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ORIGINAL ARTICLE

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 four 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. Intracortical measures were obtained using paired-pulse TMS.

Results Following a single training session, increases in corticospinal excitability were observed in both the agonist and antagonist muscles. This was accompanied by decreases in corticospinal inhibition 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.

Keywords Agonist · Antagonist · Corticospinal excitability · Corticospinal silent period · Intracortical facilitation · Short-interval cortical inhibition · Strength training

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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 Cutsem et al. 1998; Aagaard et al. 2002; Kamen and 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 and Pearce 2010; Frazer et al. 2019; Leung et al. 2015; 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, 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 et al. 2011). For example, Carolan and Cafarelli (1992) reported a 20% decrease in co-activation as early as 1-week into 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 6 months in duration (Häkkinen et al. 1998, 2000). The behavior 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 et al. 2008). Decreased levels of strength because of age or disease are also accompanied by substantial increases in co-activation (Macaluso et al. 2002; Busse et al. 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 regulates 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 (Hortobágyi and 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 and Nielsen 1989; Baldissera et al. 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 and Mambrito 1987; Mullany et al. 2002; Lévénez 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 (Hight et al. 2017), it is hypothesized 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 randomized, 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 females, age 23.38 ± 3.29; 10 males, 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 12 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. 2001).

Experimental approach

Once recruited, participants attended a familiarization session to introduce testing procedures, minimize 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 1-week rest between each condition (Fig. 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 analyzed by an independent researcher who 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 minimize 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

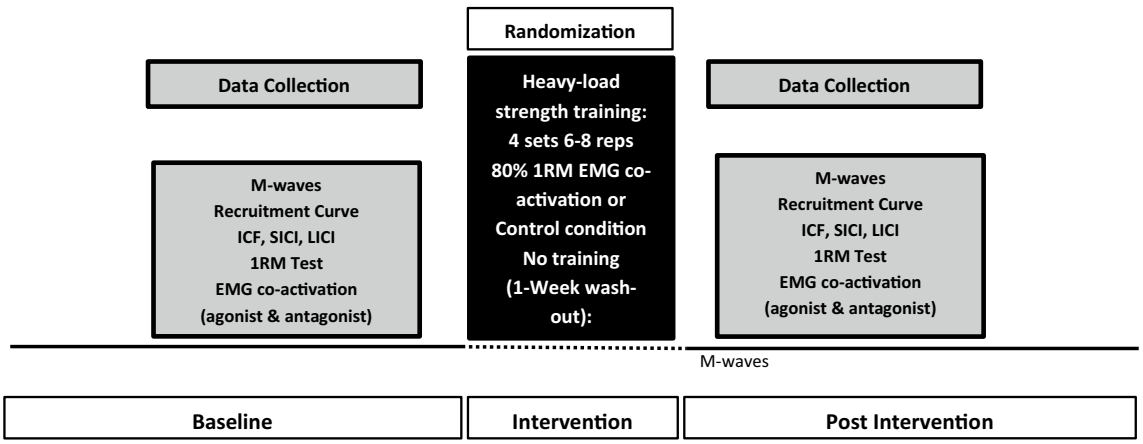

Fig. 1 **a** Schematic representation of the experimental design with measures obtained prior to and following heavy-load strength training and the control condition. Pre- and post-measures included assessment of peripheral muscle excitability (M_{MAX}), corticospinal excitability, corticospinal inhibition,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

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 four 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 inter-electrode distance of 2 cm. A grounding strap was placed around the wrist as the common reference point for all electrodes. sEMG signals were amplified (×1000), band pass filtered (high pass at 13 Hz, low pass at 1000 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 min 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

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 ± 0.64	2.24 ± 0.50	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 ± 0.98		2.56 ± 0.43	2.52 ± 0.41		3.06 ± 0.71	2.78 ± 0.57		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 ± 0.98	0.37	1.99 ± 0.36	1.86 ± 0.30	0.44	1.94 ± 0.43	1.96 ± 0.23	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 ± 0.44	2.14 ± 0.53		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

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 10 ms. 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 100 ms.

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 (Erb's point) during light background muscle activity (DS7A, Digitimer, UK). An increase in current strength was applied to Erb's 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 $5 \pm 1\%$ 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 ECR/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 analyze 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 Fig. 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 (Fig. 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 (Fig. 3a) was similar between conditions at baseline ($P > 0.05$). Following training, there was a main effect for TIME ($F_{1, 34} = 12.2$; $P = 0.001$)

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 ± 0.33	5.8 ± 0.18	< 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 ± 0.10	4.73 ± 0.12		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 ± 0.11	5.72 ± 0.11	< 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 ± 0.11	5.11 ± 0.12		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

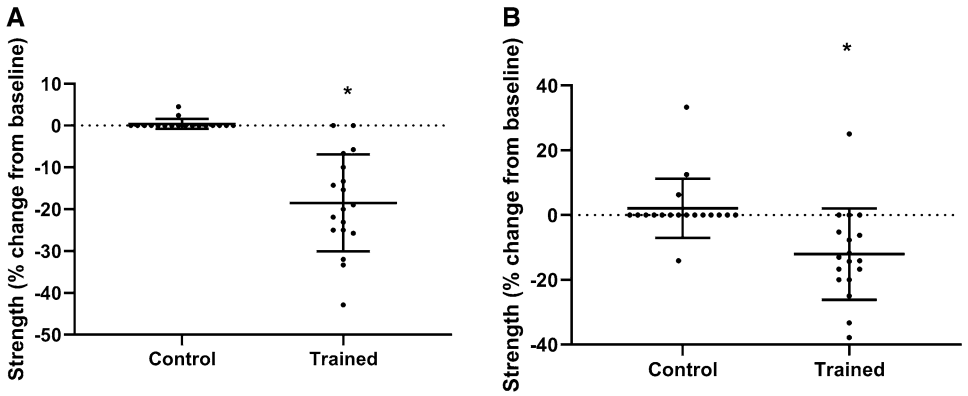

Fig. 2 Change in 1-RM strength for the agonist wrist flexors (**a**) and antagonist wrist extensor (**b**) following the control and strength training condition. *Asterisk* denotes a significant decrease in strength from baseline following heavy-load strength training for the agonist and antagonist compared to the control condition (time × condition effect)

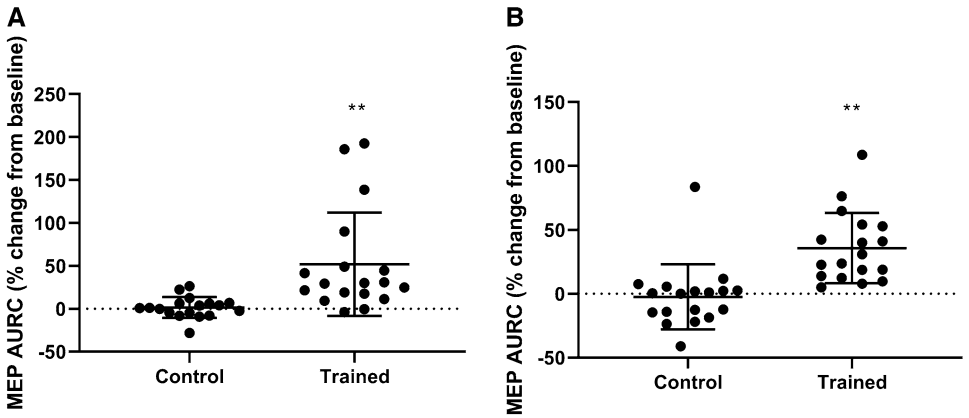

Fig. 3 Change in corticospinal excitability (percentage increase in AURC) of the trained agonist wrist flexors (mean ± SD) following heavy-load strength training (**a**) and change in corticospinal excitability (percentage increase in AURC) of the antagonist wrist extensors (mean ± SD) following heavy-load strength training (**b**). *Double asterisk* 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)

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 (Fig. 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 (Fig. 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 (Fig. 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

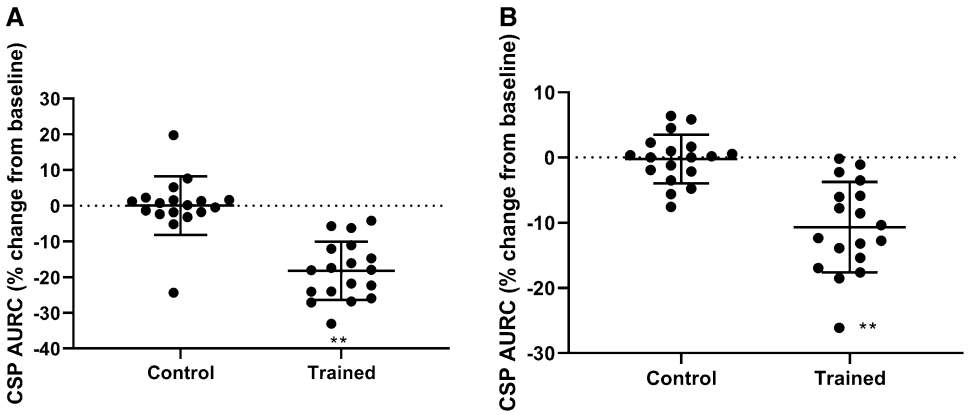

Fig. 4 Change in corticospinal inhibition (percentage decrease in silent period duration AURC) of the trained agonist wrist flexor (mean ± SD) following heavy-load strength training (**a**) and change in corticospinal inhibition (percentage decrease in silent period duration AURC) of the antagonist wrist extensors (mean ± SD) from baseline following heavy-load strength training (**b**). *Double asterisk* 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

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 (Fig. 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 (Fig. 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 (−0.87 ± 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 (six 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).

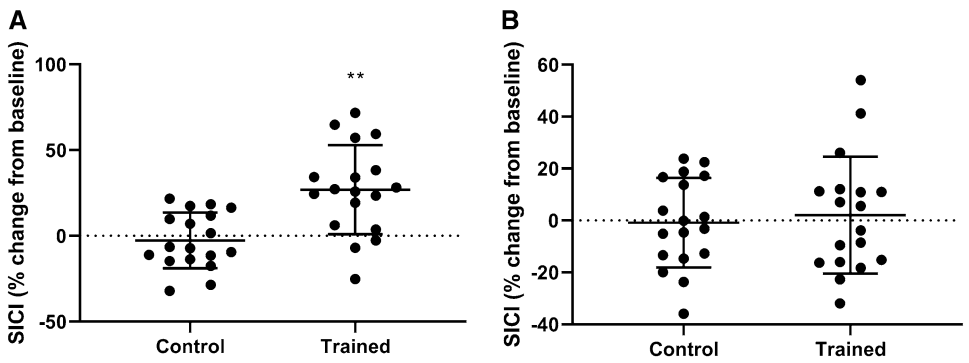

Fig. 5 Change in SICI (percentage change) of the trained agonist wrist flexor (mean ± SD) following heavy-load strength training (**a**) and change in SICI (percentage change) of the antagonist wrist extensors (mean ± SD) following heavy-load strength training (**b**). *Double asterisk* denotes a significant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

Again, for the antagonist, LICI was able to be induced in 12 of the 18 participants (six 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 (five 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 (Fig. 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 (five 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 (Fig. 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 are 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,

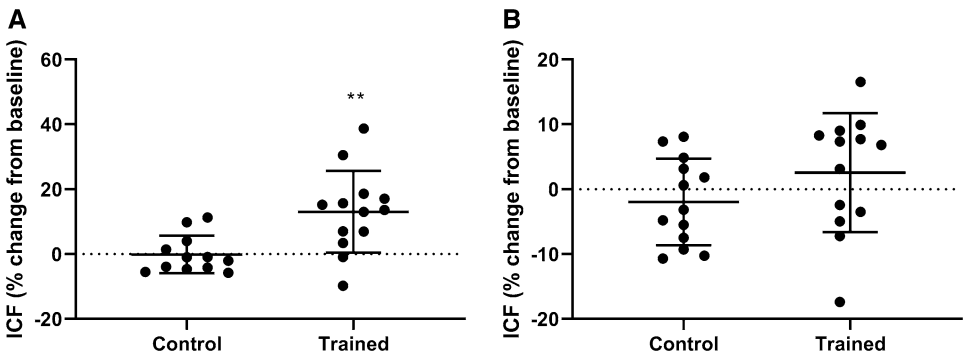

Fig. 6 Change in ICF (percentage change) of the trained agonist wrist flexor (mean ± SD) following heavy-load strength training (**a**) and change in SICI (percentage change) of the antagonist wrist extensors (mean ± SD) following heavy-load strength training (**b**). *Double asterisk* denotes a significant 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 3 Mean (± SD) co-activation data during maximal voluntary strength testing and heavy-loaded strength training

	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

*Denotes statistical significance between training sets 1 and 4 ($P = <0.05$)

these results indicate that the immediate responses of the antagonist muscle acutely following a single session of training do not reflect the suppression of antagonist activity which is typically observed following multi-week training programs (Tillin et al. 2011; Carolan and 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 behavior 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 emphasizes the key role of antagonist muscles in impairing the ability of the agonist to exert opposing forces (Carolan and 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 and 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 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 et al. 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 (Nepveu 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 and Mambrito 1987; Psek and Cafarelli 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 et al. 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 et al. 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 and Nielsen 1989; Baldissera et al. 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 (Hortobágyi and DeVita 2006). Early evidence suggested that the CNS controls the motoneurone

pools of an agonist–antagonist muscle pair as a singular pool when performing a task (De Luca and Mambrito 1987; Psek and Cafarelli 1993). More recent evidence has used coherence analysis to estimate the amount of common neural input between two muscles during voluntary movement (Ushiyama and Ushiba 2013). In addition, Dal Maso et al. (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; Lévénez et al. 2008; Psek and Cafarelli 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 and De Luca 1985) and facilitates movement accuracy (Gribble et al. 2003; Tanaka 1974). Further, antagonist behavior 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 behavior (Karst and Hasan 1987; Behm and 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 (Dal 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 (2015; Leung et al. 2015). 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 behavior during training is specific to the force used (Dal Maso et al. 2017), as is the level of intracortical inhibition (Zoghi and 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 suppressed 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. 2018; Hendy and 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 11 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 behavior of the agonist and antagonist muscle to progressive resistance training is an area that must be explored.

Author contributions JM, AF, GH and DJK conceived and designed the study. JM, AF, GH and DJK conducted experiments, analyzed data, and drafted the first version of the manuscript. AJP, SJ, JA critically revised the manuscript. All authors read and approved the manuscript.

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Compliance with ethical standards

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

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