrodes. sEMG signals were amplified (× 1,000), band pass filtered (high pass at 13 Hz, low pass at 1,000 HZ), digitized online at 2 kHz, recorded (1 s), and analyzed using Power Lab 4/35 (AD Instruments, Bella Vista, Australia). sEMG was used to record test and conditioned MEPs obtained during TMS pre and post the single bout of strength training, and also during the strength training bout to provide an estimation of muscle activity in both the FCR and ECR.

Transcranial magnetic stimulation

TMS was delivered using two Magstim 200^2 stimulators (Magstim Co., UK) to produce motor evoked potentials (MEPs) in the active FCR and ECR. The motor hotspots for both the FCR and ECR (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 five of ten stimuli produced MEP amplitudes of greater than 200 μV (Rossini et al. 1999). Following the strength training intervention, AMT was retested and adjusted if required. To ensure that 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 FCR and the ECR. For the MEPs obtained from the FCR, participants were required to maintain a wrist joint angle of 20° wrist flexion in a position of supination. 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 hand in this joint position equated to 5 ± 2% 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 ± 1% (Table 1). The MEPs obtained from the ECR were also collected during low-level isometric contractions of the wrist extensors. All stimuli were delivered during low-level isometric contraction of the wrist extensors, which were performed by maintaining a straight (180°) wrist and fingers. This equated to ~5% rmsEMG, with consistent muscle activation confirmed by recording pre-stimulus rmsEMG throughout testing (Hendy and Kidgell 2013). This level of background sEMG has been previously used to produce reliable MEP amplitudes and CSP durations (Sale and Semmler 2005; Kidgell et al. 2015) and represents 2% of maximal voluntary isometric force (MVIC). The order of testing for the construction of corticospinal excitability and inhibition recruitment curves was randomized between the FCR and the ECR.

Recruitment curves for both the FCR and ECR were constructed to determine corticospinal excitability (MEP amplitude) and corticospinal inhibition (silent period duration) before and after the heavy-load strength training bout. For a single stimulus-response curve, 10 stimuli were delivered at 130, 150 and 170% of AMT during a low-level isometric contraction of the FCR and ECR muscles. Recruitment curves were also collected during the control condition pre and following 15 minutes of quiet sitting.

To quantify short-interval intracortical inhibition (SICI), 10 single-pulse stimuli and 10 short-interval paired-pulse stimuli were delivered in a random order. The stimulator output intensity was set at 120% AMT, which was determined during familiarization and adjusted if there was a change following strength training. The conditioning stimulus for paired-pulse stimulation was set at 80% AMT, the inter-stimulus interval was 3 ms, and subsequent posterior to anterior current flow was used. To quantify intracortical facilitation (ICF), 10 single-pulse stimuli and 10 paired-pulse stimuli were delivered in a random order. The stimulator output intensity for the test response was set at 120% AMT, whilst the conditioning stimulus was set at 80% AMT and the inter-stimulus interval was adjusted to 10ms. Long-interval intracortical inhibition (LICI) was determined by a conditioning stimulus of 120% AMT followed by a test stimulus at 120% AMT with an inter-stimulus interval of 100ms.

Maximal compound muscle action potential

Direct muscle responses were obtained from the FCR and ECR muscles by supramaximal electrical stimulation (pulse width 200 μs) of the Brachial plexus (Erbs point) during light background muscle

activity (DS7A, Digitimer, UK). An increase in current strength was applied to Erbs point until there was no further increase observed in the amplitude of the EMG response (M_{MAX}). To ensure maximal responses, the current was increased an additional 20% and the average M_{MAX} was obtained from five stimuli, with a period of 6-9 s separating each stimulus. M_{MAX} was recorded at baseline and following the interventions in both the agonist and antagonist muscles to ensure that there were no changes in peripheral muscle excitability that could influence MEP amplitude.

Data analysis:

Pre-stimulus rmsEMG activity was determined in the FCR and ECR muscles 100 ms before each TMS stimulus during pre- and post-testing. Trials were discarded when the pre-stimulus rmsEMG was greater than 5 ± 1% of maximal rmsEMG and then the trial was repeated. The peak-to-peak amplitude of MEPs was measured in the right FCR and ECR muscles contralateral to the cortex being stimulated. Motor-evoked potential amplitudes were analyzed (LabChart 8 software; AD Instruments) after each stimulus and flagged automatically with a cursor, providing peak-to-peak values in mV, averaged and normalized to the M_{MAX}, and multiplied by 100. The extent of co-activation was determined by calculating the percentage of maximal ECR rmsEMG recorded during wrist flexion 1-RM strength testing, compared to the maximal ECR rmsEMG recording during wrist extension 1-RM testing.

$$\text{Co-activation} = (\text{ECR}/\text{ECR}_{MAX})/\text{ECR}/\text{FCR}) \times 100$$

Peak rmsEMG of the ECR was recorded during wrist extension 1-RM testing; the peak rmsEMG for the ECR was also recorded during wrist flexion 1-RM testing. The $\text{ECR}/\text{ECR}_{MAX}$ ratio, expressed as a percentage of total activation was then used to correctly interpret the extent of ECR/FCR ratio.

To determine the input-output properties of the corticospinal tract, the total area under the recruitment curve (AURC) was calculated via the method of trapezoidal integration using the actual data collected during the construction of corticospinal excitability (MEP amplitude) and corticospinal inhibition (silent period duration) recruitment curves for both the FCR and ECR. The experimenter was blinded to each condition during all AURC analyses. Corticospinal silent period durations were obtained from single-pulse stimuli delivered during the construction of the recruitment curve (130–170% AMT) and corticospinal silent period durations were determined by examining the duration between the onset of the MEP and the resolution of background sEMG, which was visually inspected and manually cursored. The average from 10 stimuli was used to determine corticospinal silent period durations. SICI and ICF were expressed as a percentage of the unconditioned single-pulse MEP amplitude, while LICI was calculated and expressed as a percentage of the test to conditioning MEP amplitude for each individual paired stimuli.

Statistical analysis

The number of participants required was based on power calculations for the expected changes in mean-rectified MEPs (sEMG recordings from the wrist muscles) after a single session of strength training (Hendy and Kidgell 2014). Using previous data in healthy untrained adults (Hendy and Kidgell 2014), we estimated that 11 participants would provide at least 80% power (95% confidence interval [CI]) to detect a 15% increase in mean-rectified MEPs assuming a standard deviation (SD) of 10–15% between conditions at $P < 0.05$.

All data were first screened to ensure they were normally distributed. To have sufficient data to test for questions of normality, all data from baseline motor-evoked potentials, short-interval cortical inhibition, intracortical facilitation and corticospinal silent period trials were used to establish the distributional properties. Further, the Shapiro-Wilk test suggested that SICI for the ECR in the control condition was not normally distributed ($W = 0.88$; $P = 0.03$) and ICF at baseline for the ECR in the trained condition ($W = 0.83$; $P = 0.02$). However, these violations appeared to be mild from examination of frequency histograms and detrended Q-Q plots, and were not sufficient to warrant a more conservative analytical strategy, thus it was decided to treat the data as essentially normally distributed. Subsequently, a 2 (time points) by 2 (conditions) repeated-measure ANOVA was used to determine any difference between conditions for the variables rmsEMG, CSE, CSP, SICI, ICF, LICI and voluntary strength (1-RM). If significant main effects were found, a Tukey's test was used to analyse the percentage change comparing condition interaction (control and strength training) by time. For all comparisons, effect sizes (ES) of 0.2, 0.5, and 0.8 were established to indicate small, moderate, and large comparative effects (Cohen's *d*), respectively. Prism 8 for Windows (GraphPad Software Inc, La Jolla, 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 ± SD and 95% CI.

Results

Pre-stimulus rmsEMG, maximal compounds waves and motor thresholds

There were no significant differences in M-waves between conditions at baseline and no main effects for TIME or TIME × CONDITION interactions for the agonist or antagonist muscles ($P > 0.05$; Table 1). Similarly, there were no differences at baseline between control and training conditions or following the intervention, with no main effects for TIME or TIME × CONDITION interactions detected in the agonist or antagonist muscle for pre-stimulus rmsEMG and active and resting motor thresholds ($P > 0.05$; table 2).

Strength

The percentage change in the agonist wrist flexor following either training or the control condition is presented in Figure 2A. No difference in 1-RM strength was detected between control and training

groups at baseline for the agonist wrist flexor muscle ($P > 0.05$). Following training, there was a main effect for time [($F_{1, 34} = 45.2$, $P < 0.0001$] and a TIME × CONDITION interaction [($F_{1, 34} = 46.5$, $P < 0.0001$]. Post hoc analysis revealed that a single session of strength training decreased 1-RM strength of the agonist wrist flexor by 18.51 ± 10.9% (CI -24.2 to -13.1; d = -2.68) compared to a 0.39% ± increase in the control condition (Table 1).

No differences in strength of the antagonist wrist extensor were detected between control and training groups at baseline for the antagonist wrist extensor muscle (Figure 2B, $P > 0.05$). Following training, there was a main effect for TIME [($F_{1, 34} = 6.3$, $P = 0.017$] and a TIME × CONDITION interaction [($F_{1, 34} = 12.8$, $P = 0.001$]. Post hoc analysis revealed that a single session of strength training significantly decreased 1-RM strength of the antagonist wrist extensor by 12.05% ± 14.08% (CI -22.2 to -6.11; d = 1.16) compared to a 2.11% ± 9.62% increase in the control condition (Table 1).

Changes in corticospinal excitability

Total AURC for agonist (Figure 3A) was similar between conditions at baseline ($P > 0.05$). Following training, there was a main effect for TIME [($F_{1, 34} = 12.2$; $P = 0.001$] and a TIME × CONDITION interaction ([(F1, 34 = 4.58; $P = 0.03$).]). Post hoc analysis revealed that a single session of strength training significantly increased CSE of the agonist wrist flexor by 48.05 ± 60.17% (CI -852 to -222 au; d = 0.9) compared to an 8.4 ± 10.38% increase in the control condition (CI -444 to 186 au, Table 2).

Total AURC for the antagonist were similar between conditions at baseline (Figure 3B, $P > 0.05$). Following training, there was a main effect for TIME [($F_{1, 34} = 11.7$; $P = 0.001$)] and a TIME × CONDITION interaction ([($F_{1, 34} = 14.3$; $P = 0.0006$)]). Post hoc analysis revealed that a single session of strength training significantly increased CSE of the antagonist wrist extensor by 35.82 ± 27.49% (CI -603 to -224 au, d = 1. 06) compared to a 3.65 ± 25.36% decrease in the control condition (CI -169 to 211 au, Table 2).

Changes in corticospinal inhibition

Total AURC for the agonist were similar between conditions at baseline (Figure 4A, $P > 0.05$). Following training, there was a main effect for TIME [($F_{1, 34} = 4.25$; $P = 0.04$)] and a TIME × CONDITION interaction ([($F_{1, 34} = 11.6$; $P = 0.001$)]). Post hoc analysis revealed that a single session of strength training significantly decreased the CSP of the agonist wrist flexor by 18.17 ± 8.17% (CI 0.416 to 1.69 au; d = -2.33) compared to a 4.70 ± 7.13% increase in the control condition (CI -0.898 to 0.381 au, Table 2).

Total AURC for the antagonist were similar between conditions at baseline (Figure 4B, $P > 0.05$). Following training, there was a main effect for TIME [($F_{1, 34} = 34.9$; $P < 0.0001$)] and a TIME × CONDITION interaction ([($F_{1, 34} = 31.5$; $P < 0.0001$)]). Post hoc analysis revealed that a single session of strength training significantly decreased the CSP of the antagonist wrist extensor by 8.10 ± 6.92% (CI 0.441 to 0.796 au; $d = -1.85$) compared to a 2.51 ± 3.74% increase in the control condition (CI -0.161 to 0.194 au, Table 2).

Changes in short-interval cortical inhibition

No differences in SICI were detected for the agonist at baseline between conditions (Figure 5A, $P > 0.05$). Following training, there was a main effect for TIME [($F_{1, 34} = 5.65$; $P = 0.02$)] and a TIME × CONDITION interaction ([($F_{1, 34} = 9.51$; $P = 0.0004$)]). Post hoc analysis revealed that a single session of strength training released SICI by 26.85 ± 3.85% (CI -11.7 to -2.86; $d = 1.33$) compared to the 2.65 ± 6.11% increase in the control condition (CI -3.46 to 5.34, Table 2).

No differences in SICI were detected for the antagonist at baseline between conditions (Figure 5B, $P > 0.05$). Following training, there was no effect for TIME [($F_{1, 34} = 0.23$; $P = 0.63$)] or any TIME × CONDITION interaction ([($F_{1, 34} = 0.007$; $P = 0.93$)]). SICI reduced by 2 ± 5% in the antagonist ECR muscle following training and remained unchanged following the control condition (-.87 ± 4.06%, Table 2).

Changes in long-interval intracortical inhibition

For the agonist muscle, LICI was able to be induced in 12 of the 18 participants (6 participants were excluded from further analysis due to the conditioned versus unconditioned ratio exceeding 100%). No differences were detected in LICI at baseline between conditions ($P > 0.05$). Following training, there was no effect for TIME [($F_{1, 34} = 0.034$; $P = 0.85$] or any TIME × CONDITION interaction ([($F_{1, 34} = 2.2$; $P = 0.15$, Table 2)]).

Again, for the antagonist, LICI was able to be induced in 12 of the 18 participants (6 participants were excluded from further analysis due to the conditioned versus unconditioned ratio exceeding 100%). No differences were detected in LICI at baseline between conditions ($P > 0.05$). Following training, there was no effect for TIME [$F_{1, 34} = 0.048$, $P = 0.78$] or any TIME × CONDITION interaction ([($F_{1, 34} = 0.042$; $P = 0.81$, Table 2)]).

Changes in intracortical facilitation

For the agonist muscle, ICF was able to be induced in 13 participants (5 participants were excluded from further analysis due to a ratio of less than 100%) for the agonist wrist flexor following training and the control condition (Figure 6A). No differences were detected in ICF at baseline between

conditions ($P > 0.05$). Following training, there was a main effect for TIME [($F_{1, 34} = 9.28$; $P = 0.005$)] and a TIME × CONDITION interaction ([($F_{1, 34} = 9.7$; $P = 0.004$)]). Post hoc analysis revealed that a single session of strength training increased ICF by 13.02 ± 3.50% (CI -45.5 to -2.46; $d = 1.31$) compared to the control conditions 1.08 ± 1.67% increase (CI -30.6 to 12.4, Table 2).

For the antagonist muscle, there were 13 participants (5 participants were excluded from further analysis due to a ratio of less than 100%) where ICF could be induced in the antagonist wrist extensor following the training or control condition (Figure 6B). No differences were detected in ICF at baseline between conditions ($P >0.05$). Following training, there was no effect for TIME [($F_{1, 34} = 0.034$; $P = 0.85$] or any TIME × CONDITION interaction ([($F_{1, 34} = 2.2$; $P = 0.15$, Table 2)]).

Changes in co-activation during training

Changes in co-activation from set 1 to set 4 is displayed in Table 3. There was a 63.96 ± 57.80% increase in co-activation of antagonists from set one to set four during training (CI 34.7 to 93.3, $P = 0.01$, $d = 1.02$). Co-activation of antagonists was also measured during 1-RM testing of the wrist flexors and extensors pre and post a single session of strength training. There were no significant differences between pre- and post-training in the magnitude of co-activation during strength testing (Table 3, pre: 20.51 ± 8.87, post: 21.72 ± 7.18 $P = 0.32$).

Discussion

Following a single bout of heavy-loaded strength training, the agonist and antagonist muscles experienced comparable increases in CSE and reductions in corticospinal inhibition. Intracortical assessments revealed alterations in the response of the agonist muscle following training, including an increase in ICF and a reduction in SICI. However, no such changes were detected in the antagonist muscle. Further, the sEMG activity of the antagonist muscle increased progressively during training, and peaked in the final set. Combined, these results indicate that the immediate responses of the antagonist muscle acutely following a single session of training does not reflect the suppression of antagonist activity which is typically observed following multi-week training programs (Tillin, Pain & Folland 2011; Carolan & Cafarelli 1992) and may be more indicative of its acute contribution to training. This is the first evidence for the early neural responses of the antagonist muscle following an initial strength training session, providing insight into the primary mechanisms that may dictate eventual increases in muscular strength.

The corticospinal responses of an antagonist muscle to heavy-load strength training mirror those observed in the agonist muscle

Following a single bout of heavy-loaded strength training, the agonist and antagonist muscles shared comparable increases in CSE and decreases in CSP. These responses in the agonist are aligned with recent findings (Mason et al. 2018; Leung et al. 2015; Latella et al. 2016). However, this is the first time the antagonist responses have been systematically investigated, providing insight into the corticospinal responses of muscle co-ordination following an initial bout of strength training.

Increases in CSE and reductions in CSP of the antagonist muscle following training are attributed to the behaviour of the muscle during training. The activation of the antagonist increased progressively set-by-set, and peaked in the final set. Substantial sEMG and torque-distribution evidence emphasises the key role of antagonist muscles in impairing the ability of the agonist to exert opposing forces (Carolan & Cafarelli 1992; Jarić et al. 1997), which is considered to be a protective mechanism to prevent injury (Baratta et al. 1988; Kellis 1998). This is buoyed by comprehensive evidence that as fatigue accumulates during activity, co-activation increases (Hautier et al. 2000; Psek & Cafarelli 1993). In the current study, participants were not experienced in strength training, likely leading to the accumulation of both significant muscle damage due to the eccentric component of training (Hunter et al., 2012) and substantial fatigue during training. This may have an accentuating effect, which is evidenced by a near 10% reduction in 1-RM following training. The involvement and progressive activity of the antagonist muscle during training, because of fatigue, likely provided sufficient stimulus to generate corticospinal responses akin to those of an agonist muscle, which is also fatigued during heavy-loaded strength training (Latella et al., 2016). Indeed, an increase in CSE appears to be a general property that is shared by other types of motor training, including ballistic and skill training (Classen et al. 1998; Cirillo, Todd & Semmler 2011), as well as strength training (Leung et al. 2015; Mason et al. 2018). Importantly, increases in CSE might not be sensitive to factors such as training load or training type (Leung et al. 2015). Further, increases in CSE and decreases in inhibitory markers have been detected in muscles not directly involved in training following both aerobic and strength training sessions (Nepvue et al. 2017; Leung et al. 2015). Thus, it appears as though the excitable elements of the corticospinal system are easily manipulated/facilitated through training, which extends to the antagonist muscle. This is perhaps unsurprising given the shared cortical inputs between agonist and antagonist muscles (De Luca & Mambirto et al. 1987; Psek & Cafarelli et al. 1993). Another explanation for the increase in CSE is that early exposure to a novel task such as externally-paced, heavy-loaded strength training is analogous to learning a new skill. In this case, the skill requires muscular co-ordination between agonists, synergists and antagonists, and the process of acquiring the appropriate motor command strategies is reminiscent of motor learning (Carroll, Riek & Carson 2001). Thus, it is

conceivable that the corticospinal responses of the antagonist muscle resemble those seen following a single bout of skill training, including an increase in CSE and a decrease in CSP (Leung et al. 2015; Classen et al. 1998; Cirillo, Todd & Semmler 2011).

Although not as frequently investigated, reductions in CSP have also been detected following both heavy-load strength training in the agonist muscle (Mason et al., 2018; Latella et al., 2016). Given evidence that the motoneurones innervating the antagonist muscle are inhibited in harmony with the activation of agonist motoneurones (Crone & Nielsen 1989; Baldissera, Hultborn & Illert 2011; Gorassini et al. 2002), it is perhaps unexpected that the current study observed a decrease in corticospinal inhibition as opposed to an increase.

A bout of heavy-loaded strength training has differential effects on motor cortical circuitry projecting to the antagonist muscle

In agreement with previous findings, the agonist muscle observed increases in ICF, a release in SICI and no change in LICI immediately following training (Leung et al. 2015; Mason et al. 2018; Latella et al. 2016; Manca et al. 2016). However, the intracortical measures of the antagonist muscle were uninfluenced by a single session of heavy-loaded strength training. This is in contrast to the corticospinal markers of excitability and inhibition of the antagonist, which were modulated by training. These results bring into question the locus of the modulation of antagonistic responses following training, by indicating a differential response of the corticospinal and intracortical circuitry of the M1.

The activity of the antagonist muscle during training is likely the result of complex interactions between cortical and spinal mechanisms (Hortobagyi & Devita 2006). Early evidence suggested that the CNS controls the motorneurone pools of an agonist-antagonist muscle pair as a singular pool when performing a task (De Luca & Mambirto et al. 1987; Psek & Cafarelli et al. 1993). More recent evidence has used coherence analysis to estimate the amount of common neural input between two muscles during voluntary movement (Ushiyama & Ushiba 2013). In addition, Dal Maso and colleagues (2017) determined that the M1 directly regulates both agonist and antagonist muscles during isometric knee flexion at different torques, validating previous work that indicated involvement of distinct cortical control of antagonist muscles (Mullany et al. 2002; Levenez et al. 2008; Psek & Cafarelli et al. 1993). Despite the evidence that supraspinal mechanisms are responsible for antagonist co-ordination, only measures involving spinal circuitry elements were influenced following a single bout of training in the current study. The differential responses between the agonist and antagonist muscle, as well as between the corticospinal and intracortical circuitry of the antagonist muscle, could be explained by a range of factors, including the sensitivity of intracortical factors to training type and the varying functions of the antagonist muscle. The antagonist muscle has a number of functional roles. While it is

well established that the antagonist muscle inhibits agonist movement during contraction, it also aids in joint stability (Rao et al. 2009; Basmajian & De Luca 1985) and facilitates movement accuracy (Gribble et al. 2003; Tanaka 1974). Further, antagonist behaviour during movement and training is specific to a number of factors. Training load, contraction intensity, velocity, range of motion and contraction type all influence antagonist behaviour (Karst & Hasan 1987; Behm & Sale 1993). Recent research has indicated that cortical input to antagonist muscles is specific to the biomechanical demands as well as the difficulty of the task (Nandi et al. 2019), and that independent cortical control of antagonist muscles occur according to the function of the muscle (Del Maso et al. 2017) and phase of force production (Desmyttere et al. 2018). Adjustment of any of these training factors might induce more substantial responses, including modulation of intracortical circuits. However, the externally paced, dynamic and heavy-loaded nature of training in the current study has been repeatedly demonstrated to be a potent modulator of corticospinal responses over other training prescriptions (Kidgell et al. 2010; Kidgell et al. 2015; Leung et al. 2015; Mason et al. 2017). Another factor likely involved in the differential results between the corticospinal and intracortical assessments of the antagonist muscle is the sensitivity of intracortical measures to the specific elements of the task. While corticospinal factors appear to be easily manipulated by all types of training, intracortical factors, appear to be more task dependent. For example, recent research has demonstrated that although CSE and CSP are manipulated immediately following a single bout of heavy- and light-load strength training, SICI is only released following heavy-loaded training (Mason et al. 2019). Further, cortical control of antagonist behaviour during training is specific to the force used (Dal Maso et al. 2017), as is the level of intracortical inhibition (Zoghi & Nordstrom 2007). Thus, although central factors are evidently involved in antagonist activation during training, and changes in co-activation of the antagonist muscle underpin improvements in strength following multiple training sessions, the activity of the antagonist muscle during the current study may not have been sufficient to induce substantial and/or detectable responses in intracortical markers.

It is important to note that the acute corticospinal responses following a single session do not necessarily reflect the more chronic modulations of corticospinal response following multi-week training programs. For example, in the agonist muscle, a single bout of training increases CSE and has no influence on SICI, whereas multi-week training programs typically produce no enhancements of CSE but a release in SICI of the agonist (Kidgell et al., 2017). The current study is potentially in line with this notion, by observing increases in CSE and a period of disinhibition immediately following training. These responses may be incongruent with the longer-term supressed responses of the antagonist muscle which may be expected with the downregulation of antagonist activity accompanying improvements in muscular strength. There is early evidence to suggest that shifts in co-activation during training are observable following just a single session of training (Hight et al. 2017); however, this is yet to be thoroughly examined.

Despite its novel contribution to the literature, the current study is not without limitations. Most antagonist studies have investigated the relationships between knee flexors and extensors, and the ability of TMS to generate intracortical responses from a wrist extensor is not well reported. Therefore, any potential intracortical effects were potentially undetectable. Further, each muscle group likely has a unique antagonist profile and response, potentially leading to differential corticospinal effects following training. For example, a majority of antagonist strength training studies use lower limb muscles. However, the selection of wrist extensors and flexors is teleological a sensible choice to investigate this paradigm because of the common use of wrist flexors in TMS literature (Mason et al. 2017; Mason et al. 2018; Hendy & Kidgell 2013; Nuzzo et al. 2016) and the problematic nature of assessing intracortical measures from the quadriceps (Brownstein et al. 2018). Further, the training setup was different to the TMS testing conditions, which may influence the result (Brownstein et al. 2018). Lastly, generating intracortical measures such as ICF and LICI has been demonstrated to be fickle in nature, as evidenced by only eleven participants generating a detectable facilitation response in this study, and very few studies having reported ICF and LICI following either acute or longer-term strength training, as highlighted by a recent review (Kidgell et al., 2017).

The findings of this study provide the first evidence for the initial corticospinal responses of an antagonist muscle immediately following heavy-load strength training in an untrained population. The involvement of the antagonist muscle during training produced corticospinal responses that mirrored those observed in the agonist muscle, including an increase in CSE and cSP. However, intracortical measures from the antagonist muscle remained uninfluenced by training, while the agonist muscle experienced motor cortical facilitation and disinhibition. These results provide growing evidence of the agonist muscle responses to training, and importantly provide insight into how corticospinal pathways respond to muscle co-ordination during an initial training session, which may be a critical determinant of strength development. Given the difference in response reported here from an acute bout of strength training in comparison to multiple strength training sessions, the behaviour of the agonist and antagonist muscle to progressive resistance training is an area that must be explored.

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Compliance with ethical standards

Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

References

Aagaard P, Simonsen EB, Andersen JL, Magnusson P, Dyhre-Poulsen P (2002) Increased rate of force development and neural drive of human skeletal muscle following resistance training. J Appl Physiol 93:1318-1326.

Baldissera F, Hultborn H, Illert M (2011) Integration in spinal neuronal systems. Com Physiol 509-595. 10.1002/cphy.cp010212.

Baratta R, Solomonow M, Zhou B H, Letson D, Chuinard R, D'ambrosia R (1988) Muscular coactivation: the role of the antagonist musculature in maintaining knee stability. Am J Sports Med 16: 113-122.

Basmajian J V, De Luca C J (1985) Description and analysis of the EMG signal. Muscles alive: their functions revealed by electromyography. Baltimore: Williams & Wilkins, USA.

Bazzucchi I, Riccio M E, Felici F (2008) Tennis players show a lower coactivation of the elbow antagonist muscles during isokinetic exercises. J Electromyo Kinesiol 18: 752-759.

Behm DG, Sale DG (1993) Velocity specificity of resistance training. Sports Med 15: 374-388.

Bertolasi L, Priori A, Tinazzi M, Bertasi V, Rothwell J C (1998) Inhibitory action of forearm flexor muscle afferents on corticospinal outputs to antagonist muscles in humans. J Physiol 511: 947-956.

Brownstein CG, Ansdell P, Škarabot J, Frazer A, Kidgell DJ, Howatson G, Thomas, K (2018) Motor cortical and corticospinal function differ during an isometric squat compared with isometric knee extension. Exp Physiol 103:1251-1263.

Busse M E, Wiles C M, Van Deursen RWM (2005) Muscle co-activation in neurological conditions. Phys Ther Rev 10: 247-253.

Capaday C, Devanne H, Bertrand L, Lavoie BA (1998) Intracortical connections between motor cortical zones controlling antagonistic muscles in the cat: a combined anatomical and physiological study. Exp Brain Res 120: 223-232.

Capaday C, Ethier C, Van Vreeswijk C (2013) On the functional organization and operational principles of the motor cortex. Front Neural Circ 7:66.

Carolan B, Cafarelli E. (1992) Adaptations in coactivation after isometric resistance training. J Appl Physiol 73: 911-917.

Carroll TJ, Riek S, Carson RG (2001) Neural adaptations to resistance training. Sports Med 31:829-840.

Christie A, Fling B, Crews RT, Mulwitz LA, Kamen G (2007) Reliability of motor-evoked potentials in the ADM muscle of older adults. J Neuro Meth 164: 320-324.

Cirillo J, Todd G, Semmler JG (2011) Corticomotor excitability and plasticity following complex visuomotor training in young and old adults. Eur J Neurosci 34: 1847-1856.

Classen J, Liepert J, Wise SP, Hallett M, Cohen LG (1998) Rapid plasticity of human cortical movement representation induced by practice. J Neurophyiol 79: 1117-1123.

Crone C, Nielsen JENS (1989) Spinal mechanisms in man contributing to reciprocal inhibition during voluntary dorsiflexion of the foot. J Phsyiol 416: 255-272.

Dal Maso F, Longcamp M, Cremoux S, Amarantini D (2017) Effect of training status on beta-range corticomuscular coherence in agonist vs. antagonist muscles during isometric knee contractions. Exp Brain Res 235: 3023-3031.

De Luca C J, Mambrito B (1987) Voluntary control of motor units in human antagonist muscles: coactivation and reciprocal activation.J Neurophysiol 58: 525-542.

Desmyttere G, Mathieu E, Begon M, Simoneau-Buessinger E, Cremoux S (2018) Effect of the phase of force production on corticomuscular coherence with agonist and antagonist muscles. Uro J Neurosci 48: 3288-3298.

Frazer A K, Howatson G, Ahtiainen JP, Avela J, Rantalainen T, Kidgell DJ (2019) Priming the motor cortex with anodal transcranial direct current stimulation affects the acute inhibitory corticospinal responses to strength training. J Strength Cond Res 33: 307-317.

Gorassini M, Yang JF, Siu M, Bennett DJ (2002) Intrinsic activation of human motoneurons: reduction of motor unit recruitment thresholds by repeated contractions. J Neurophysiol 87: 1859-1866.

Gribble PL, Mullin LI, Cothros N, Mattar A (2003) Role of cocontraction in arm movement accuracy. J Neurophysiol 89: 2396-2405.

Häkkinen K, Alen M, Kallinen M, Newton RU, Kraemer WJ (2000) Neuromuscular adaptation during prolonged strength training, detraining and re-strength-training in middle-aged and elderly people. Eur J Appl Phyiol 83: 51-62.

Häkkinen K, Kallinen M, Izquierdo M, Jokelainen K, Lassila H, Malkia E, Alen M (1998) Changes in agonist-antagonist EMG, muscle CSA, and force during strength training in middle-aged and older people. J Appl Phyiol 84: 1341-1349.

Hallett M (2000) Transcranial magnetic stimulation and the human brain. Nature 406: 147.

Hautier CA, Arsac LM, Deghdegh K, Souquet J, Belli, A, Lacour JR (2000) Influence of fatigue on EMG / force ratio and cocontraction in cycling. Med Sci Sports Exerc 32: 839-843.

Hendy AM, Kidgell DJ (2013) Anodal tDCS applied during strength training enhances motor cortical plasticity. Med Sci Sports Exerc 45:1721-1729.

Hendy AM, Kidgell DJ (2014) Anodal-tDCS applied during unilateral strength training increases strength and corticospinal excitability in the untrained homologous muscle. Exp Brain Res 232: 3243-3252.

Hight, RE, Beck, TW, Bemben, DA, & Black, CD (2017) Adaptations in antagonist co-activation: Role in the repeated-bout effect. PloS one 12(12), e0189323.

Hortobágyi T, DeVita P (2006) Mechanisms responsible for the age-associated increase in coactivation of antagonist muscles. Ex Sport Sci Rev 34: 29-35.

Jarić S, Radovanović S, Milanović S, Ljubisavljević M, Anastasijević R (1997) A comparison of the effects of agonist and antagonist muscle fatigue on performance of rapid movements. Eur J Appl Physiol 76: 41-47.

Kamen G, Knight CA (2004. Training-related adaptations in motor unit discharge rate in young and older adults. J Geront Ser A: Biol Sci Med 59: 1334-1338.

Karst GM, Hasan Z (1987) Antagonist muscle activity during human forearm movements under varying

kinematic and loading conditions. Exp Brain Res 67: 391-401.

Keel JC, Smith MJ, Wassermann EM (2001) A safety screening questionnaire for transcranial magnetic stimulation. Clin Neurophysiol 112:720

Keen DA, Yue GH, Enoka RM (1994) Training-related enhancement in the control of motor output in elderly humans. J Appl Physiol 77: 2648-2658.

Kellis E (1998) Quantification of quadriceps and hamstring antagonist activity. Sports Med 25: 37-62.

Kidgell DJ, Bonanno DR, Frazer AK, Howatson G, Pearce AJ (2017) Corticospinal responses following strength training: a systematic review and meta-analysis. Eur J Neurosci 46: 2648-2661.

Kidgell DJ, Frazer AK, Rantalainen T, Ruotsalainen I, Ahtiainen JP, Avela J, Howatson G (2015) Increased cross-education of muscle strength and reduced corticospinal inhibition following eccentric strength training. Neurosci 300: 566-575.

Kidgell D J, Pearce A J (2010) Corticospinal properties following short-term strength training of an intrinsic hand muscle. Hum Mov Sci 29: 631-641.

Kidgell D J, Stokes MA, Pearce AJ (2011) Strength training of one limb increases corticomotor excitability projecting to the contralateral homologous limb. Motor cont 15: 247-266.

Latella C, Hendy AM, Pearce AJ, Vander Westhuizen D, Teo WP (2016). The time-course of acute changes in corticospinal excitability, intra-cortical inhibition and facilitation following a single-session heavy strength training of the biceps brachii. Front Hum Neurosci 10: 607.

Latella C, Kidgell DJ, Pearce AJ (2012) Reduction in corticospinal inhibition in the trained and untrained limb following unilateral leg strength training. Eur J Apply Physiol 112: 3097-3107.

Latella C, Teo WP, Harris D, Major B, Vander Westhuizen D, Hendy AM (2017) Effects of acute resistance training modality on corticospinal excitability, intra-cortical and neuromuscular responses. Eur J Apply Physiol 117: 2211-2224.

Lévénez M, Garland SJ, Klass M, Duchateau J (2008) Cortical and spinal modulation of antagonist coactivation during a submaximal fatiguing contraction in humans. J Neurophysiol 99: 554-563.

Leung M, Rantalainen T, Teo WP, Kidgell DJ (2017) The corticospinal responses of metronome-paced, but not self-paced strength training are similar to motor skill training. Eur J Apply Physiol 117: 2479-2492.

Leung M, Rantalainen T, Teo WP, Kidgell DJ (2015) Motor cortex excitability is not differentially modulated following skill and strength training. Neurosci 305:99-108.

Macaluso A, Nimmo MA, Foster JE, Cockburn M, McMillan NC, De Vito G (2002) Contractile muscle volume and agonist-antagonist coactivation account for differences in torque between young and older women. Muscle Nerve 25: 858-863.

Manca A, Cabboi MP, Ortu E, Ginatempo F, Dragone D, Zarbo IR, Deriu F (2016) Effect of contralateral strength training on muscle weakness in people with multiple sclerosis: proof-of-concept case series. Phys Ther 96: 828-838.

Mason J, Frazer AK, Pearce AJ, Goodwill AM, Howatson G, Jaberzadeh S, Kidgell DJ (2018) Determining the early corticospinal-motoneuronal responses to strength training: a systematic review and meta-analysis. Rev Neurosci https://doi.org/10.1515/revneuro-2018-0054.

Mason J, Frazer AK, Jaberzadeh S, Ahtiainen J, Avela A, Rantalainen T, Leung M, Kidgell DJ (2019). Determining the corticospinal responses to single bouts of skill and strength training. J Strength Cond Res. In press.

Morita H, Crone C, Christenhuis D, Petersen NT, Nielsen JB (2001) Modulation of presynaptic inhibition and disynaptic reciprocal Ia inhibition during voluntary movement in spasticity. Brain 124: 826-837.

Mullany H, O'Malley M, Gibson ASC, Vaughan C (2002) Agonist–antagonist common drive during fatiguing knee extension efforts using surface electromyography. J Electromyo Kinesiol 12: 375-384.

Nandi T, Hortobágyi T, van Keeken HG, Salem GJ, Lamoth C J (2019) Standing task difficulty related increase in agonist-agonist and agonist-antagonist common inputs are driven by corticospinal and subcortical inputs respectively. Sci Reports 9: 2439.

Nepveu JF, Thiel A, Tang A, Fung J, Lundbye-Jensen J, Boyd LA, Roig M (2017) A single bout of

high-intensity interval training improves motor skill retention in individuals with stroke. Neurorehab Neural Rep 31: 726-735.

Nielsen JB (2004) Sensorimotor integration at spinal level as a basis for muscle coordination during voluntary movement in humans. J Apply Physiol 96: 1961-1967.

Nuzzo JL, Barry BK, Gandevia SC, Taylor JL (2016) Acute strength training increases responses to stimulation of corticospinal axons. Med Sci Sports Exerc 48: 139-150.

Oldfield R (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97–113

Osternig LR, Hamill J, Lander JE, Robertson R (1986) Co-activation of sprinter and distance runner muscles in isokinetic exercise. Med Sci Sports Exerc 18: 431-435.

Psek JA, Cafarelli E (1993) Behavior of coactive muscles during fatigue. J Appl Physiol 74: 170-175.

Rao G, Amarantini D, Berton E (2009) Influence of additional load on the moments of the agonist and antagonist muscle groups at the knee joint during closed chain exercise. J Electromyo Kinesiol 19: 459-466.

Rossini PM, Rossi S, Pasqualetti P, Tecchio F (1999) Corticospinal excitability modulation to hand muscles during movement imagery. Cereb Cortex 9:161–167.

Sale DG (1988) Neural adaptation to resistance training. Med Sci Sports Exerc, 20: S135-45.

Sale MV, Semmler JG (2005) Age-related differences in corticospinal control during functional isometric contractions in left and right hands. J Apply Physiol 99: 1483-1493.

Selvanayagam VS, Riek S, Carroll TJ (2011) Early neural responses to strength training. J Apply Physiol 111: 367-375.

Škarabot J, Mesquita RN, Brownstein CG, Ansdell P (2019) Myths and Methodologies: How loud is the story told by the transcranial magnetic stimulation-evoked silent period? Exp Phsyiol.

Tanaka R (1974) Reciprocal Ia inhibition during voluntary movements in man. Exp Brain Res 21: 529-540.

Tillin NA, Pain MT, Folland JP (2011) Short-term unilateral resistance training affects the agonist–antagonist but not the force–agonist activation relationship. Muscle Nerve 43: 375-384.

Ushiyama J, Ushiba J (2013) Resonance between cortex and muscle: A determinant of motor precision? Clin Neurophysiol 124:5-7.

Van Cutsem M, Duchateau J, Hainaut K (1998) Changes in single motor unit behaviour contribute to the increase in contraction speed after dynamic training in humans. J Physiol 513: 295-305.

Yacyshyn AF, Woo EJ, Price MC, McNeil CJ (2016) Motoneuron responsiveness to corticospinal tract stimulation during the silent period induced by transcranial magnetic stimulation. Exp Brain Res 234: 3457-3463.

Zoghi M, Nordstrom MA (2007) Progressive suppression of intracortical inhibition during graded isometric contraction of a hand muscle is not influenced by hand preference. Exp Brain Res 177: 266-274.

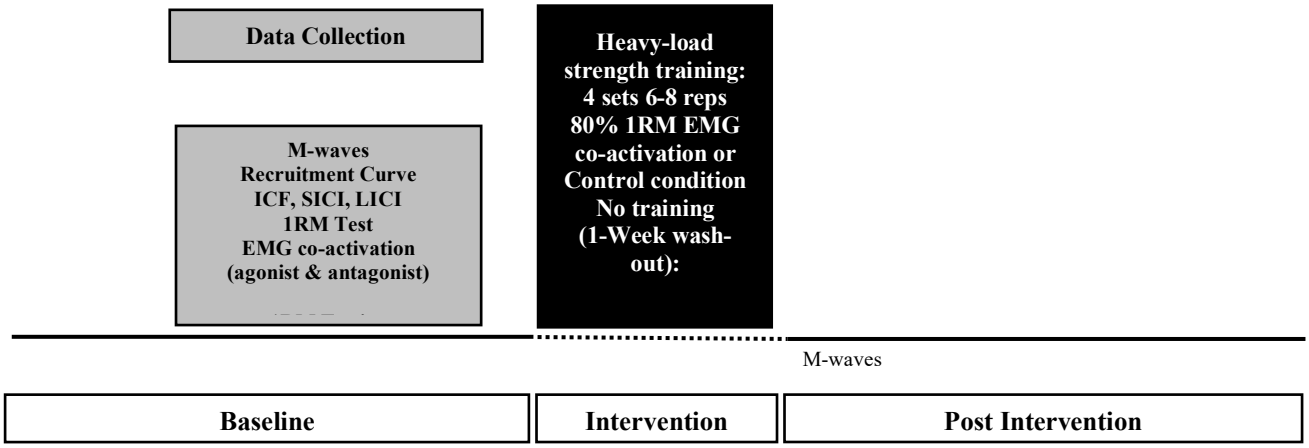

Figure 1: (A) Schematic representation of the experimental design with measures obtained prior to and following heavy-load strength training and the control condition. Pre- and post-measures included assessment of peripheral muscle excitability (M_{MAX}), corticospinal excitability, corticospinal inhibition, short-interval intracortical inhibition, long-interval cortical inhibition and intracortical facilitation of the wrist flexors and extensors.

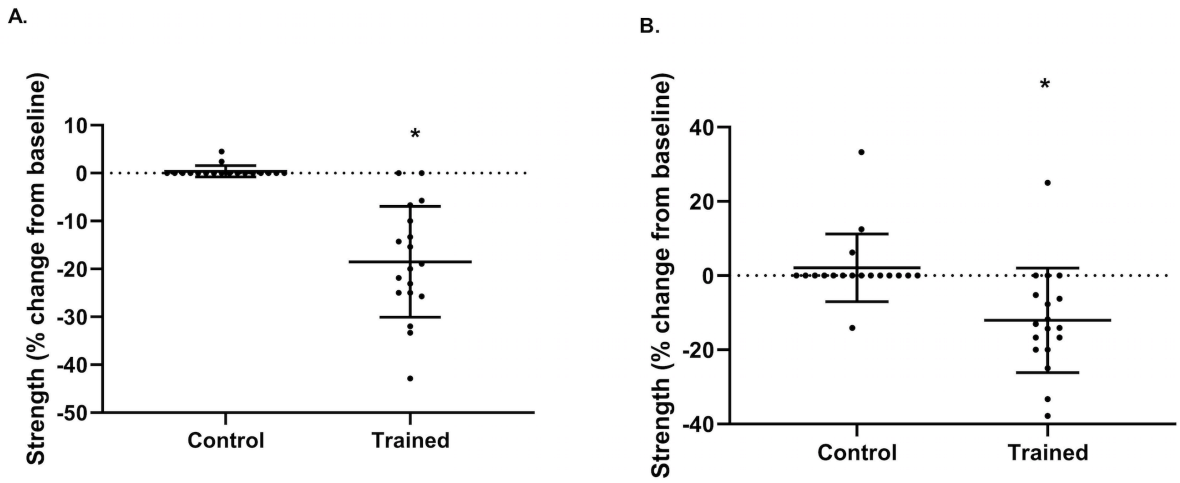

Figure 2: Change in 1-RM strength for the agonist wrist flexors **(A)** and antagonist wrist extensor **(B)** following the control and strength training condition.* Denotes a significant decrease in strength from baseline following heavy-load strength training for the agonist and antagonist compared to the control condition (time × condition effect).

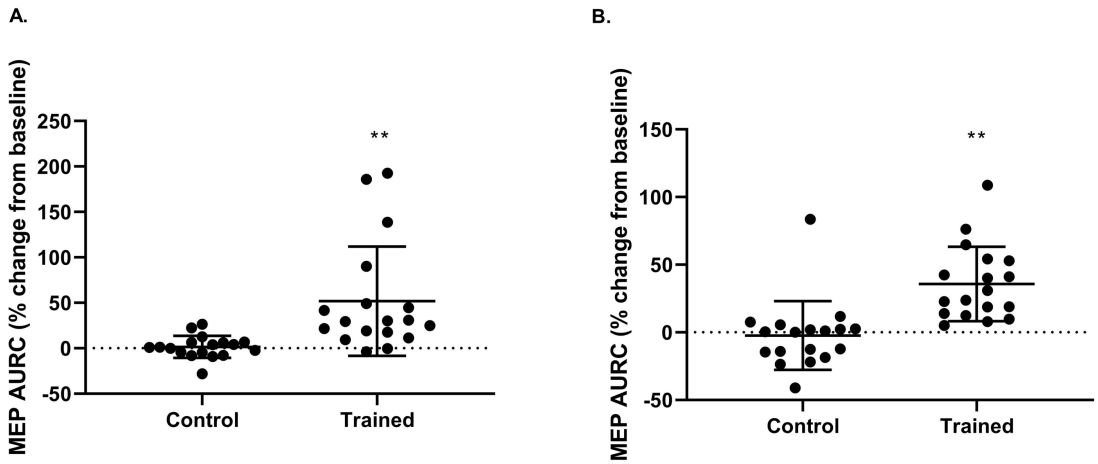

Figure 3: Change in corticospinal excitability (percentage increase in AURC) of the trained agonist wrist flexors (mean ± SD) following heavy-load strength training **(A)** and change in corticospinal excitability (percentage increase in AURC) of the antagonist wrist extensors (mean ± SD) following heavy-load strength training **(B)**. **Denotes a significant increase in corticospinal excitability from baseline following heavy-load strength training (within-time effect) for the agonist and antagonist and compared to the control condition (tine × condition effect).

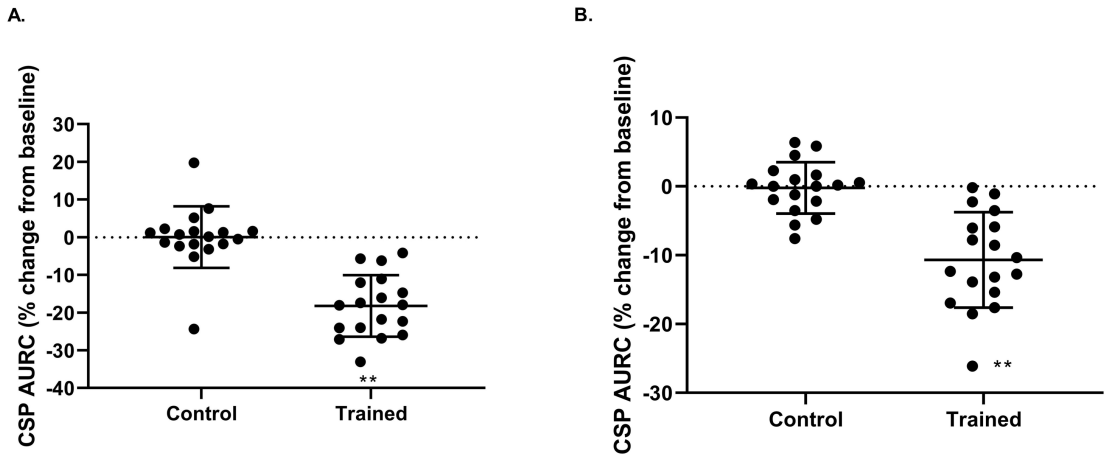

Figure 4: Change in corticospinal inhibition (percentage decrease in silent period duration AURC) of the trained agonist wrist flexor (mean ± SD) following heavy-load strength training **(A)** and change in corticospinal inhibition (percentage decrease in silent period duration AURC) of the antagonist wrist extensors (mean ± SD) from baseline following heavy-load strength training **(B)**. **Denotes a significant decrease in corticospinal inhibition from baseline following heavy-load strength training compared to the control condition (time × condition effect) for the agonist and antagonist.

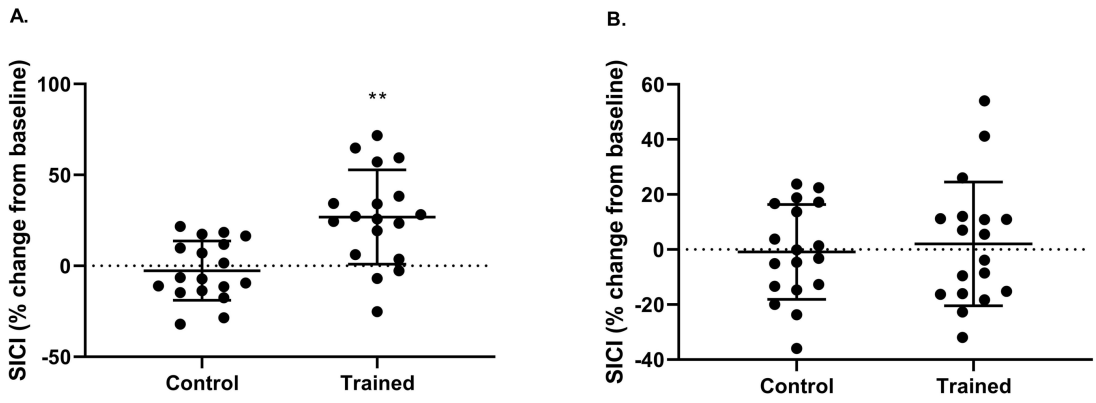

Figure 5: Change in SICI (percentage change) of the trained agonist wrist flexor (mean ± SD) following heavy-load strength training **(A)** and change in SICI (percentage change) of the antagonist wrist extensors (mean ± SD) following heavy-load strength training **(B)**. **Denotes a significant release in SICI from baseline following heavy-load strength training for the agonist only compared to the control condition (time × condition effect).

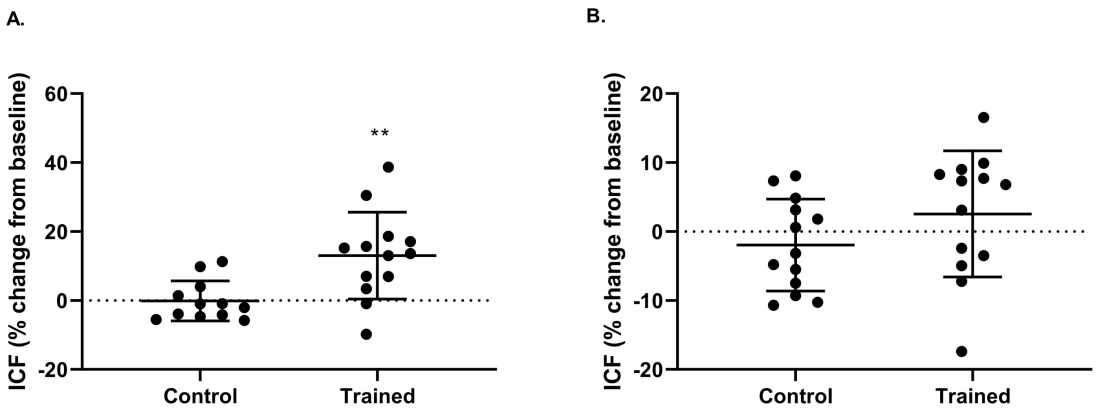

Figure 6: Change in ICF (percentage change) of the trained agonist wrist flexor (mean ± SD) following heavy-load strength training **(A)** and change in SICI (percentage change) of the antagonist wrist extensors (mean ± SD) following heavy-load strength training **(B)**. **Denotes a significant increase in ICF from baseline following heavy-load strength training for the trained agonist muscle only compared to the control condition (time × condition effect).

Table 1. Mean (± SD) for AMT stimulus intensity, M_{MAX}, single- and paired--pulse TMS pre-stimulus *rms*EMG and 1-RM for wrist flexion and extension prior to and following a single session of strength training.

	AMT SI (%)			**M_{MAX} (mV)**			**SP *rms*EMG (% rmsEMGmax)**			**PP *rms*EMG (% rmsEMGmax)**			**1-RM**		
	Pre	**Post**	**P-value**	**Pre**	**Post**	**P-value**	**Pre**	**Post**	**P-value**	**Pre**	**Post**	**P-value**	**Pre**	**Post**	**P-value**
Control Condition Agonist	39.40 ± 2.87	38.42 ± 2.99	0.34	6.37 ± 1.31	6.34 ± 1.01	0.11	2.41± 0.61	2.47± 0.46	0.36	2.18 ± .64	2.24 ± .50	0.23	16.97 ± 4.57	17.03 ± 4.56	<0.001
Training Condition Agonist	37.93 ± 2.72	36.65 ± 2.69		7.03 ± 1.01	6.18 ± .98		2.56 ± 0.43	2.52 ± 0.41		3.06 ± .71	2.78 ± .57		17.83± 4.30	14.23 ± 4.33	
Control Condition Antagonist	42.93 ± 3.32	43.50 ± 3.89	0.51	6.13 ± 1.11	5.99 ± .98	0.37	1.99 ± 0.36	1.86 ± 0.30	0.44	1.94 ± .43	1.96 ± .23	0.38	12.10 ± 3.33	12.29 ± 3.29	0.001
Training Condition Antagonist	40.92 ± 3.08	41.00 ± 3.02		6.33 ± 1.23	6.08 ± 1.13		2.01 ± 0.18	2.08 ± 0.24		2.17 ± .44	2.14 ± .53		13.39 ± 4.27	11.74 ± 4.17	

AMT SI: active motor threshold stimulus intensity, 1-RM: one-repetition-maximum. Single (SP) and paired pulse (PP) *rms*EMG was pooled across stimulus intensities.

Table 2. Mean (± SD) for the agonist wrist flexor and antagonist wrist extensor prior to and following a single session of strength training.

	MEP curve (Au)			Corticospinal silent period curve (Au)			SICI (%test response)			LICI (%test response)			ICF (% test response)		
	Pre	Post	P-value	Pre	Post	P-value	Pre	Post	P-value	Pre	Post	P-value	Pre	Post	P-value
Control Group Agonist	870 ± 93.28	943 ± 95.2	0.03	5.54 ± .33	5.8 ± .18	<0.01	23.36 ± 4.81	24.41 ± 4.96	<0.01	43.97± 18.02	43.50± 16.83	0.15	116.79 ± 4.0	116.62 ± 4.5	<0.01
Training Group Agonist	999 ± 130.39	1479 ± 195.28		5.78 ± .10	4.73 ± .12		26.22 3.67	33.49 ± 5.20		46.54 21.70	47.55 22.13		116.9 ± 3.44	131.63 ± 4.56	
Control Group Antagonist	905 ± 105.00	872 ± 78.11	<0.01	5.58 ± .11	5.72 ± .11	<0.01	26.82 ± 4.96	27.06 ± 5.11	0.93	42.04 ± 23.13	42.43 ± 21.79	0.81	118.56 ± 3.54	116.14 ± 3.78	0.15
Training Group Antagonist	885 ± 90.22	1285 ± 158.32		5.56 ± .11	5.11 ± .12		29.26 ± 3.57	28.76 ± 3.30		38.67± 17.98	39.35 ± 19.23		116.58 4.60	119.70 ± 5.90	

MEP (au): motor-evoked potential arbitrary unit, SICI: short-interval cortical inhibition, LICI: long-interval cortical inhibition, ICF: Intracortical facilitation.

Table 3. Mean (± SD) co-activation data during maximal voluntary strength testing and heavy-loaded strength training. * denotes statistical significance between training sets 1 and 4 (P=<0.05)

	Strength test baseline	Strength test post	Training set 1	Training set 2	Training set 3	Training set 4
Antagonist co-contraction index (%)	20.51 ± 8.87	21.72 ± 718	13.25 ± 5.02	15.04 ± 4.80	18.96 ± 4.96	21.86* ± 7.16